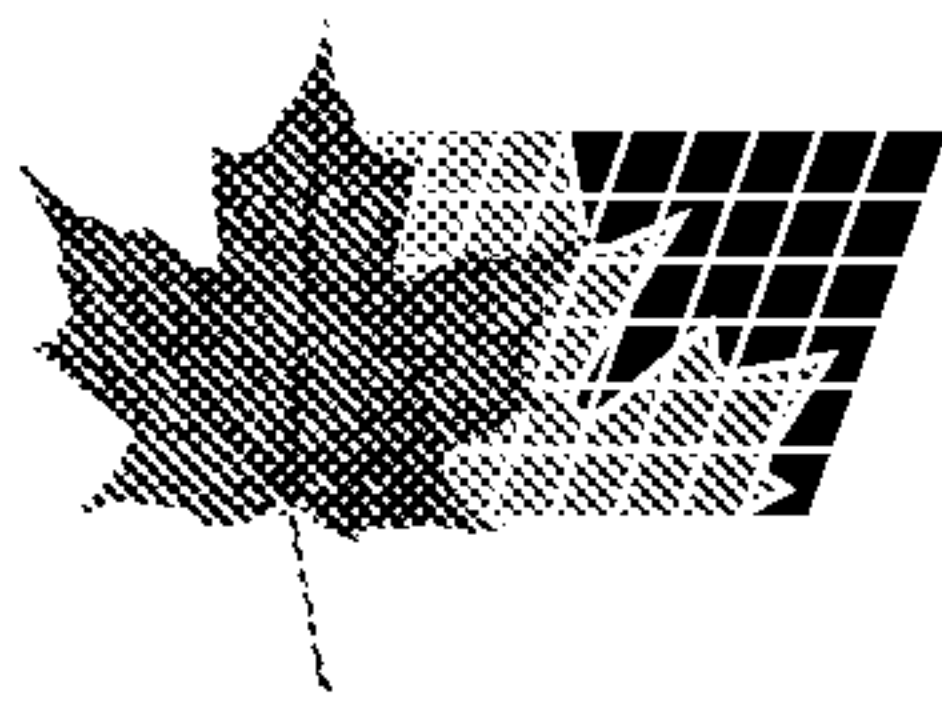
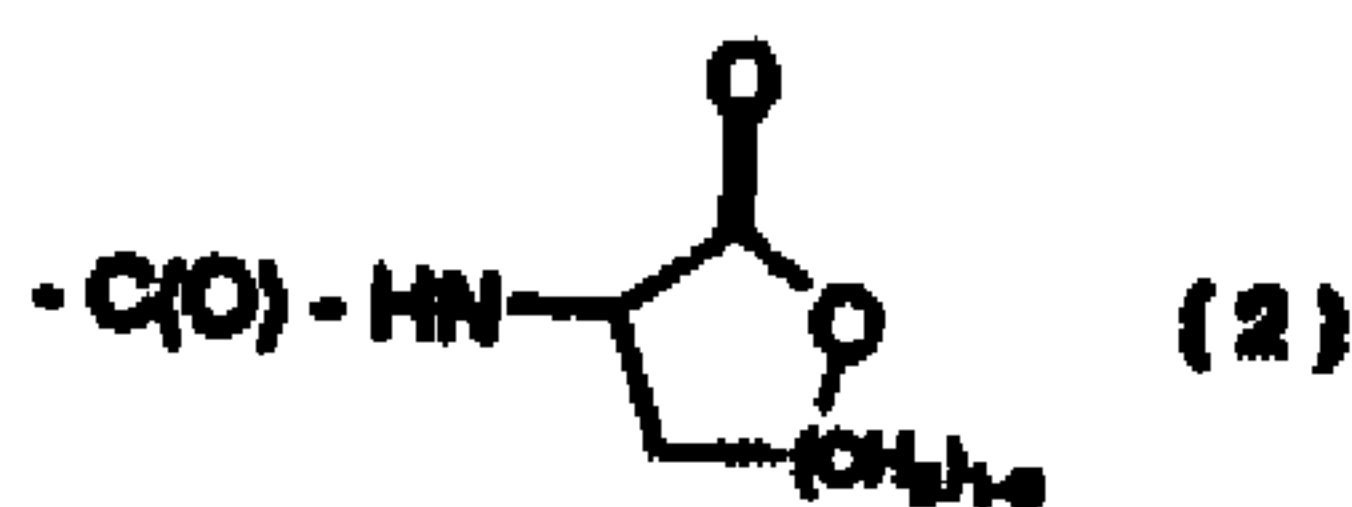
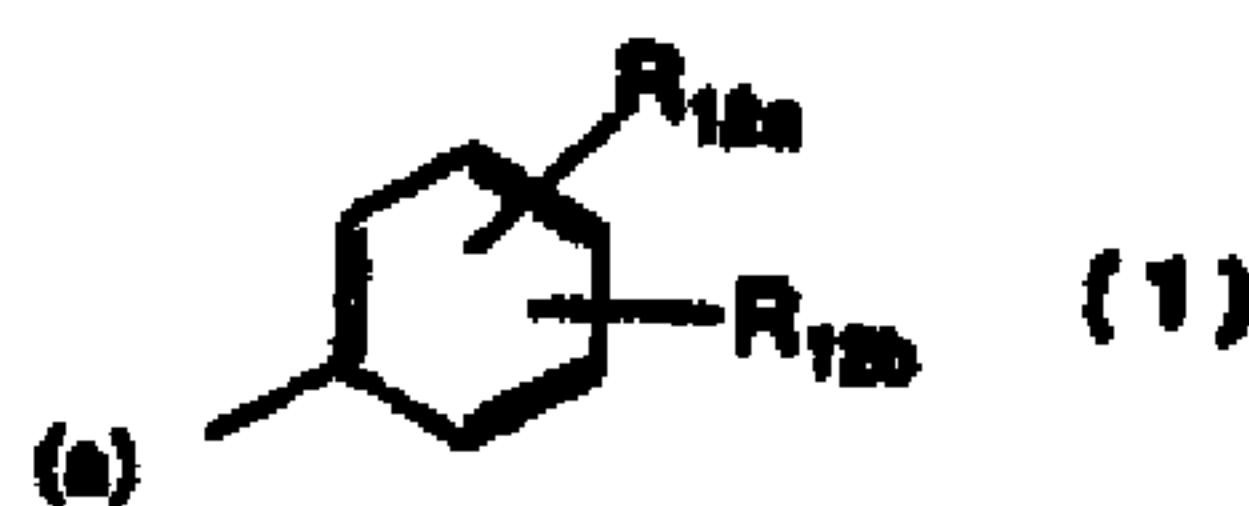
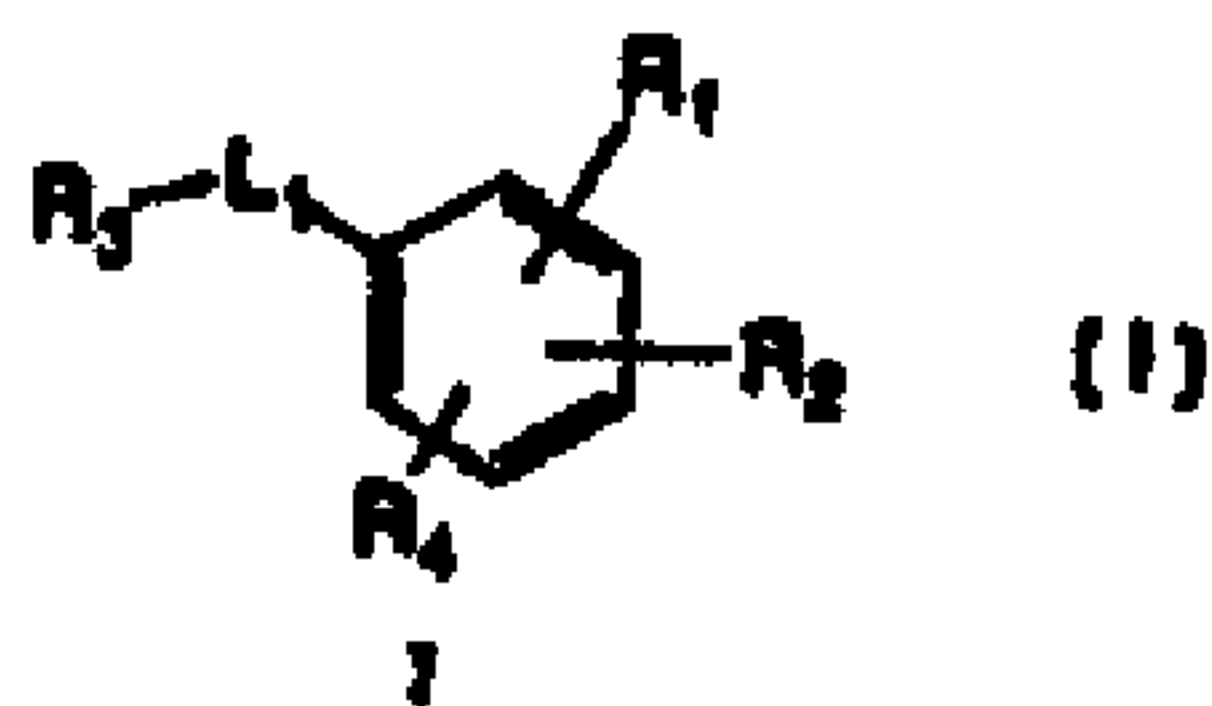
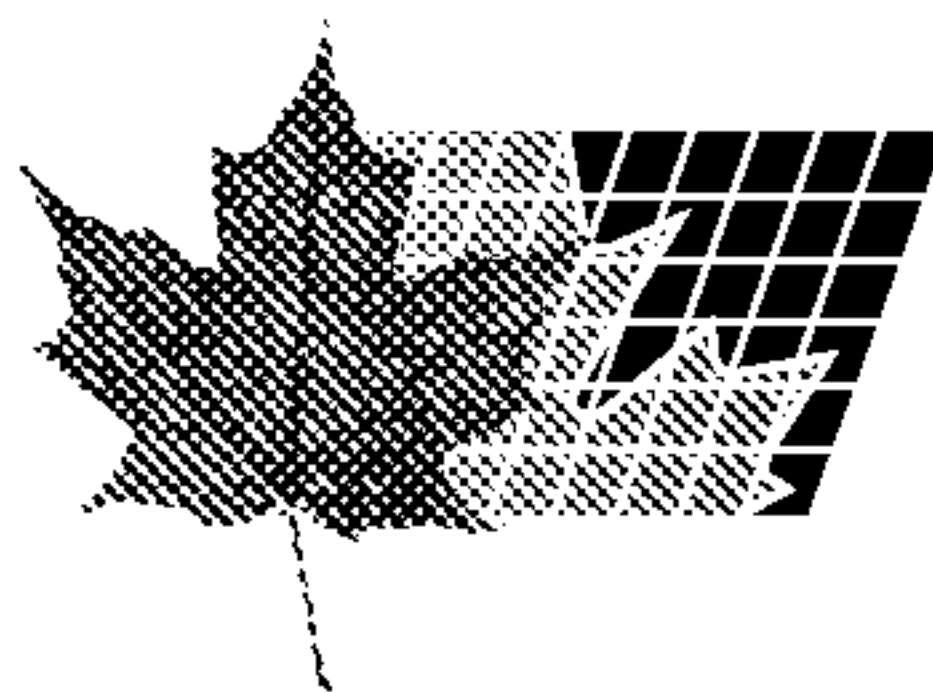




- (72) SEBTI, SAID M., US
(72) HAMILTON, ANDREW D., US
(72) AUGERI, DAVID J., US
(72) BARR, KENNETH J., US
(72) LARSEN, JOHN J., US
(72) DONNER, BERNARD G., US
(72) FAKHOURY, STEPHEN A., US
(72) JANOWICK, DAVID A., US
(72) KALVIN, DOUGLAS M., US
(72) LIU, GANG, US
(72) O'CONNOR, STEPHEN J., US
(72) SHEN, WANG, US
(72) SORENSEN, BRYAN K., US
(72) SZCZEPANKIEWICZ, BRUCE G., US
(72) WASICK, JAMES I., US
(72) ROSENBERG, SAUL H., US
(72) SWENSON, ROLF E., US
(72) SULLIVAN, GERARD M., US
(72) TASKER, ANDREW S., US
(72) WINN, MARTIN, US
(71) UNIVERSITY OF PITTSBURGH, US
(51) Int.Cl.⁷ A61K 31/38, C07D 233/54, A61K 31/505, C07C 303/00,
C07C 309/00, C07C 307/00, C07D 333/00, C07D 307/00,
C07C 313/00, C07C 311/00, A61K 31/495, A61K 31/445, A61K 31/44
(30) 1997/05/07 (08/852,858) US
(54) **INHIBITEURS DE PROTEINES ISOPRENYLE TRANSFERASES**
(54) **INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES**





(57) Cette invention se rapporte à des composés représentés par la formule (I) ou à un sel pharmaceutiquement acceptable de ces composés. Dans la formule (I), R_1 est (a) hydrogène, (b) alkyle inférieur, (c) alkényle, (d) alcoxy, (e) thioalcoxy, (f) halo, (g) haloalkyle, (h) aryle $-L_2-$ et (i) $-L_2-$ hétérocyclique; R_2 est sélectionné dans le groupe constitué par (a) le composé représenté par la formule (1), (b) $-C(O)NH-CH(R_{14})-C(O)OR_{15}$, (c) le composé représenté par la formule (2), (d) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$, (e) $-C(O)NH-CH(R_{14})$ -tétrazolyne, (f) $-C(O)NH$ -hétérocycle et (g) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$; R_3 est aryle ou hétérocyclique substitué ou non substitué, cycloalkényle ou cycloalkyle substitué ou non substitué, le composé représenté par la formule (3) et $-P(W)R^{R3}R^{R3'}$; R_4 est hydrogène, alkyle inférieur, haloalkyle, halogène, aryle, arylalkyle, hétérocycle ou (hétérocycle)alkyle; L_1 est absent ou est sélectionné parmi (a) $-L_4-N(R_5)-L_5-$, (b) $-L_4-O-L_5-$, (c) $-L_4-S(O)_n-L_5-$, (d) $-L_4-L_6-C(W)-N(R_5)-L_5-$, (e) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$, (f) $-L_4-N(R_5)-C(W)-L_7-L_5-$, (g) $-L_4-N(R_5)-S(O)_p-L_7-L_5-$, (h) alkylène éventuellement substitué, (i) alkénylène éventuellement substitué, (j) alkynylène éventuellement substitué, (k) une liaison covalente, (l) le composé représenté par la formule (4), et (m) le composé représenté par la formule (5). Ces composés sont des inhibiteurs de protéines isoprényle transférases. L'invention se rapporte également à des compositions permettant d'inhiber les protéines isoprényle transférases et à un procédé d'inhibition des protéines isoprényle transférases.

(57) Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R_1 is (a) hydrogen, (b) lower alkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl $-L_2-$, and (i) heterocyclic $-L_2-$; R_2 is selected from (a) formula (1), (b) $-C(O)NH-CH(R_{14})-C(O)OR_{15}$, (c) formula (2), (d) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$, (e) $-C(O)NH-CH(R_{14})$ -tetrazolyl, (f) $-C(O)NH$ -heterocyclic, and (g) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$; R_3 is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, formula (3), and $-P(W)R^{R3}R^{R3'}$; R_4 is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L_1 is absent or is selected from (a) $-L_4-N(R_5)-L_5-$, (b) $-L_4-O-L_5-$, (c) $-L_4-S(O)_n-L_5-$, (d) $-L_4-L_6-C(W)-N(R_5)-L_5-$, (e) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$, (f) $-L_4-N(R_5)-C(W)-L_7-L_5-$, (g) $-L_4-N(R_5)-S(O)_p-L_7-L_5-$, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :

A61K 31/38, 31/39, 31/40, 31/415, 31/42,
31/425, 31/44, 31/445, 31/495, 31/505,
31/095, 31/18, C07D 207/09, 233/54,
239/24, 241/04, 263/02, 277/28, 307/00,
333/00, 209/10, C07C 303/00, 307/00,
309/00, 311/00, 313/00

A1

(11) International Publication Number:

WO 98/50029

(43) International Publication Date: 12 November 1998 (12.11.98)

(21) International Application Number: PCT/US98/09296

(22) International Filing Date: 7 May 1998 (07.05.98)

(30) Priority Data:

08/852,858

7 May 1997 (07.05.97)

US

(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Office of Technology Transfer, 911 Williams Pitt Union, Pittsburgh, PA 15260 (US).

(72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle, Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1 White Pine Lane, Guilford, CT 06437 (US). AUGERI, David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US). BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago, IL 60640-4143 (US). DONNER, Bernard, G.; 1901 McRae Lane, Mundelein, IL 60060 (US). FAKHOURY, Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US). JANOWICK, David, A.; 37070 Ganster Road, Beach Park, IL 60087 (US). KALVIN, Douglas, M.; 1201 Lockwood Drive, Buffalo Grove, IL 60089 (US). LARSEN,

John, J.; 10542 Altegld Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard M.; 2214 North Sunrise Drive, Round lake Beach, Illinois 60073 (US). SZCZEPANKIEWICZ, Bruce G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, Illinois 60030 (US). TASKER, Andrew S.; 6251 Eagle Ridge Drive, Gurnee, Illinois 60031 (US). WASICK, James I.; 28440 Dorie Lane, Waterford, Wisconsin 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, Illinois 60015 (US).

(74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman, Intellectual Property Group of Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

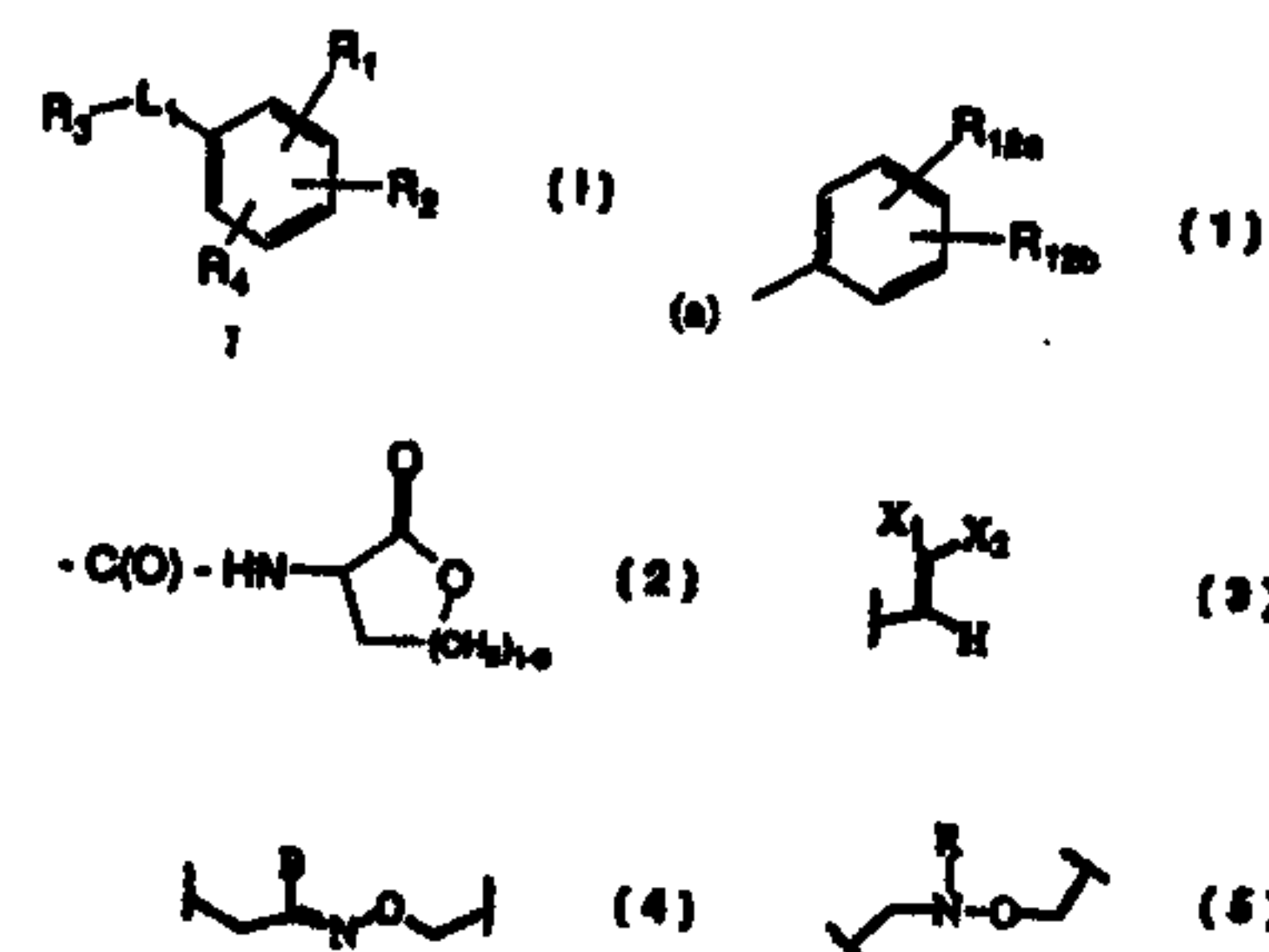
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

(57) Abstract

Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R₁ is (a) hydrogen, (b) lower alkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl -L₂-, and (i) heterocyclic -L₂-; R₂ is selected from (a) formula (1), (b) -C(O)NH-CH(R₁₄)-C(O)OR₁₅, (c) formula (2), (d) -C(O)NH-CH(R₁₄)-C(O)NHSO₂R₁₆, (e) -C(O)NH-CH(R₁₄)-tetrazolyl, (f) -C(O)NH-heterocyclic, and (g) -C(O)NH-CH(R₁₄)-C(O)NR₁₇R₁₈; R₃ is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, formula (3), and -P(W)R^{R3}R^{R3'}; R₄ is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L₁ is absent or is selected from (a) -L₄-N(R₅)-L₅-, (b) -L₄-O-L₅-, (c) -L₄-S(O)_n-L₅-, (d) -L₄-L₆-C(W)-N(R₅)-L₅-, (e) -L₄-L₆-S(O)_m-N(R₅)-L₅-, (f) -L₄-N(R₅)-C(W)-L₇-L₅-, (g) -L₄-N(R₅)-S(O)_p-L₇-L₅-, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.



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INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

5

Technical Field

10 The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

15

Background of the Invention

Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

25 Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, I-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

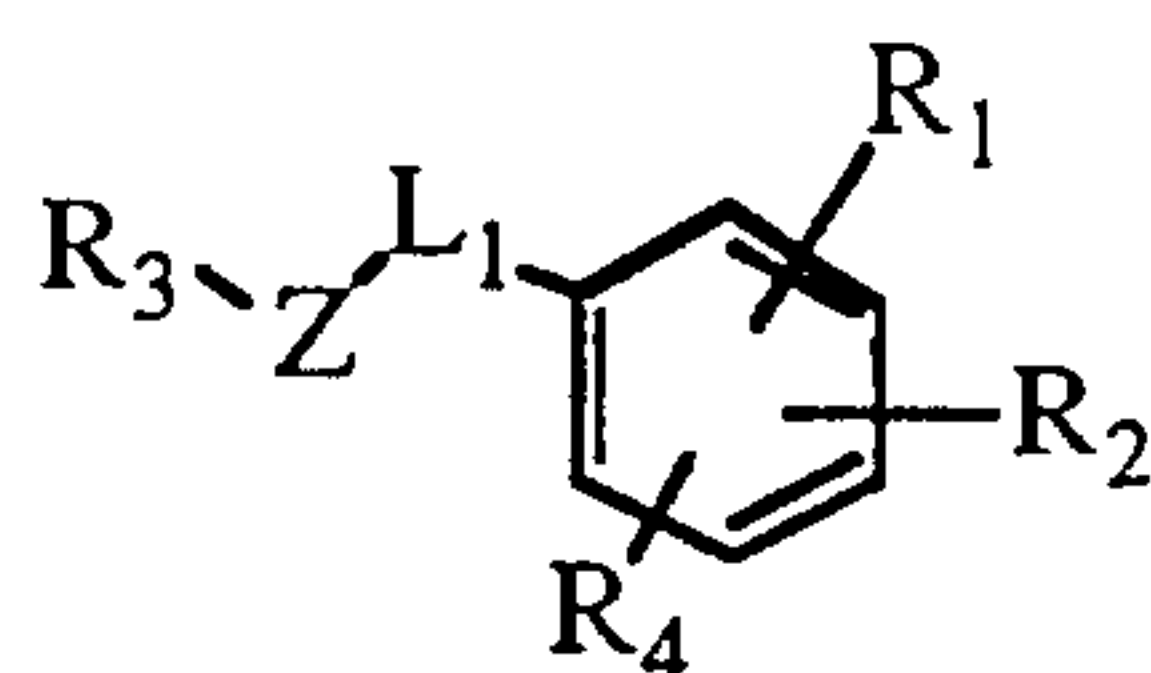
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There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

35

Summary of the Invention

In its principle embodiment, the invention provides a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

R₁ is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl-L₂- wherein aryl is selected from the group consisting of

- (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the group consisting of

alkenyl,

alkynyl,

alkoxy,

aryl,

carboxy,

cyano,

halogen,

haloalkyl,

hydroxy,

hydroxyalkyl,

loweralkyl,

nitro,

N-protected amino, and

-NRR' wherein R and R' are independently selected

from the group consisting of

hydrogen and

75 loweralkyl,

oxo (=O), and

thioalkoxy and

L₂ is absent or is selected from the group consisting of

-CH₂-,

80 -CH₂CH₂-,

-CH(CH₃)-,

-O-,

-C(O)-,

-S(O)_q wherein q is 0, 1 or 2, and

85 -N(R)-, and

(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is

unsubstituted or substituted with 1, 2, 3 or 4 substituents

independently selected from the group consisting of

(a) loweralkyl,

90 (b) hydroxy,

(c) hydroxyalkyl,

(d) halogen

(e) cyano,

(f) nitro,

95 (g) oxo (=O),

(h) -NRR',

(i) N-protected amino,

(j) alkoxy,

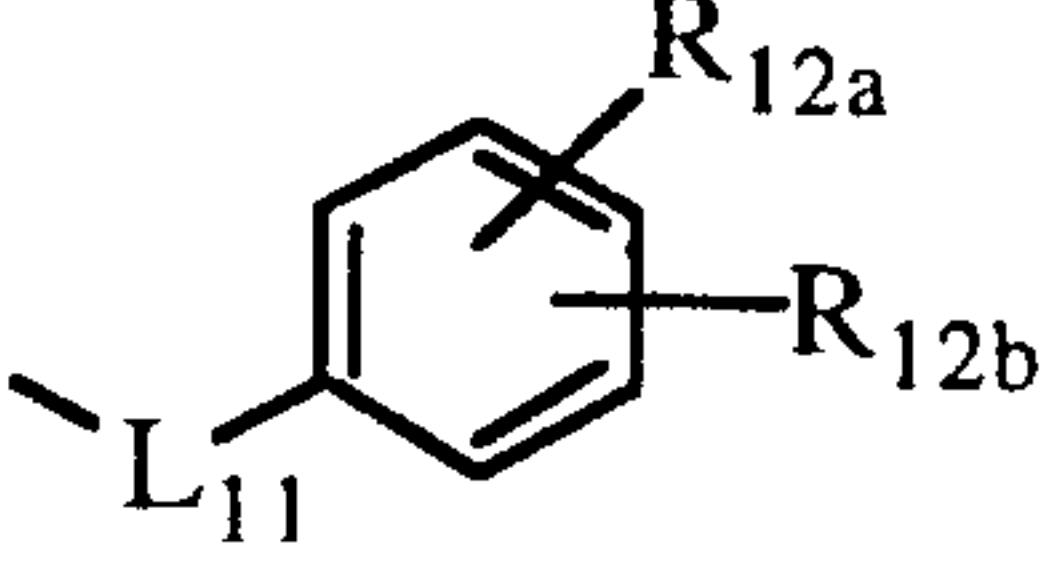
(k) thioalkoxy,

100 (l) haloalkyl,

(m) carboxy, and

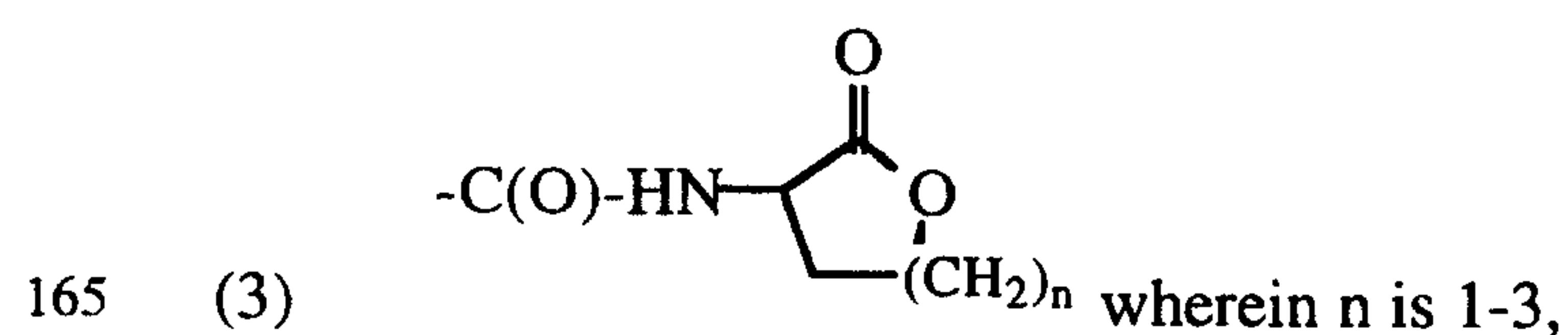
(n) aryl;

R₂ is selected from the group consisting of

- 105 (1)  wherein L_{11} is selected from the group consisting of
- (a) a covalent bond,
 - (b) $-C(W)N(R)-$ wherein R is defined previously and W is selected from the group consisting of O and S ,
 - 110 (c) $-C(O)-$,
 - (d) $-N(R)C(W)-$,
 - (e) $-CH_2O-$,
 - (f) $-C(O)O-$, and
 - (g) $-CH_2N(R)-$,
 - 115 R_{12a} is selected from the group consisting of
 - (a) hydrogen,
 - (b) loweralkyl, and
 - (c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group consisting of
 - 120 hydrogen and
 - a carboxy-protecting group, and
 - R_{12b} is selected from the group consisting of
 - (a) hydrogen and
 - (b) loweralkyl,
 - 125 with the proviso that R_{12a} and R_{12b} are not both hydrogen,

- (2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously, R_v is selected from the group consisting of
- (a) hydrogen and
 - 130 (b) loweralkyl,
 - R_{15} is selected from the group consisting of
 - (a) hydrogen,
 - (b) alkanoyloxyalkyl,
 - (c) loweralkyl, and
 - 135 (b) a carboxy-protecting group, and
 - R_{14} is selected from the group consisting of
 - (a) alkoxyalkyl,
 - (b) alkoxyarylalkyl,

- 140 (c) alkoxycarbonylalkyl,
 (d) alkylsulfinylalkyl,
 (e) alkylsulfonylalkyl,
 (f) alkynyl,
 (g) aminoalkyl,
 (h) aminocarbonylalkyl,
 145 (i) aminothiocarbonylalkyl,
 (j) aryl,
 (k) arylalkyl,
 (l) carboxyalkyl,
 (m) cyanoalkyl,
 150 (n) cycloalkyl,
 (o) cycloalkylalkoxyalkyl,
 (p) cycloalkylalkyl,
 (q) (heterocyclic)alkyl,
 (r) hydroxyalkyl,
 155 (s) hydroxyarylalkyl,
 (t) loweralkyl,
 (u) sulfhydrylalkyl,
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
 unsubstituted or substituted with 1, 2, 3, or 4
 160 substituents selected from the group consisting of
 halogen,
 (w) thioalkoxyalkylamino, and
 (x) thiocycloalkyloxyalkyl,



- (4) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_{14} is defined previously
 and R_{16} is selected from the group consisting of
 170 (a) loweralkyl,
 (b) haloalkyl,
 (c) aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently

- 175 selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
180 oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
185 haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
190 selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
195 cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
200 alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;
- 205
- (5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted
or substituted with loweralkyl or haloalkyl,
- (6) -L₁₁-heterocycle,

210

- (7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously and R_{17} and R_{18} are independently selected from the group consisting of

215

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

220

- (8) $-C(O)OR_{15}$, and

- (9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

225

L_1 is absent or is selected from the group consisting of

- (1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group consisting of

230

- (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

235

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents, with the proviso that no two hydroxyls are attached to the same carbon,

240

alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of

245

halogen and
 cycloalkyl,
 alkylsilyloxy,
 250 alkyl[S(O)_q],
 alkyl[S(O)_q]alkyl,
 aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently
 selected from the group consisting of
 255 alkoxy wherein the alkoxy is unsubstituted or
 substituted with substituents selected
 from the group consisting of cycloalkyl,
 aryl,
 arylalkyl,
 260 aryloxy wherein the aryloxy is unsubstituted or
 substituted with 1, 2, 3, 4, or 5
 substituents independently selected from
 the group consisting of,
 halogen,
 265 nitro, and
 -NRR',
 cycloalkyl,
 halogen,
 loweralkyl,
 270 hydroxyl,
 nitro,
 -NRR', and
 -SO₂NRR',
 arylalkoxy wherein the arylalkoxy is unsubstituted or
 275 substituted with substituents selected from the
 group consisting of alkoxy,
 arylalkyl,
 arylalkyl[S(O)_q]alkyl,
 aryl[S(O)_q],
 280 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
 unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents independently selected from
 alkoxy and

285 loweralkyl,
 arylalkoxyalkyl wherein the arylalkoxyalkyl is
 unsubstituted or substituted with substituents
 selected from the group consisting of
 alkoxy, and
 halogen,
 290 aryloxy,
 aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
 substituted with substituents selected from the
 group consisting of halogen,
 carboxyl,
 295 $-C(O)NR_C R_D$ wherein R_C and R_D are independently
 selected from the group consisting of
 hydrogen,
 loweralkyl, and
 alkoxycarbonyl or
 300 R_C and R_D together with the nitrogen to which
 they are attached form a ring selected
 from the group consisting of
 morpholine,
 piperidine,
 305 pyrrolidine
 thiomorpholine,
 thiomorpholine sulfone, and
 thiomorpholine sulfoxide,
 wherein the ring formed by R_C and R_D
 310 together is unsubstituted or
 substituted with 1 or 2
 substituents independently
 selected from the group consisting
 of alkoxy and alkoxyalkyl,
 315 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
 substituted with 1 or 2 substituents selected from
 the group consisting of alkenyl,
 cyclolalkoxy,
 cycloalkoxycarbonyl,
 320 cyclolalkoxyalkyl,

cyclolalkyl wherein the cycloalkyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting
of aryl,
325 loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
330 cycloalkylalkyl,
cycloalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
335 substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
340 independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
unsubstituted or substituted with 1 or 2
substituents independently selected from
345 the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2
350 substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or
355 substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of

360 alkanoyl,
 alkoxy,
 carboxaldehyde,
 haloalkyl,
 halogen,
 loweralkyl,
 nitro,
 365 -NRR', and
 thioalkoxy,
 arylalkyl,
 aryloxy,
 cycloalkoxyalkyl,
 370 cycloalkyl,
 cycloalkylalkyl,
 halogen,
 heterocycle,
 hydroxyl,
 375 loweralkyl wherein the loweralkyl is
 unsubstituted or substituted with 1, 2, or
 3 substituents independently selected
 from the group consisting of
 heterocycle,
 380 hydroxyl,
 with the proviso that no two hydroxyls
 are attached to the same carbon,
 and
 -NR^{R3}R^{R3'} wherein R^{R3} and R^{R3'} are
 385 independently selected from the
 group consisting of
 hydrogen
 aryl,
 loweralkyl,
 390 aryl,
 arylalkyl,
 heterocycle,
 (heterocyclic)alkyl,
 cycloalkyl, and

430

-O-NH-R,

$\text{—O—N}=\begin{matrix} \text{J}' \\ \text{J} \end{matrix}$ wherein J and J' are independently selected

from the group consisting of

435

loweralkyl and

arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

440

oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

445

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

450

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

455

sulfhydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

460

(b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R₅ is selected from the group consisting of

hydrogen,

465

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

group consisting of aryl,

alkoxy,
 alkoxyalkyl,
 470 alkoxycarbonyl wherein the alkoxycarbonyl is
 unsubstituted or substituted with 1, 2 or 3
 substituents independently selected from the
 group consisting of
 aryl and
 475 halogen,
 alkylaminocarbonylalkyl wherein the
 alkylaminocarbonylalkyl is unsubstituted or
 substituted with 1 or 2 substituents
 independently selected from the group consisting
 480 of aryl,
 (anthracenyl)alkyl,
 aryl,
 arylalkoxy,
 arylalkyl wherein the arylalkyl is unsubstituted or
 485 substituted with 1, 2, 3, 4, or 5 substituents
 independently selected from the group
 consisting of
 alkoxy,
 aryl,
 490 carboxyl,
 cyano,
 halogen,
 haloalkoxy,
 haloalkyl,
 495 nitro,
 oxo, and
 -L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
 (aryl)oyl wherein the (aryl)oyl is unsubstituted or
 substituted with substituents selected from the
 500 group consisting of halogen,
 aryloxycarbonyl,
 carboxaldehyde,
 -C(O)NRR',
 cycloalkoxycarbonyl,

- 505 cycloalkylaminocarbonyl,
cycloalkylaminothiocarbonyl,
cyanoalkyl,
cycloalkyl,
cycloalkylalkyl wherein the cycloalkylalkyl is
- 510 unsubstituted or substituted with 1 or 2 hydroxyl
substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,
(cycloalkyl)oyl,
- 515 (9,10-dihydroanthracenyl)alkyl wherein the
(9,10-dihydroanthracenyl)alkyl is unsubstituted
or substituted with 1 or 2 oxo substituents,
haloalkyl,
heterocycle,
- 520 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents selected from the group consisting of
loweralkyl,
(heterocyclic)oyl,
- 525 loweralkyl, wherein the loweralkyl is unsubstituted
or substituted with substituents selected from the
group consisting of -NRR',
-SO₂-A, and
thioalkoxyalkyl;
- 530 (2) -L₄-O-L₅-,
- (3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
or 2,
- 535 (4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
R₆ is selected from the group consisting of
- (a) hydrogen,
(b) loweralkyl,
540 (c) aryl,
(d) arylalkyl,

- (e) heterocycle,
 (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 (h) cycloalkylalkyl, and
 545 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R₆)- wherein R₆ is selected from the group
 550 consisting of
 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 555 heterocycle,
 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- (5) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
 560
 (6) -L₄-L₆-N(R₅)-S(O)_m-L₅-,
 (7) -L₄-N(R₅)-C(W)-L₇-L₅- wherein L₄, R₅, W, and L₅ are
 565 defined previously and L₇ is absent or is selected from the group
 consisting of -O- and -S-,
 (8) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or
 substituted with 1 or 2 substituents independently selected from
 570 the group consisting of
 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 575 (e) cyclolakyl,
 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and
 (h) hydroxy,

580 (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- (a) aryl,
- (b) arylalkyl,
- 585 (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
- (d) heterocycle,
- 590 (e) (heterocycle)alkyl,
- (f) hydroxyalkyl,
- (g) cyclolalkyl,
- (h) cycloalkylalkyl,
- (i) alkylthioalkyl, and
- 595 (j) hydroxy,

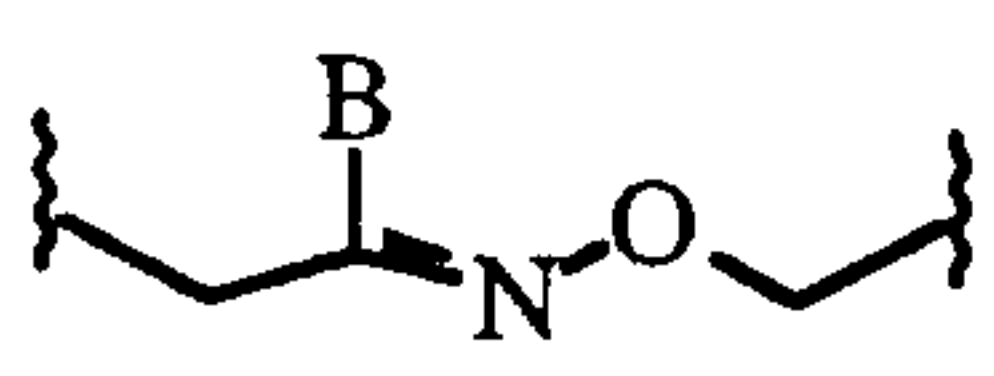
(10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- 600 (a) aryl,
- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolalkyl,
- 605 (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

(11) -L₄-heterocycle-L₅-,

610

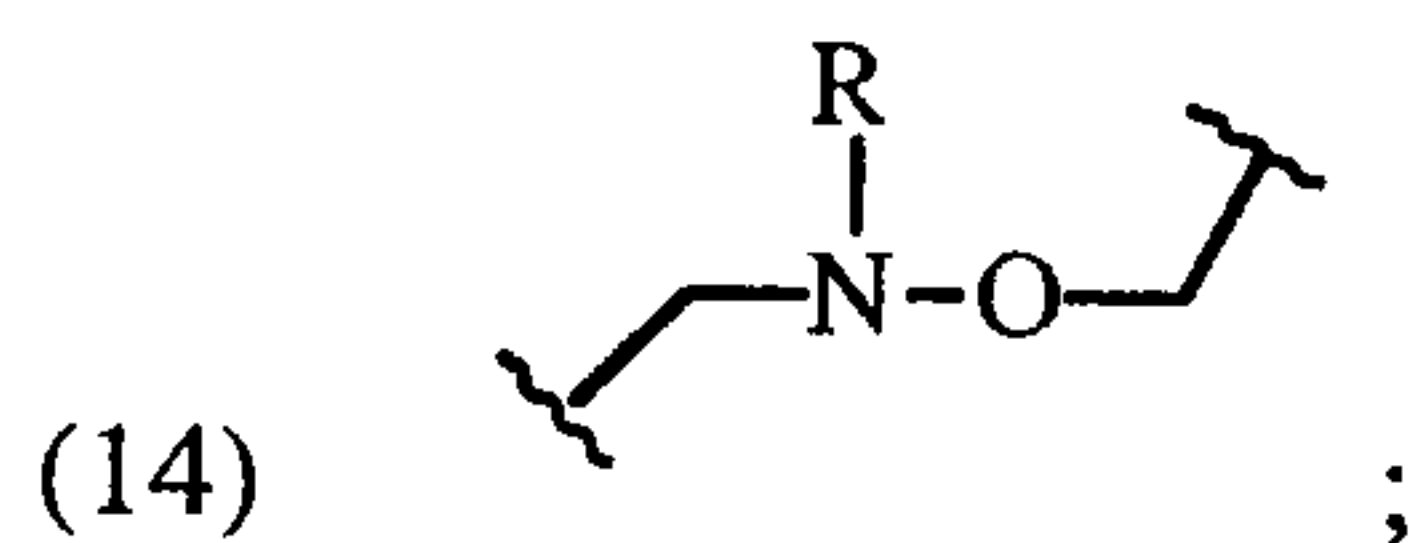
(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and

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615 arylalkyl, and



Z is selected from the group consisting of

- 620 (1) a covalent bond,
 (2) -O-,
 (3) -S(O)_q-, and
 (4) -NR_Z- wherein R_Z is selected from the group consisting of
 (a) hydrogen
 625 (b) loweralkyl,
 (c) aryl,
 (d) arylalkyl,
 (e) heterocycle,
 (f) (heterocyclic)alkyl,
 630 (g) cyclolalkyl, and
 (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,
 635 (2) aryl,
 (3) fluorenyl,
 (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

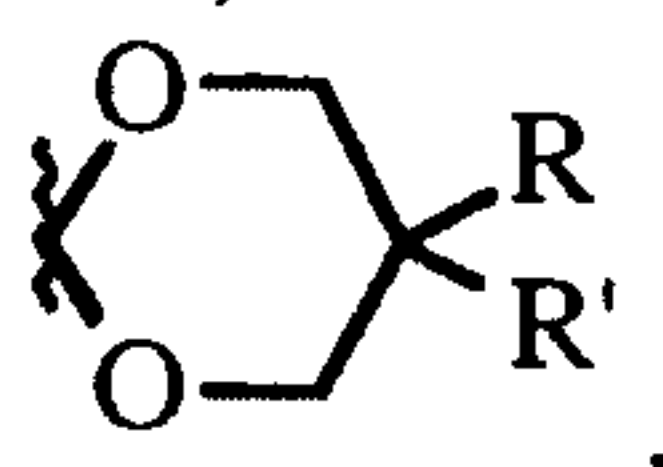
- 640 (a) alkanoyl,
 (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1,
 2, 3, 4, or 5 substituents independently selected from the
 group consisting of
 halogen,
 645 aryl, and
 cycloalkyl,
 (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or
 substituted with 1 or 2, 3, 4 or 5 substituents
 independently selected from the group consisting of

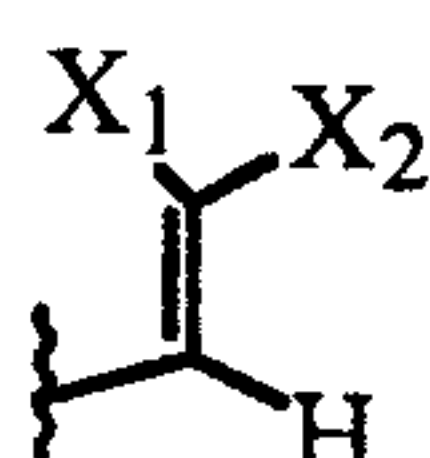
- 650 aryl and
cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of
- 655 aryl, and
cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3,
- 660 4, or 5 substituents independently selected from the
group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted
with 1 or 2 substituents selected from the group
- 665 consisting of cycloalkyl,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
- 670 nitro,
-NRR', and
thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or
- 675 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
- 680 (j) (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR'' wherein R is defined previously and R'' is
- 685 selected from the group consisting of
hydrogen,

- loweralkyl, and
carboxyalkyl,
- 690 (o) cyano,
(p) cyanoalkyl,
(q) cycloalkyl,
(r) cycloalkylalkyl,
(s) cycloalkoxyalkyl,
(t) halogen,
- 695 (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,
- 700 (v) heterocycle,
(w) hydroxyl,
(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,
- 705 (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
with substituents selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,
- 710 -NR³R^{3'}, and
-P(O)(OR)(OR'),
- (z) nitro,
(aa) -NRR',
(bb) oxo,
- 715 (cc) -SO₂NR_A'R_B' wherein R_A' and R_B' are independently selected
from the group consisting of
hydrogen,
(aryl)oyl,
loweralkyl, and
- 720 heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, or 3 substituents
independently selected from the group consisting
of loweralkyl,

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- 725 (dd) sulfhydryl, and
(ee) thioalkoxy,
- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with
1, 2, 3, 4 or 5 substituents selected from the group consisting of
730 (a) alkoxy,
(b) aryl,
(c) arylalkoxy
(d) aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
selected from the group consisting of halogen,
735 (e) loweralkyl,
(f) halogen,
(g) $\text{NR}^3\text{R}^3'$,
(h) oxo, and
(i) ,
740
- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted
with 1, 2, 3 or 4 substituents independently selected from the
group consisting of
745 (a) loweralkyl,
(b) alkoxy,
(c) halogen,
(d) aryl,
(e) aryloxy,
(f) alkanoyl, and
750 (g) $\text{NR}^3\text{R}^3'$,

- (7)  wherein X_1 and X_2 together are cycloalkyl wherein the
cycloalkyl is unsubstituted or substituted with 1 or 2 substituents
selected from the group consisting of aryl, and

755

- (8) $-\text{P}(\text{W})\text{R}^3\text{R}^3'$; and

R₄ is selected from the group consisting of

- (1) hydrogen,
- 760 (2) loweralkyl,
- (3) haloalkyl
- (4) halogen,
- (5) aryl,
- (6) arylalkyl,
- 765 (7) heterocycle,
- (8) (heterocyclic)alkyl
- (9) alkoxy, and
- (10) -NRR'; or

770 **L₁, Z, and R₃** together are selected from the group consisting of

- (1) aminoalkyl,
- (1) haloalkyl,
- (2) halogen,
- (3) carboxaldehyde, and
- 775 (4) (carboxaldehyde)alkyl, and
- (5) hydroxyalkyl,

with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a
780 pharmaceutically acceptable carrier.

In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting
785 protein isoprenyl transferases (i.e., protein farnesyltransferase and/or geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase,
790 protein geranylgeranyltransferase or both.

In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

795 In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a therapeutically effective amount of a compound of the invention alone or in combination with another chemotherapeutic agent

800 In yet another aspect of the present invention is disclosed a method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

805 The compounds of the invention can comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is hereby incorporated herein by reference.

810

Detailed Description

Definitions of Terms

815 As used herein the terms "Cys," "Glu," "Leu," "Lys," "Met," "nor-Leu," "nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine, norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As used herein these amino acids are in their naturally occurring L- form.

820 As used herein, the term "carboxy protecting group" refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference). Examples of esters
830 useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21

of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference.

Representative carboxy protecting groups are C₁ to C₈ loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted
 835 derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the
 840 like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-
 850 (phenoxyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as
 855 t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the
 860 like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl
 865 ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an

alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{29}C(O)-$ wherein R_{29} is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{71}-NH-$ wherein R_{71} is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to $R_{29}C(O)-O-$ wherein R_{29} is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include -CH=CH₂, -CH₂CH=CH₂, -C(CH₃)=CH₂,
 905 -CH₂CH=CHCH₃, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also
 910 containing at least one carbon-carbon double bond. Examples of alkenylene include -CH=CH-, -CH₂CH=CH-, -C(CH₃)=CH-, -CH₂CH=CHCH₂-, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention
 915 can be optionally substituted.

The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to R₃₀O- wherein R₃₀ is loweralkyl as
 920 defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

925 The term "alkoxyalkoxy" as used herein refers to R₃₁O-R₃₂O- wherein R₃₁ is loweralkyl as defined above and R₃₂ is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously
 930 defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R₆₆-C(O)-O- wherein R₆₆ is an alkoxyalkyl group.

935 The term "alkoxyarylalkyl" as used herein refers to a an arylalkyl group to which is attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of

940 alkoxy carbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like. The alkoxy carbonyl groups of this invention can be optionally substituted. The alkoxy carbonyl groups of this invention can be optionally substituted.

The term "alkoxy carbonyl alkyl" as used herein refers to an alkoxy carbonyl group as previously defined appended to a lower alkyl radical. Examples of alkoxy carbonyl alkyl
945 include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The alkoxy carbonyl alkyl groups of this invention can be optionally substituted.

The term "alkoxy carbonyl amino alkyl" as used herein refers to a lower alkyl radical to which is appended $R_{69}-NH-$ wherein R_{69} is an alkoxy carbonyl group. The alkoxy carbonyl amino alkyl groups of this invention can be optionally substituted.

950 The term "alkoxy carbonyloxy alkyl" as used herein refers to a lower alkyl radical to which is appended $R_{63}-O-$ wherein R_{63} is an alkoxy carbonyl group. The alkoxy carbonyloxy alkyl groups of this invention can be optionally substituted.

The term "alkyl amino" as used herein refers to $R_{35}NH-$ wherein R_{35} is a lower alkyl group, for example, methyl amino, ethyl amino, butyl amino, and the like. The alkyl amino
955 groups of this invention can be optionally substituted.

The term "alkyl amino alkyl" as used herein refers a lower alkyl radical to which is appended an alkyl amino group. The alkyl amino alkyl groups of this invention can be optionally substituted.

The term "alkyl aminocarbonyl amino alkyl" as used herein refers to a lower alkyl
960 radical to which is appended $R_{70}-C(O)-NH-$ wherein R_{70} is an alkyl amino group. The alkyl aminocarbonyl amino alkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene,
965 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be optionally substituted.

The term "alkyl silyloxy" as used herein refers to a lower alkyl group to which is attached $-OSiR_W'R_X'R_Y'$ wherein R_W' , R_X' , and R_Y' are selected from the group consisting of lower alkyl.

970 The term "alkyl sulfinyl" as used herein refers to $R_{33}S(O)-$ wherein R_{33} is a lower alkyl group. The alkyl sulfinyl groups of this invention can be optionally substituted.

The term "alkyl sulfinyl alkyl" as used herein refers to an alkyl group to which is attached a alkyl sulfinyl group. The alkyl sulfinyl alkyl groups of this invention can be optionally substituted.

975 The term "alkyl sulfonyl" as used herein refers to $R_{34}S(O)_2-$ wherein R_{34} is a lower alkyl group. The alkyl sulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be optionally substituted.

980 The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include $-C\equiv CH$, $-CH_2C\equiv CH$, $-CH_2C\equiv CCH_3$, and the like. 985 The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include $-C\equiv C-$, 990 $-CH_2C\equiv C-$, $-CH_2C\equiv CCH_2-$, and the like. The alkynylene groups of this invention can be optionally substituted.

The term "amino" as used herein refers to $-NH_2$.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this 995 invention can be optionally substituted.

The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

1000 The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is appended an amino group. The aminoalkyl groups of this invention can be optionally substituted.

The term "aminothiocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocarbonylcarbonyl ($C=S$) group. The aminothiocarbonyl groups of this invention can be optionally substituted.

1005 The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aryloxy group (i.e., $R_{61}-C(O)O-$ wherein R_{61} is an aryl group). The aryloxyalkyl groups of this invention can be optionally substituted.

1010 The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy,

alkoxycarbonyl, haloalkyl-C(O)-NH-, haloalkenyl-C(O)-NH- and carboxamide. In
 1015 addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is
 appended an aryl group. The arylalkenyl groups of this invention can be optionally
 substituted.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl
 1020 radical to which is appended $R_{68}-O-C(O)-O-$ wherein R_{68} is an arylalkenyl group. The
 arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached
 an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is
 1025 appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl,
 hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this
 invention can be optionally substituted.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to
 which is appended an arylalkylcarbonyloxy group (i.e., $R_{62}C(O)O-$ wherein R_{62} is an
 1030 arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally
 substituted.

The term "aryloxy" as used herein refers to an aryl group attached to the parent
 molecular group through an oxygen atom. The aryloxy groups of this invention can be
 optionally substituted.

1035 The term "aryloxycarbonyl" as used herein refers to an aryloxy group attached to the
 parent molecular group through a carbonyl group. The aryloxycarbonyl groups of this
 invention can be optionally substituted.

The term "aryloyl" as used herein refers to an aryl group attached to the parent
 molecular group through a carbonyl group. The aryloyl groups of this invention can be
 1040 optionally substituted.

The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl
 radical to which is appended $R_{67}-O-C(O)-O-$ wherein R_{67} is an arylalkyl group. The
 arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1045 The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is
 appended $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxyalkyl groups of this invention
 can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy radical to which is
 appended $R_{65}-O-$ wherein R_{65} is an aryl group. The arylalkoxy groups of this invention
 can be optionally substituted.

1050 The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of
1055 this invention can be optionally substituted.

The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{75}-S-$ wherein R_{75} is an aryloxyalkyl group. The
1060 aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-C(O)-O-$ wherein R_{65} is an aryl group. The aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1065 The term "arylsulfonyl" as used herein refers to $R_{36}S(O)_2-$ wherein R_{36} is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to $R_{37}S(O)_2O-$ wherein R_{37} is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to $-COOH$.

1070 The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy ($-COOH$) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano ($-CN$) group. The cyanoalkyl groups of this invention can be
1075 optionally substituted.

The term "carboxaldehyde" as used herein used herein refers to $-CHO$.

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

1080 The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e., $R_{60}-C(O)-$ wherein R_{60} is a cycloalkyl group).

1085 The cycloalkanoylalkyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1090 The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

1095 The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

1100 The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

1105 The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{O})-$ wherein R_{60} is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

1110 The term "cycloalkylaminothiocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{S})-$ wherein R_{60} is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

1115 The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1120 The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like.

1125 The cycloalkylalkyl groups of this invention can be optionally substituted.

The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{64}-O-C(O)-O-$ wherein R_{64} is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1130 The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

1135 The term "dialkylamino" as used herein refers to $R_{38}R_{39}N-$ wherein R_{38} and R_{39} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

1140 The term "dialkyaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{73}-C(O)-$ wherein R_{73} is a dialkylamino group. The dialkyaminocarbonylalkyl groups of this invention can be optionally substituted.

The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo ($=O$) groups. The dioxoalkyl groups of this invention can be optionally substituted.

1145 The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

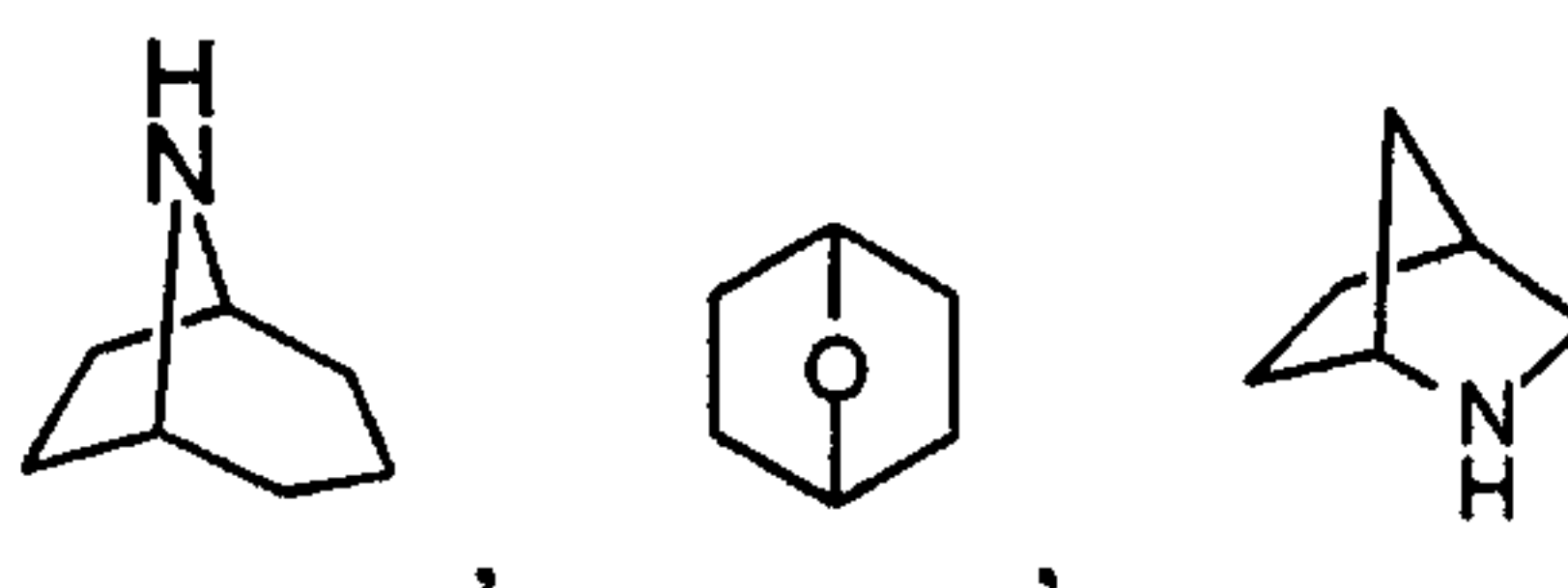
The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

1150 The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

1155 The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

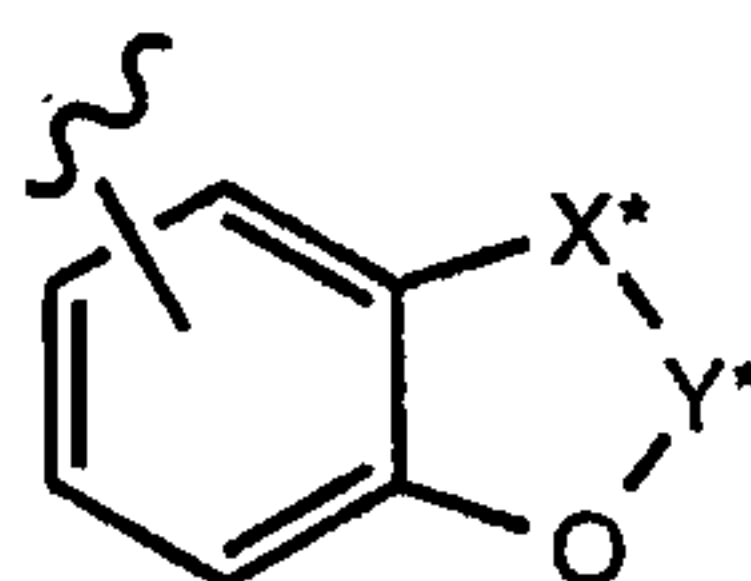
The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring

1160 containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two
 or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur
 atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one
 oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent
 positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent
 nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom;
 1165 two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2
 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term
 "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the
 above heterocyclic rings is fused to one or two rings independently selected from the group
 consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a
 1170 cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl,
 isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics
 include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl,
 imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl,
 piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl,
 1175 morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl,
 indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl,
 thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl,
 tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl,
 tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl,
 1180 benzofuranyl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein
 a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

1185 Heterocyclics also include compounds of the formula



wherein X* is -CH₂-, -CH₂O- or -O- and Y* is -C(O)- or -(C(R''))_v - wherein R'' is
 hydrogen or C₁-C₄-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl
 and the like.

- 1190 Heterocyclics can be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of
- a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino, g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four
- 1195 loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) -SO₃H, w) loweralkyl, x) alkoxycarbonyl, y) -C(O)NH₂, z) -C(S)NH₂, aa) -C(=N-OH)NH₂, bb) aryl-L₁₆-C(O)- wherein L₁₆ is an alkenylene radical, cc) -S-L₁₇-C(O)OR₄₀ wherein L₁₇ is an alkylene radical which is unsubstituted or substituted with one or two
- 1200 substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₂ is loweralkyl) and R₄₀ is hydrogen or a carboxy-protecting group, dd) -S-L₁₈-C(O)NR₄₃R₄₄ wherein L₁₈ is an alkylene radical which is unsubstituted or substituted with one or two
- 1205 substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₃ and R₄₄ are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L₁₉-CN wherein L₁₉ is an alkylene radical, ff) -S-L₂₀-R₄₅ wherein L₂₀ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R₄₅ is
- 1210 hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L₂₁-R₄₆ wherein L₂₁ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the
- 1215 alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₆ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group
- 1220 consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) -O-S(O)₂-R₄₇ wherein R₄₇ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) -S(O)₂-NH-R₄₈ wherein R₄₈ is
- 1225 aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or

- substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) $-C(=NOR_{49})C(O)OR_{50}$ wherein R_{49} is hydrogen or loweralkyl and R_{50} is hydrogen or a carboxy-protecting group, oo) alkoxycarbonylalkyl, pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn) $R_{53}-L_{22}-$, wherein L_{22} is alkenylene or alkynylene and R_{53} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp) $R_{54}-N=N-$ wherein R_{54} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qqq) $=N-R_{55}$ wherein R_{55} is hydrogen, aryl, heterocyclic, $-S(O)_2$ -aryl or $-S(O)_2$ -heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N(R_{56})- or arylalkyl-N(R_{56})- wherein R_{56} is hydrogen or an N-protecting group, ttt) aryl-sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) $=C(CN)(C(O)NH_2)$, www) $=C(CN)(C(O)O$ -loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH- L_{23} - wherein L_{23} is an alkylene group, eeee) heterocyclicalkyl-NH- L_{24} - wherein L_{24} is an alkylene group, ffff) aryl-S(O)₂-NH- L_{25} - wherein L_{25} is an alkylene group, gggg) heterocyclic-S(O)₂-NH- L_{26} - wherein L_{26} is an alkylene group, hhhh) aryl-C(O)-NH- L_{27} - wherein L_{27} is an alkylene group and iiiii) heterocyclic-C(O)-NH- L_{28} -

wherein L_{28} is an alkylene group, $jjjj) R_{yy}(CH_2)_n-X-Y-Z-(CH_2)_m$ wherein R_{yy} is
 1265 cycloalkyl, aryl and loweralkyl, n and m are independently 0-2, Z is O or absent, Y is
 absent, CH_2 , $CHOH$ or $C(O)$, with the proviso that when X is O, Z is absent and with the
 proviso that when Z is O, X is absent and with the proviso that when Y is $CHOH$, X and Z
 are absent.

The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is
 1270 attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally
 substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as
 defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic
 alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The
 1275 (heterocyclic)alkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the
 parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this
 invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is
 1280 attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can
 be optionally substituted.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group
 to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention
 can be optionally substituted.

1285 The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical
 to which is appended $R_{72}-C(O)-O-$ wherein R_{72} is a heterocyclic group. The
 heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to $-OH$.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is
 1290 appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally
 substituted.

The term "hydroxyarylalkyl" as used herein refers to a arylalkyl group to which is
 appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be
 optionally substituted.

1295 The term "hydroxythioalkoxy" as used herein refers to $R_{51}S-$ wherein R_{51} is a
 hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally
 substituted.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl
 groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-

1300 butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

1305 The term "nitro" as used herein refers to $-\text{NO}_2$.

The term "oxo" as used herein refers to $(=\text{O})$.

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo $(=\text{O})$ group. The oxoalkyloxy groups of this invention can be optionally substituted.

1310 The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a $-\text{O}-\text{NR}-\text{C}(\text{O})-\text{R}'$ group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a $-\text{O}-\text{NR}^{\text{R}_3}-\text{C}(\text{O})-\text{R}$ group wherein R^{R_3} is arylalkyl and R is loweralkyl.

1315 The term "oxyaminocarbonylalkyl" as used herein refers to $-\text{O}-\text{NH}-\text{C}(\text{O})-\text{R}$ group wherein R is loweralkyl.

The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to $-\text{SH}$.

1320 The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to $\text{R}_{52}\text{S}-$ wherein R_{52} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

1325 The thioalkoxy groups of this invention can be optionally substituted.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

1330 The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

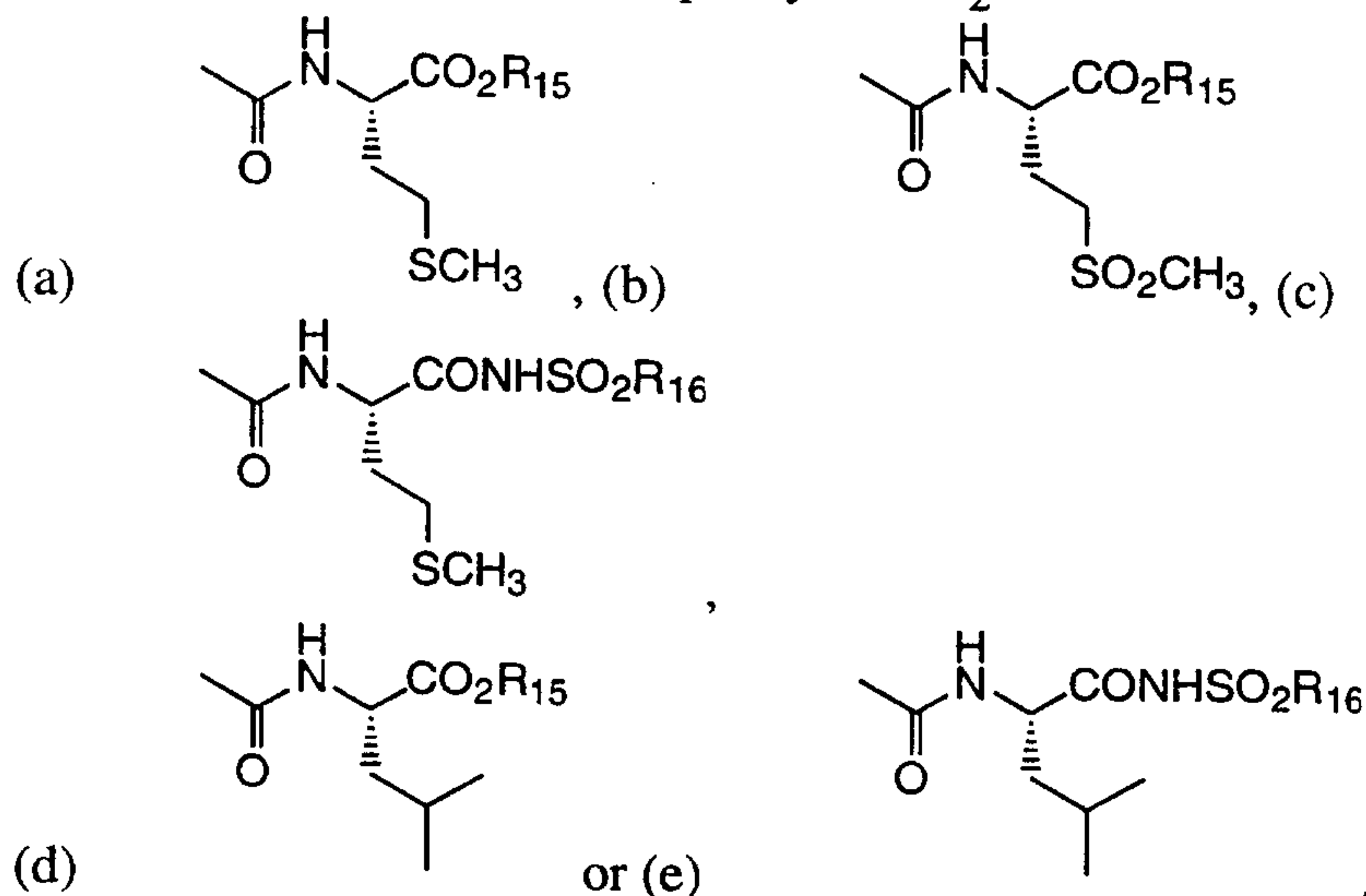
1335 The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_2 , R_{14} , R_{15} and R_{16} are defined above.

1340

More preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is

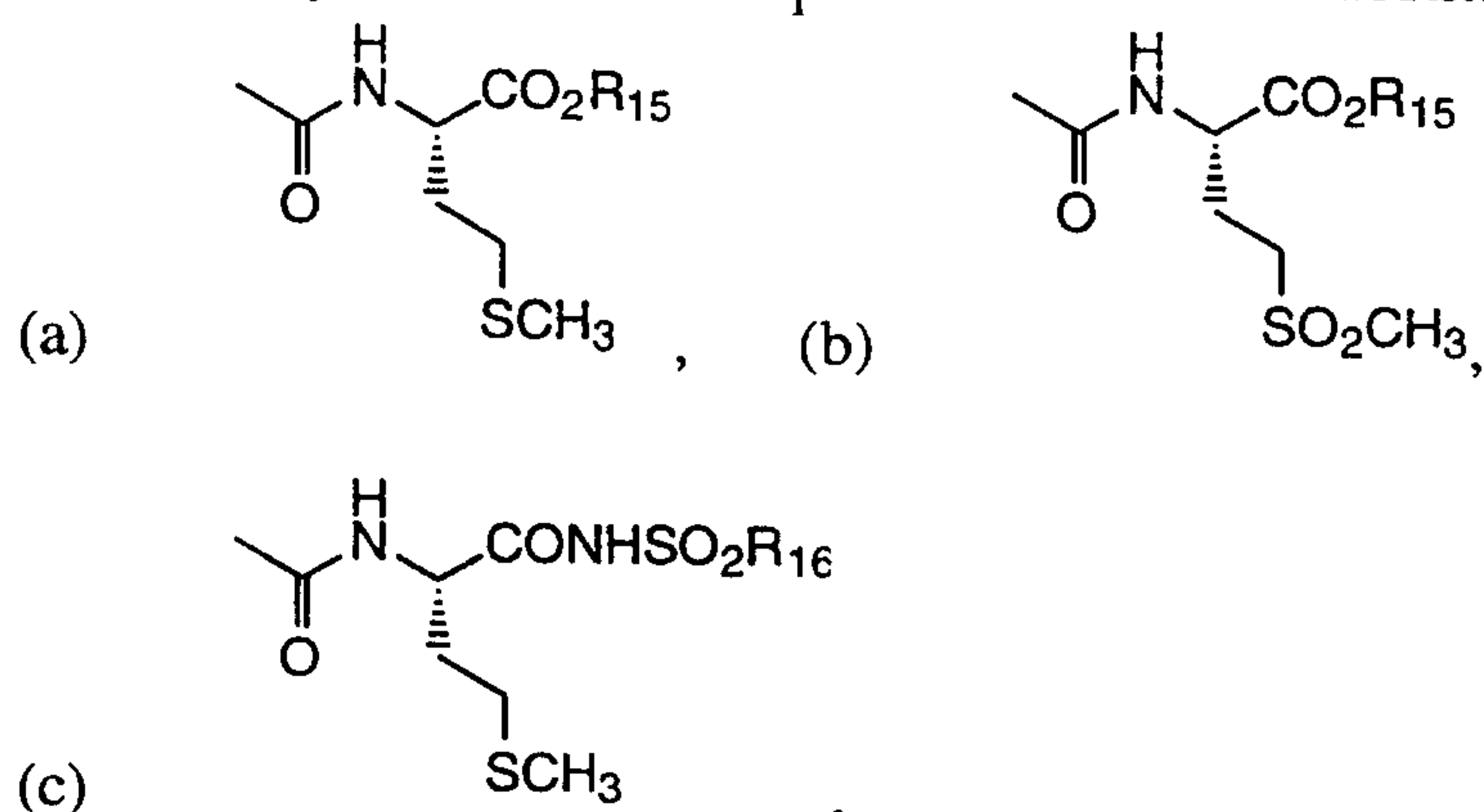


1345

Still more preferred compounds have formula I wherein R_3 is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

1350

Still more preferred compounds of the invention have the structure defined immediately above wherein R_1 is unsubstituted or substituted phenyl and R_2 is



1355

Tables 1-5

In Vitro Potencies of Representative Compounds

1385 Table 1. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-5} M	Example	% inhibition at 1×10^{-5} M
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

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380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at 1X10 ⁻⁶ M	Example	% inhibition at 1X10 ⁻⁶ M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

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209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

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252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70

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290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

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329	98	810	89
330	98	812	94
331	98	813	95
332	26	816	87
333	99	824	90
334	93	831	92
343	72	832	80
344	95	834	55
345	91	835	96
346	98	844	92
347	95	846	85
348	66	850	90
349	99	862	95
379	21	866	62
541	37	867	71
542	67	868	89
544	35	872	74
545	88	878	95
546	97	879	95
547	91	886	35
550	96	889	95
	78	902	85
728			
552	88	903	78
553	92	908	88
554	96	910	42
555	85	911	65
556	99	918	97
557	93	923	78
560	91	924	77
561	91	925	87
564	98	926	69
565	94	936	
			69
566	98	937	95
568	93	962	> 50

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569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

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Table 3. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-7} M	Example	% inhibition at 1×10^{-7} M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

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511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

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593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at 1X10 ⁻⁸ M	Example	% inhibition at 1X10 ⁻⁸ M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

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820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80

Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at 1×10^{-6} M
388	> 50% inhibition at 1×10^{-7} M
389	> 50% inhibition at 1×10^{-6} M
390	> 50% inhibition at 1×10^{-5} M
392	> 50% inhibition at 1×10^{-5} M
399	> 50% inhibition at 1×10^{-6} M
953	> 50% inhibition at 1×10^{-6} M
955	> 50% inhibition at 1×10^{-7} M
962	> 50% inhibition at 1×10^{-7} M
964	> 50% inhibition at 1×10^{-6} M
966	> 50% inhibition at 1×10^{-6} M
967	> 50% inhibition at 1×10^{-6} M
969	> 50% inhibition at 1×10^{-5} M
974	> 50% inhibition at 1×10^{-5} M

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Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as * (0.1 mM) or ** (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

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1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

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1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

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1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

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1113		55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

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1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

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1181		82*	1383		88*
1182		92**	1384		69**
1183		79**	1385		93*
1184		84**	1386		88*
1185		85**	1387		82**
1186		93**	1392		93*
1187		93**	1397		87**
1188		93**	1398		81*
1189		74**	1399		94
1190		95**	1400		95
1191		85**			
1192		91*			
1193		95**			
1194		78**			
1195		94*			
1196		87*			
1197		85*			
1198		86*			

* % inhibition at 0.1 μ M** % inhibition at 0.01 μ M

1400

Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranygeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

1410

FTase

³H-Farnesyldiphosphate (final concentration 0.6 μ M), H-Ras (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01% Triton X-100) to give

1415 a final volume of 50 μ L. The mixture was brought to 37 °C, enzyme was added, and the
reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the
reaction, and the mixture was allowed to stand for 15 minutes at room temperature then
diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass
microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass
1420 filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The
radioisotope retained on the glass fiber filter was counted to reflect the activity of the
enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a
suitable range of inhibitor concentrations.

1425 GGTase I

³H-geranylgeranyldiphosphate (final concentration 0.5 μ M), H-Ras-CVLL (final
concentration 5.0 μ M) and the test compound (various final concentrations from a stock
solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50
mM Tris-HCl (pH 7.2), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01%
1430 Triton X-100) to give a final volume of 50 μ L. The mixture was brought to 37 °C, treated
with enzyme, and incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the
reaction, and the mixture was allowed to stand for 15 minutes at room temperature then
diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass
microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass
1435 filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The
radioisotope retained on the glass fiber filter was counted to reflect the activity of the
enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a
suitable range of inhibitor concentrations.

Additionally, the ability of the compounds of the invention to inhibit prenylation in
1440 whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor
xenograft in mice could be demonstrated according to the methods described in PCT Patent
Application No. WO95/25086, published September 21, 1995, which is hereby
incorporated herein by reference.

1445 Pharmaceutical Compositions

The compounds of the present invention can be used in the form of pharmaceutically
acceptable salts derived from inorganic or organic acids. These salts include, but are not
limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate,
benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate,
1450 cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate,

glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e., protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as osteosarcoma, osteoid osteoma, liposarcoma, hemangioma and hemangiosarcoma; melanomas such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myloblastic and chronic mylocytic.

1490 The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., *Drugs Exptl. Clin. Res.* 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Gueritte-Voegelein F., Lavelle F., *Cancer Res.* 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., *Acta Pathol. Microbiol. Scand.* 77, 758 (1969), which are hereby incorporated
1495 herein by reference.

 These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. *Circ. Res.* 73: 264-268 (1993), Mitsuka, M. et al.
1500 *Circ. Res.* 73: 269-275 (1993) and Santoian, E.C. et al. *Circulation* 88: 11-14 (1993), which are hereby incorporated herein by reference.

 For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more
1505 preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

 For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit
1510 compositions may contain such amounts of submultiples thereof to make up the daily dose.

 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

 It will be understood, however, that the specific dose level for any particular patient
1515 will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

 The compounds of the present invention may be administered orally, parenterally,
1520 sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills may also be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.

While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al.,
1565 Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is hereby incorporated herein by reference. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethylenimines (thiotepa, hexamethylmelamine); folic
1570 acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside); purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin,
1575 taxol and brequinar).

The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference or by such therapeutically useful amounts as would be known to one of ordinary
1580 skill in the art.

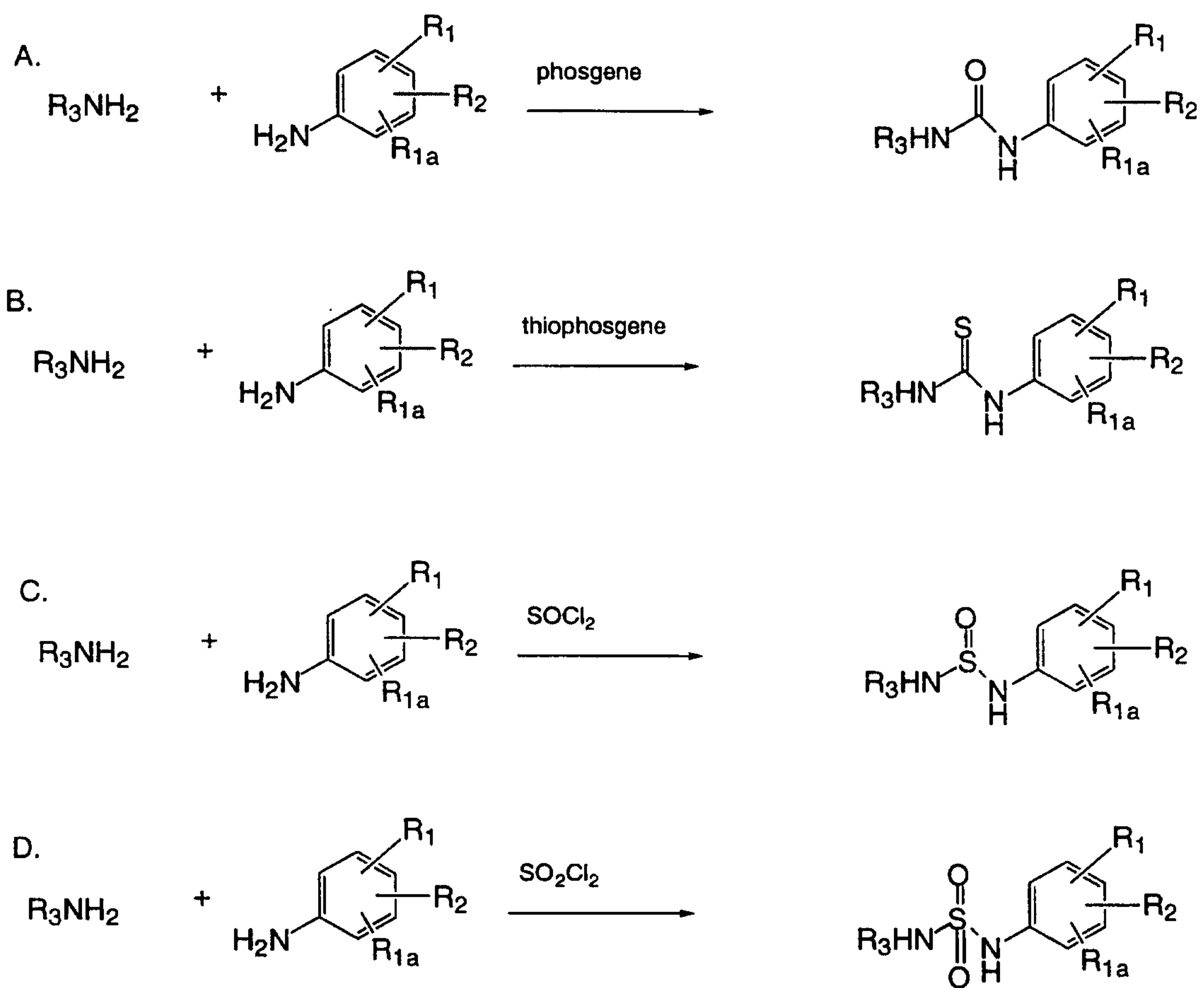
The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain a desired therapeutic response depending on the route of administration, severity of the
1585 disease and the response of the patient.

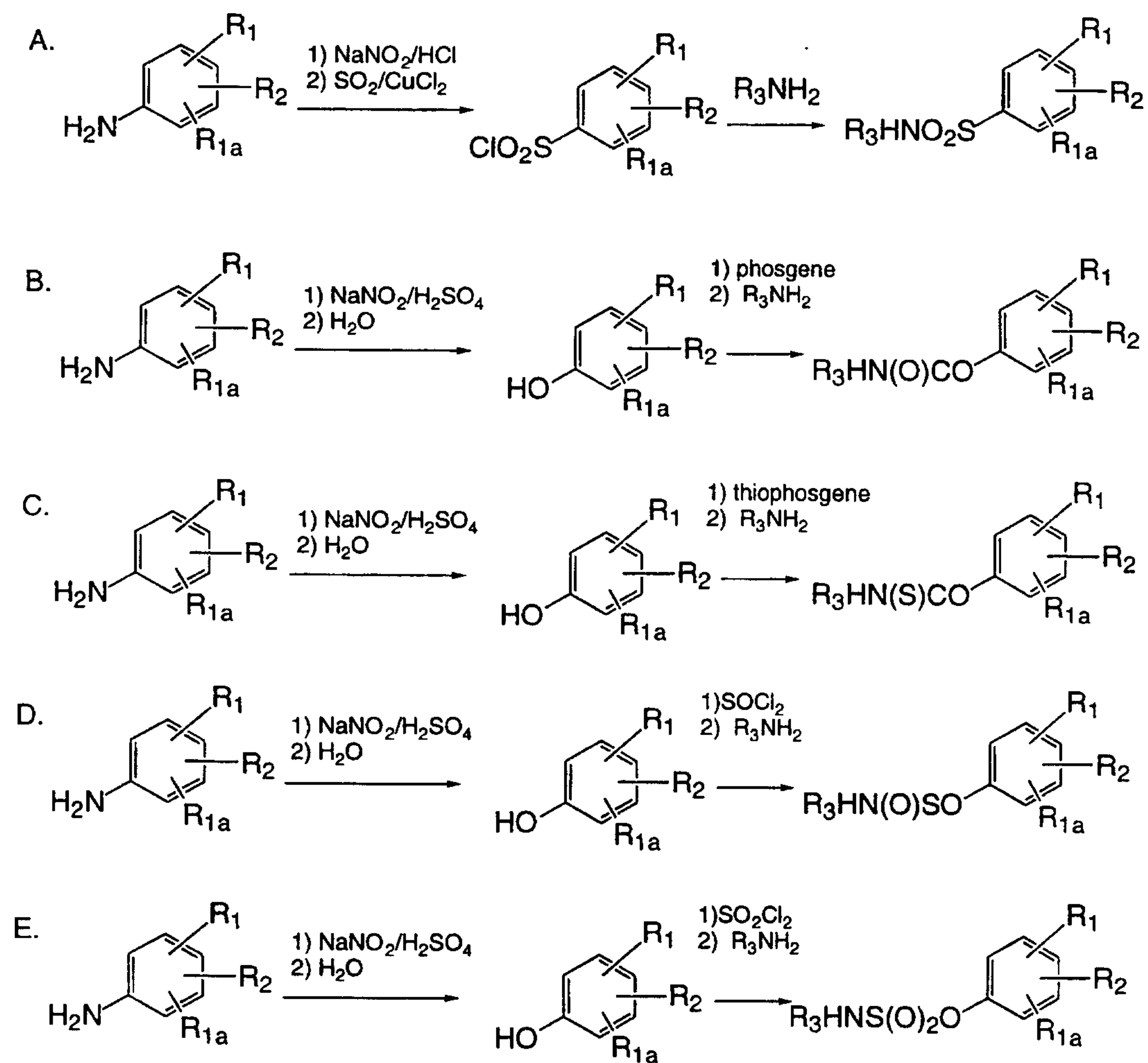
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

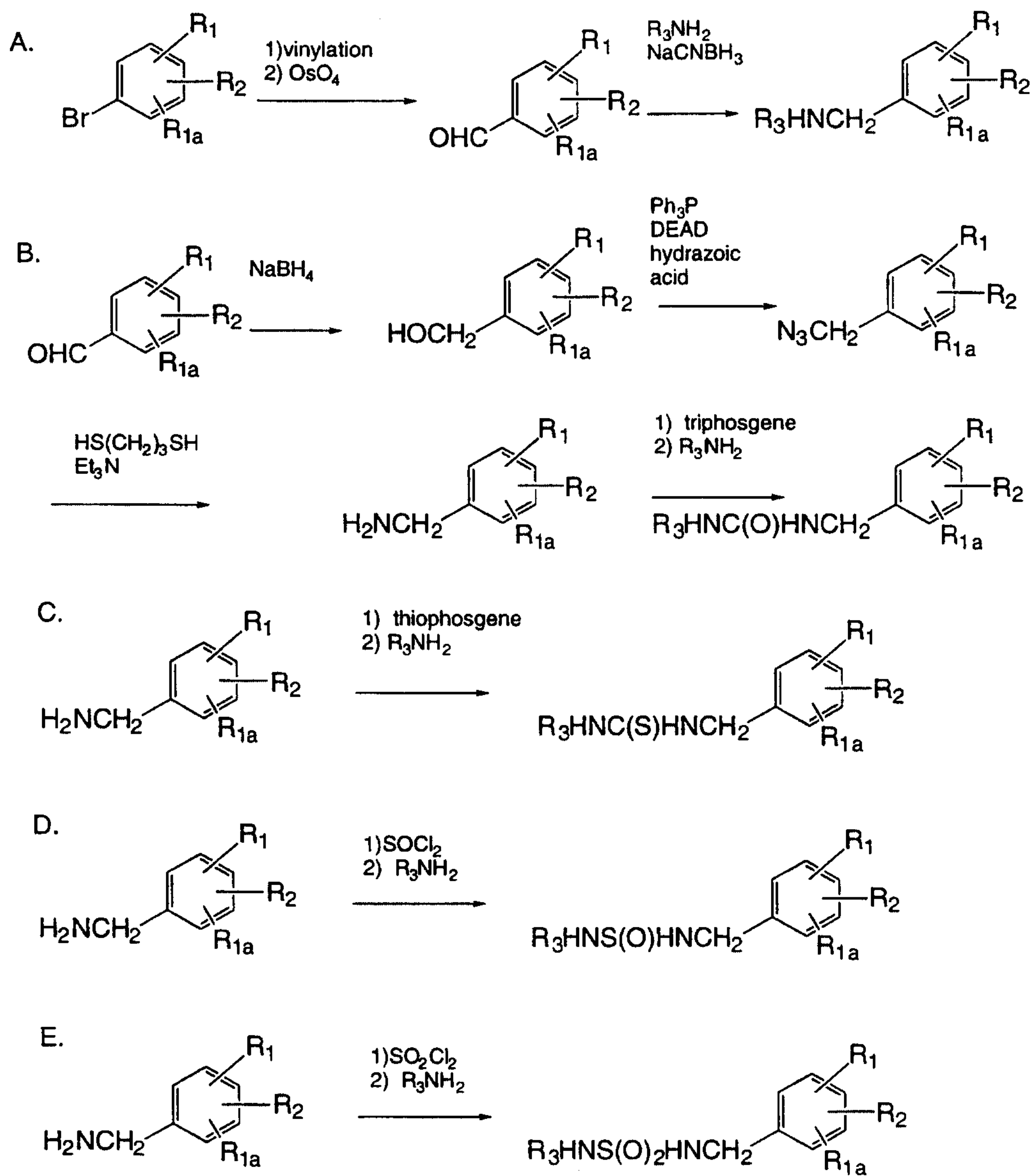
1590 Preparation of the Compounds of the Invention

In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

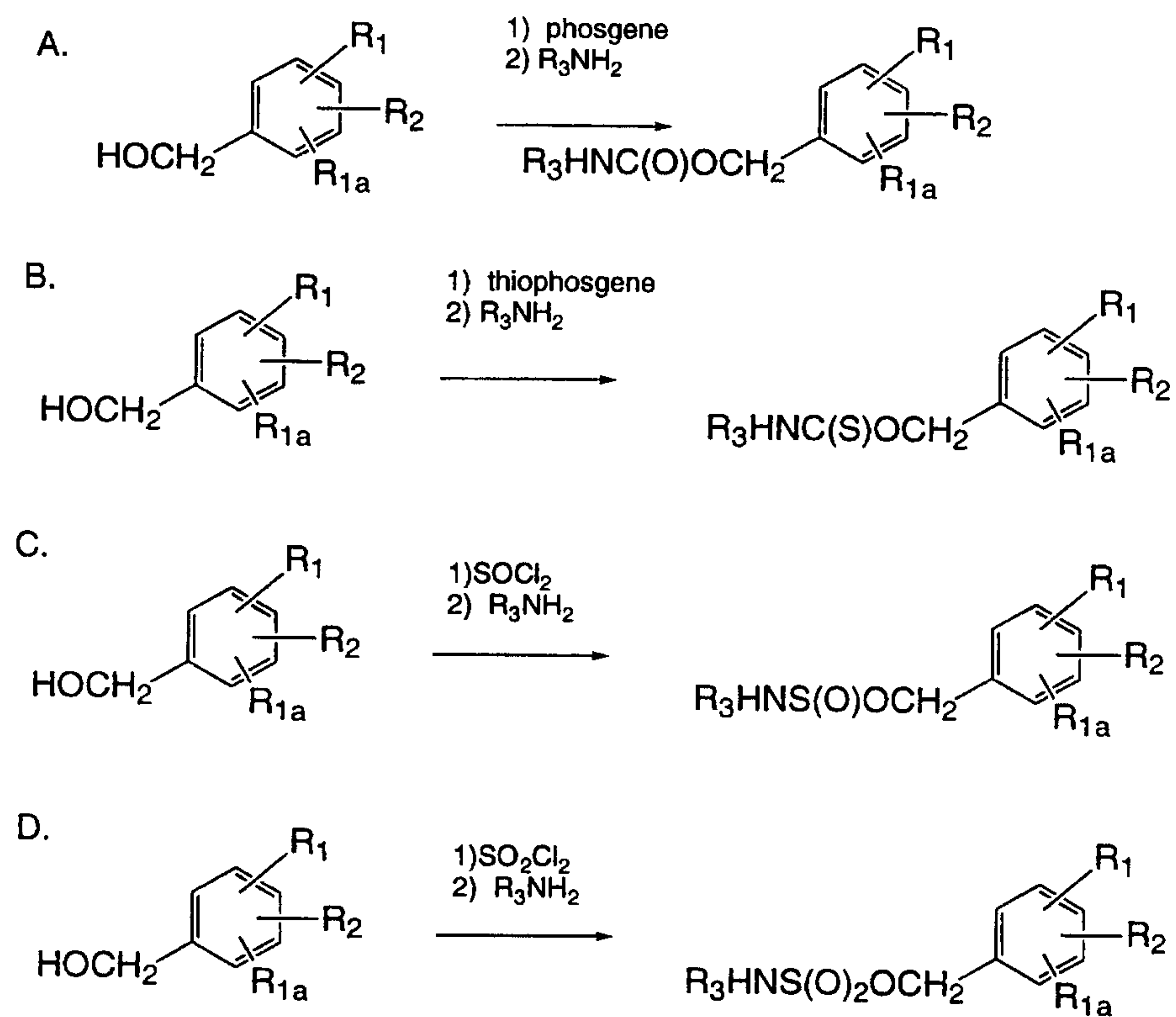
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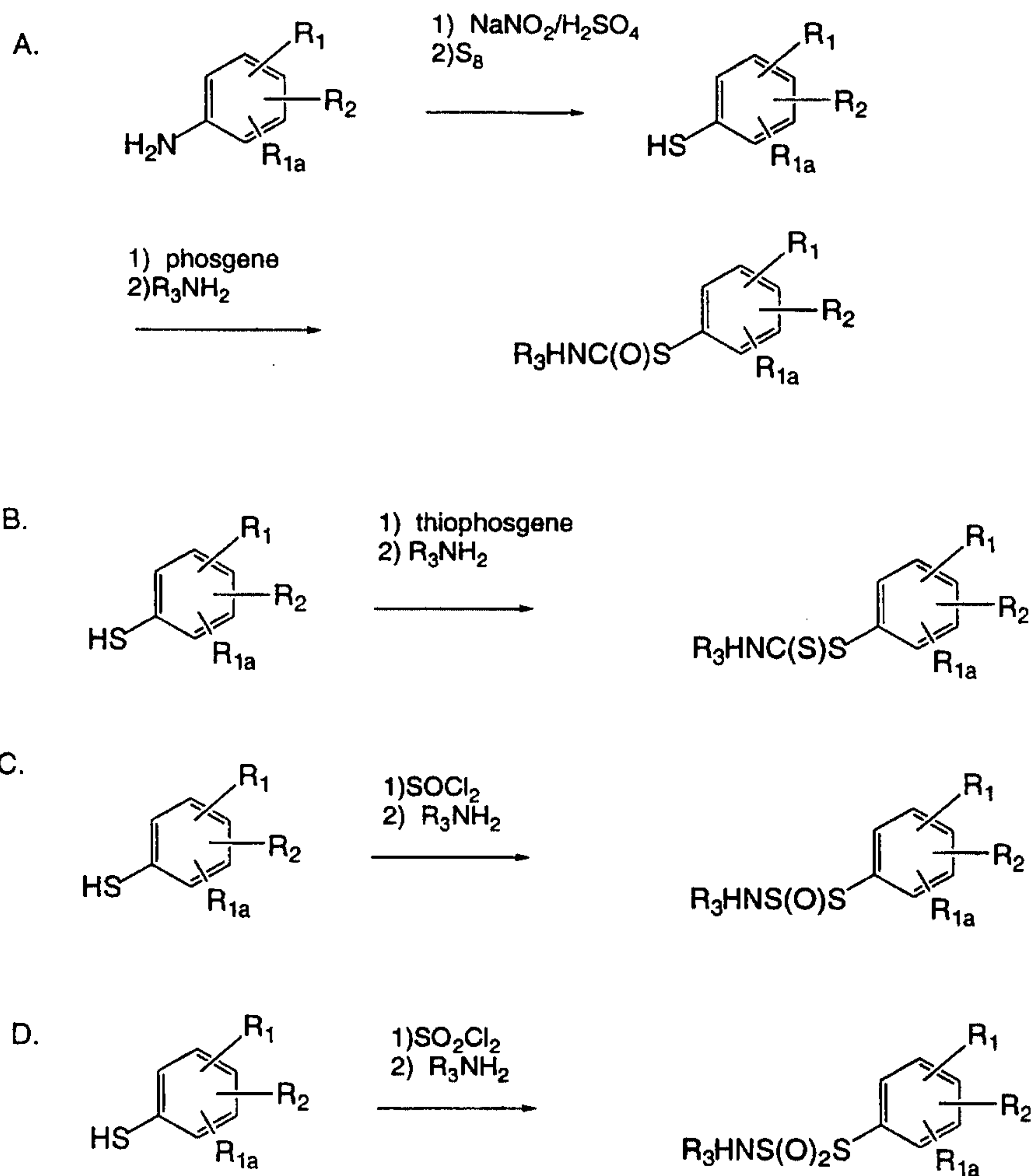
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SCHEME 2

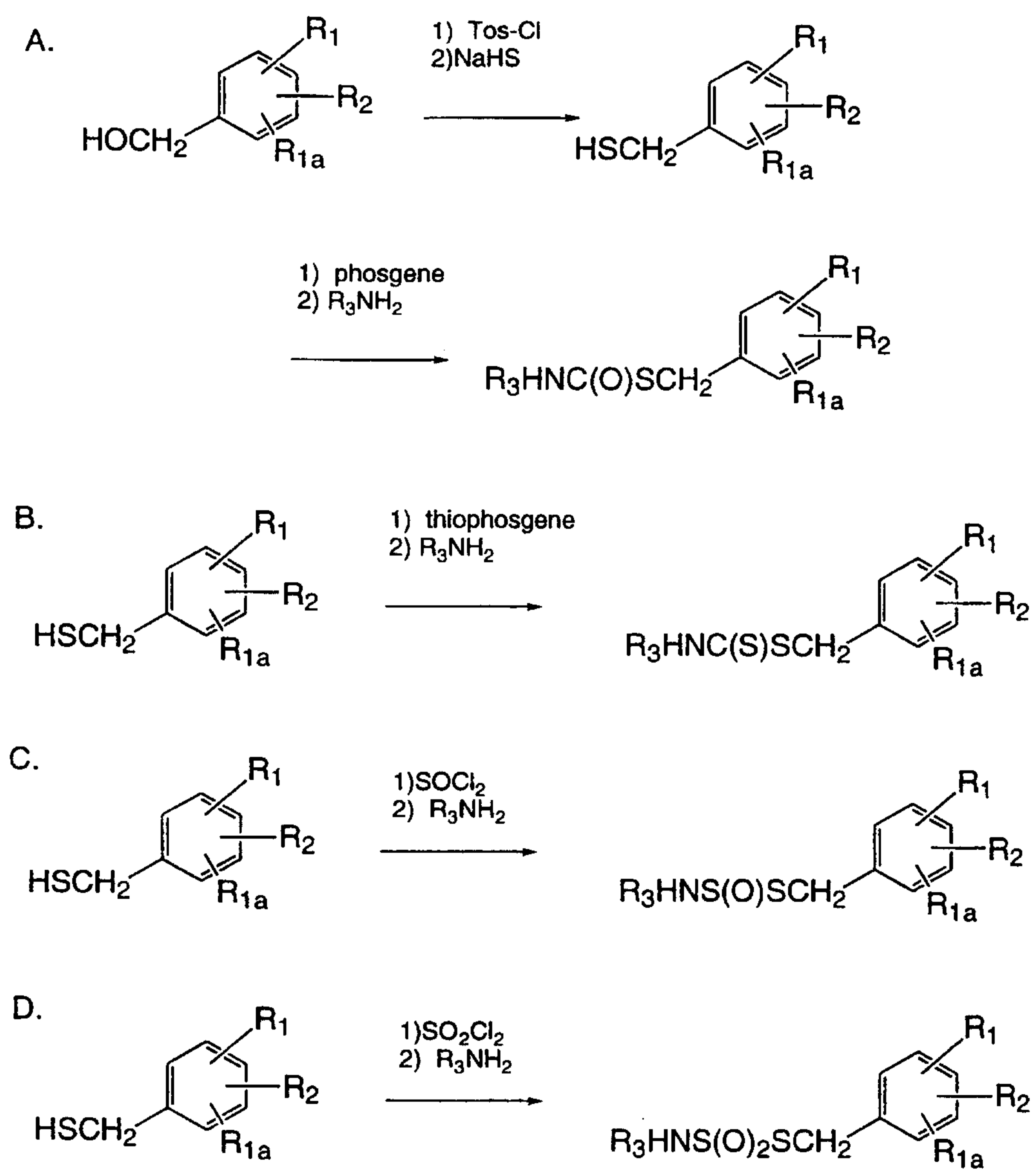
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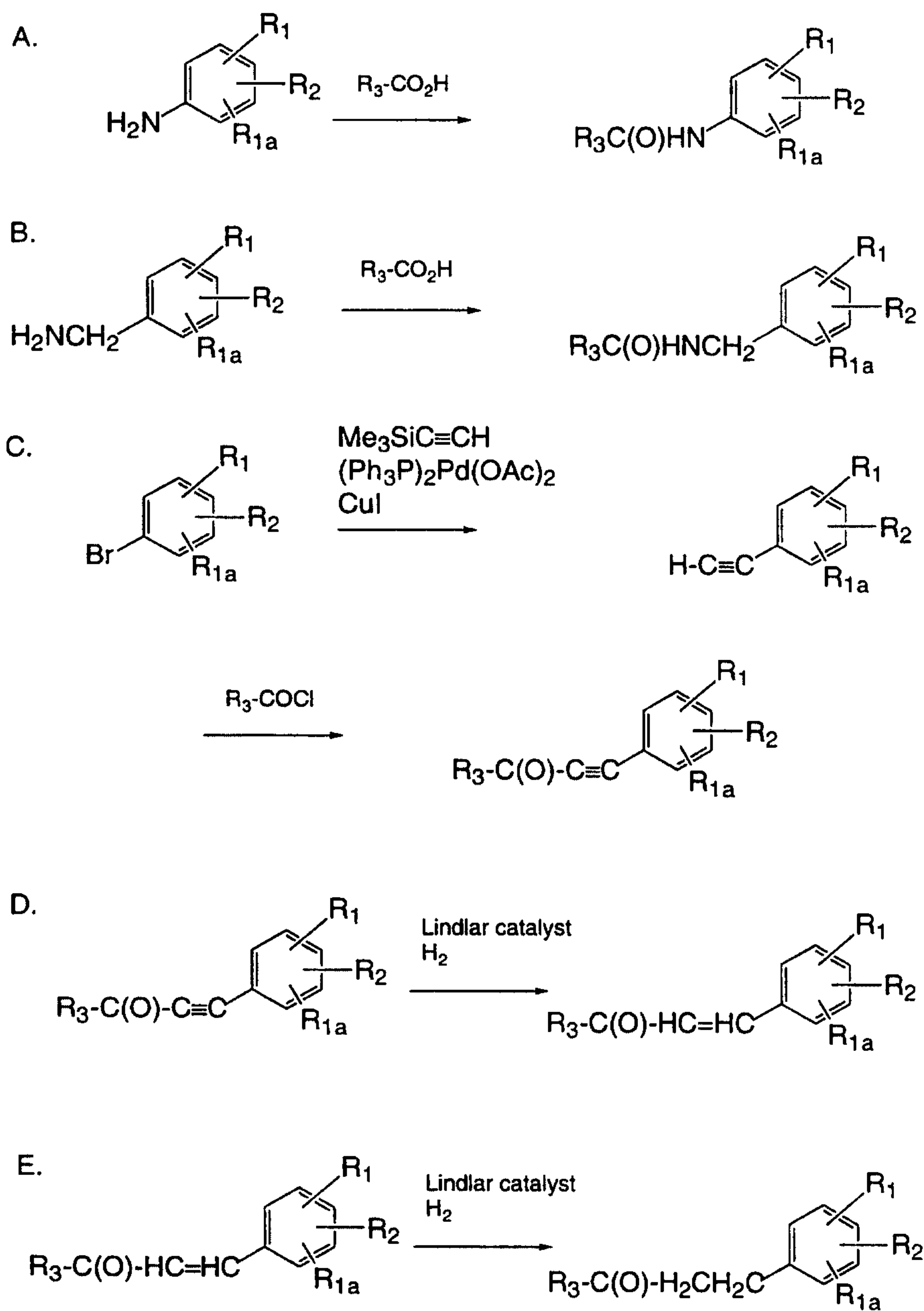
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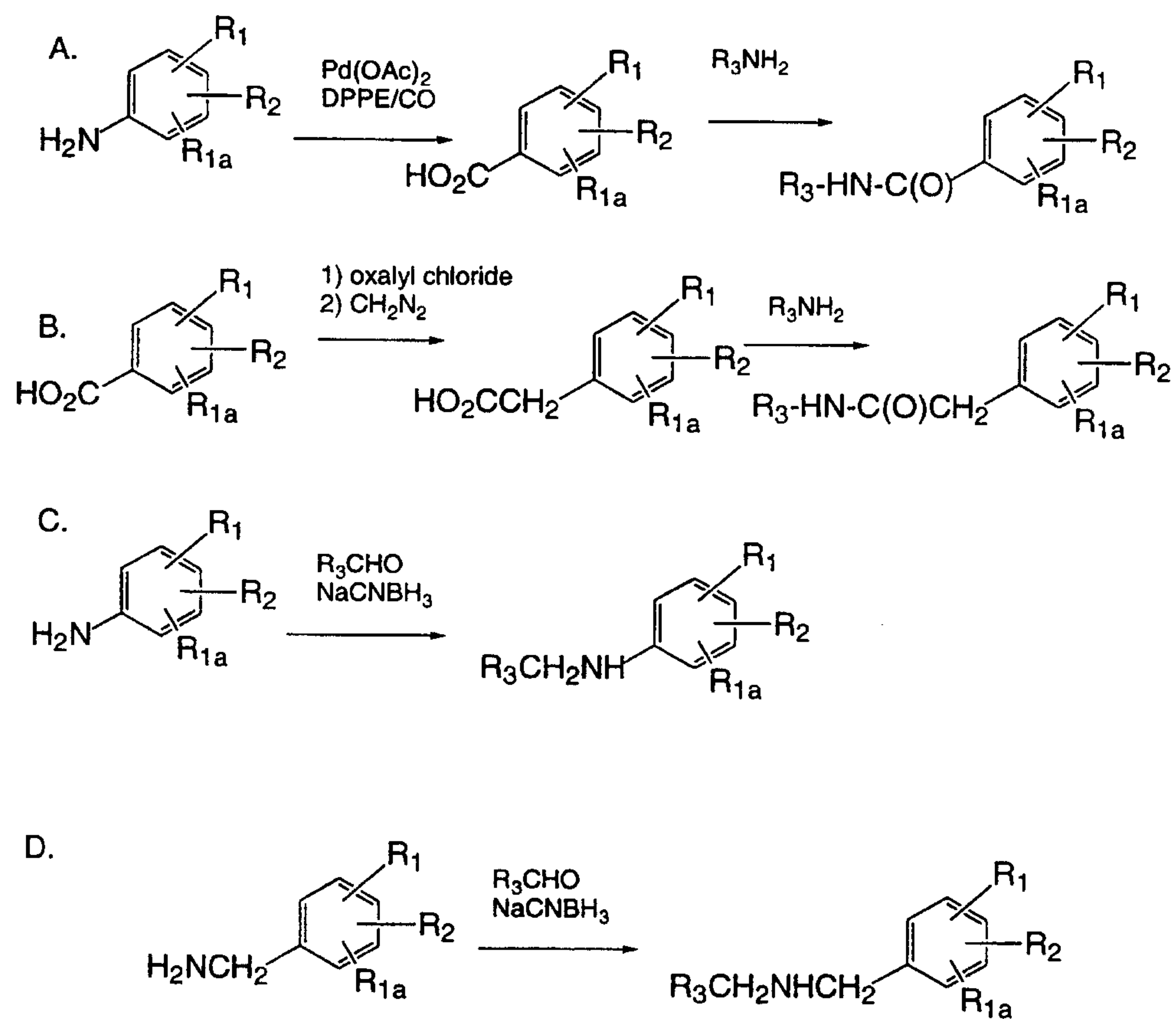
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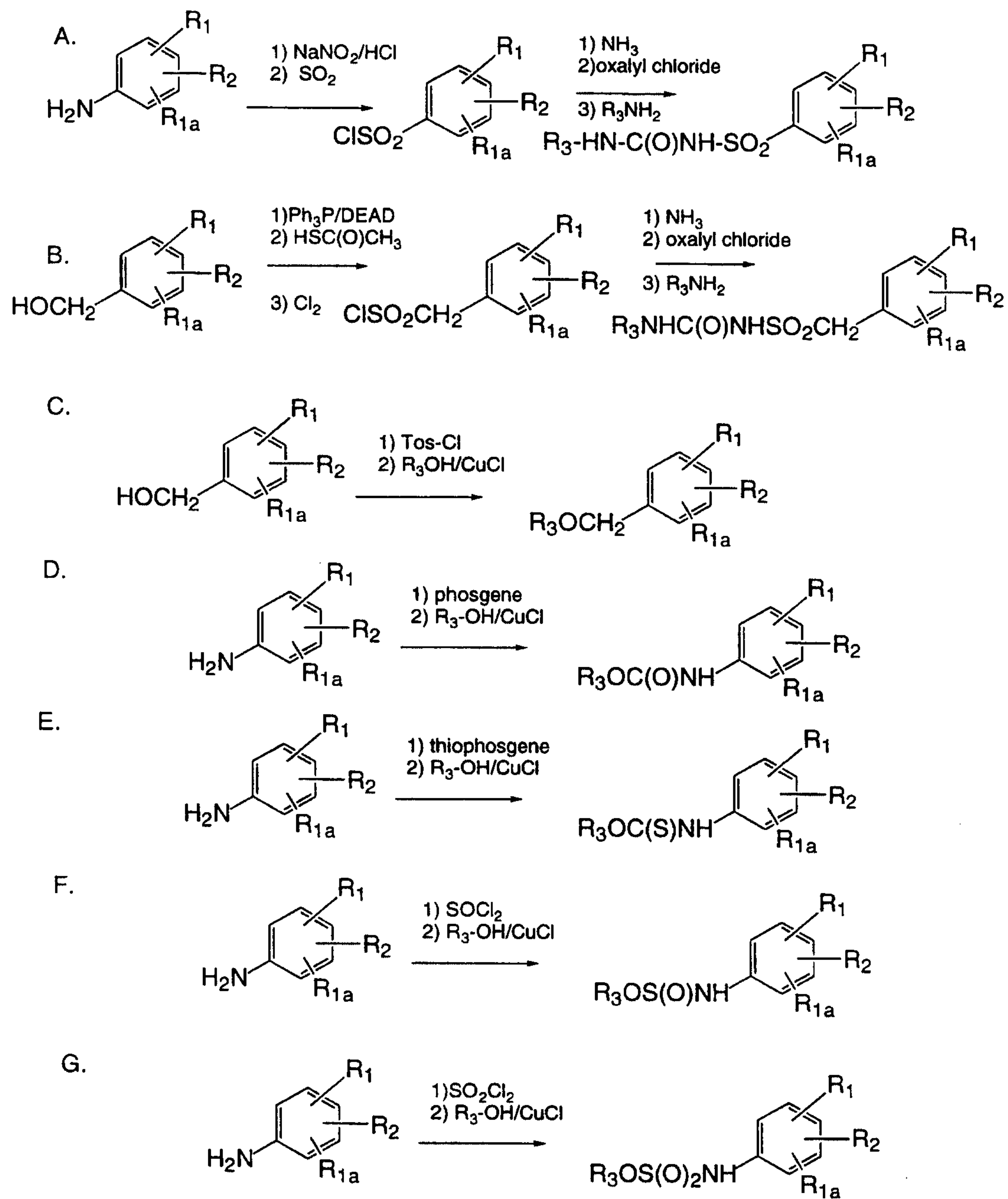
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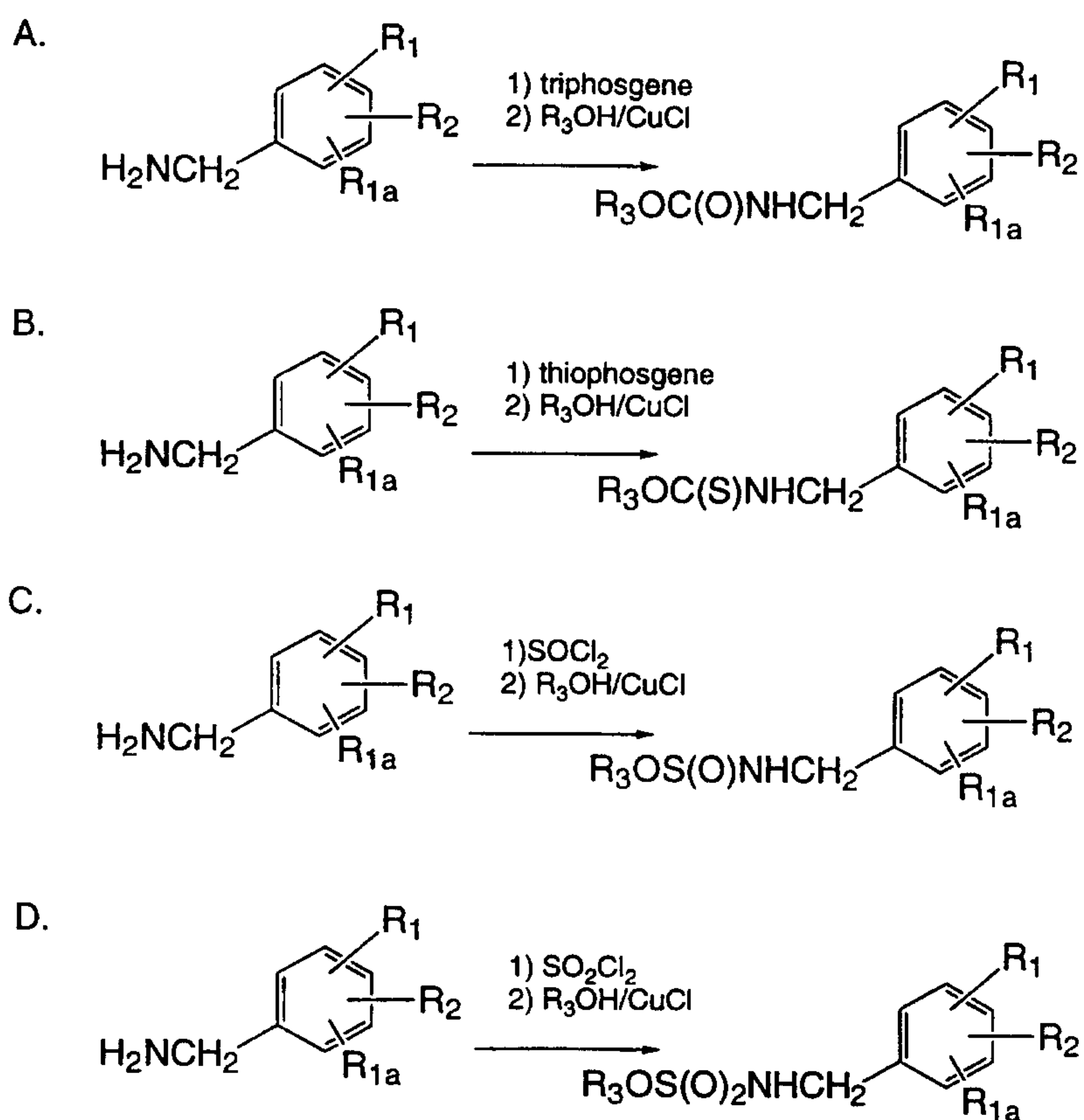
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SCHEME 6

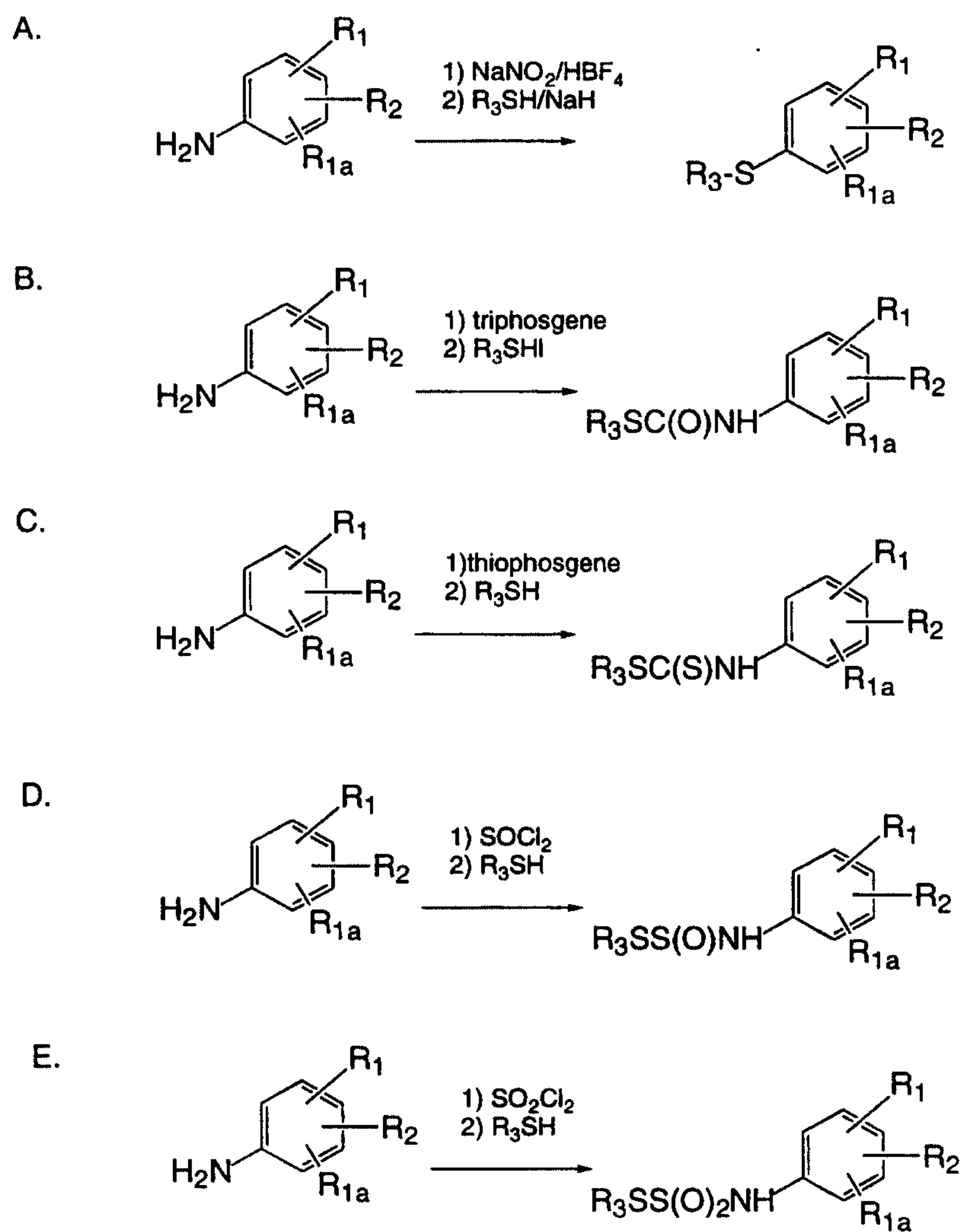
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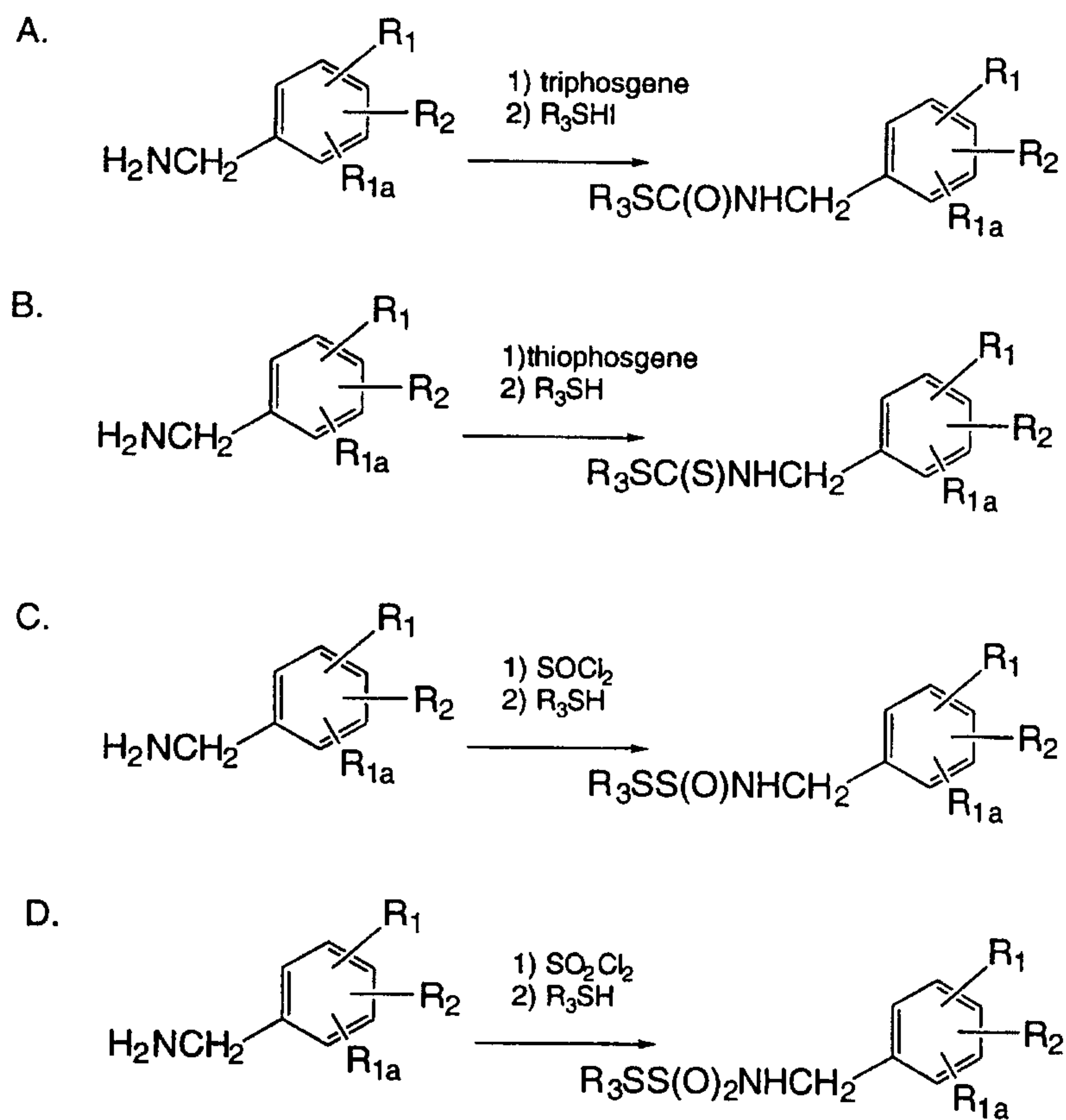
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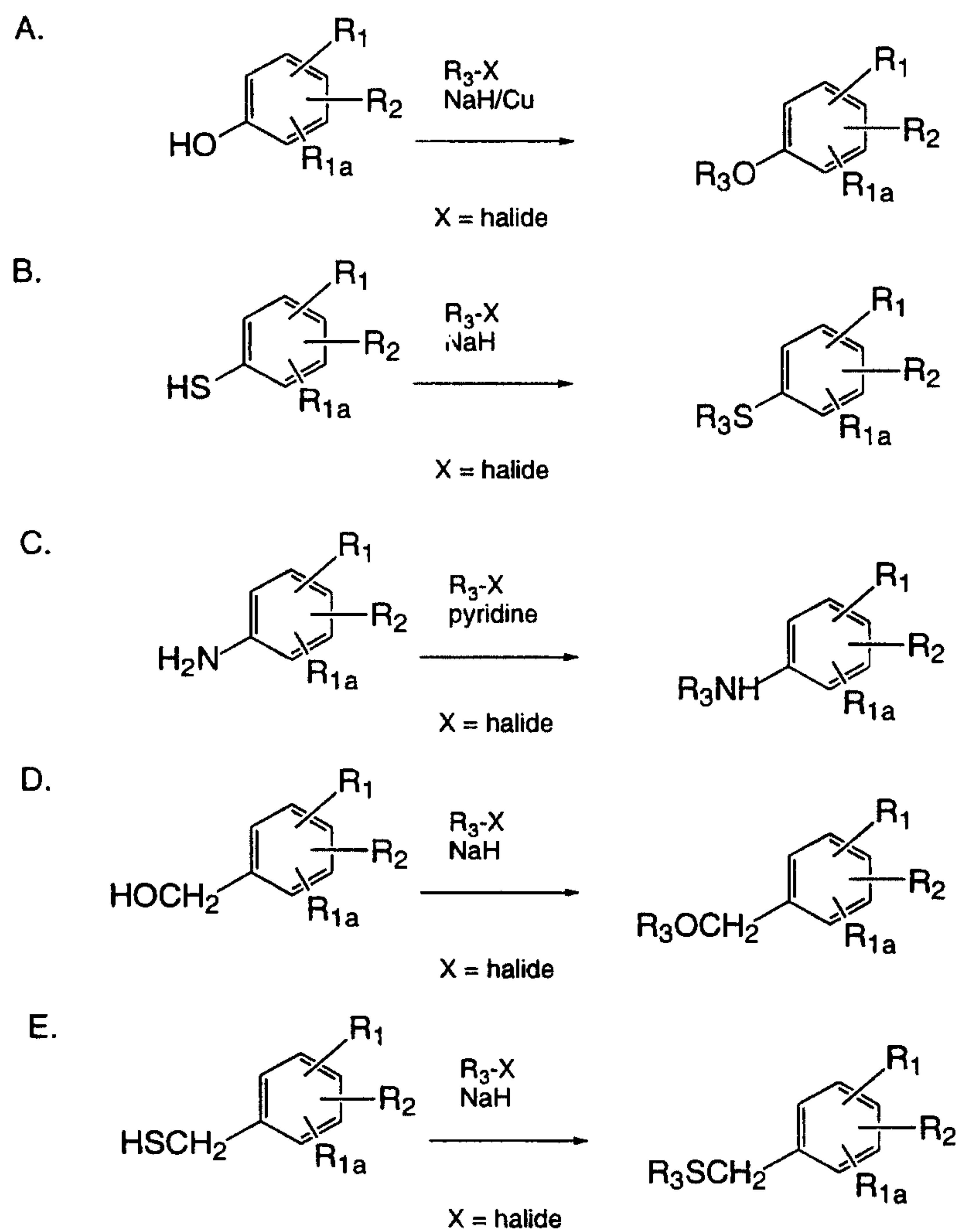
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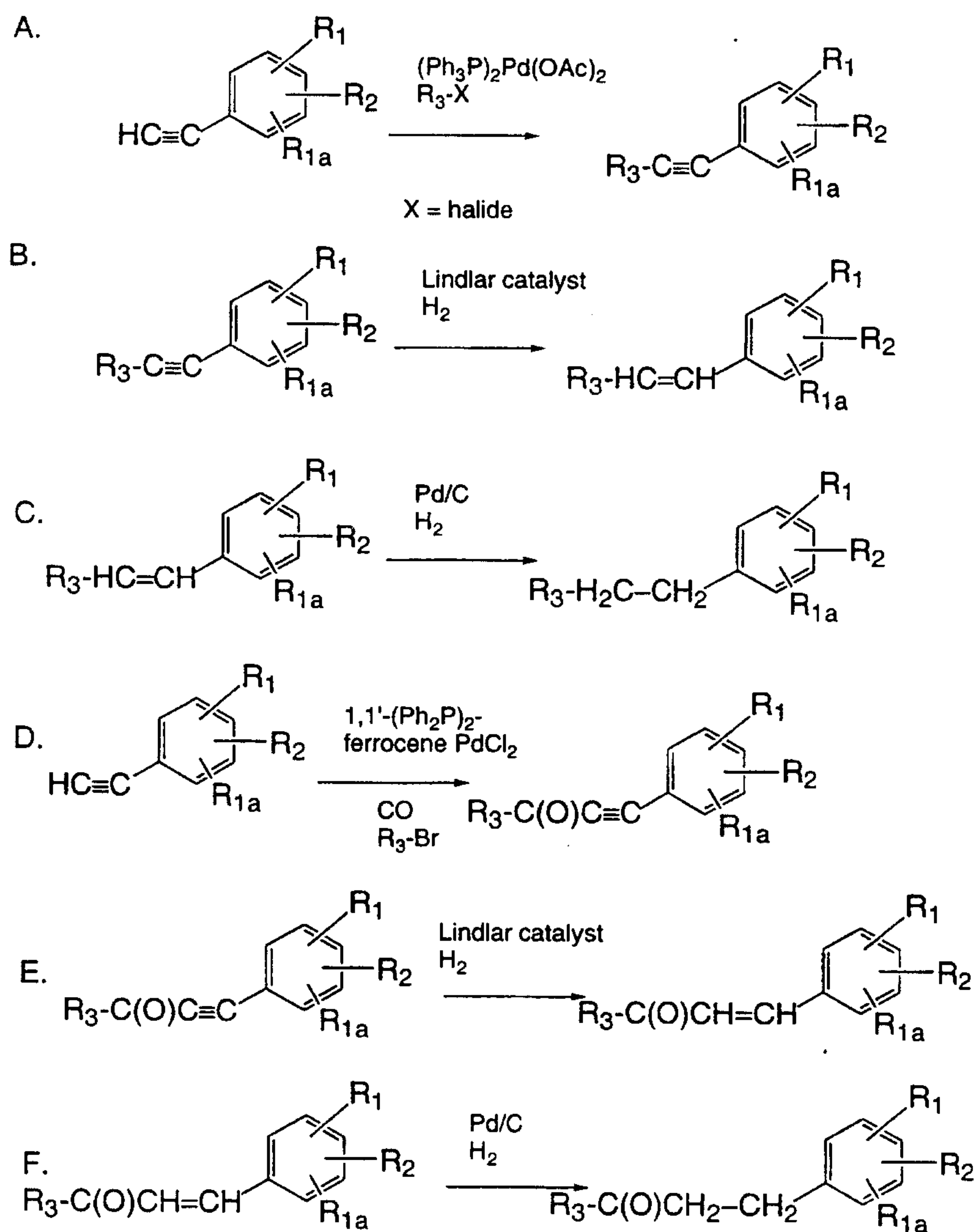
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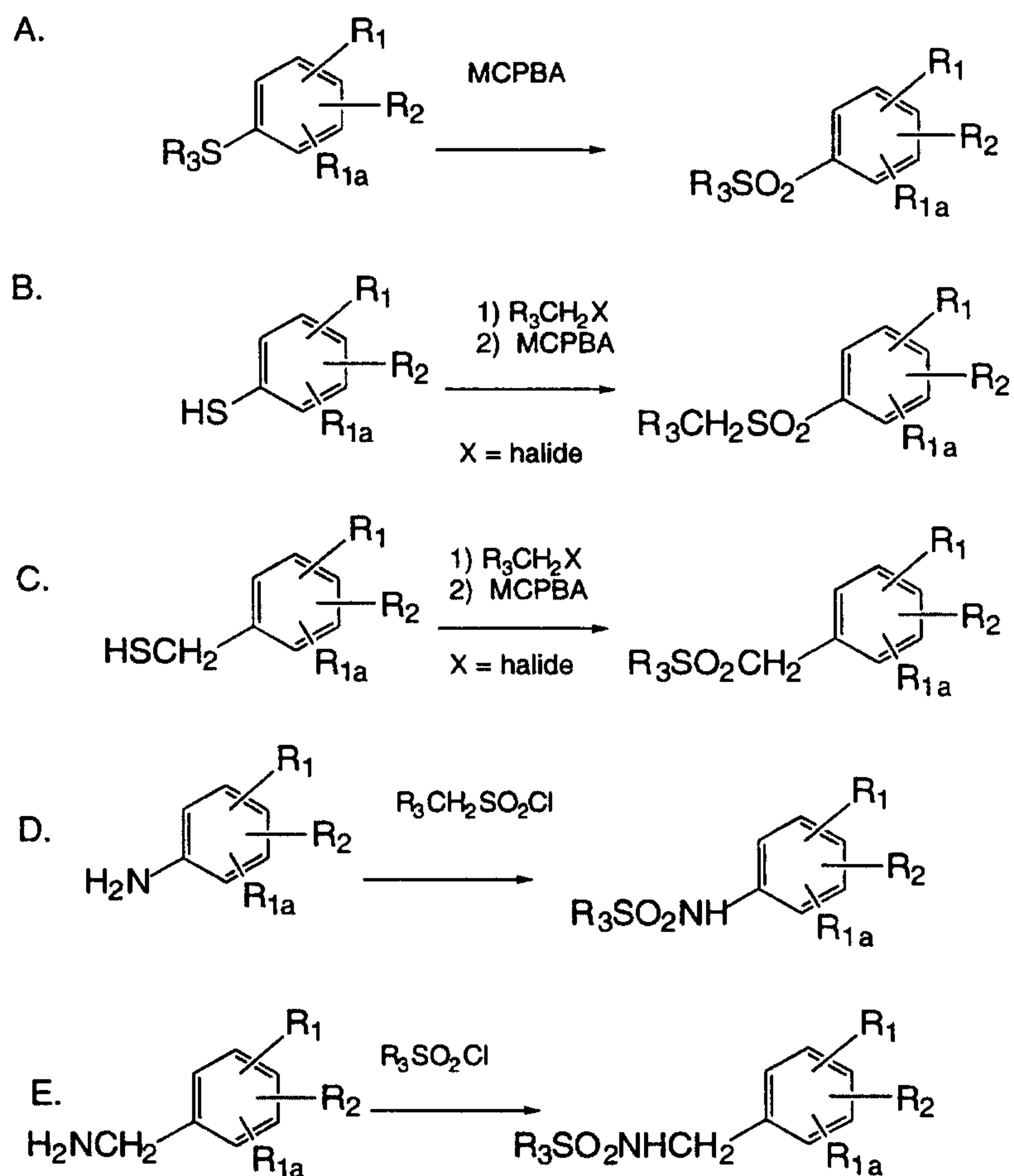
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SCHEME 11

SCHEME 12

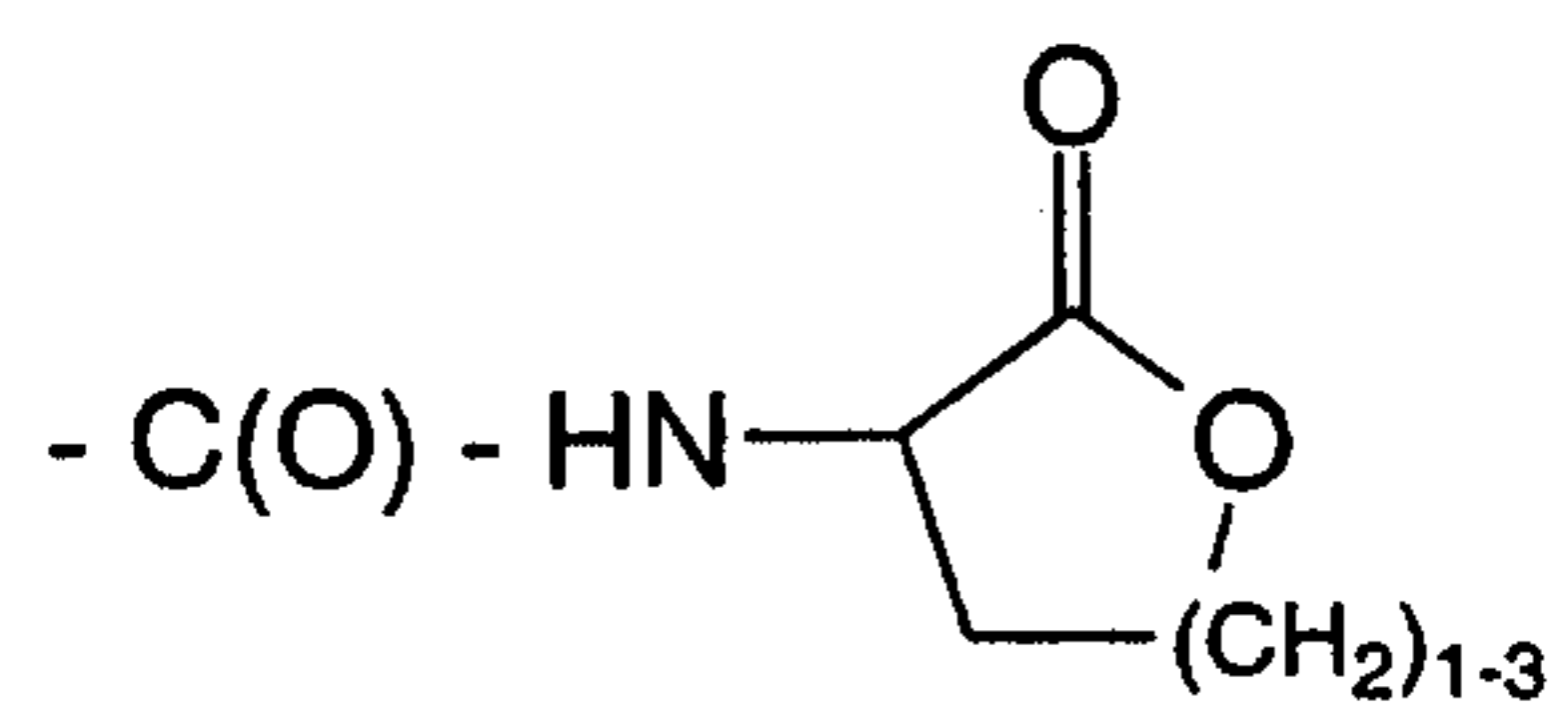
SCHEME 13

SCHEME 14

SCHEME 15

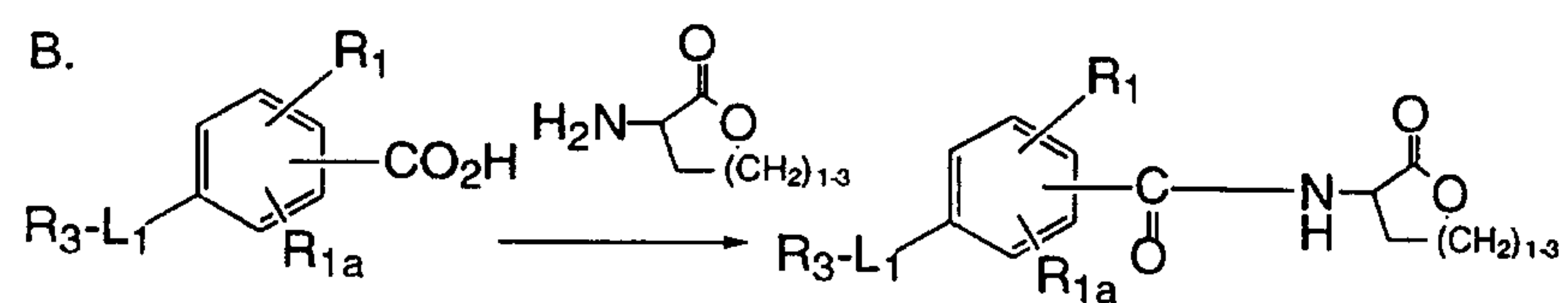
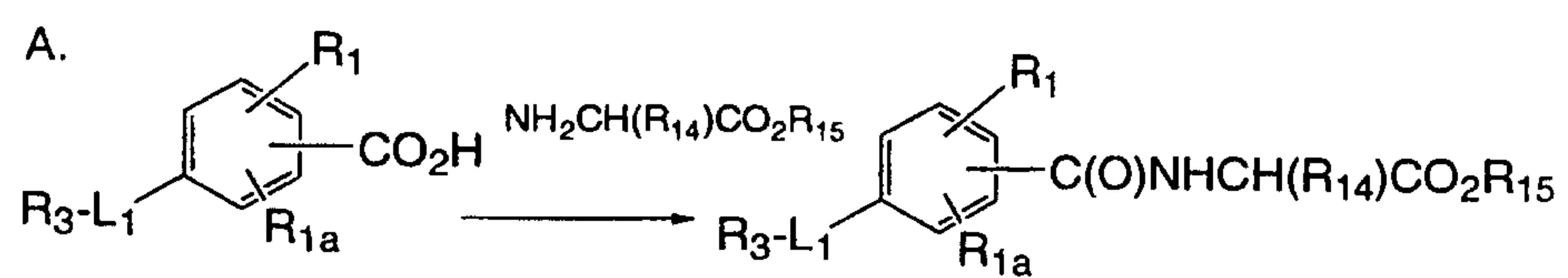
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Scheme 16 illustrates an alternative method for preparing compounds wherein R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or



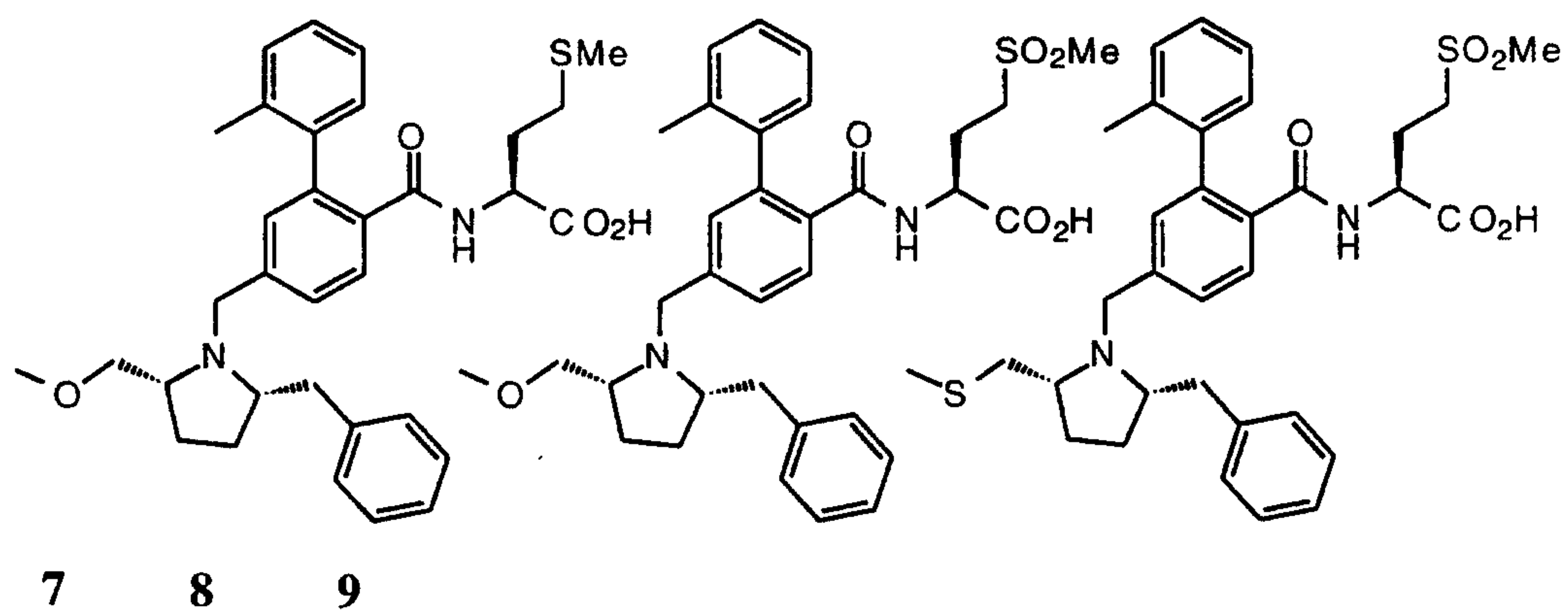
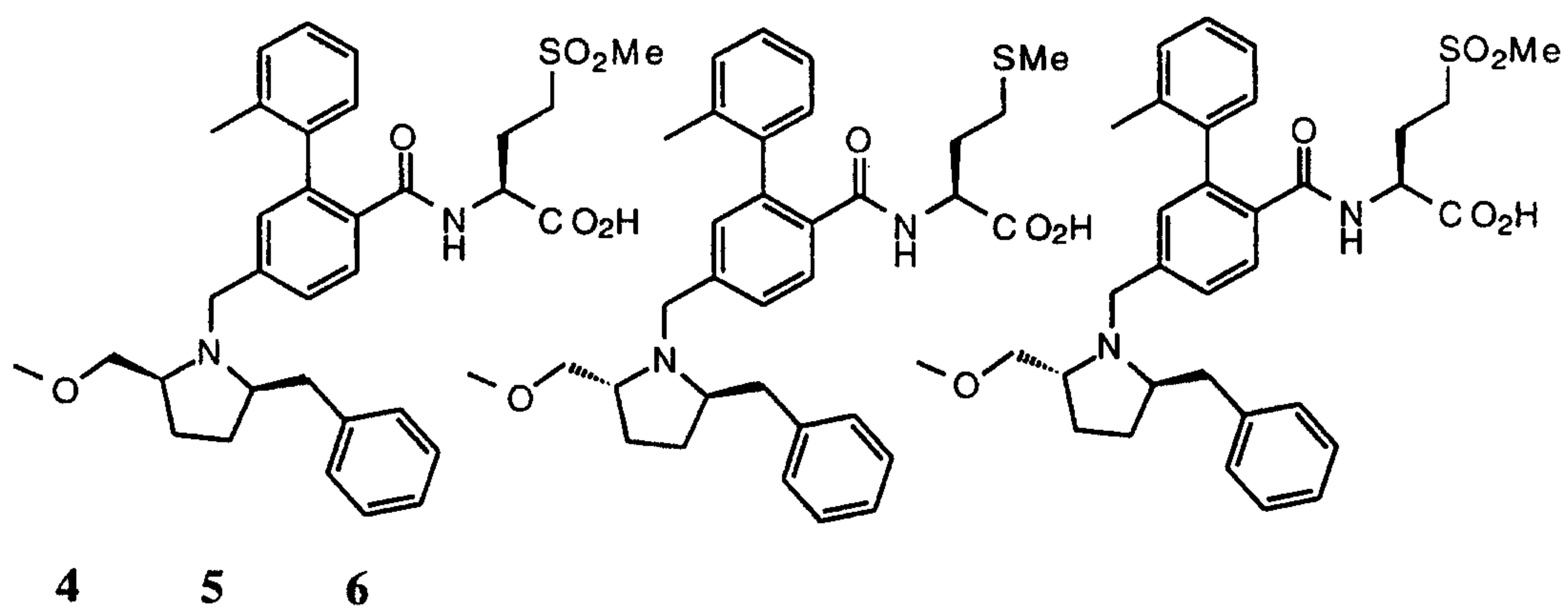
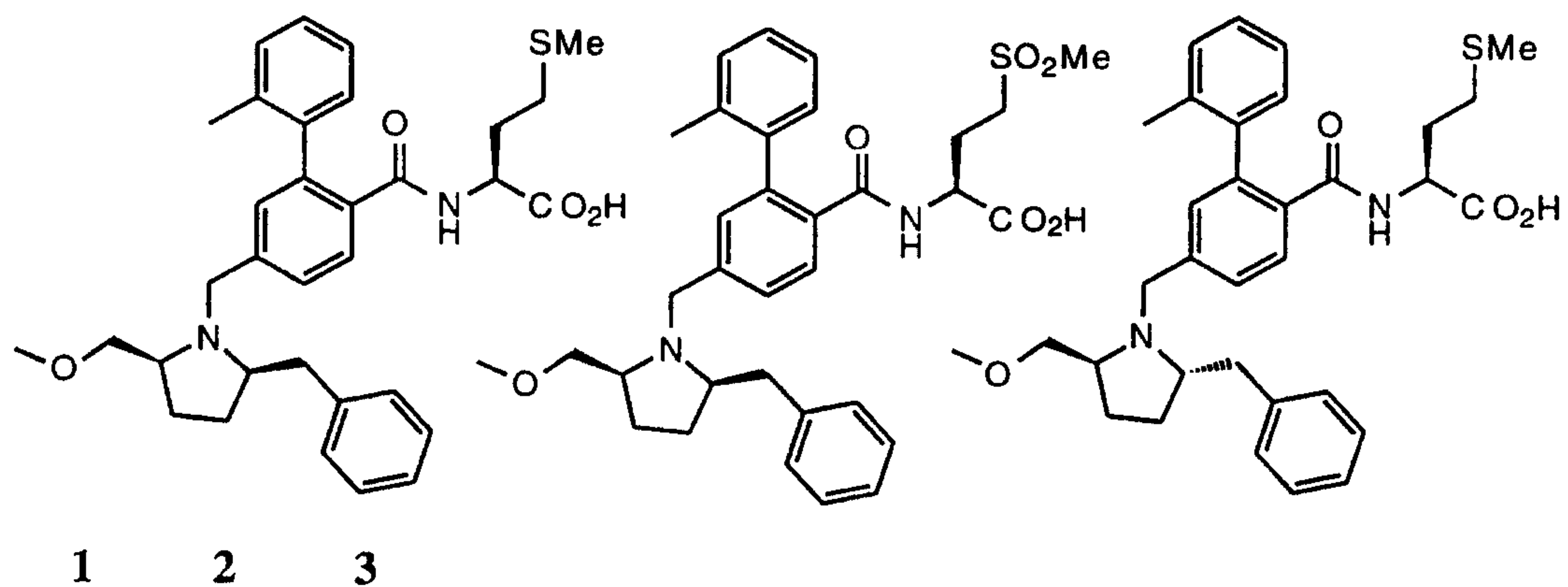
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as defined above.

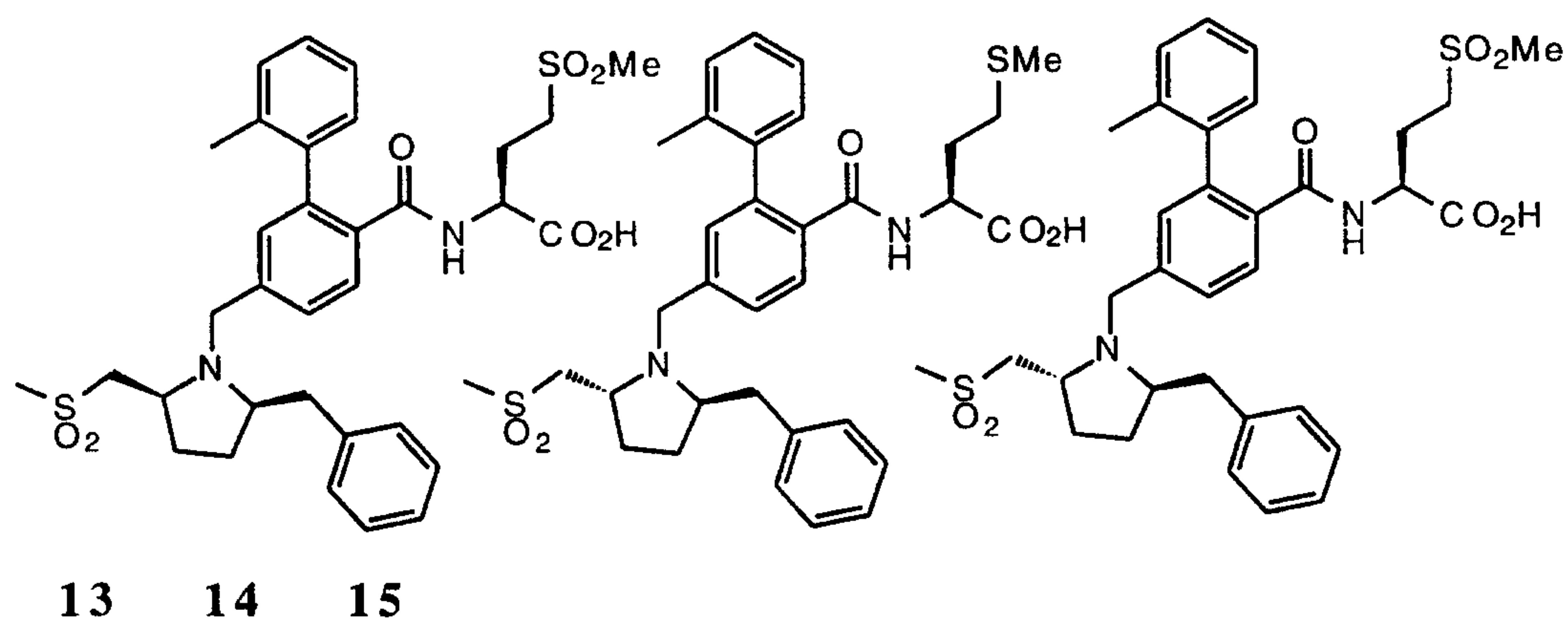
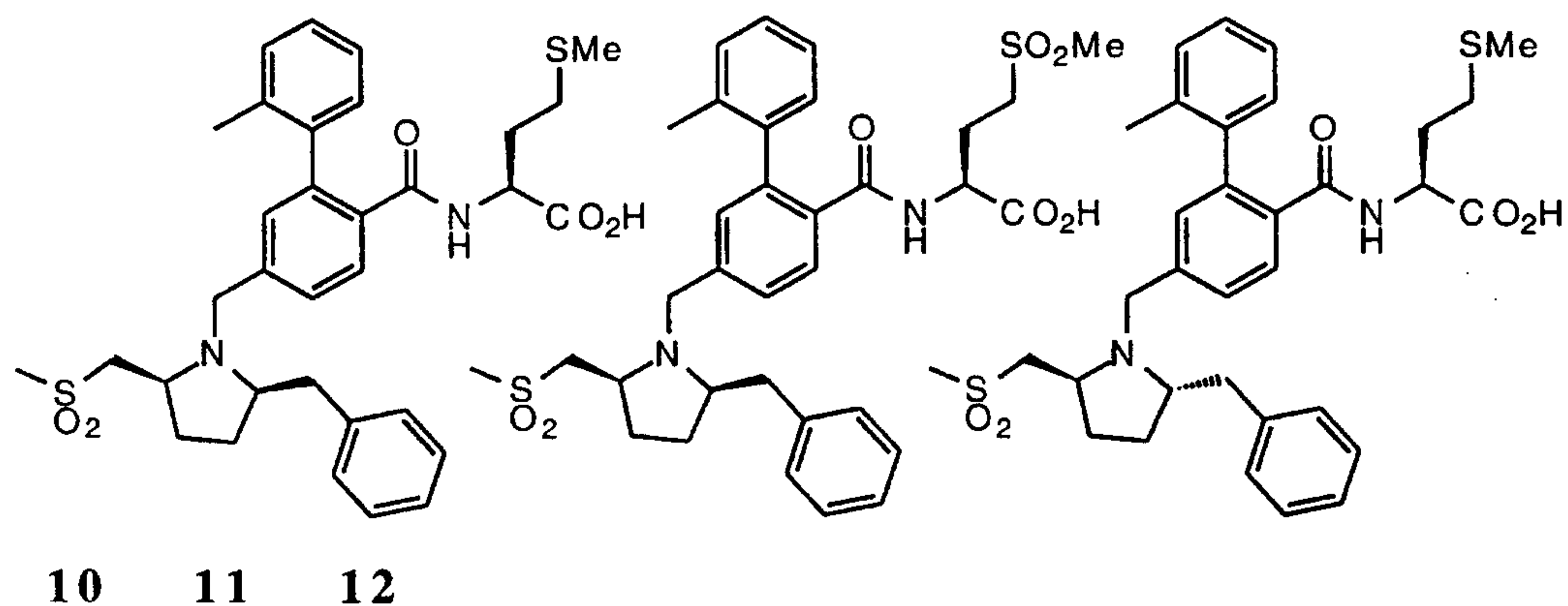
SCHEME 16

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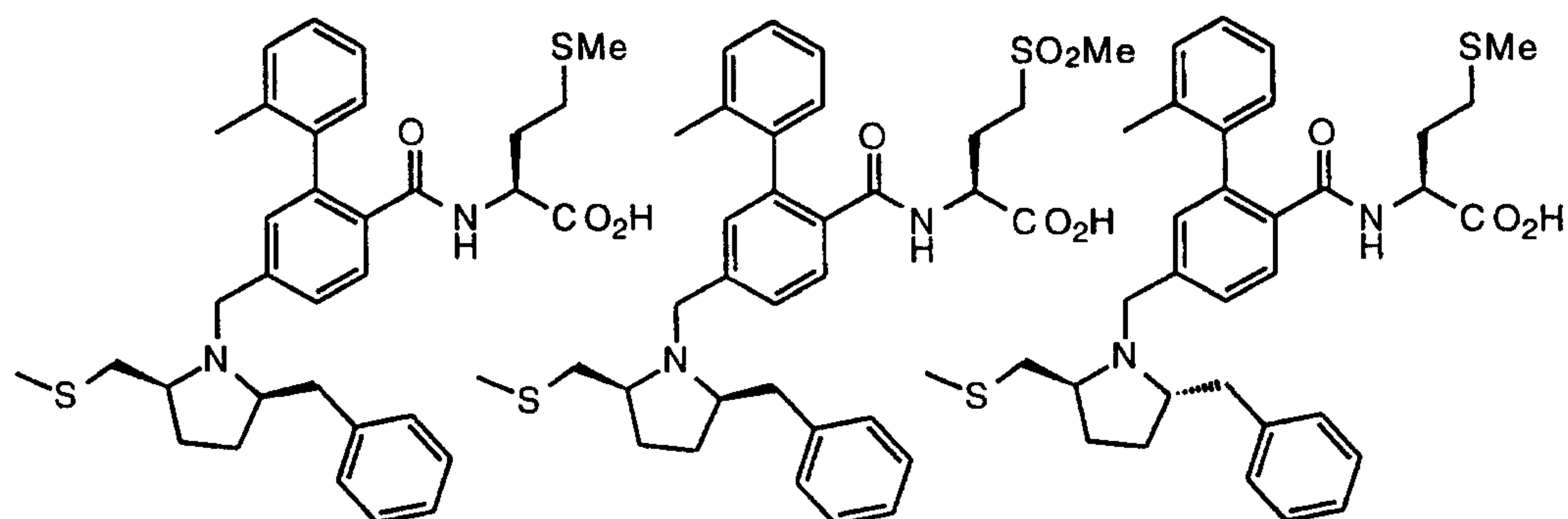
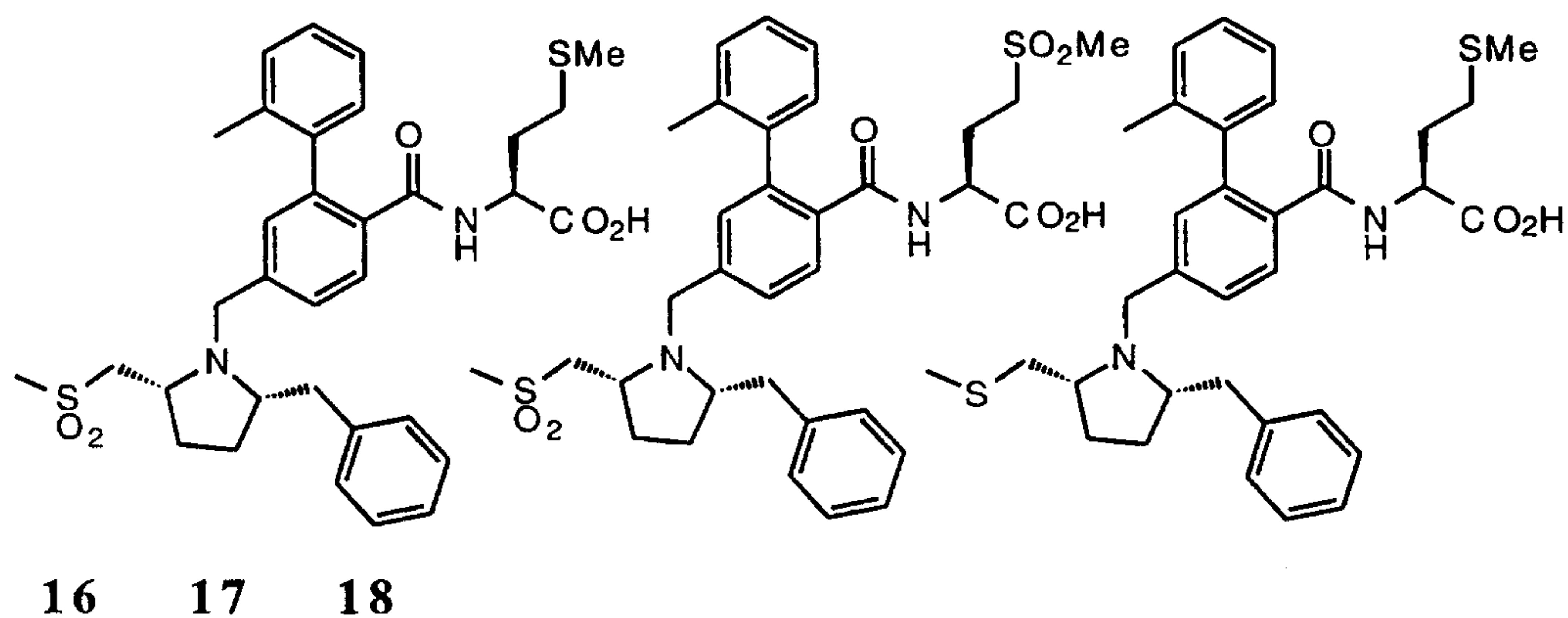
Table 6. Amines of the Type A(B)N-L₁



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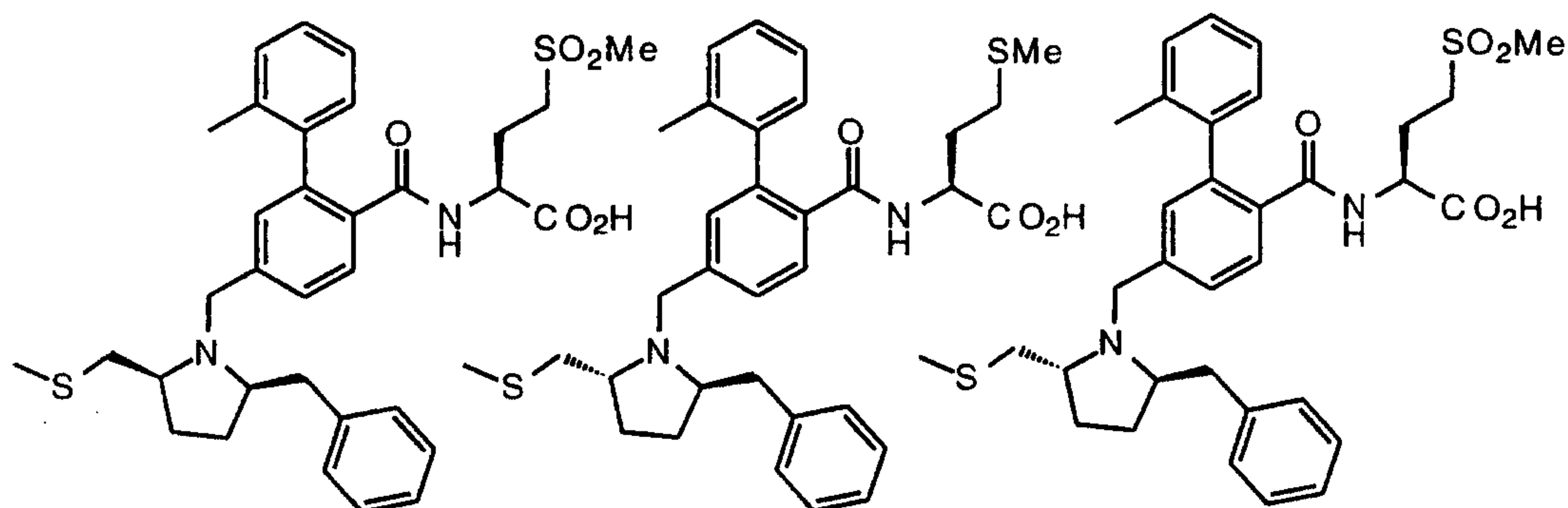


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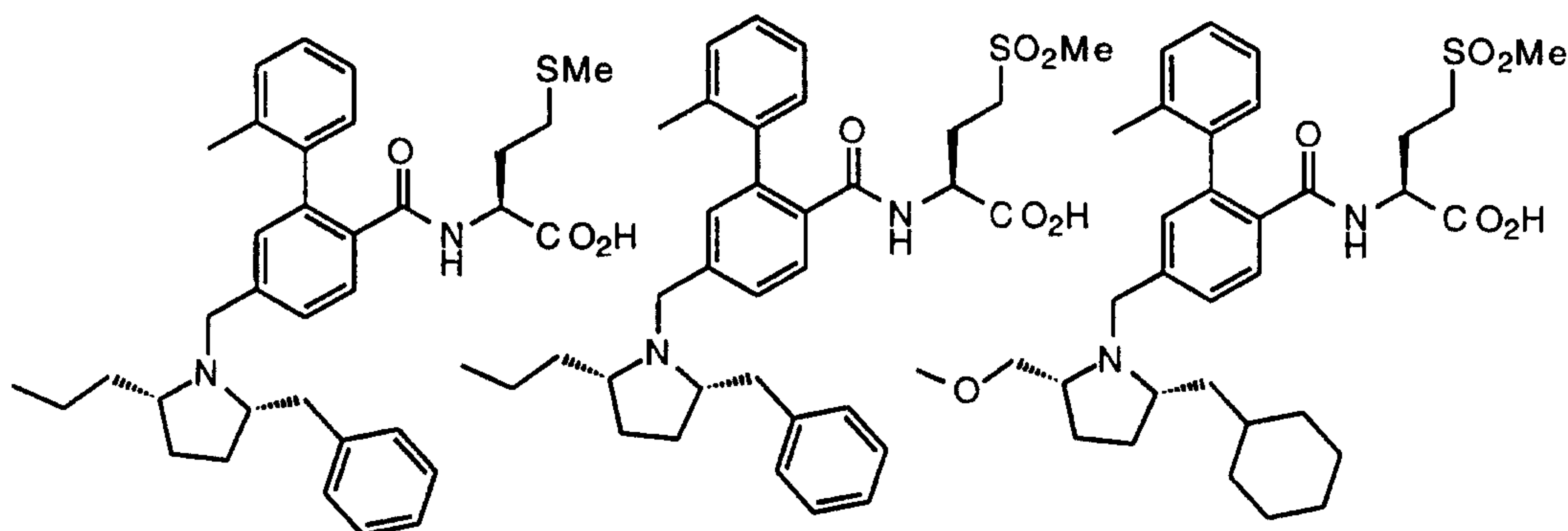
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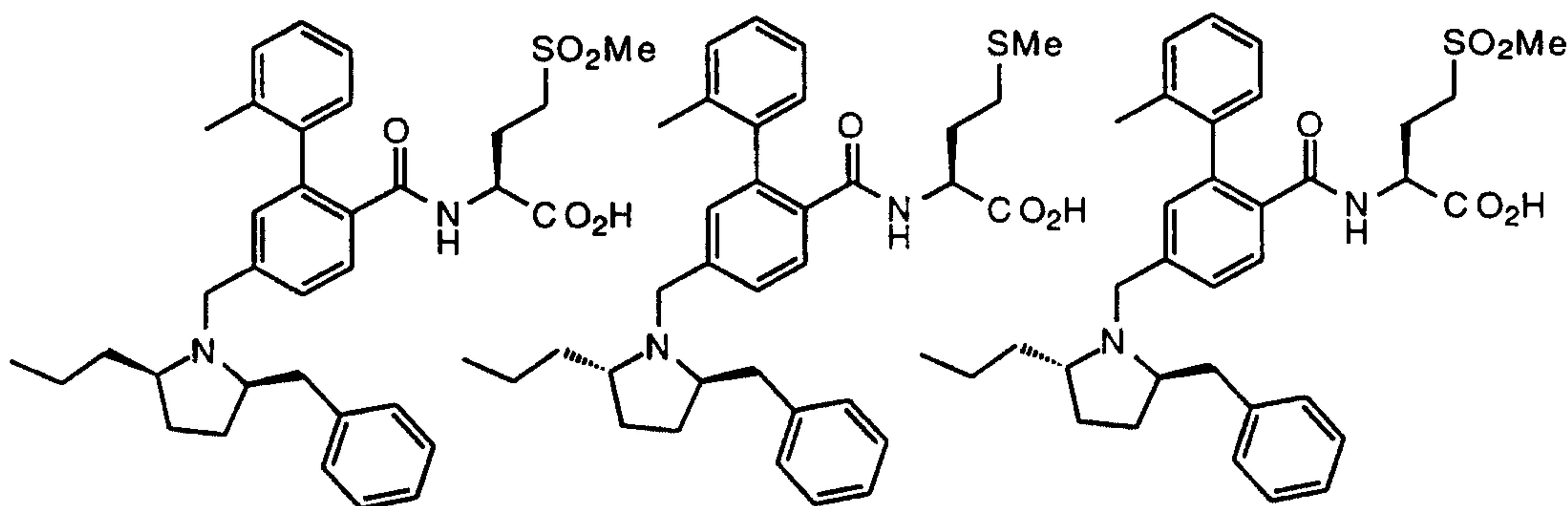


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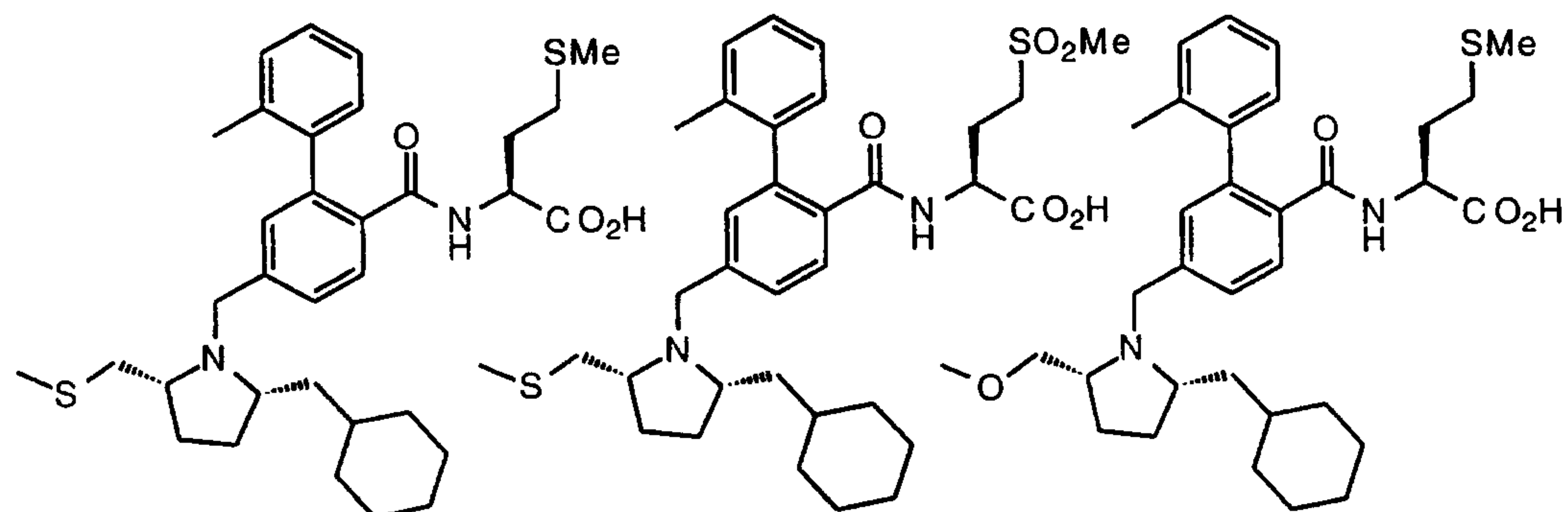
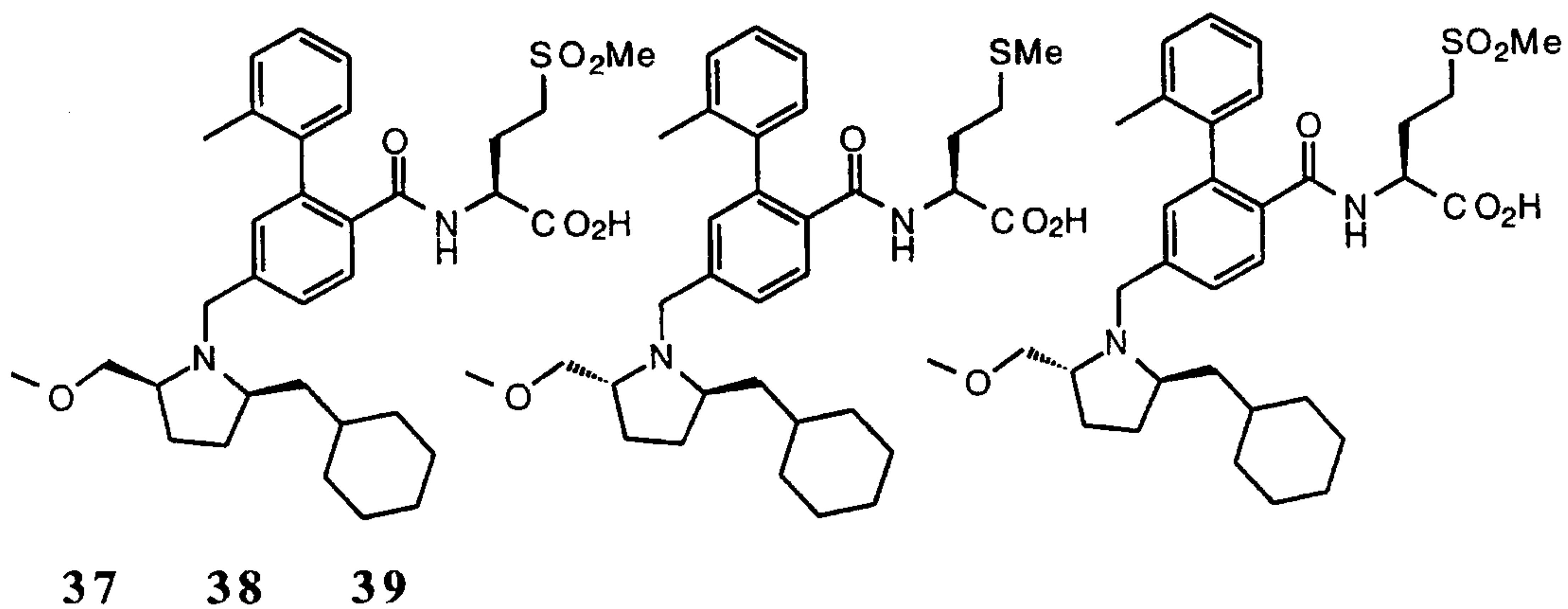
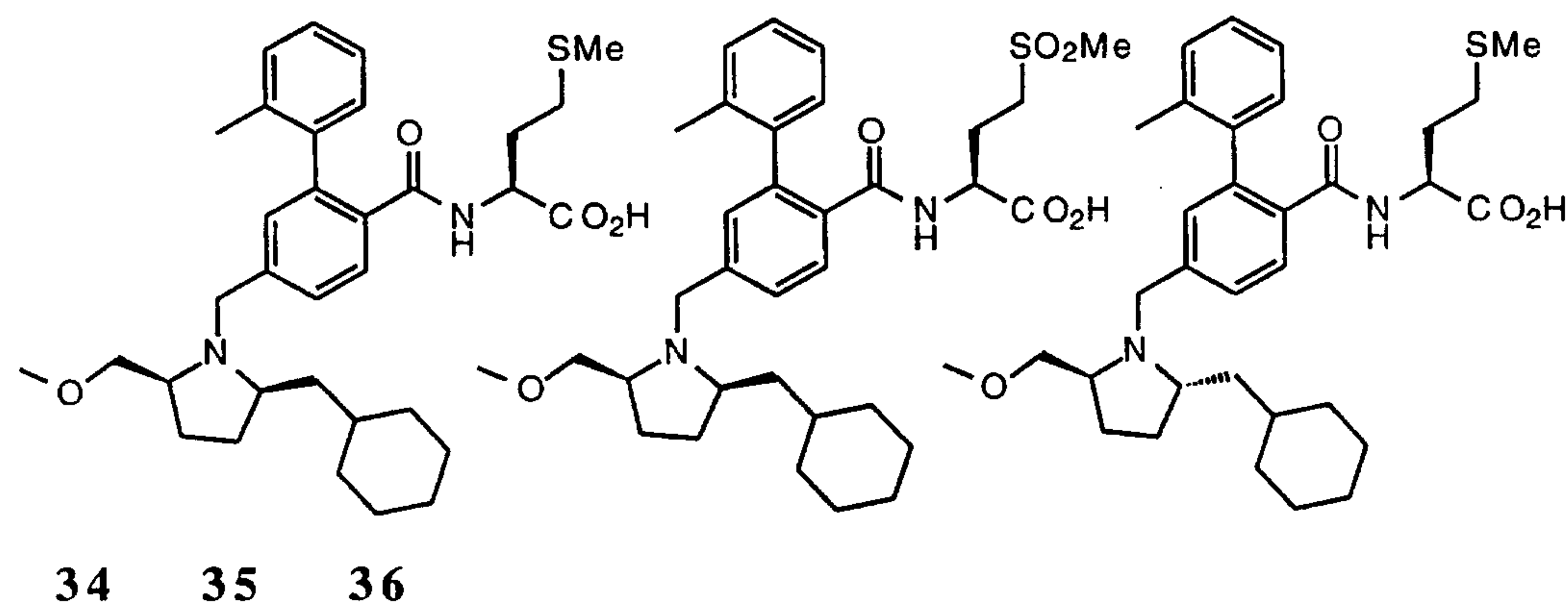
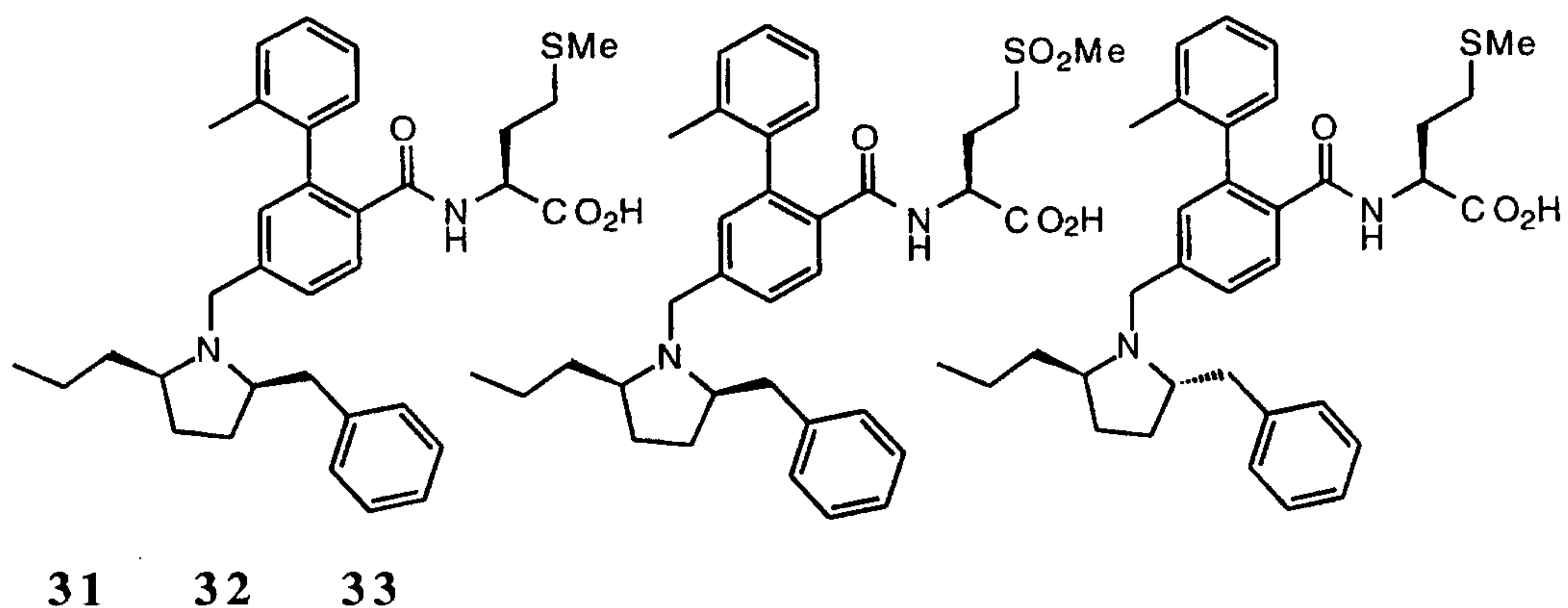


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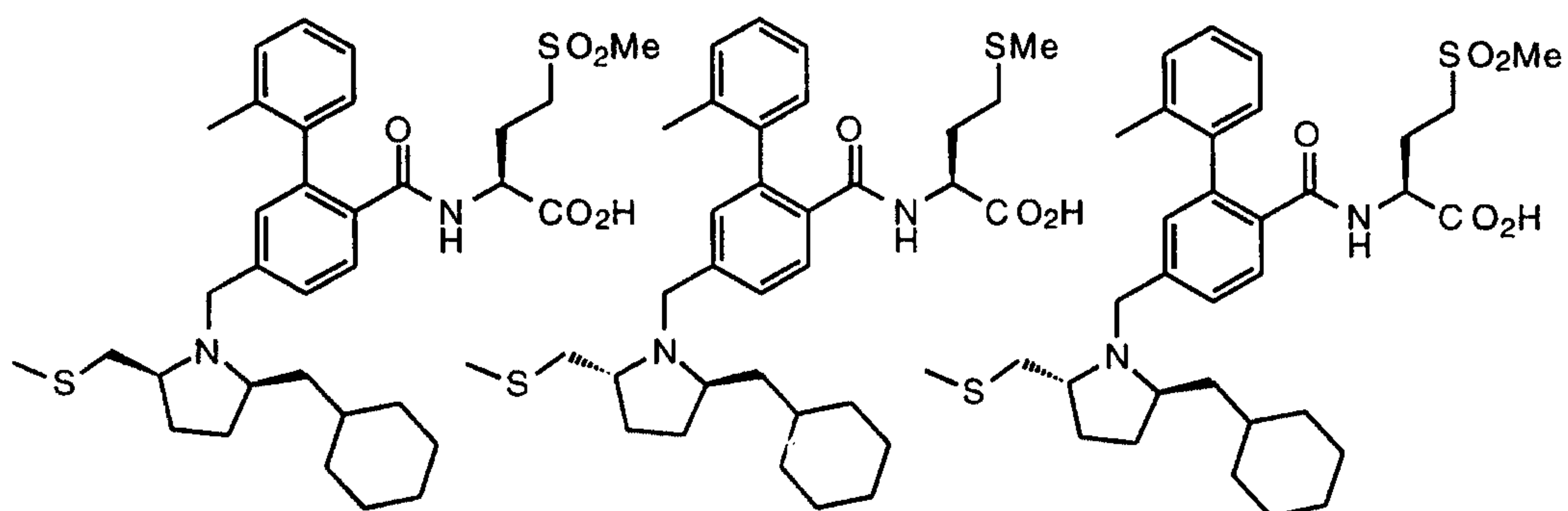


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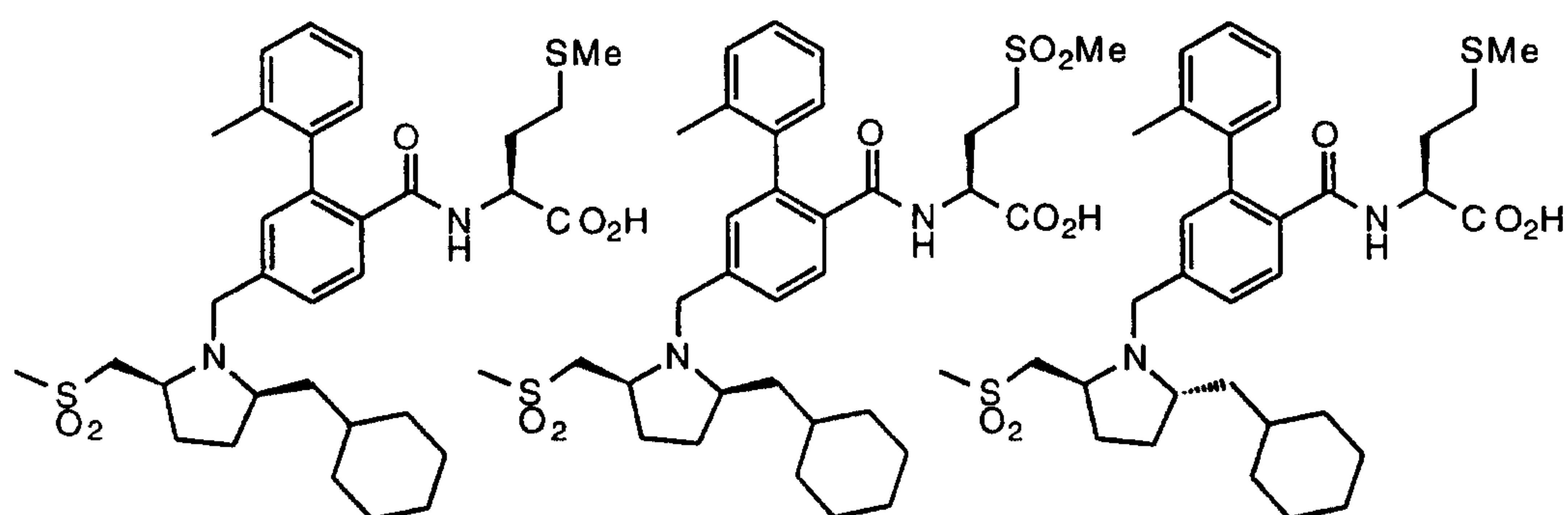


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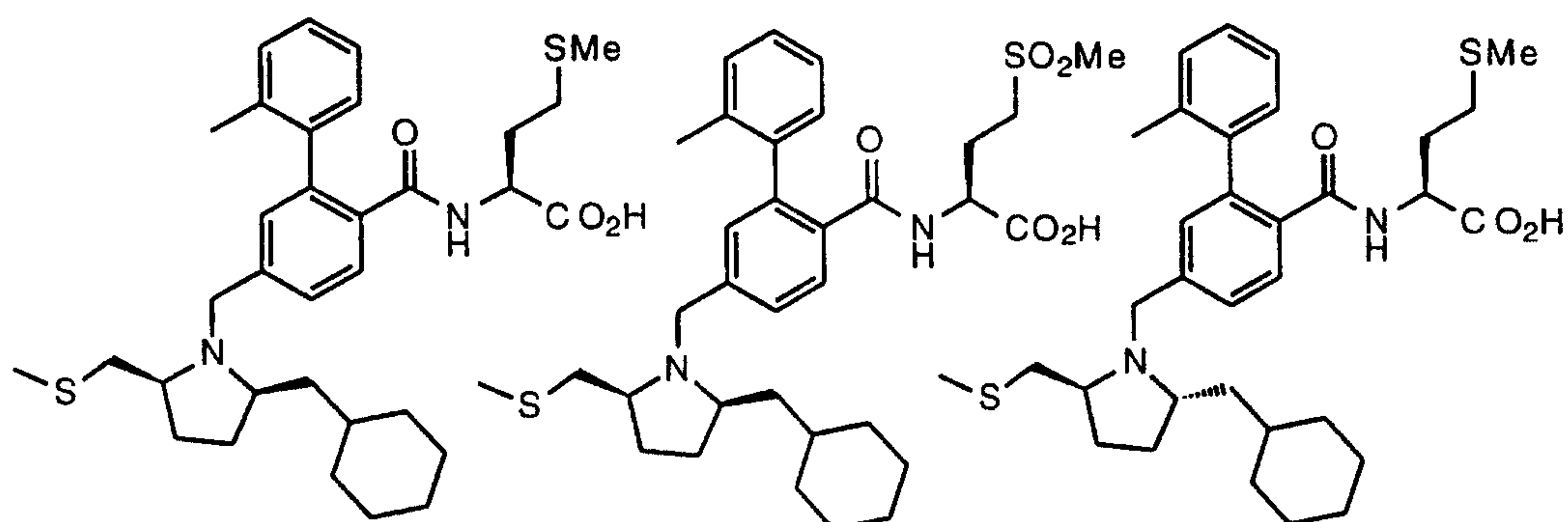


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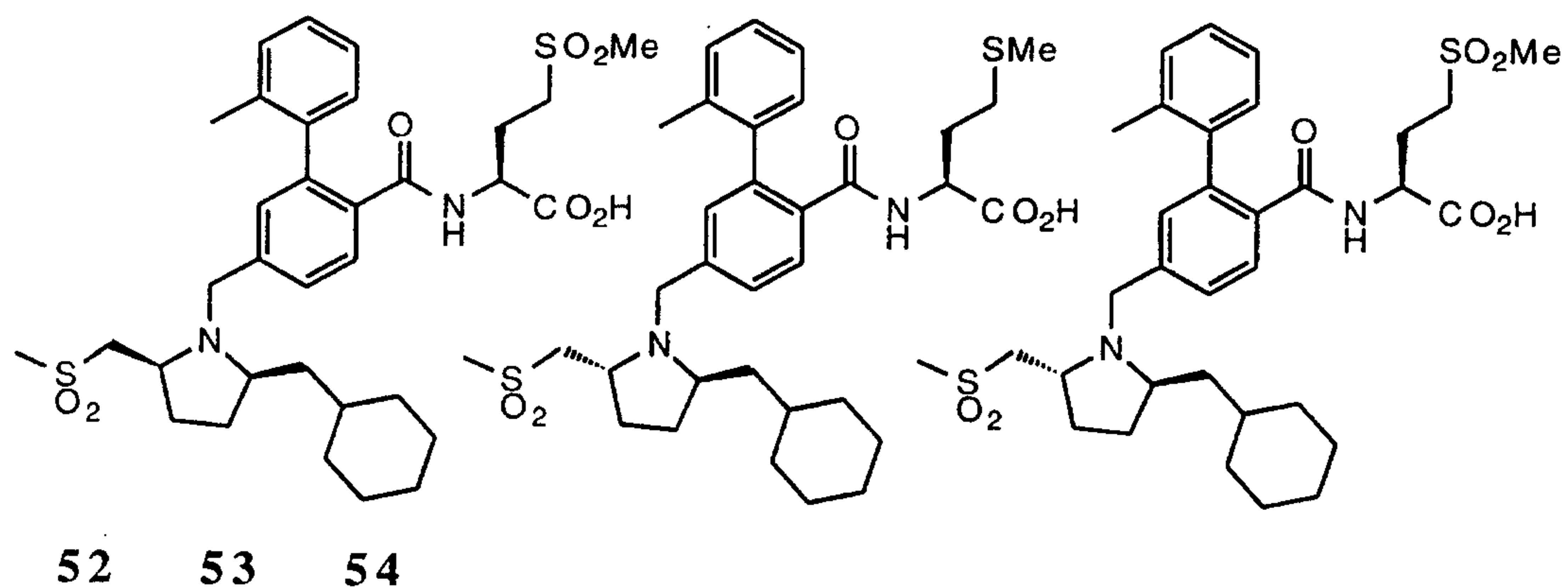
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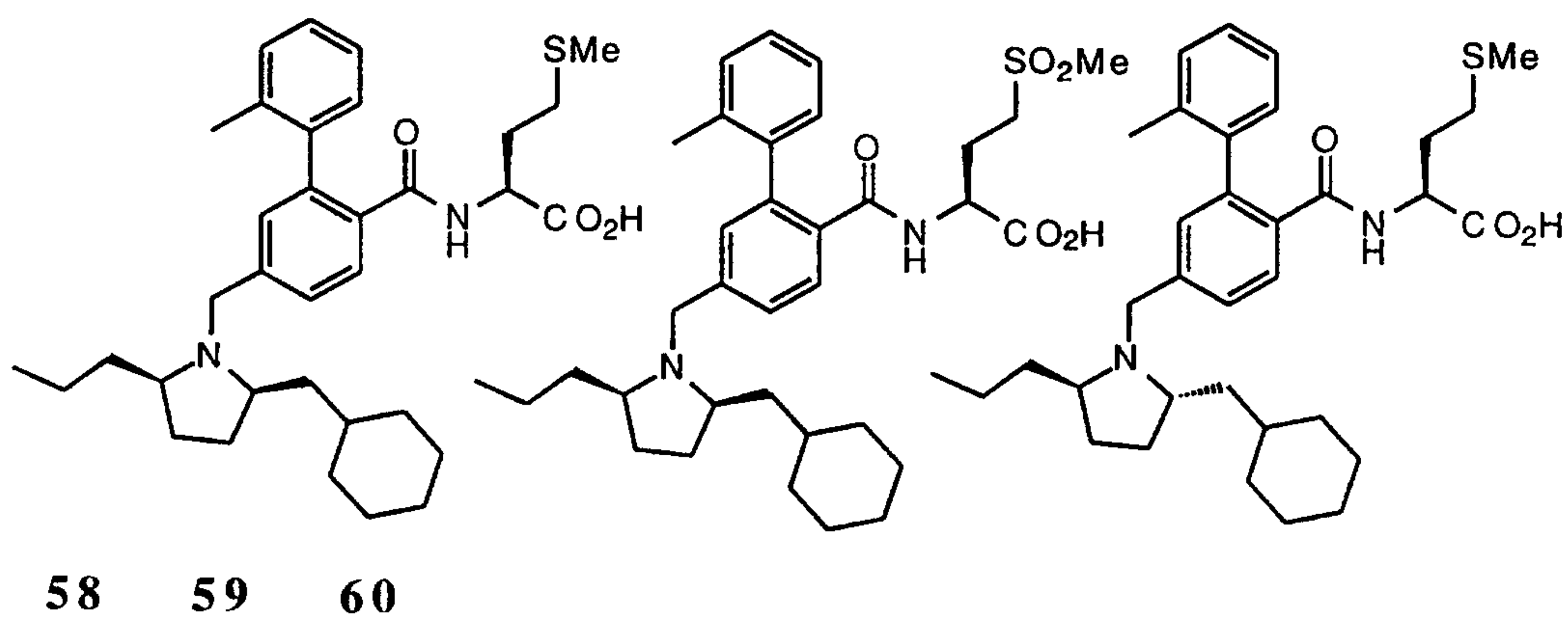
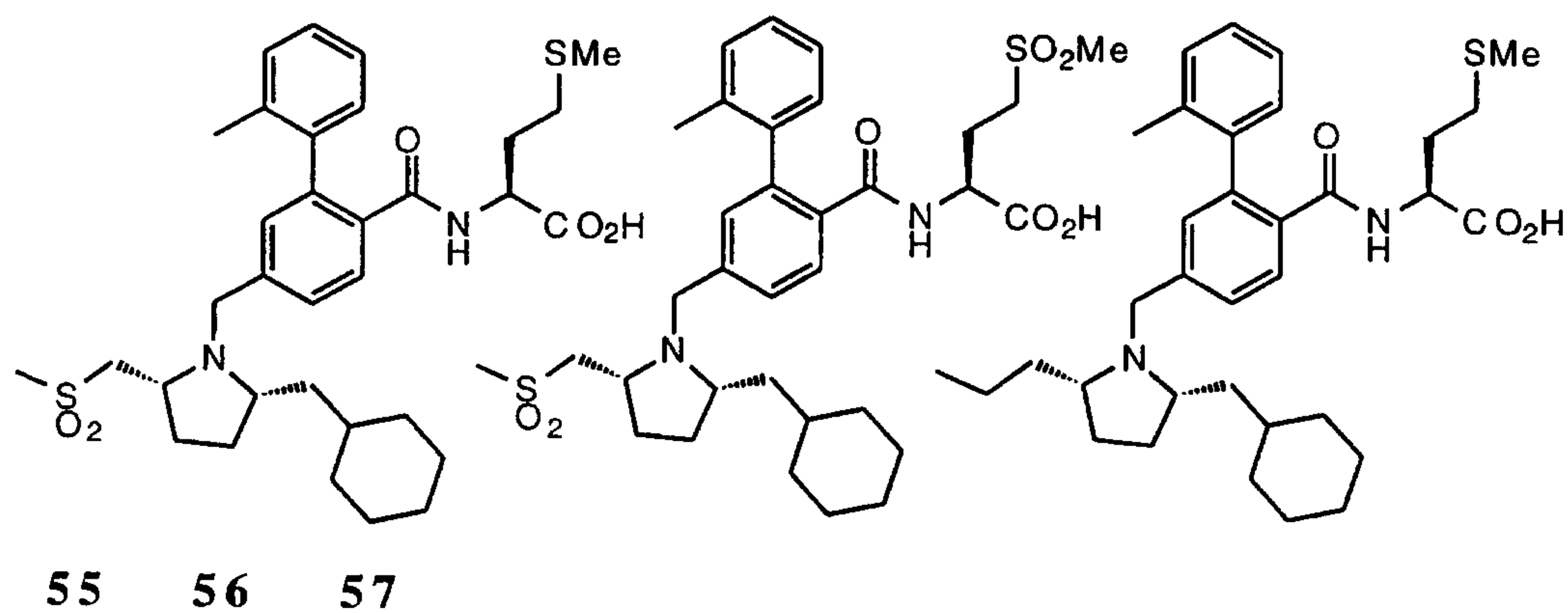
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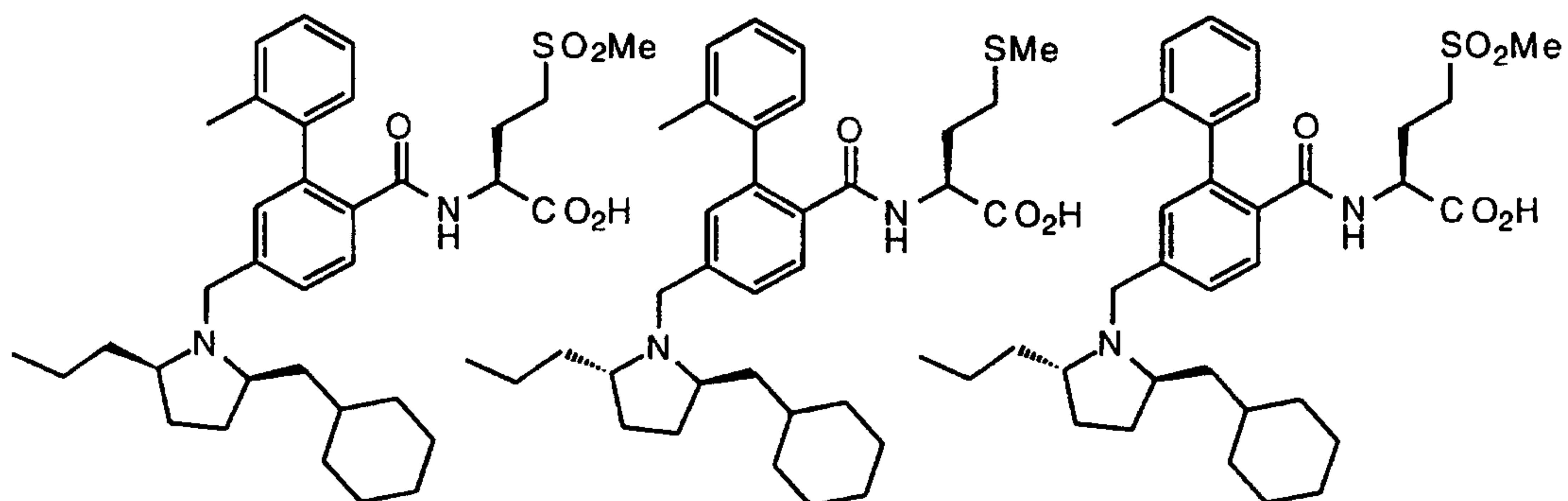




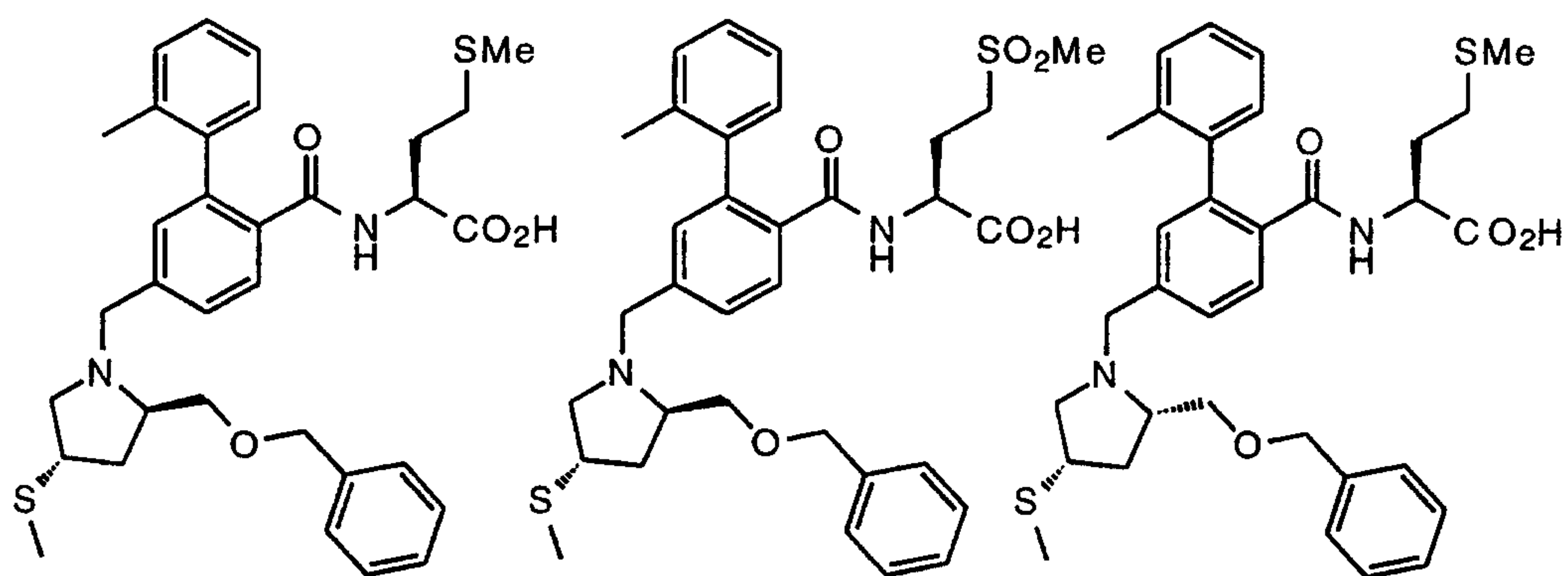
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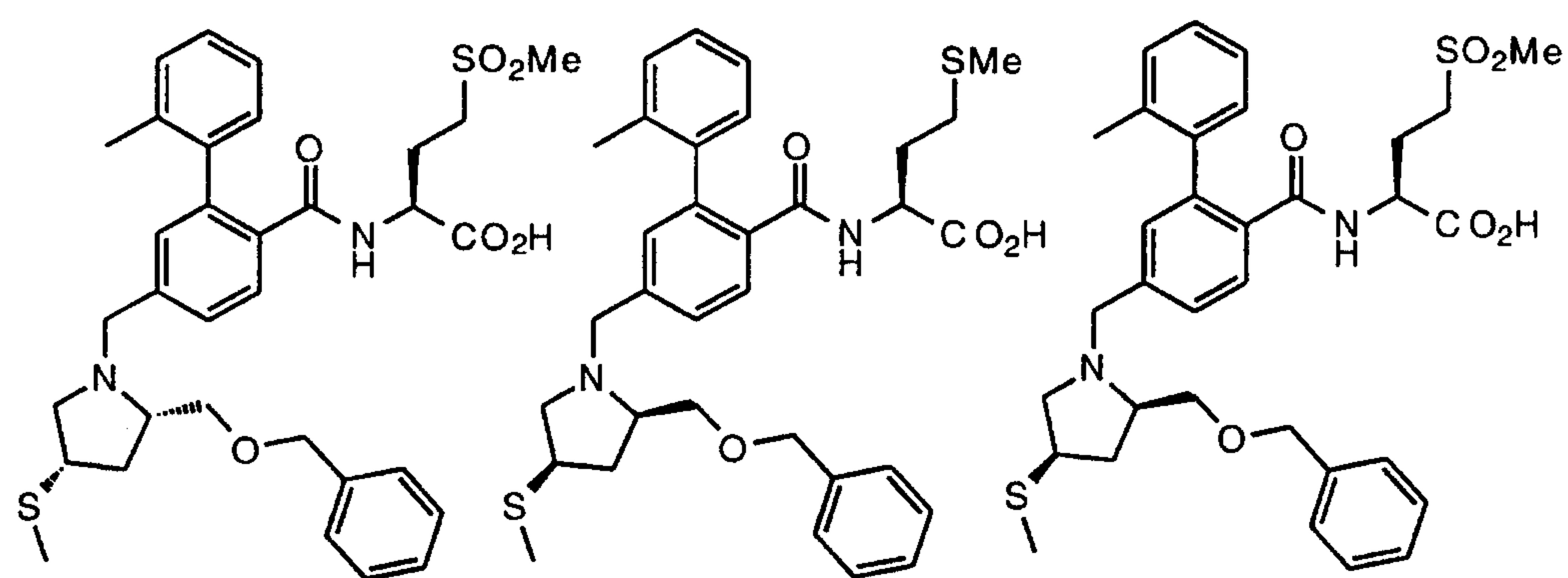


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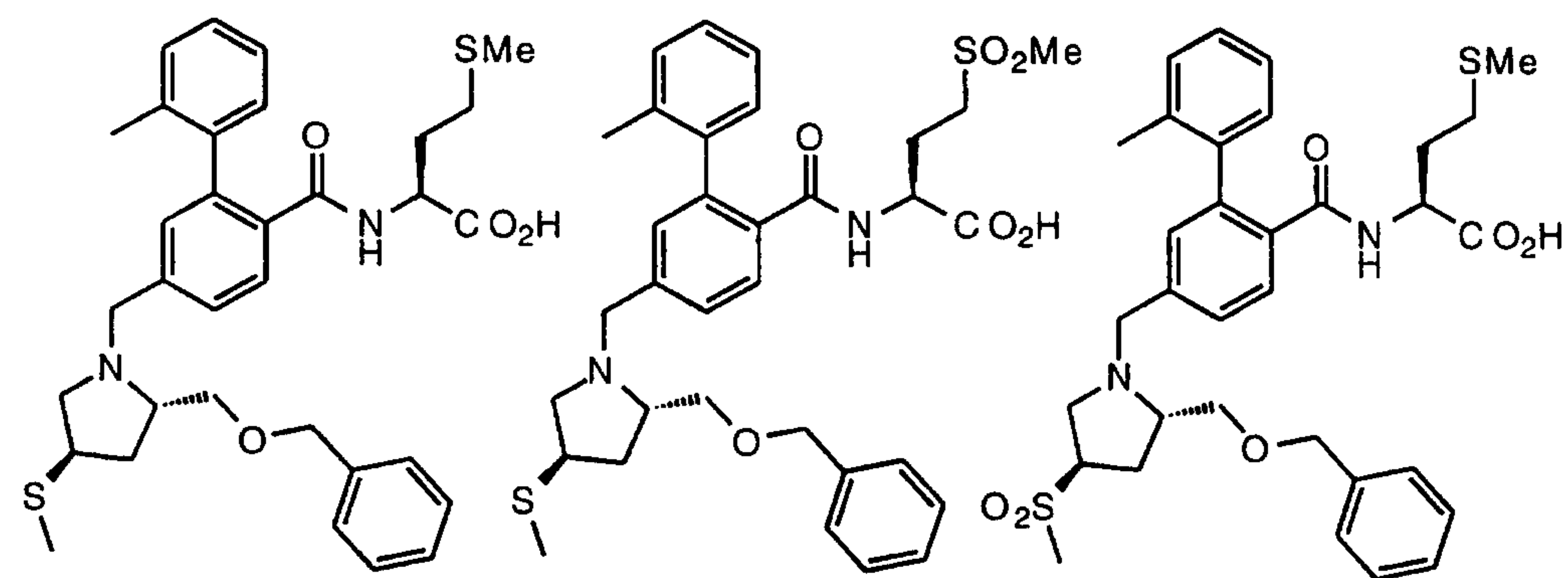


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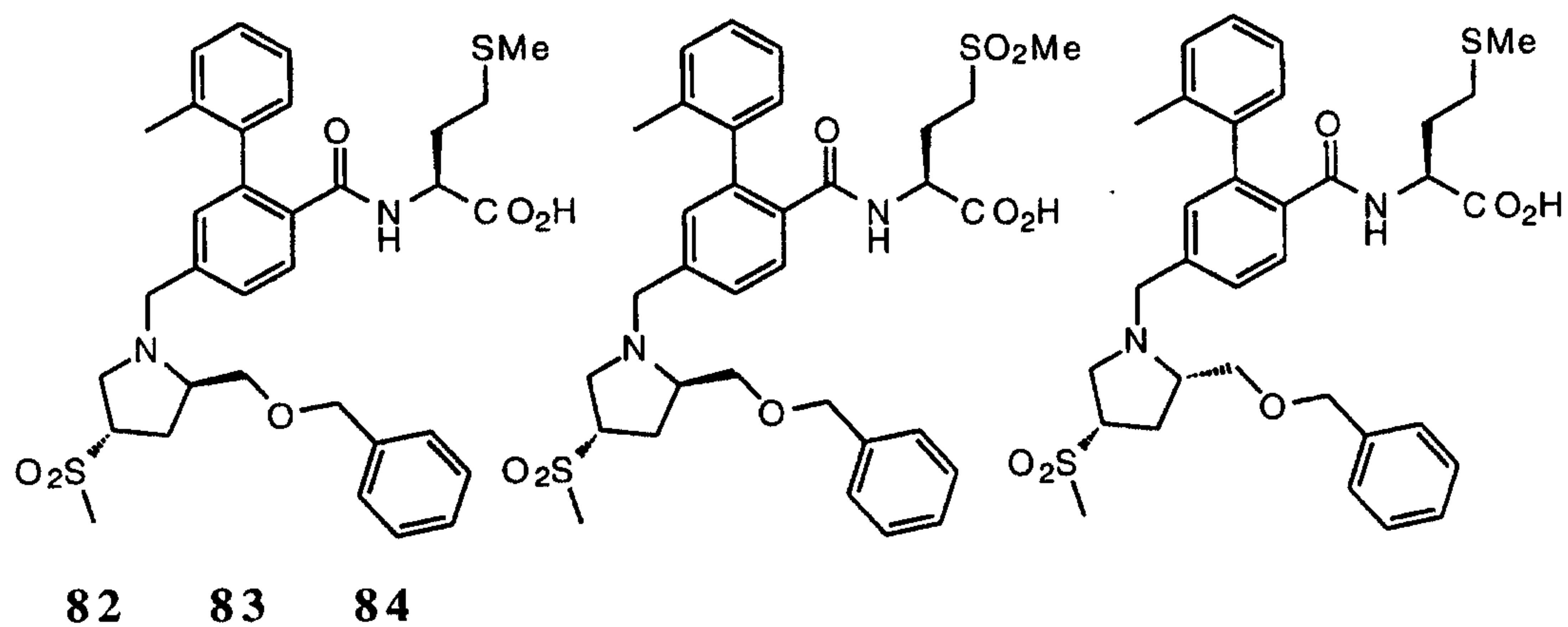


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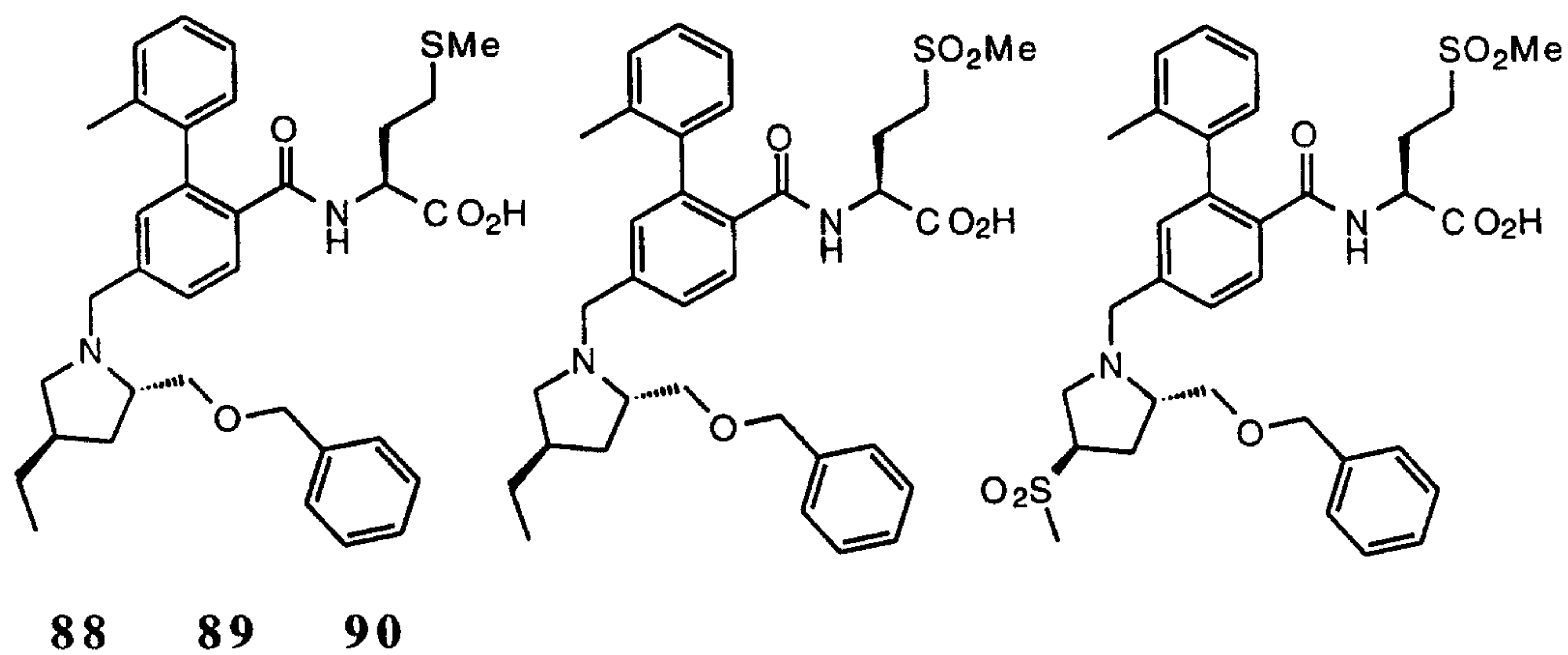
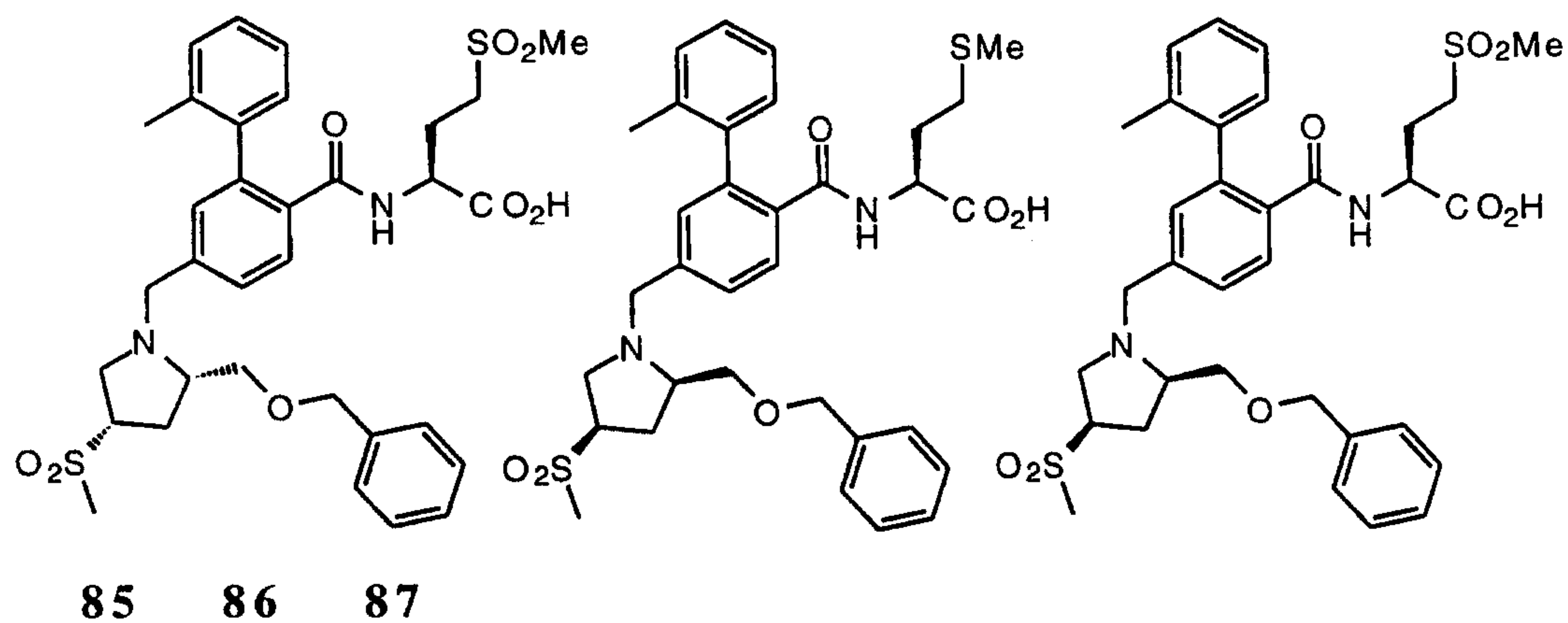
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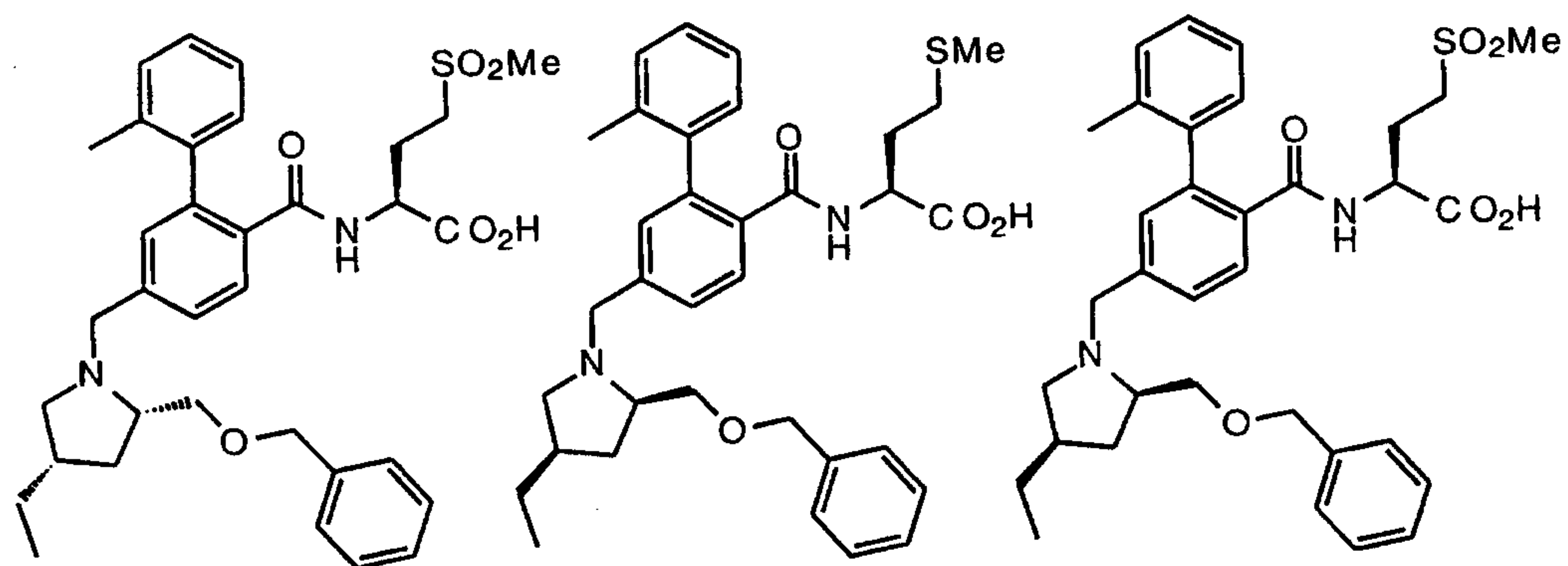
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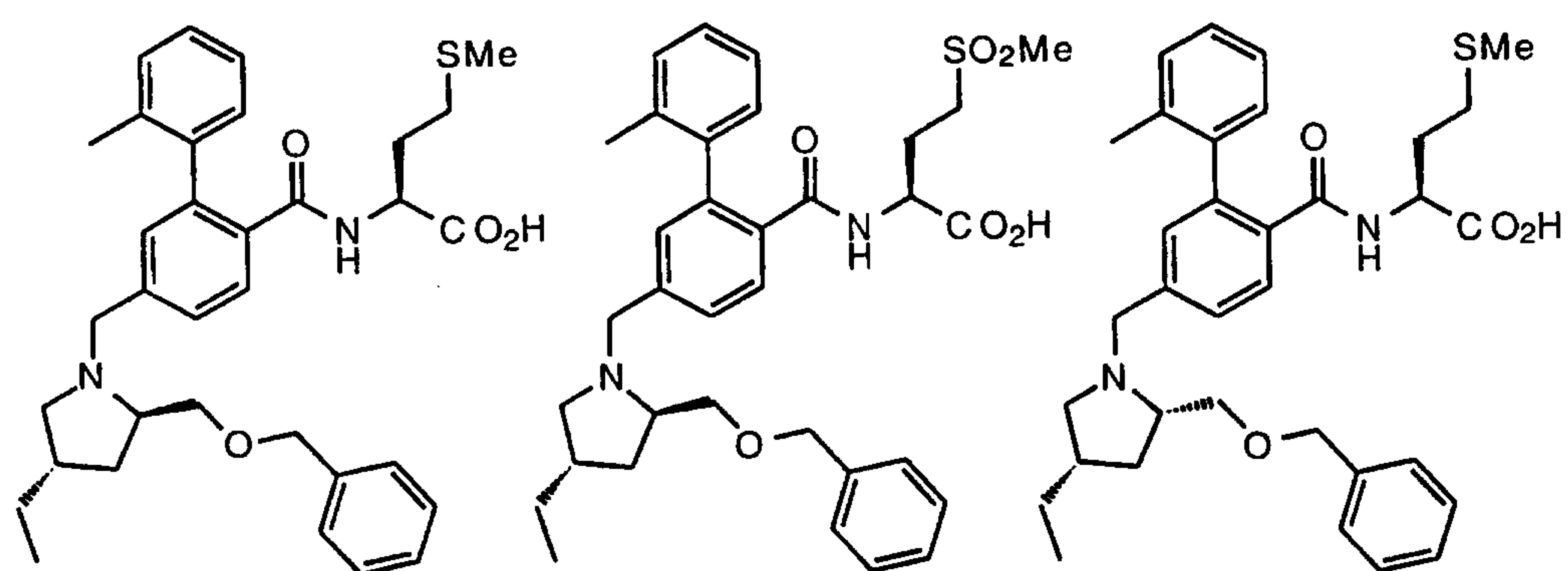
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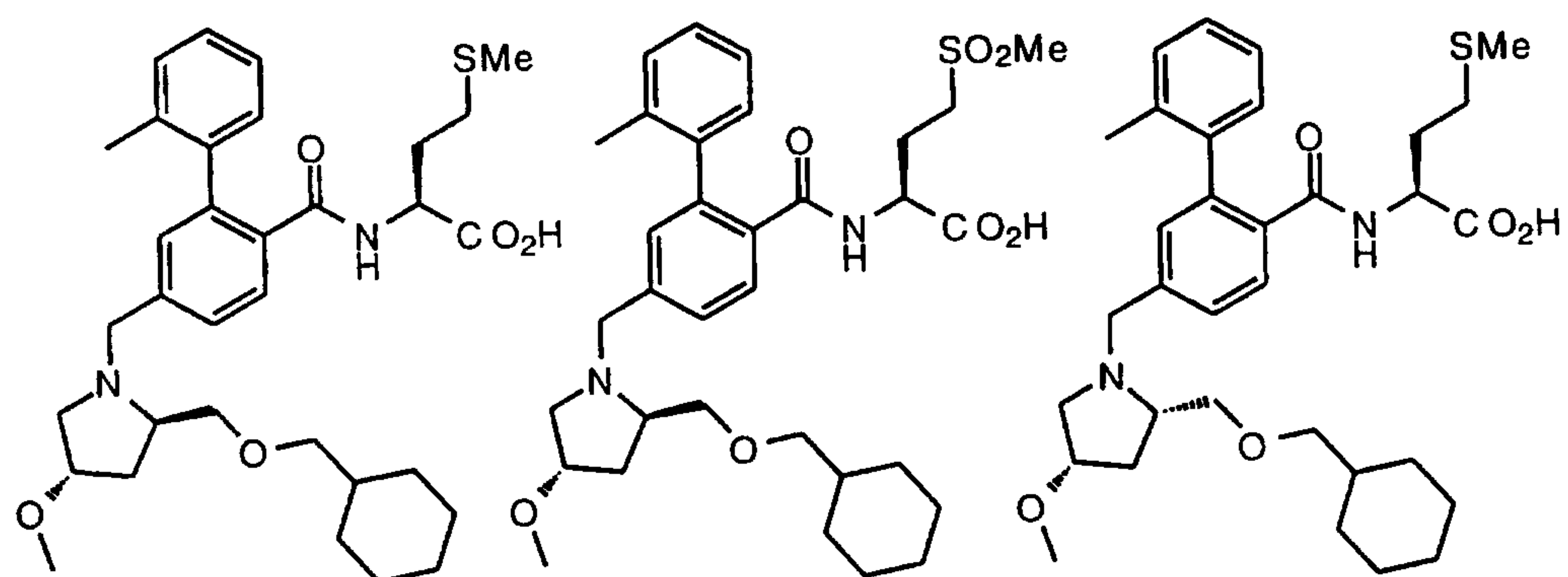
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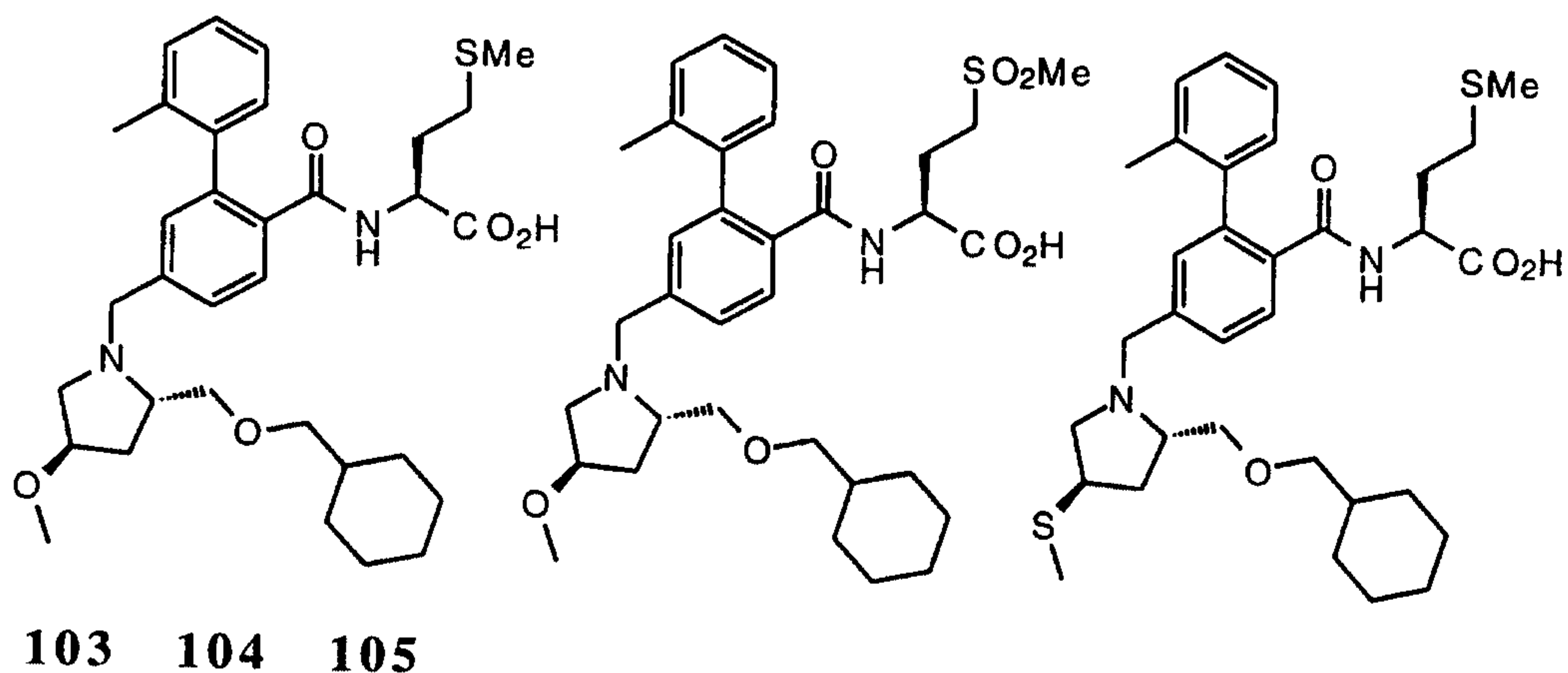
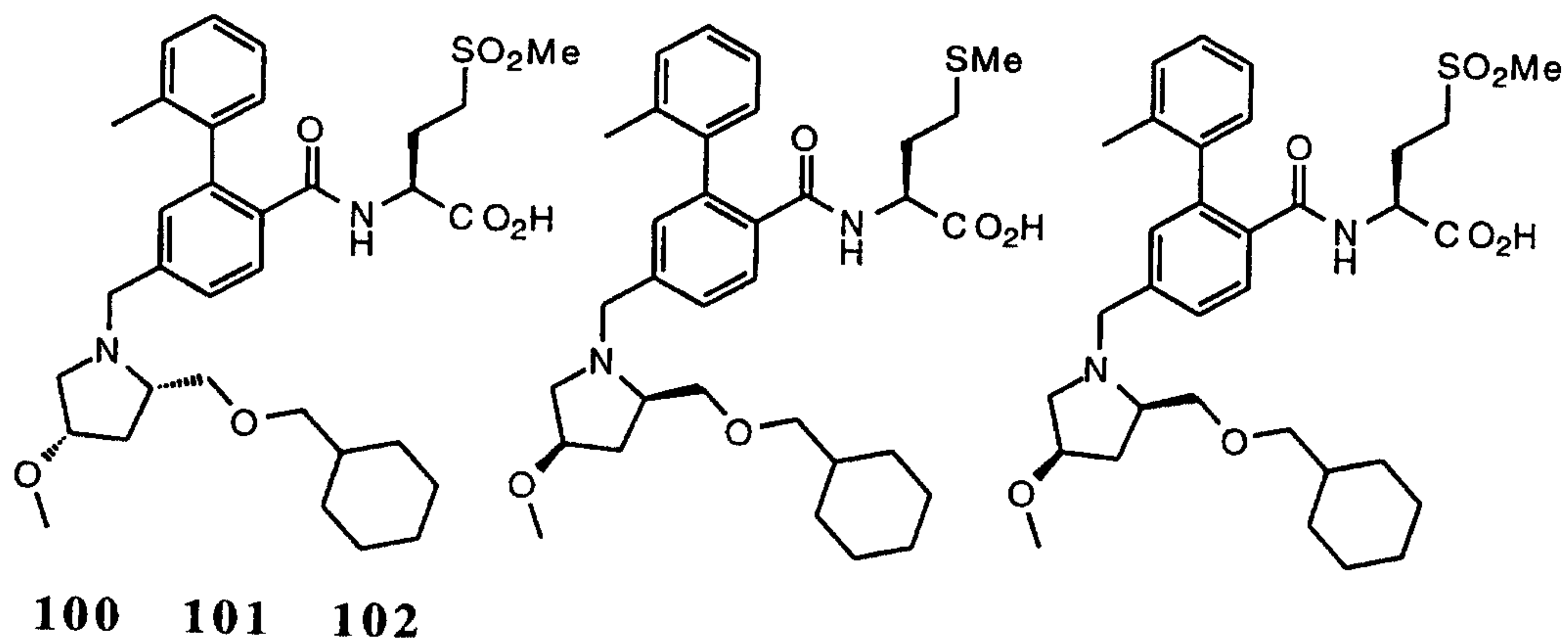
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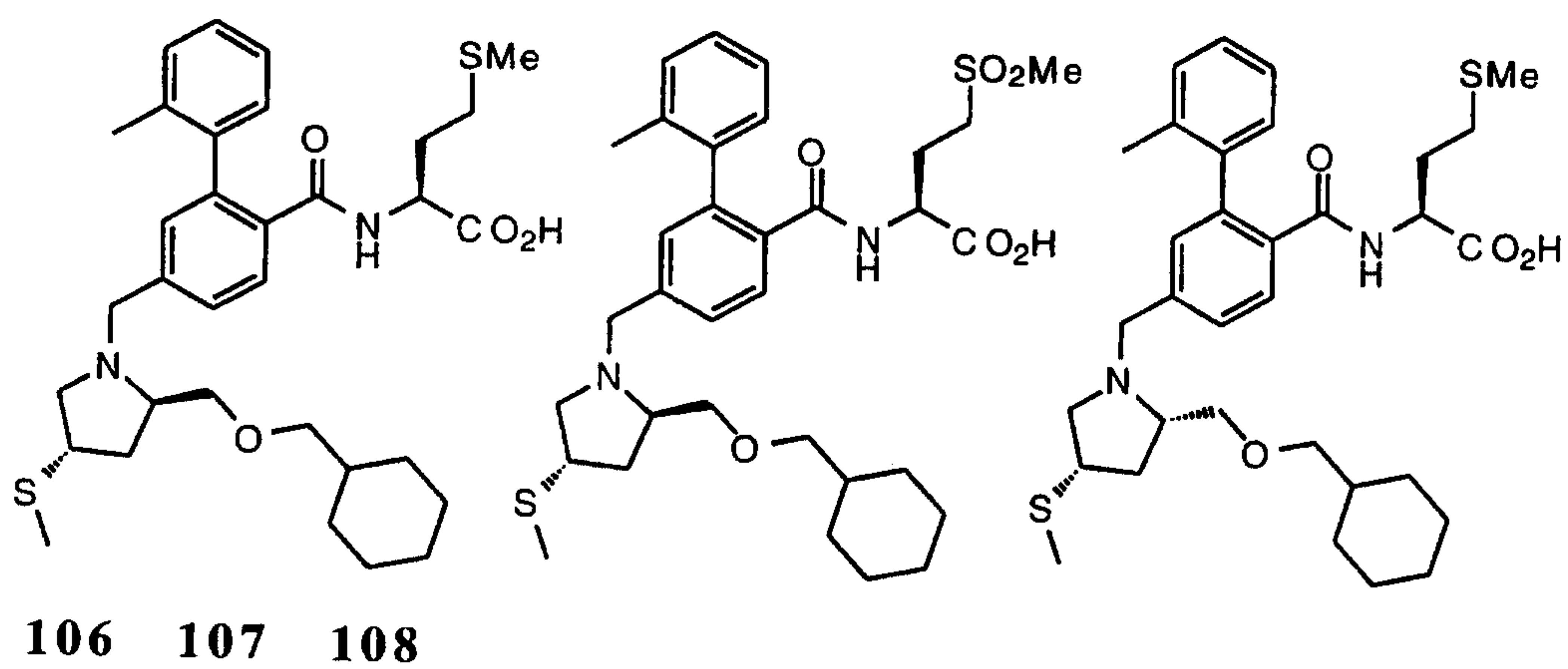
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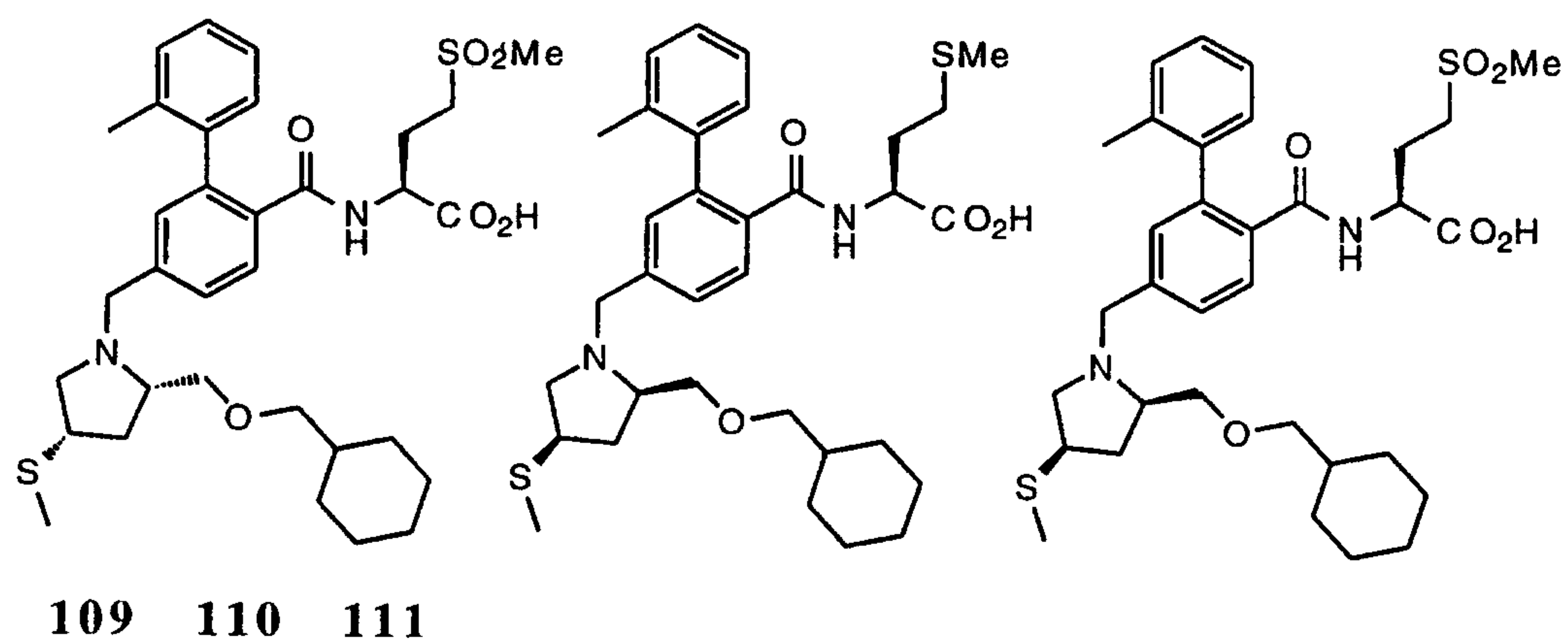
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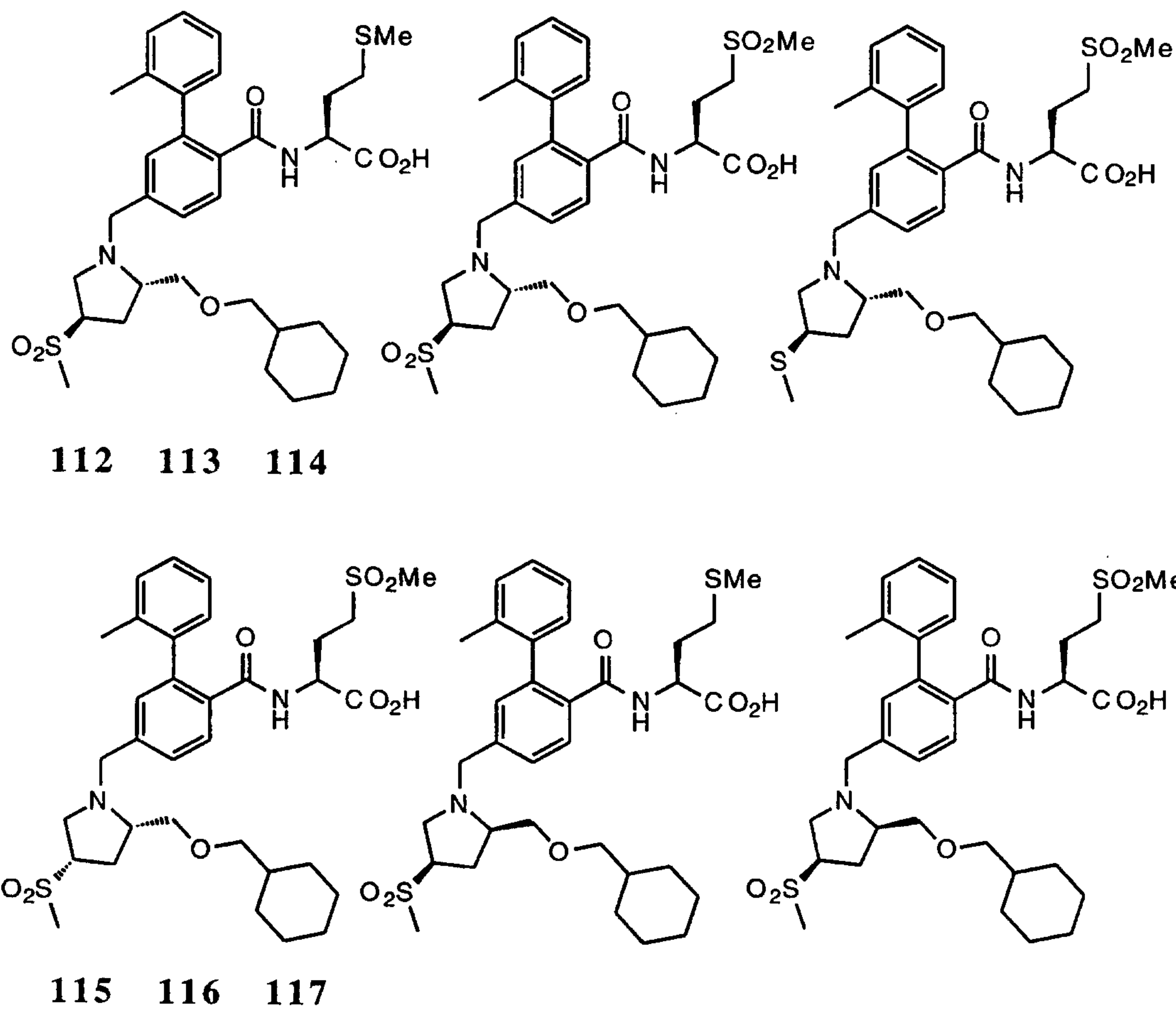
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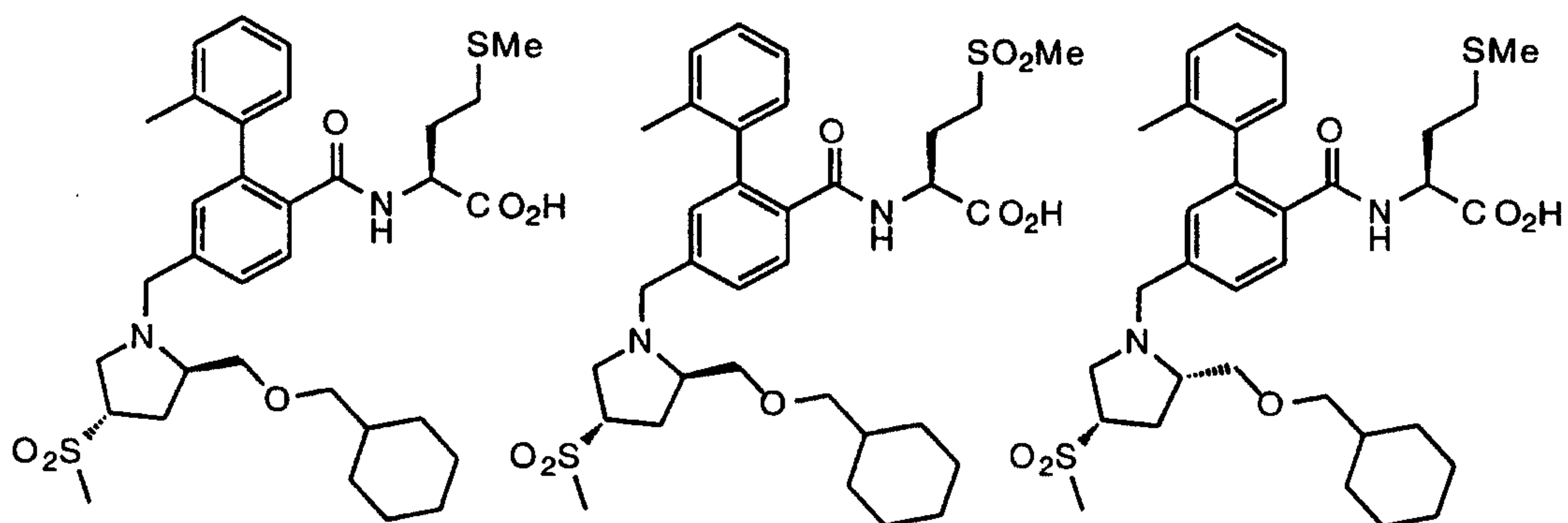


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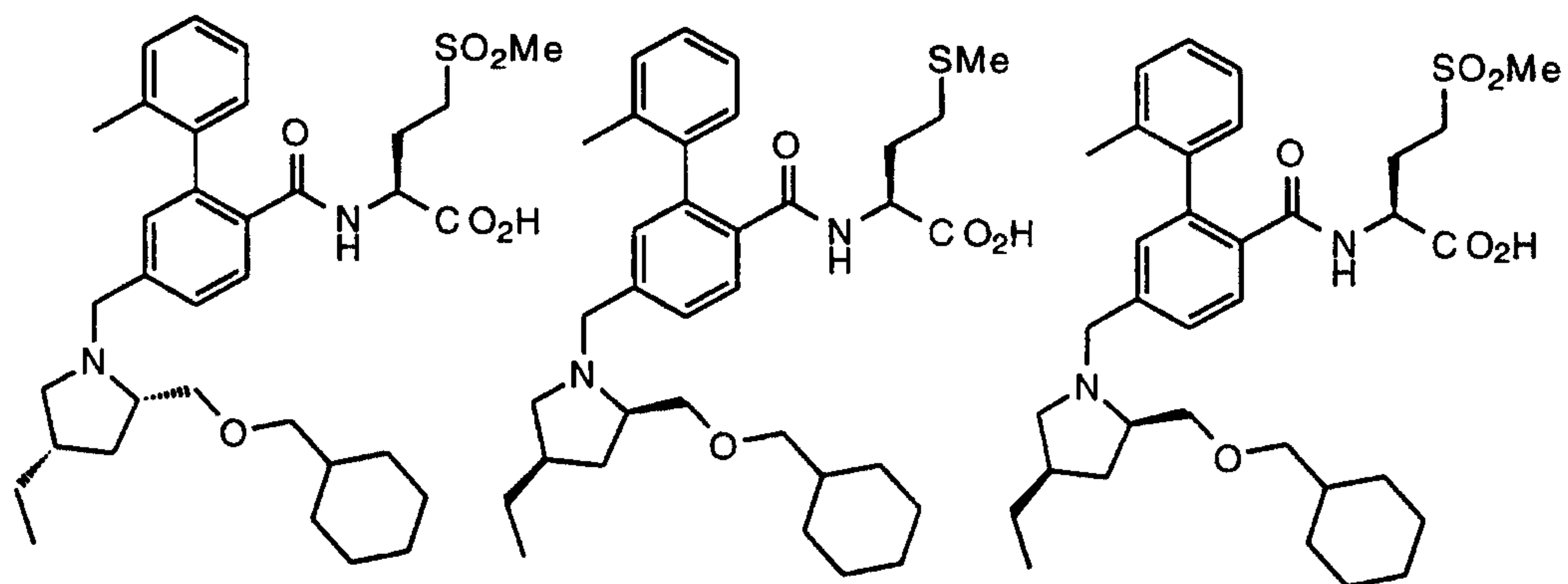
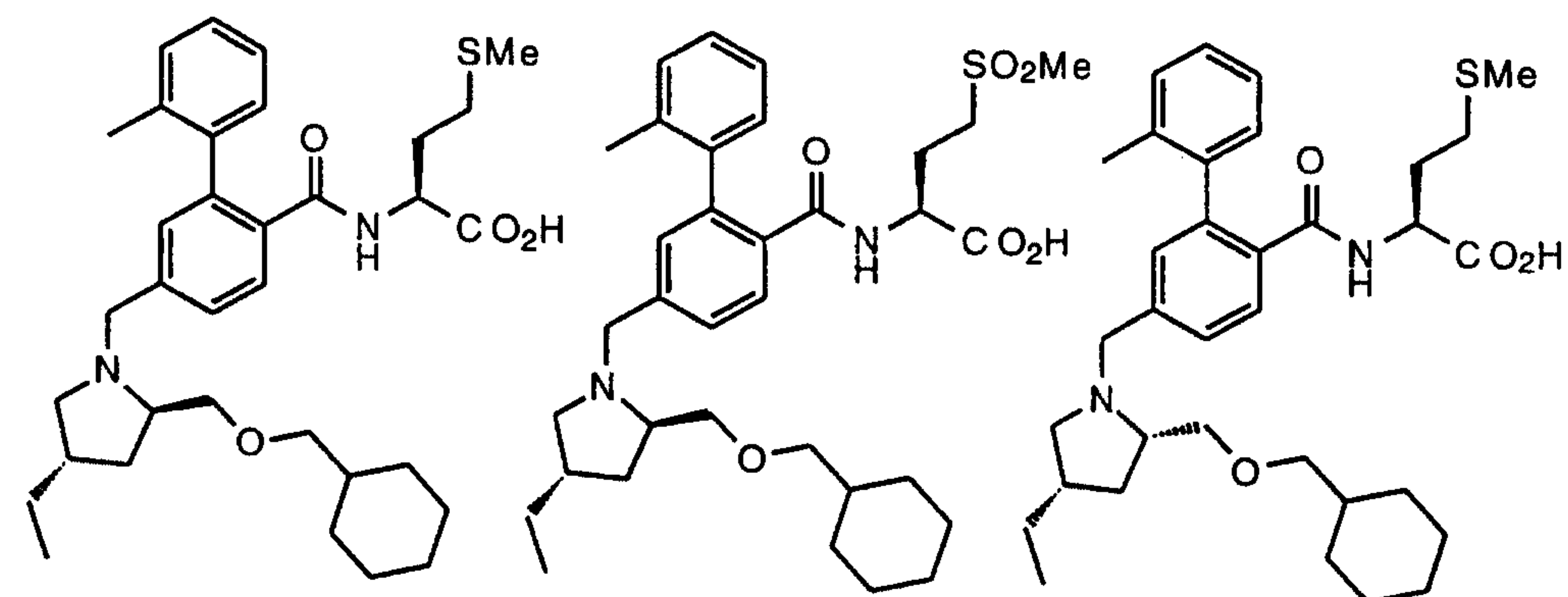


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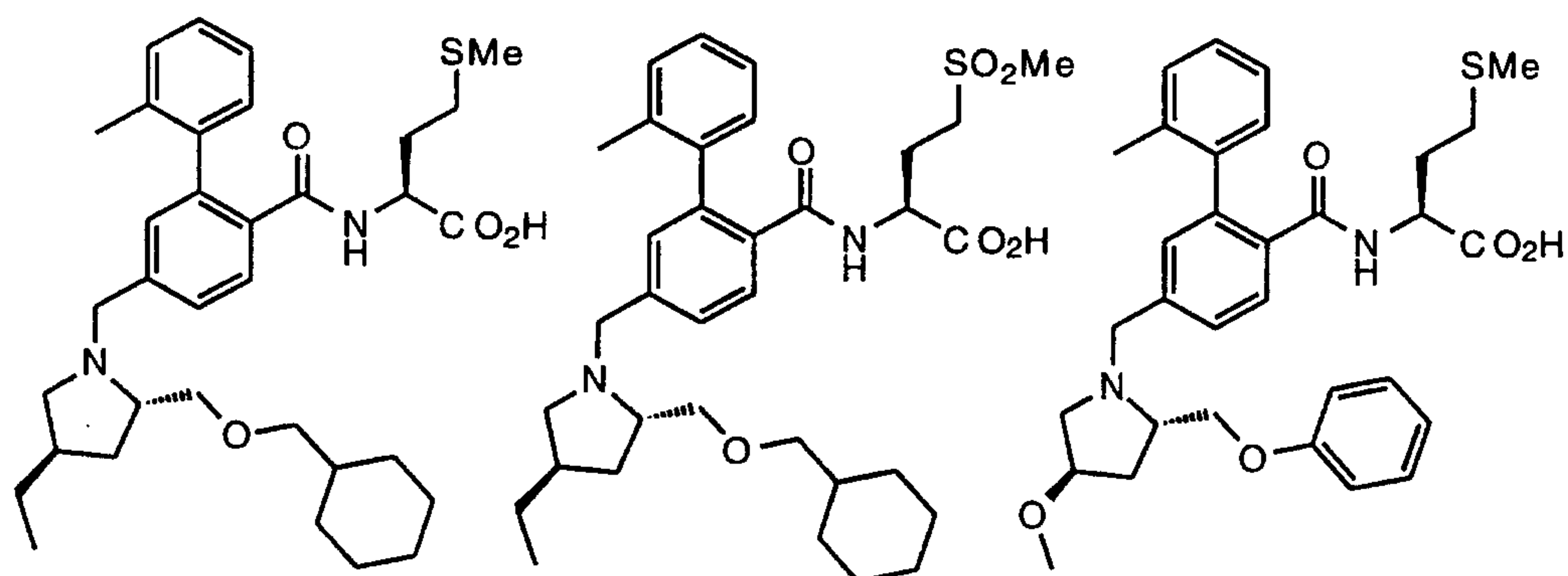
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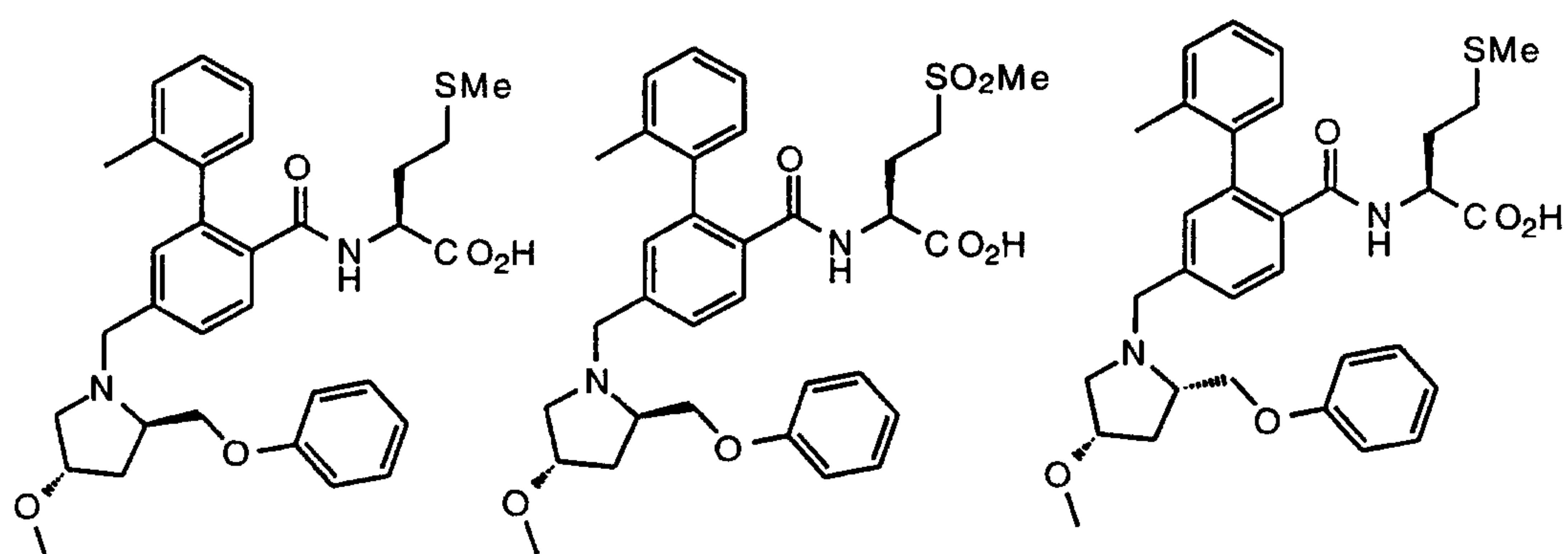
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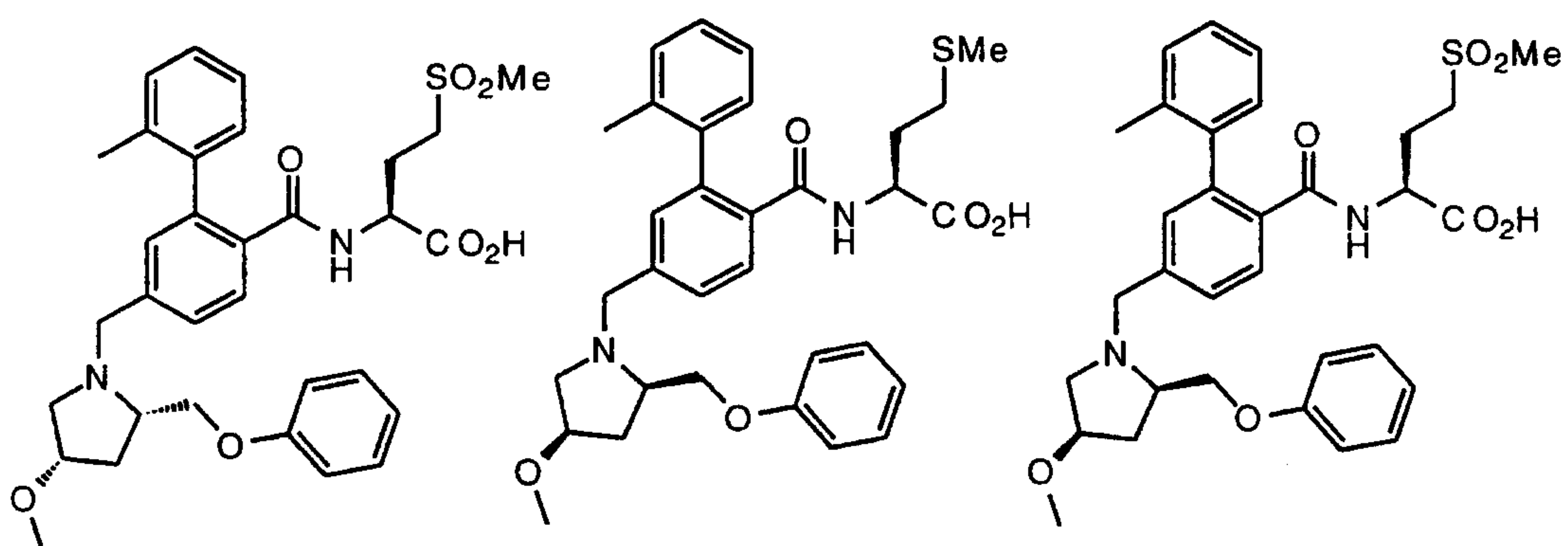


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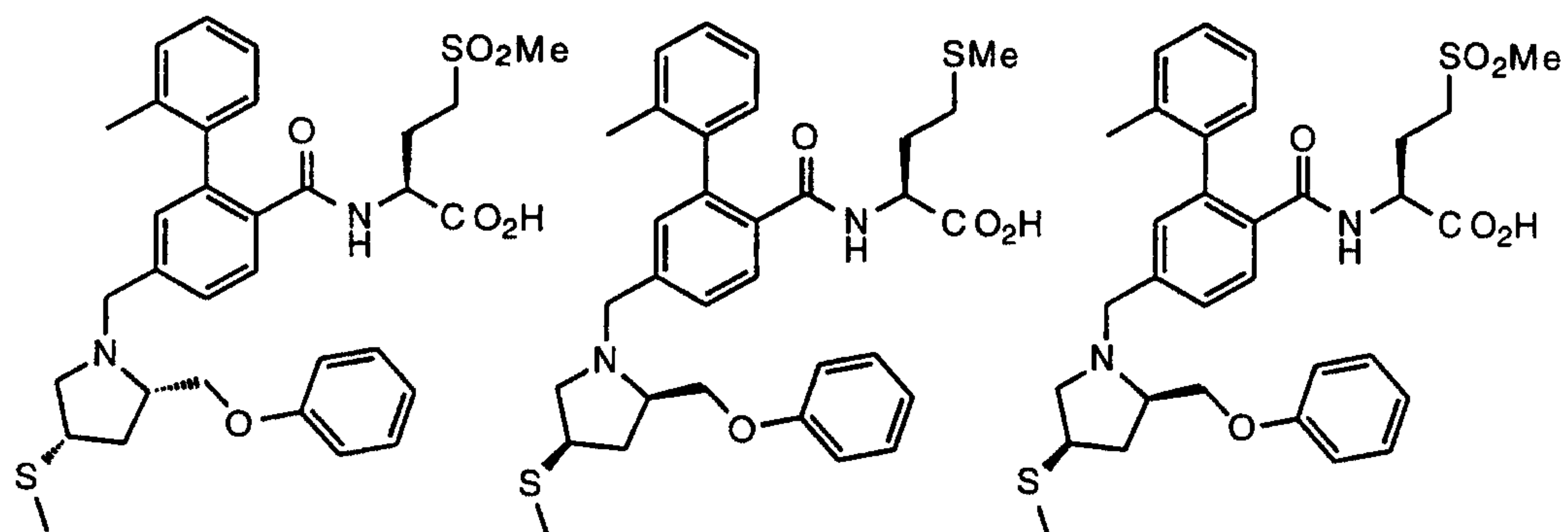
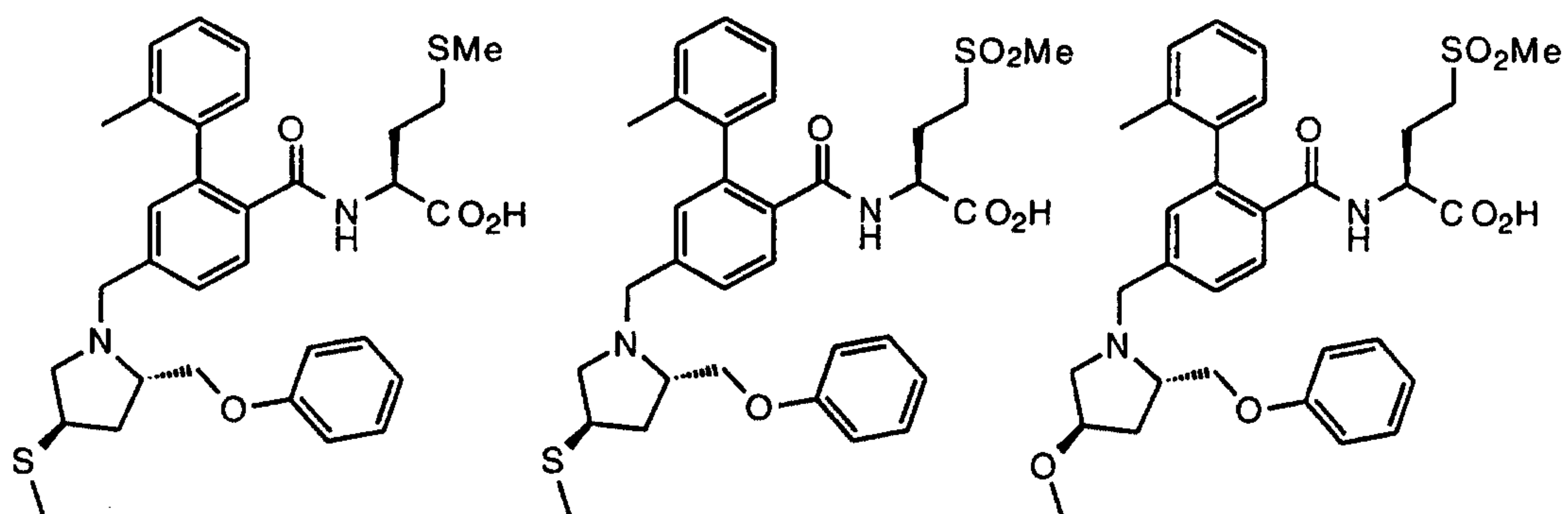
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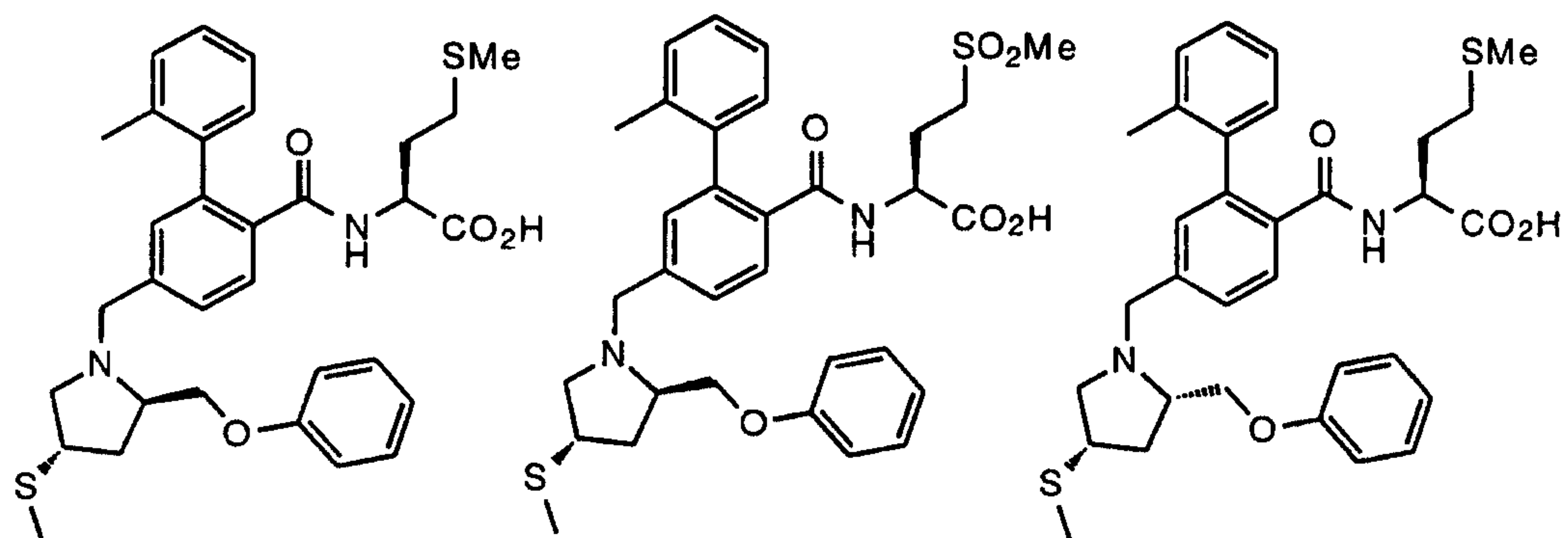


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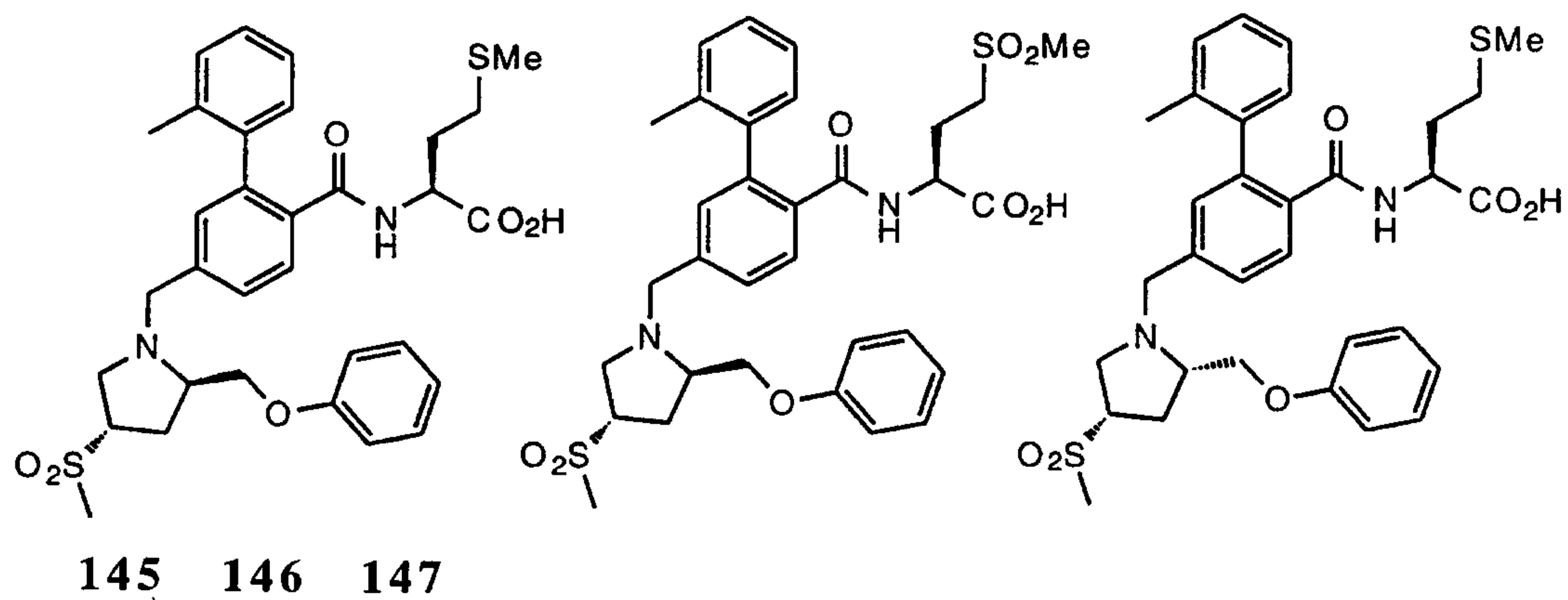
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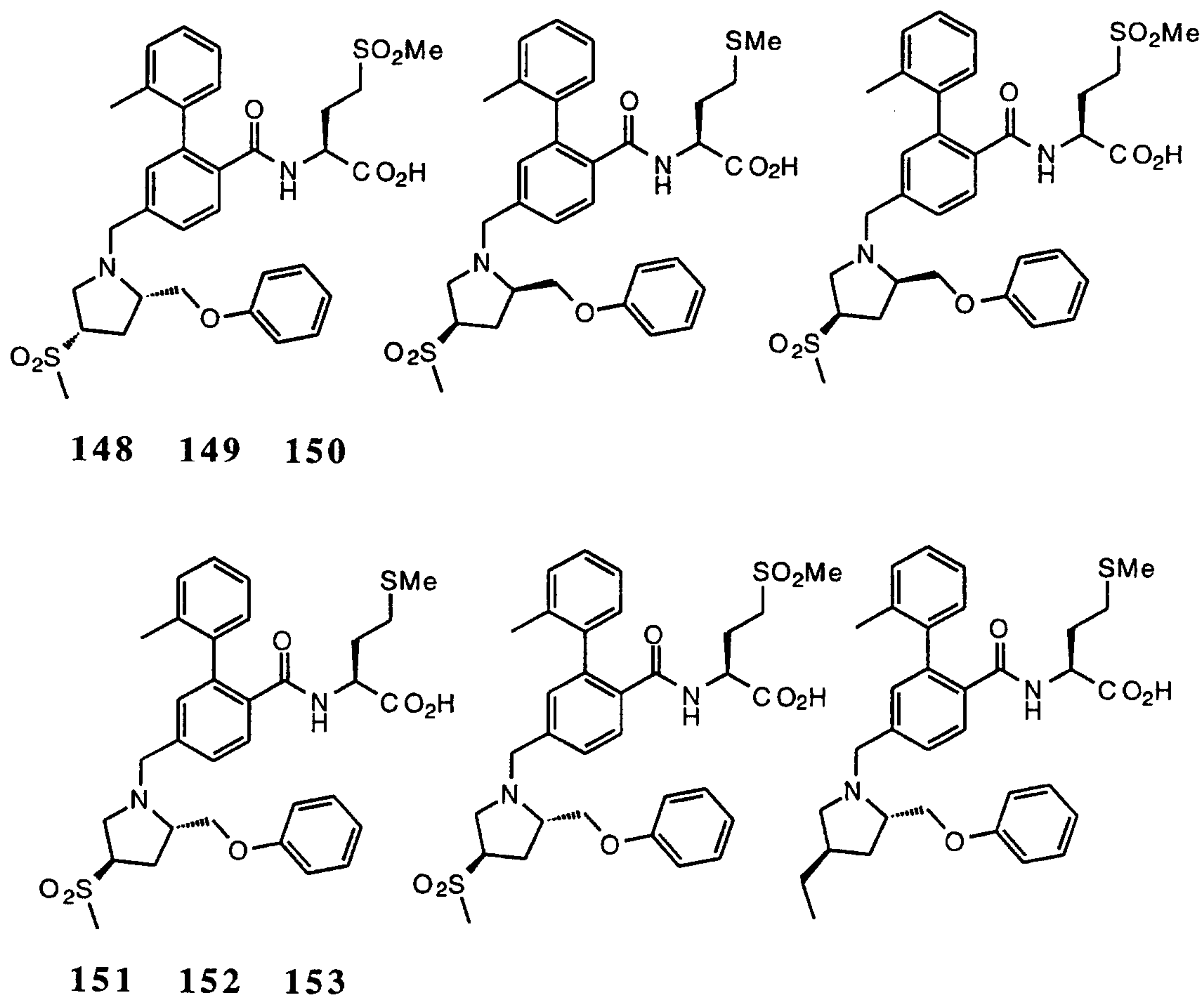
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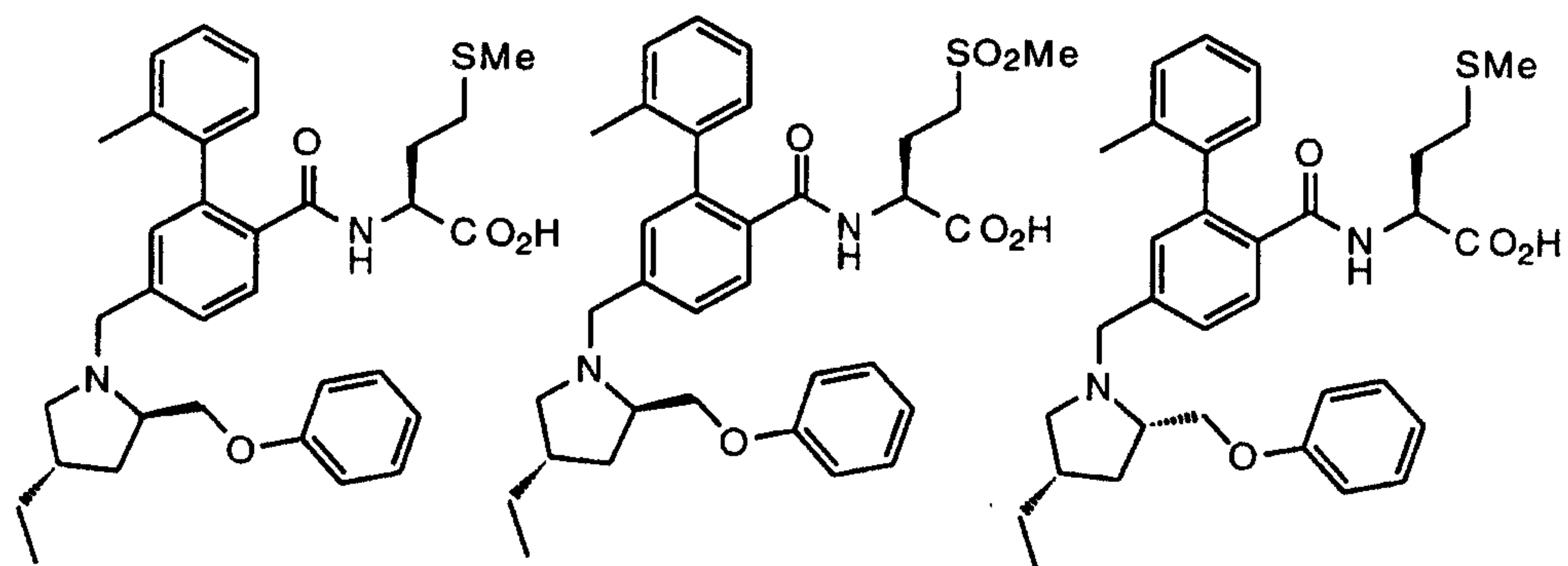


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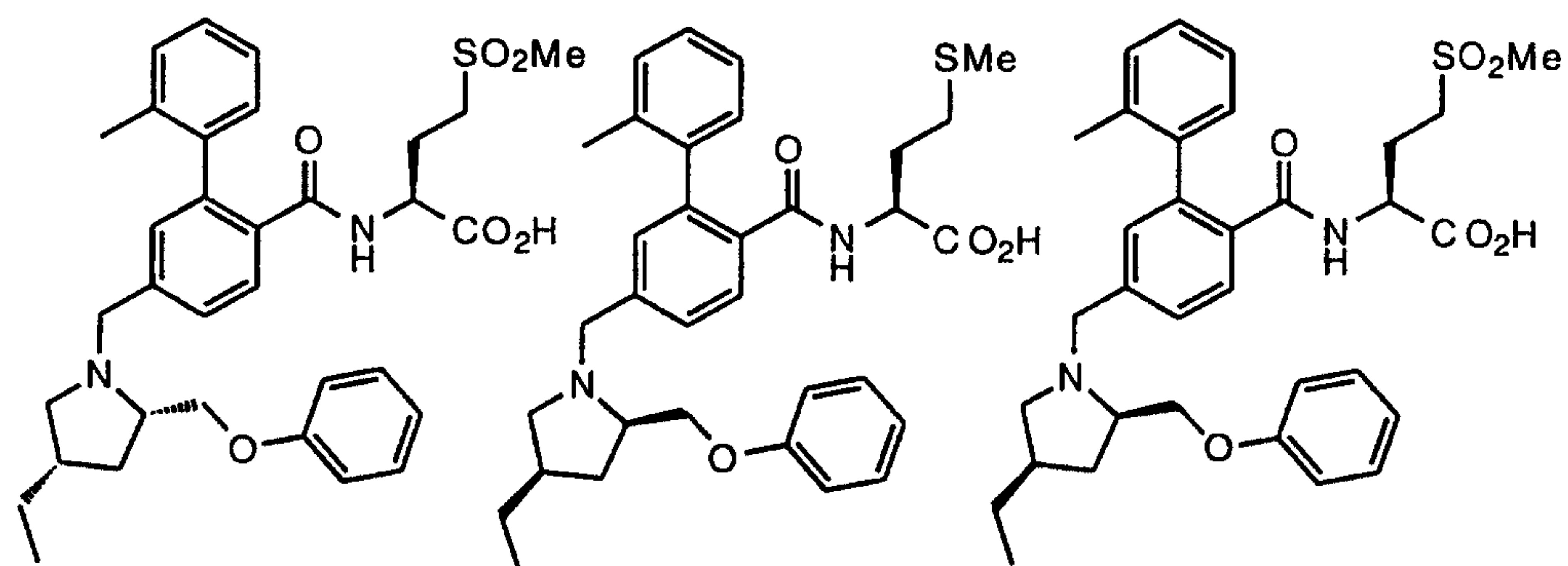
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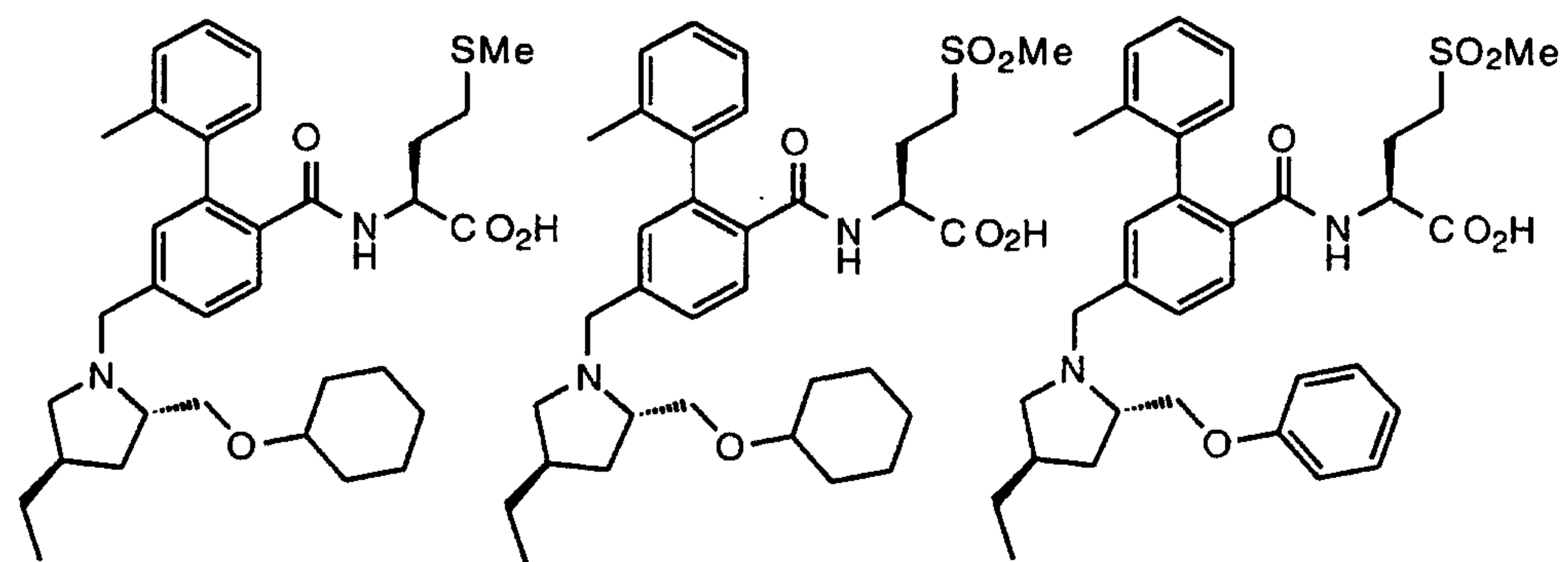


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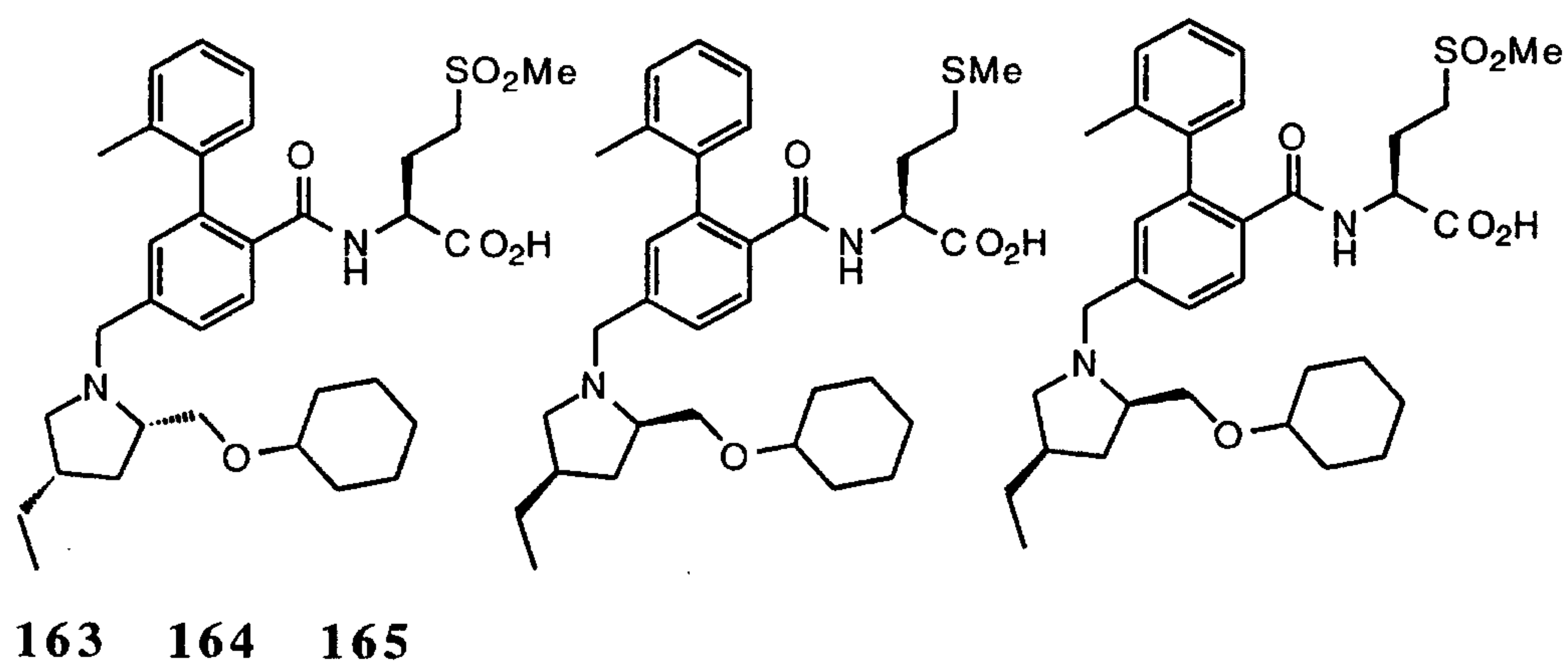


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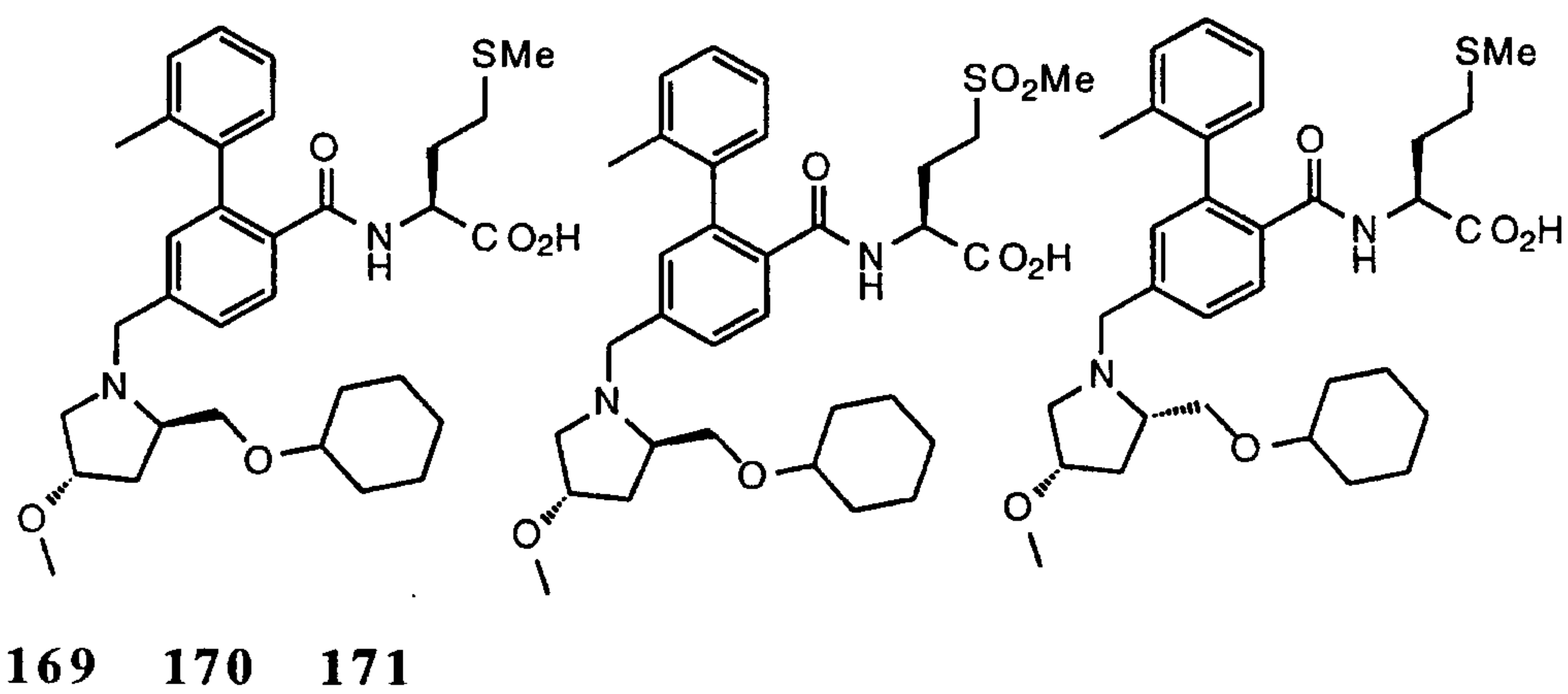
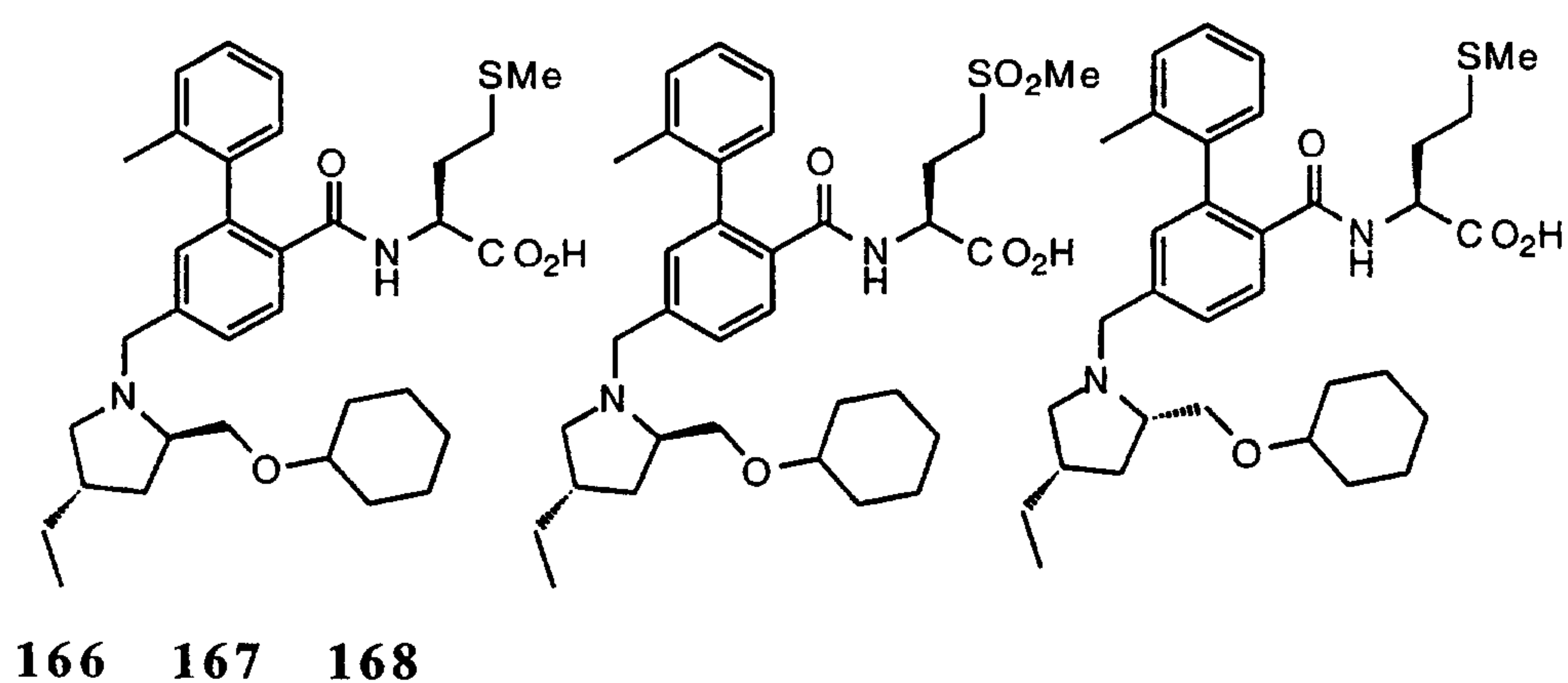


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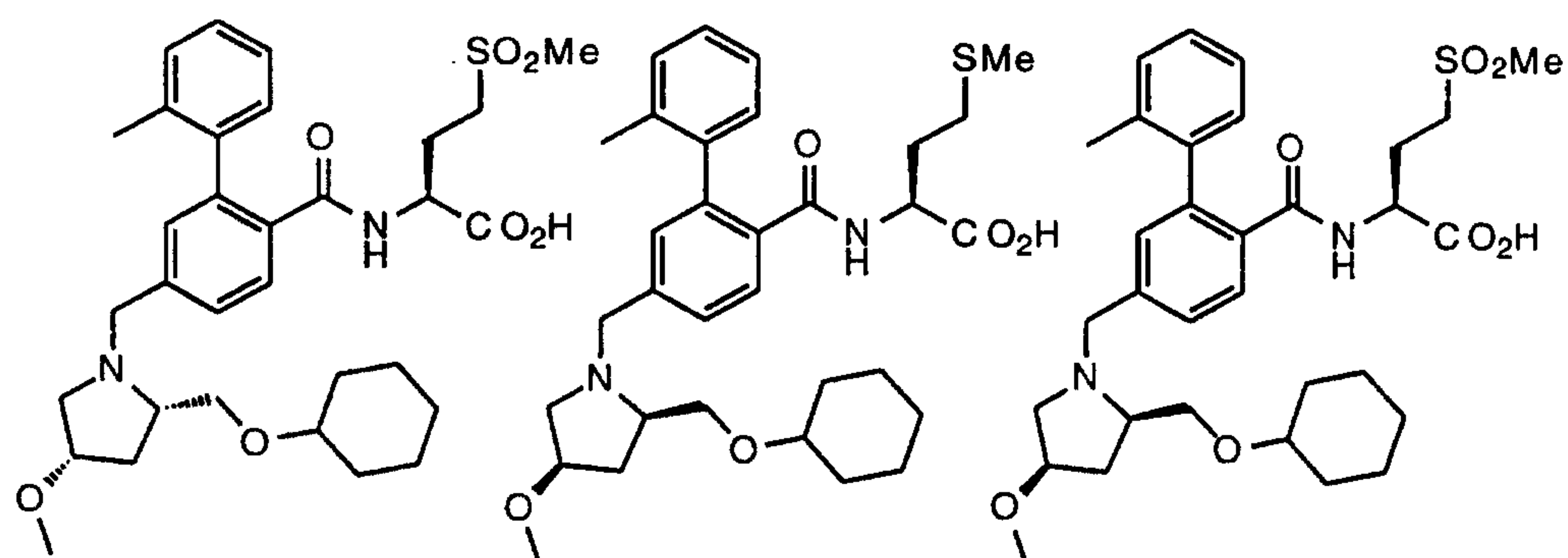
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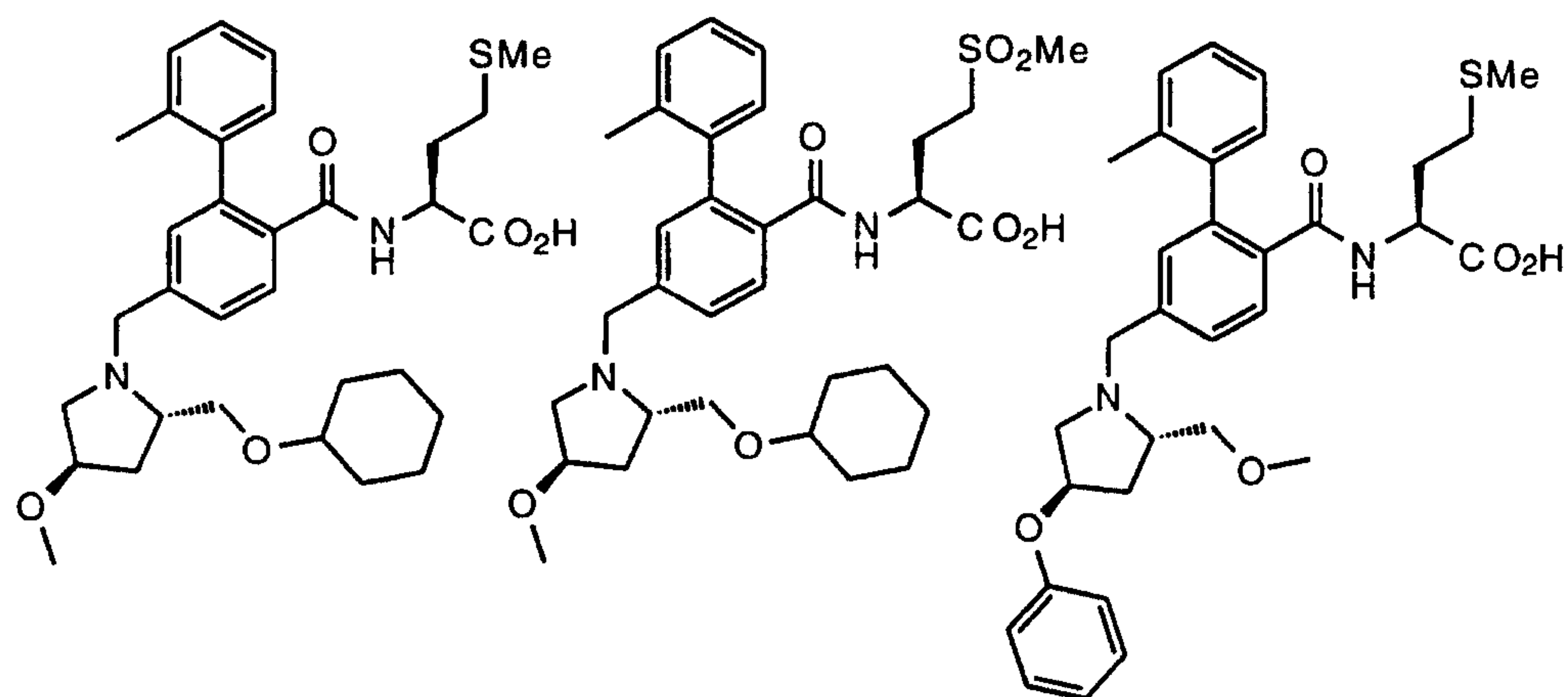
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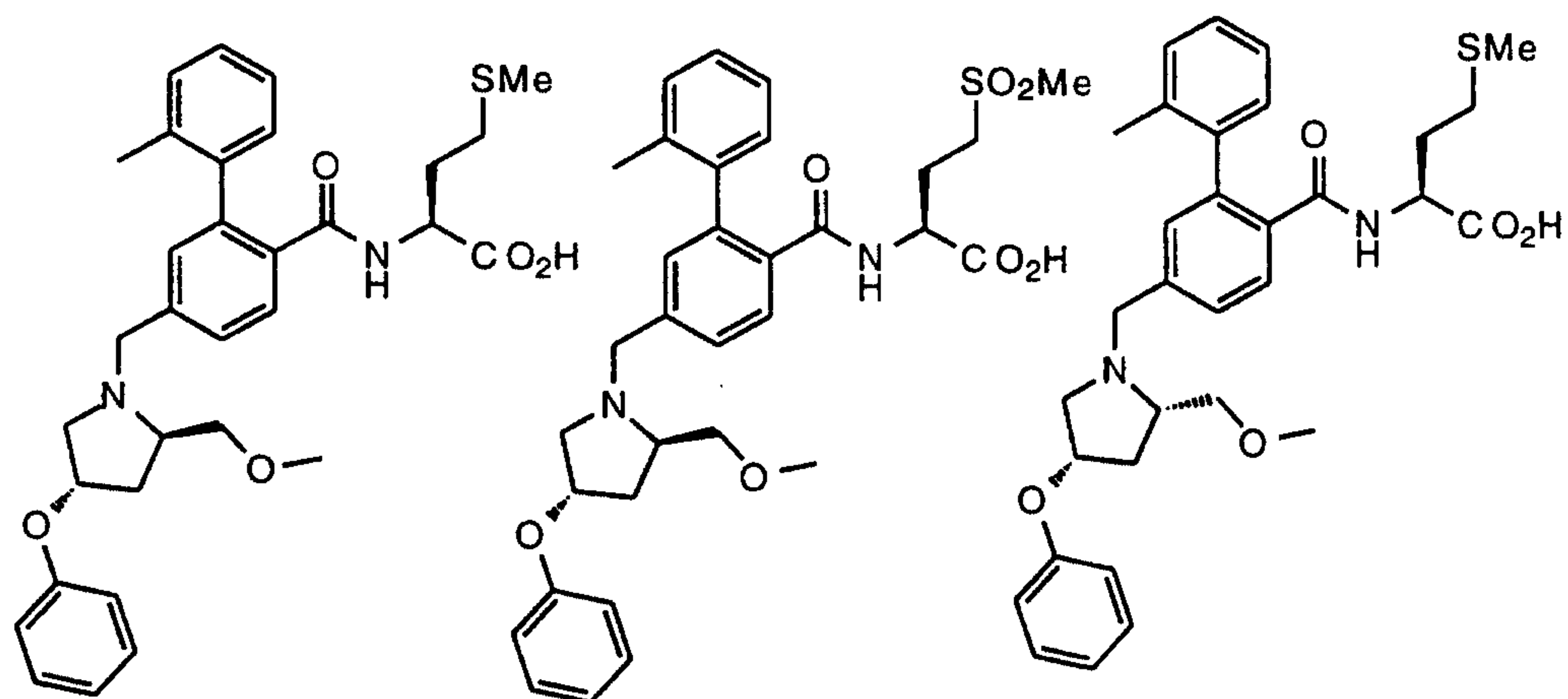
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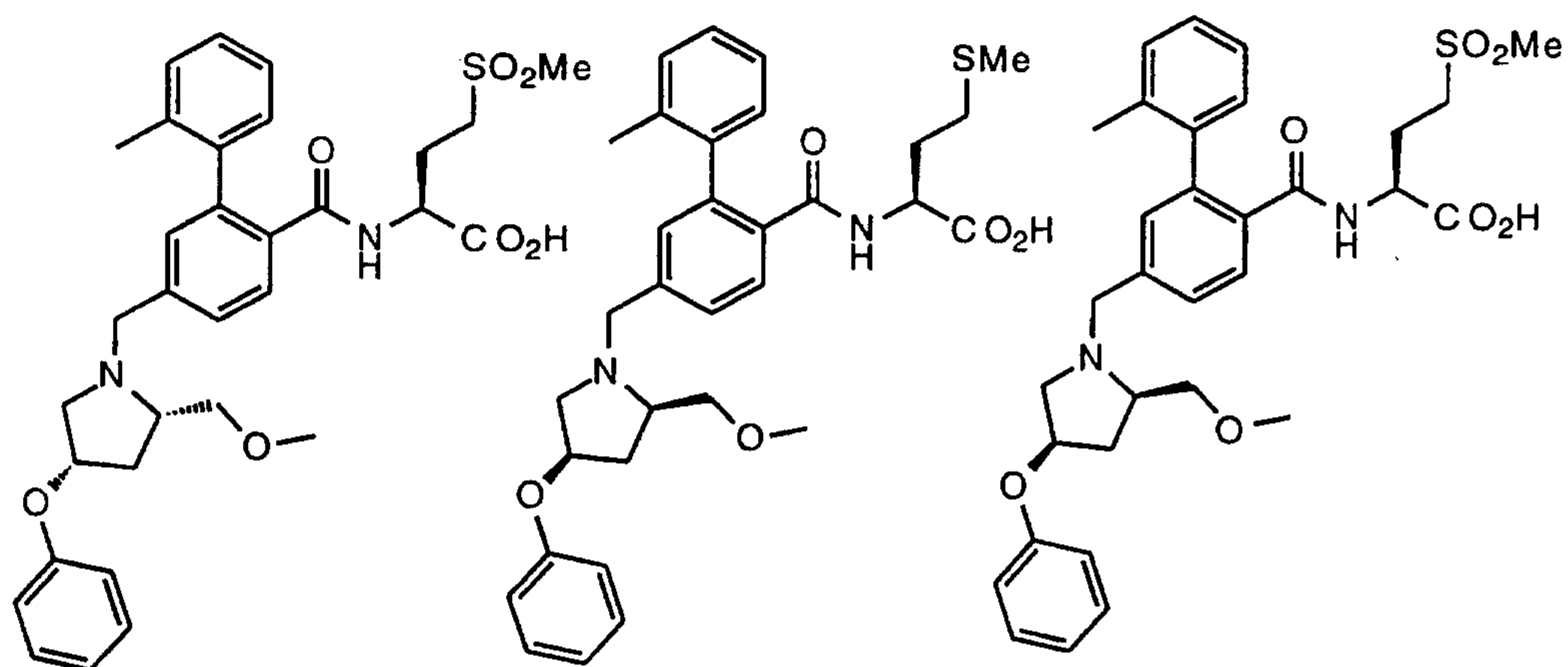
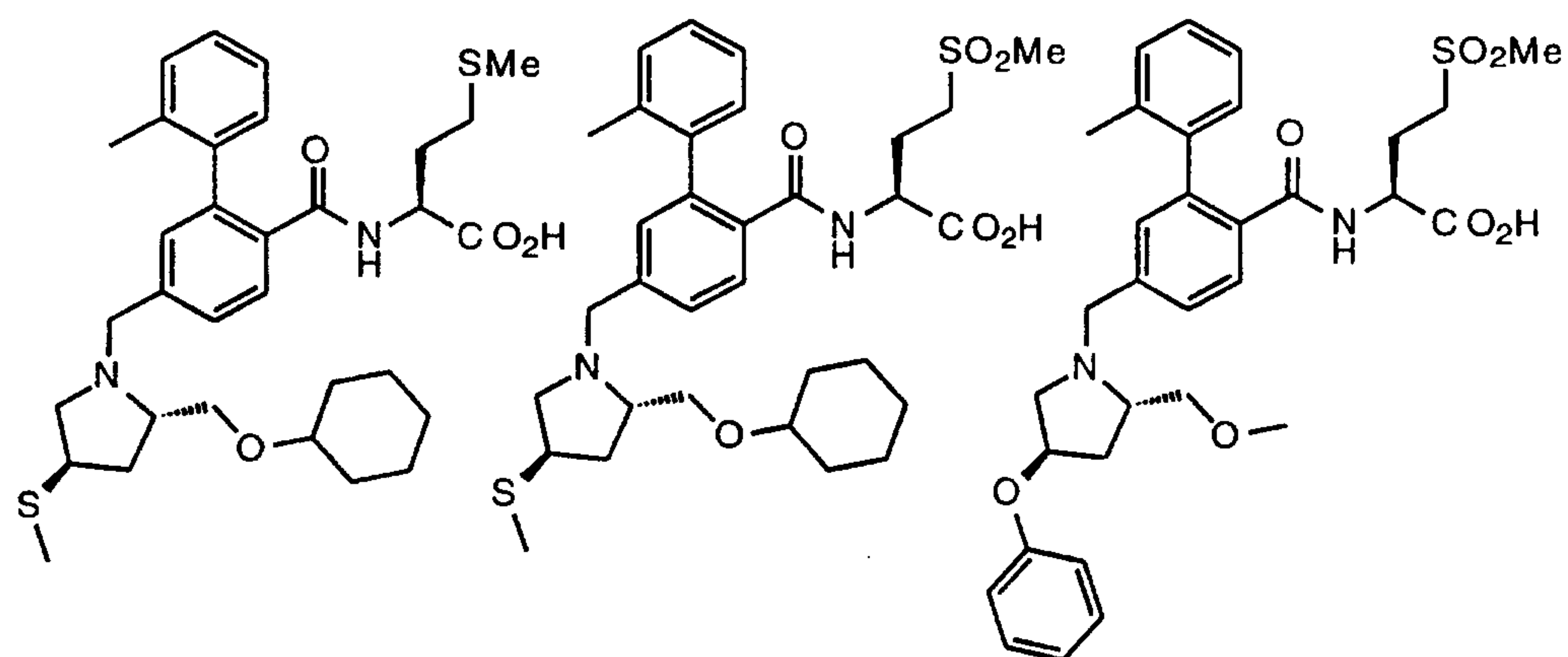
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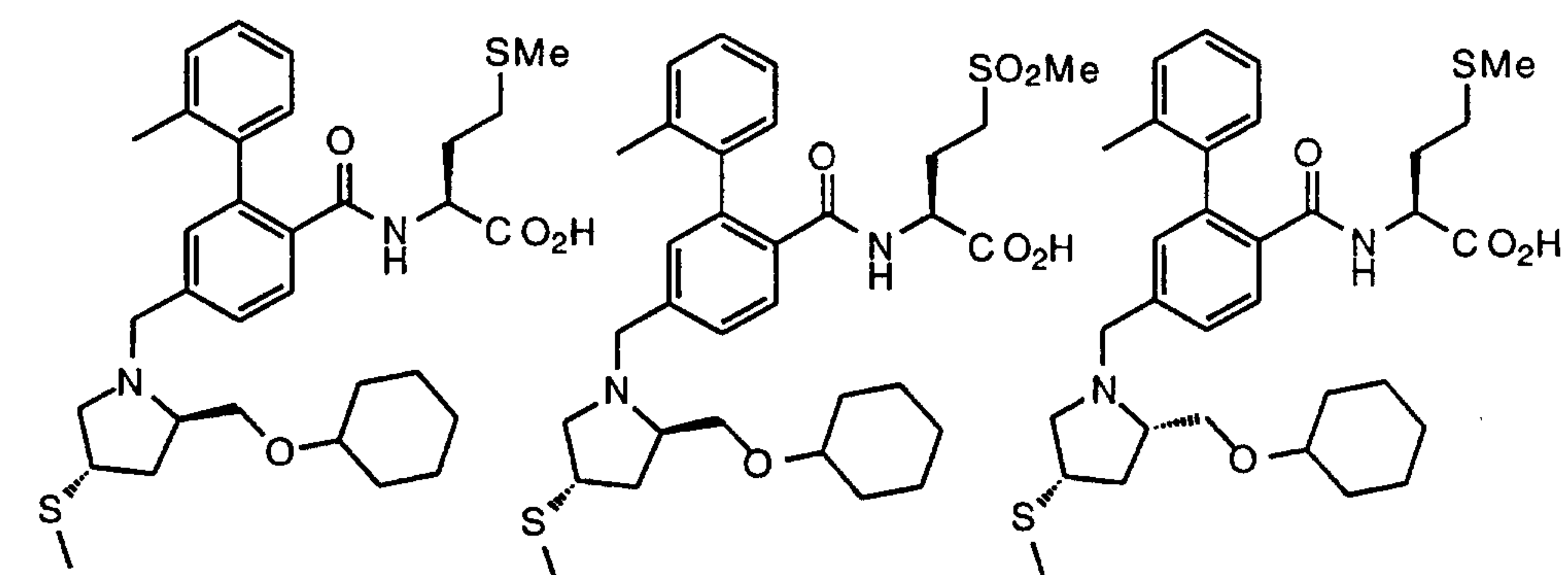
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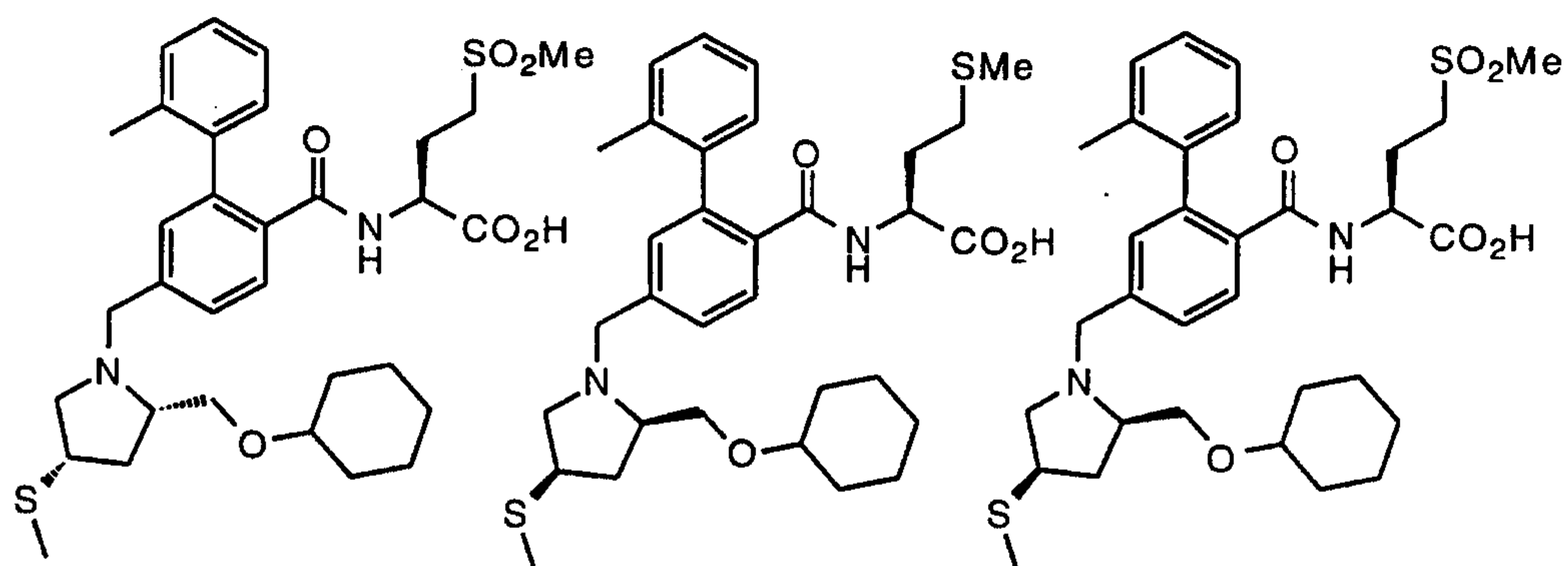


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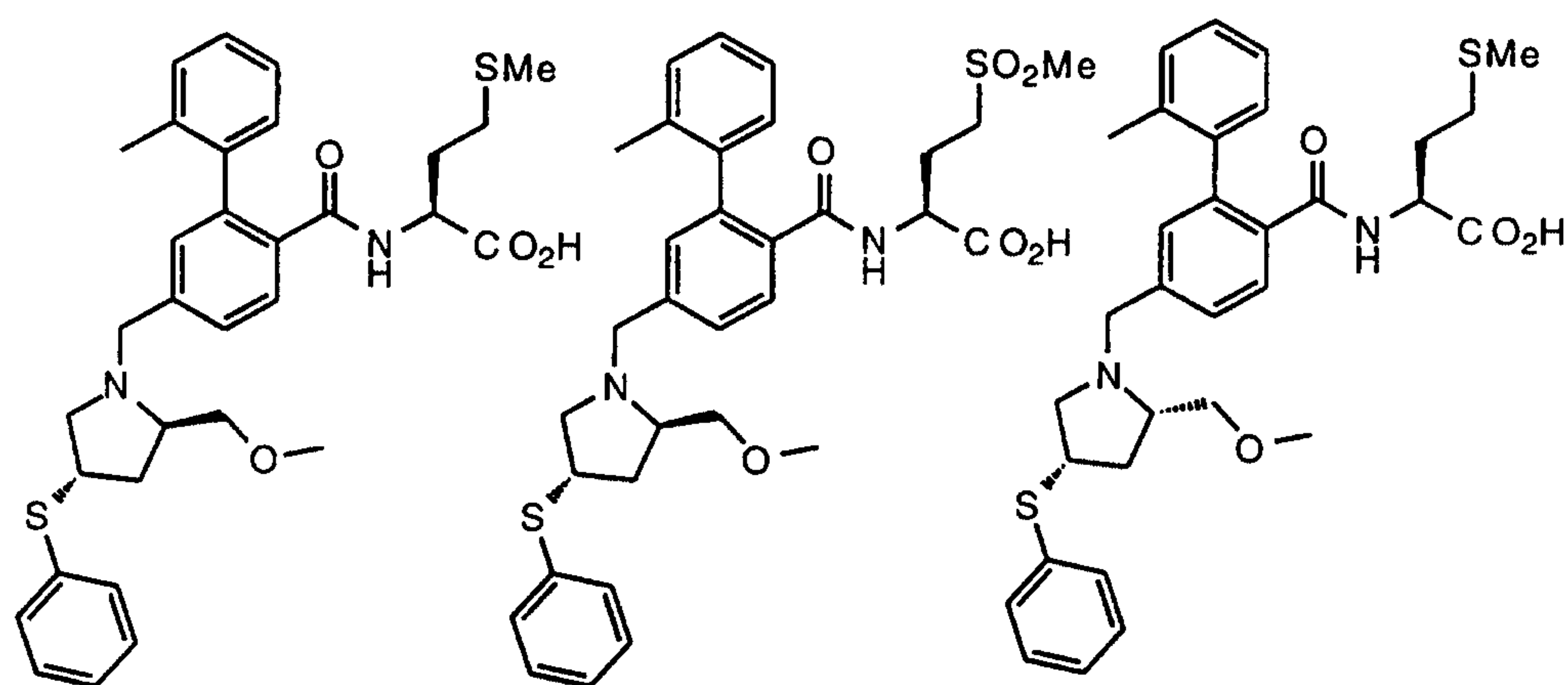
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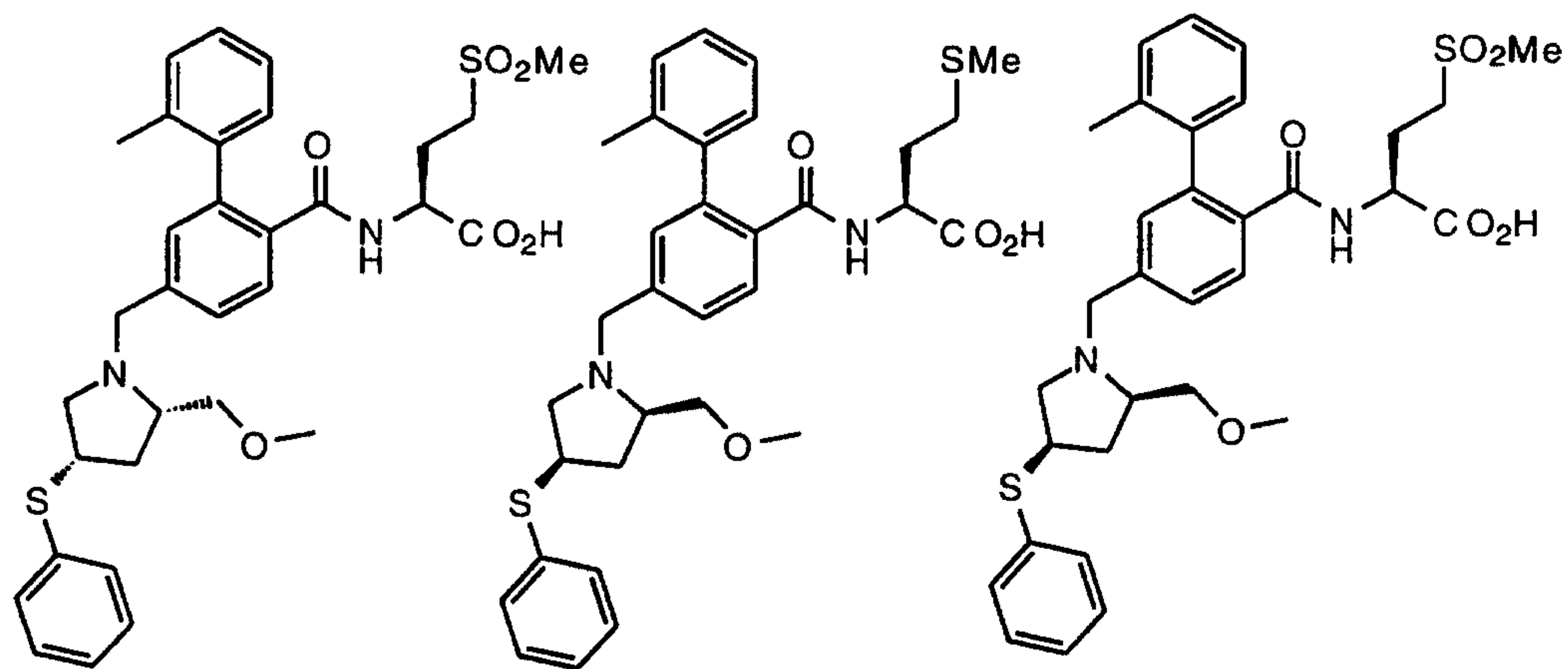
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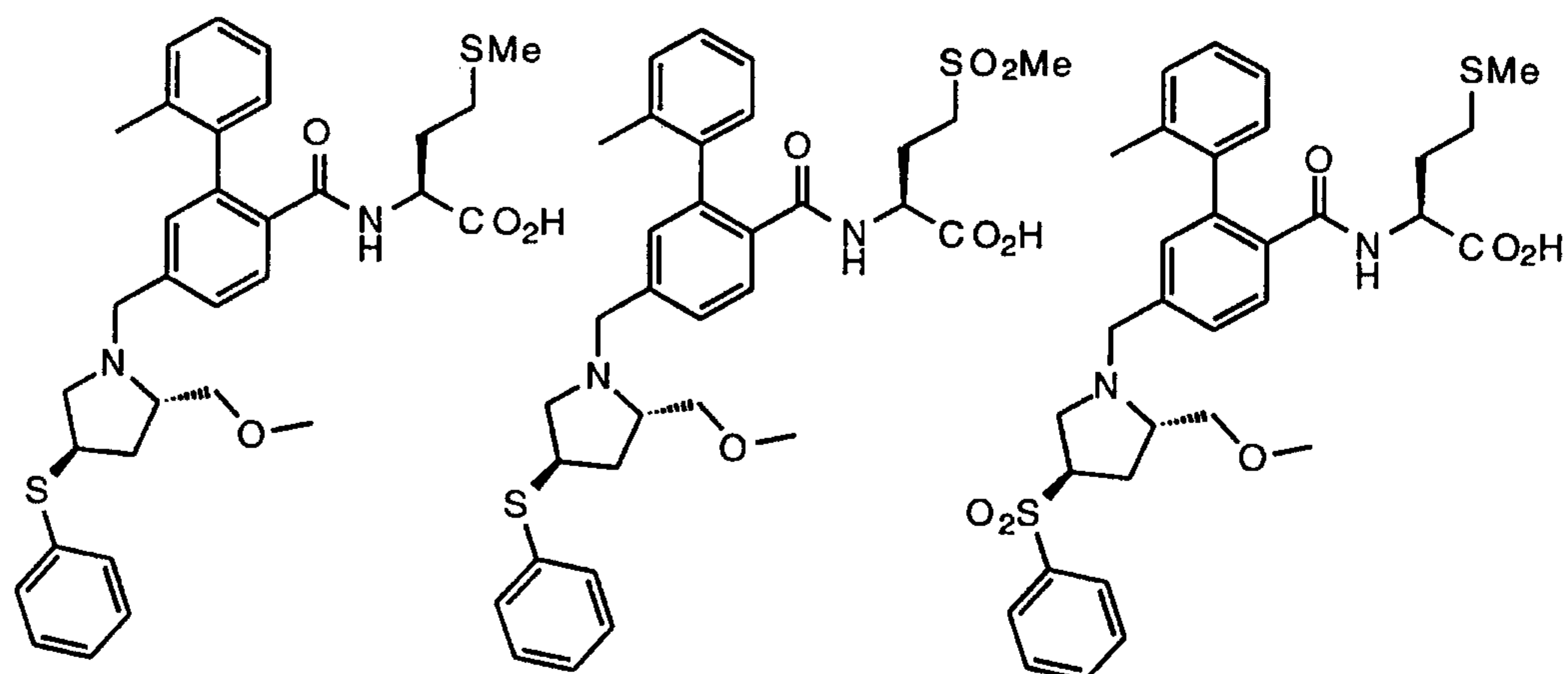


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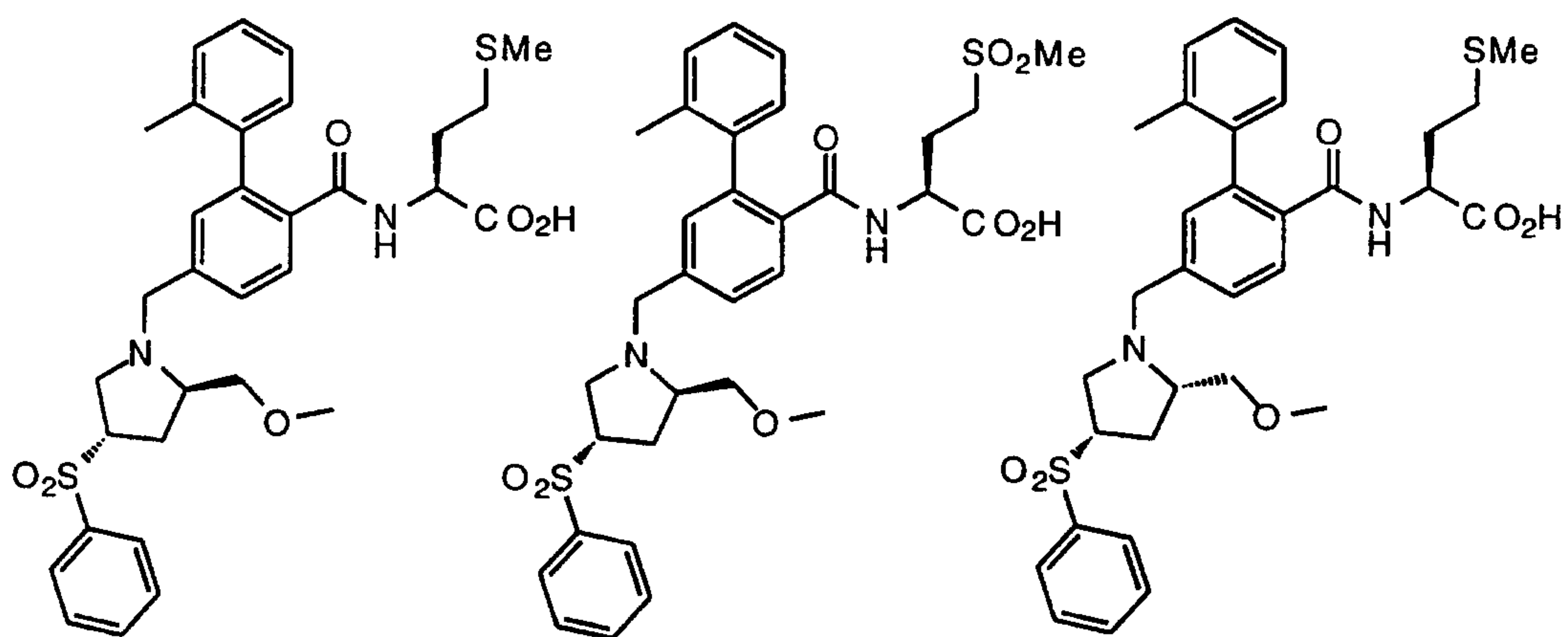
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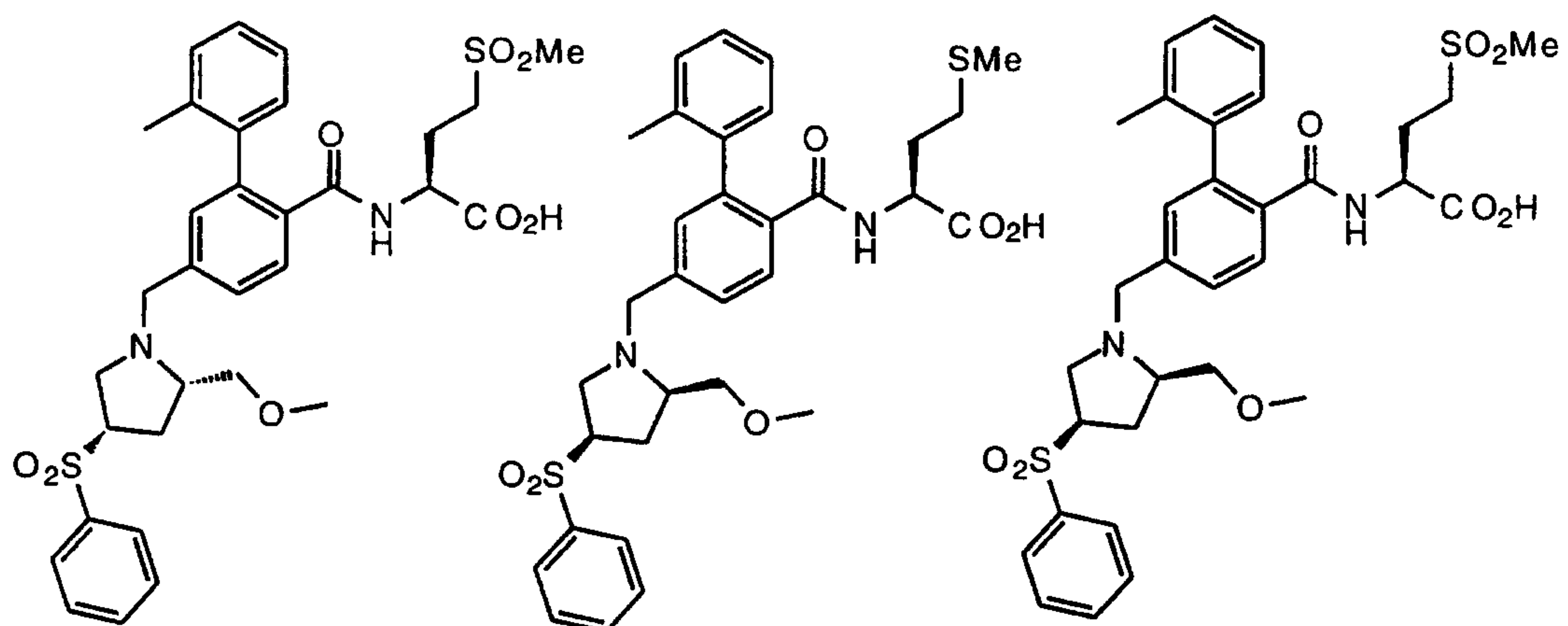


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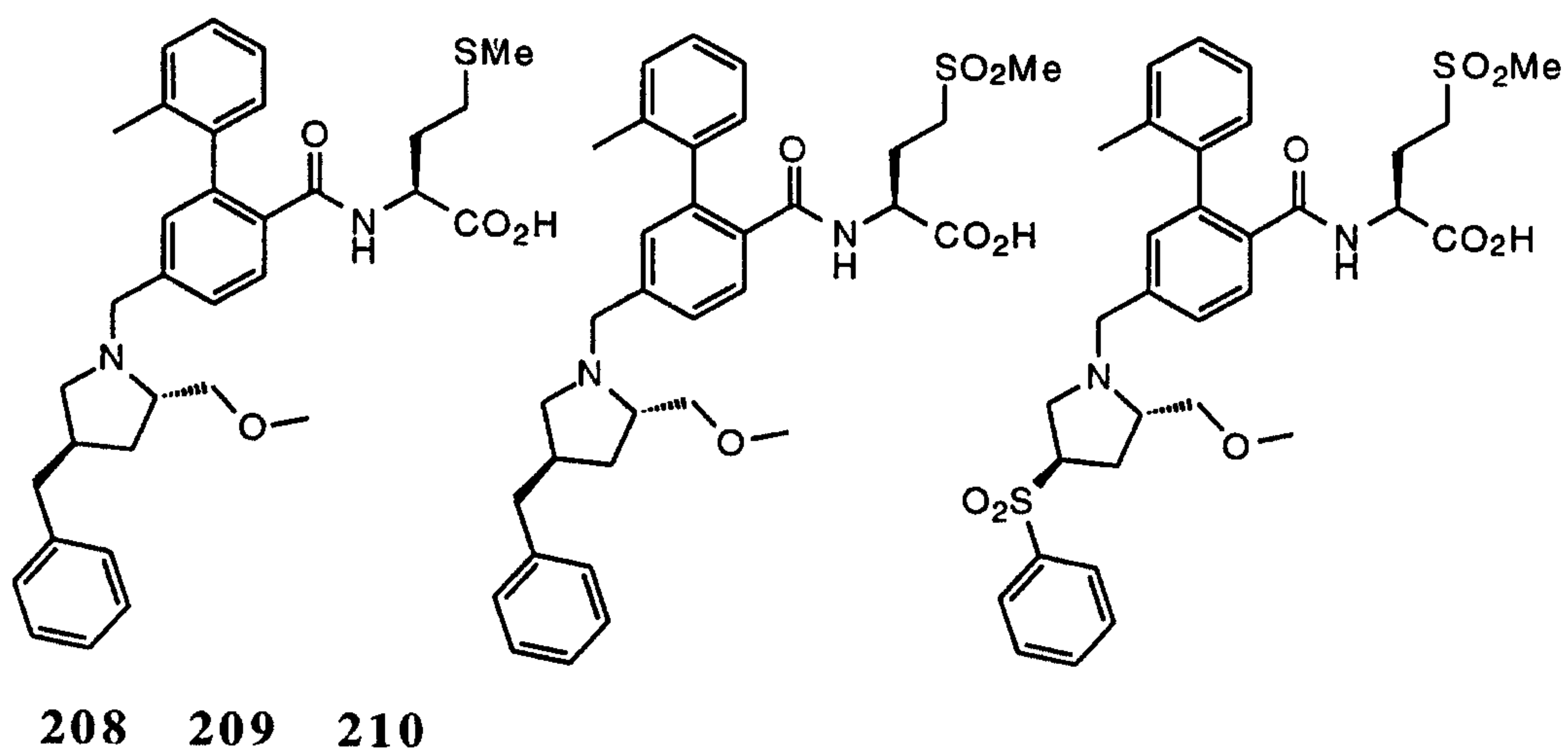


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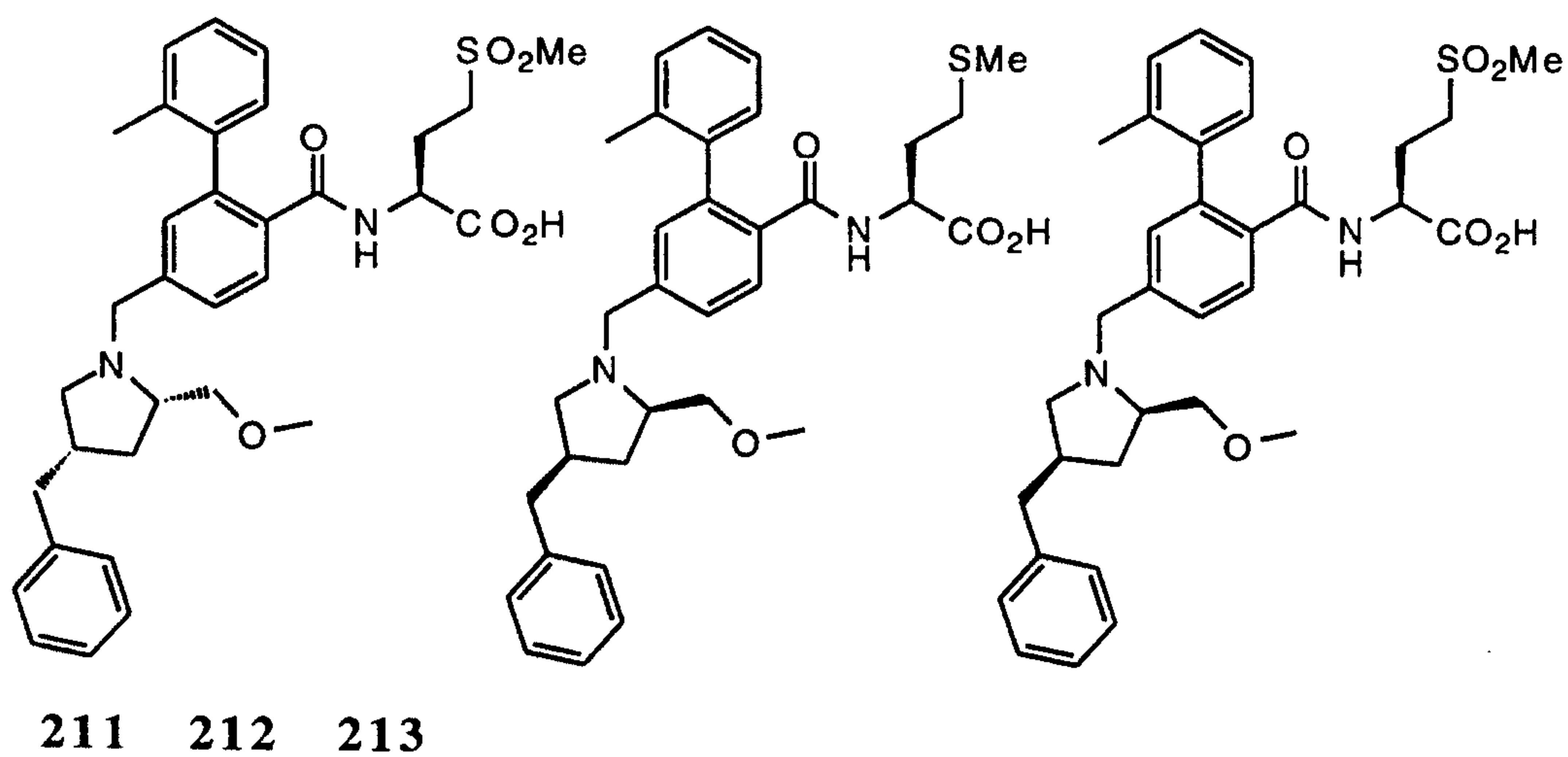


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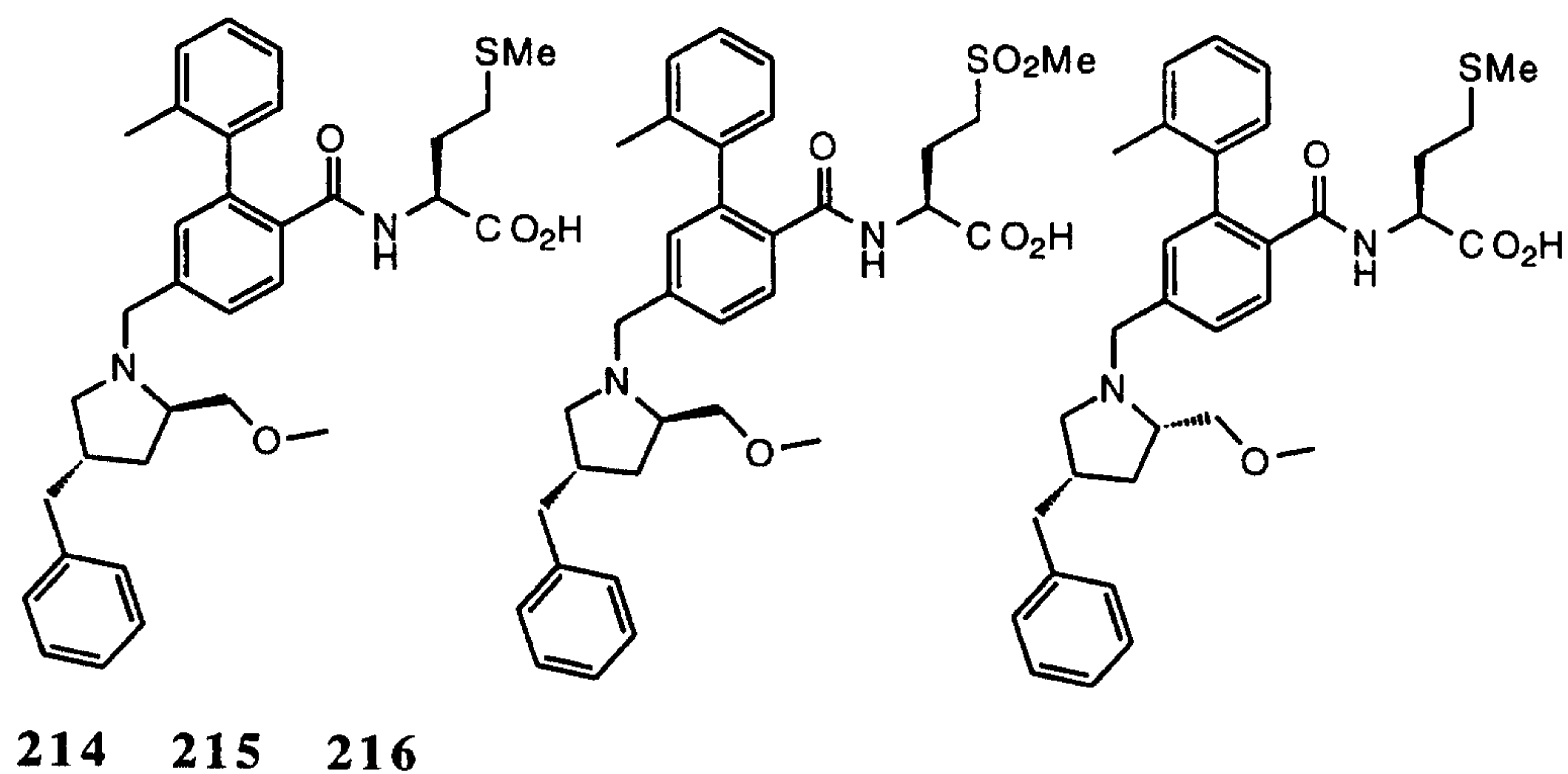
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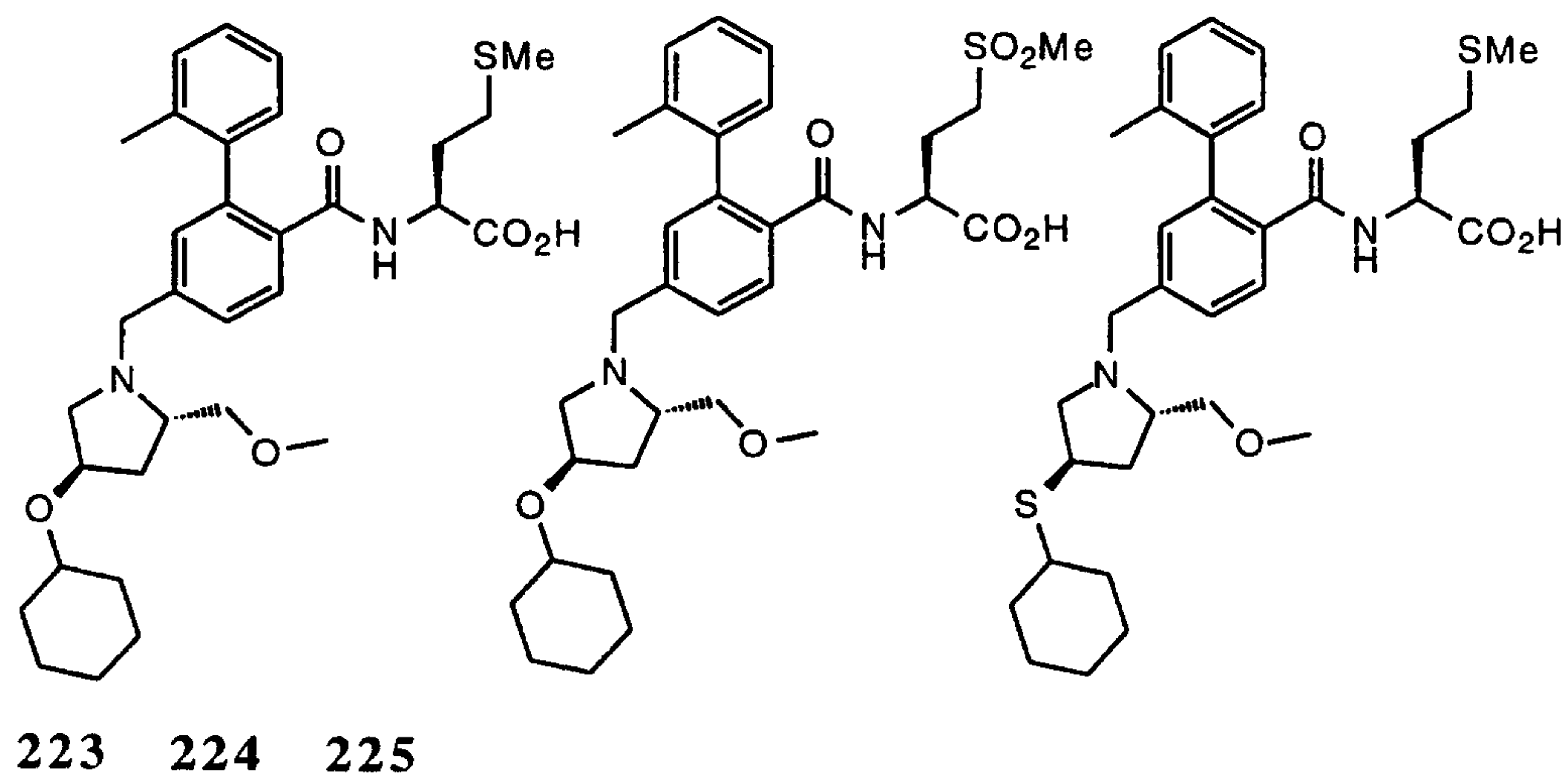
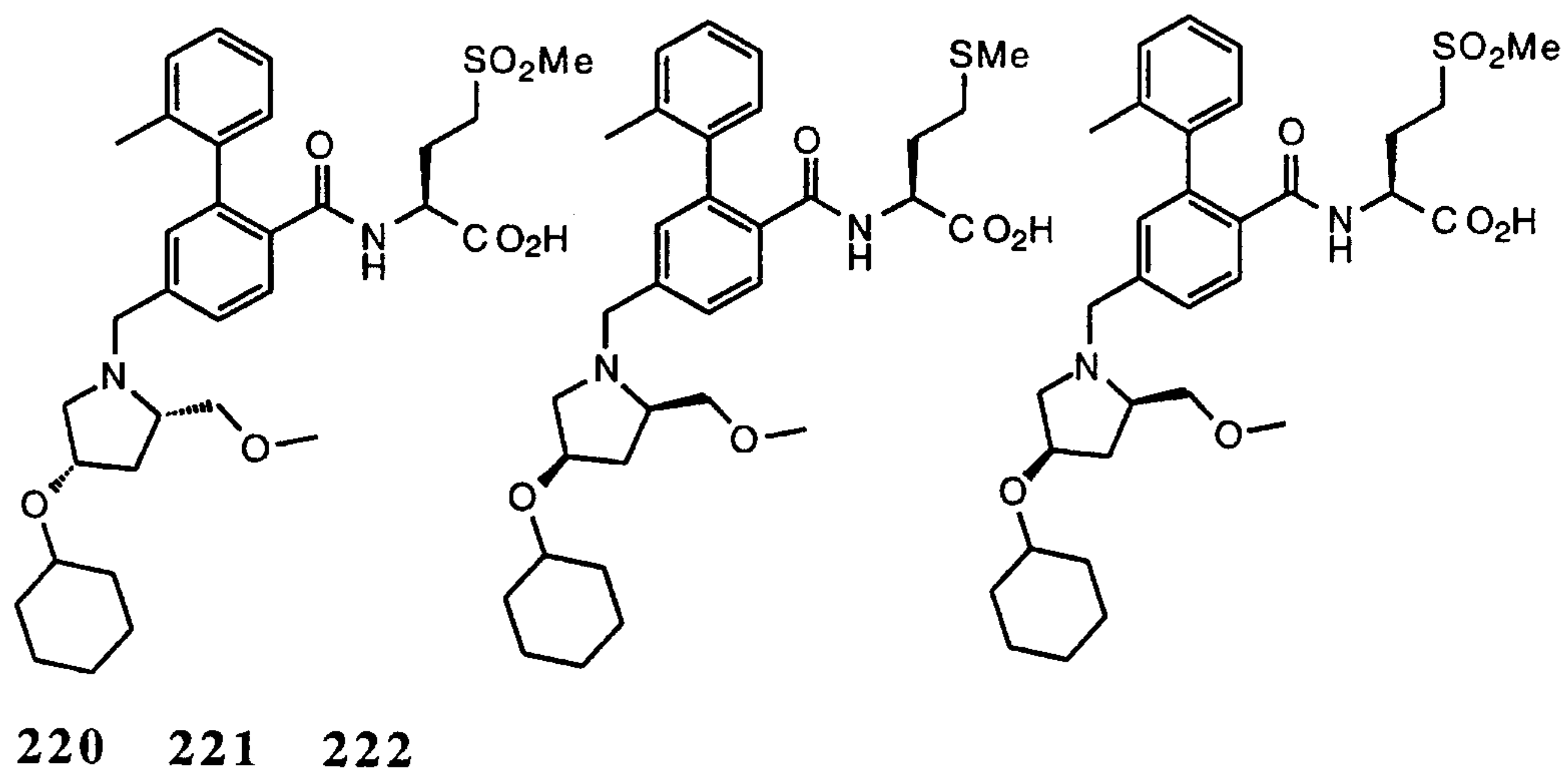
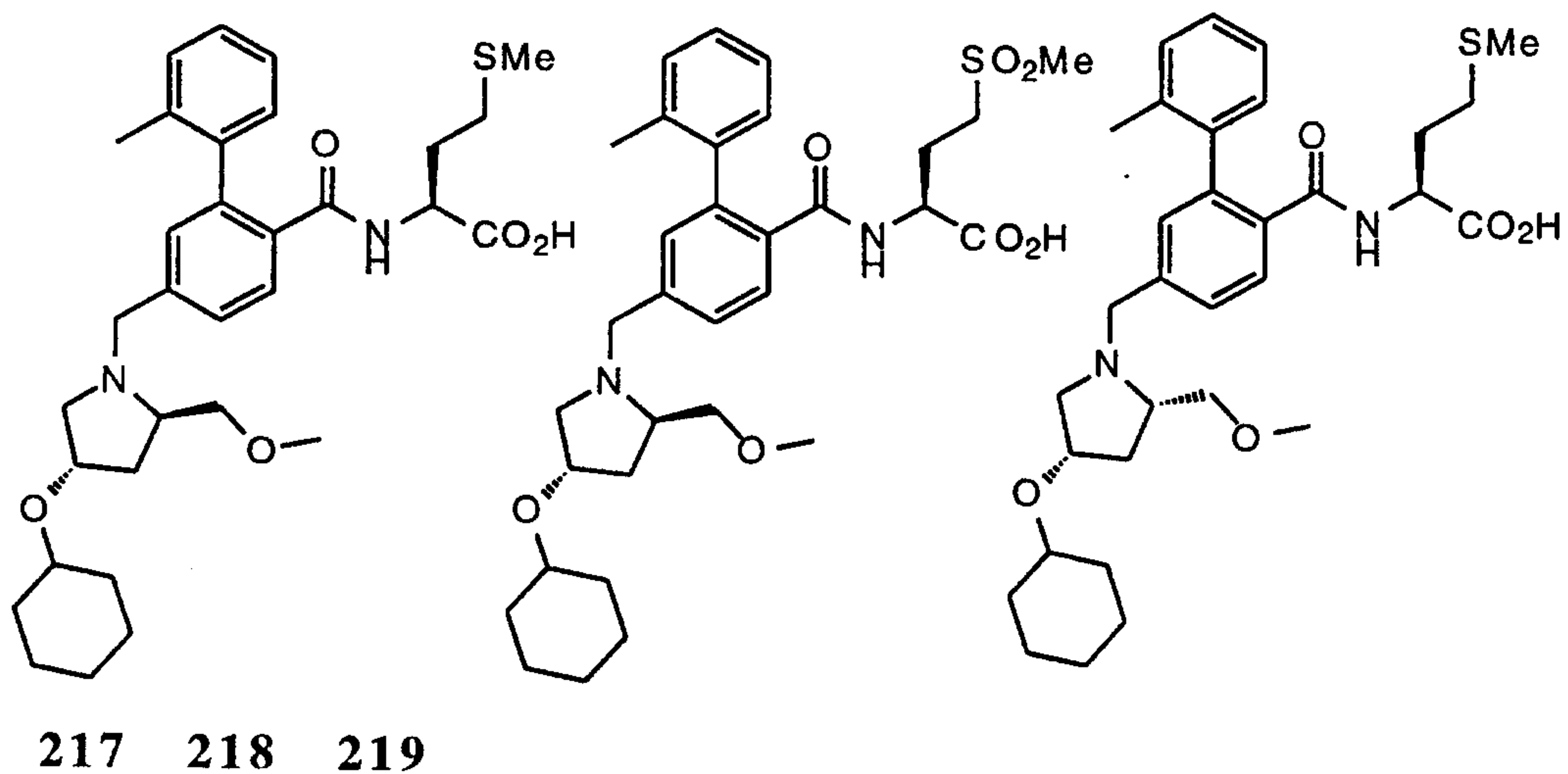


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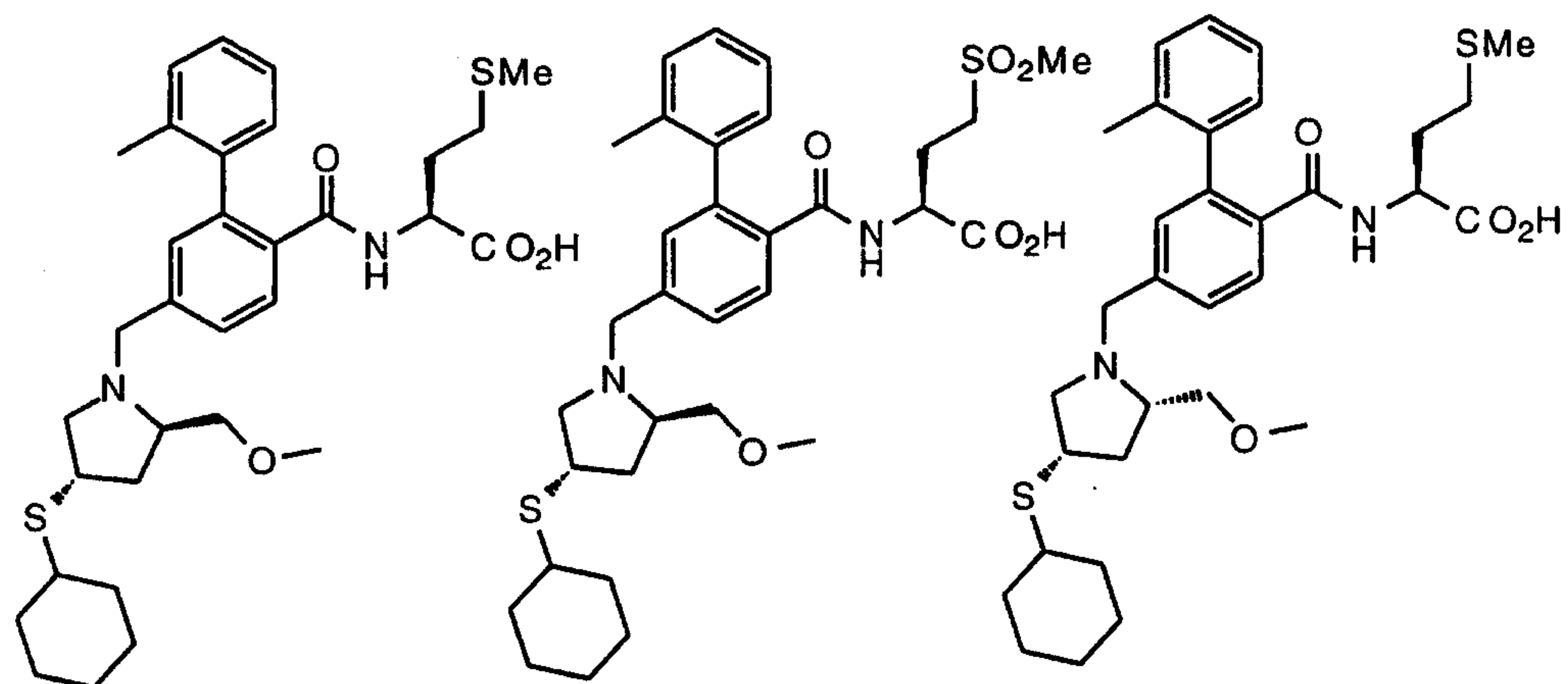
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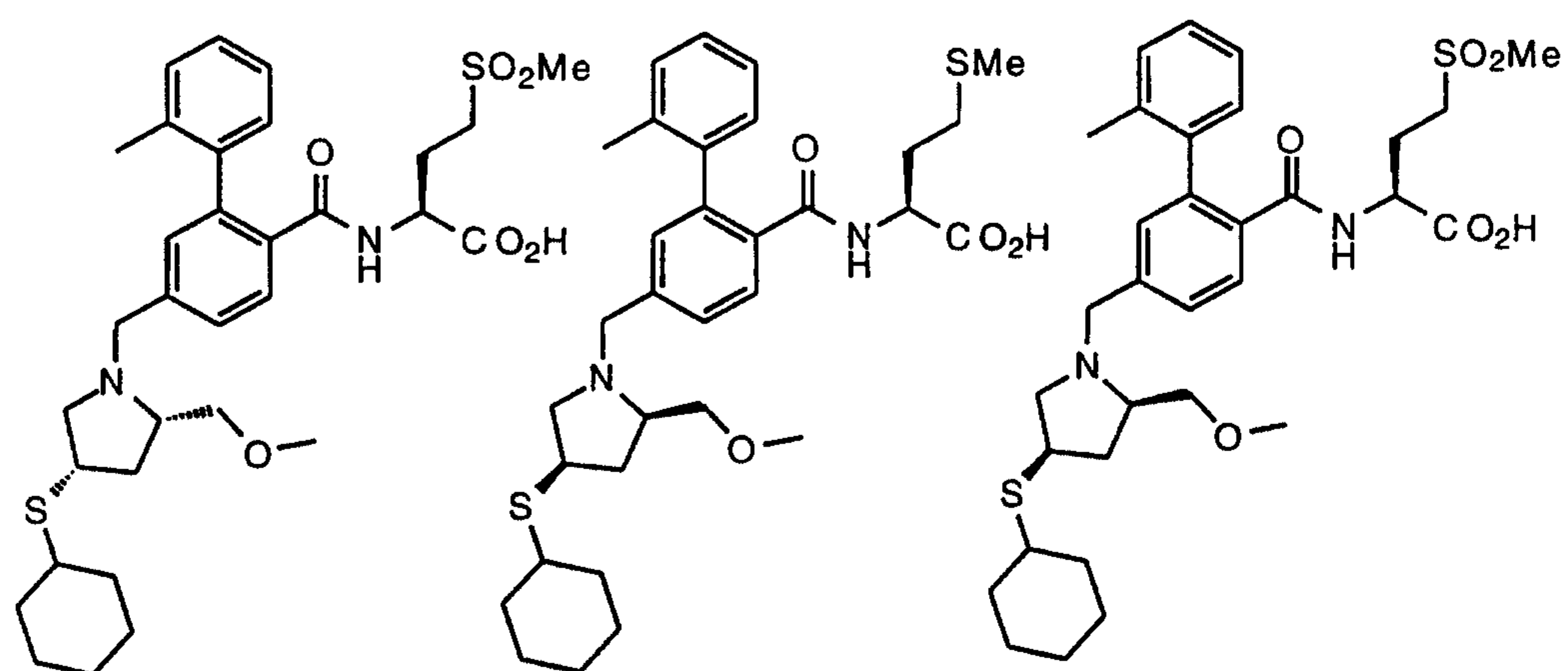


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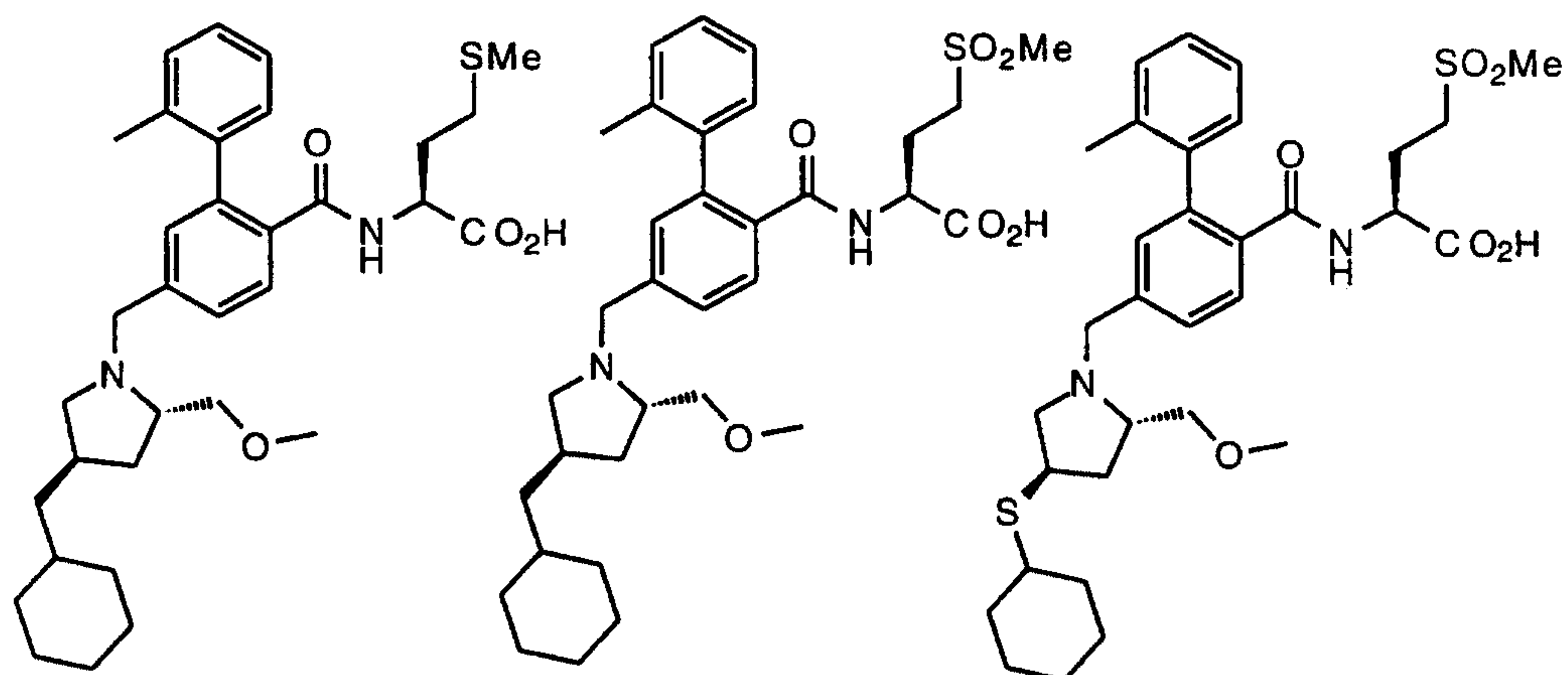


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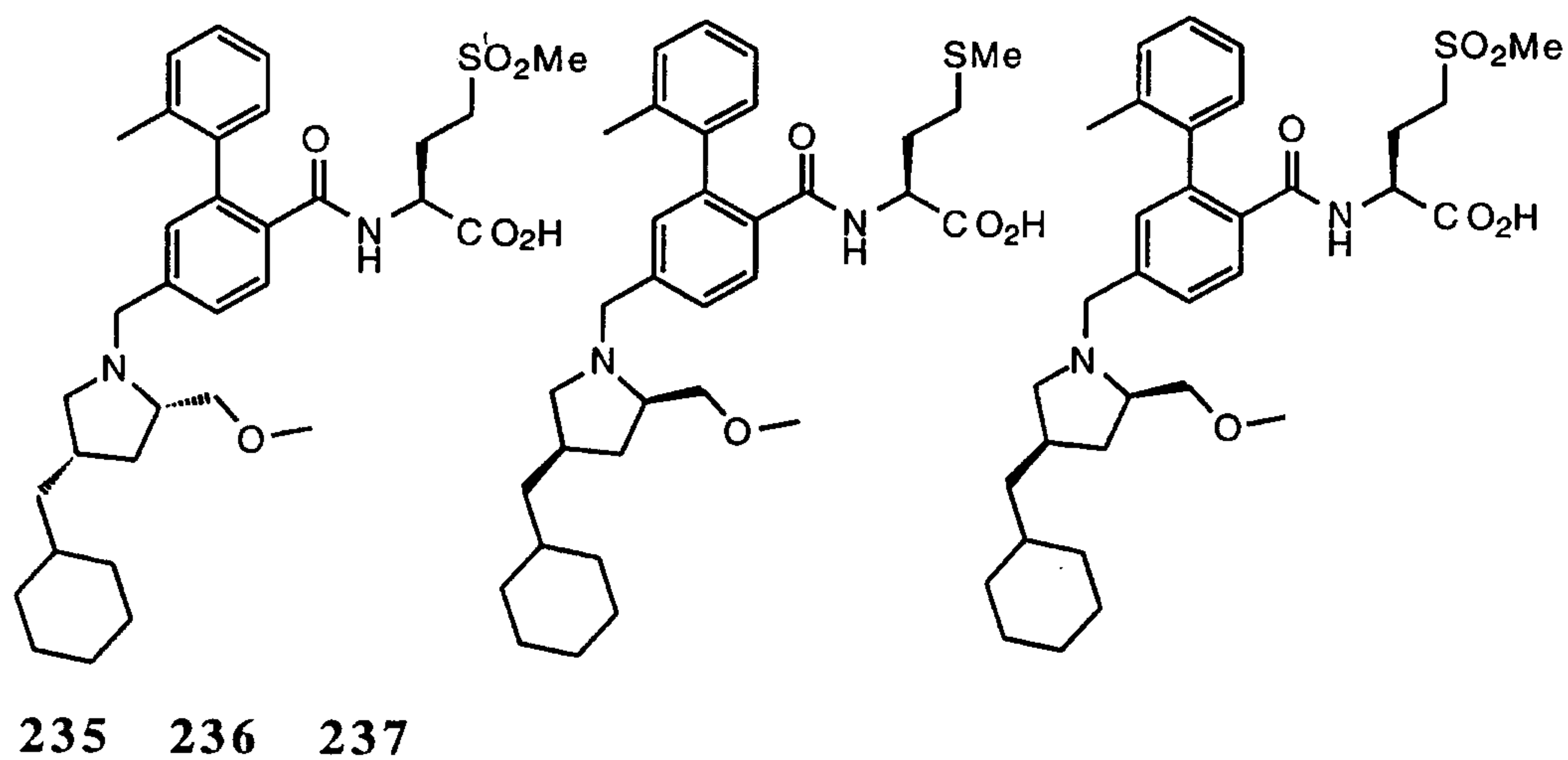
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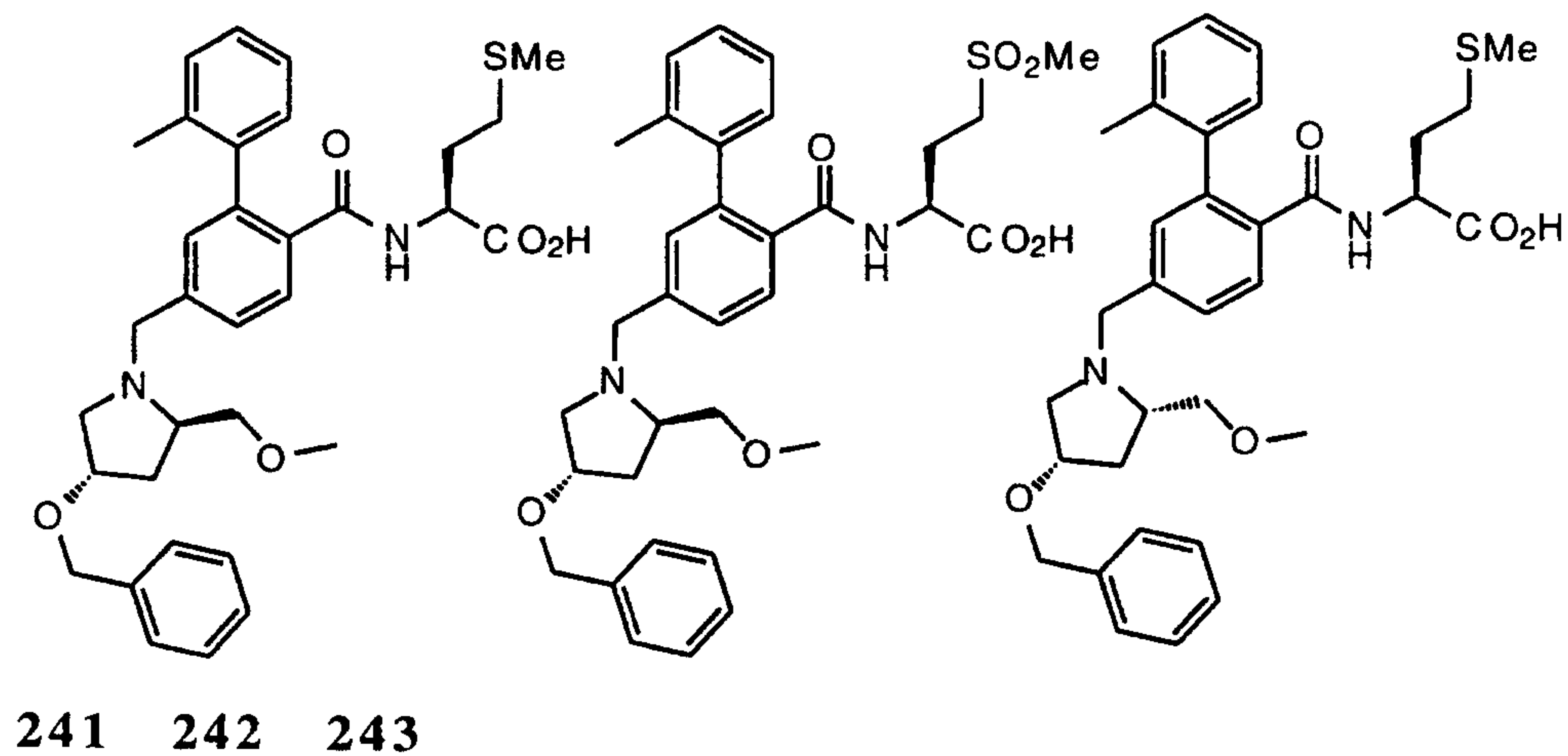
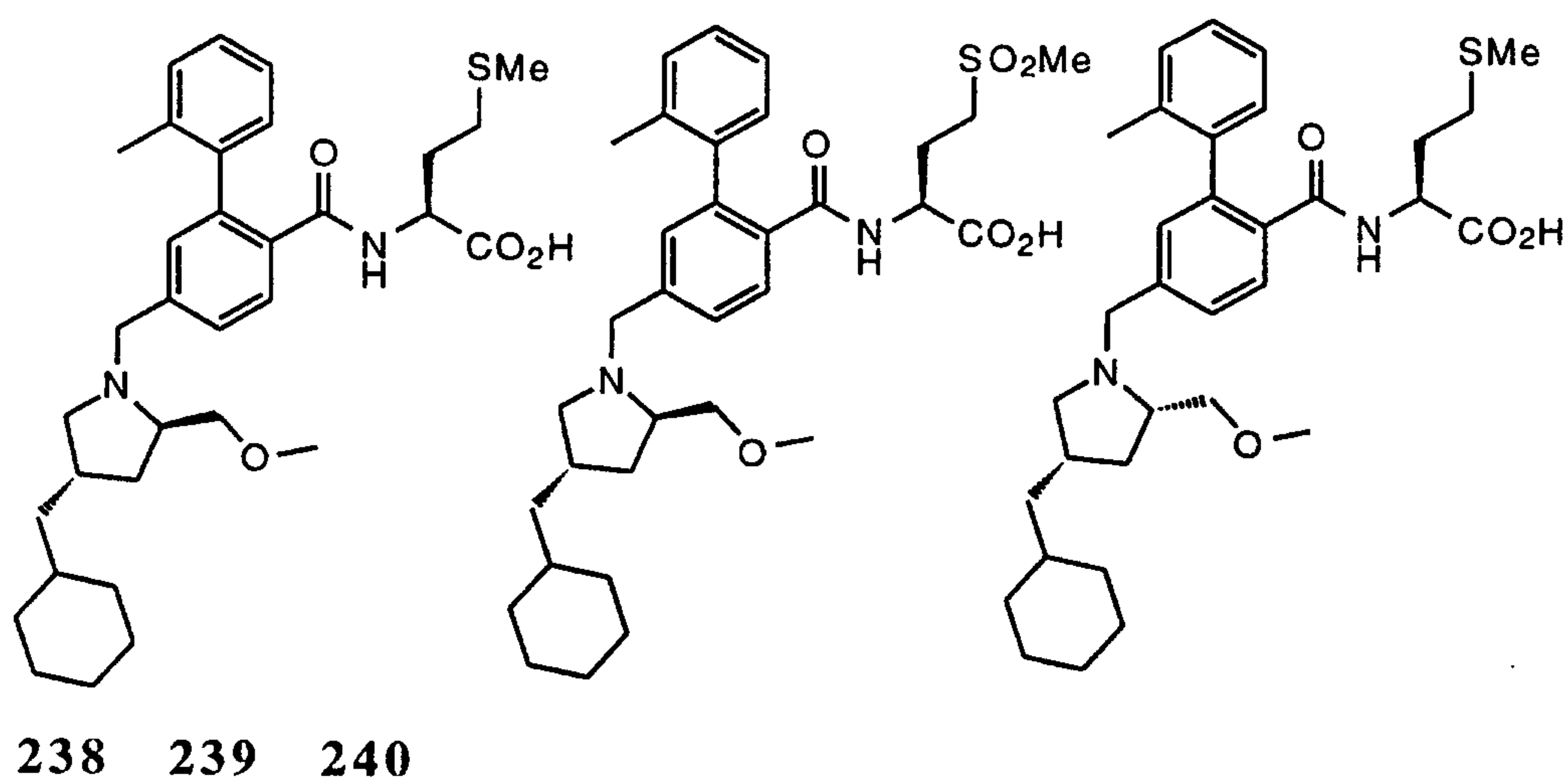


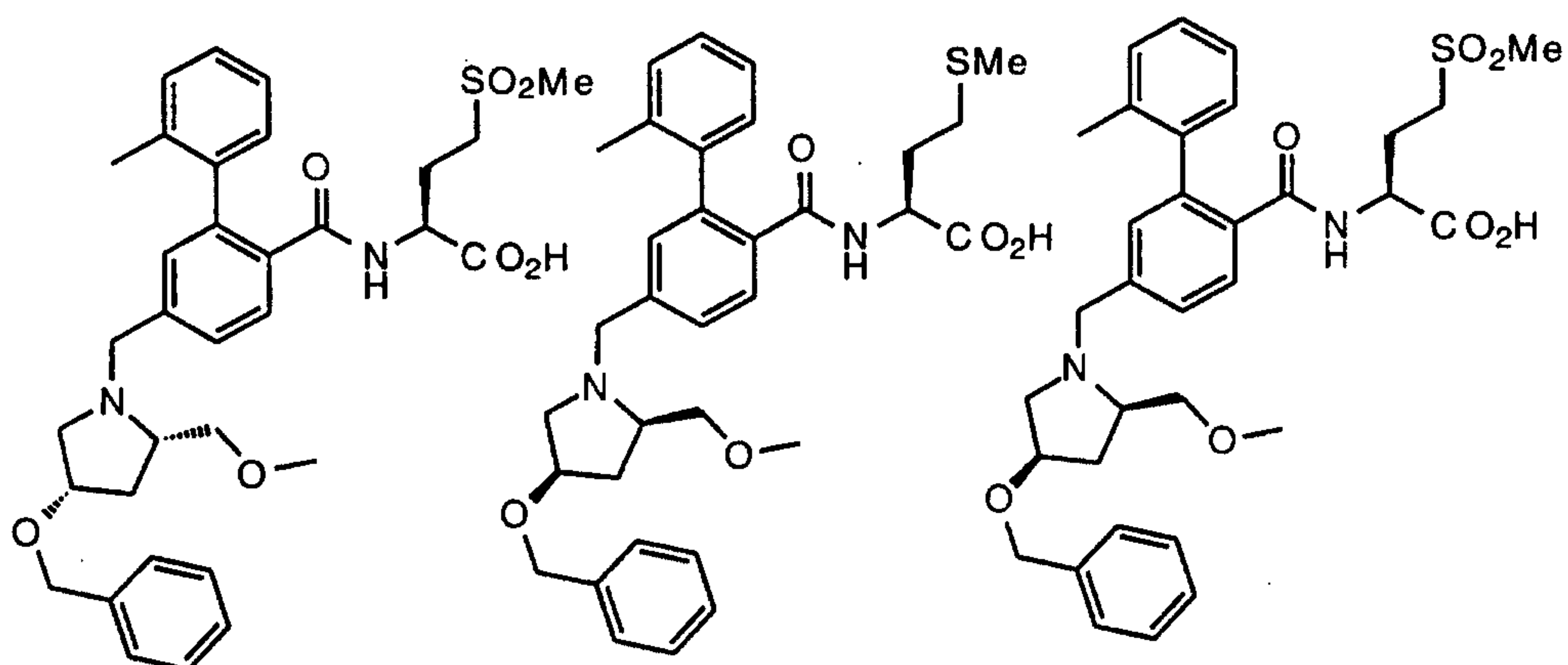
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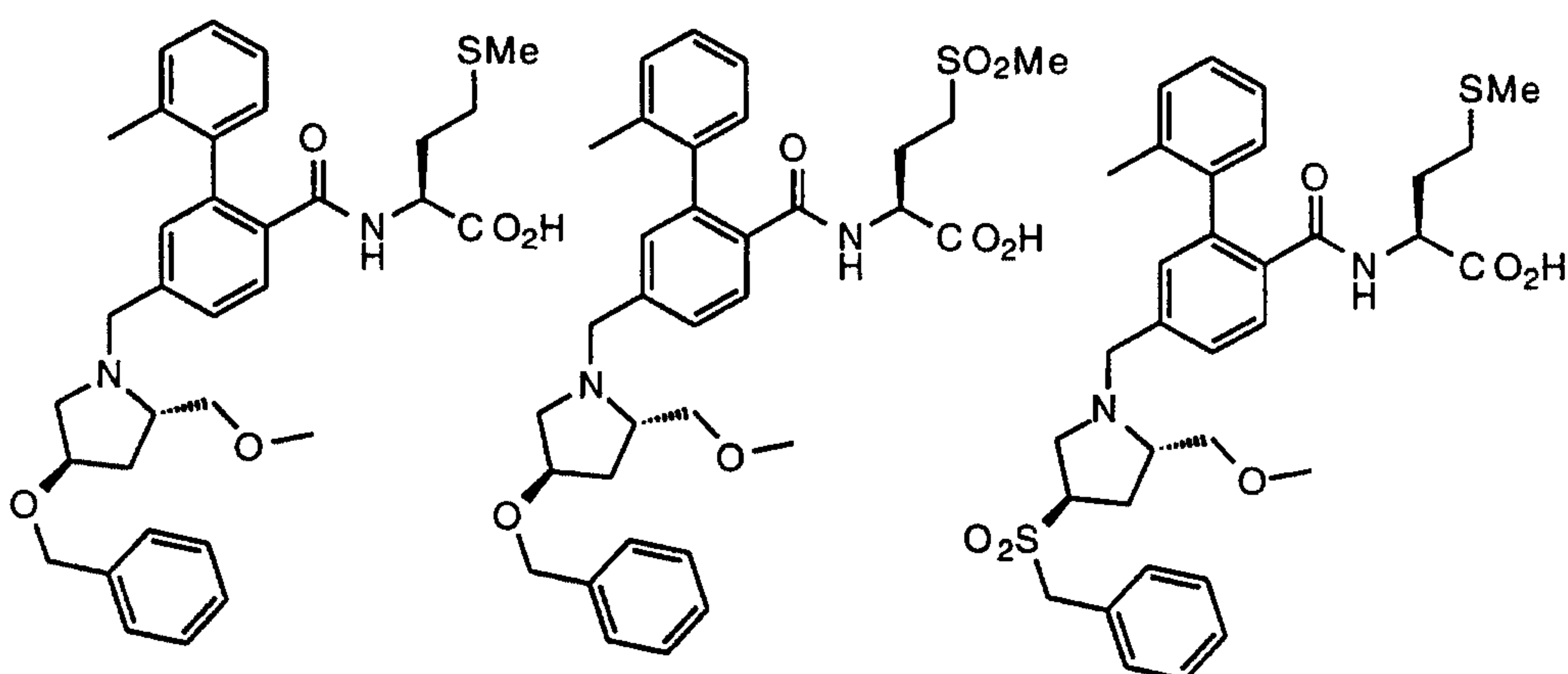
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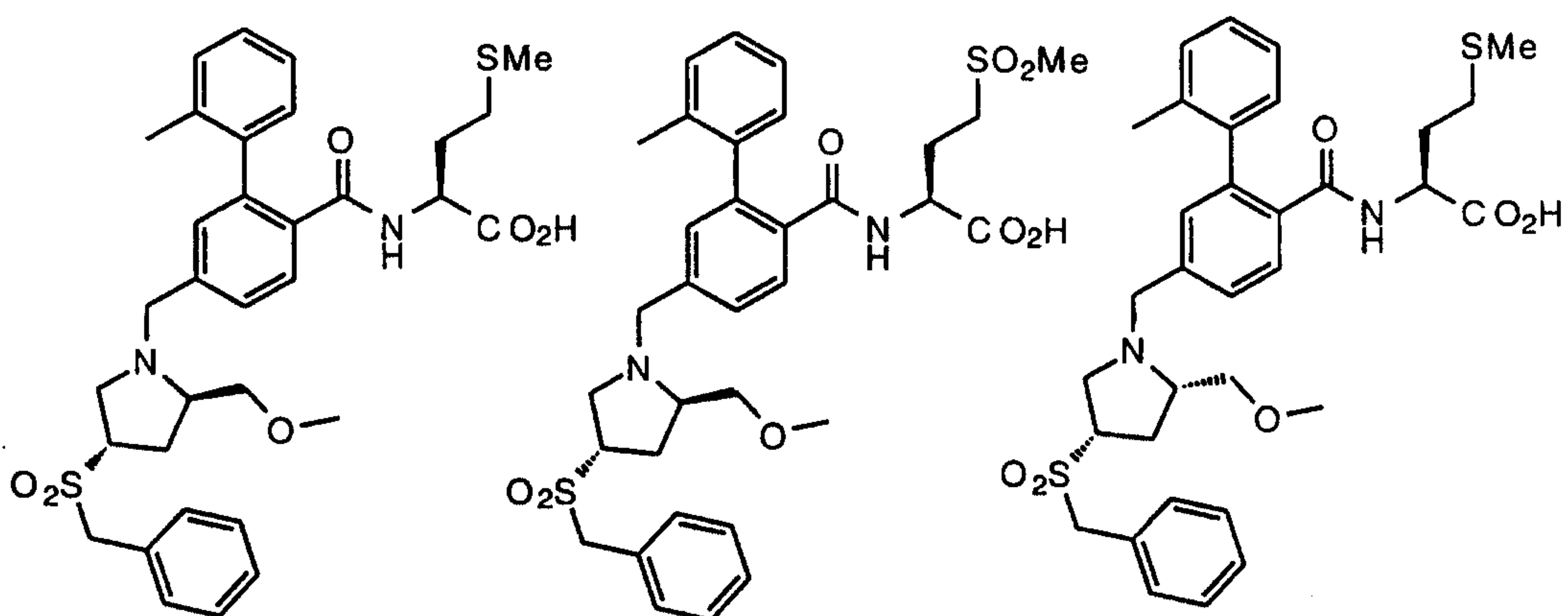


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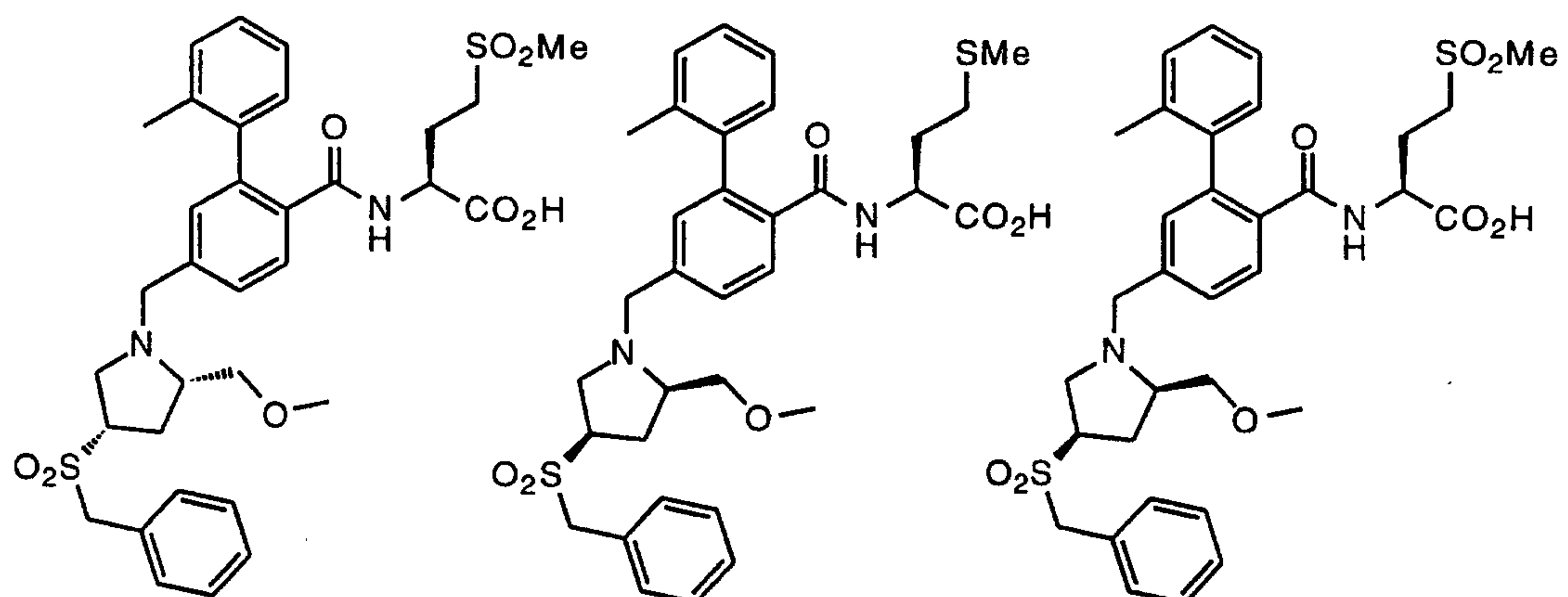


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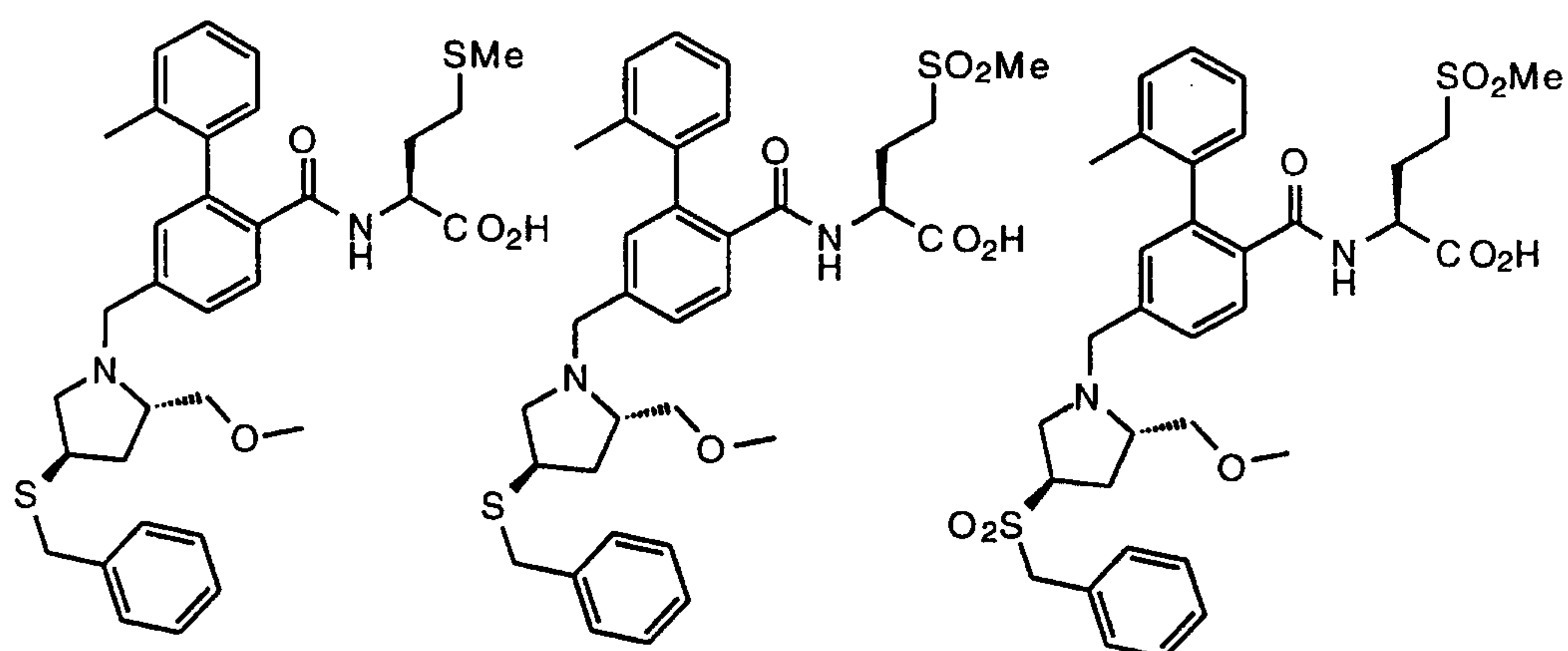


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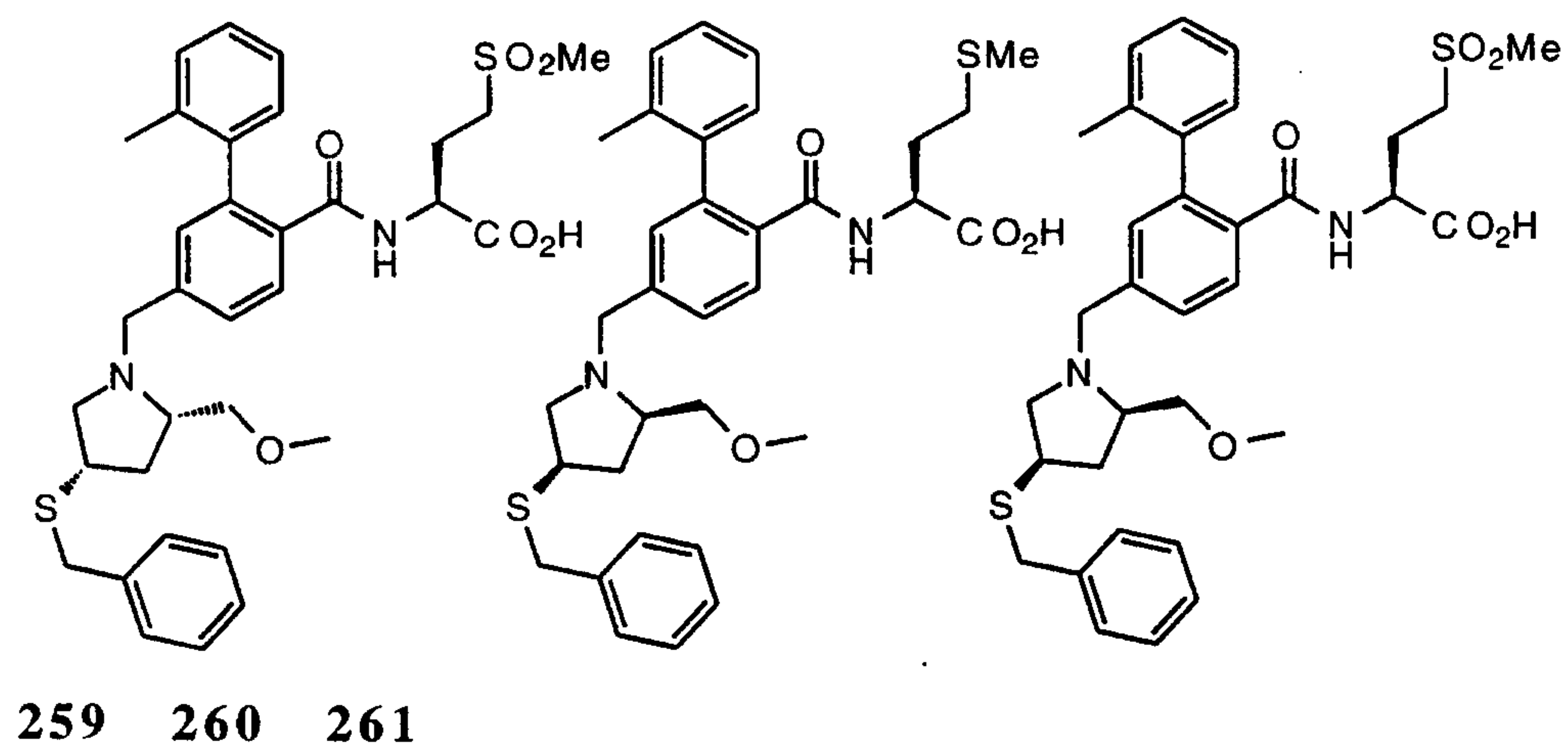
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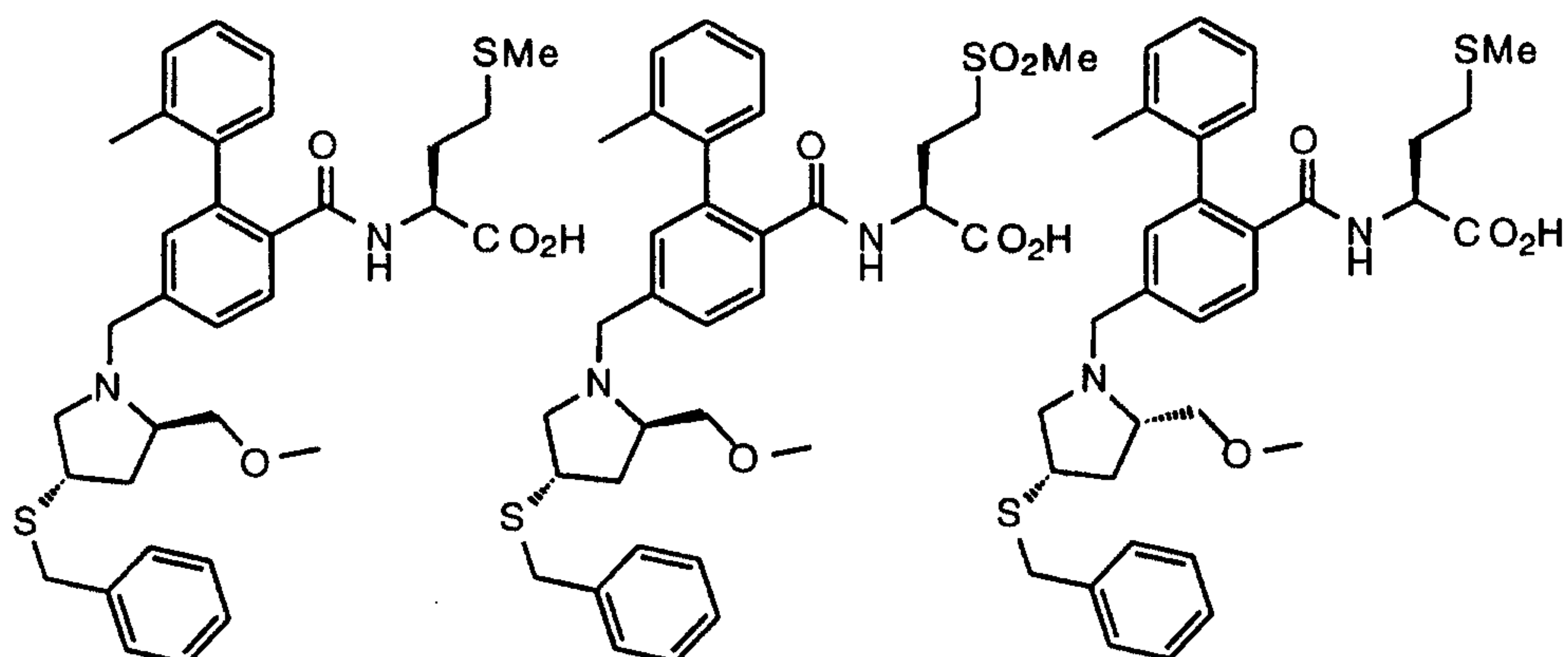


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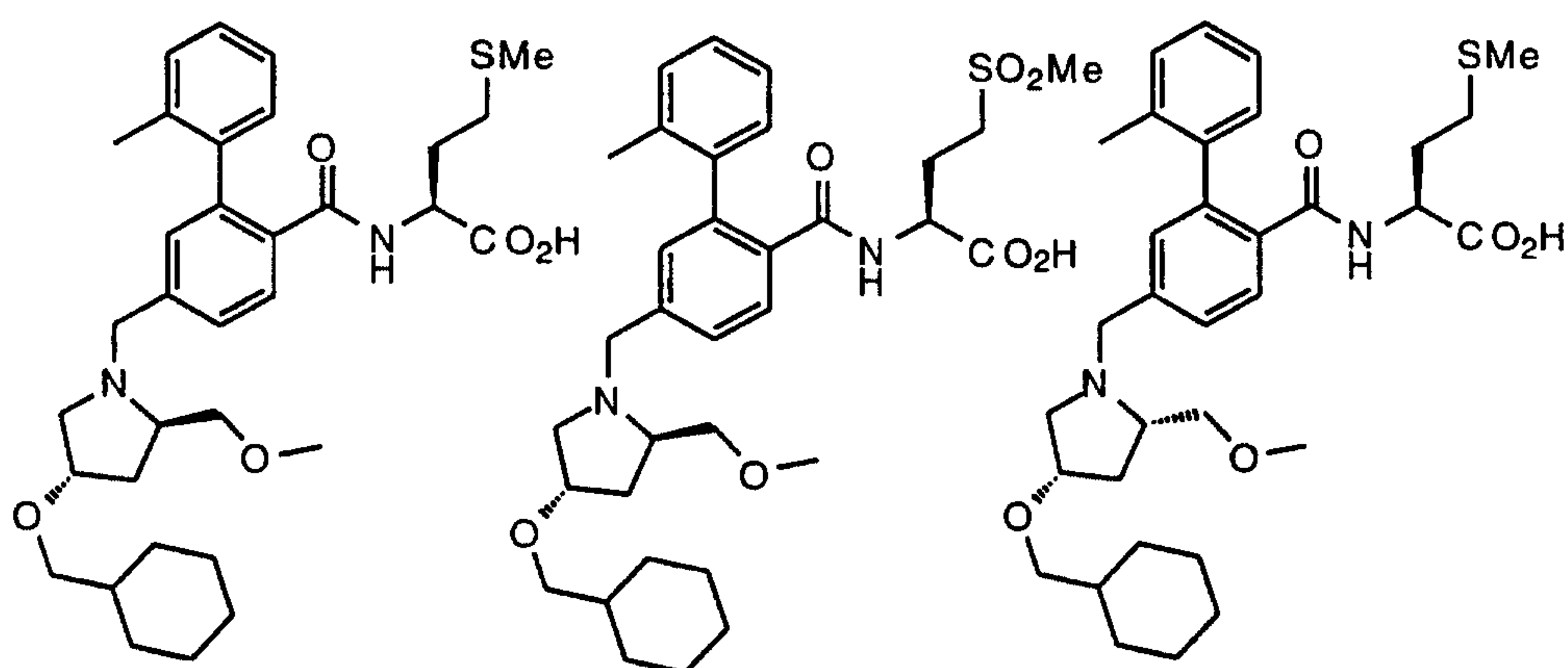


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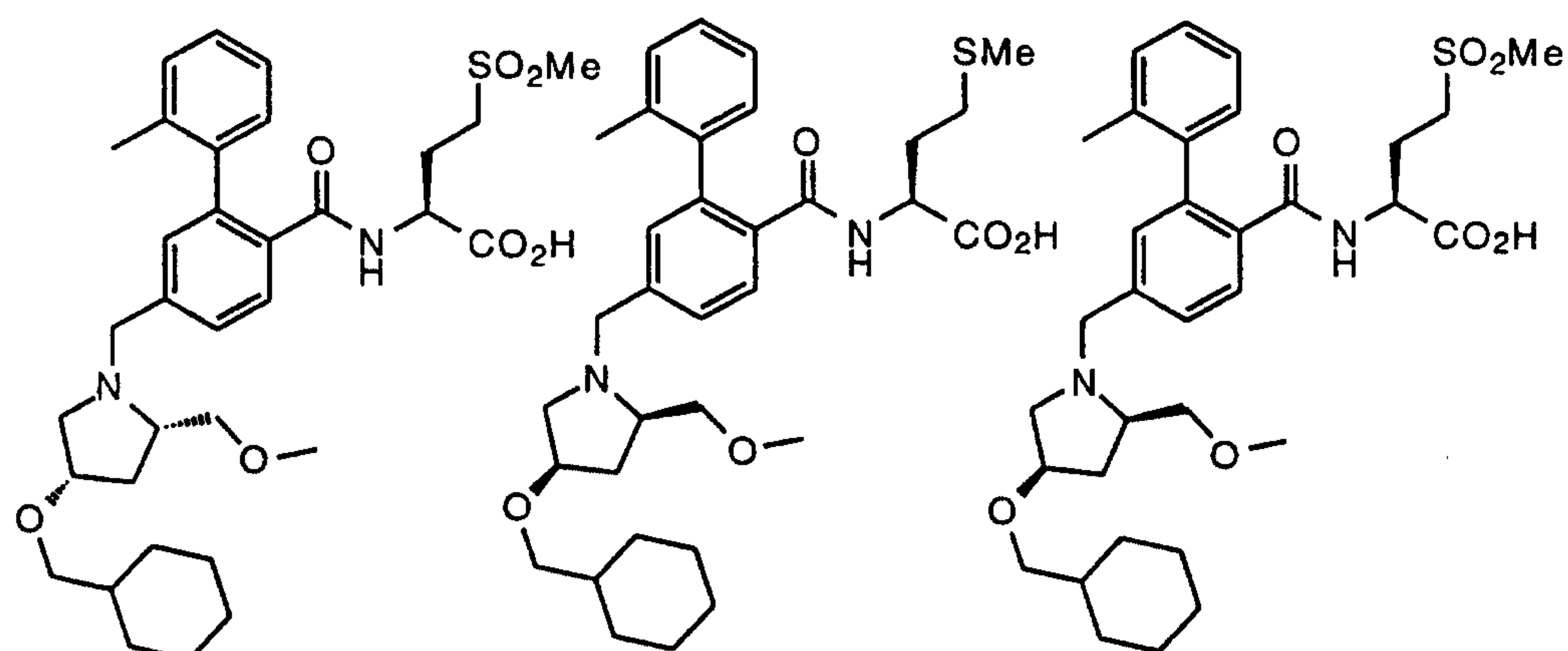




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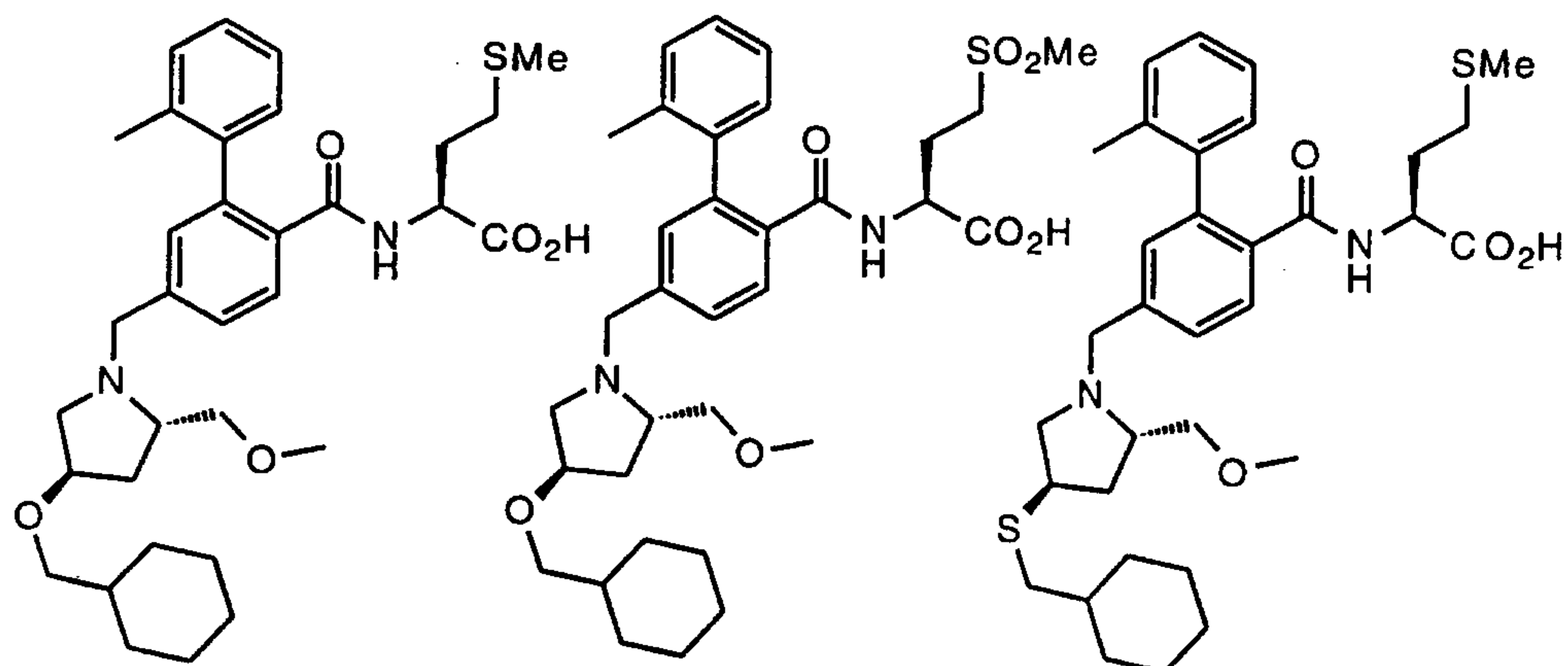
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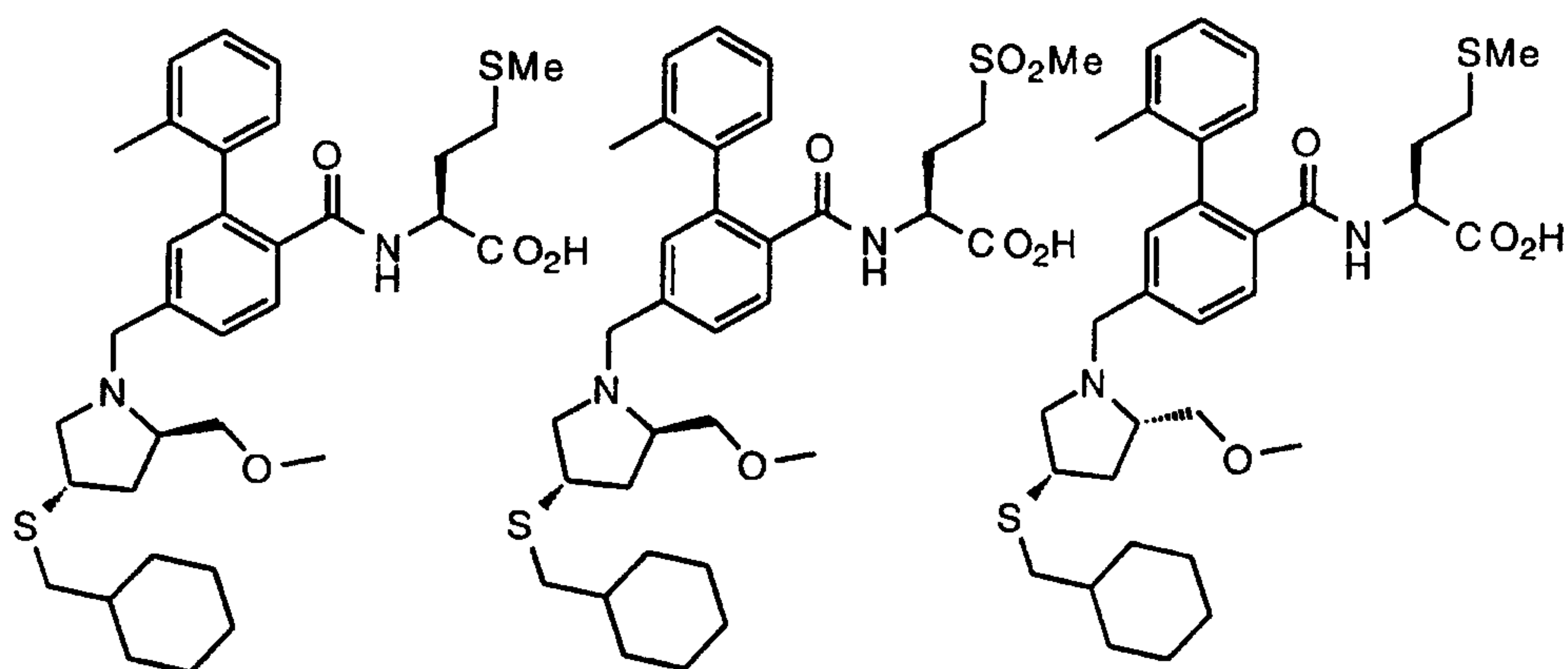
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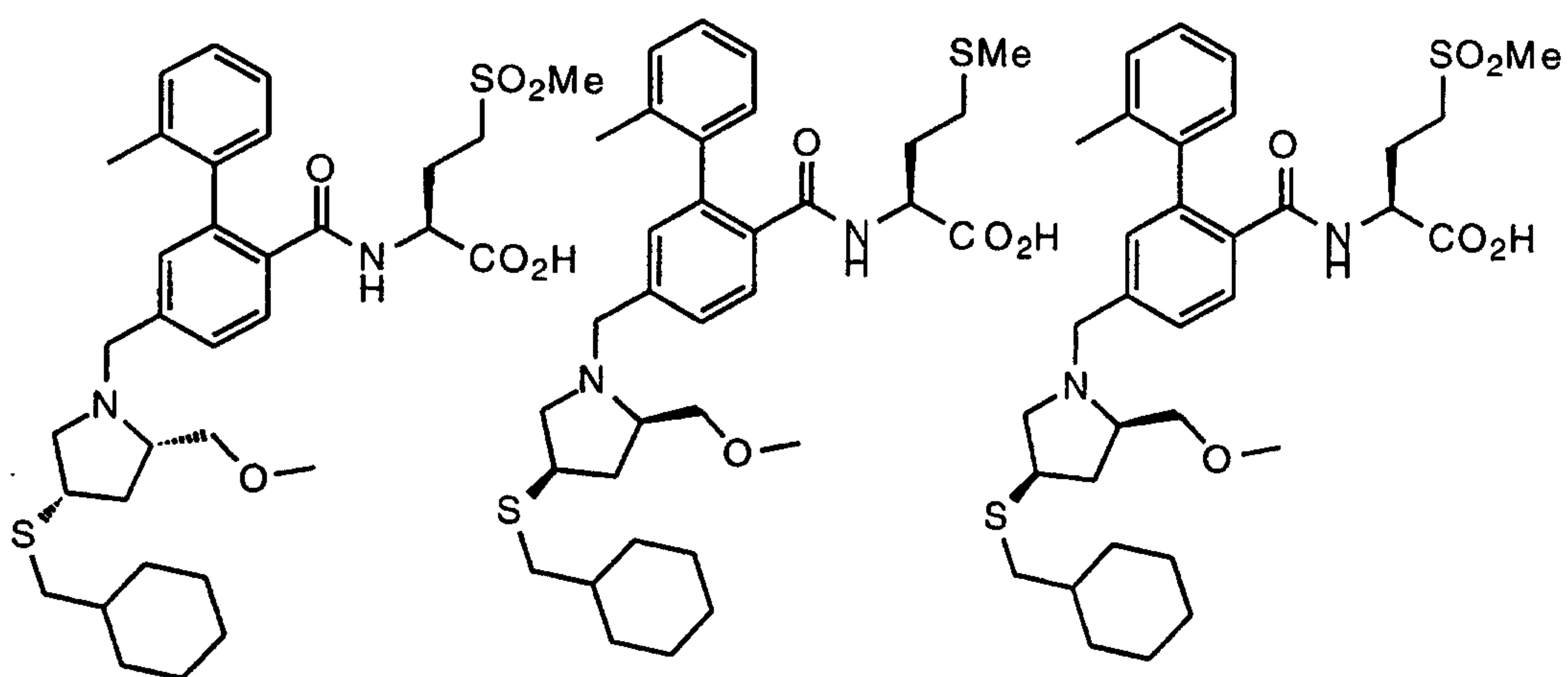
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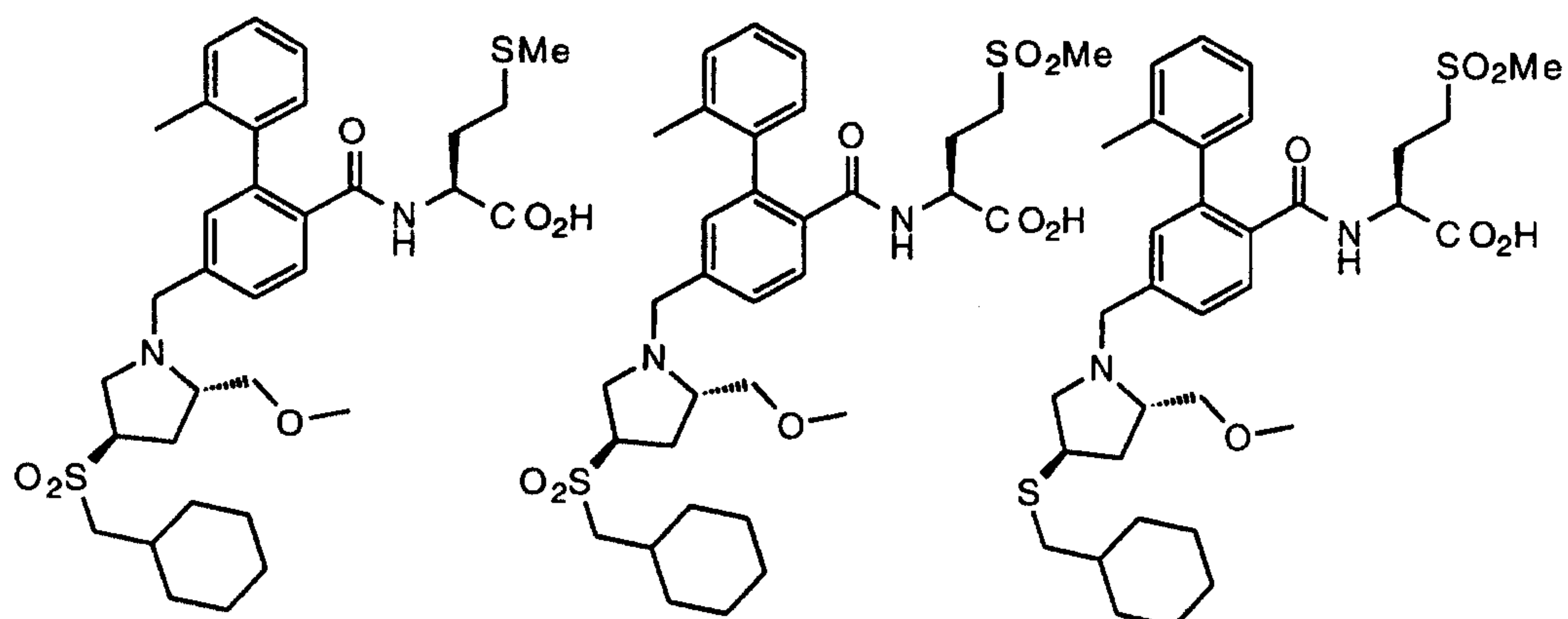
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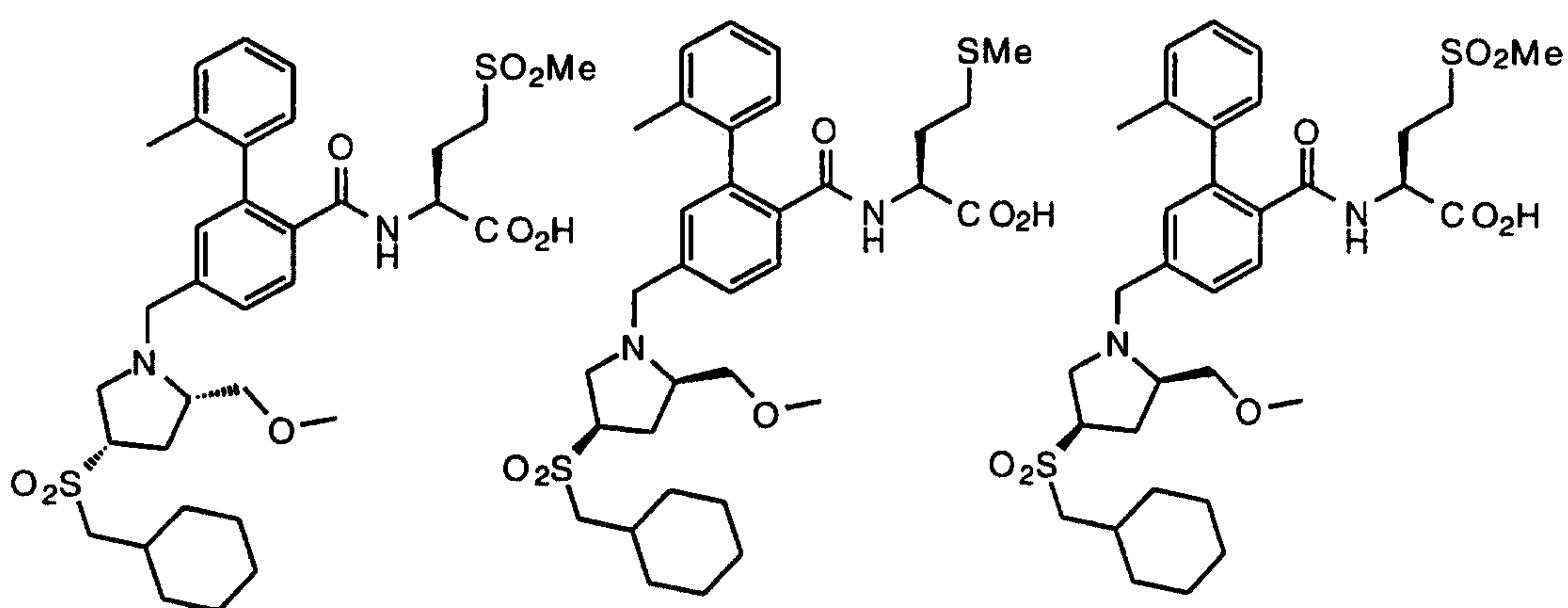


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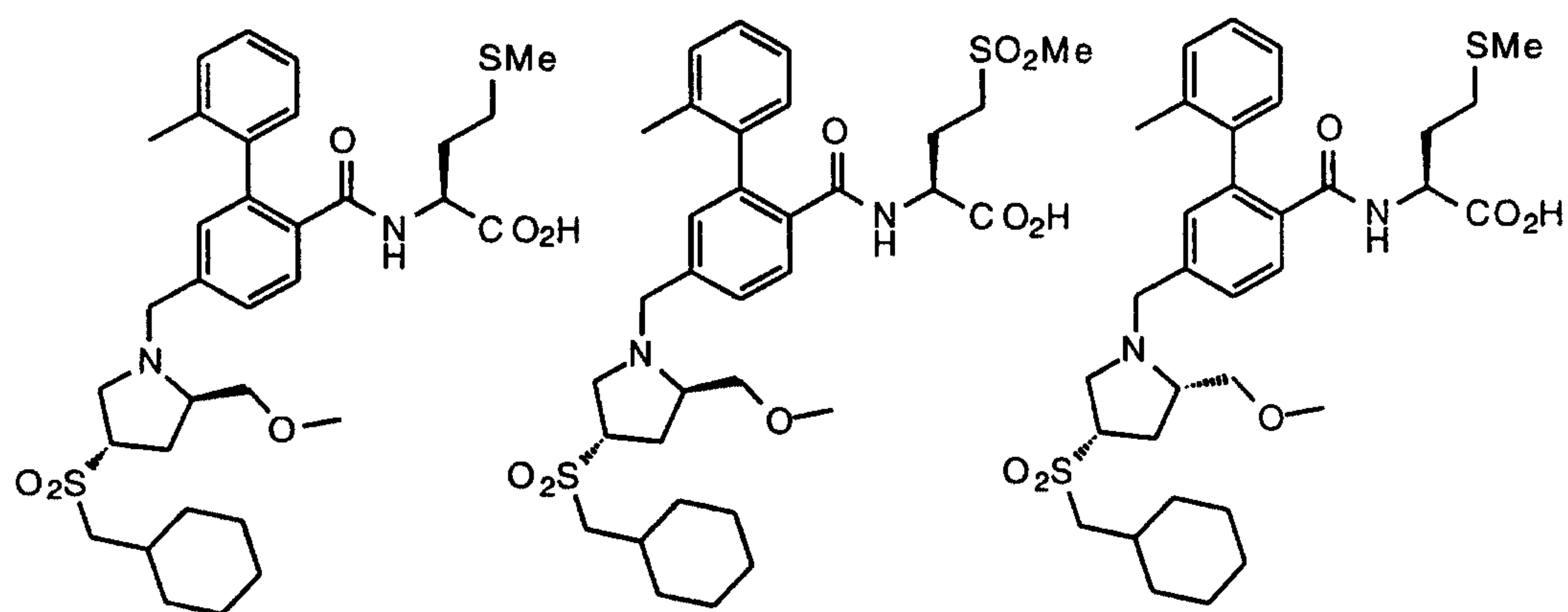
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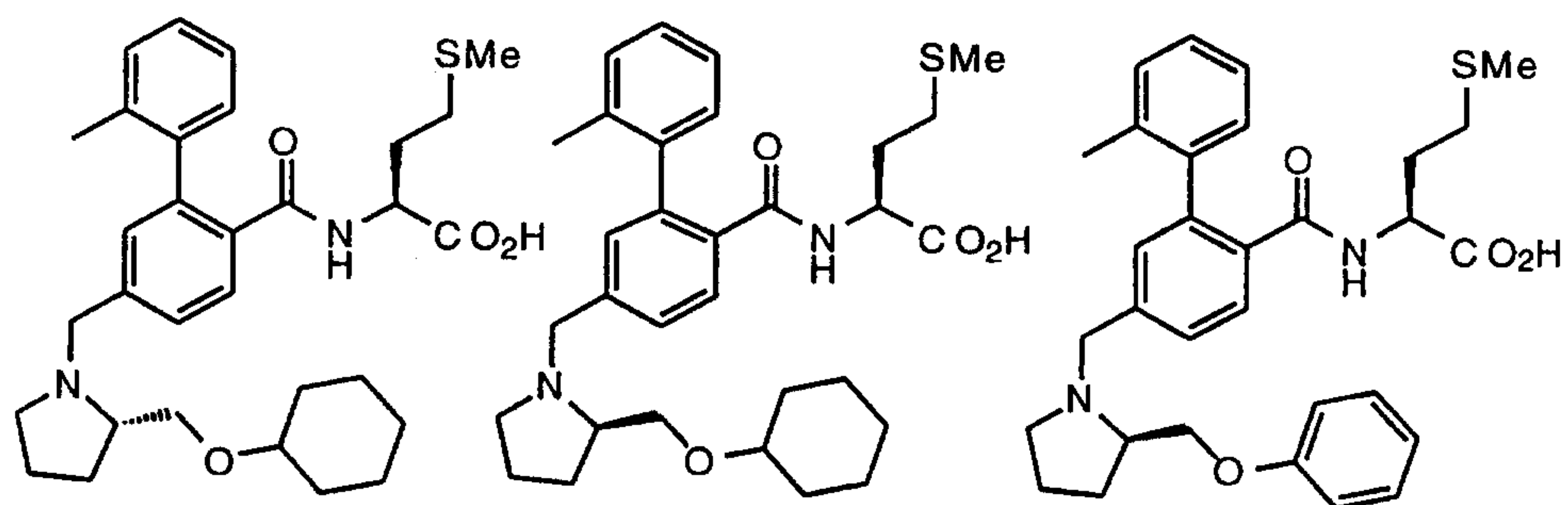
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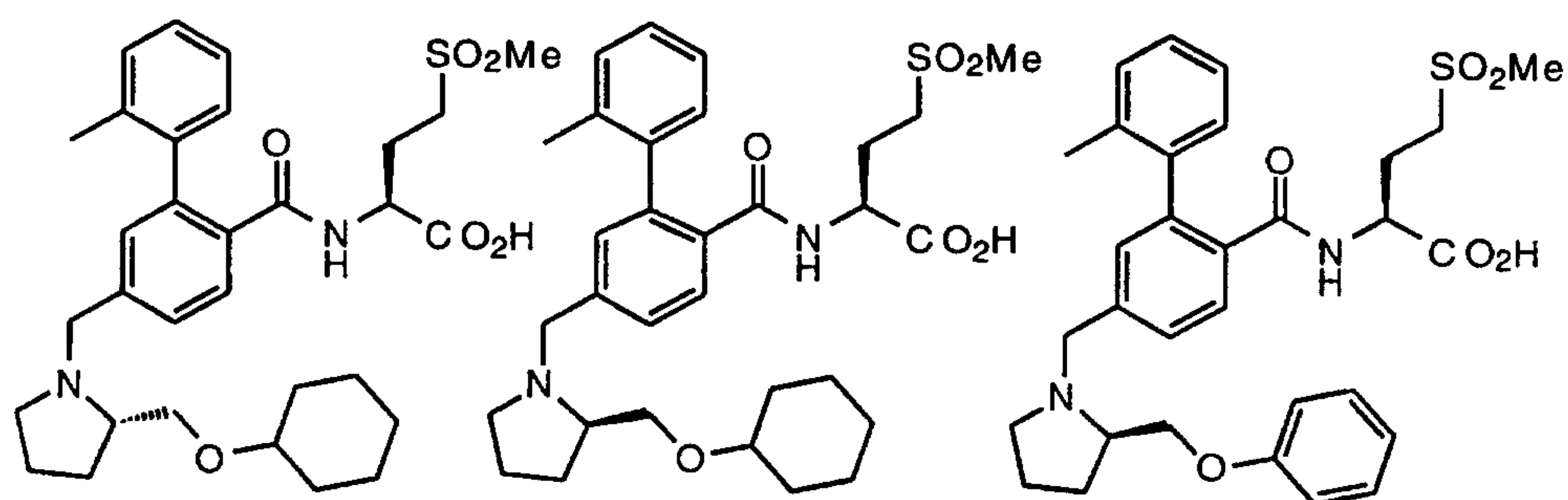
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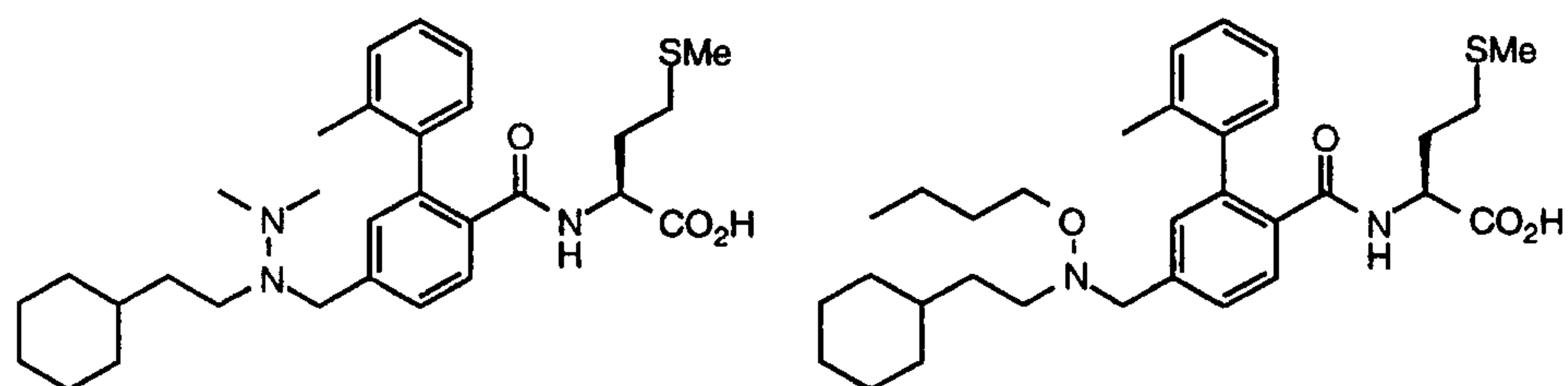


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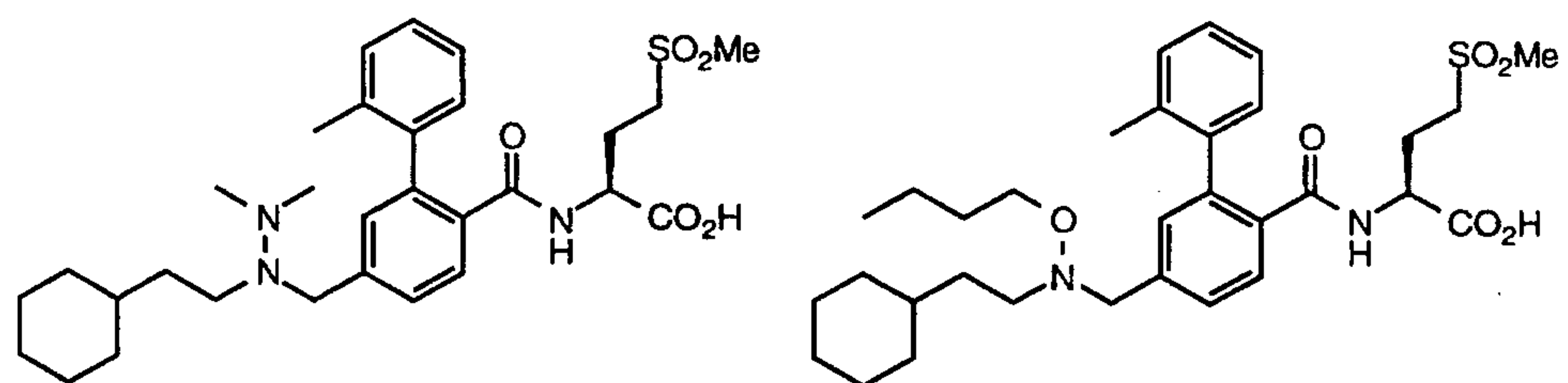


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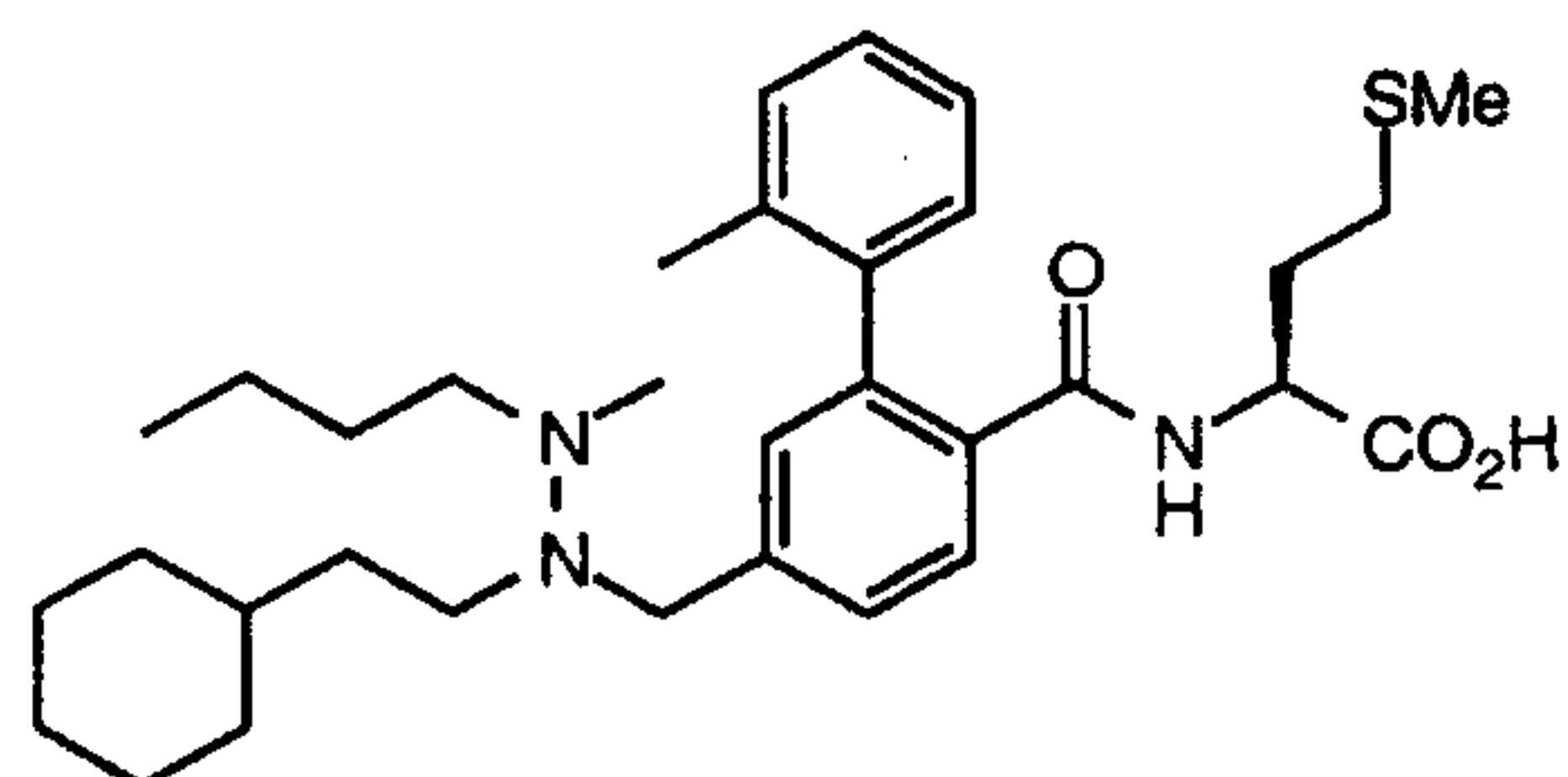


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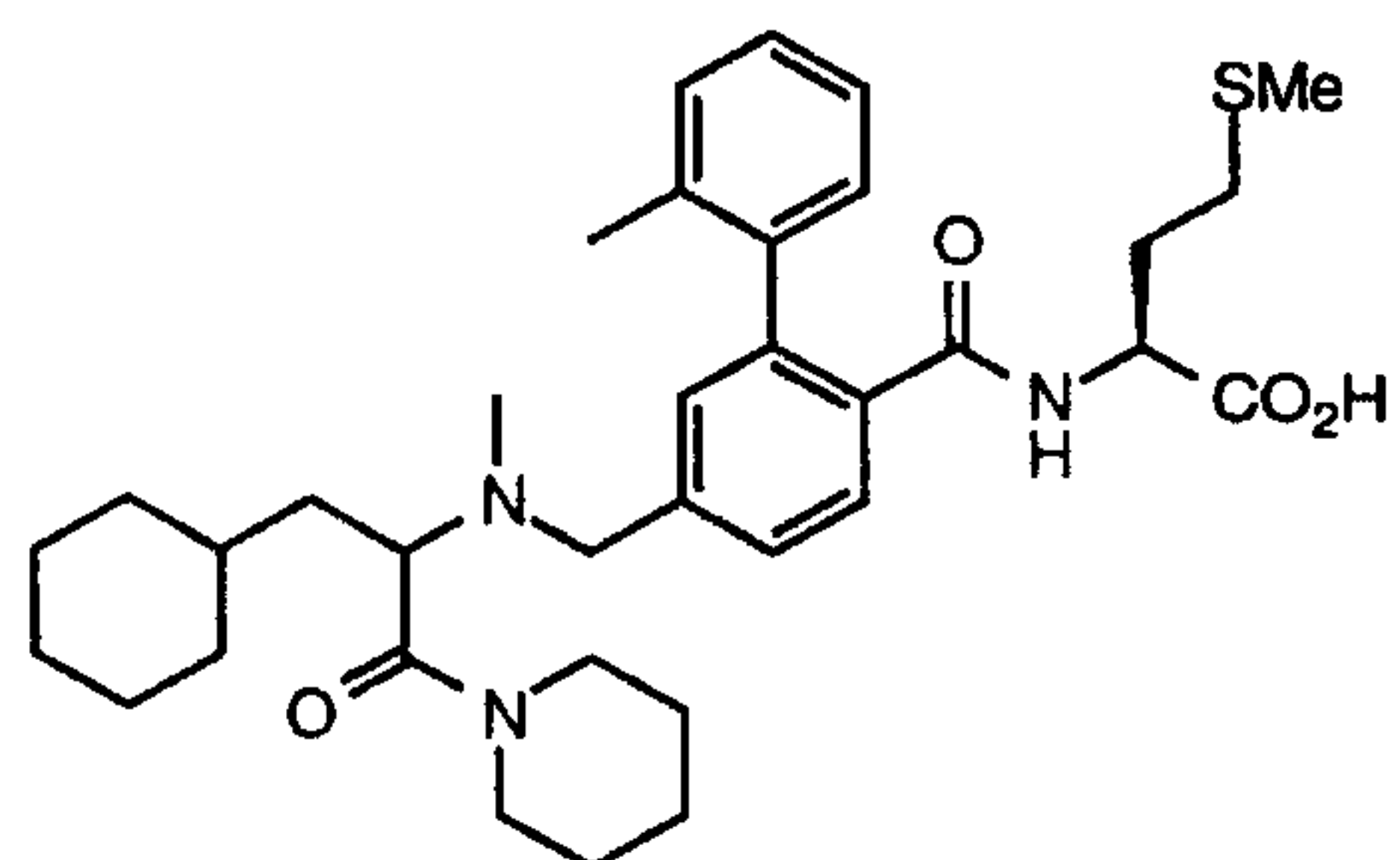
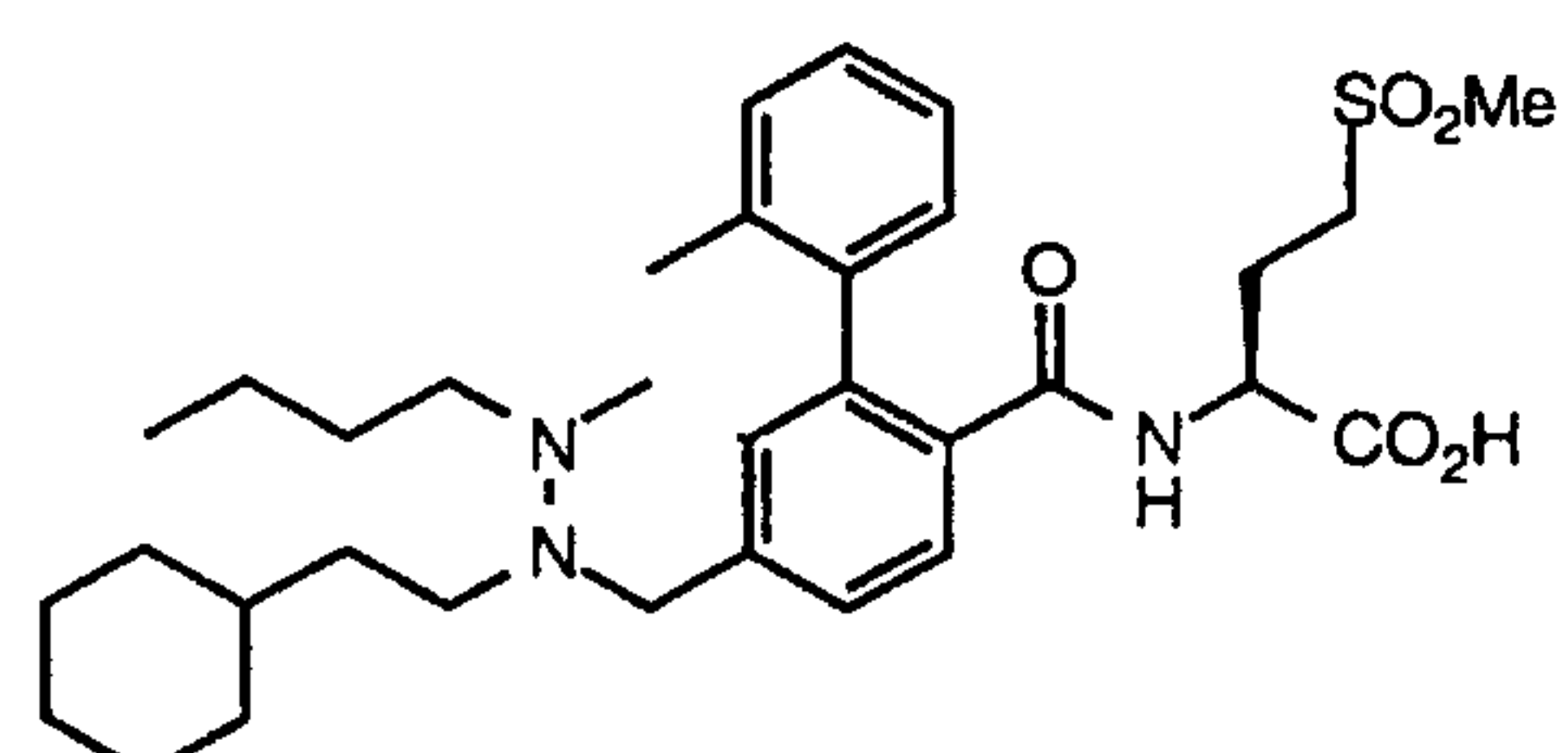
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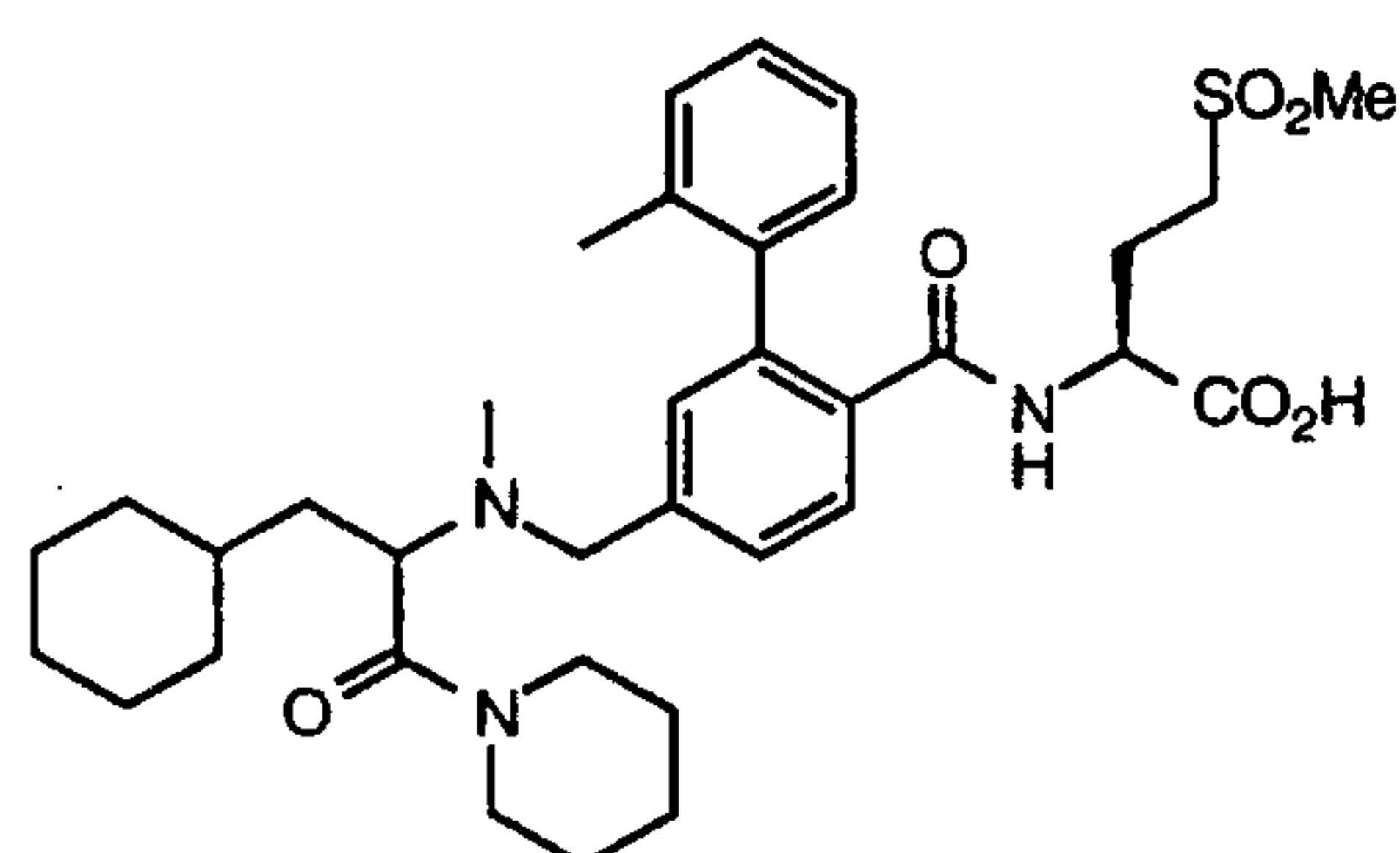
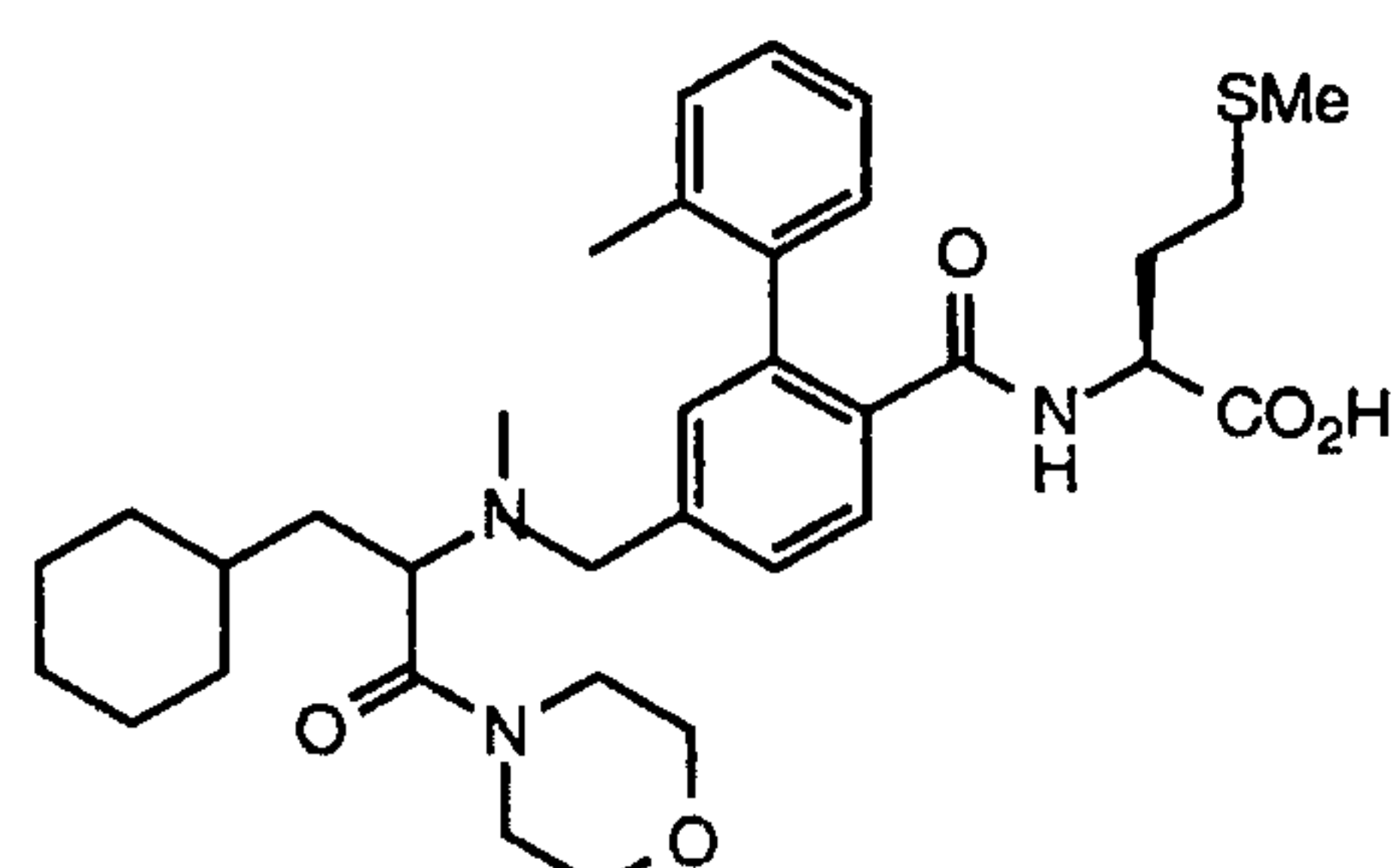
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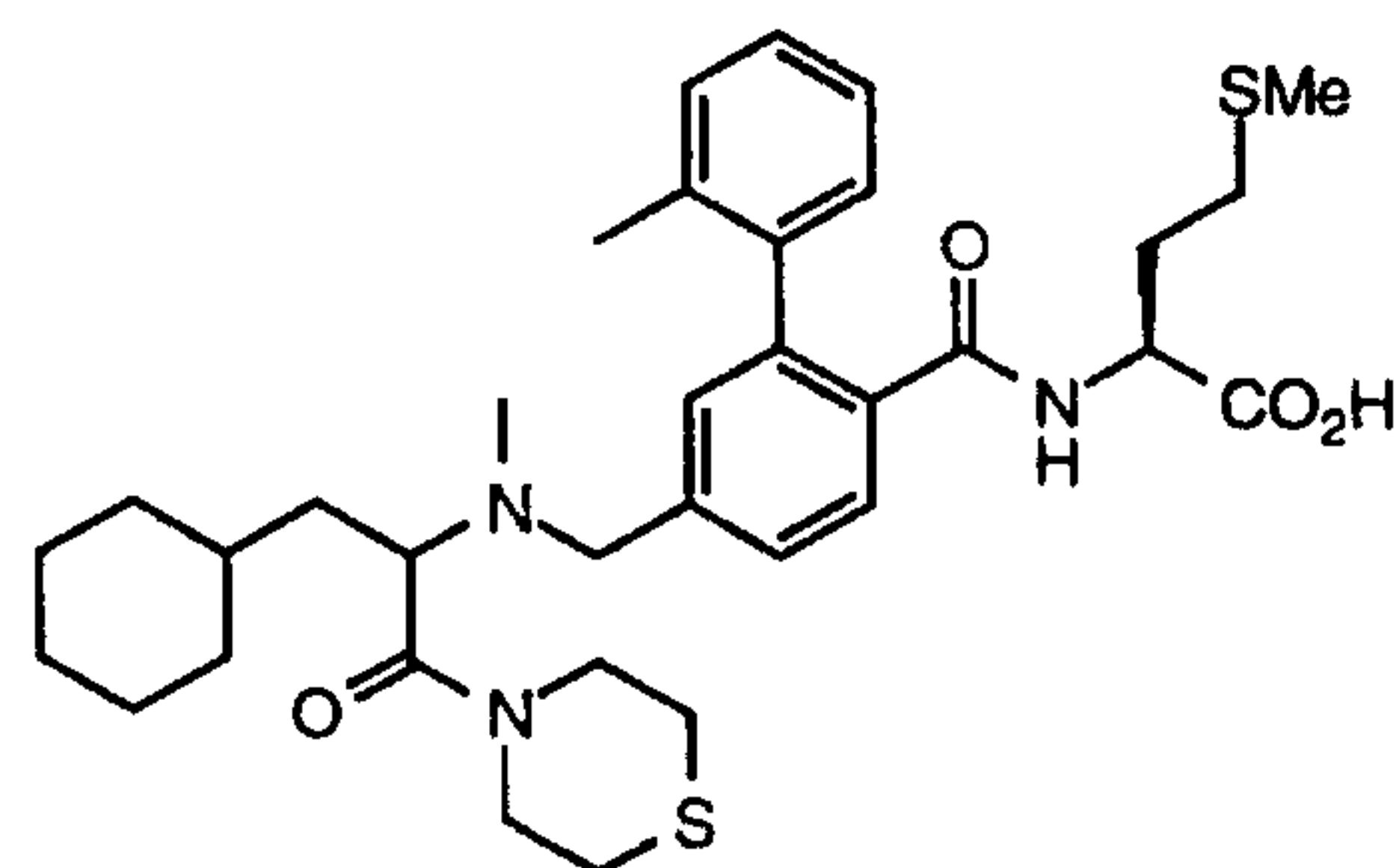
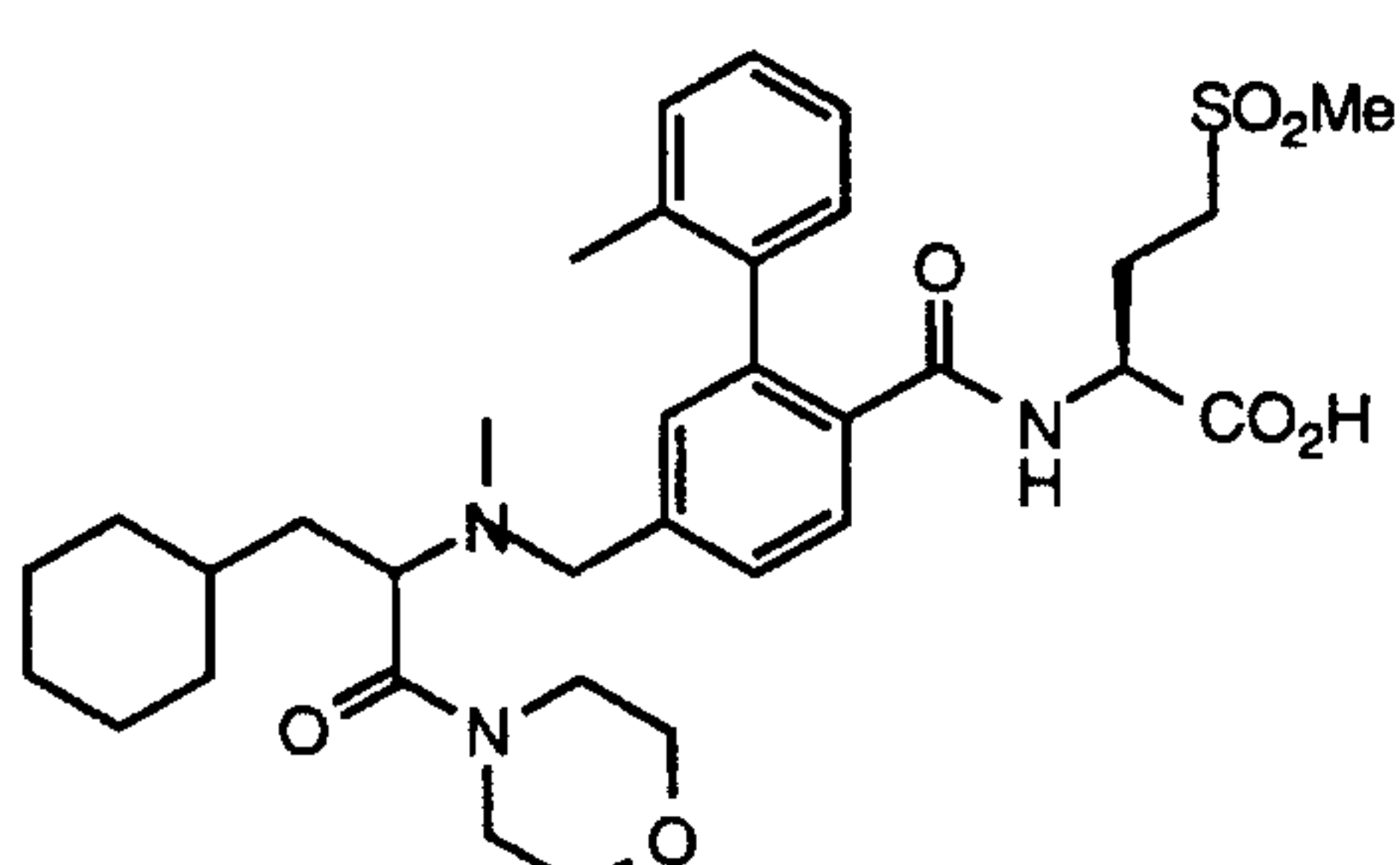
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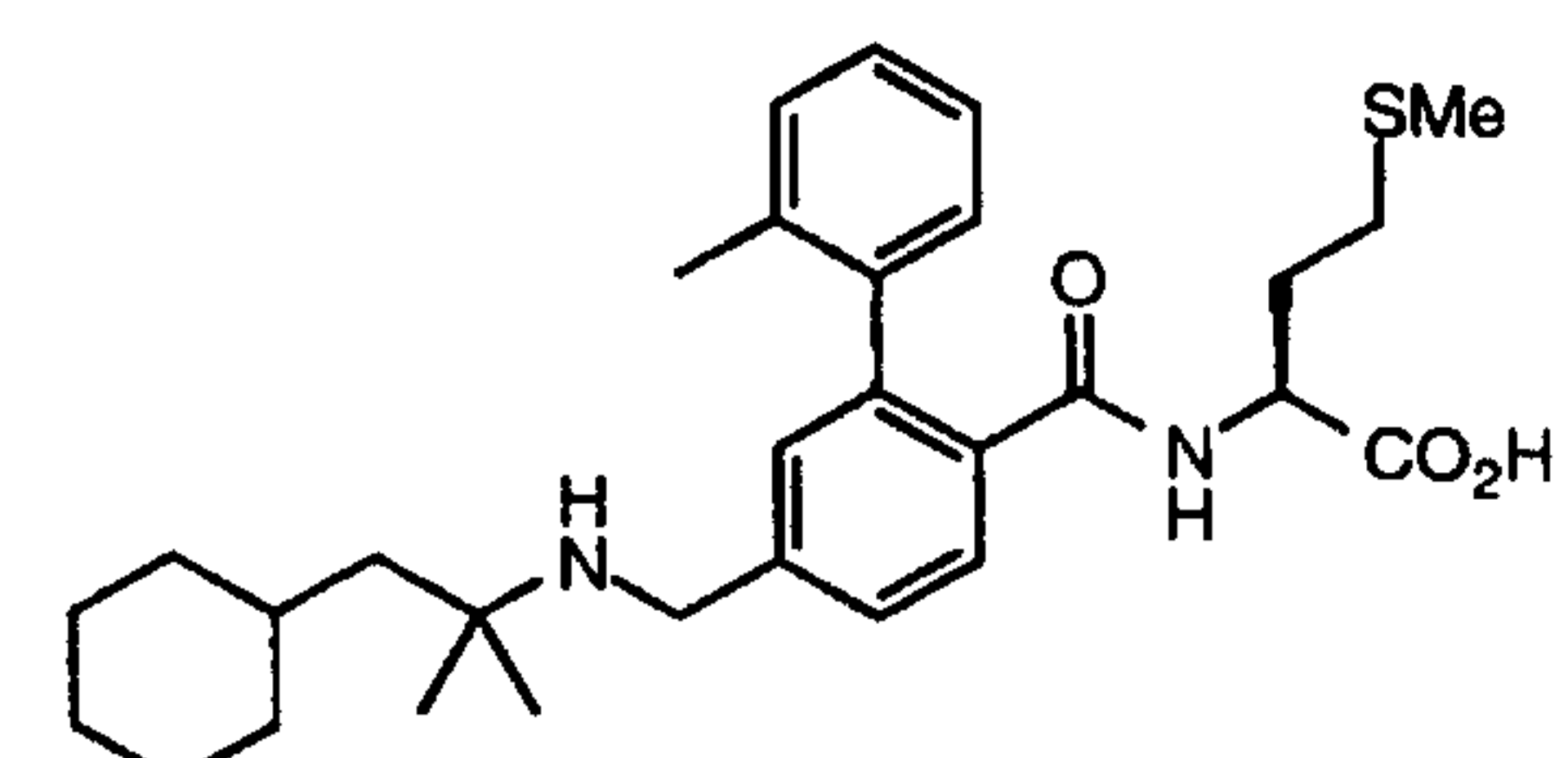
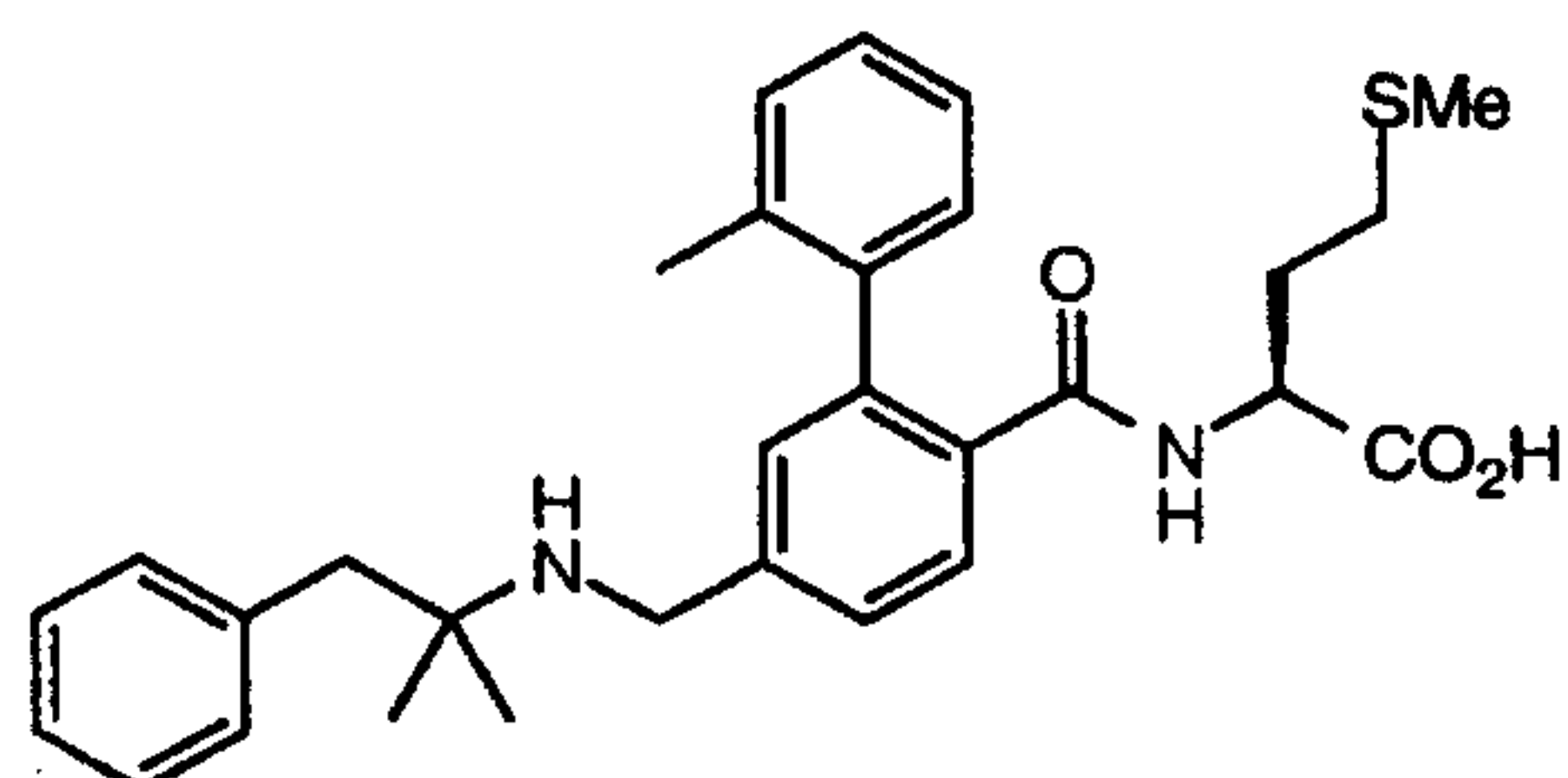
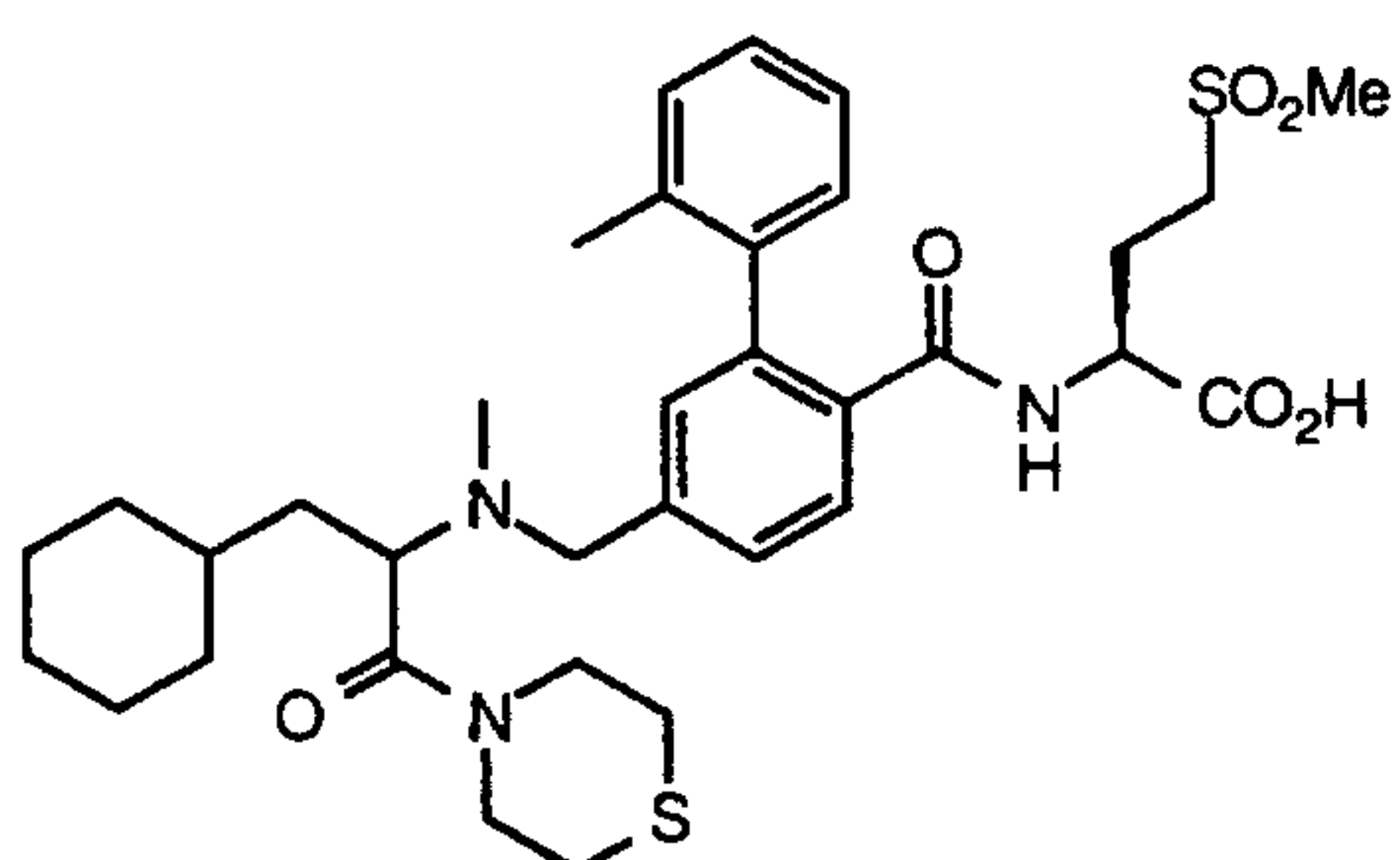
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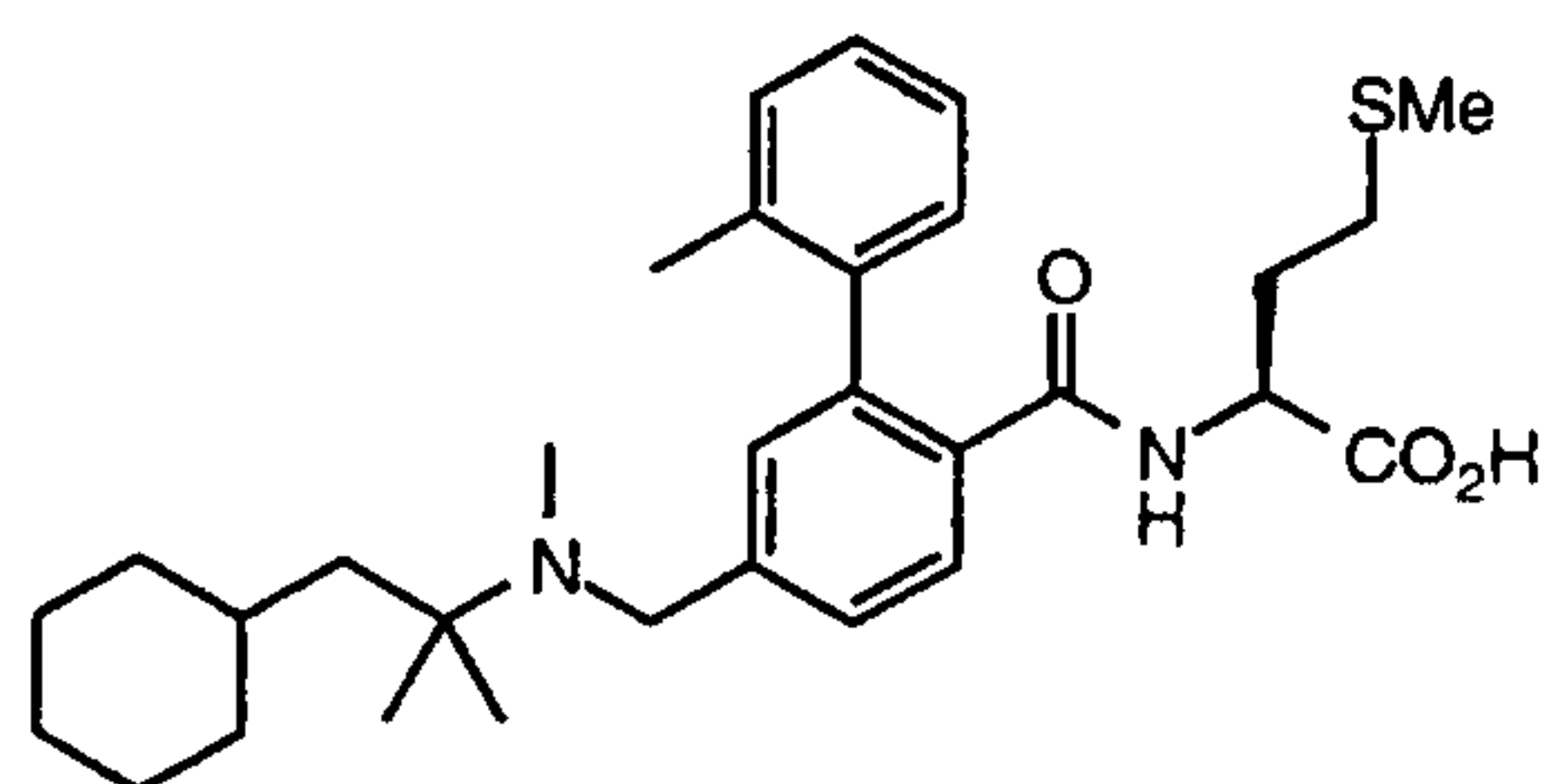
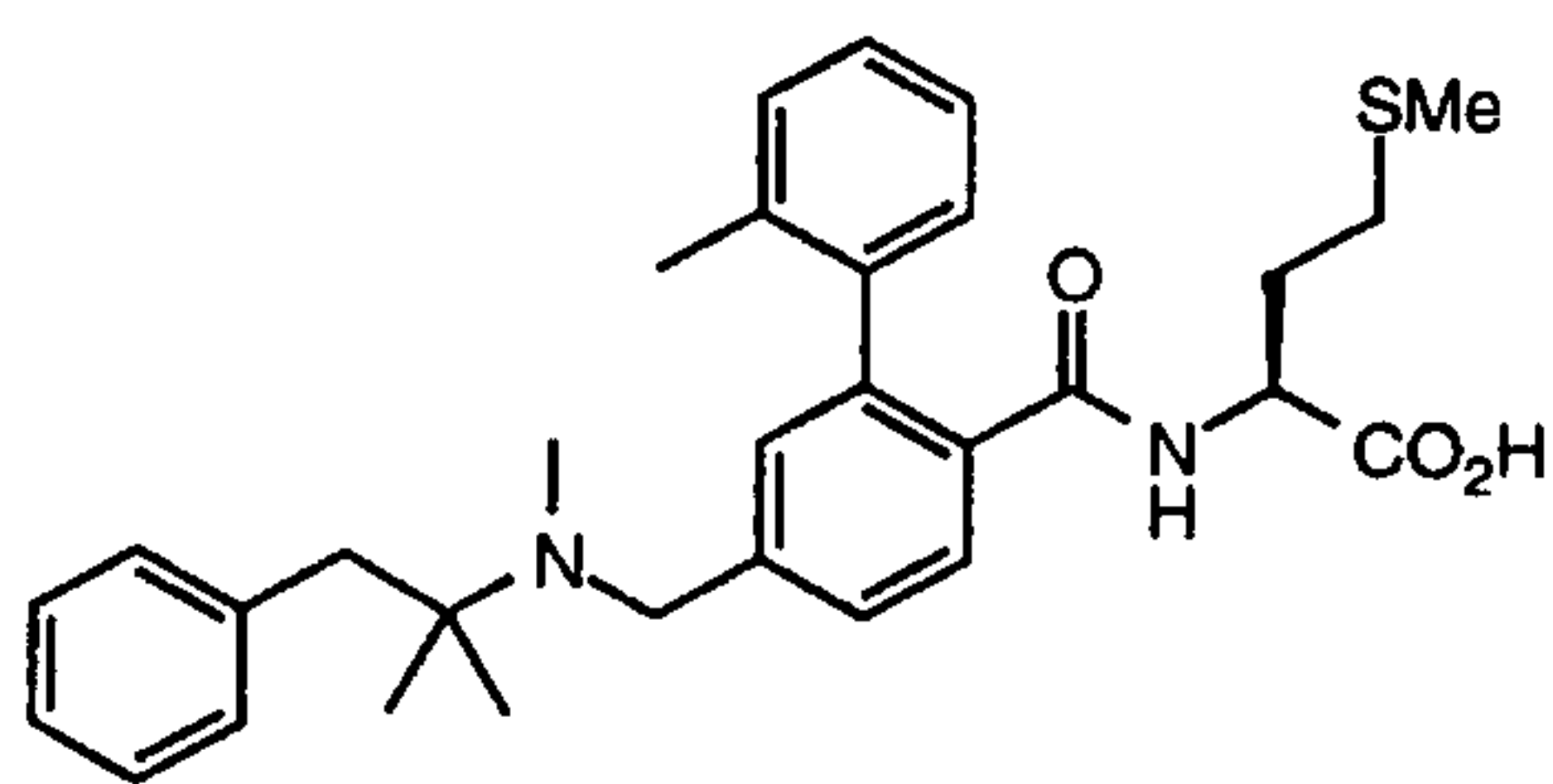


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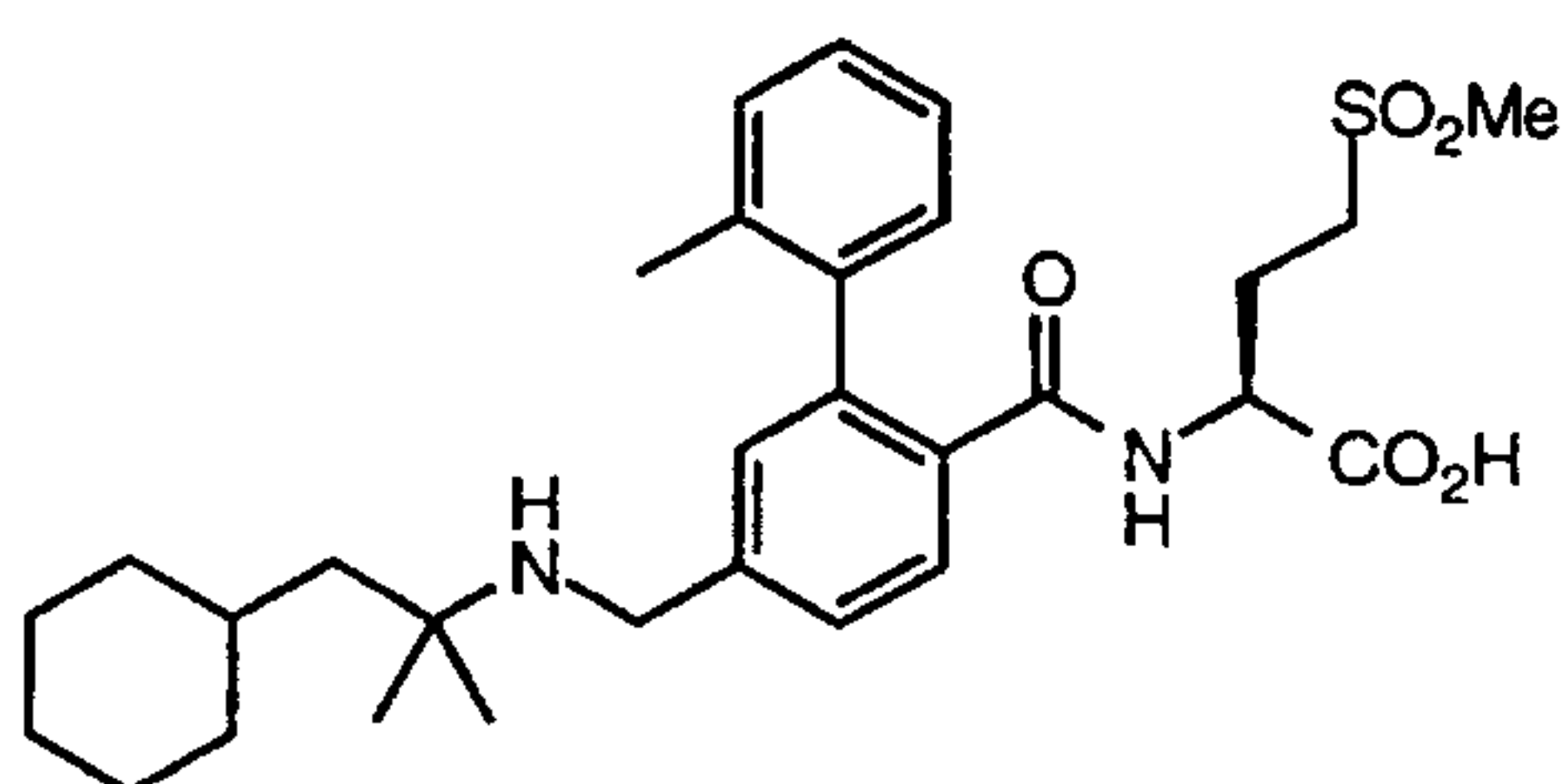
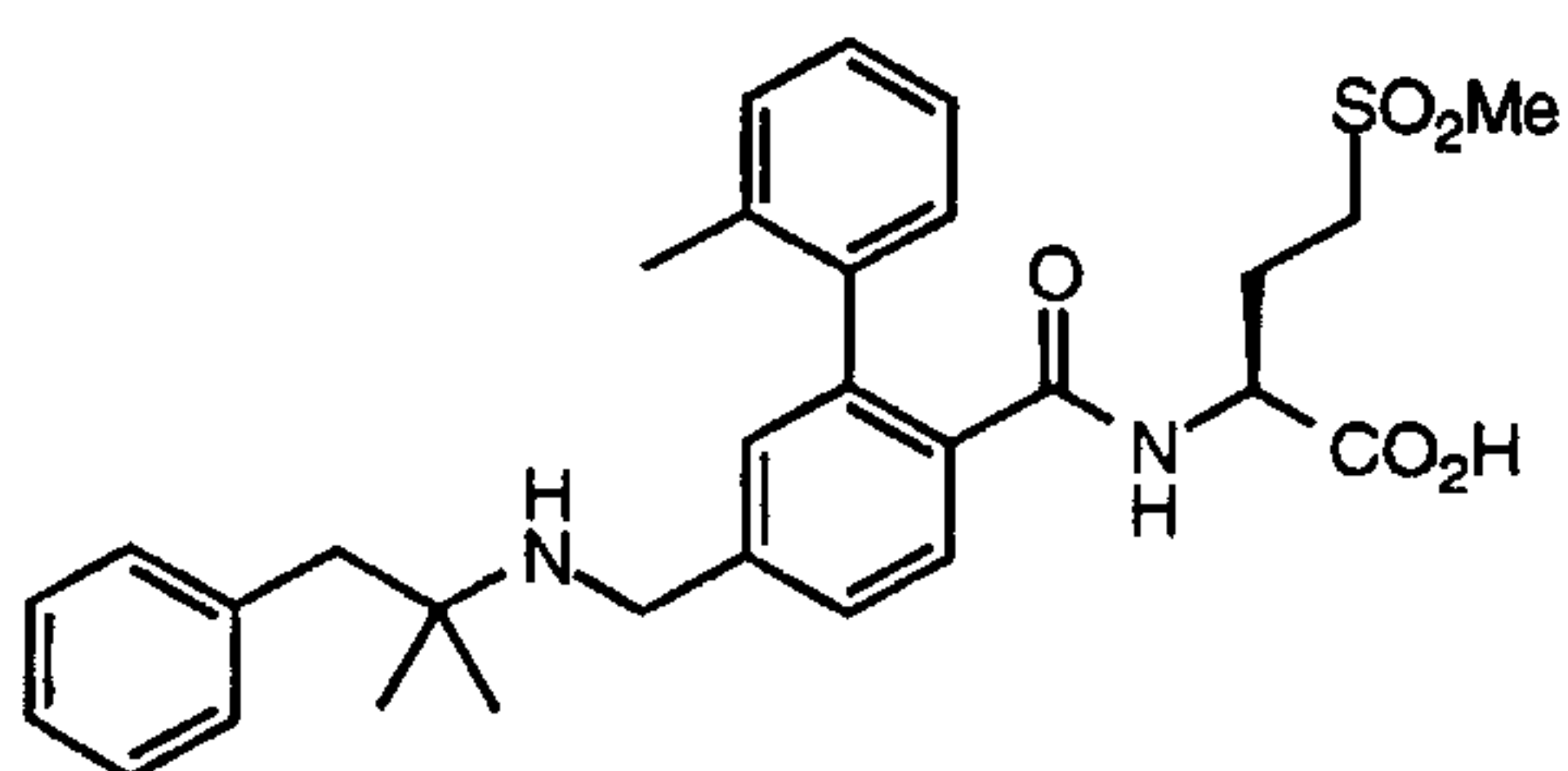
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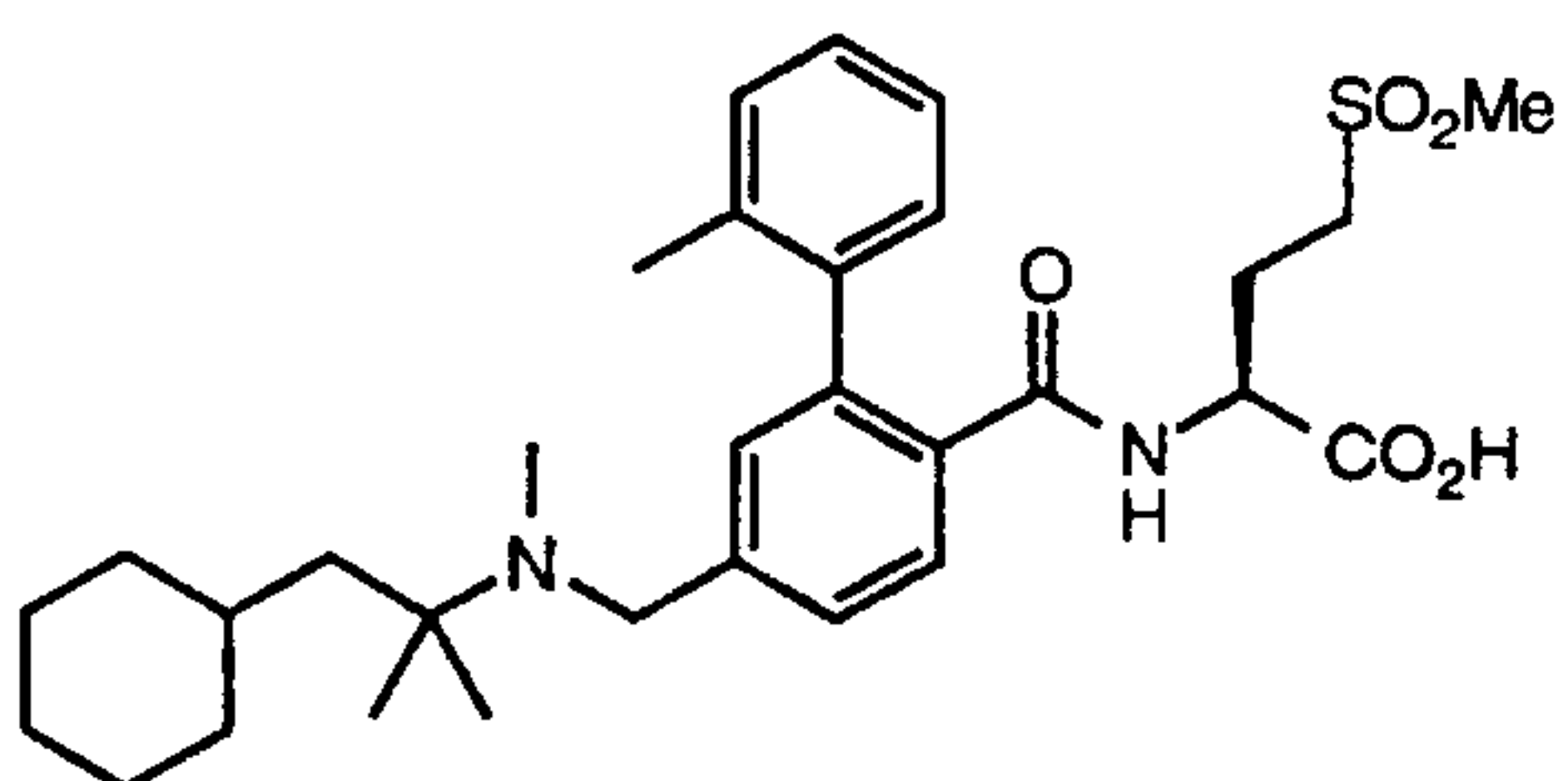
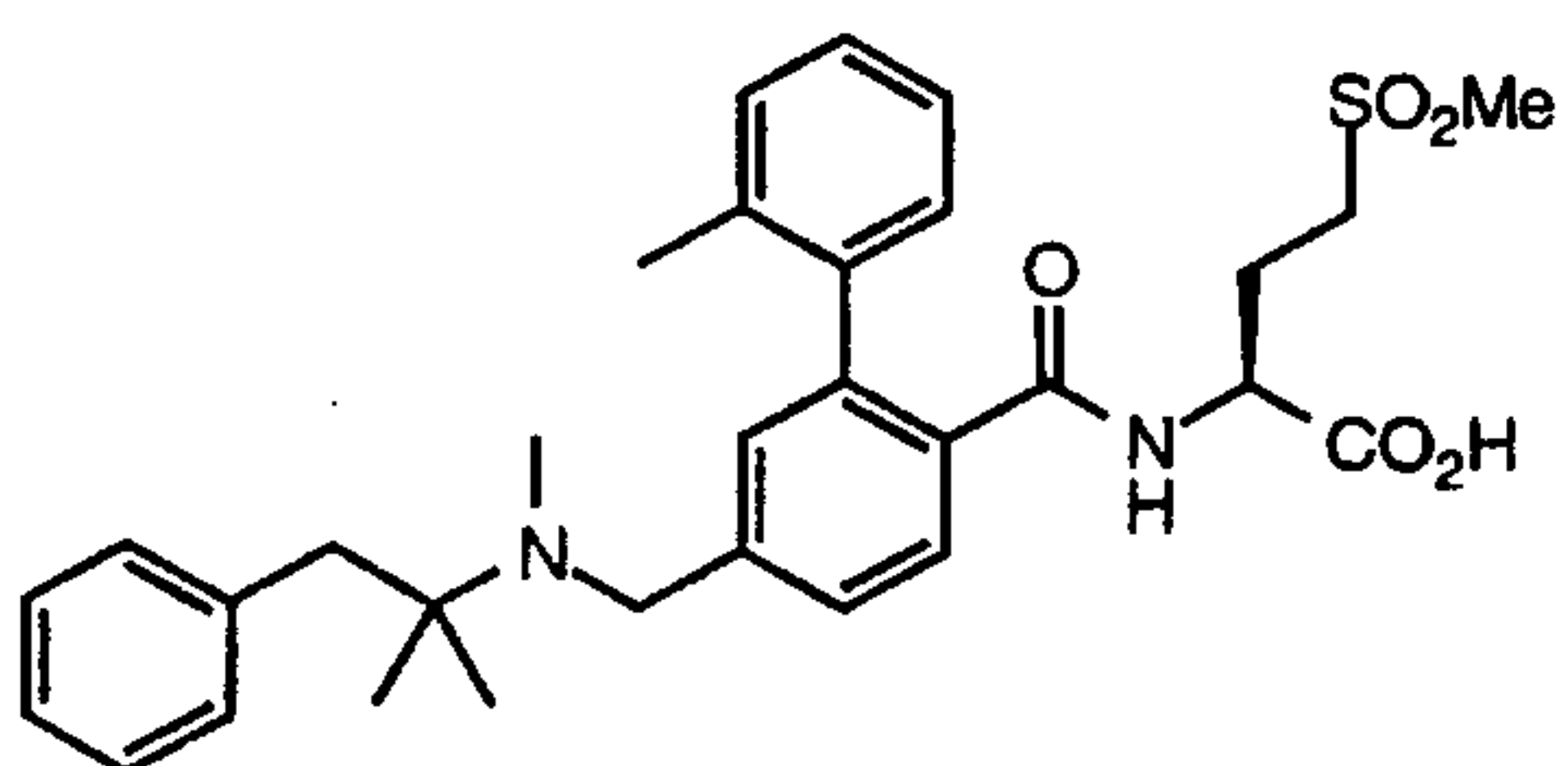


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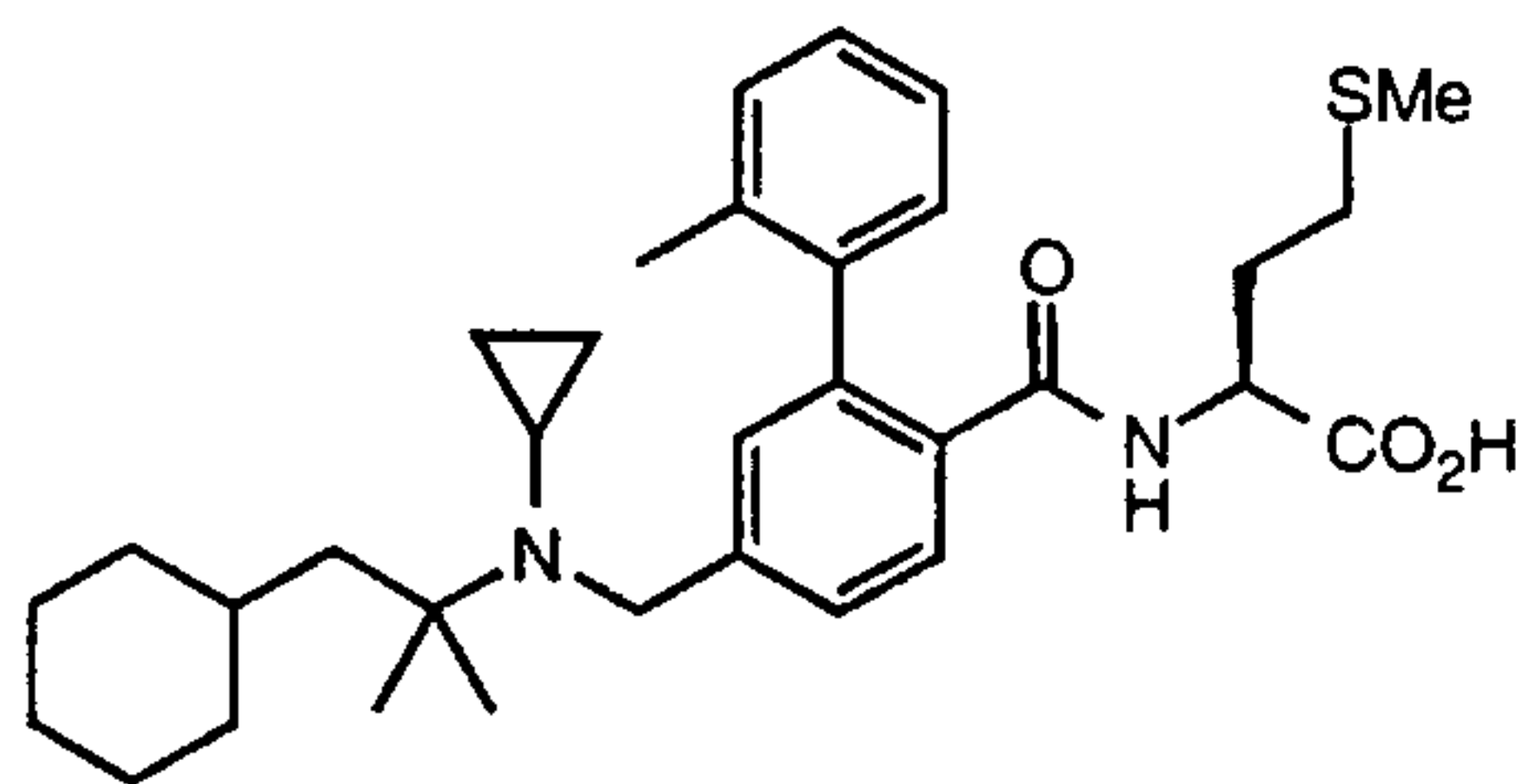
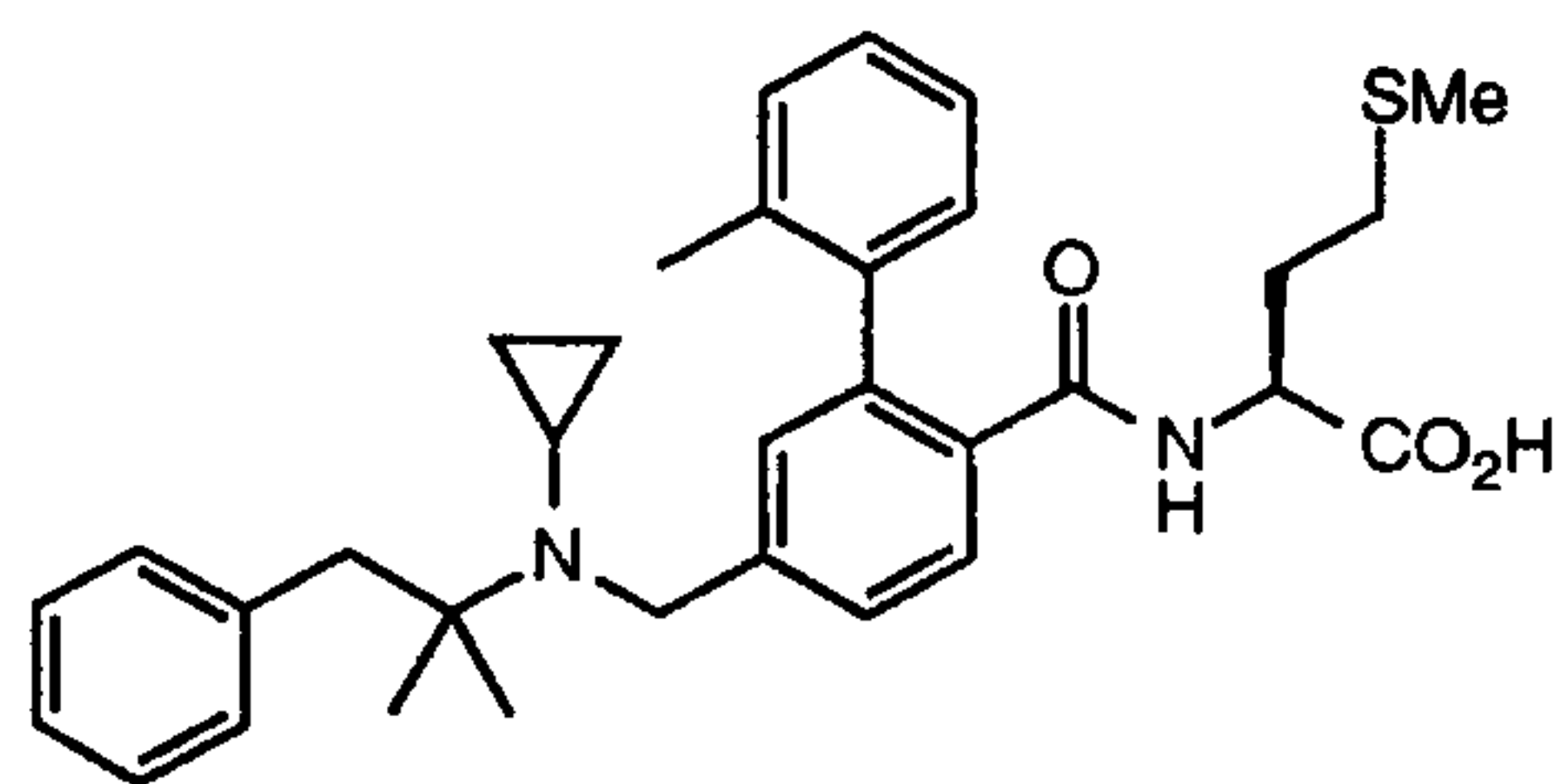


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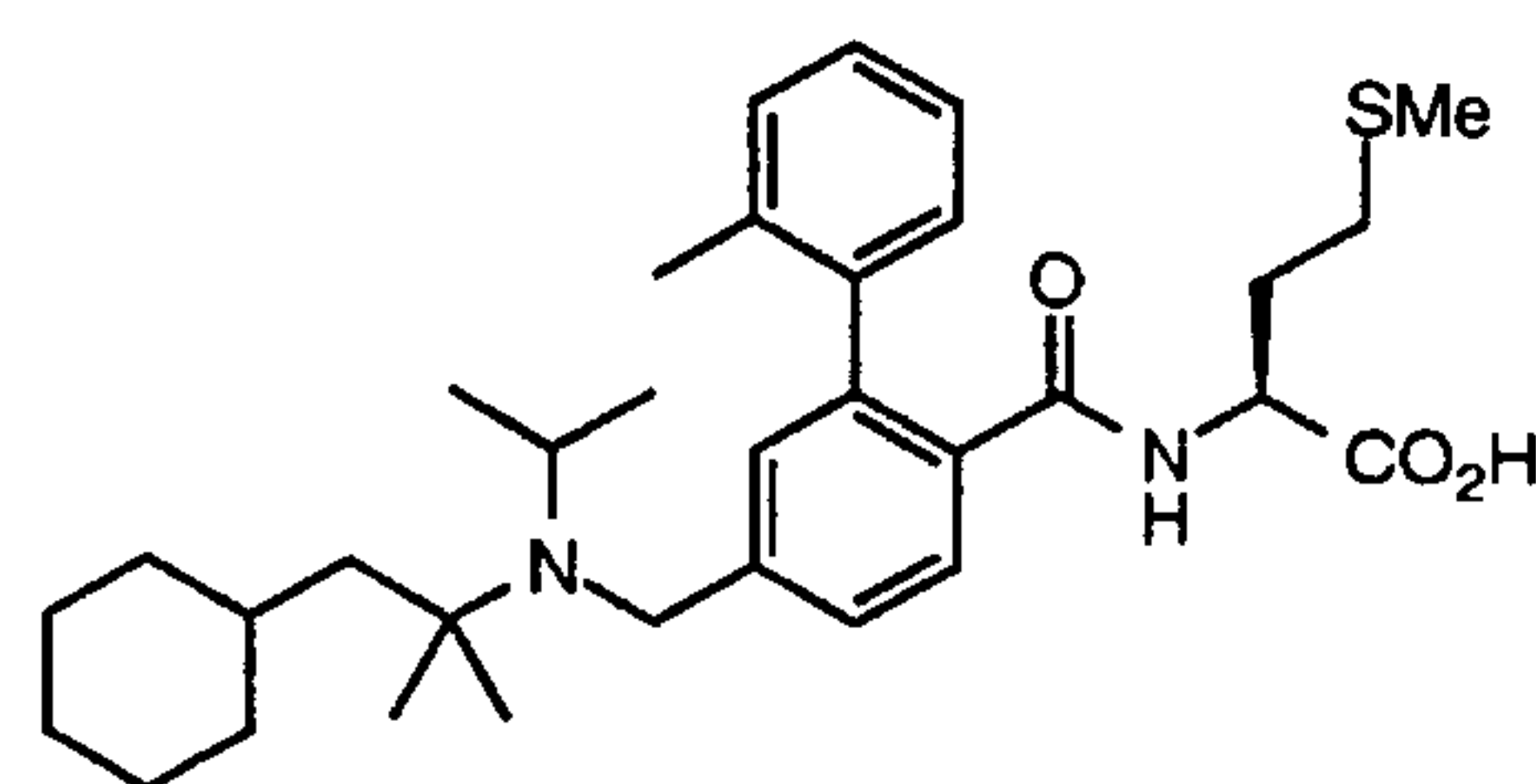
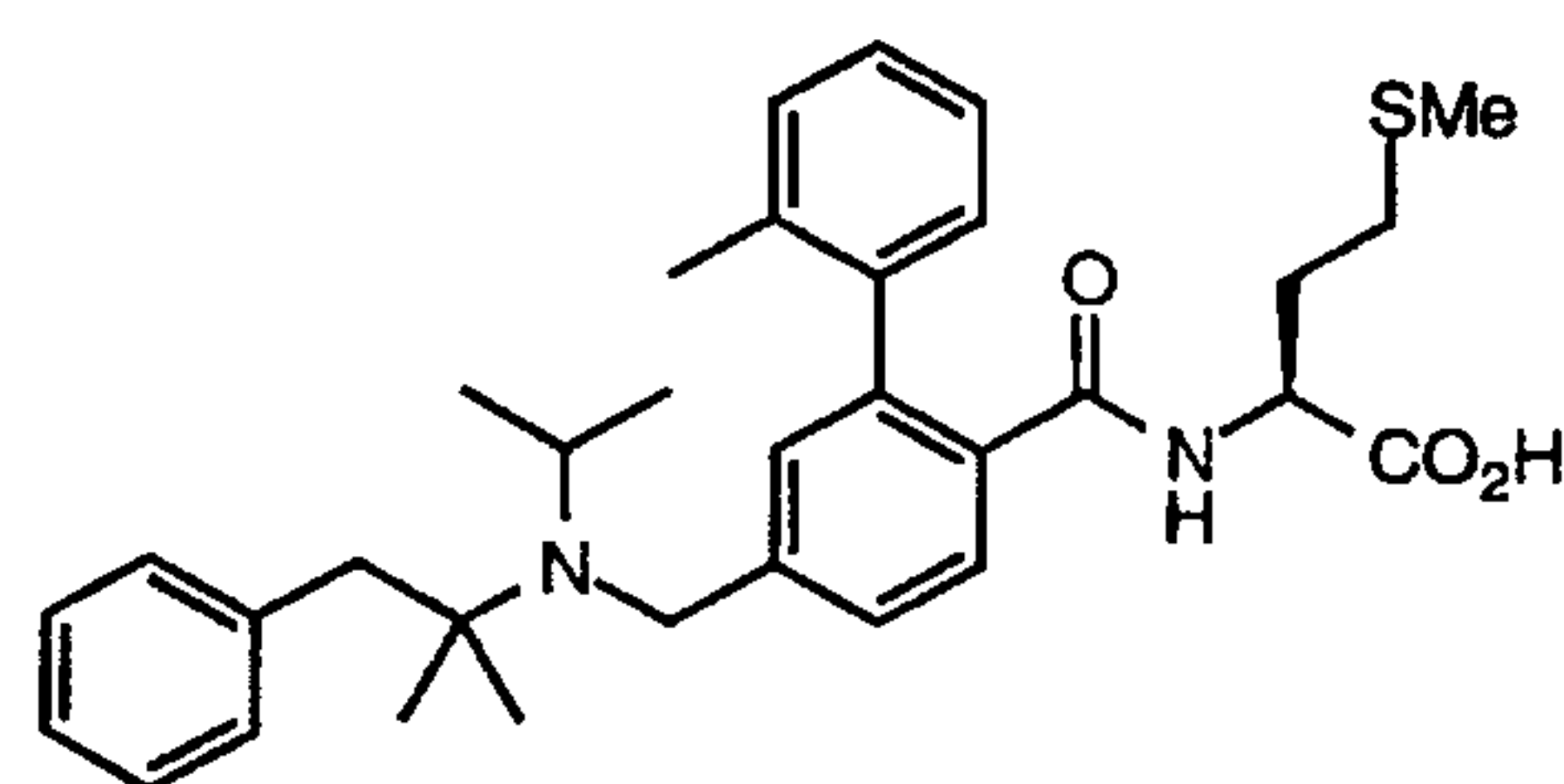


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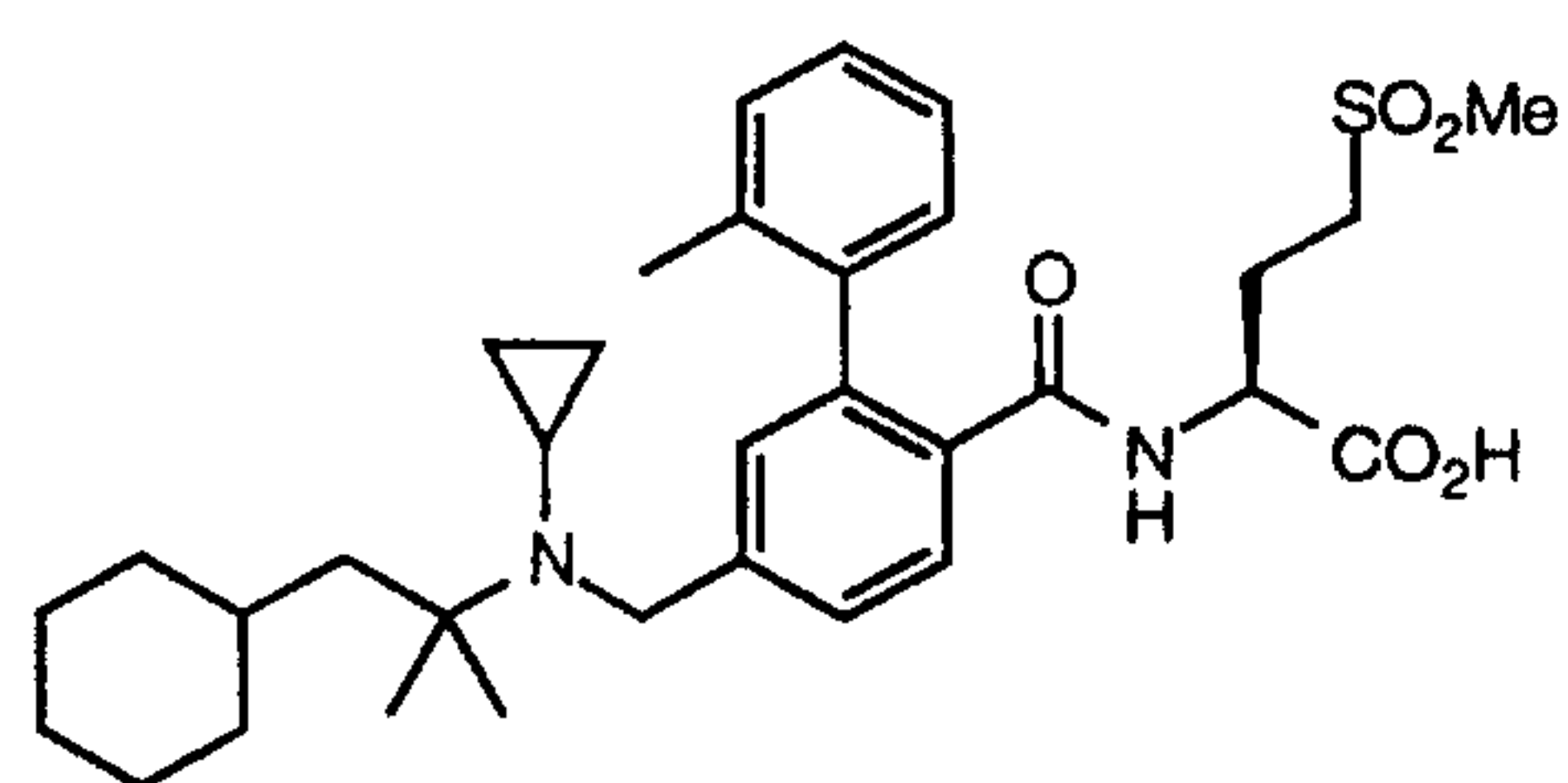
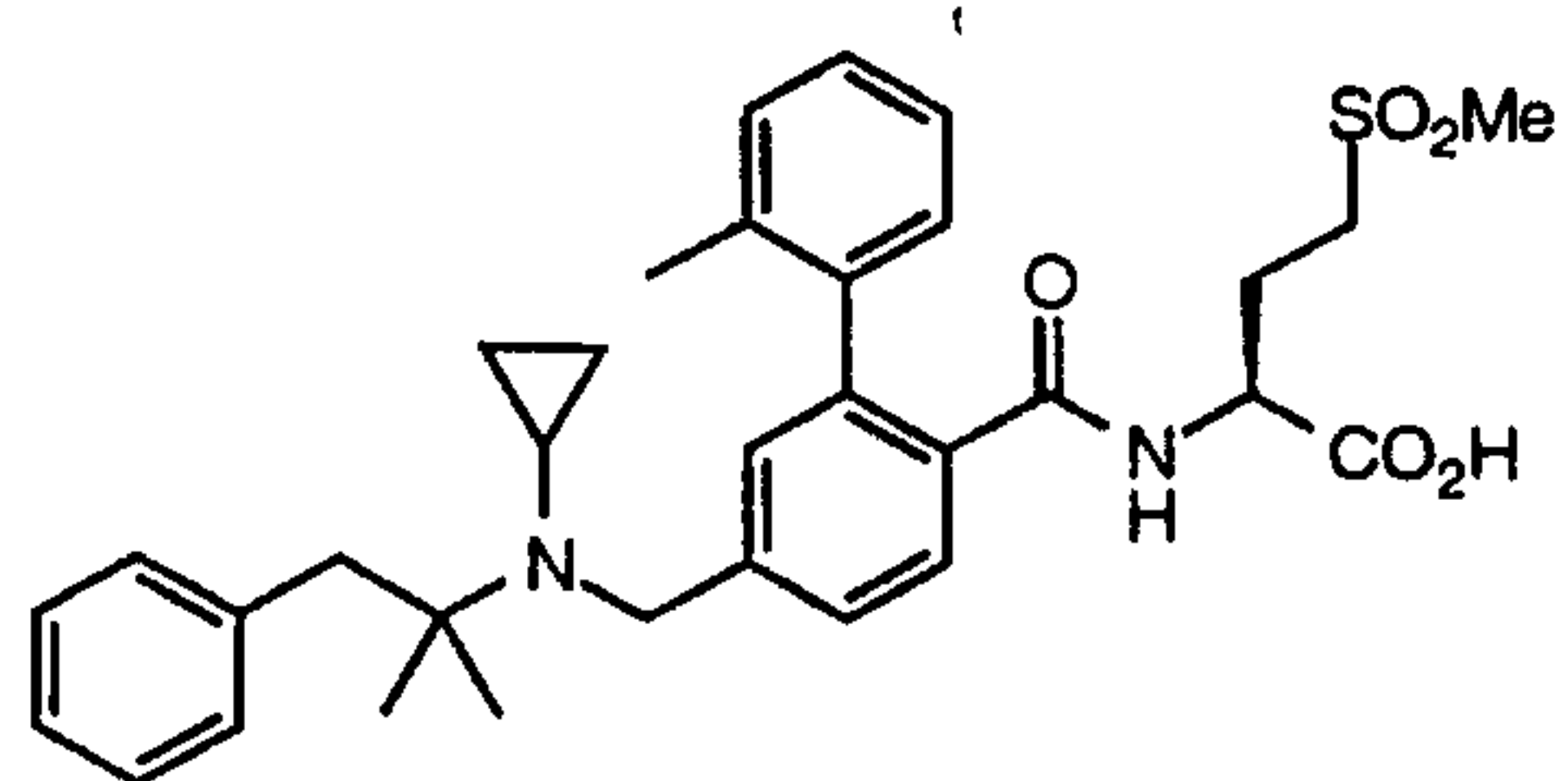


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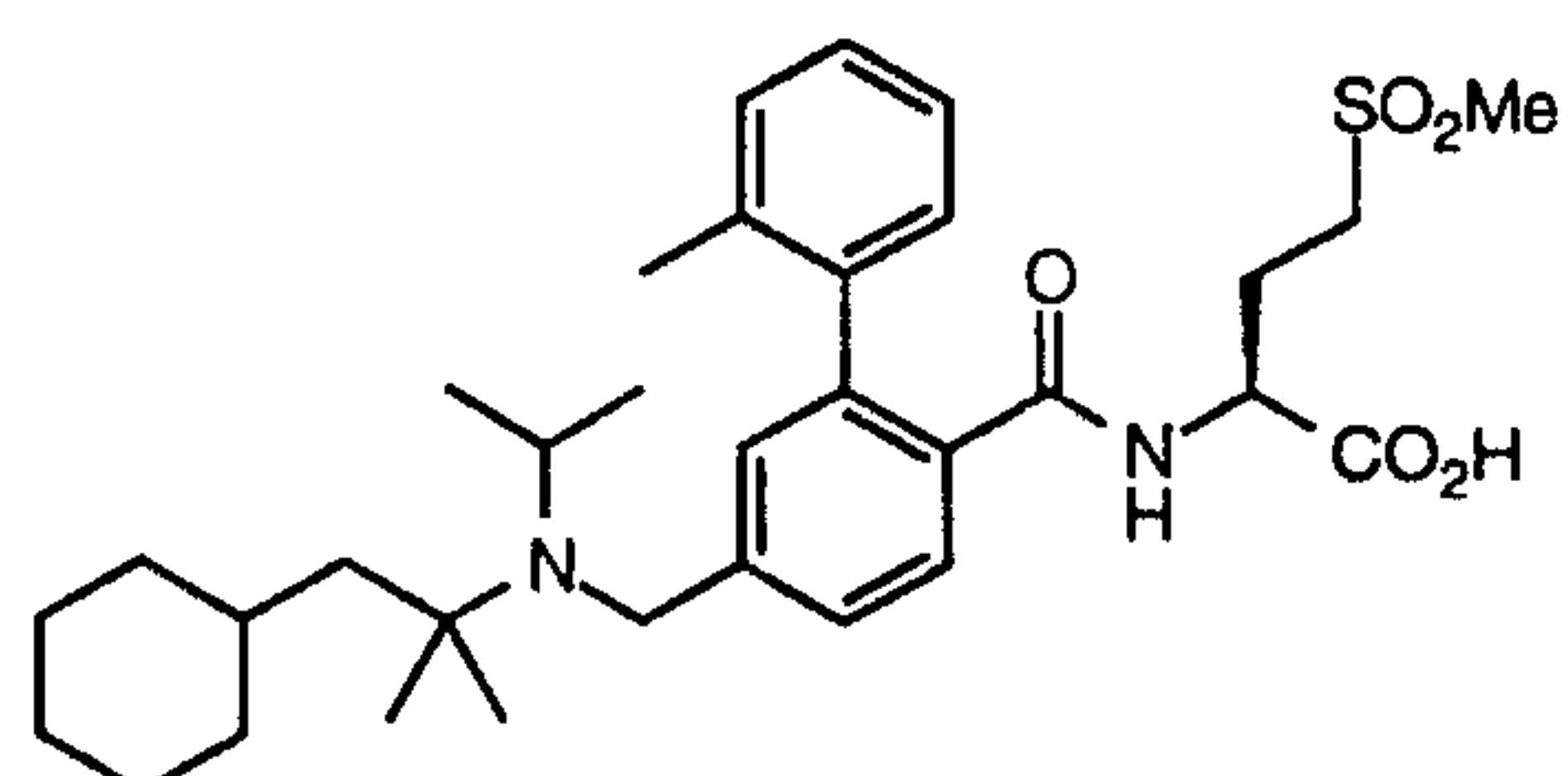
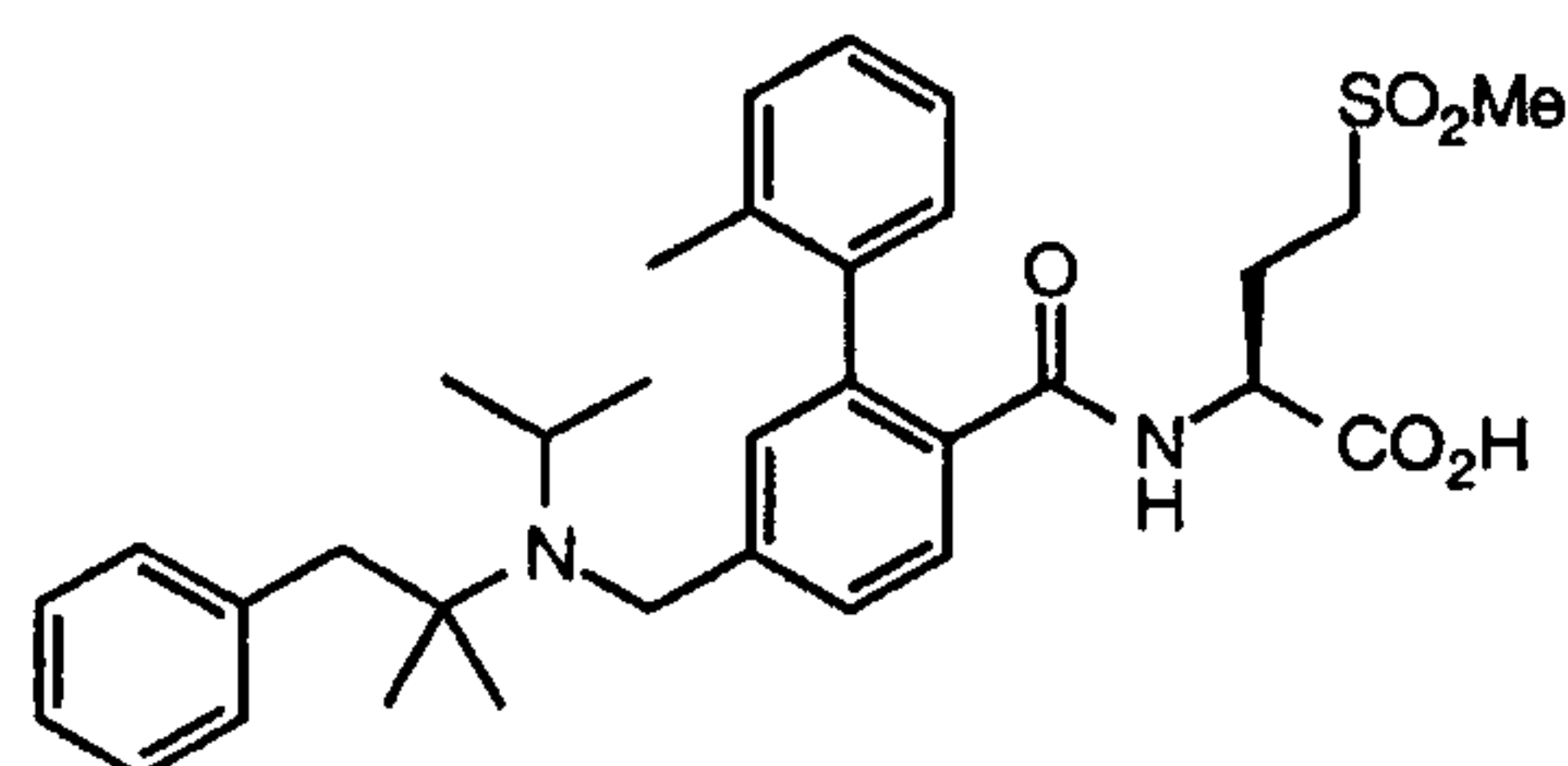
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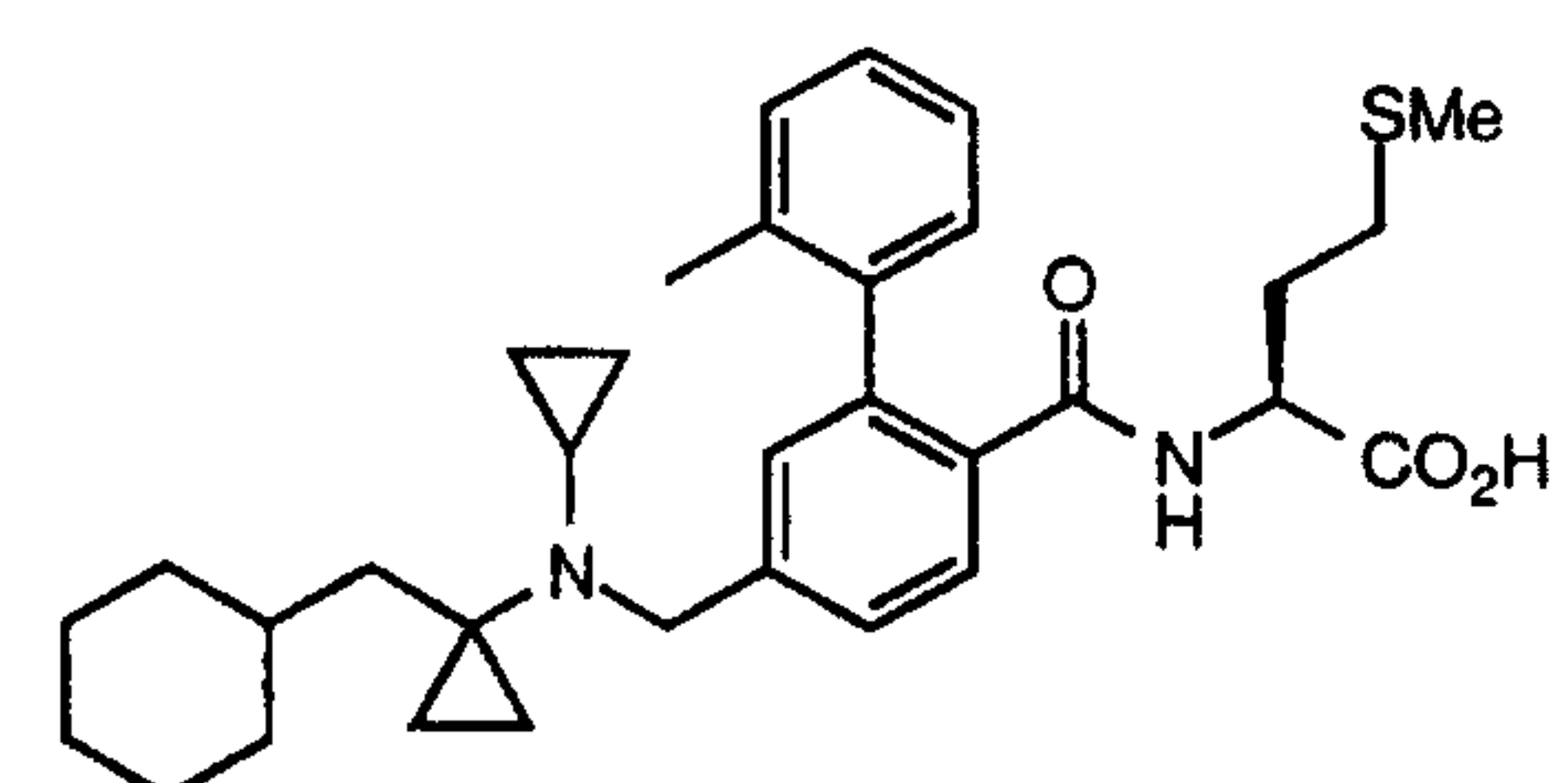
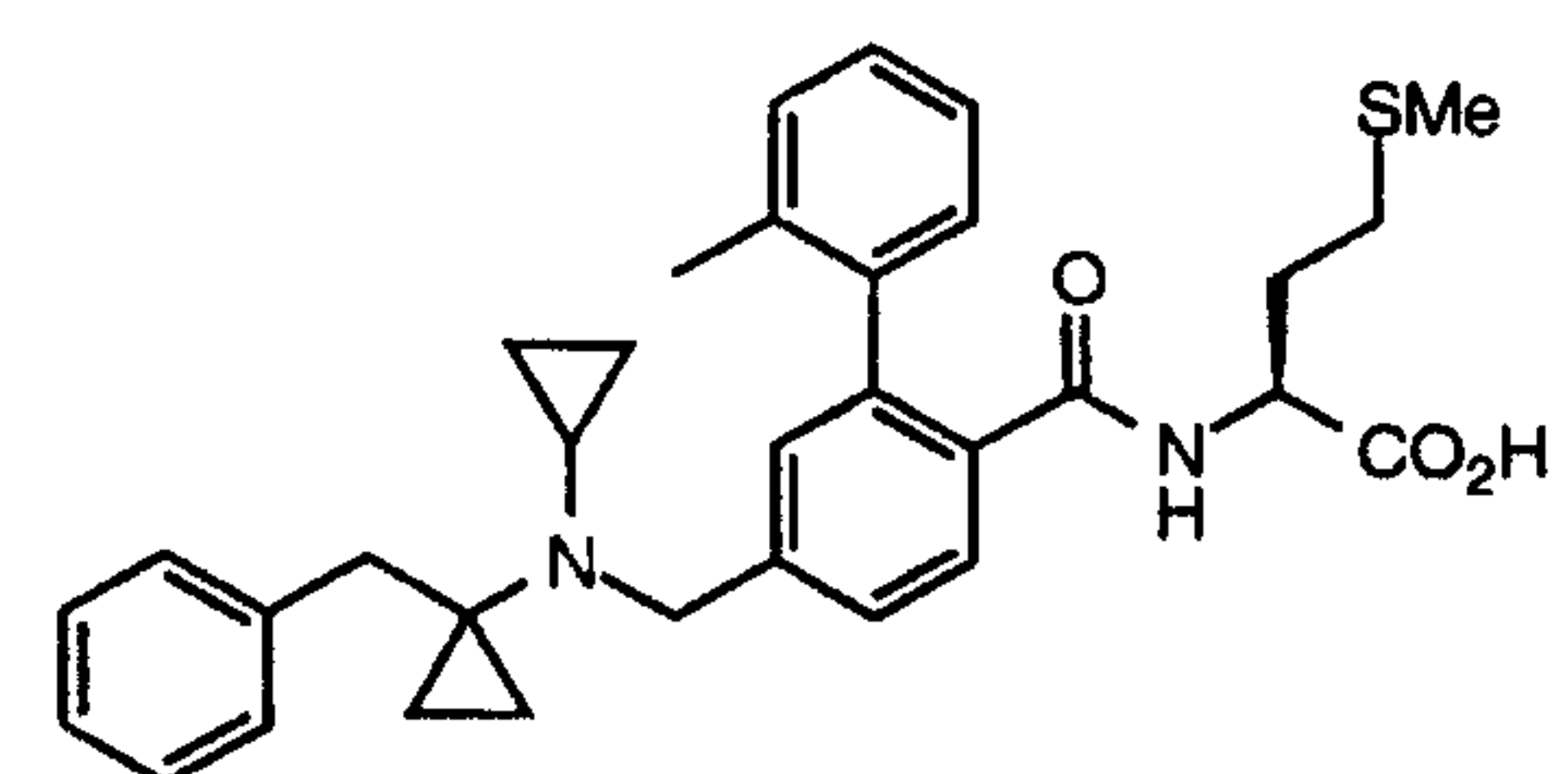


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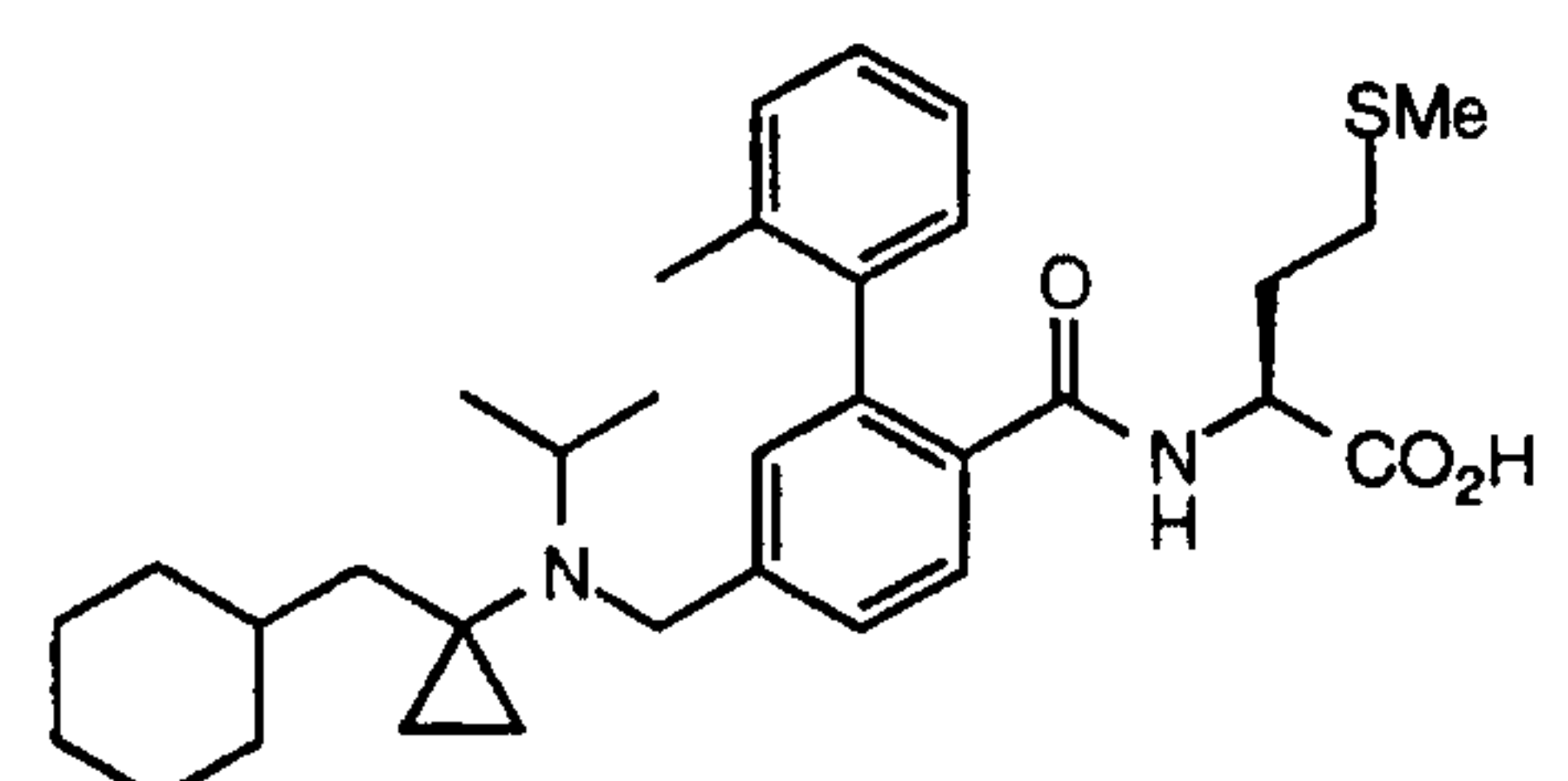
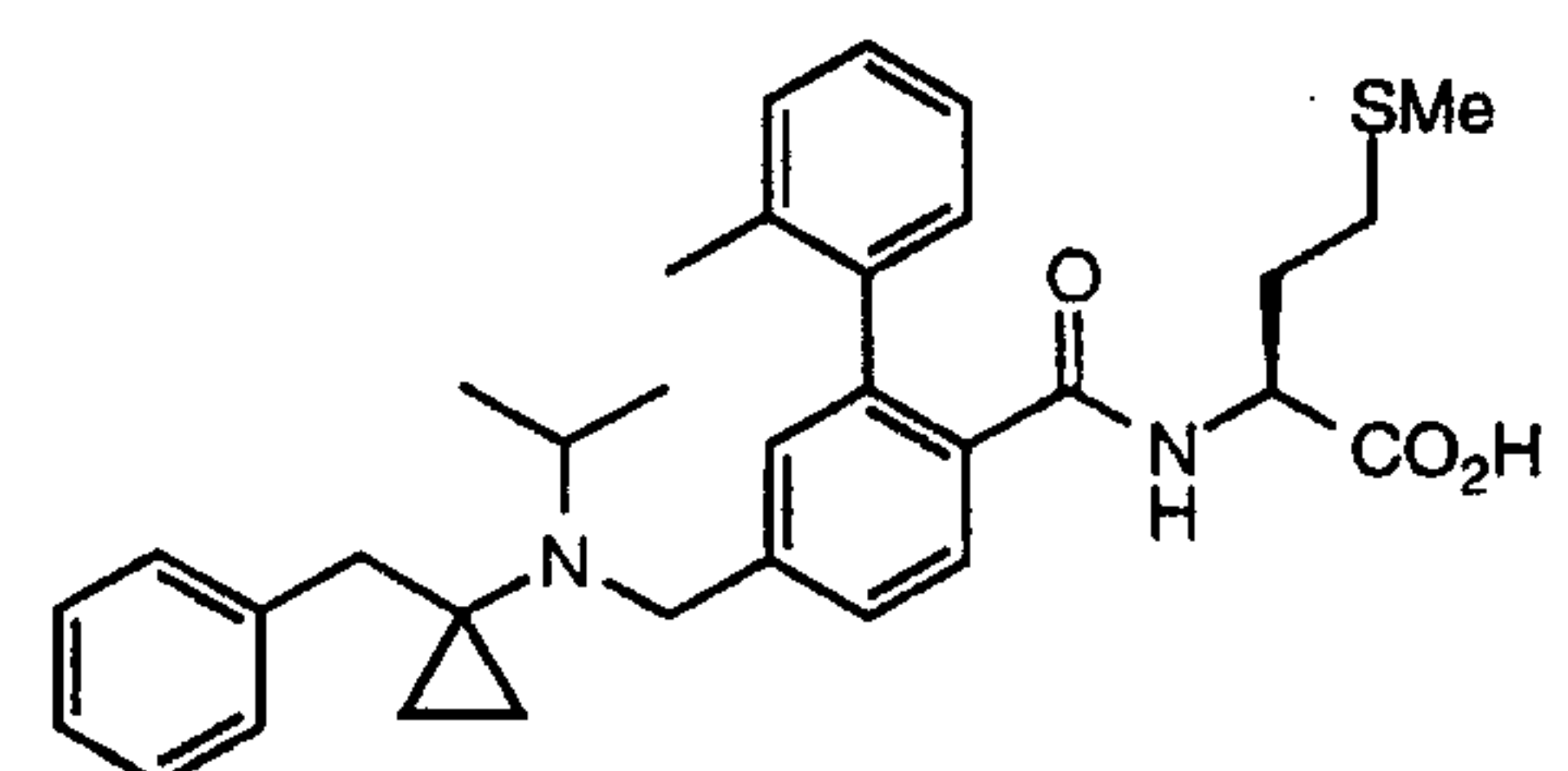


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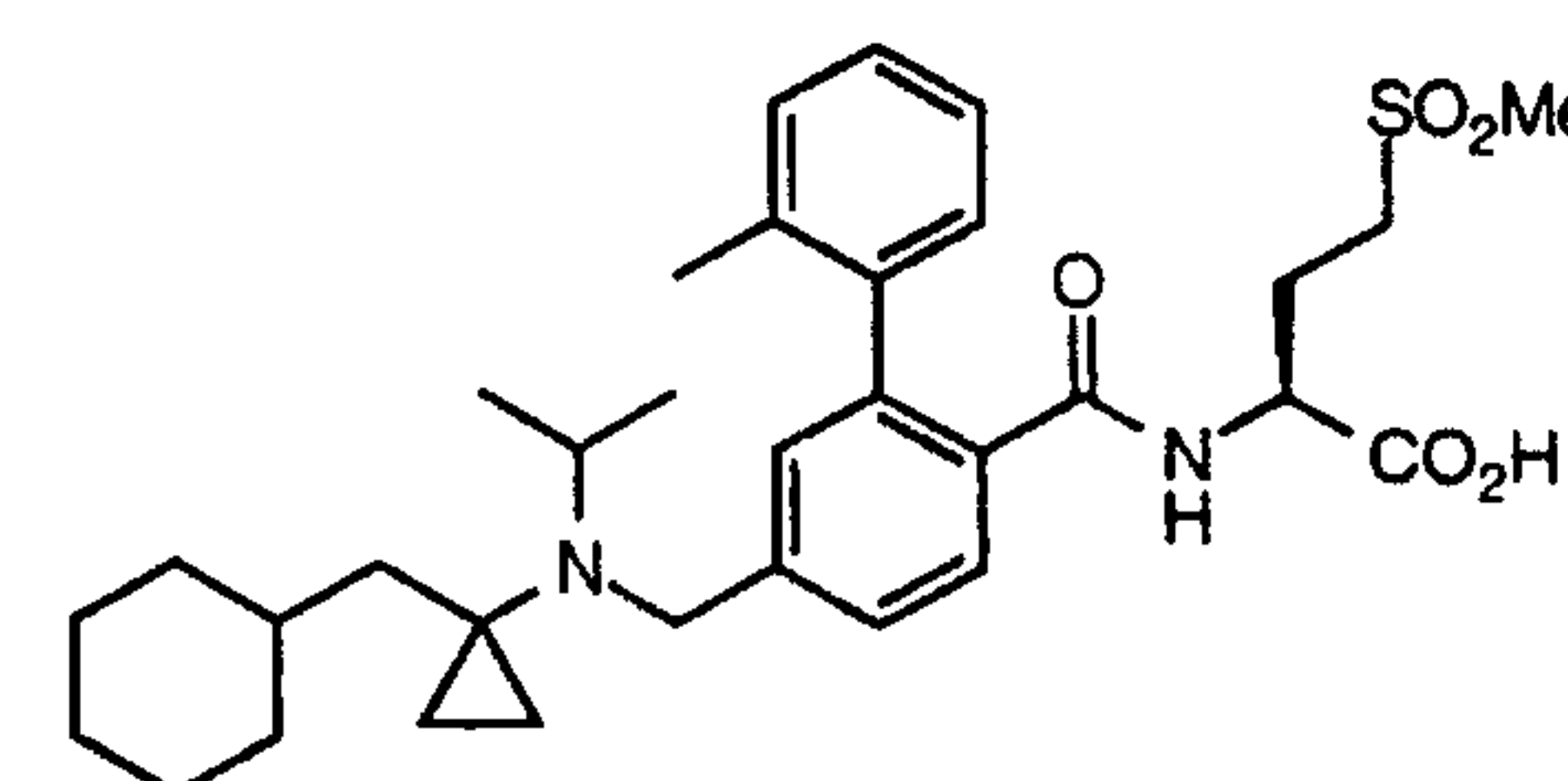
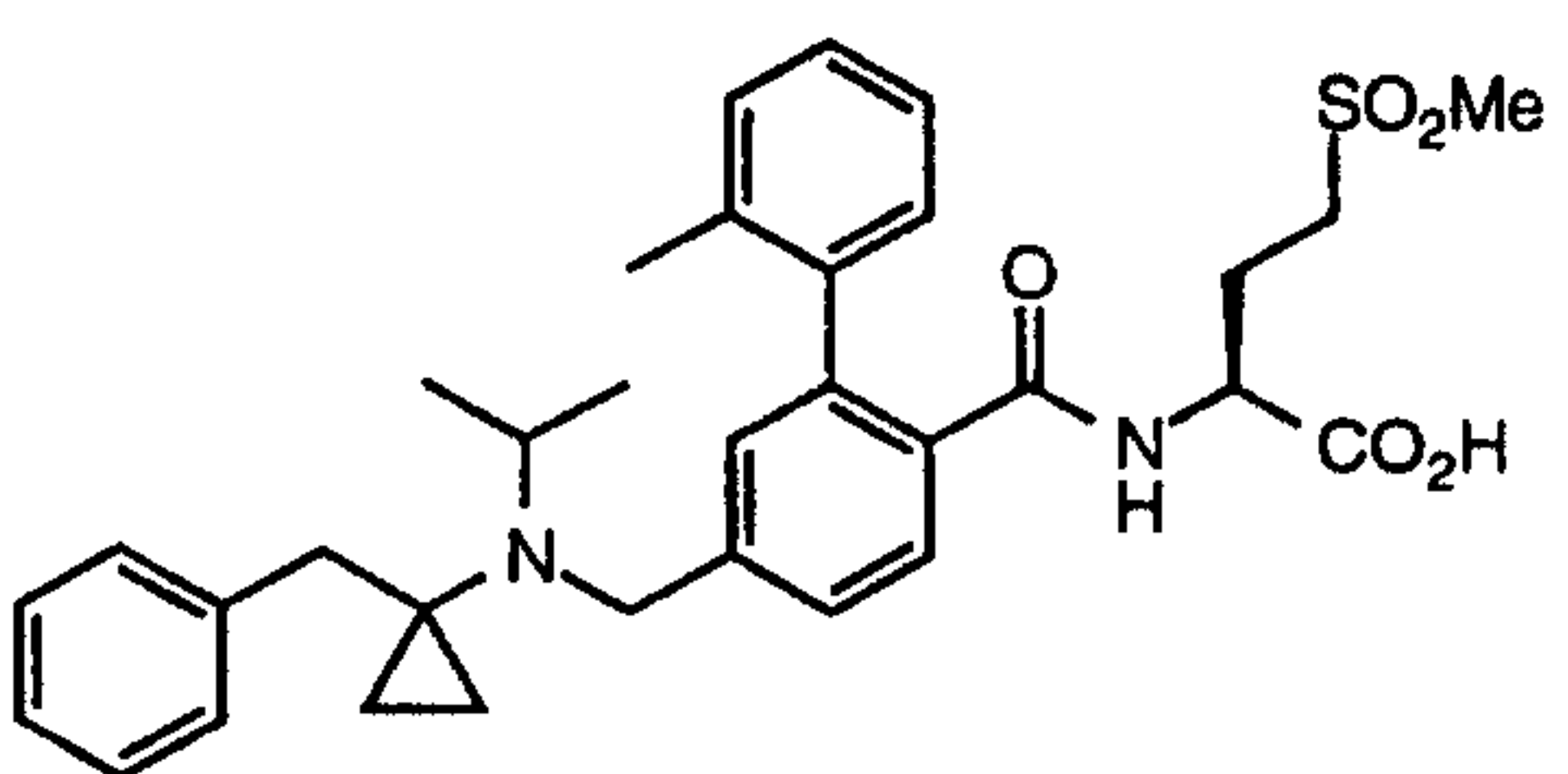


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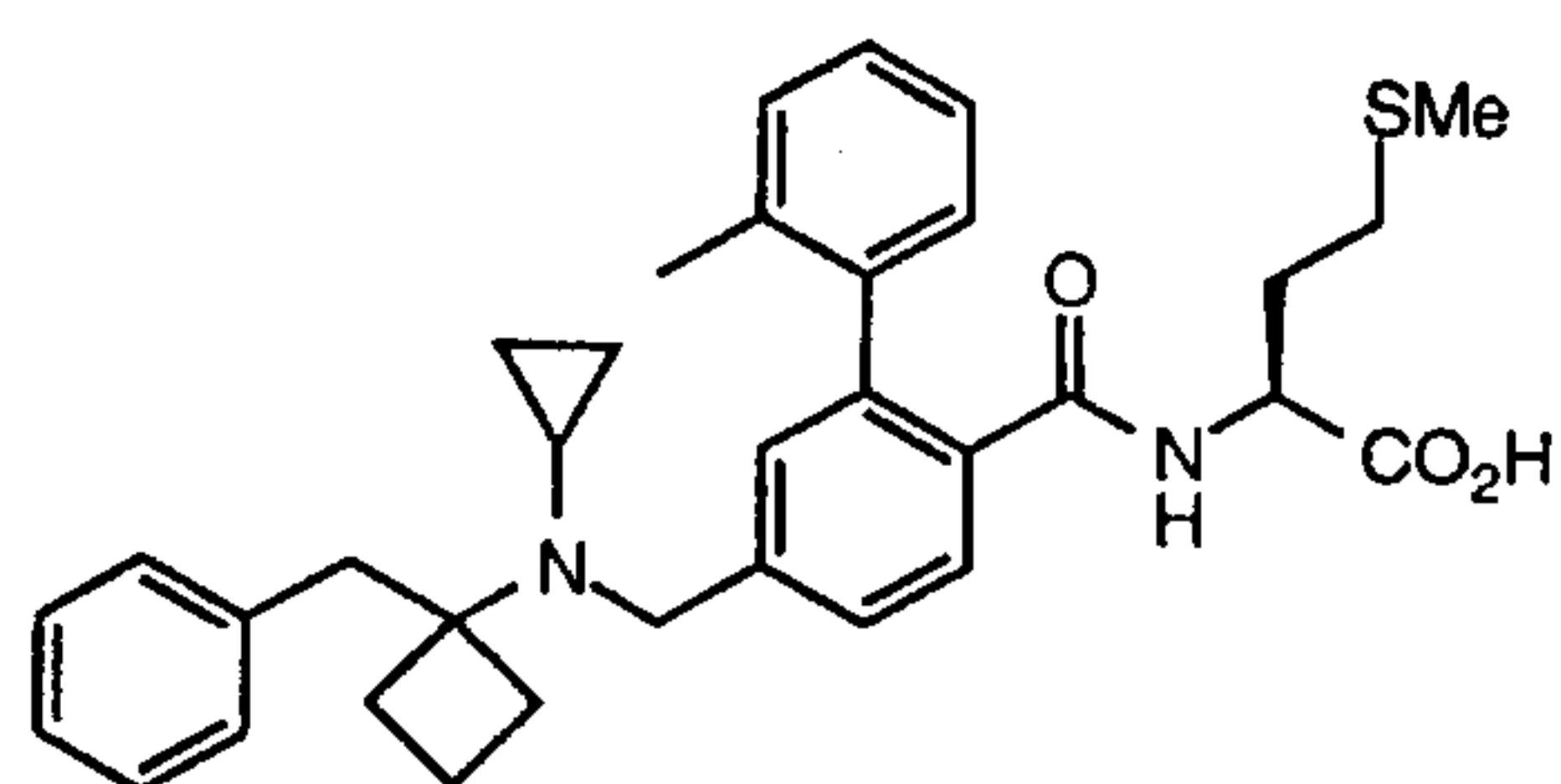


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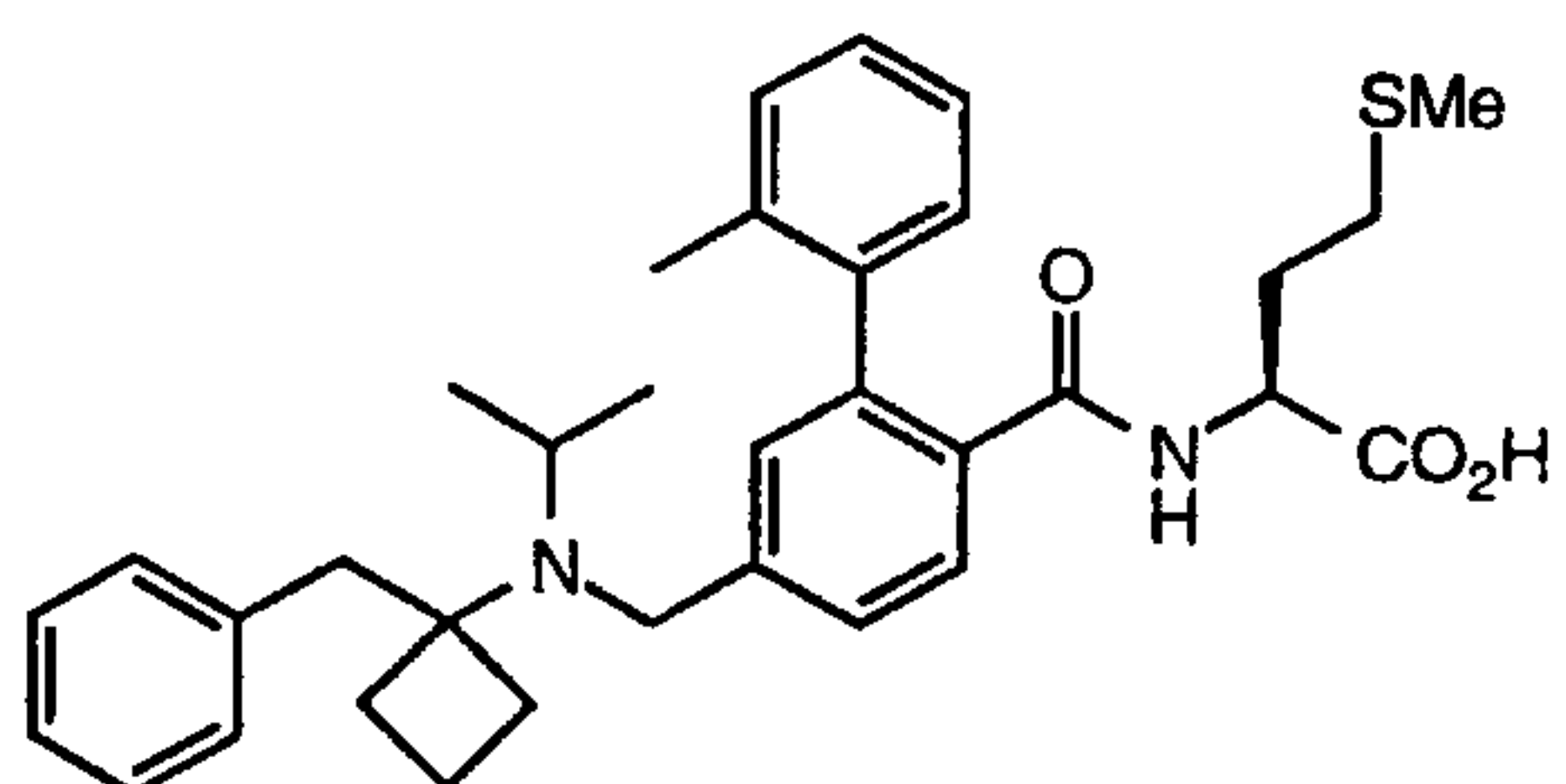
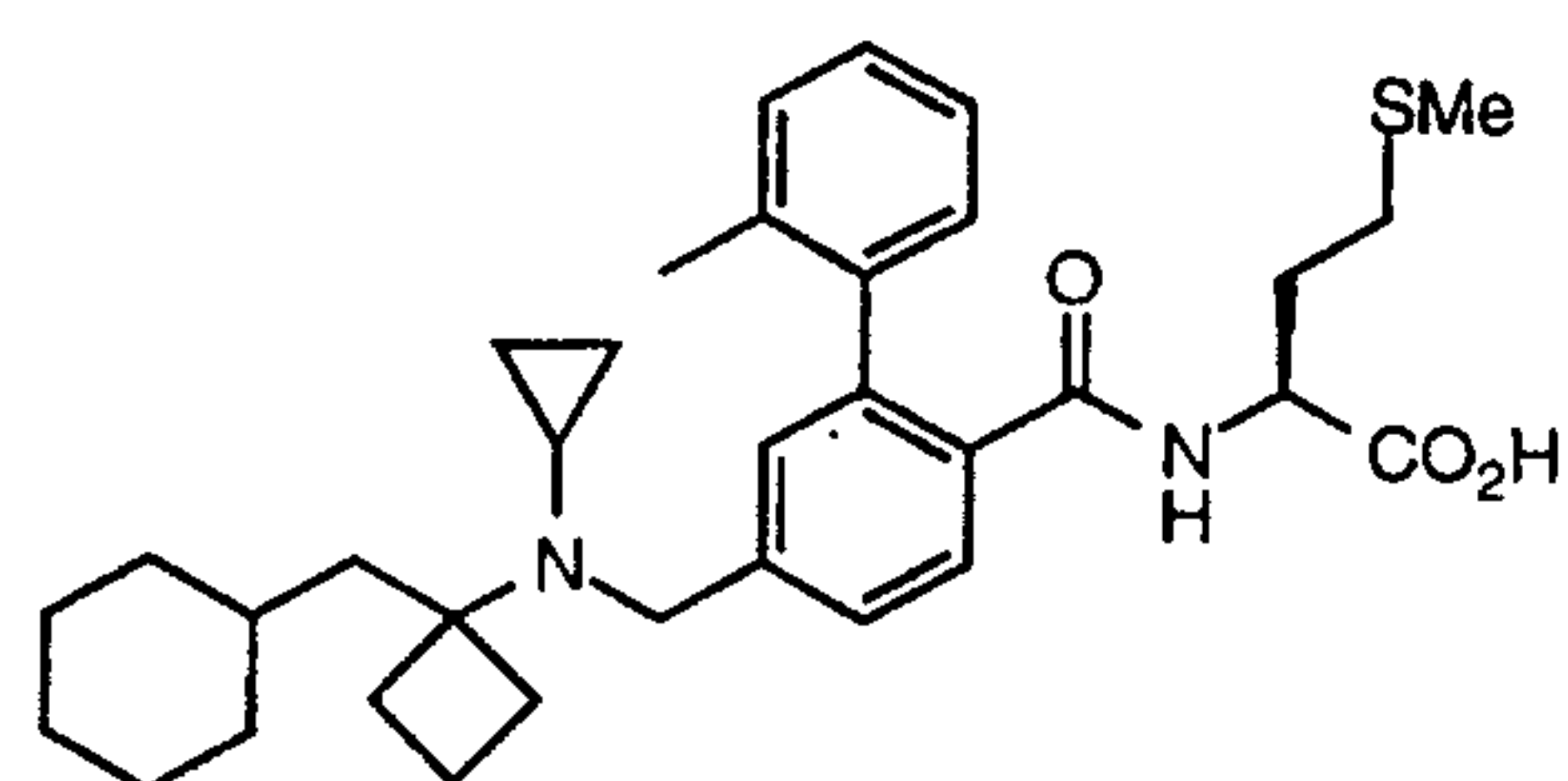
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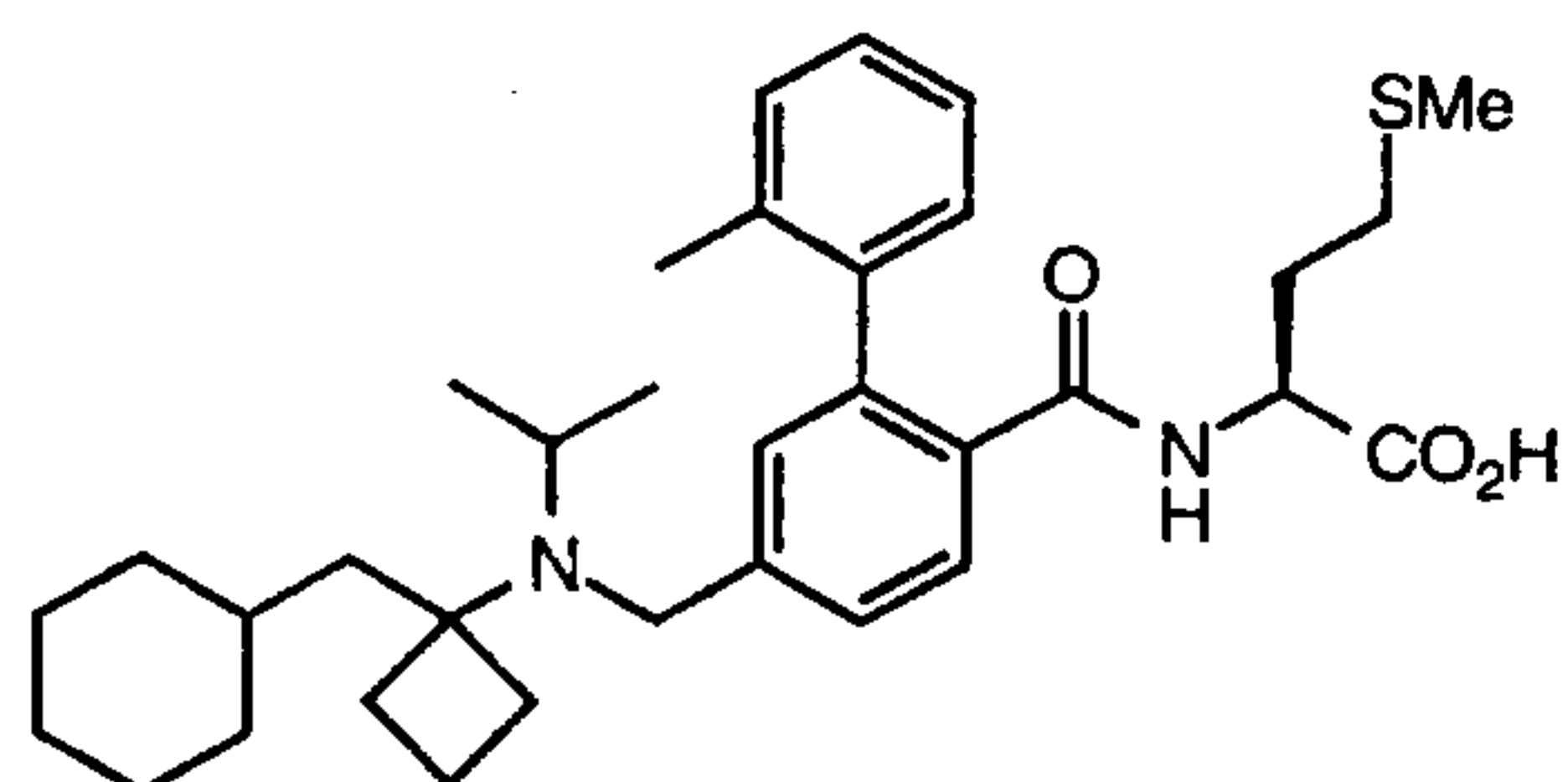
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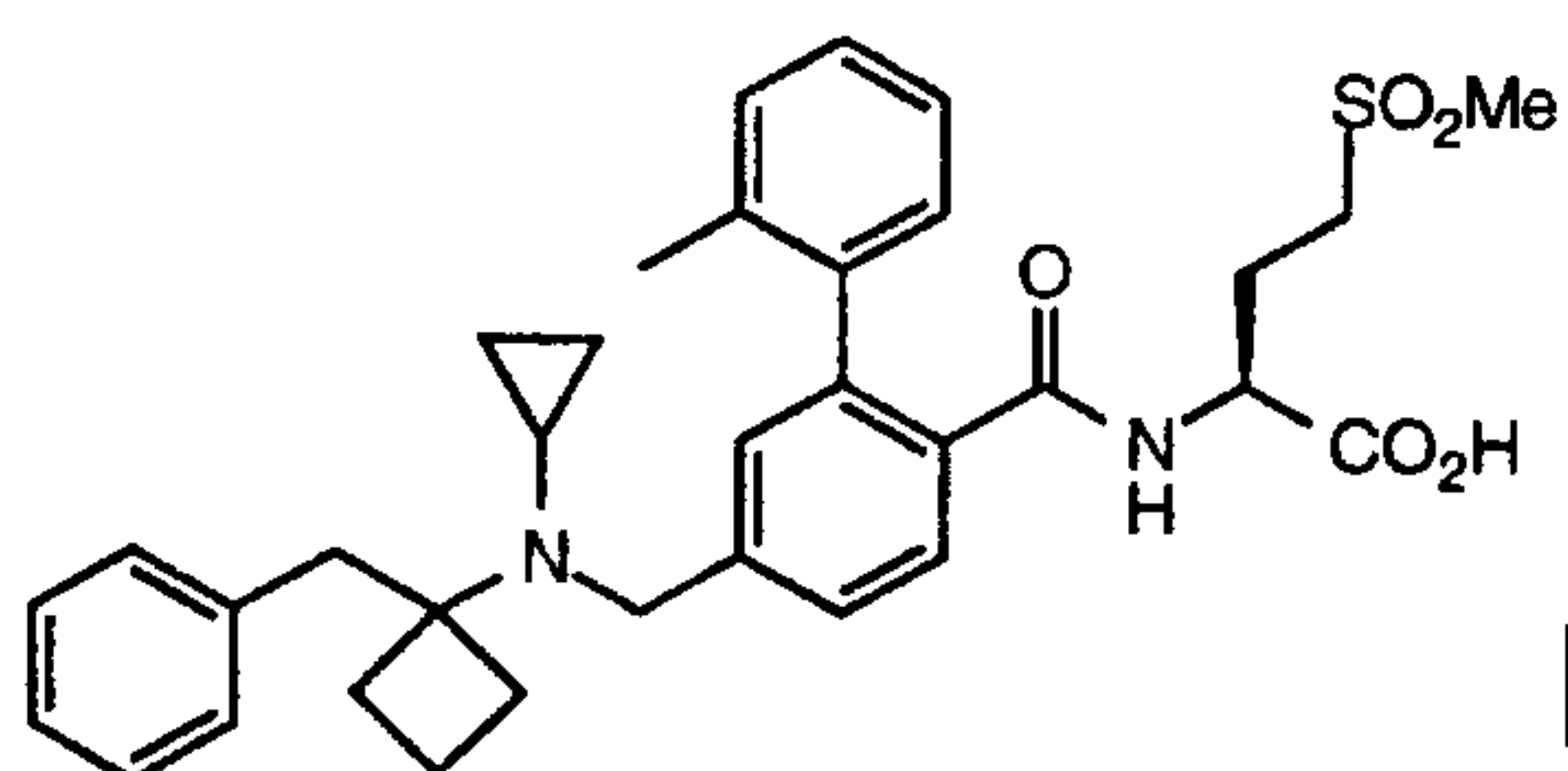
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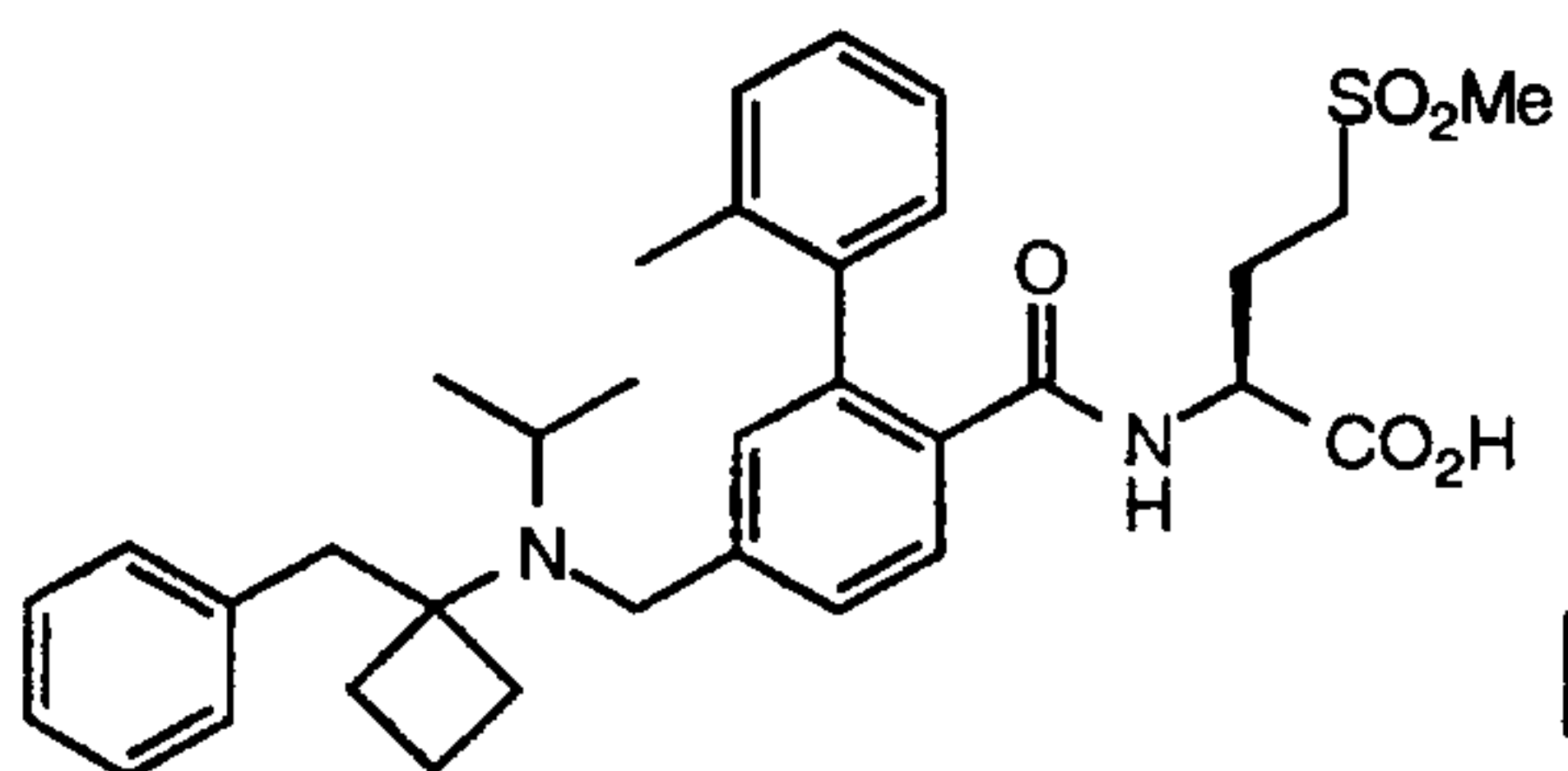
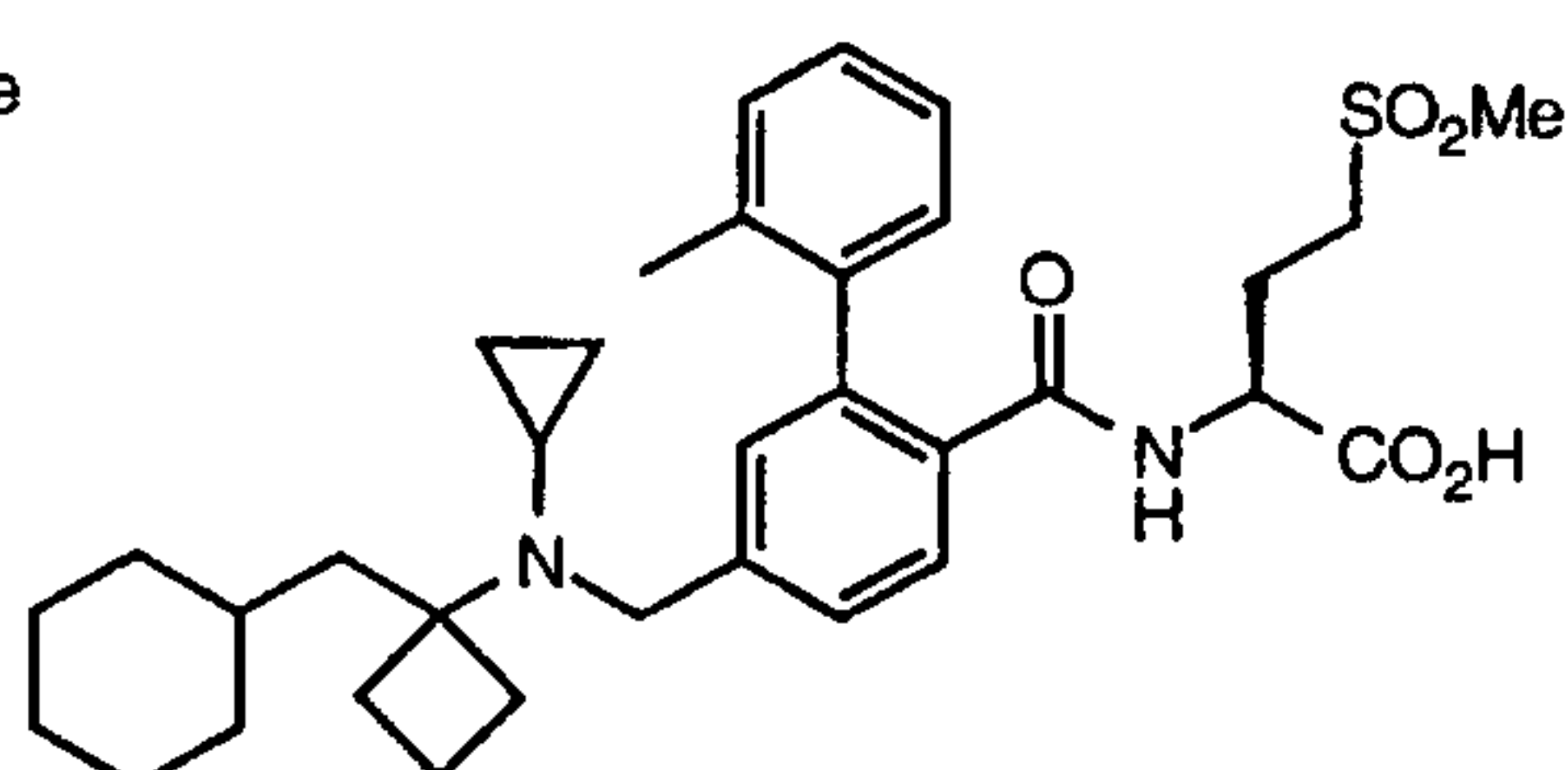
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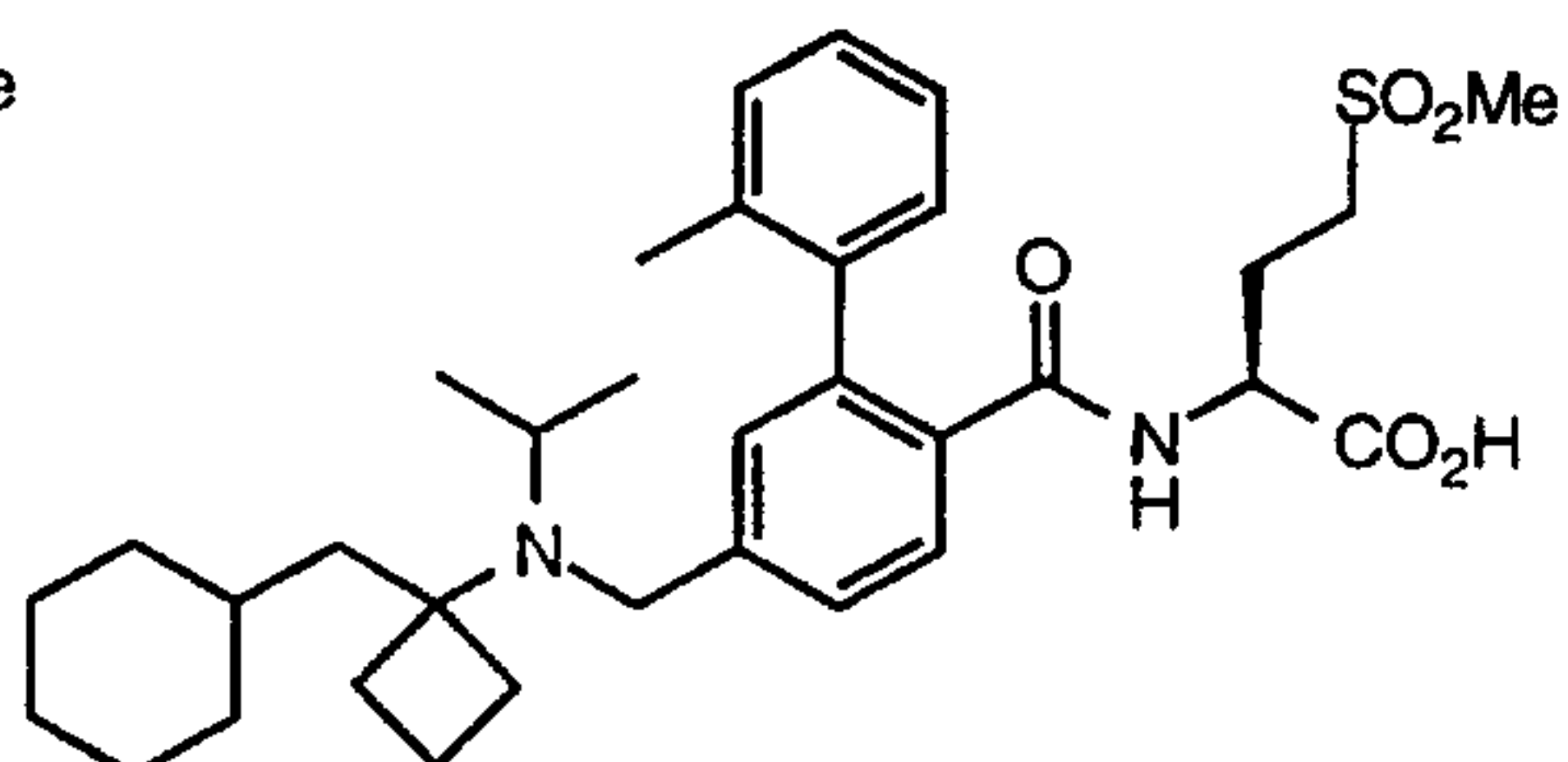
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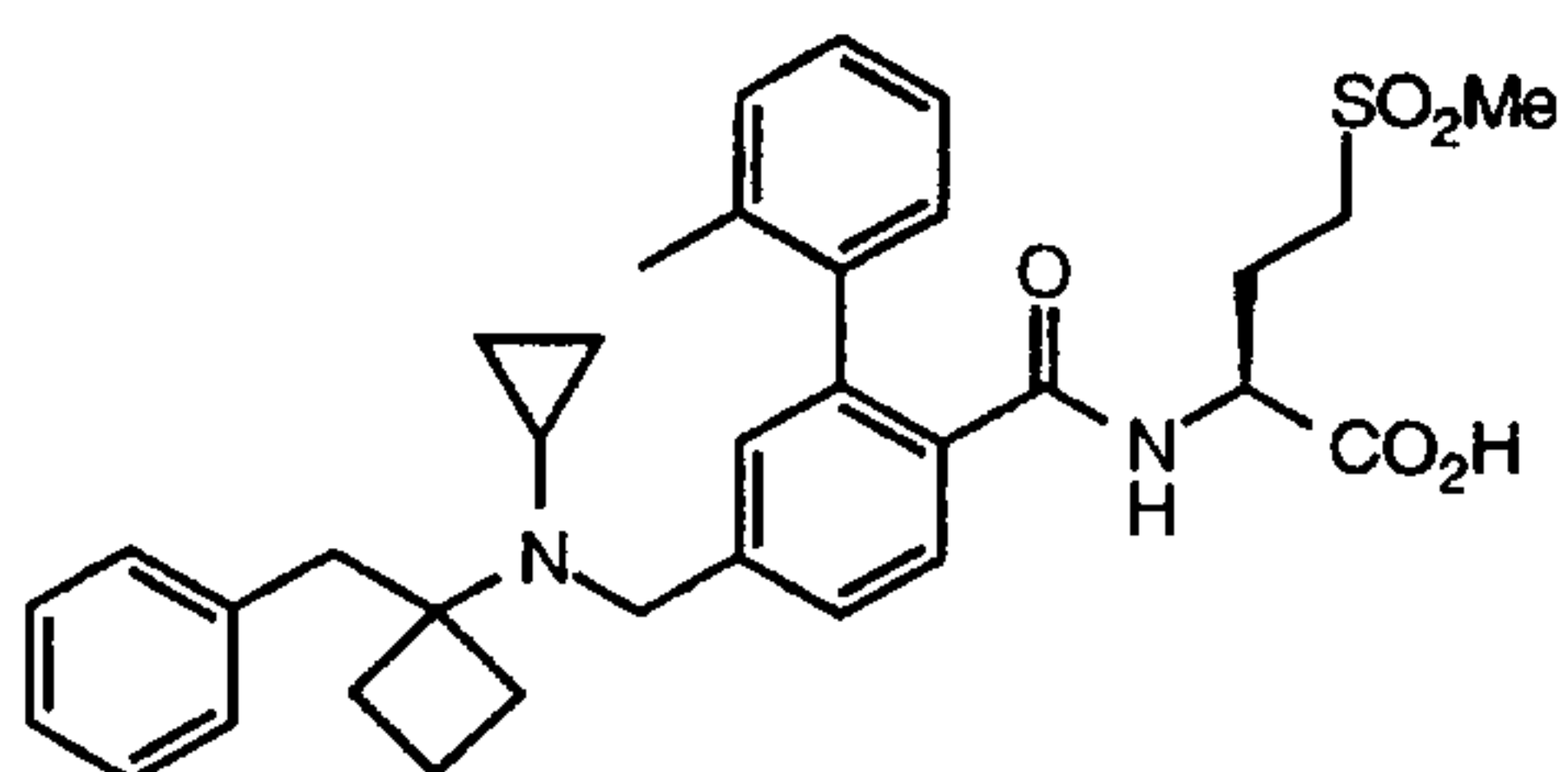
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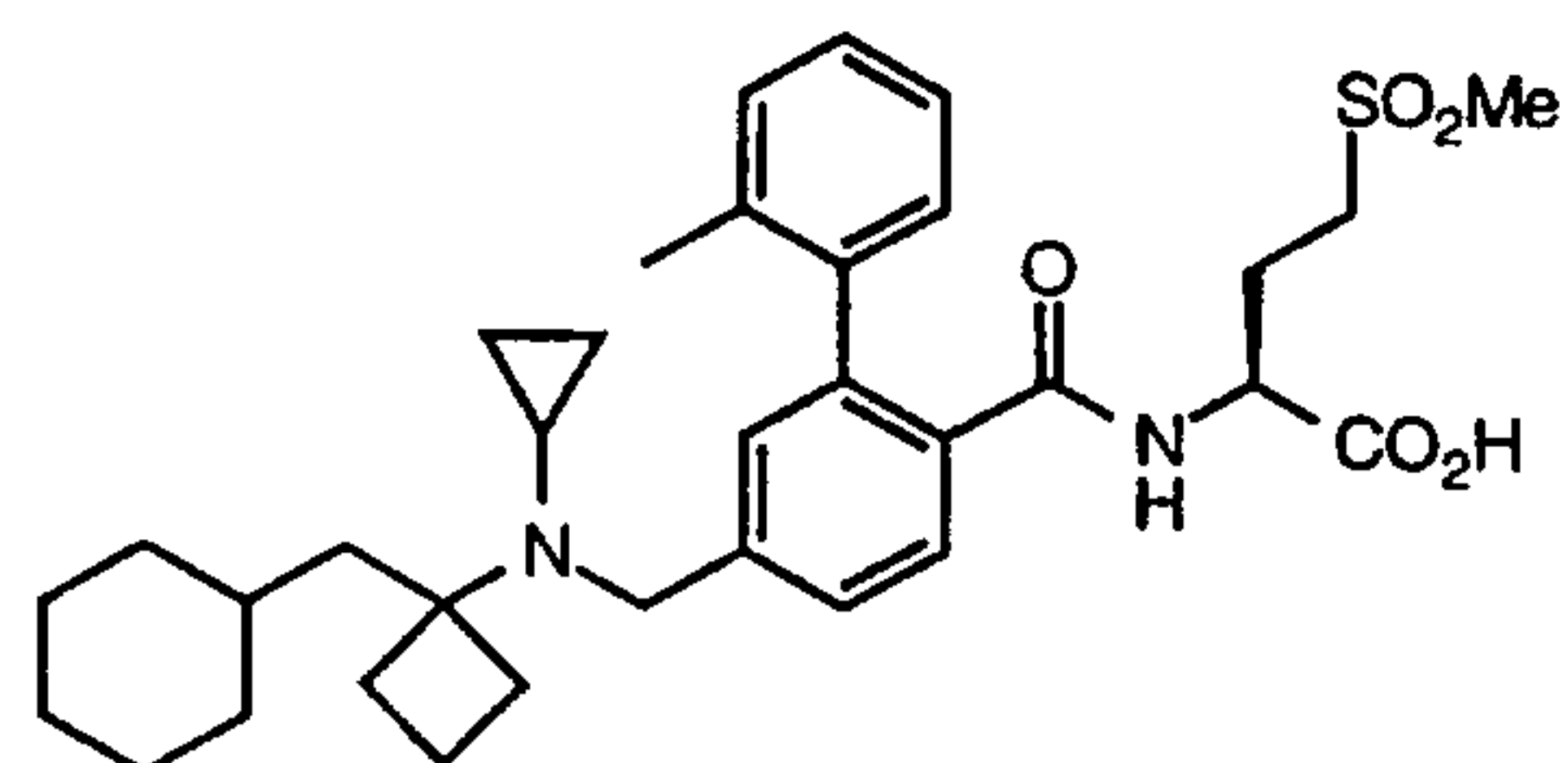
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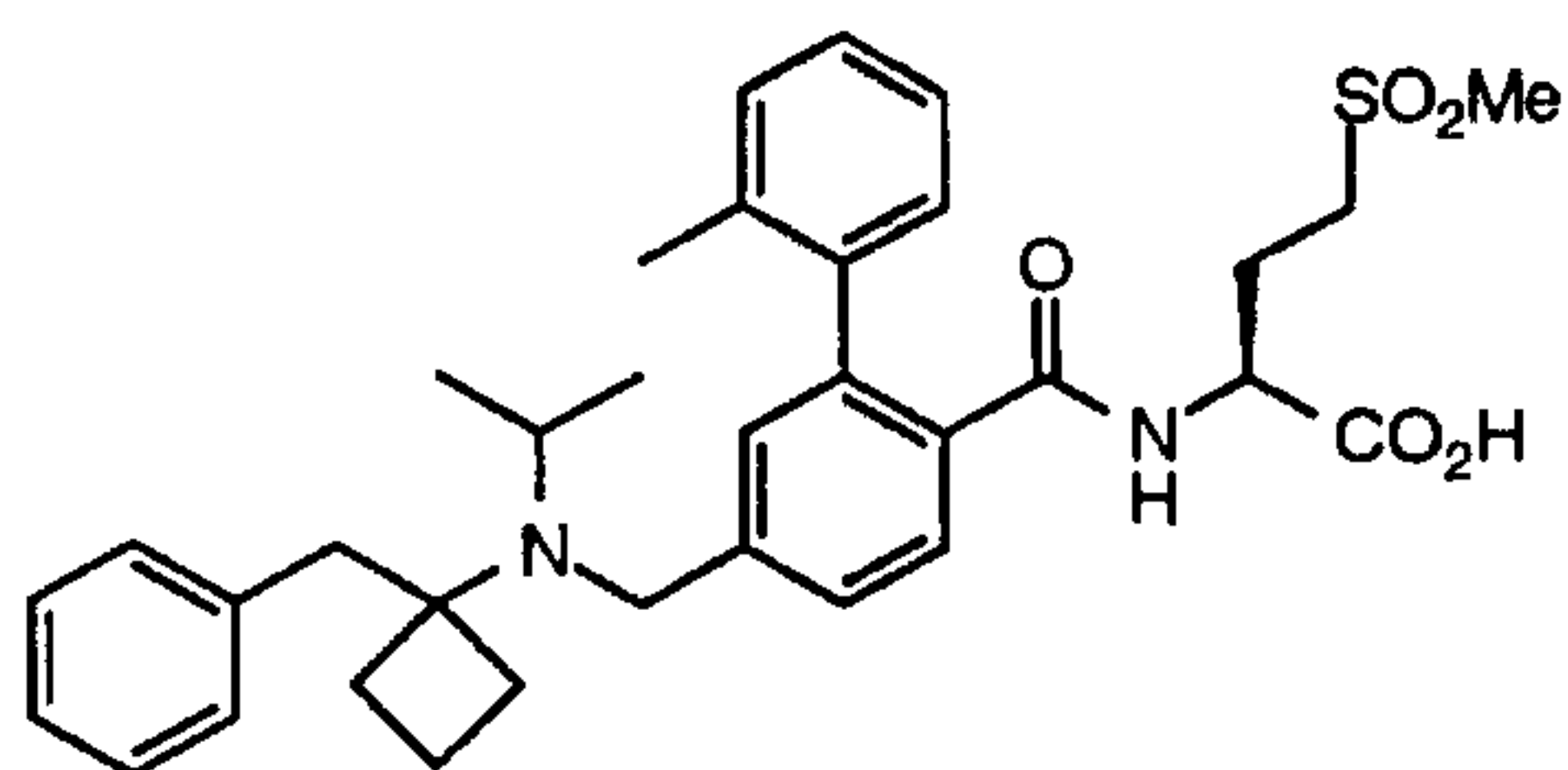
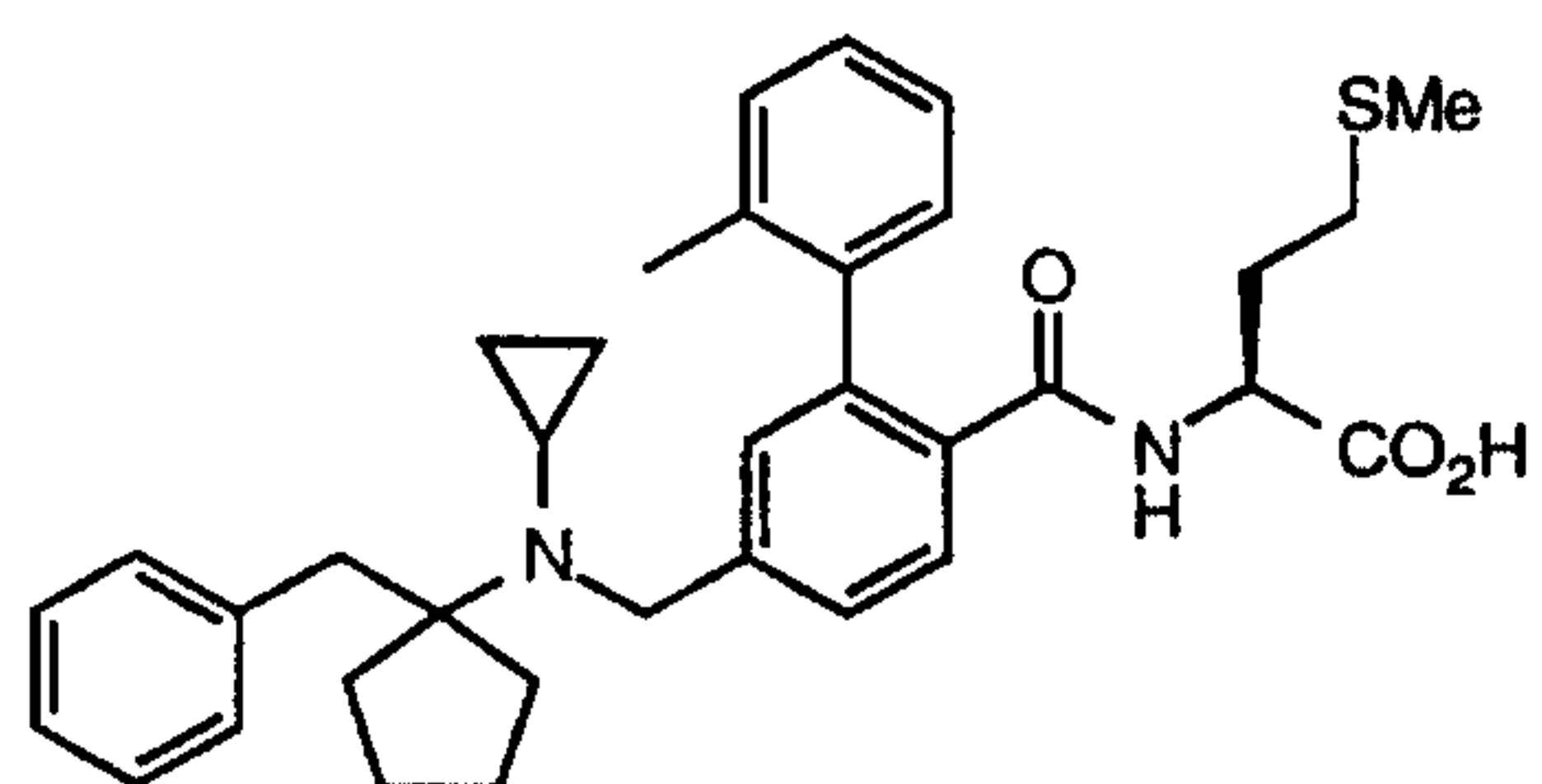
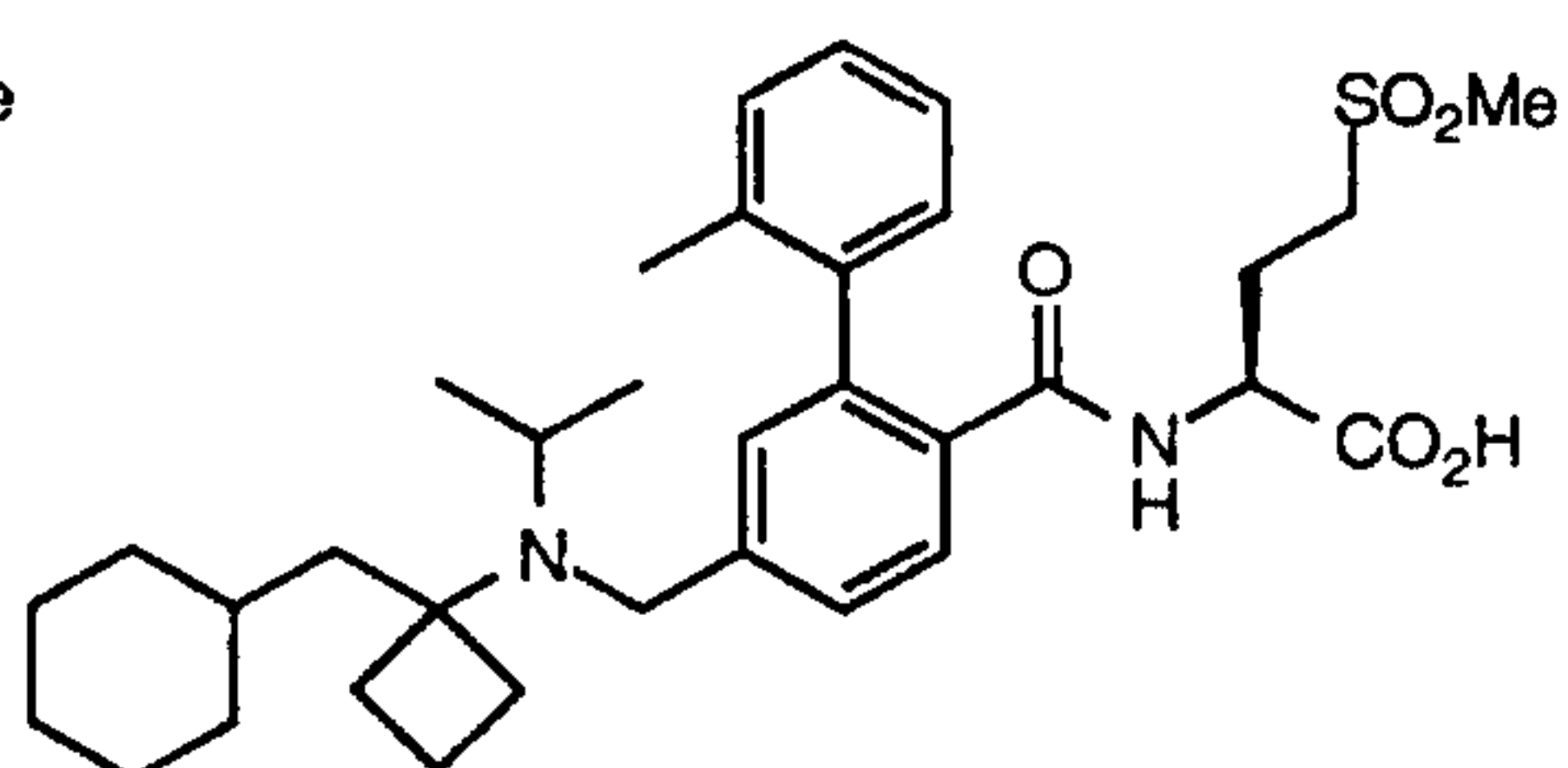
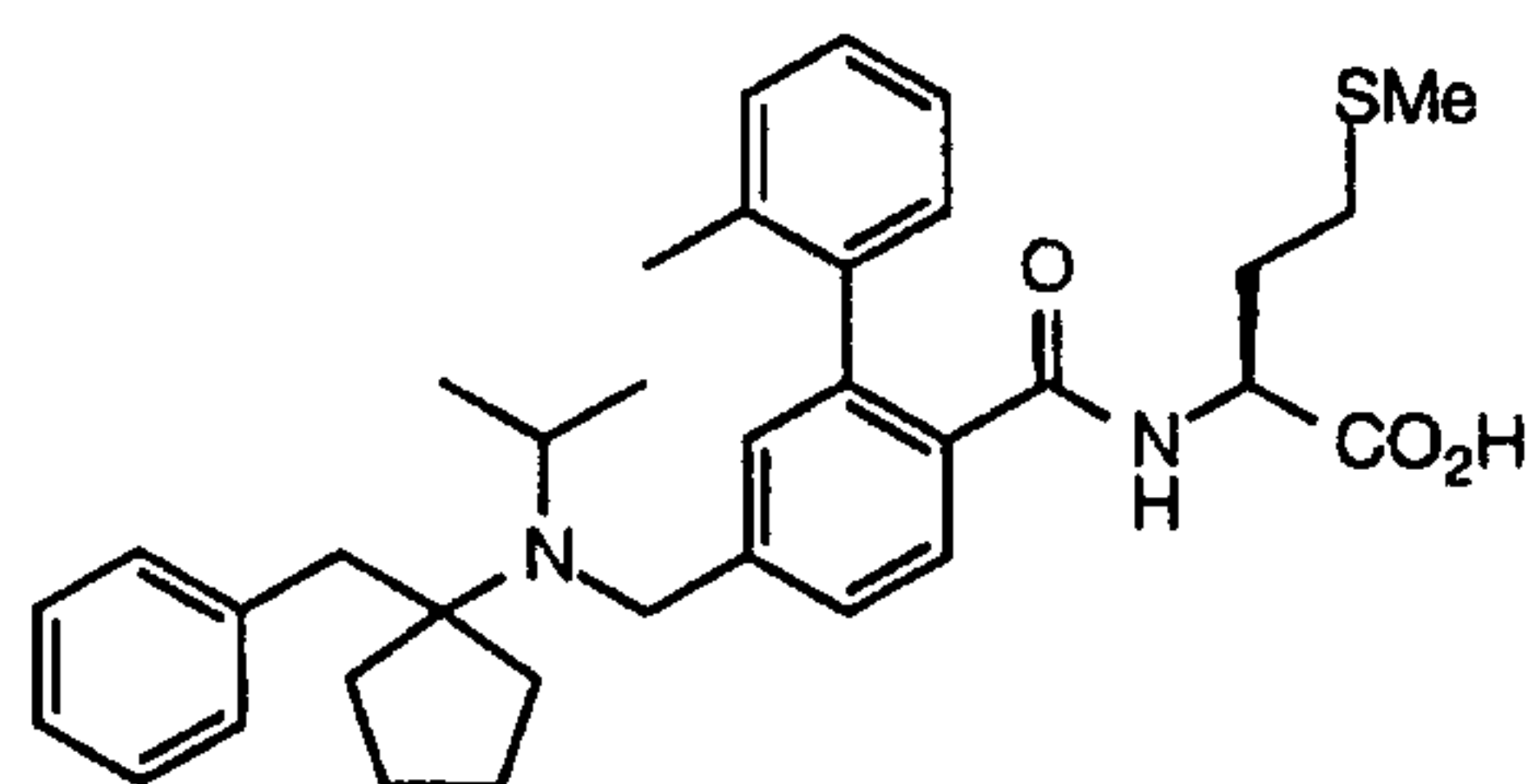
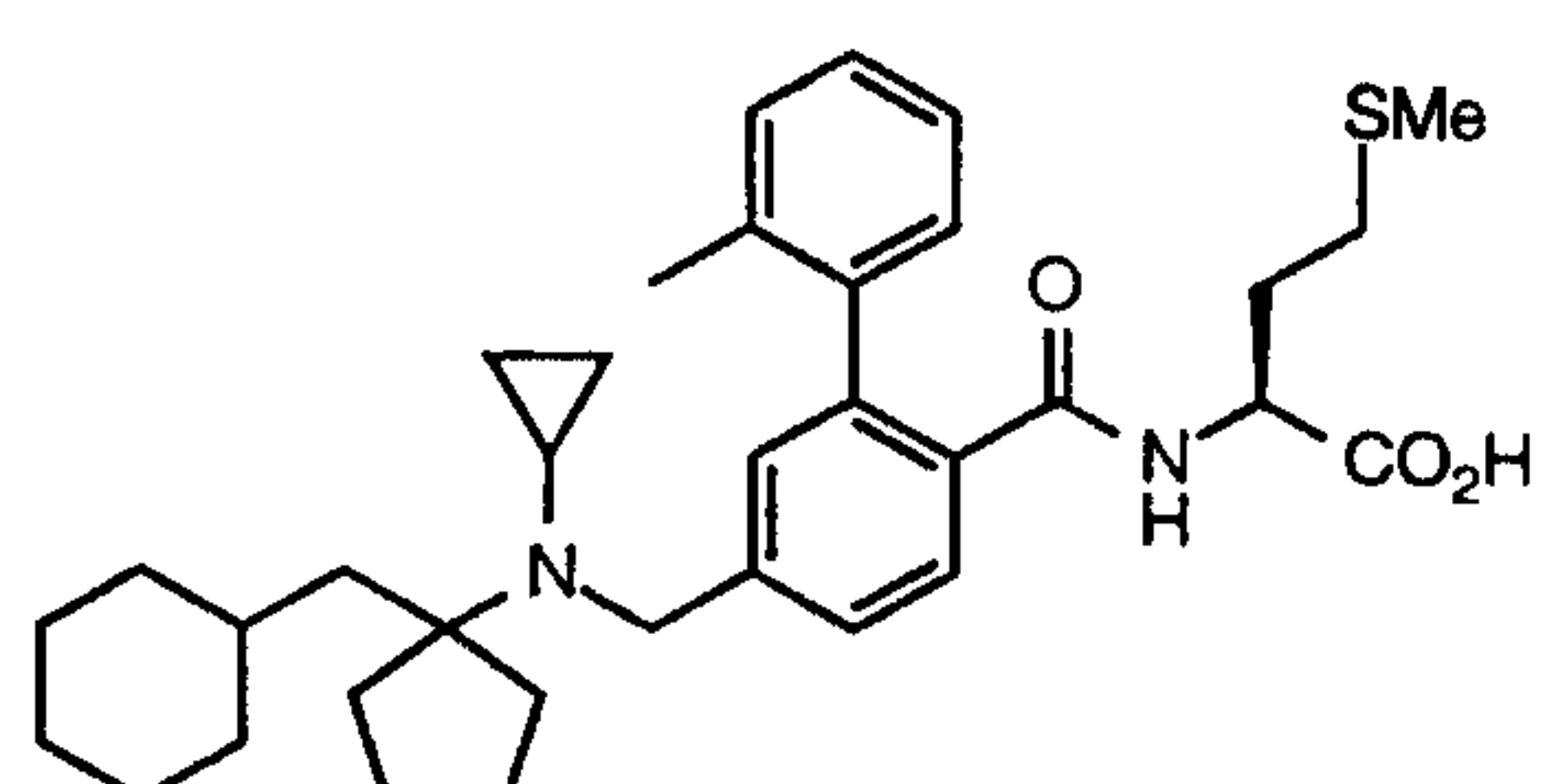
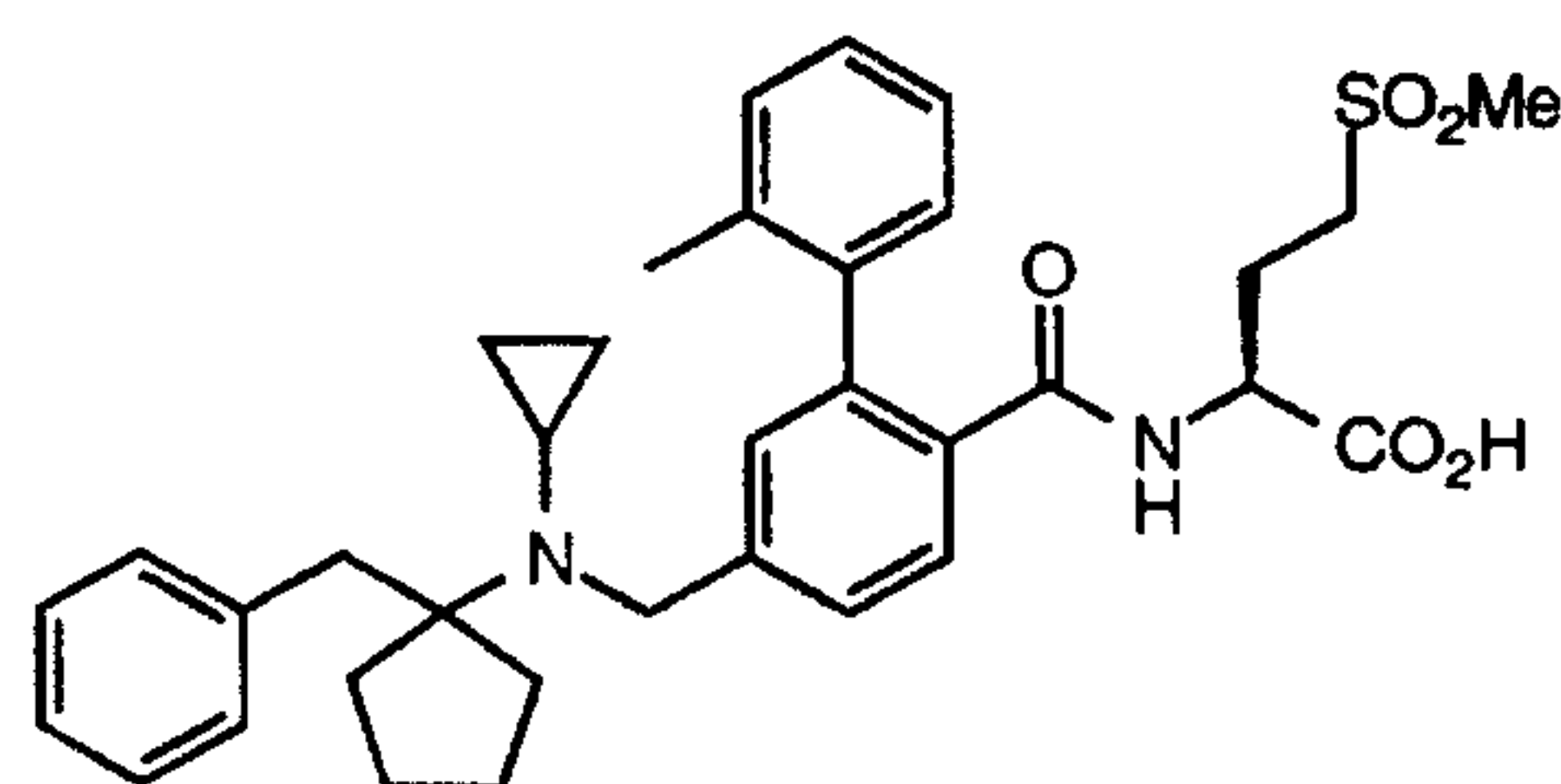
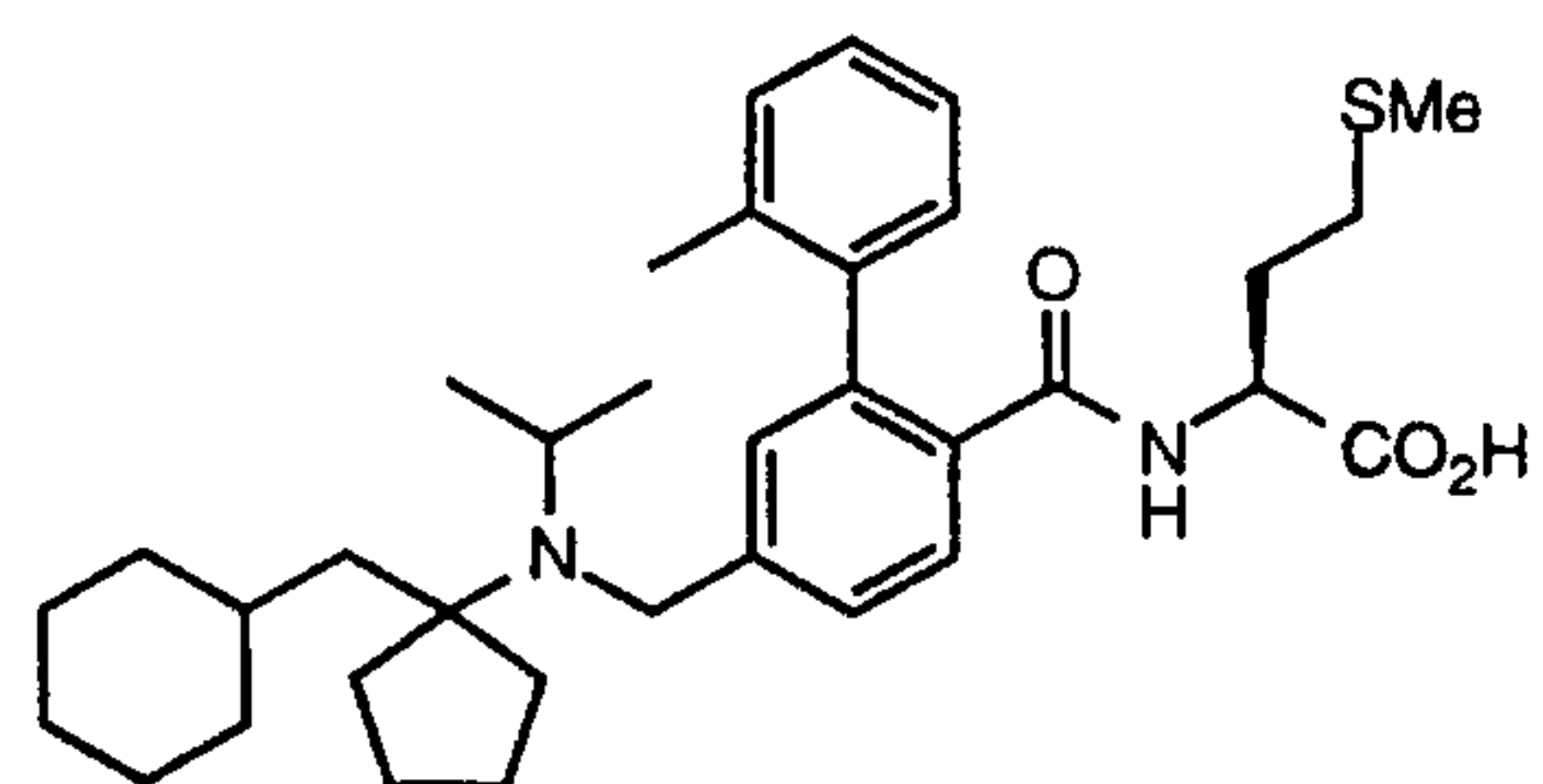
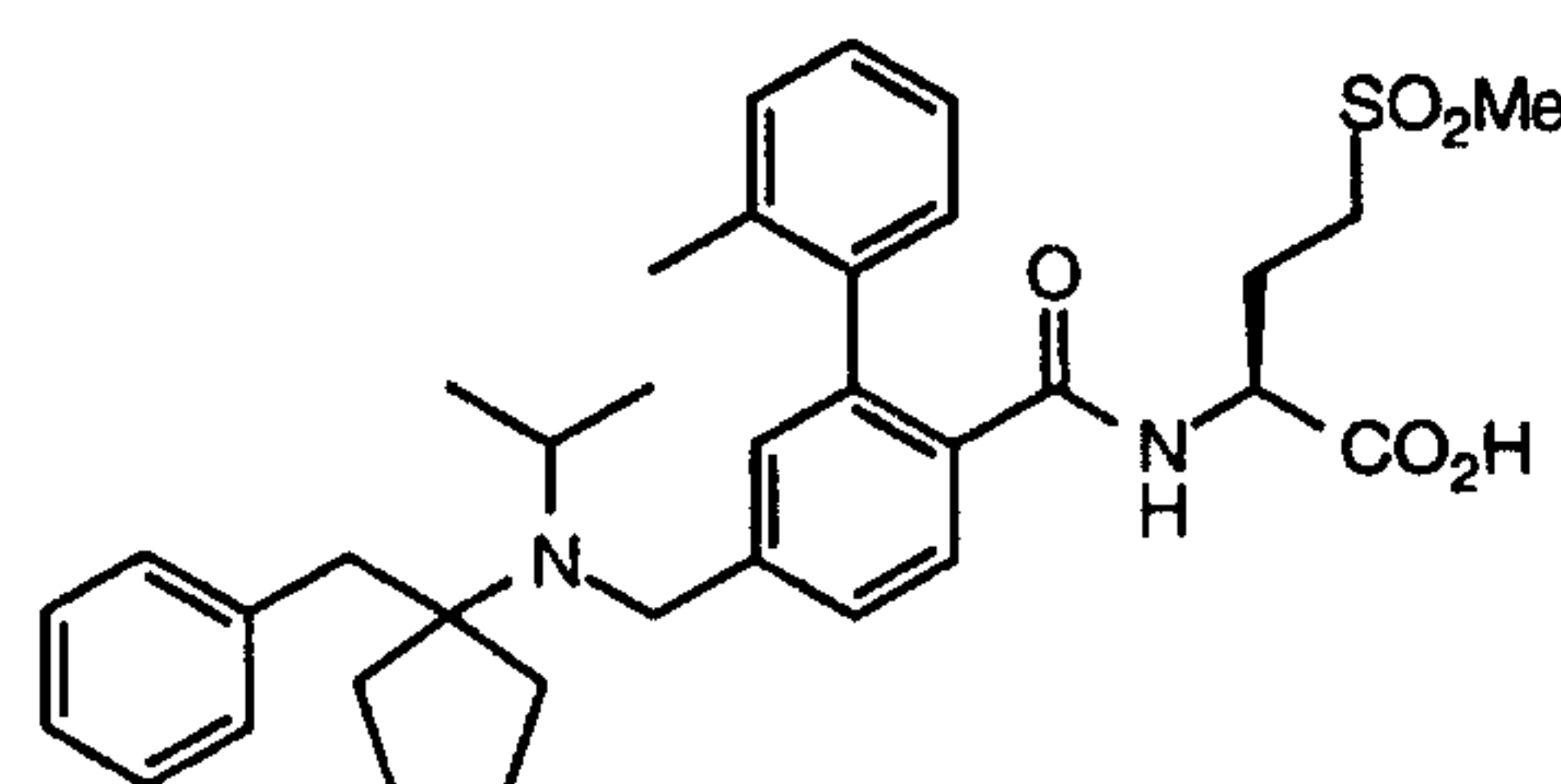
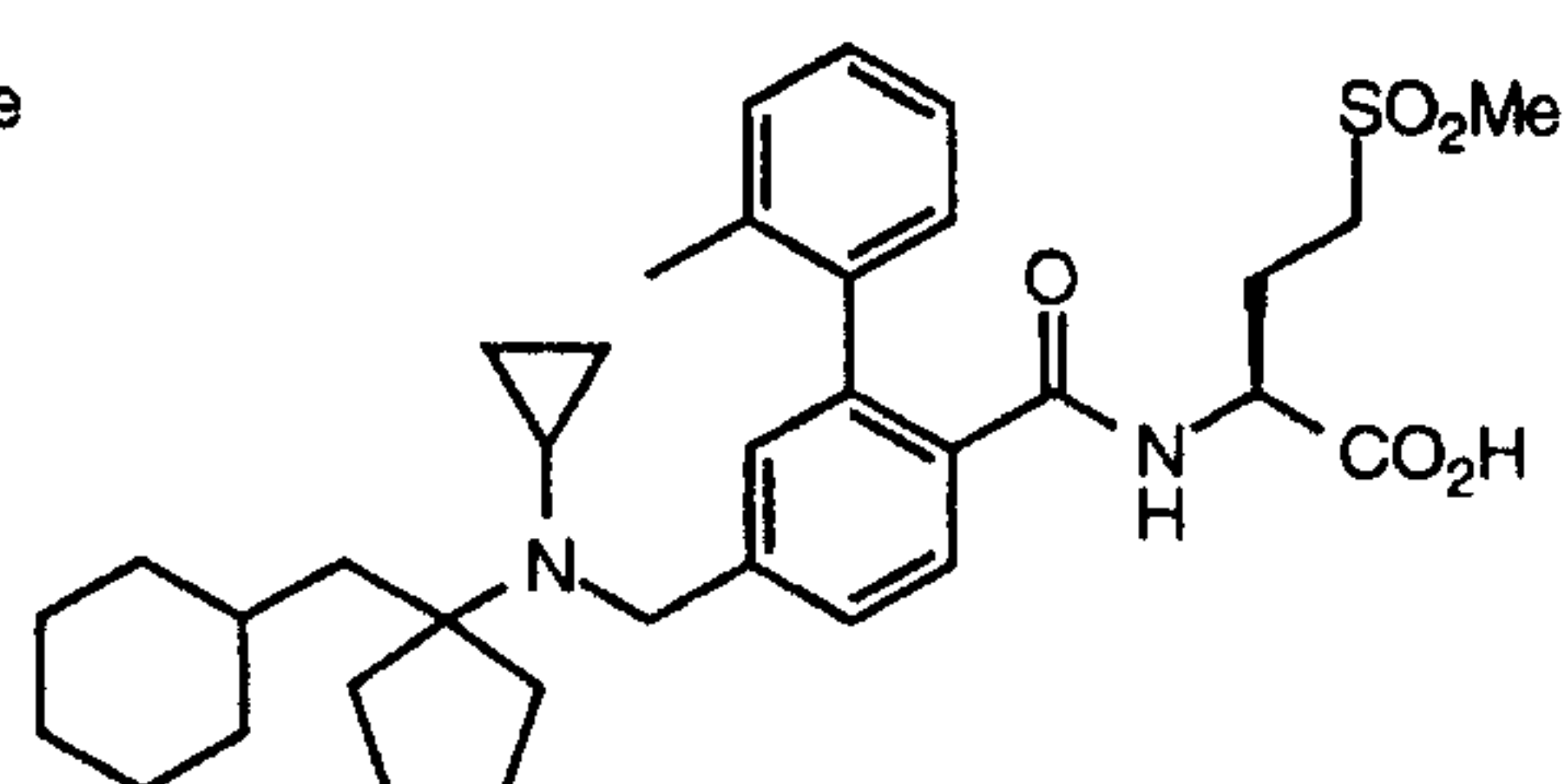
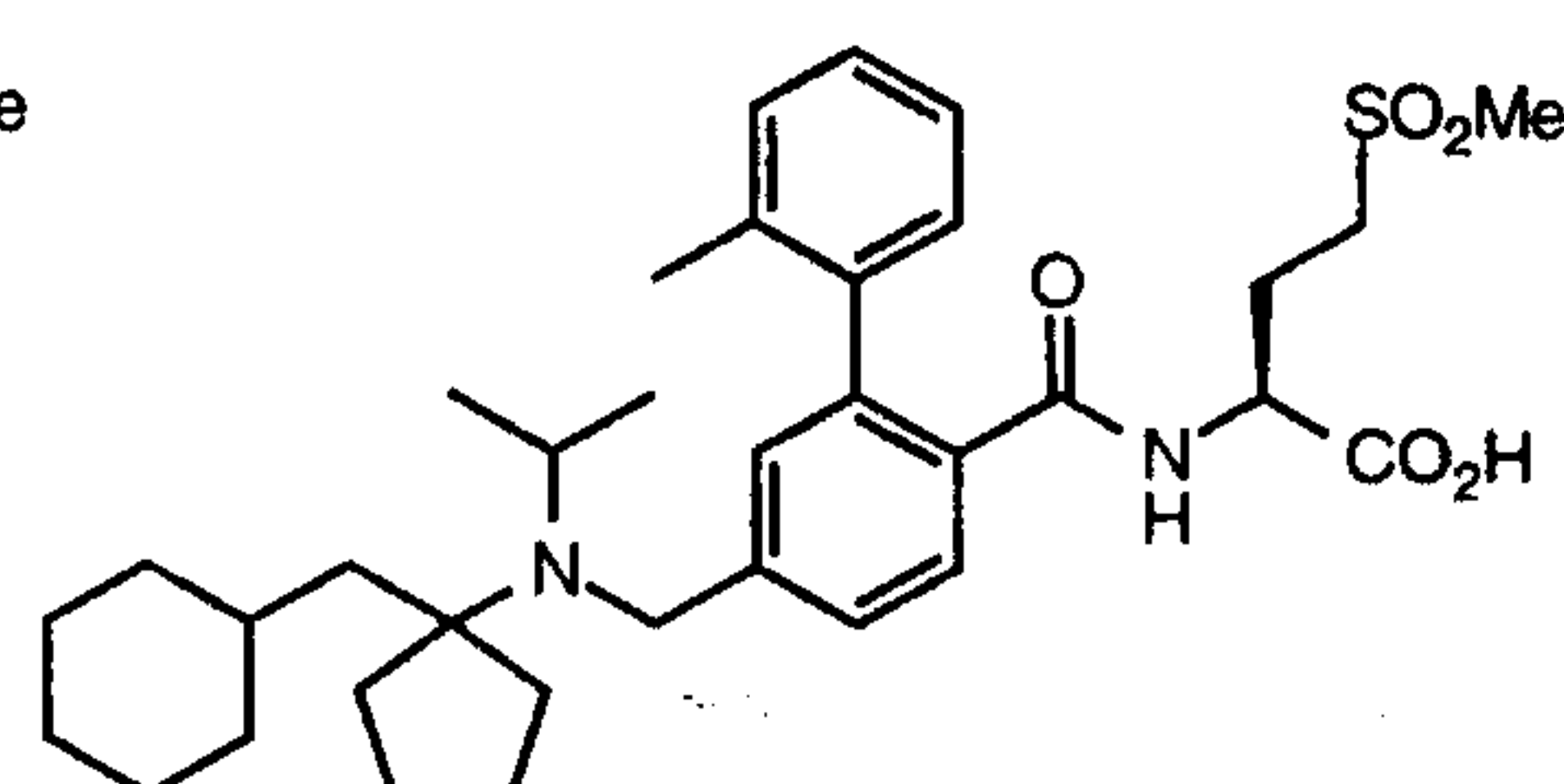
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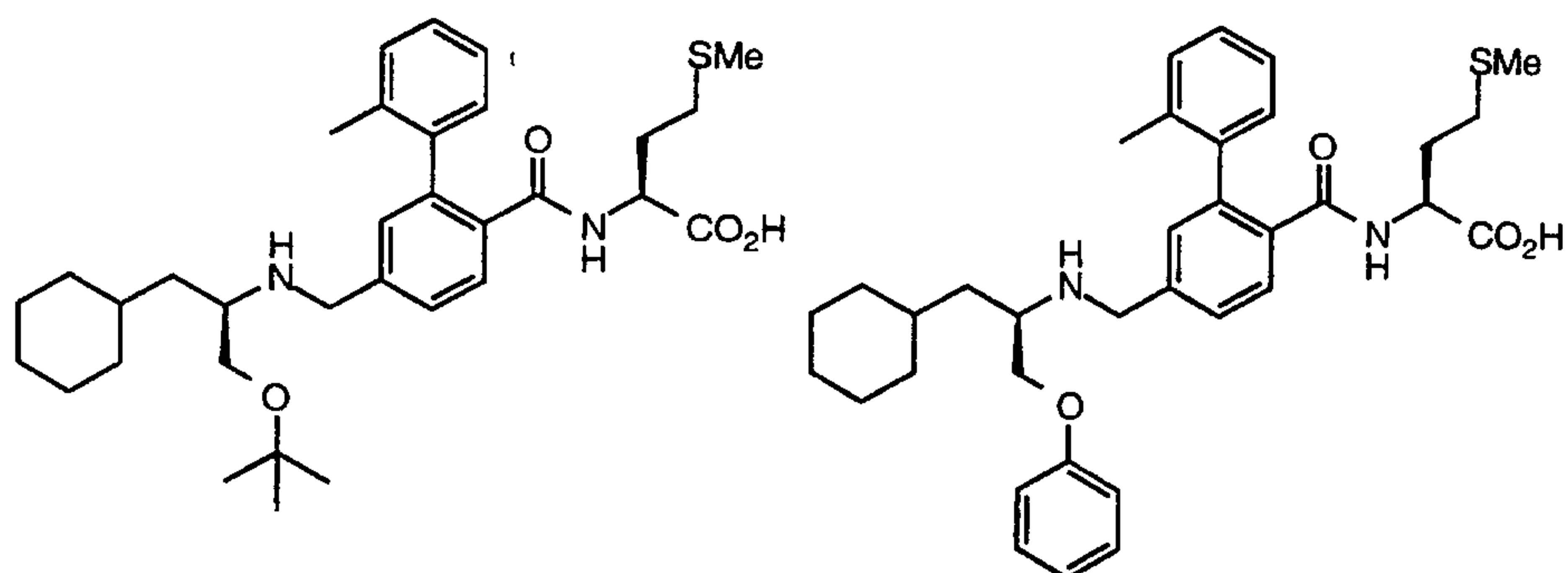


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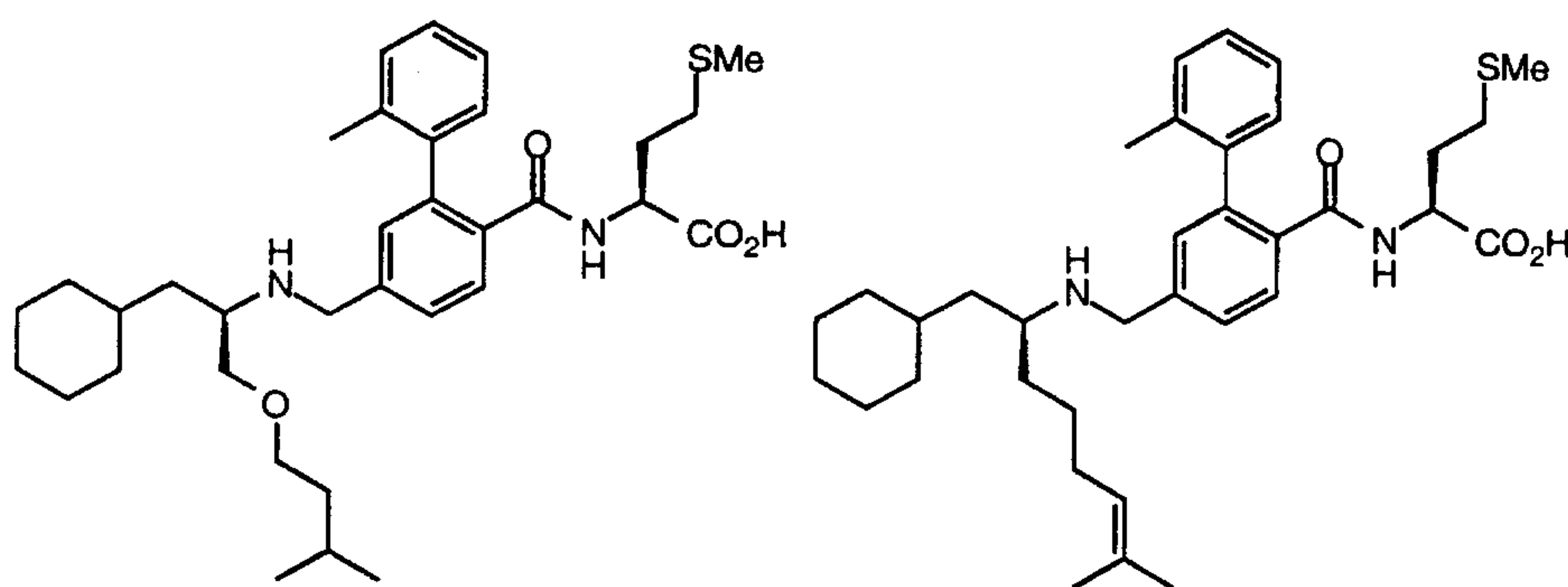
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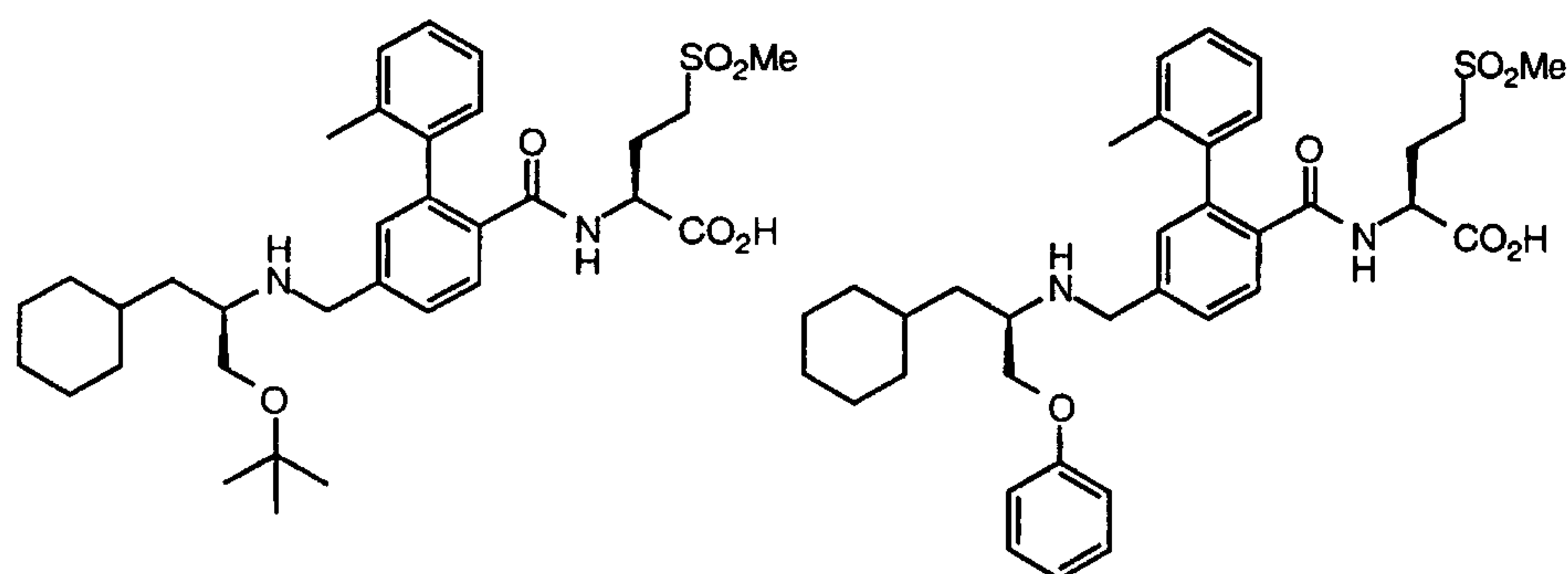
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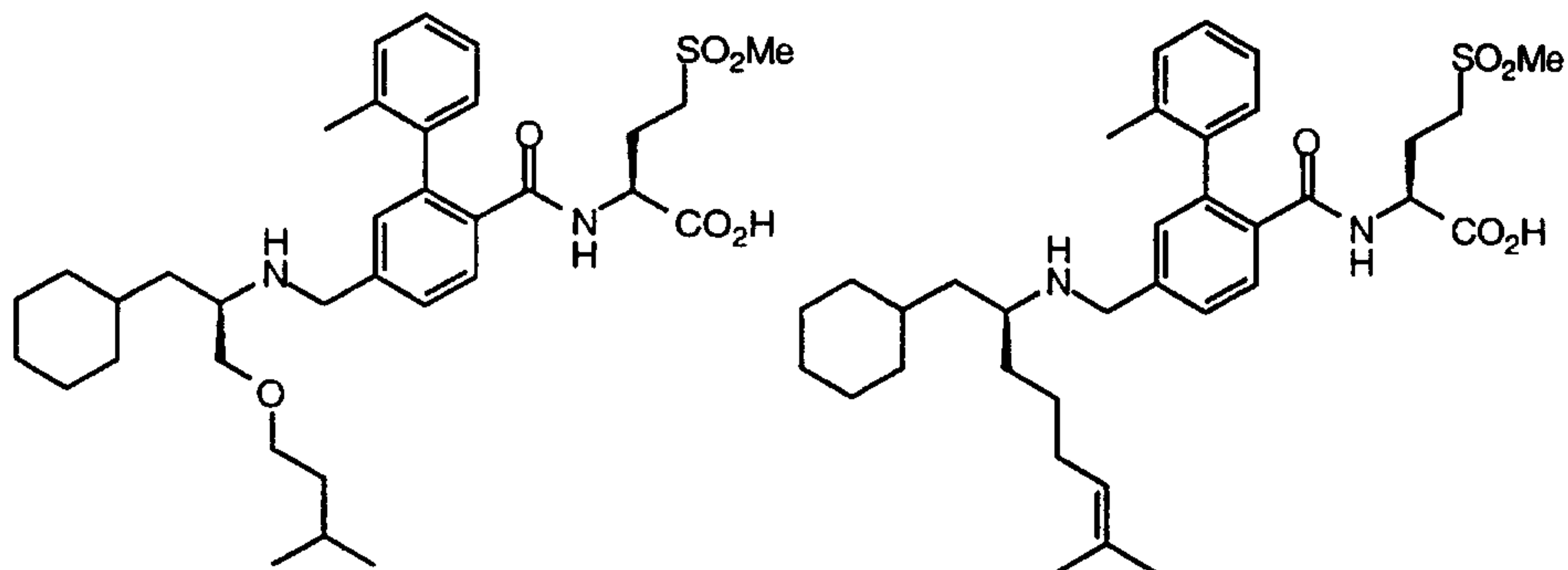
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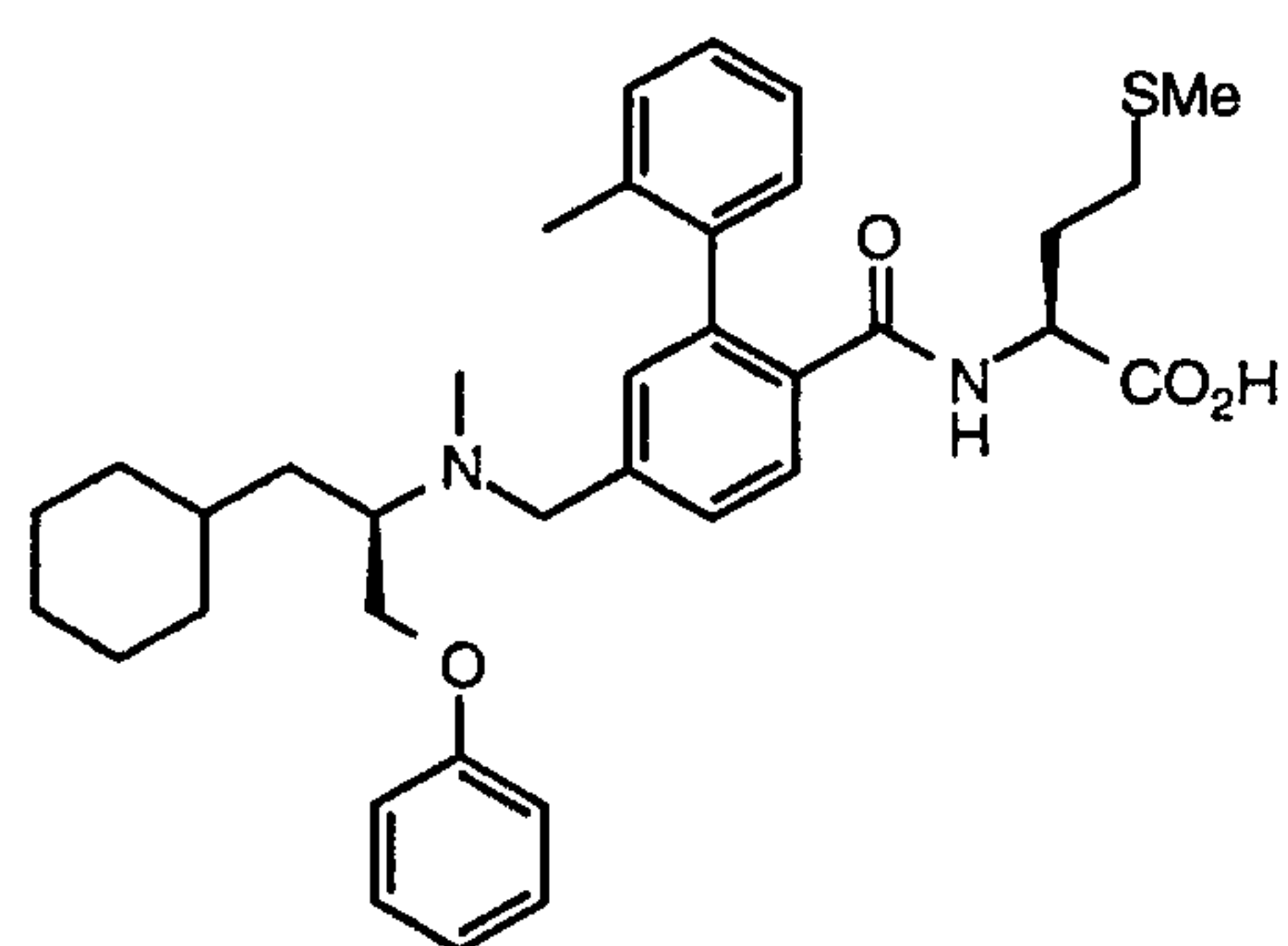
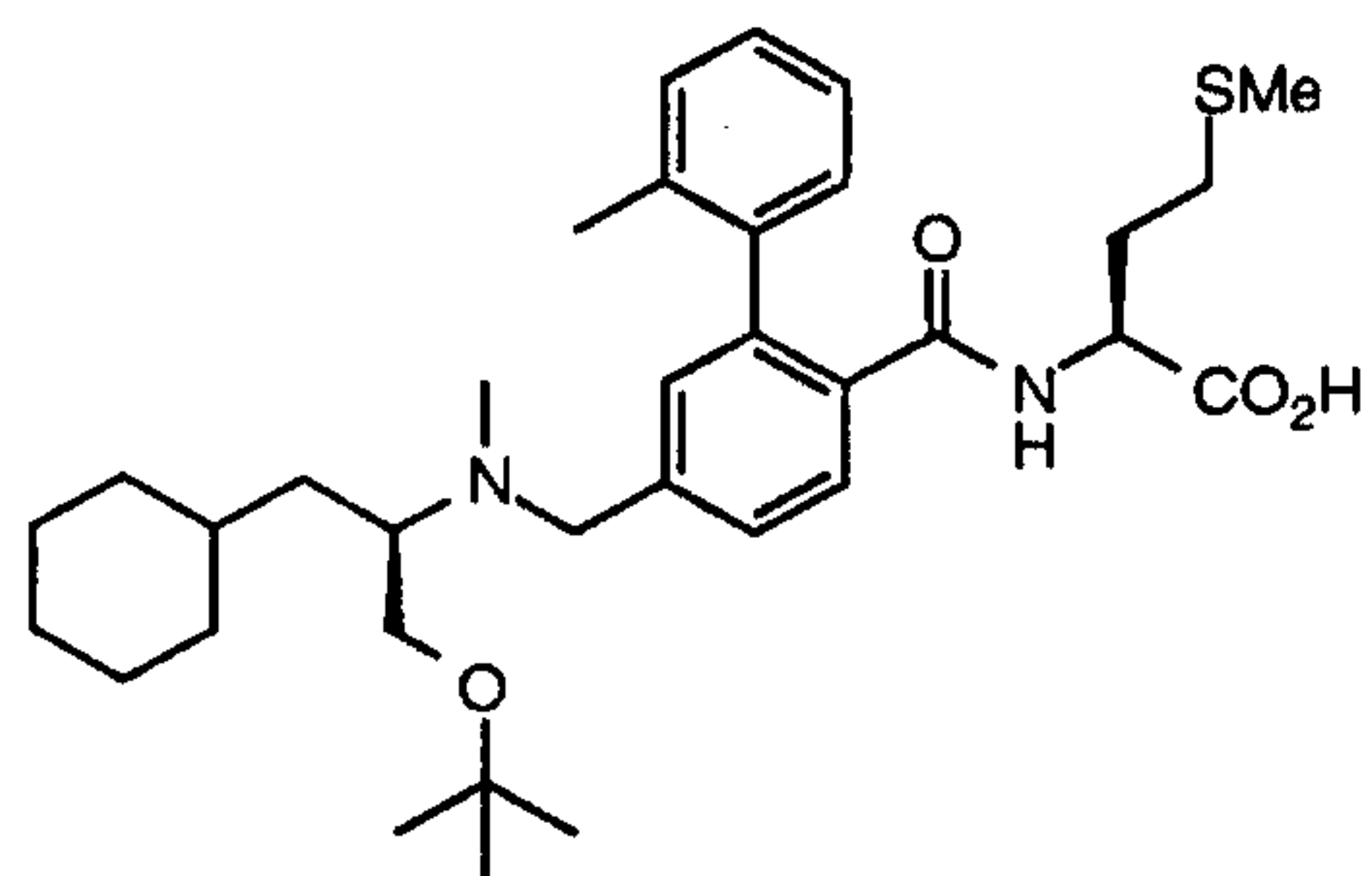
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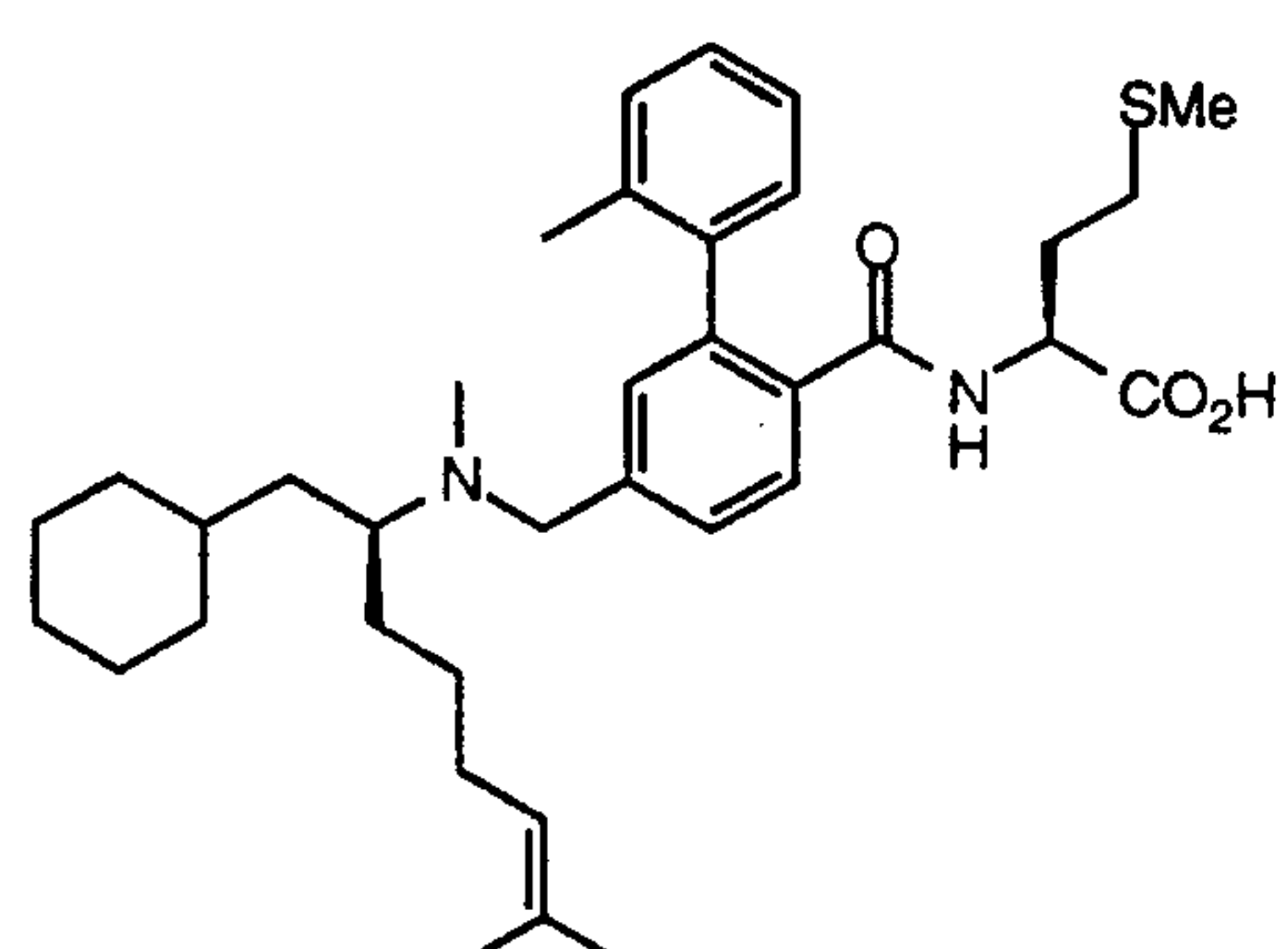
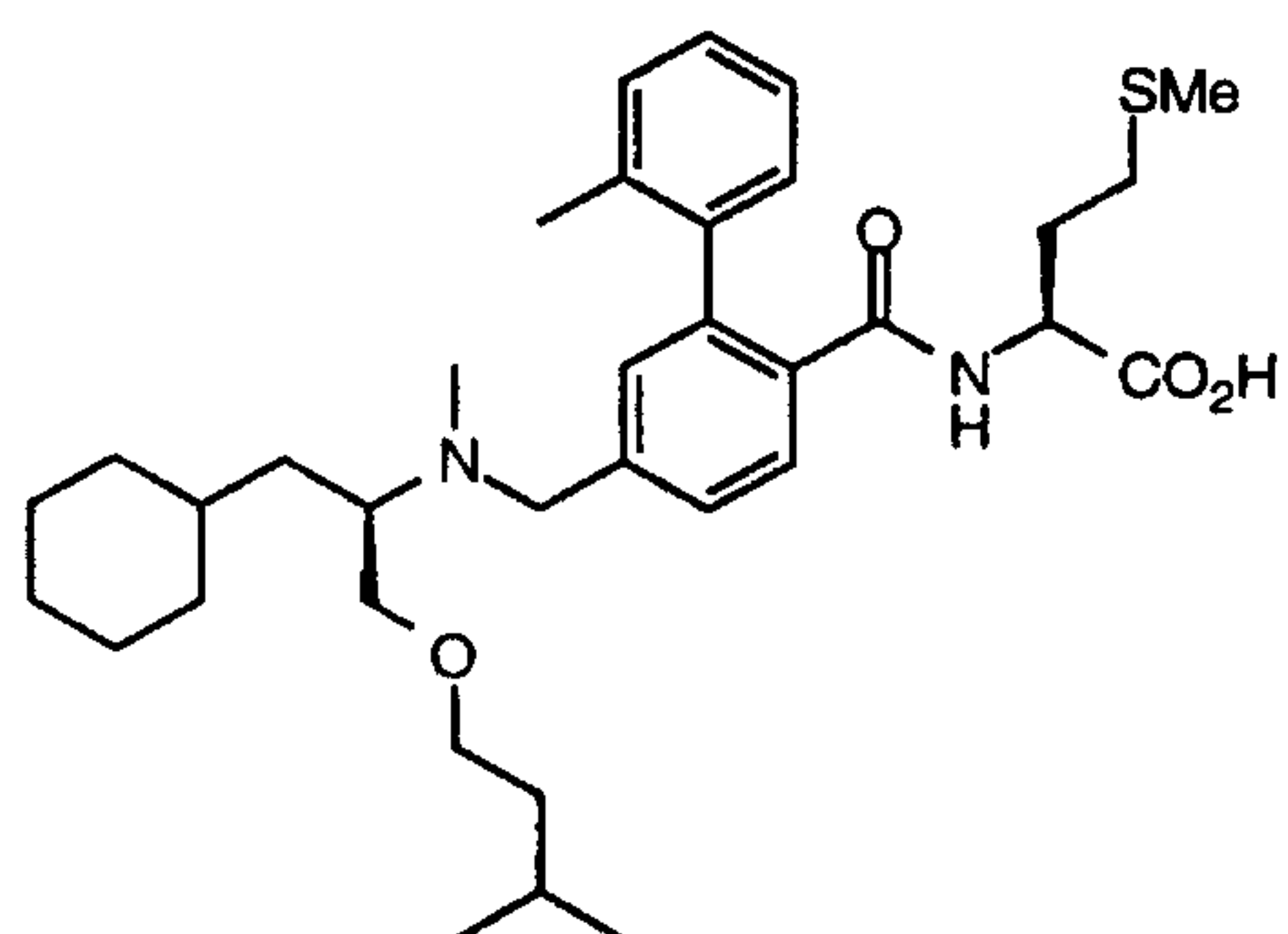
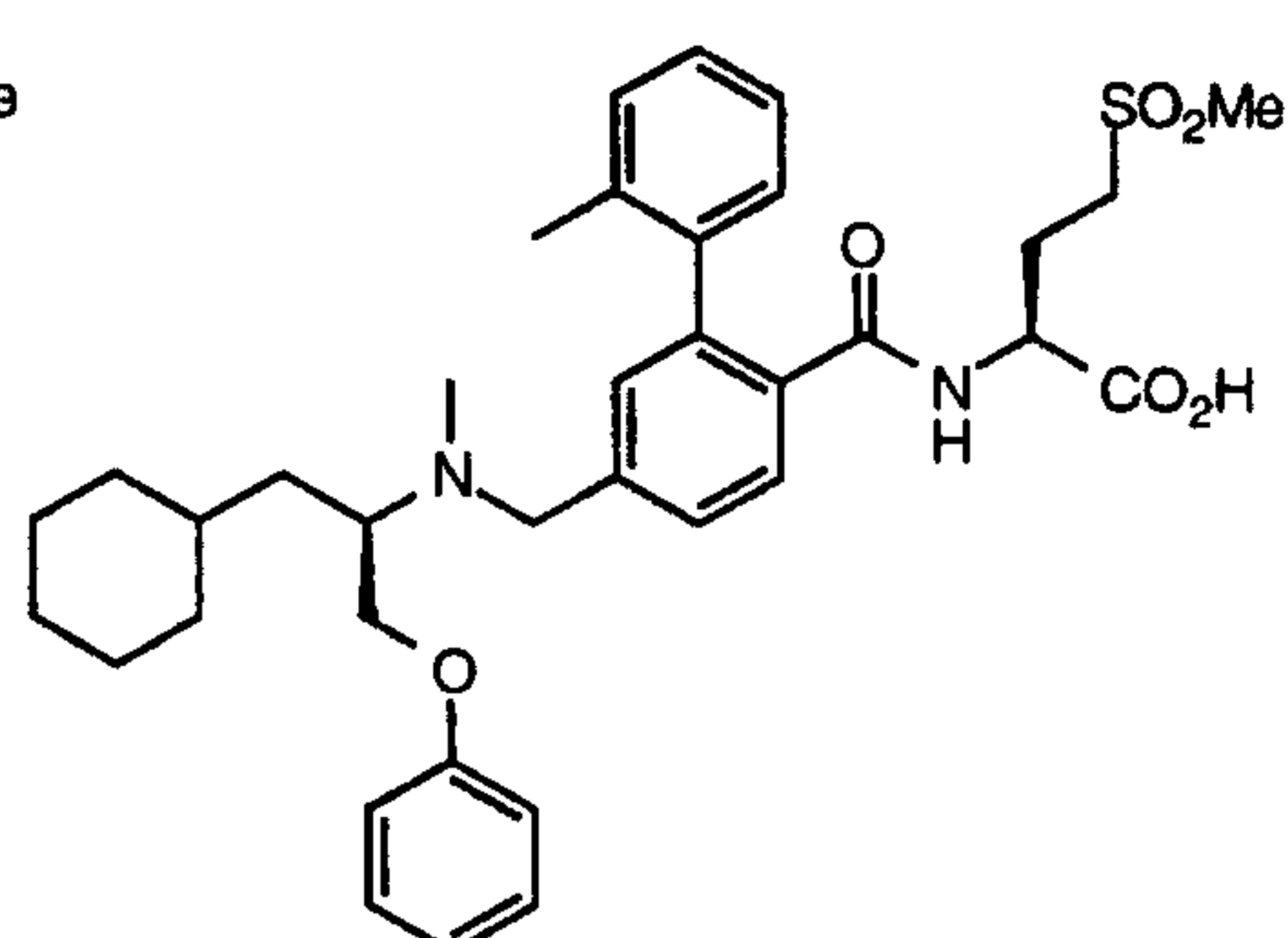
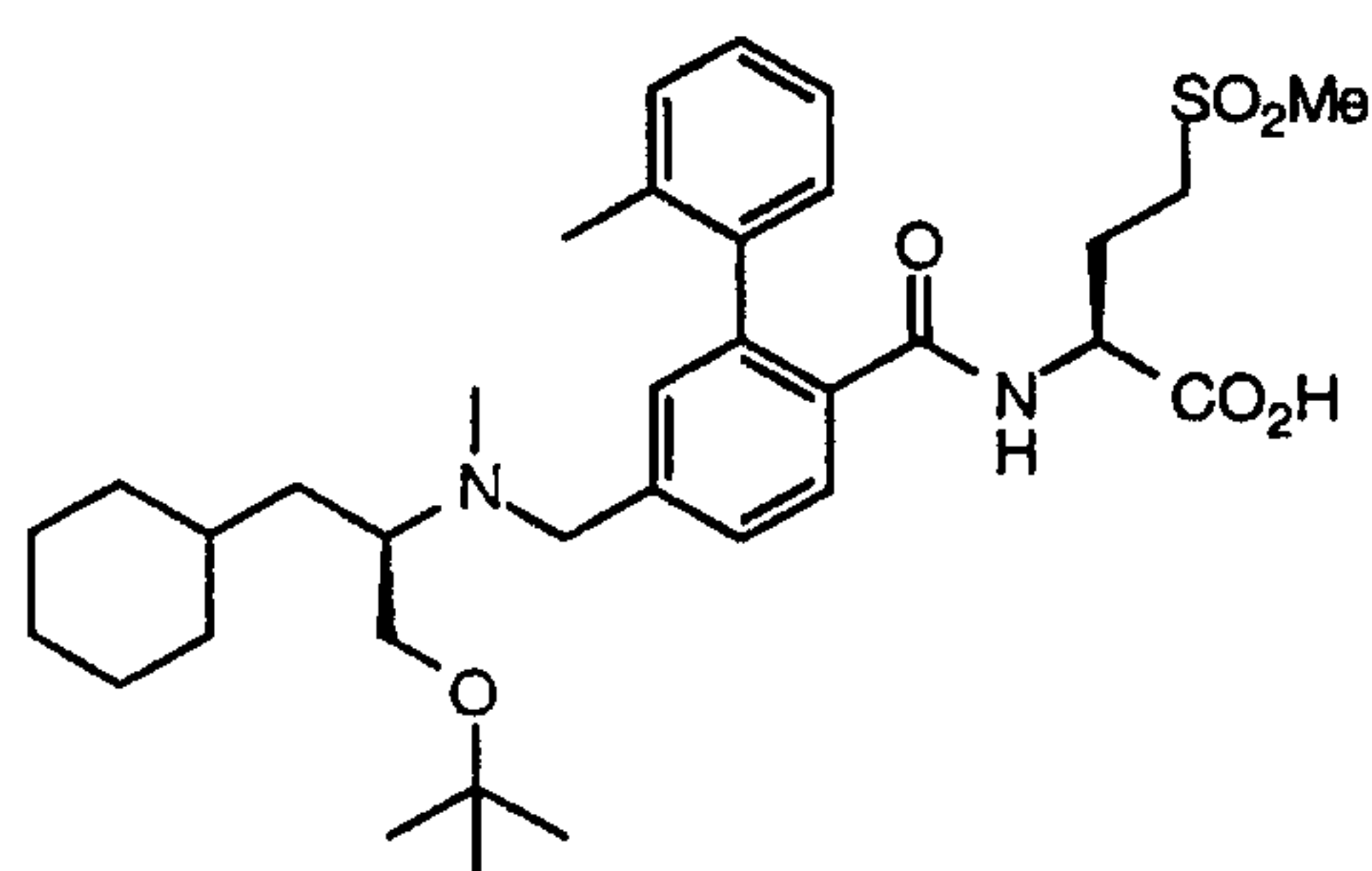
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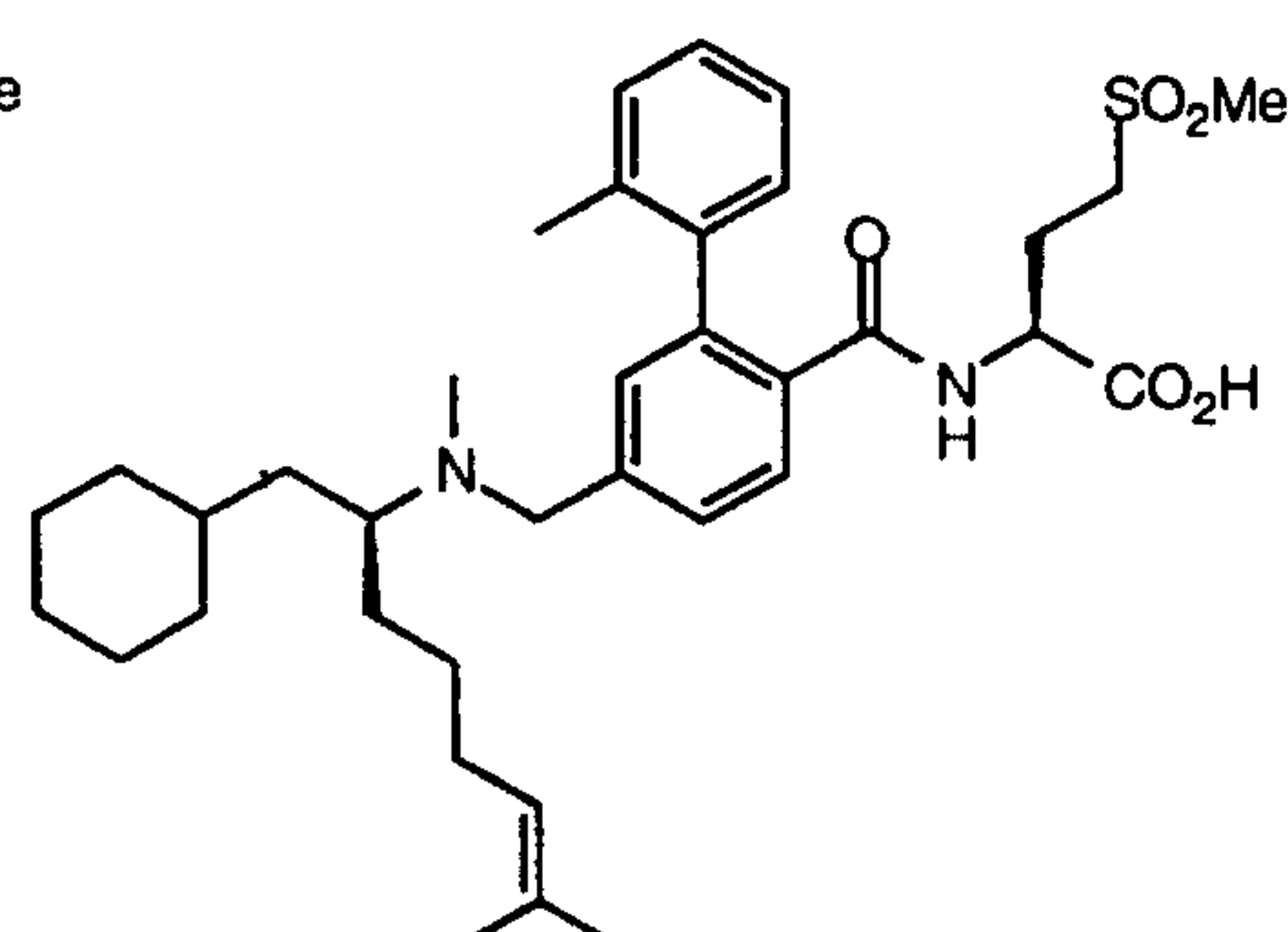
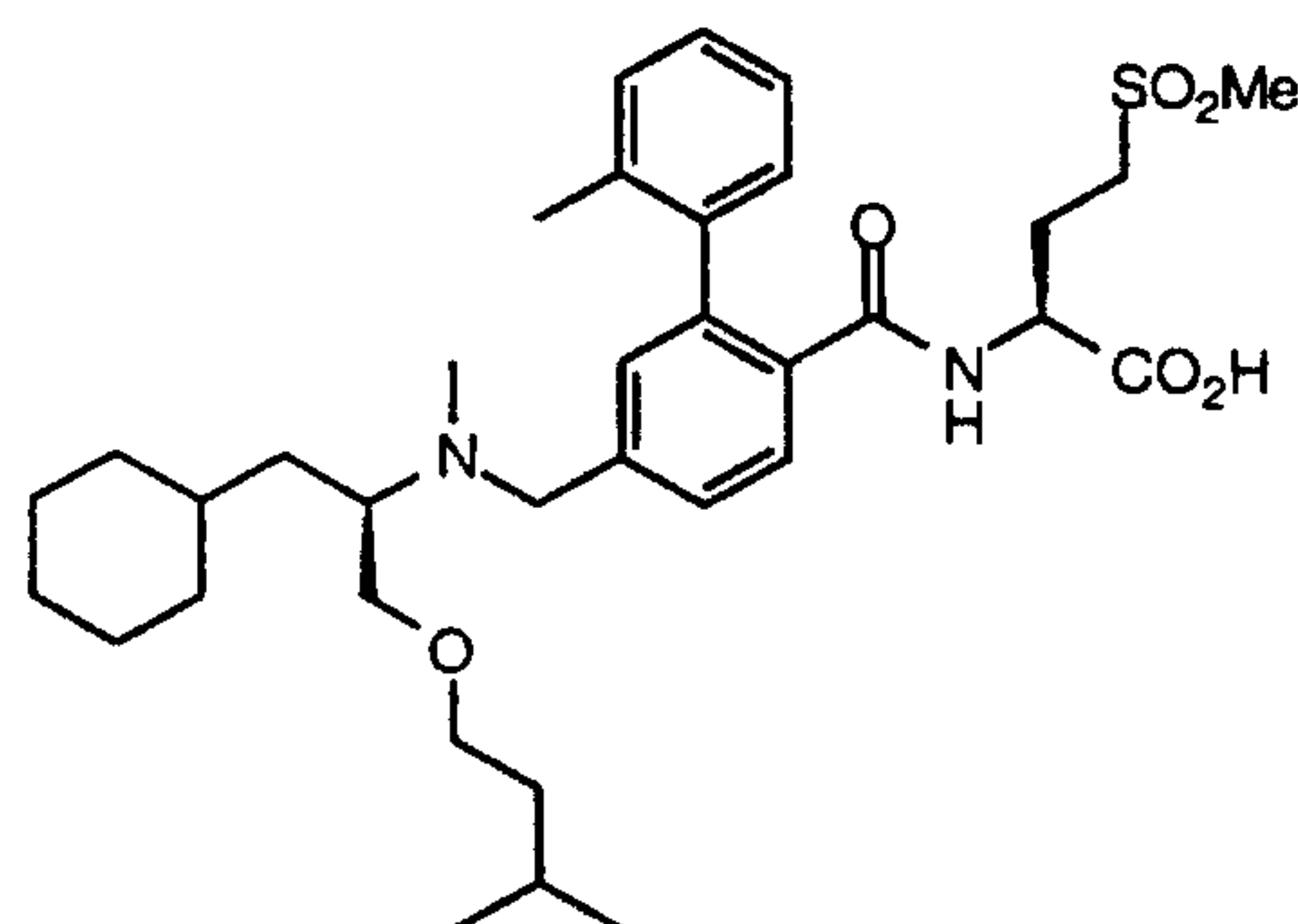
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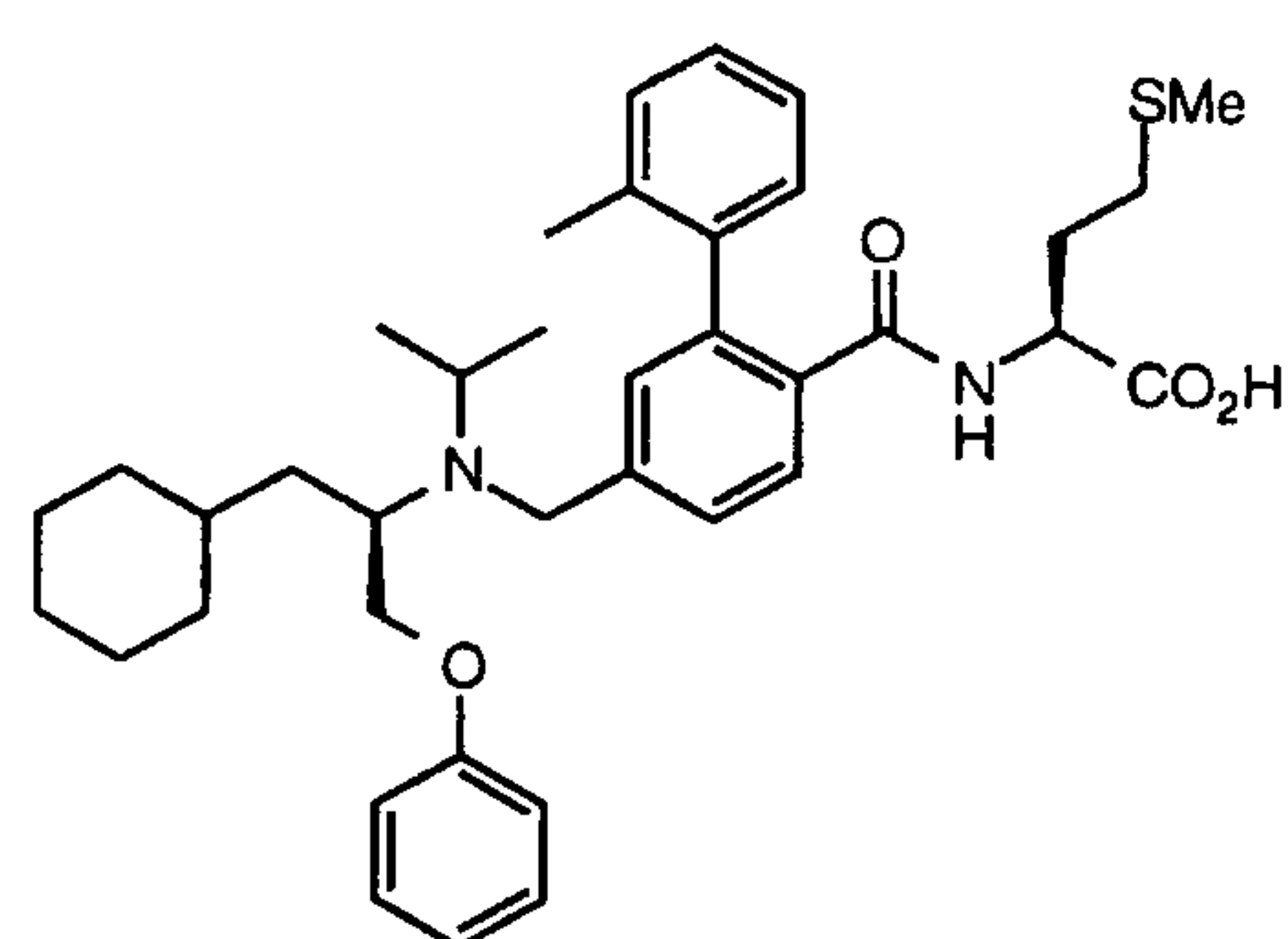
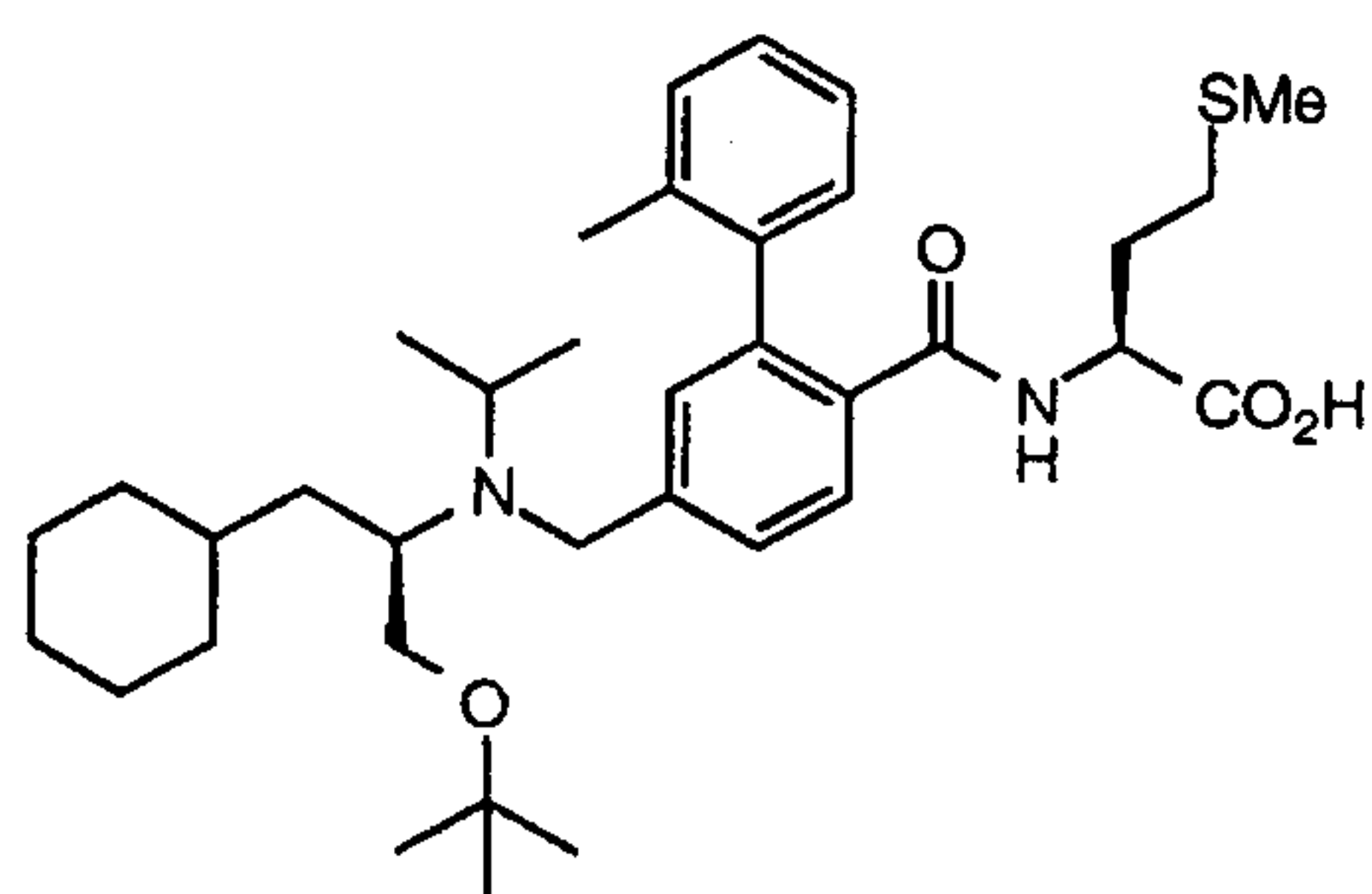
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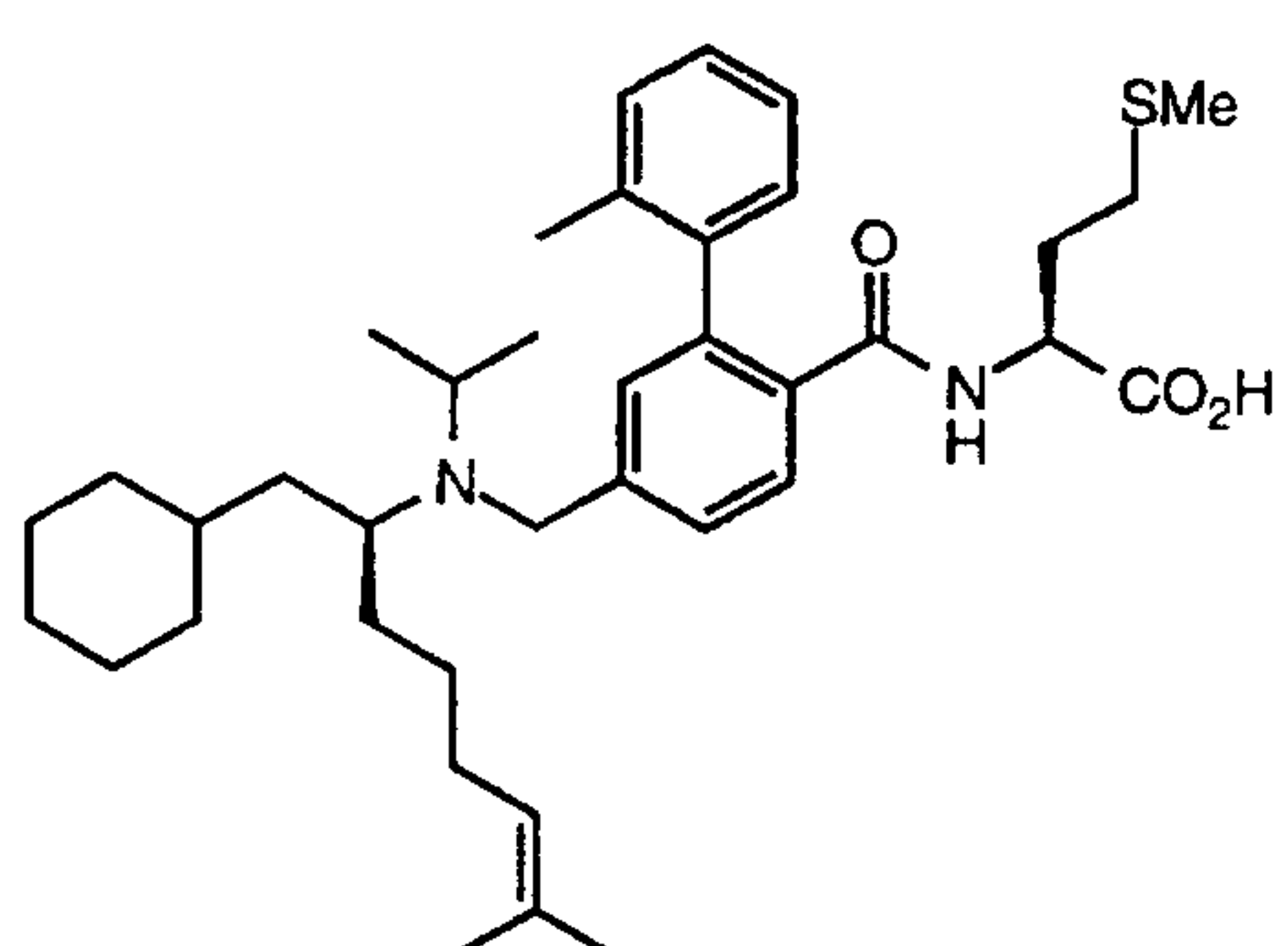
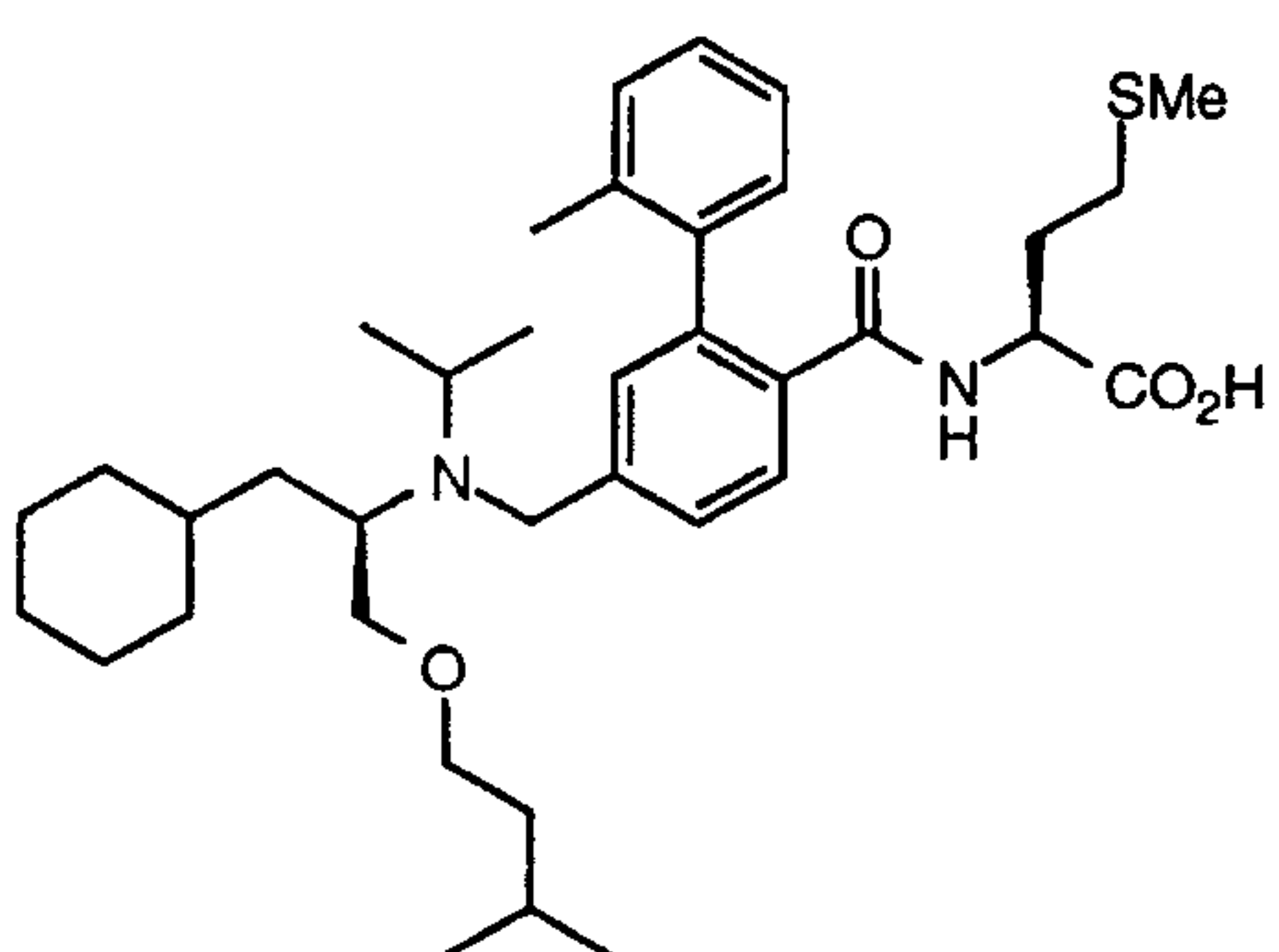
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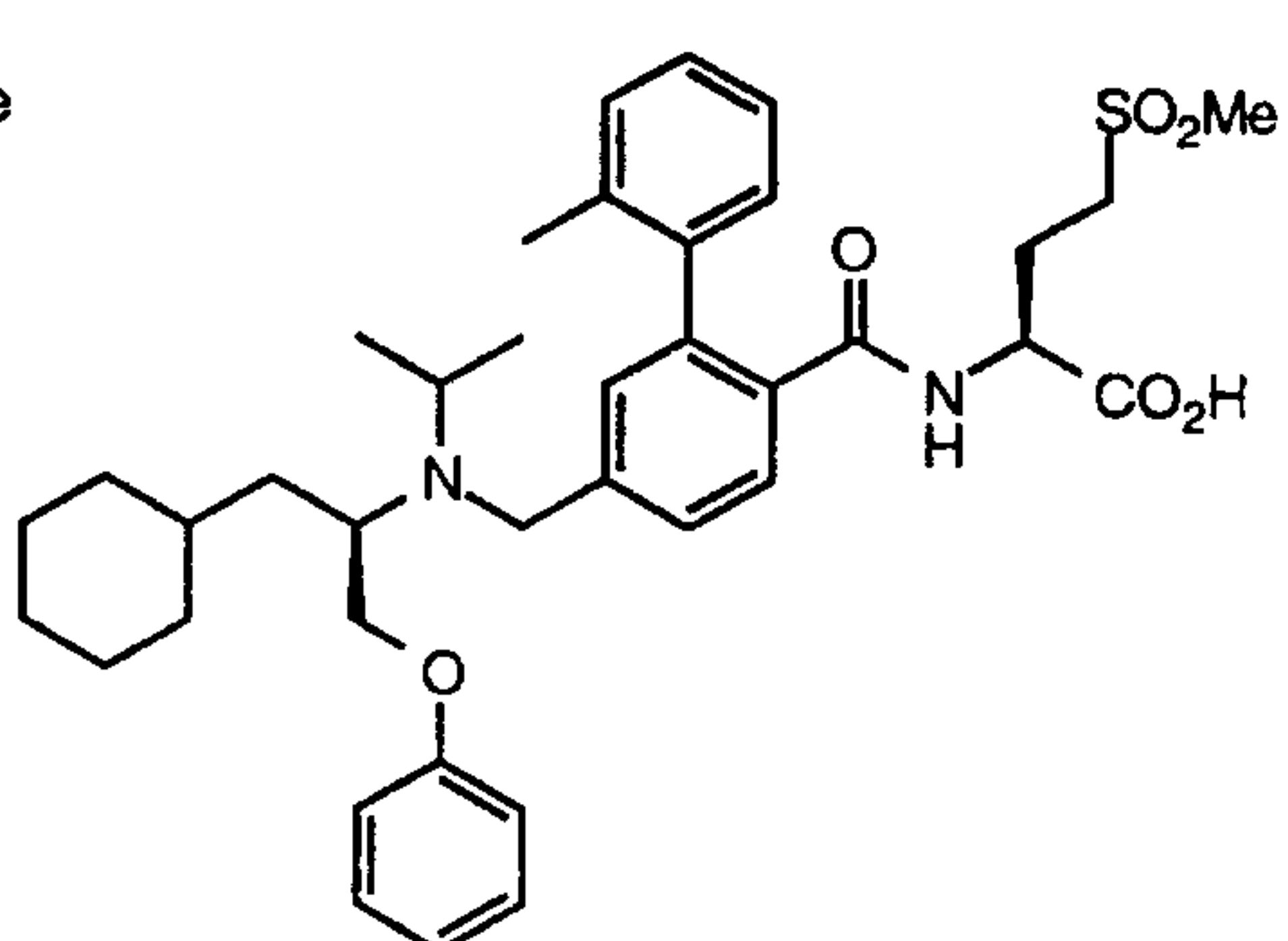
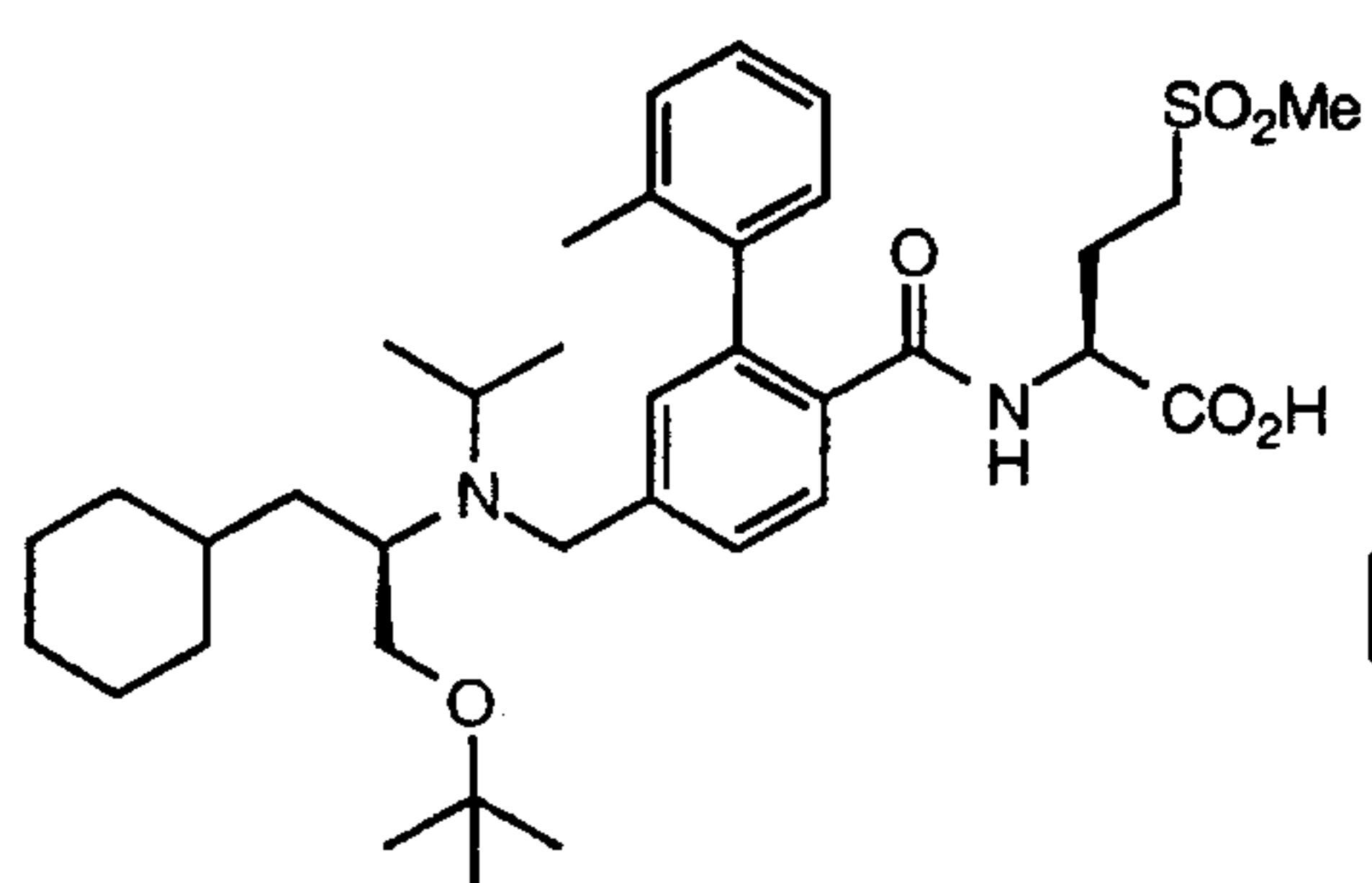
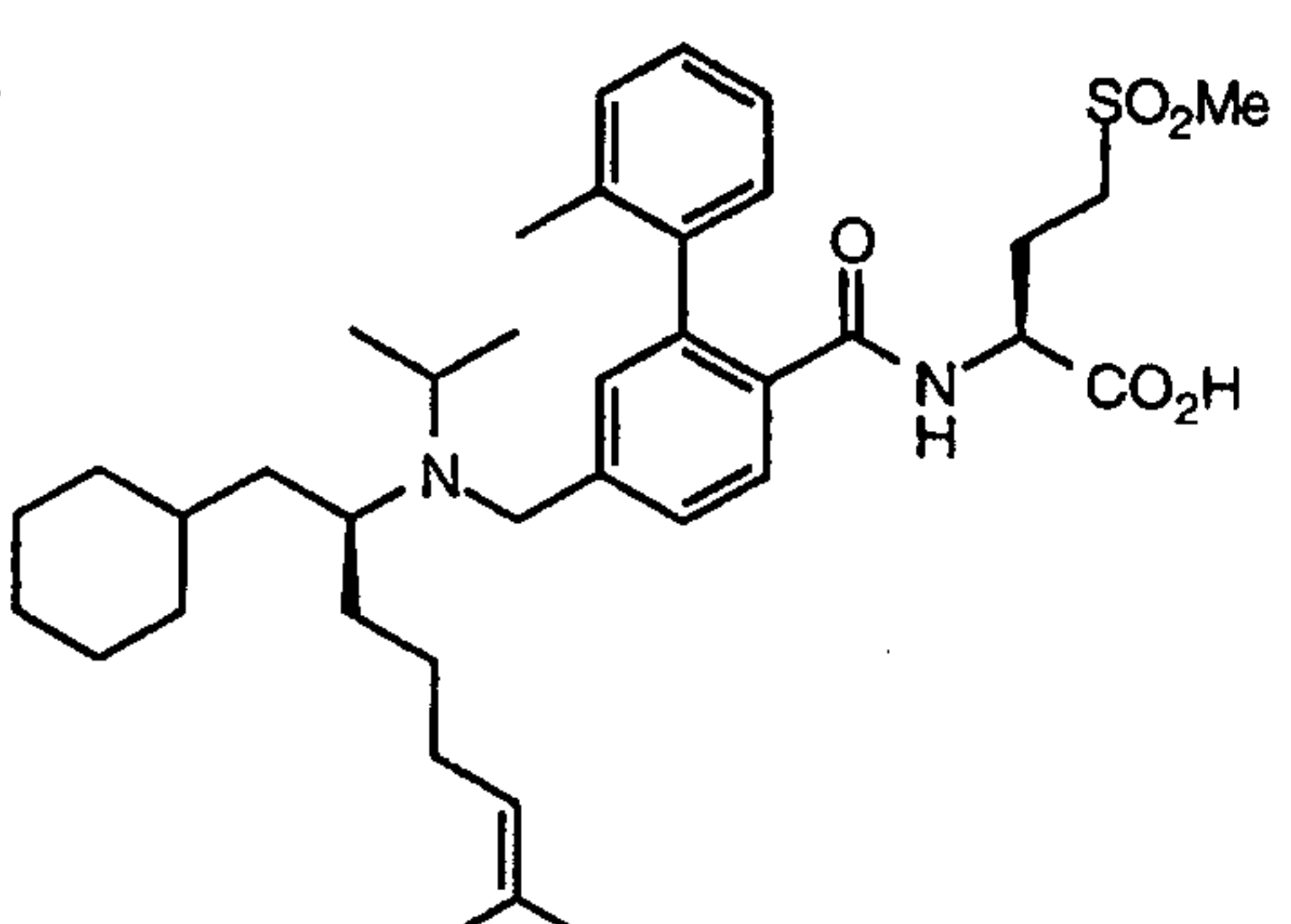
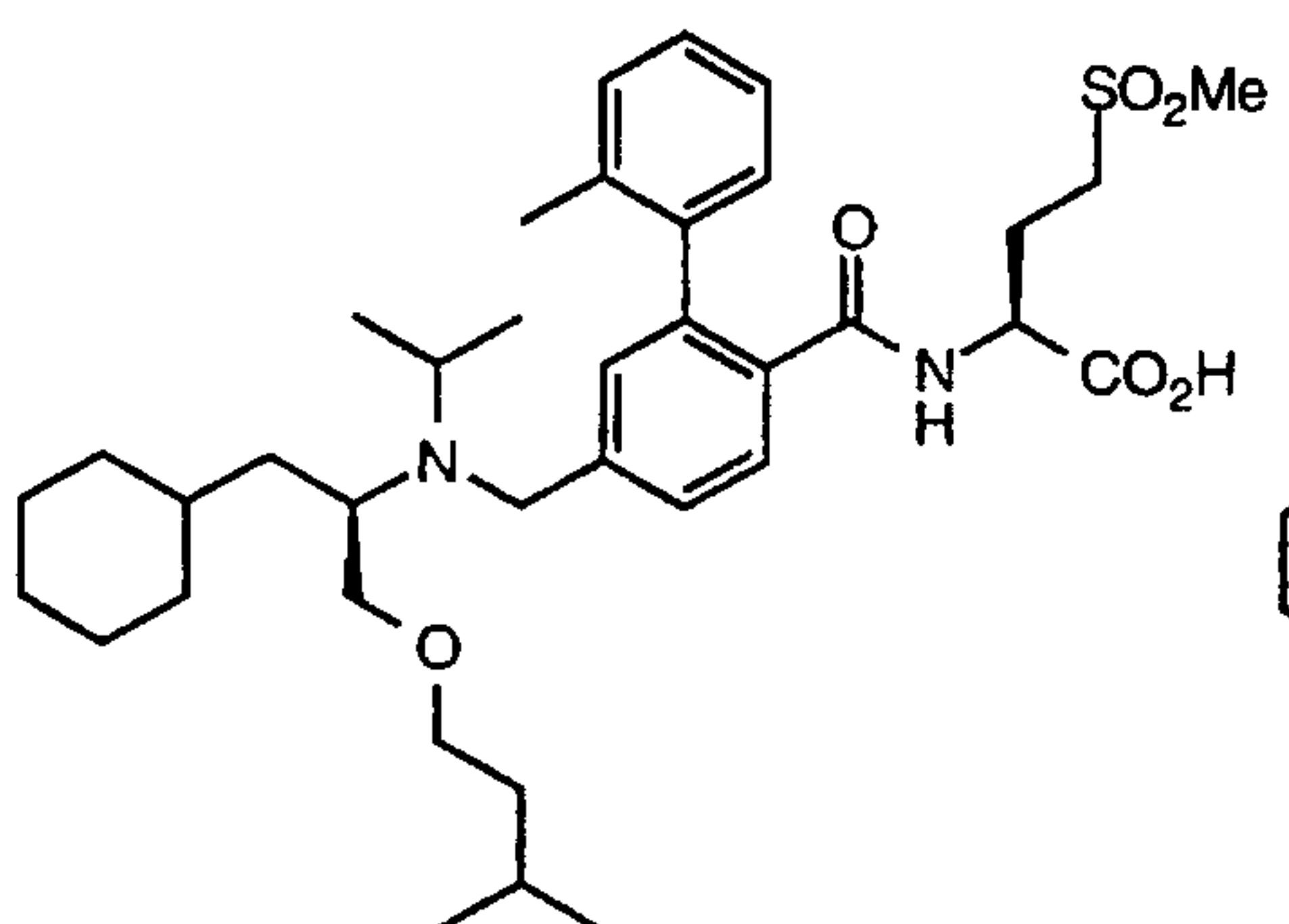
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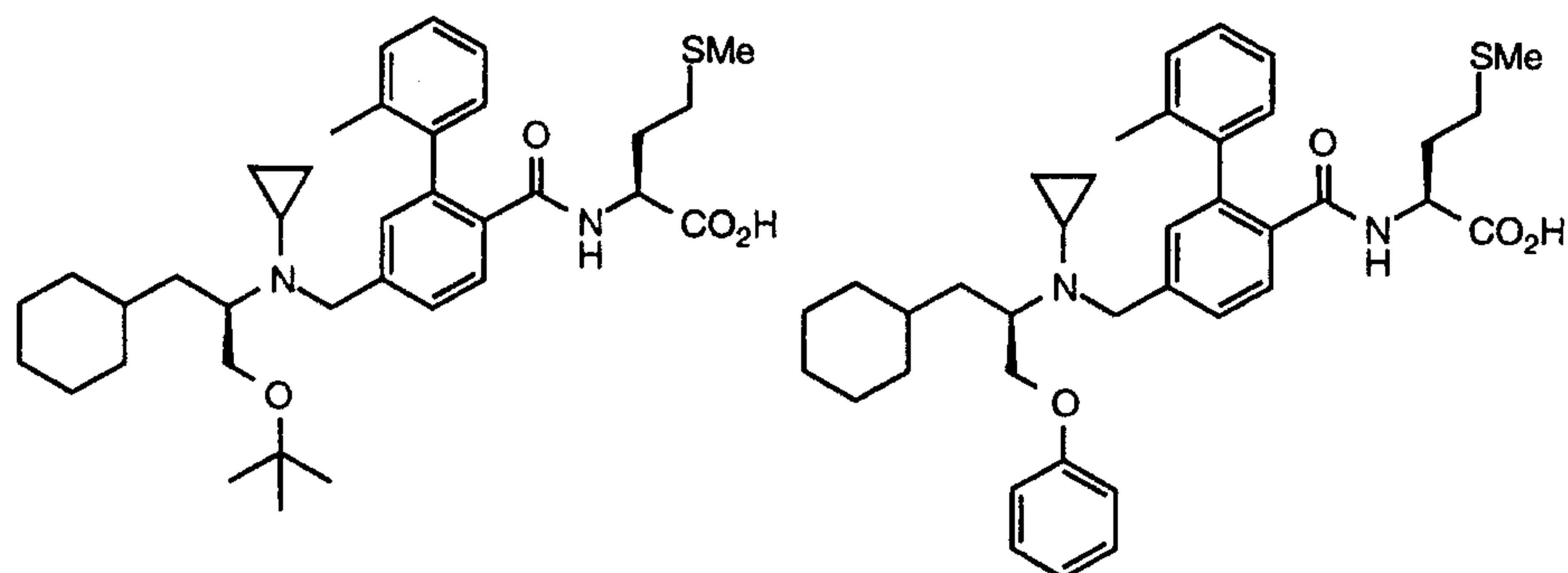
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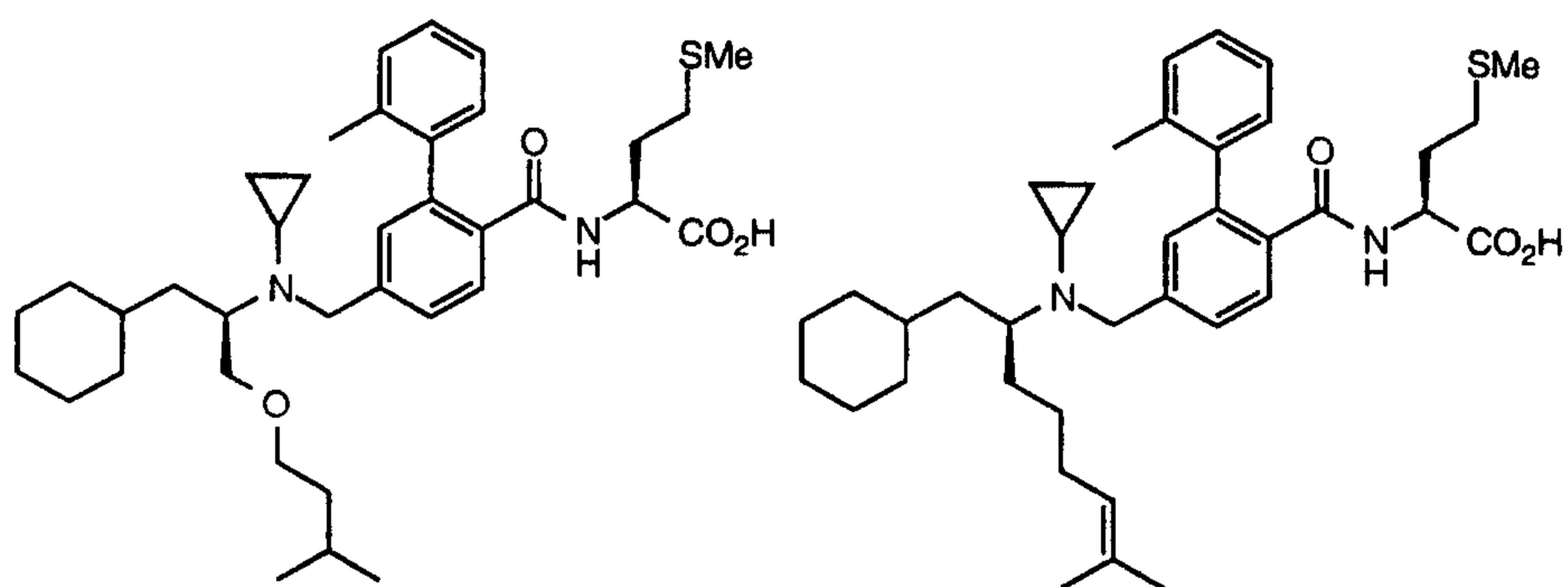
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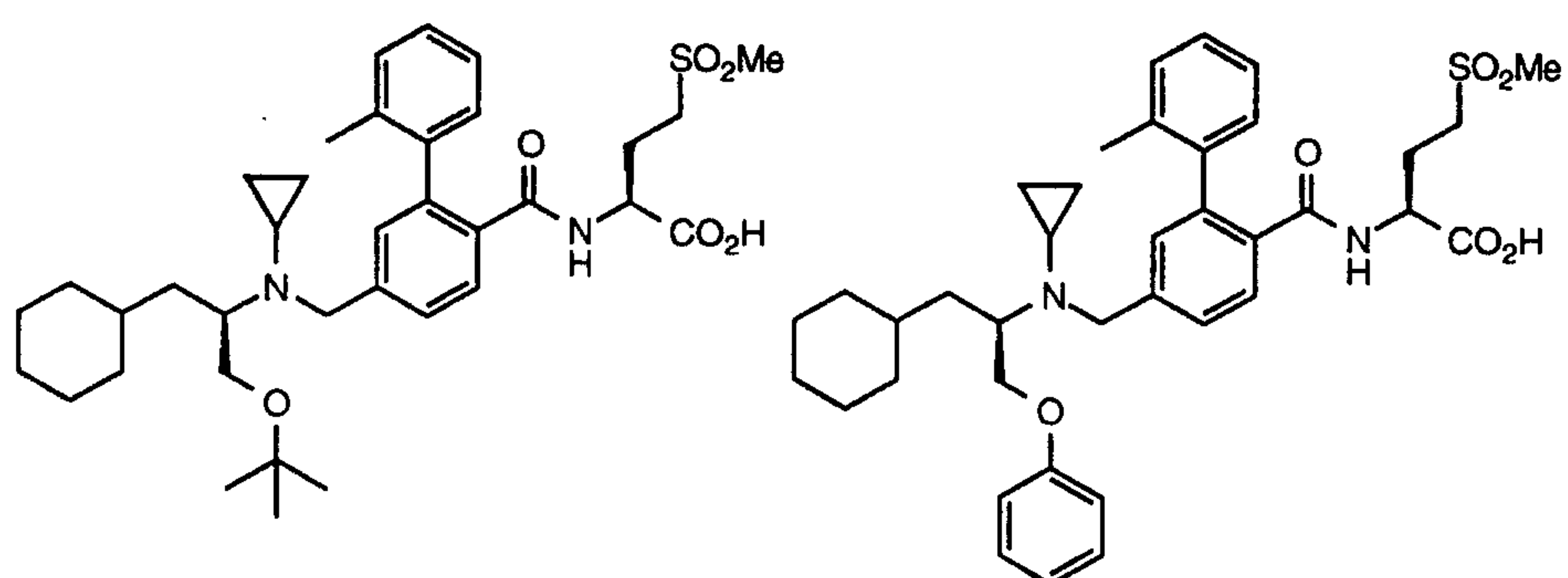
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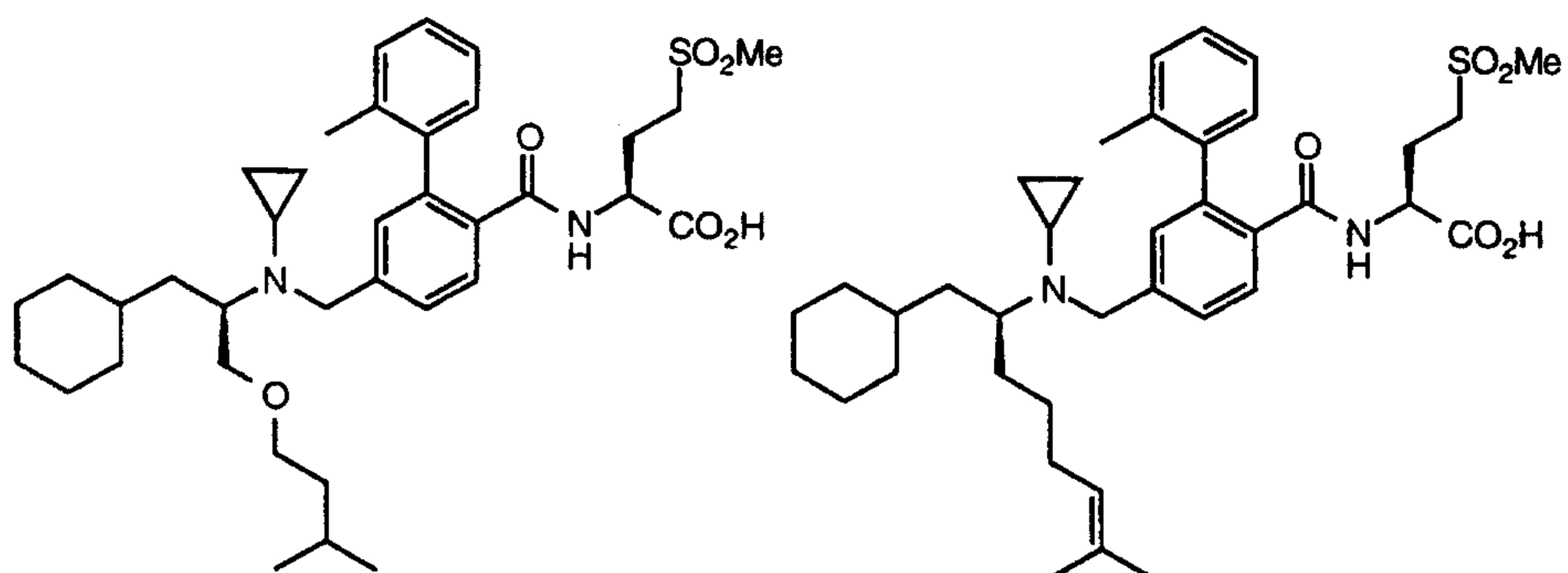
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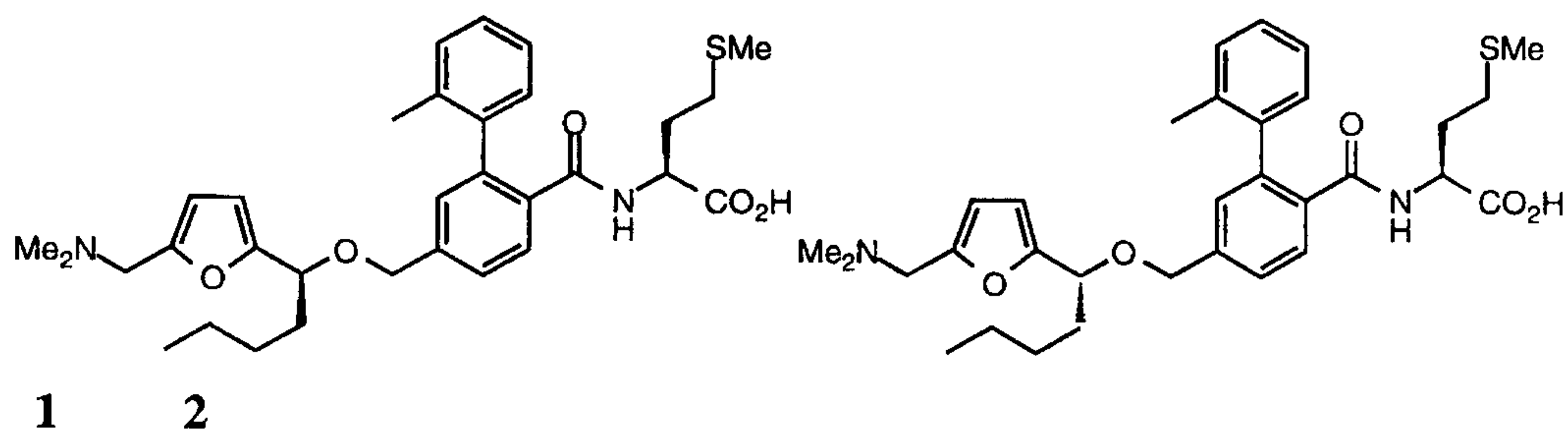
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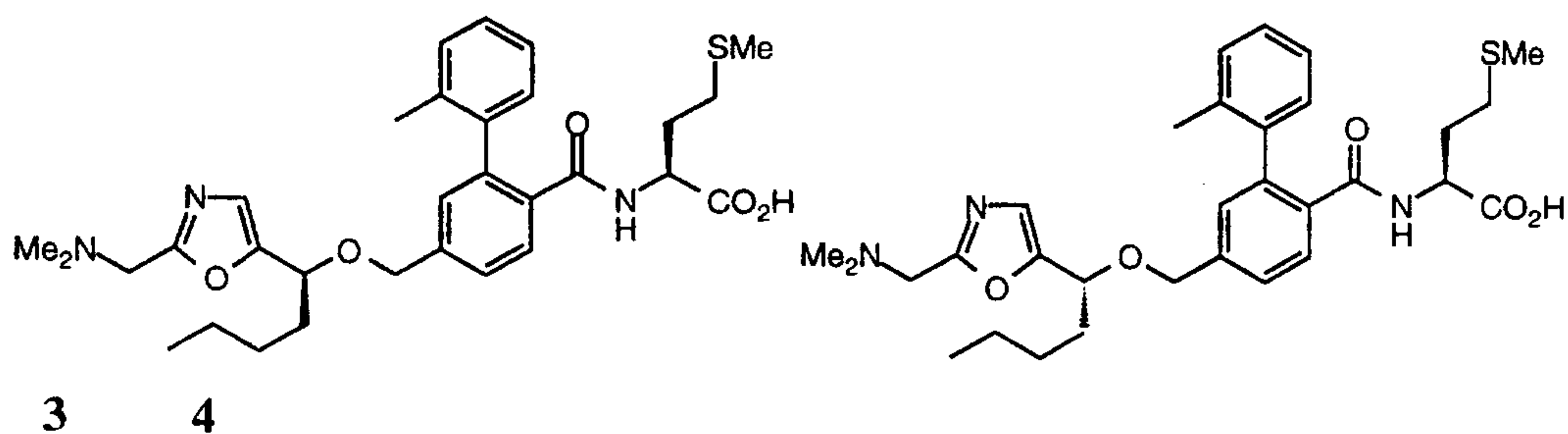
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Table 7. Ethers of the Type A-OL₁

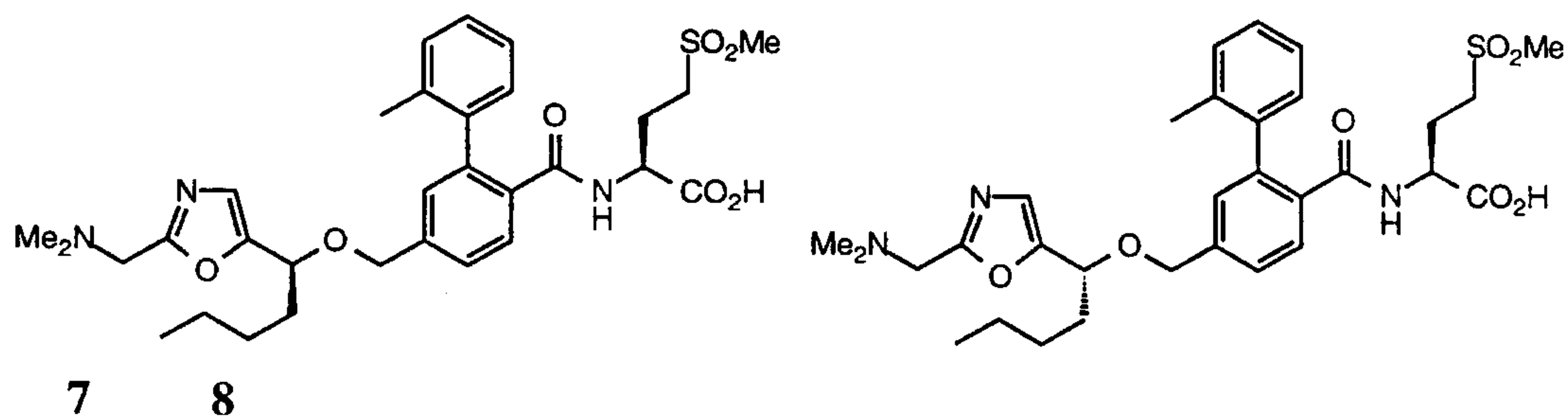
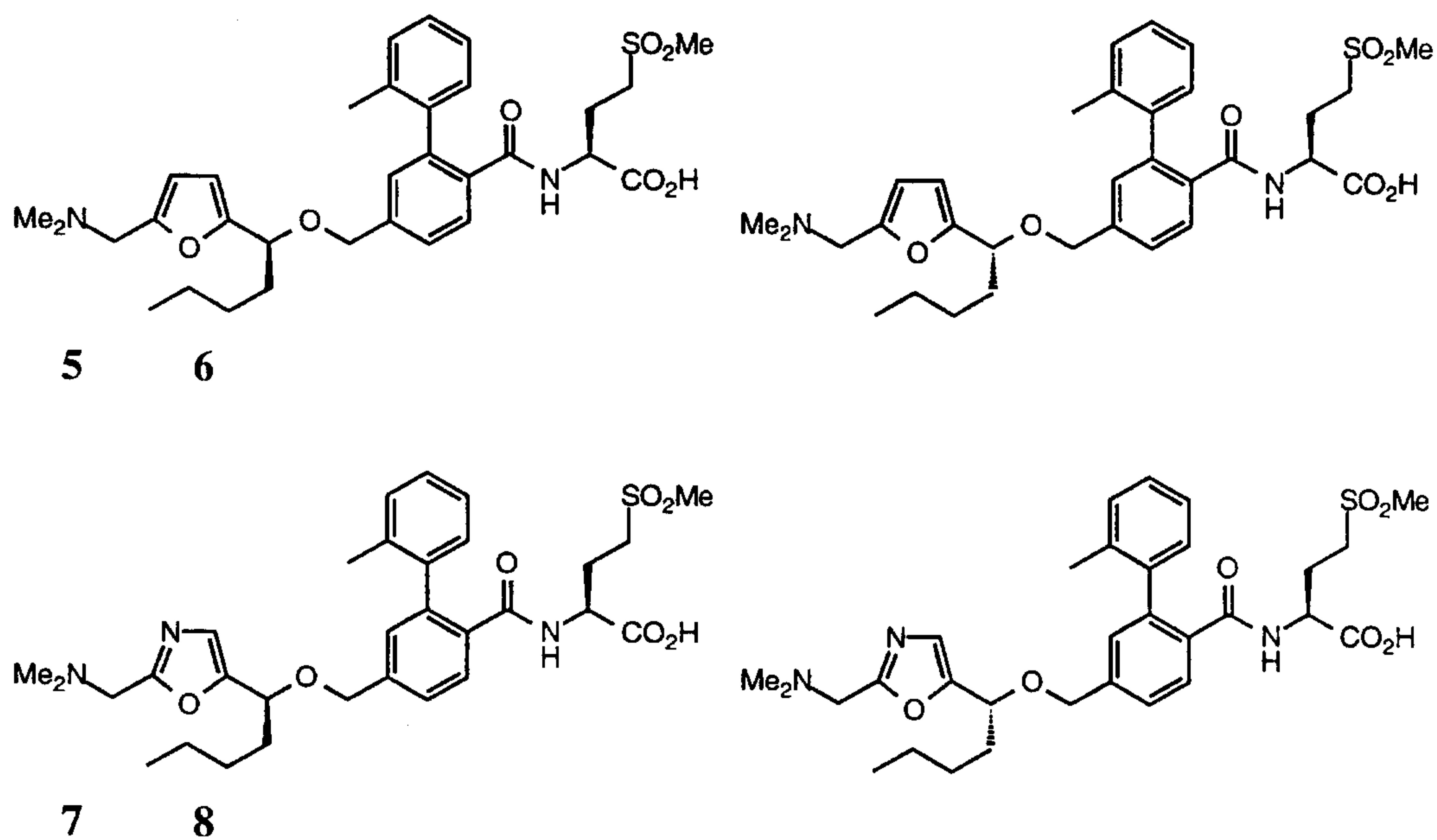
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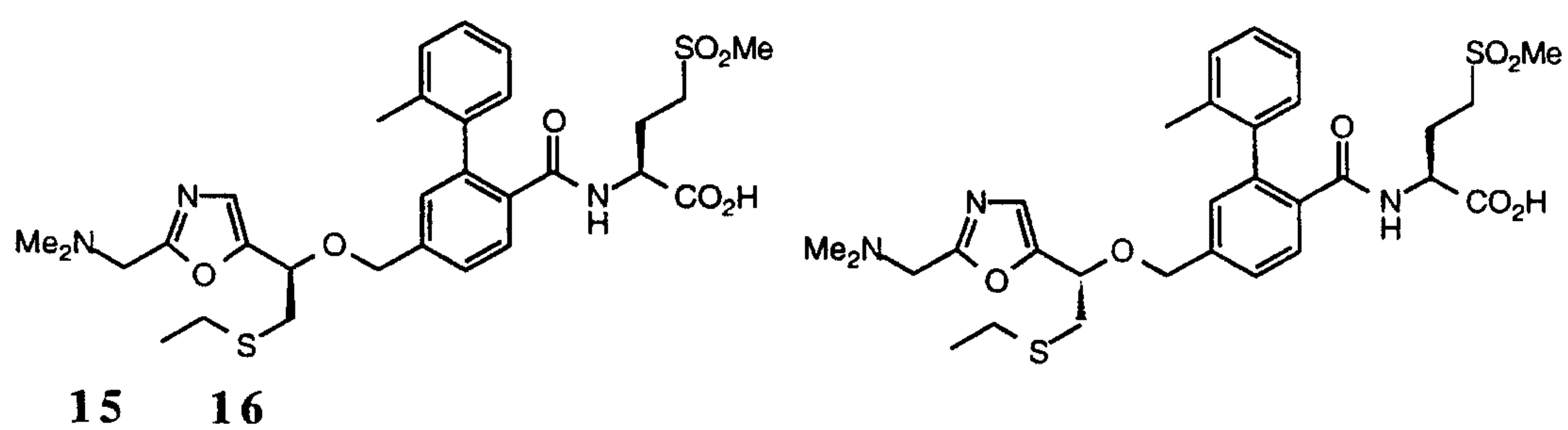
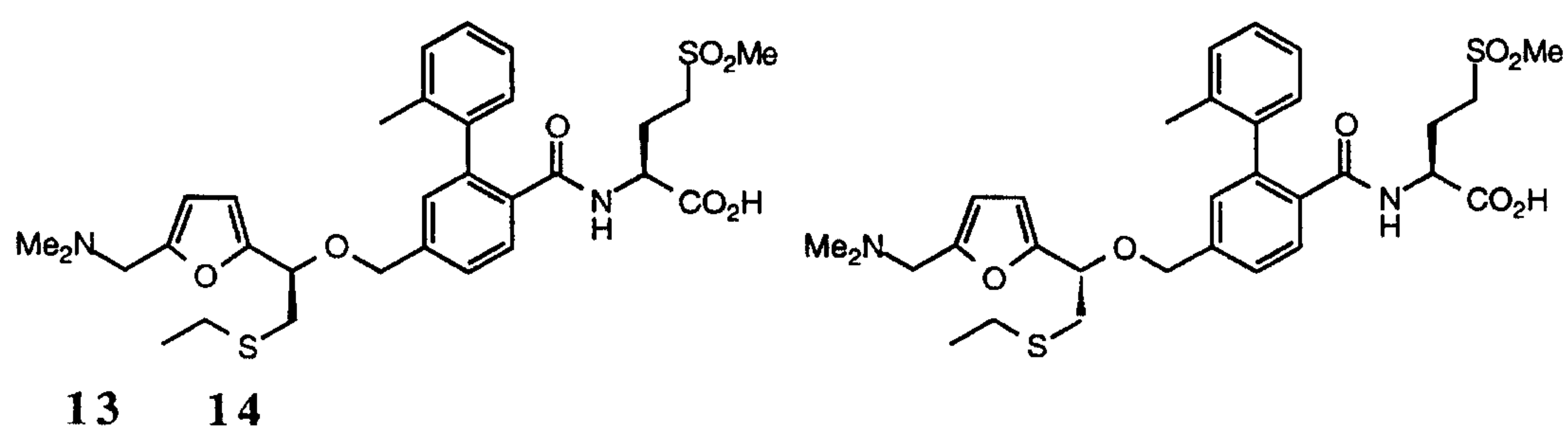
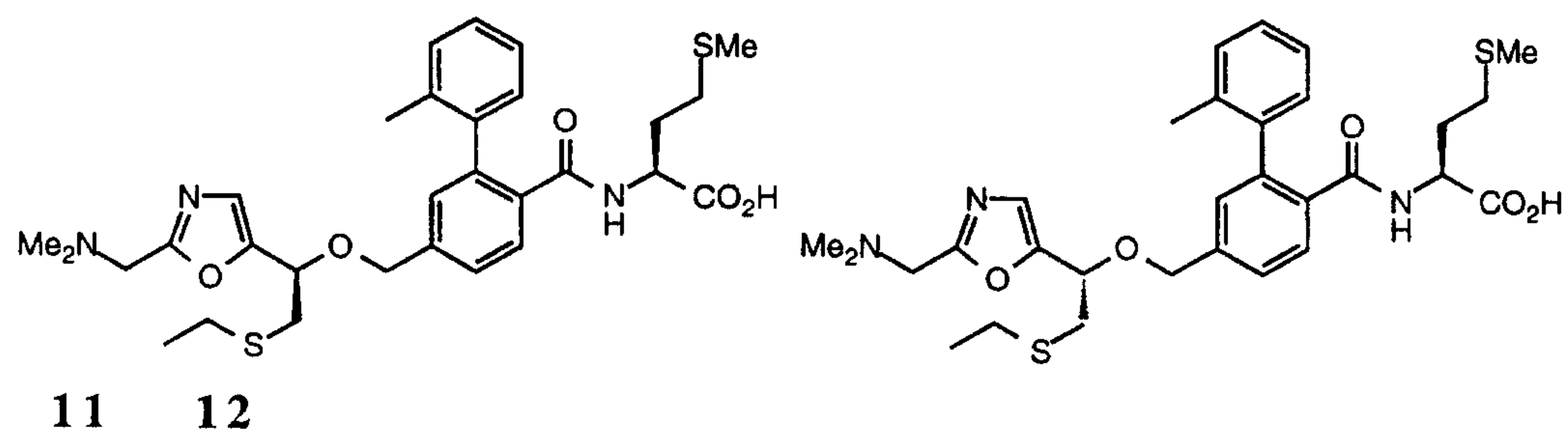
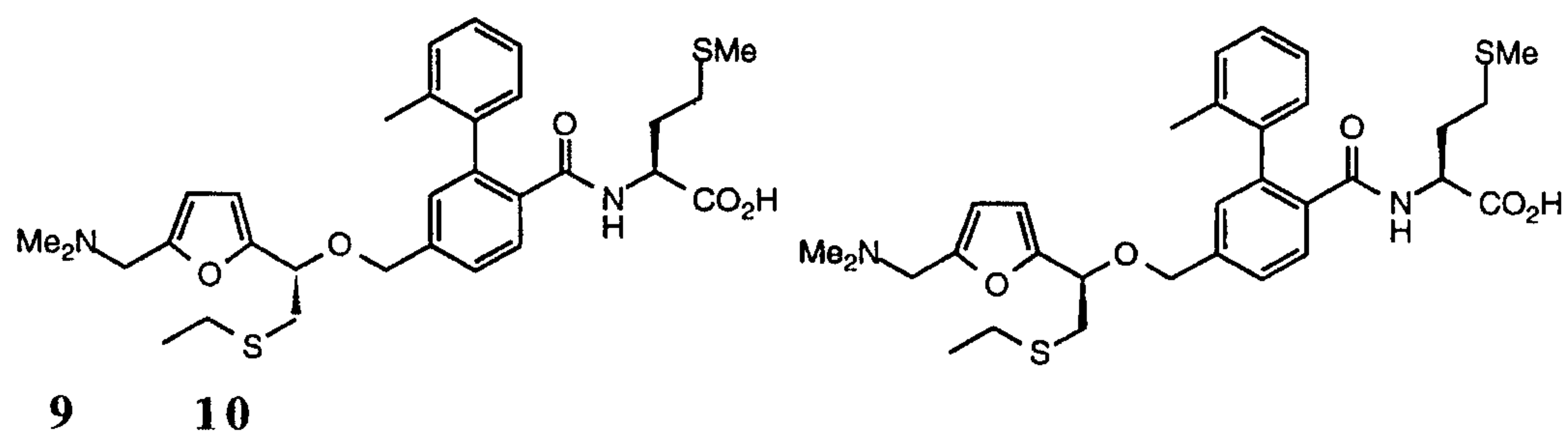


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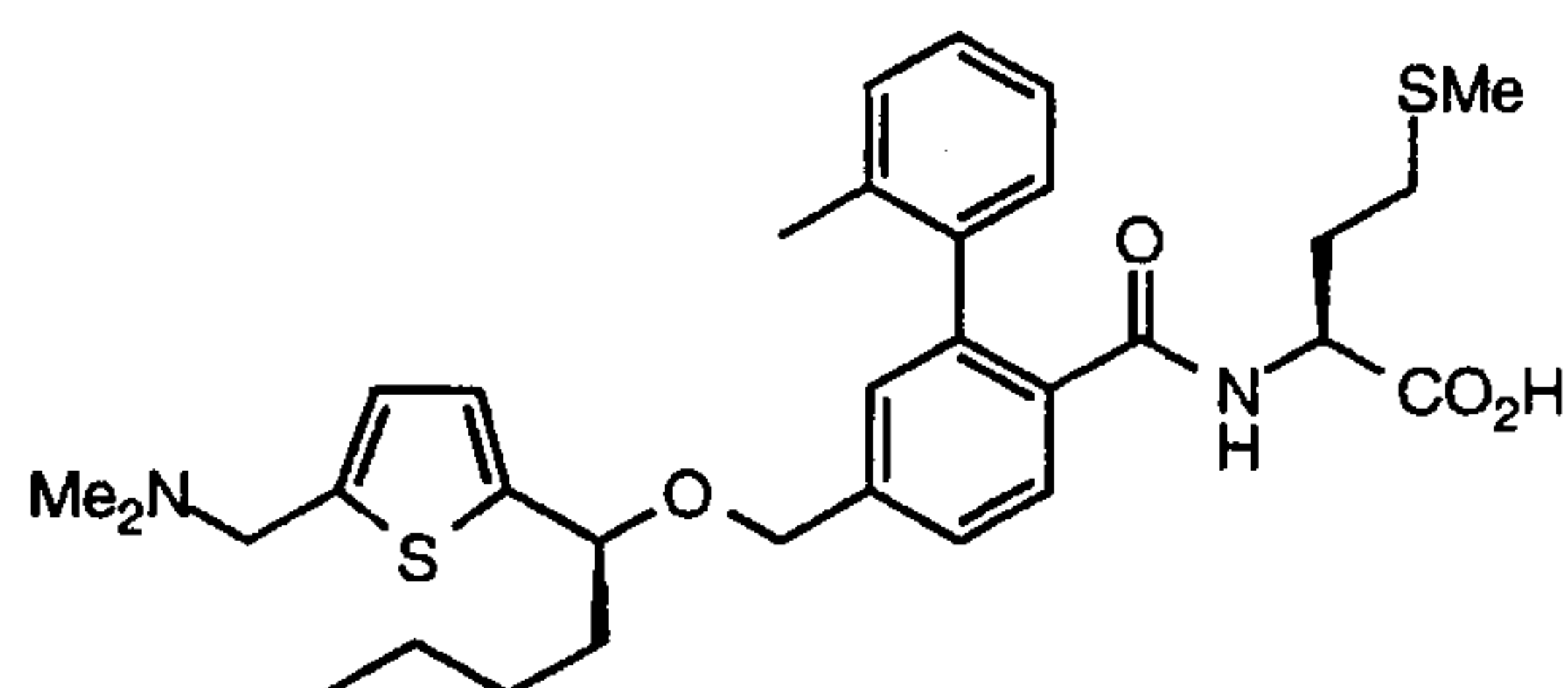
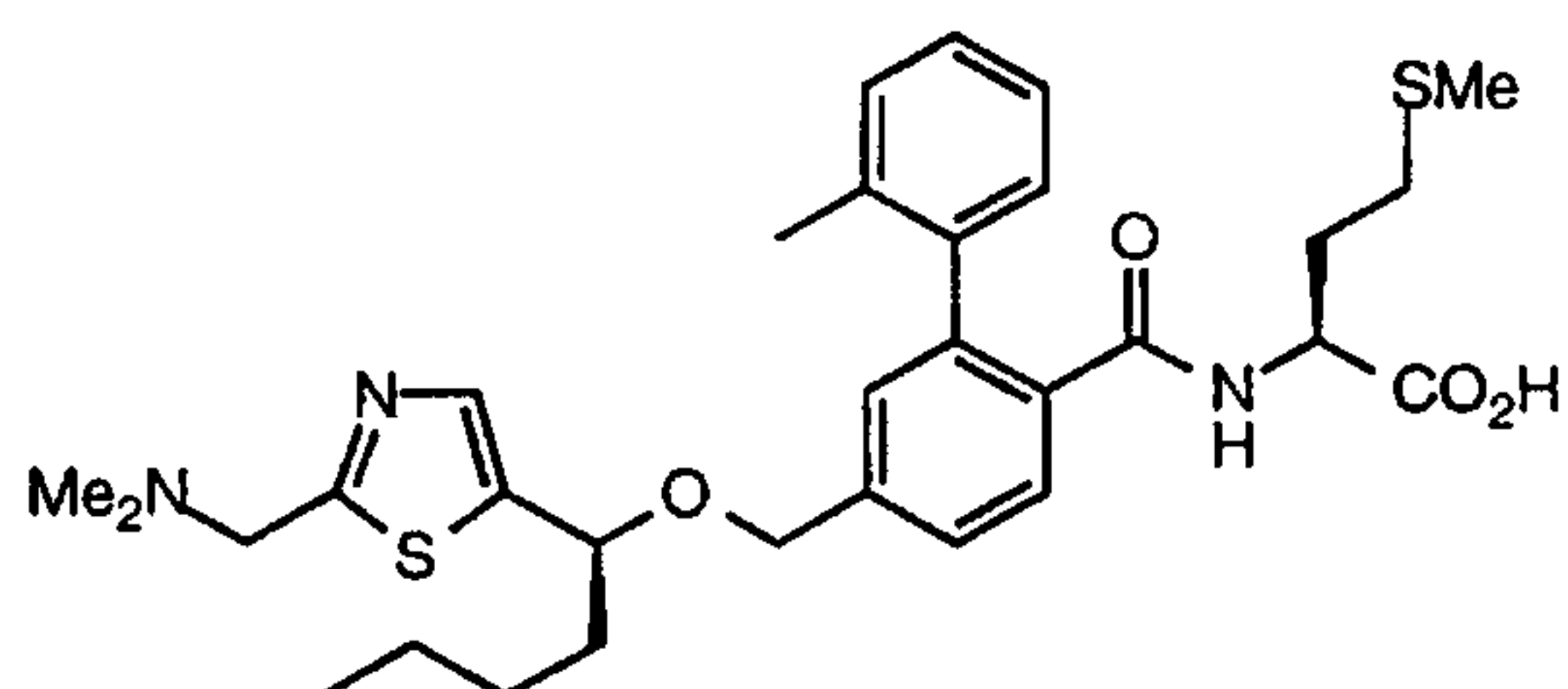
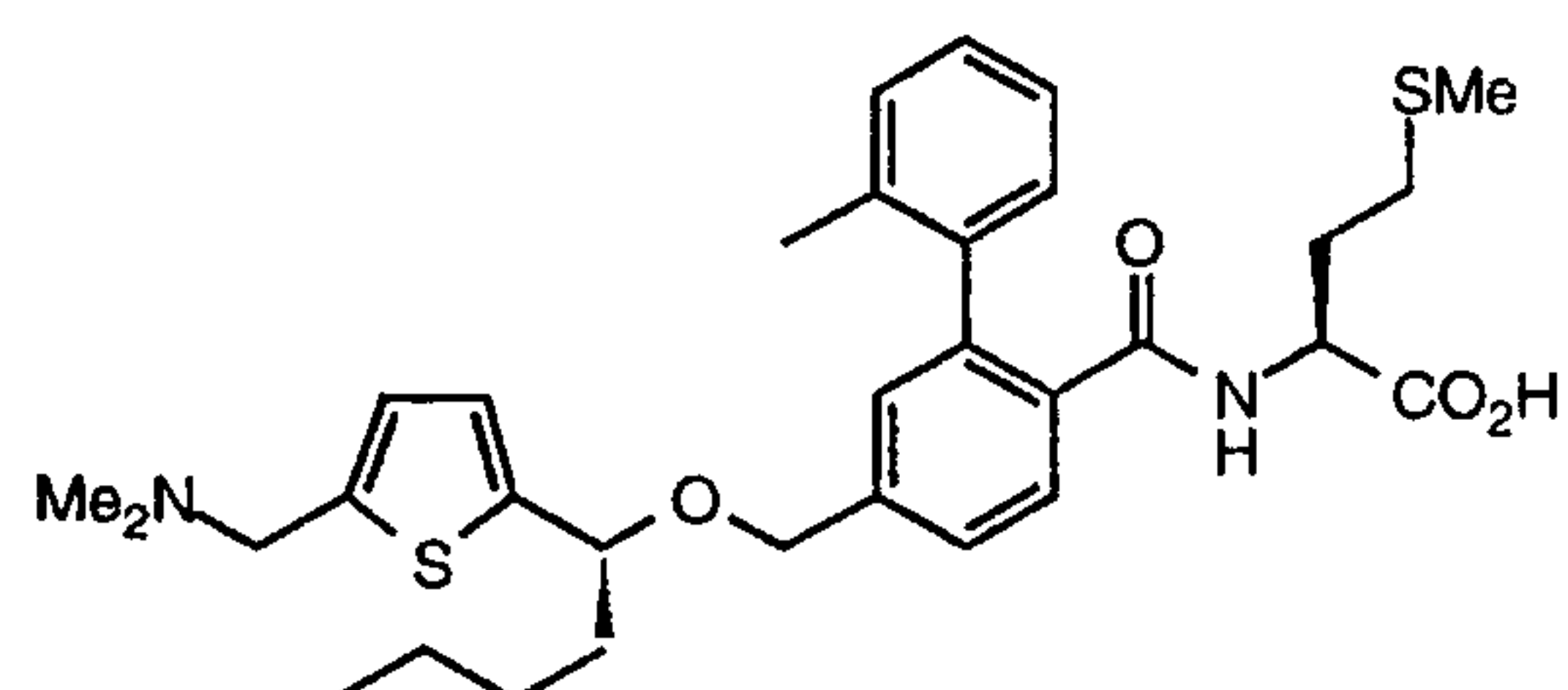
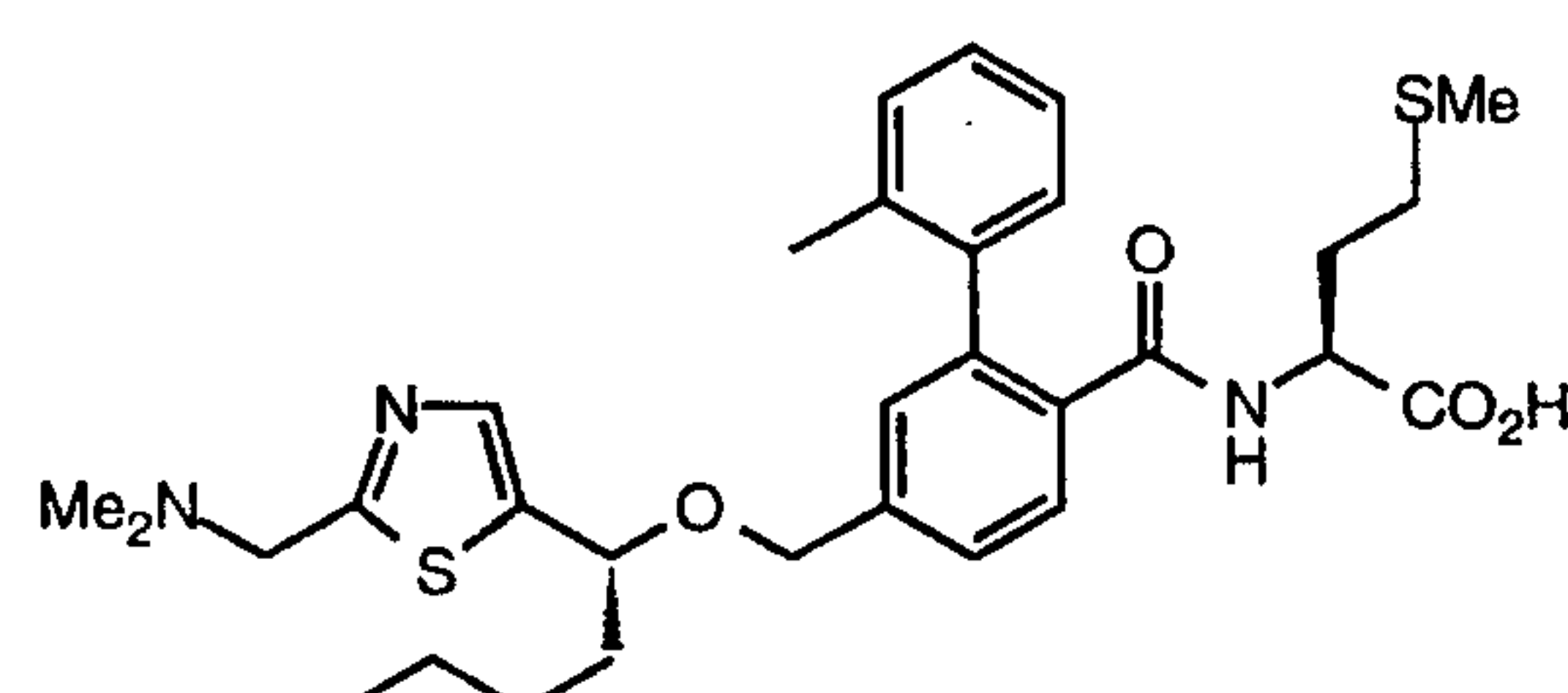
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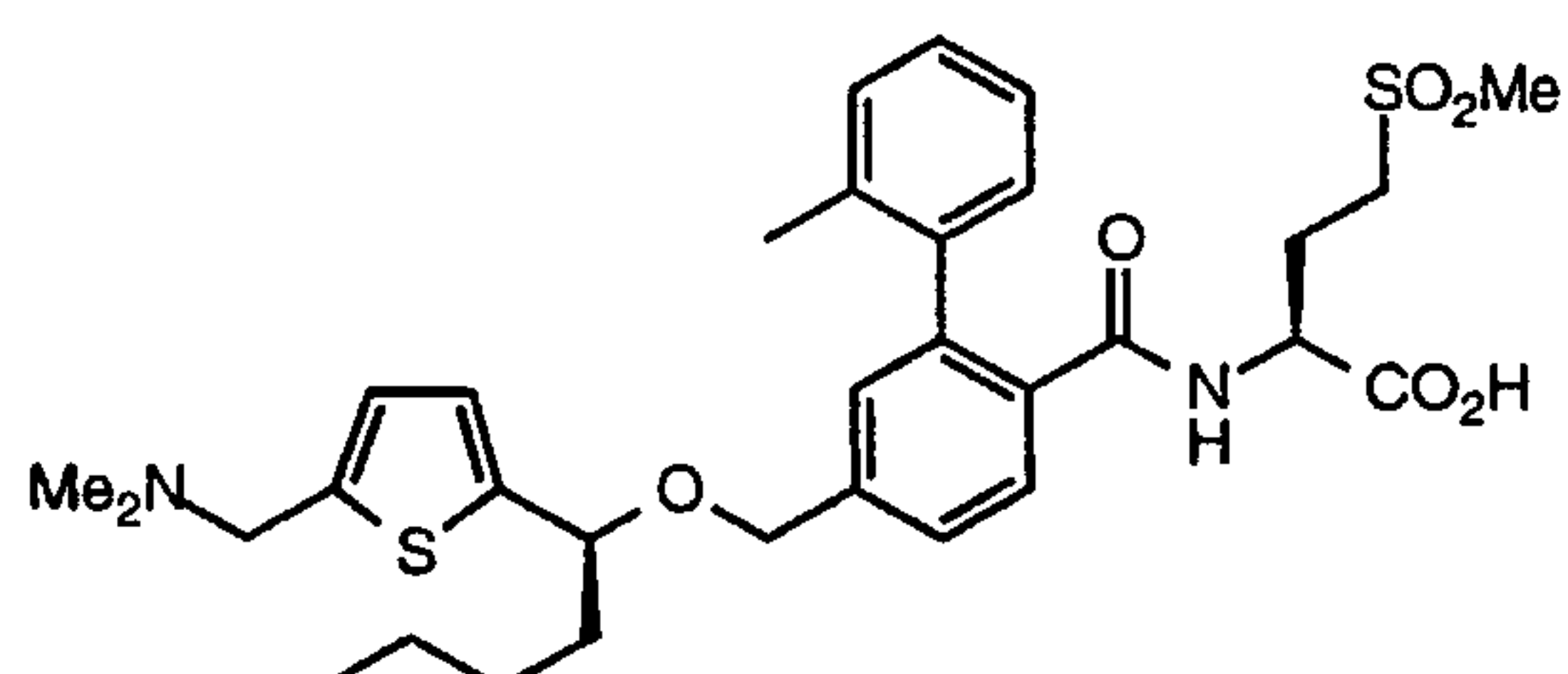
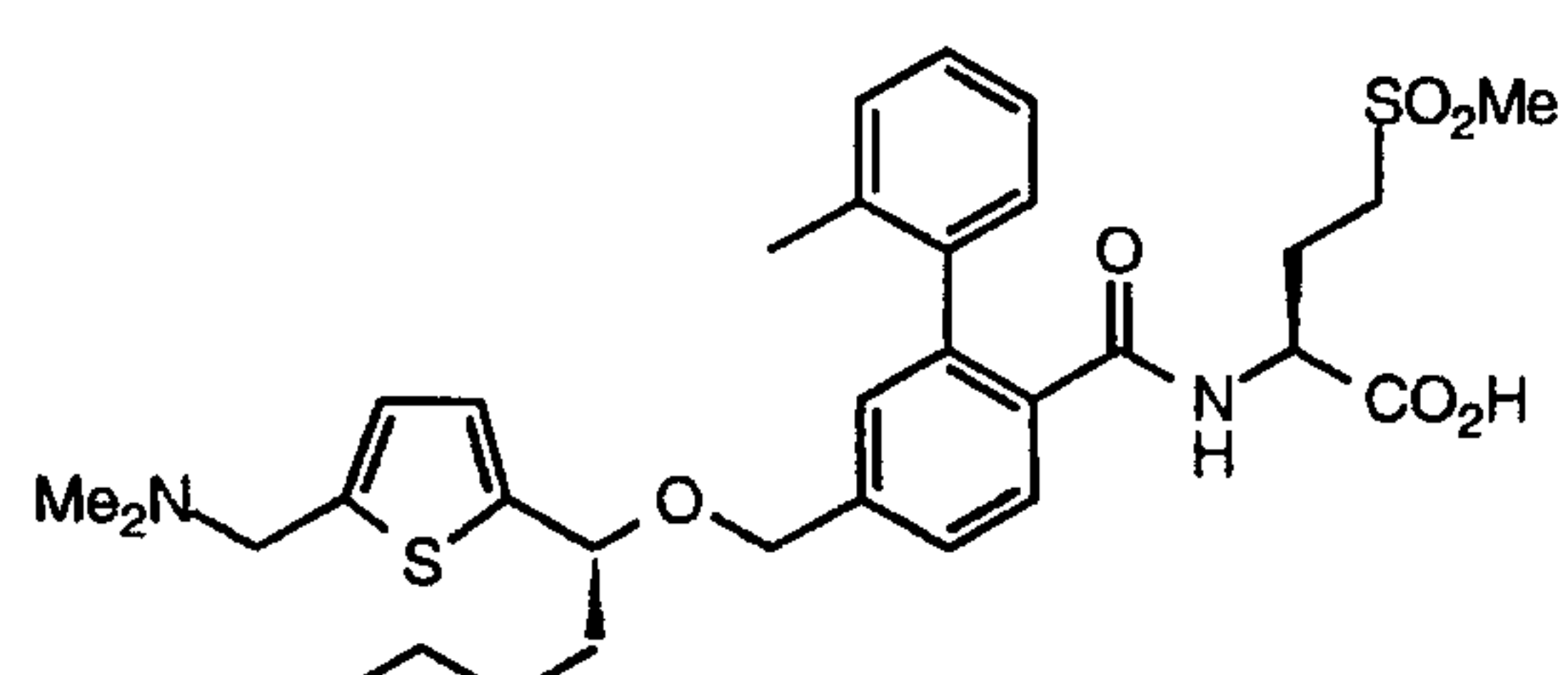


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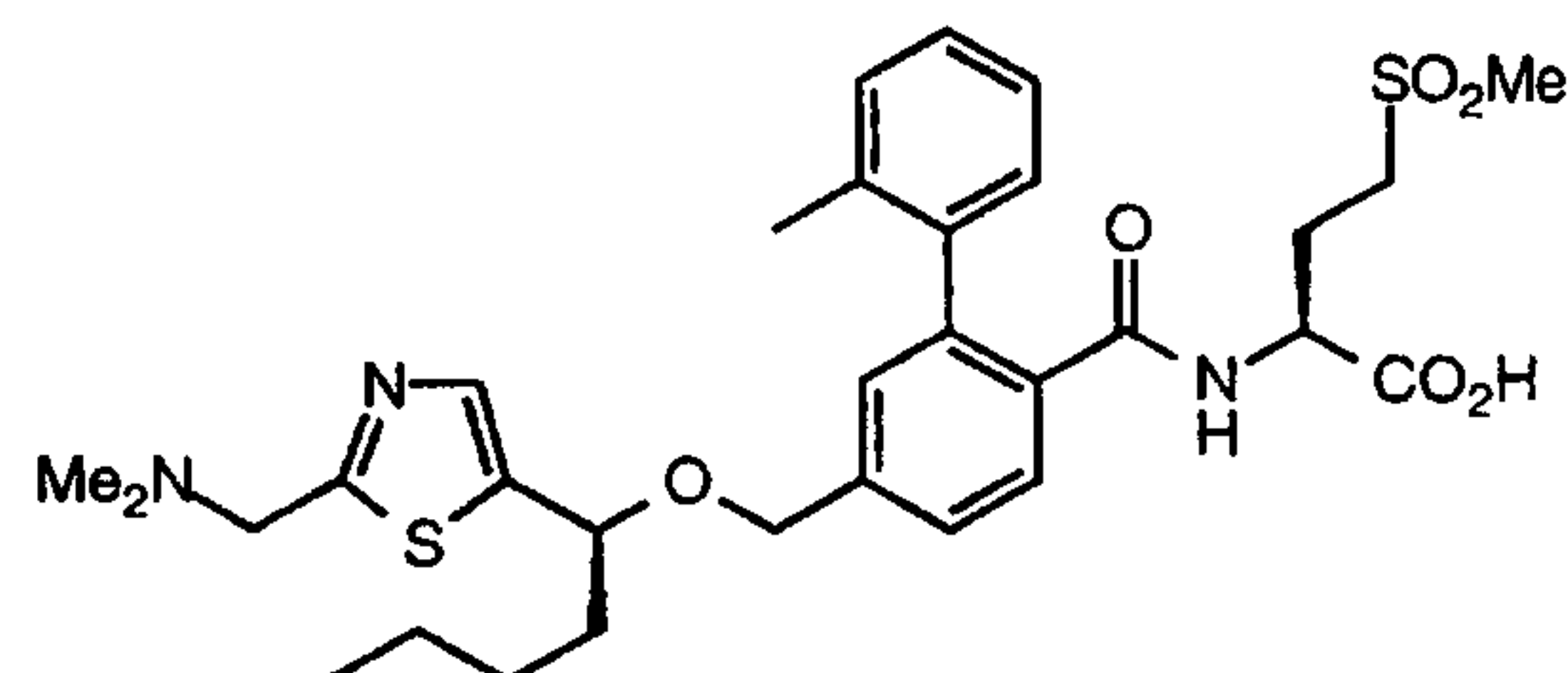
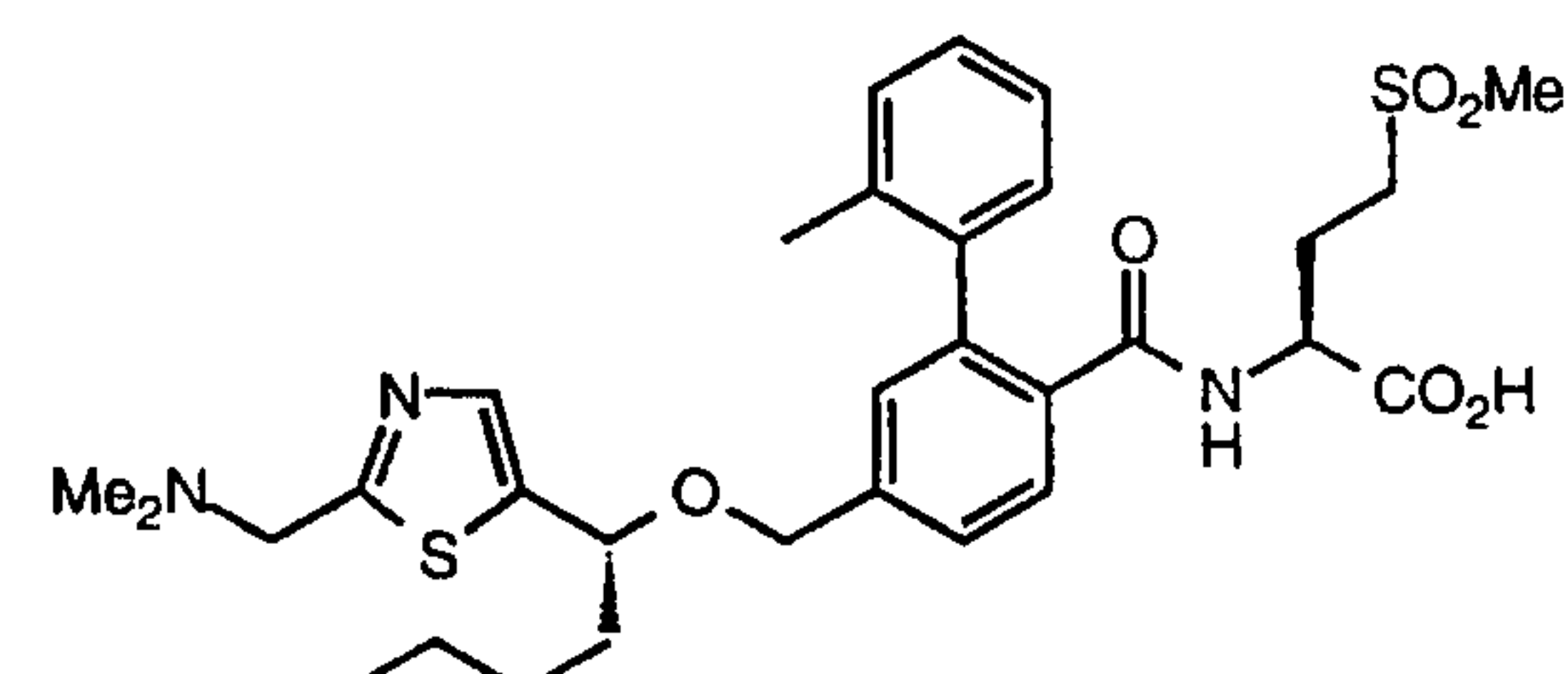
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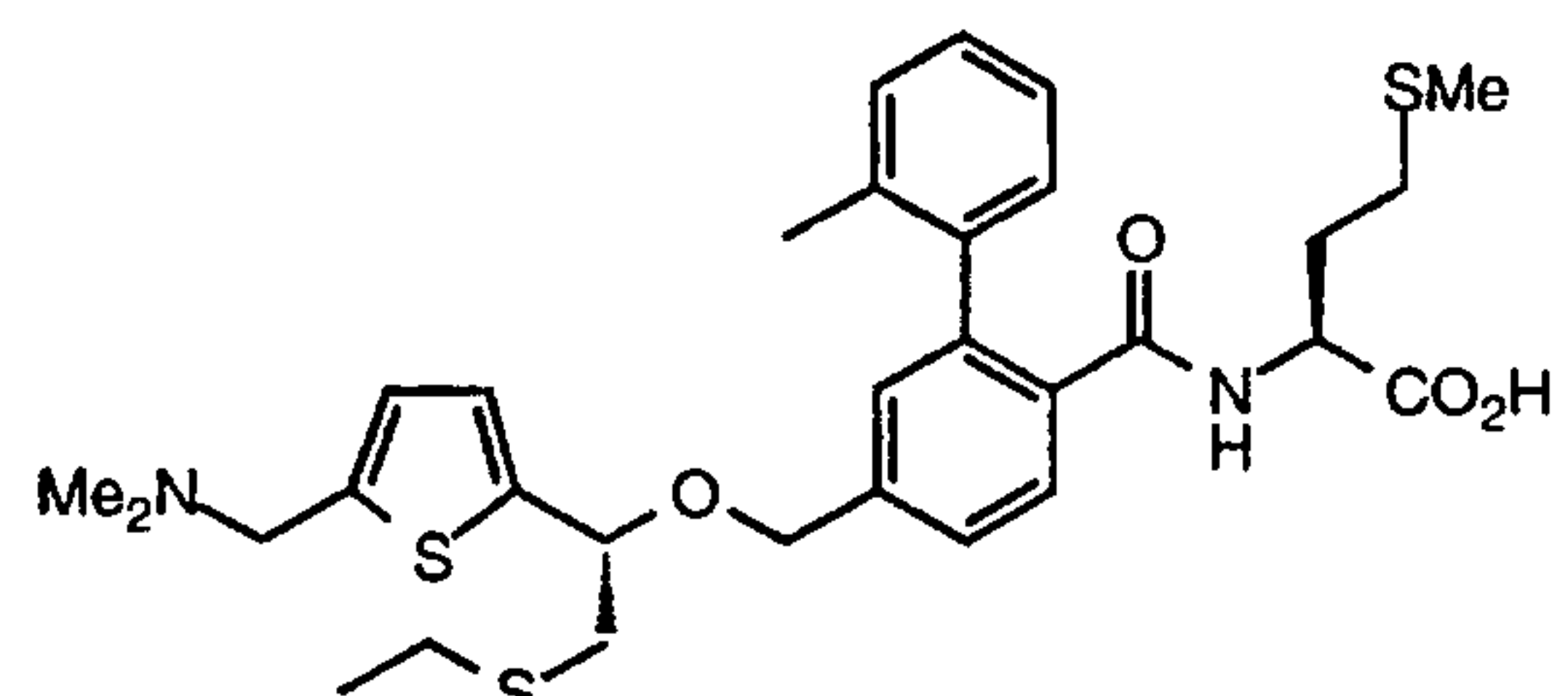
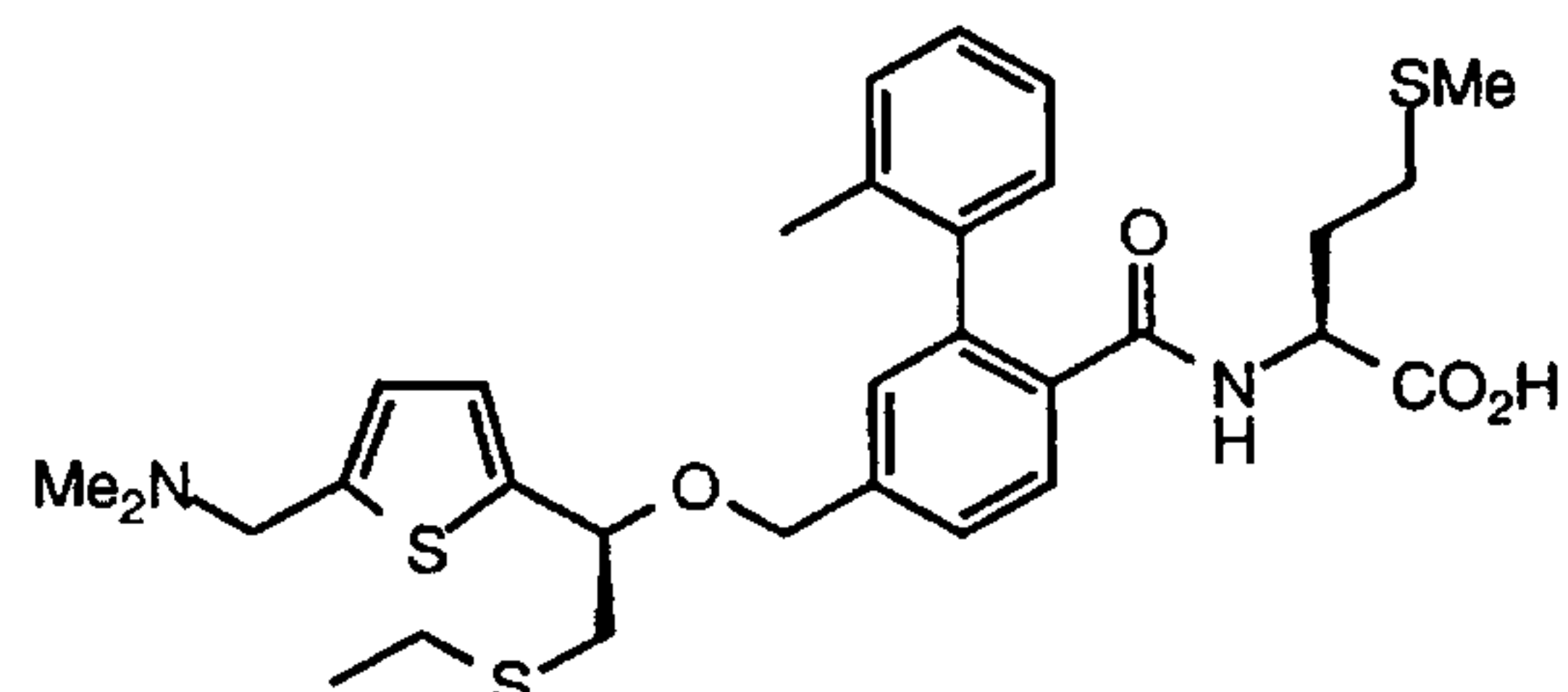
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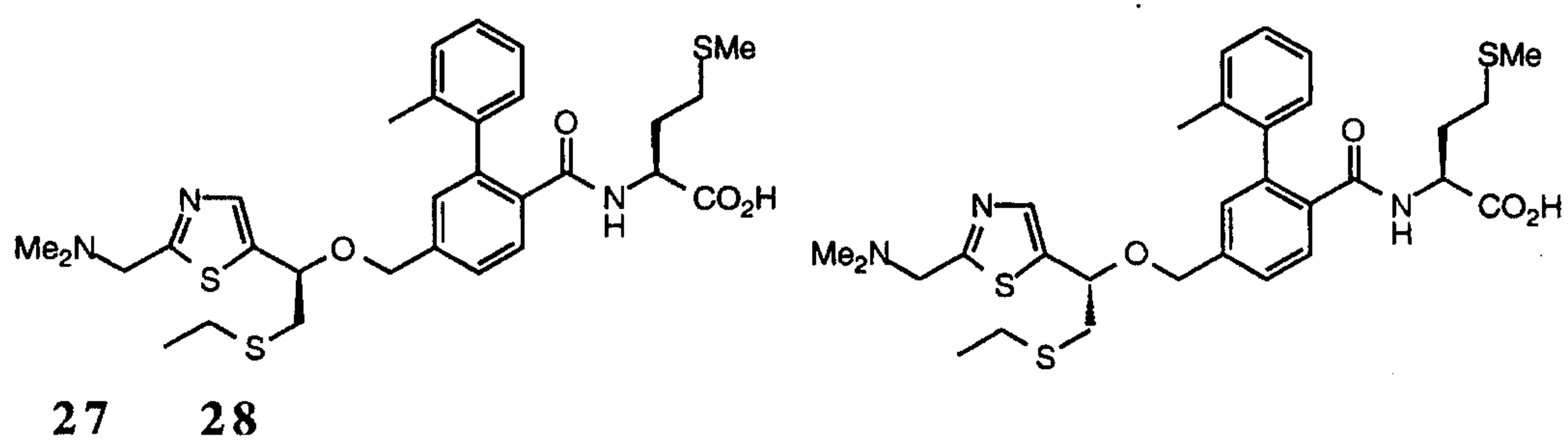


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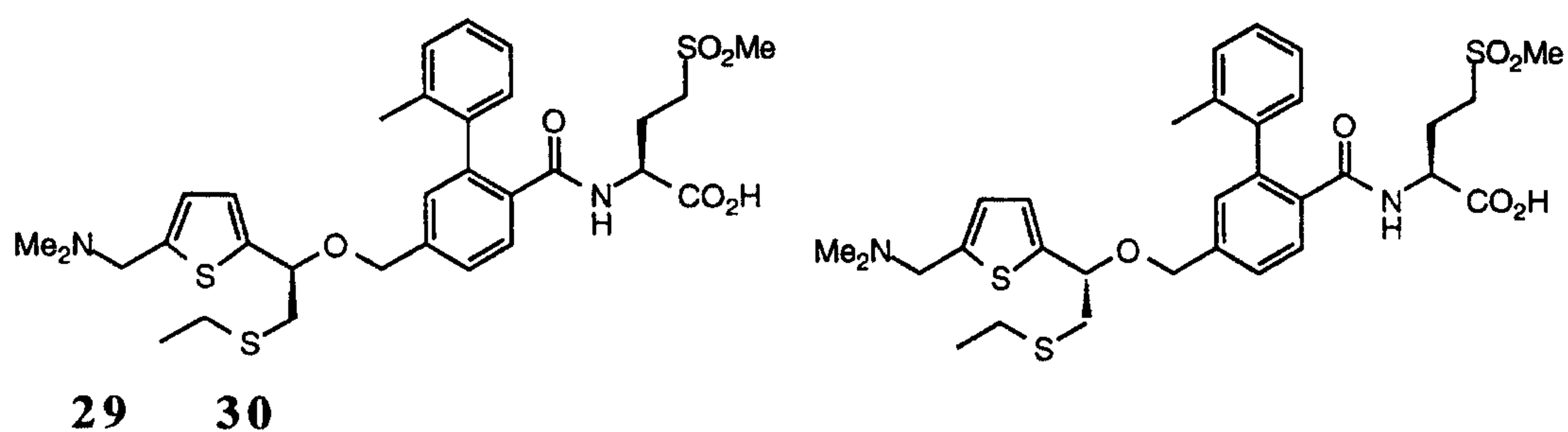
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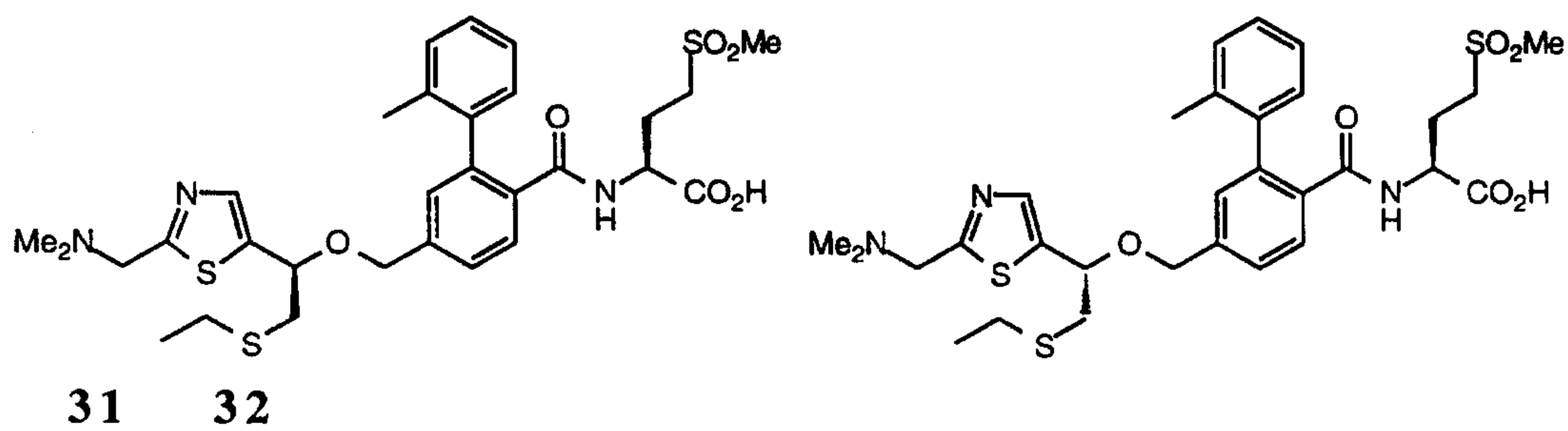
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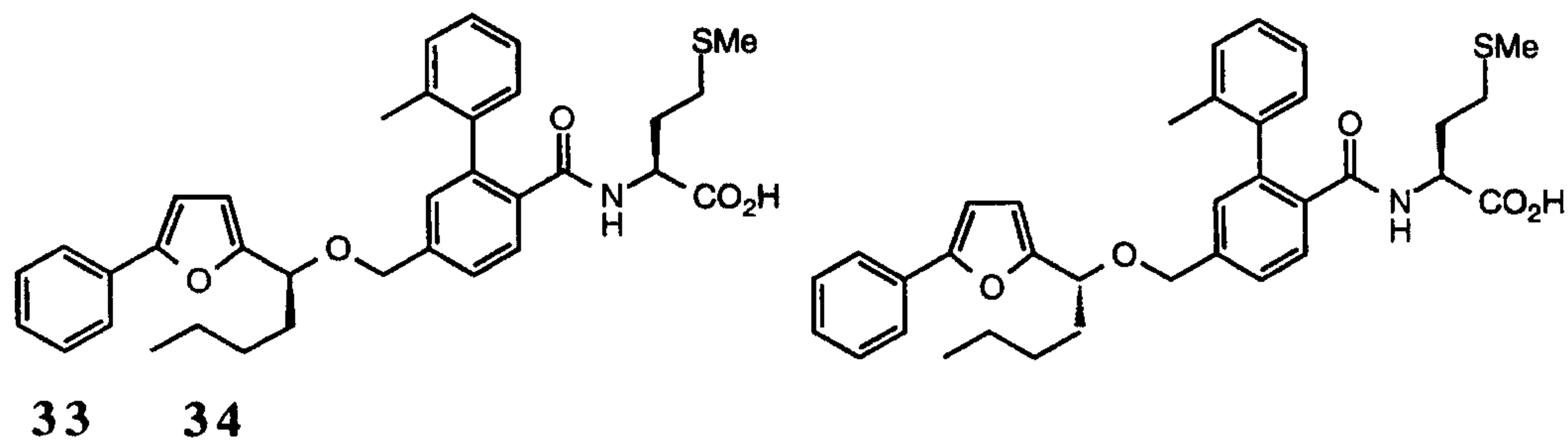
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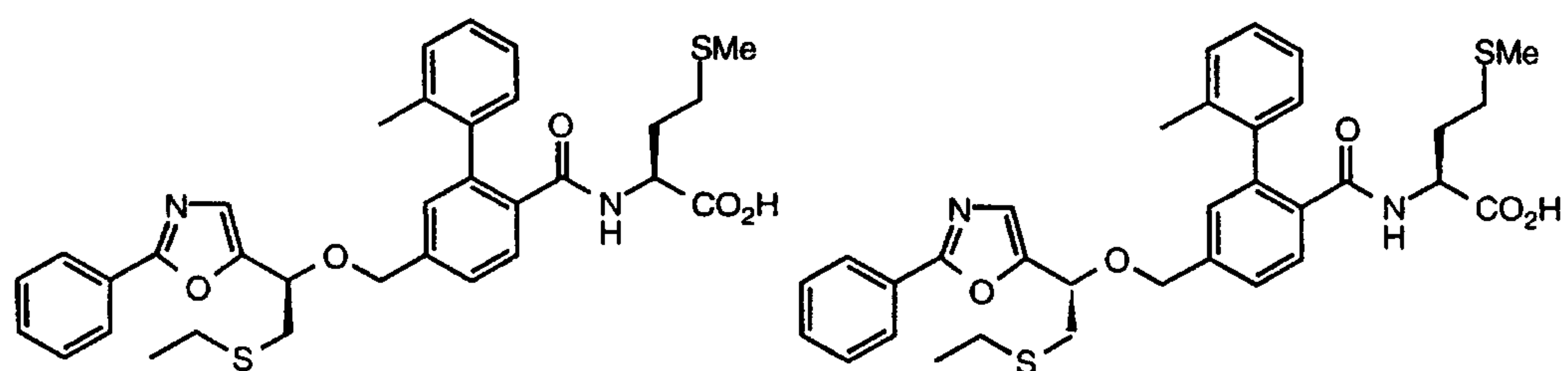
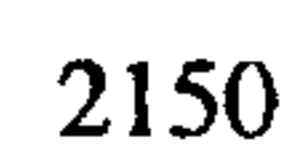
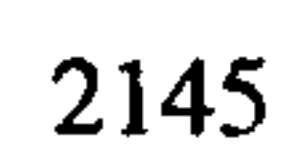
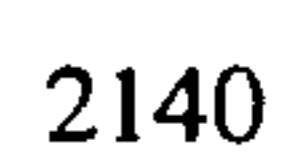


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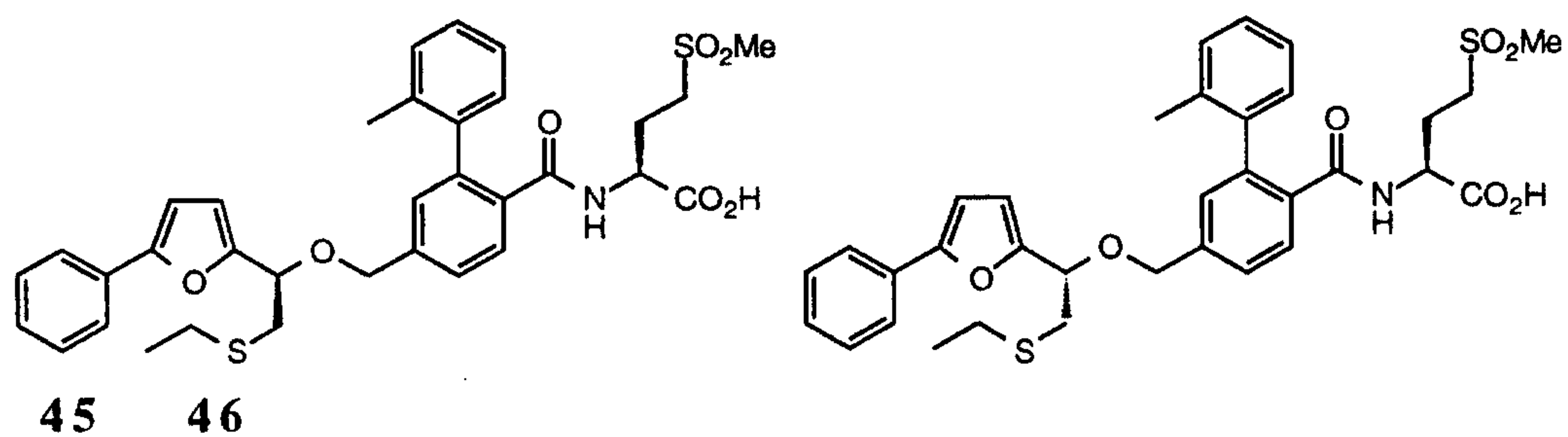
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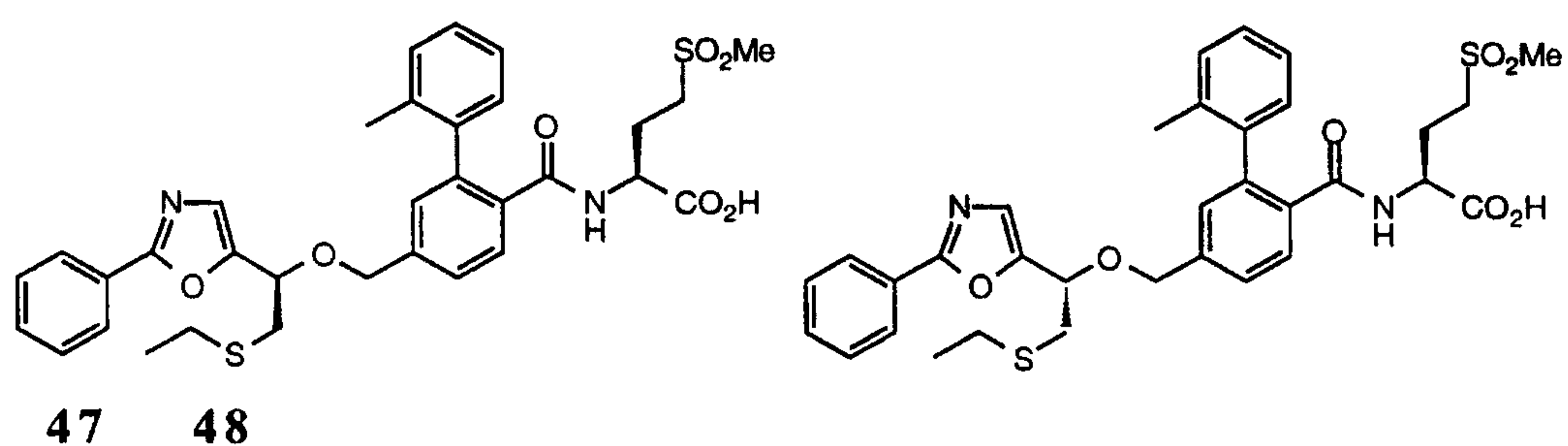


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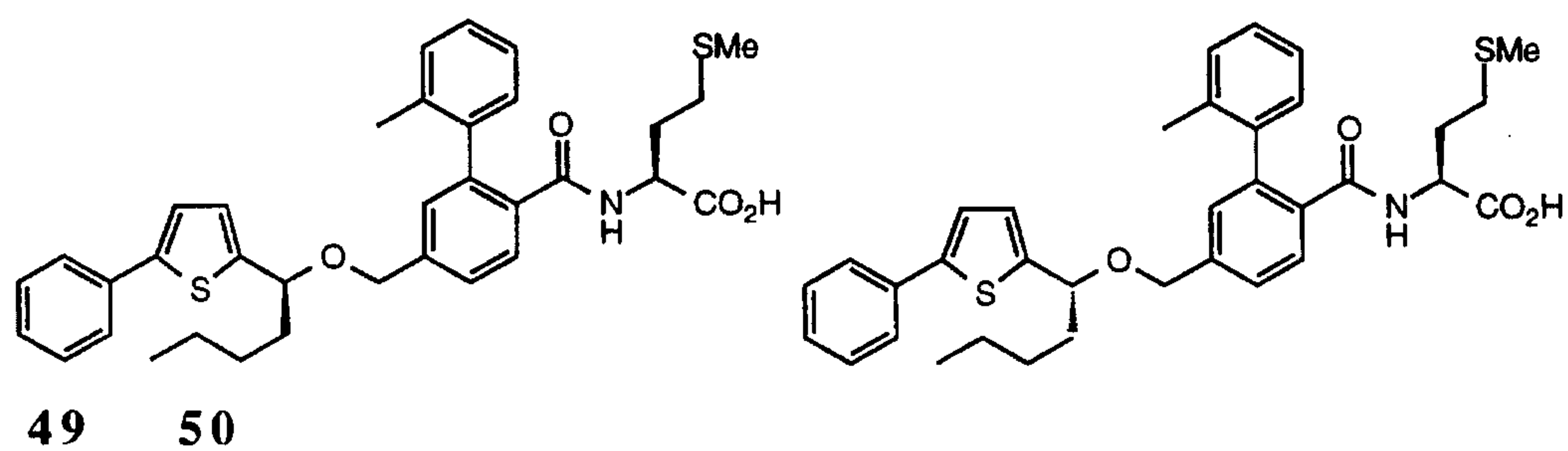
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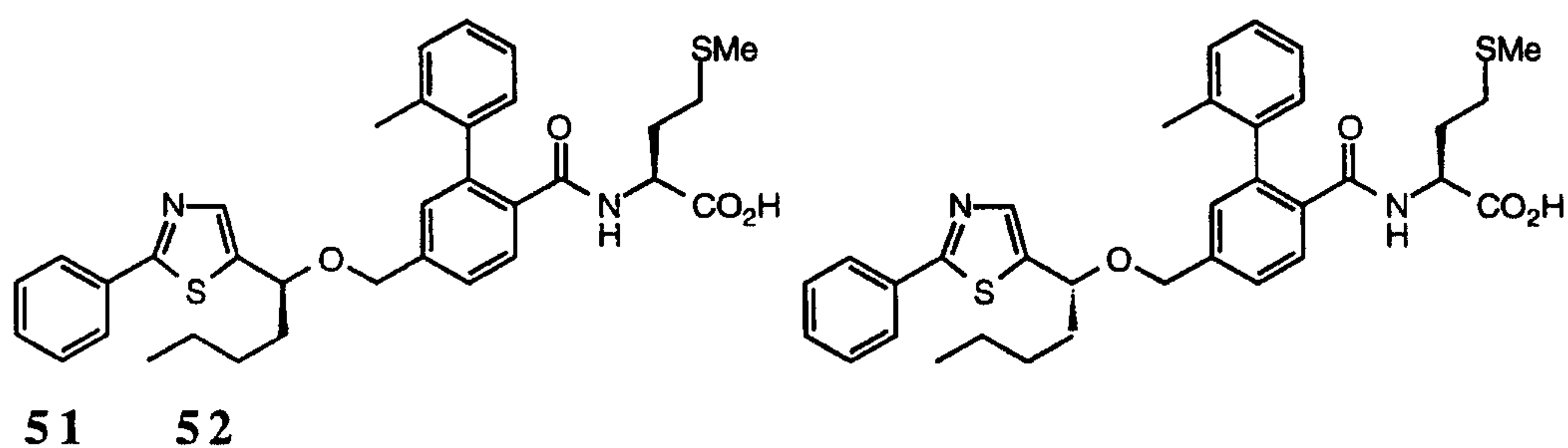
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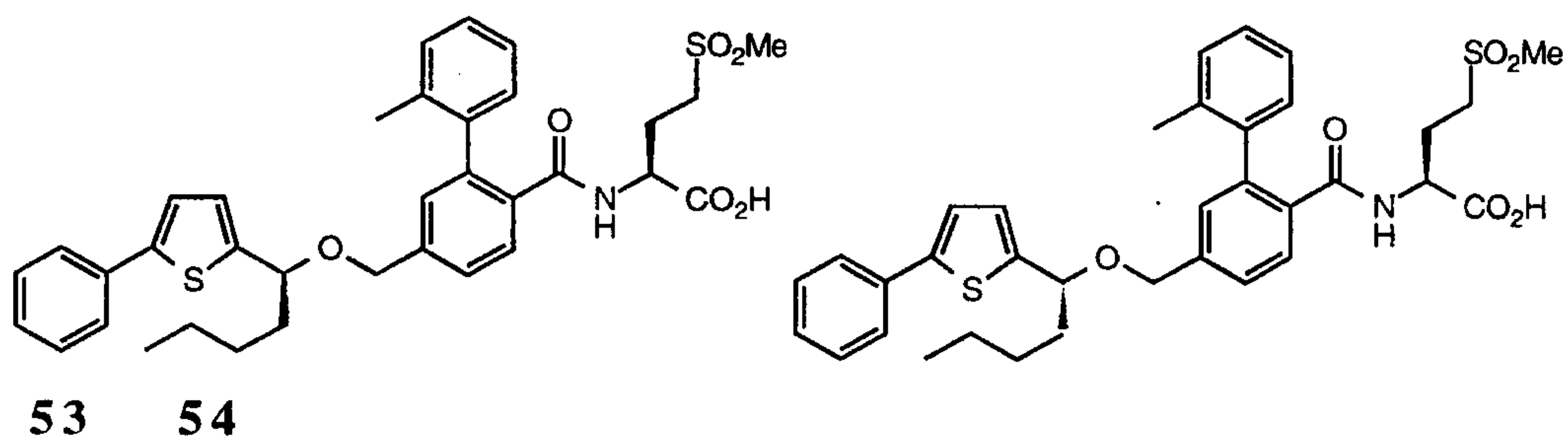


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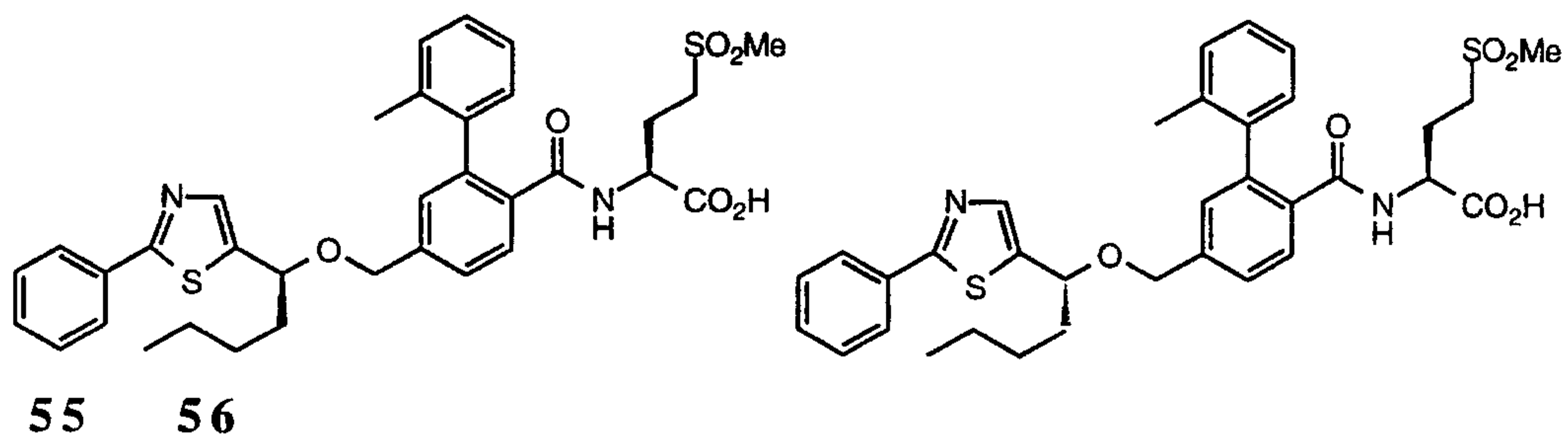


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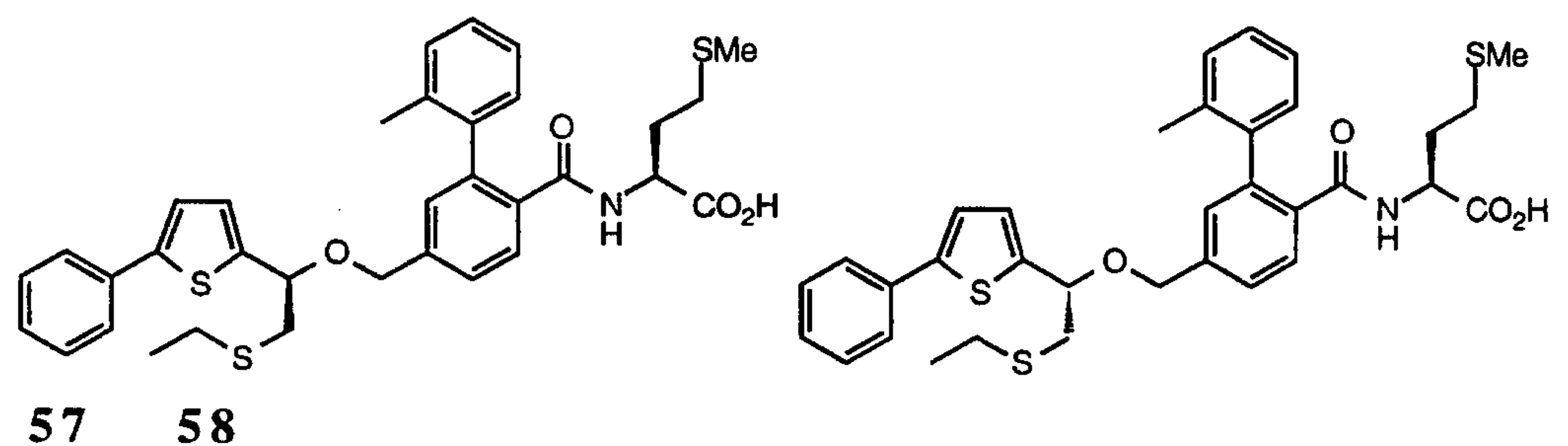




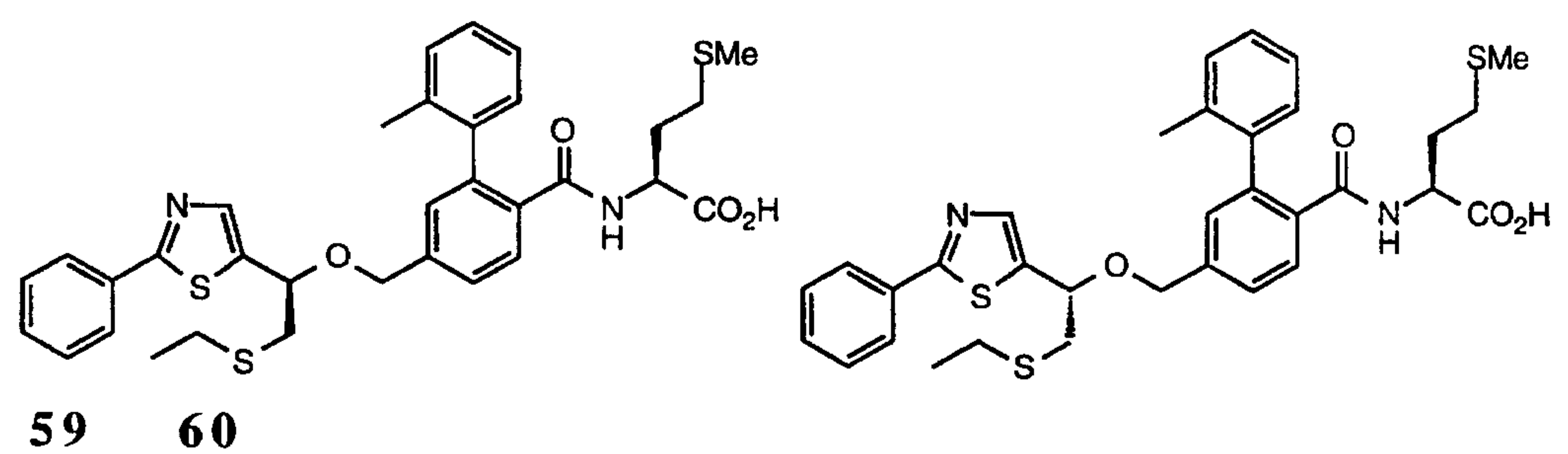
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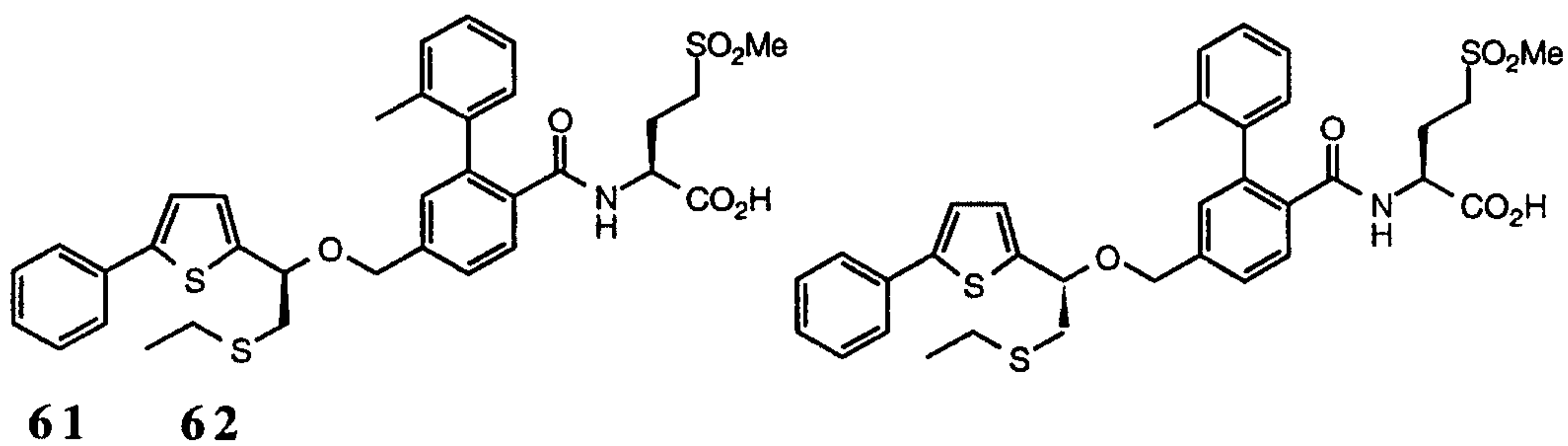


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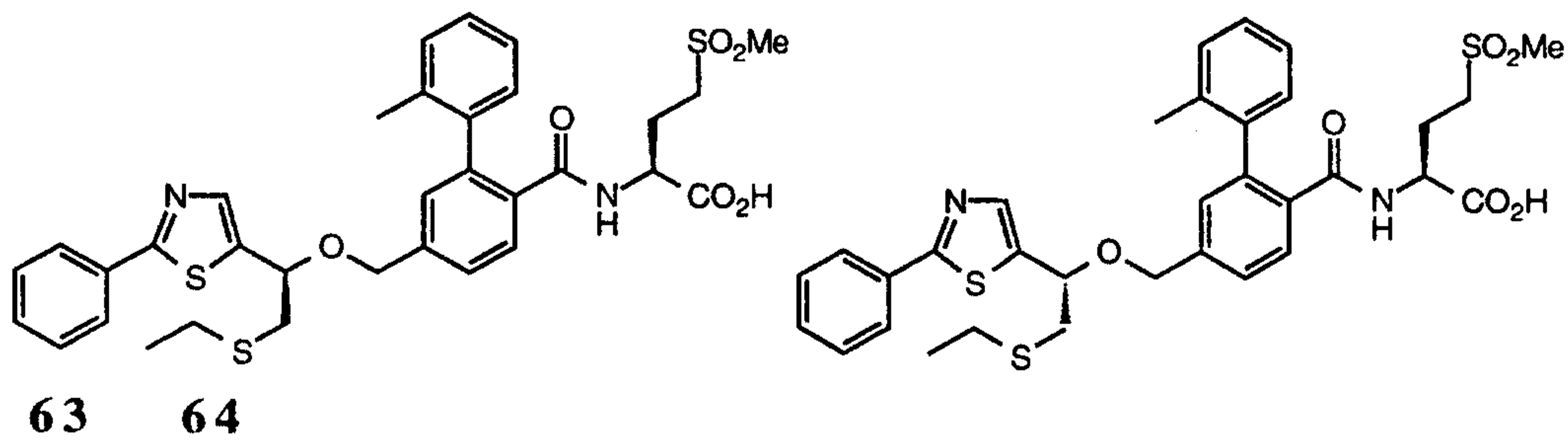


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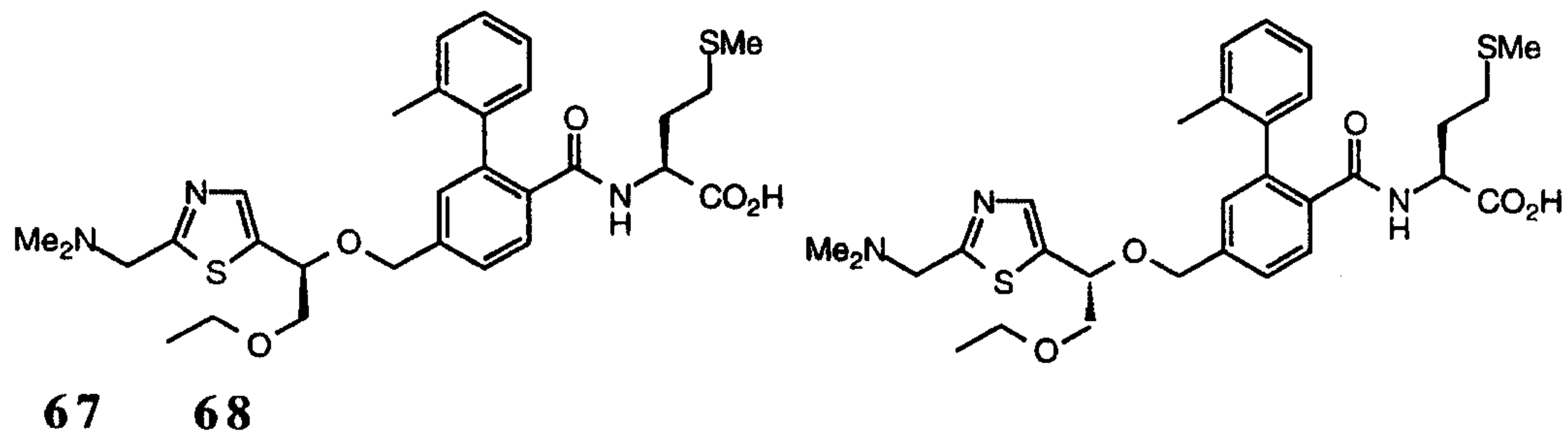
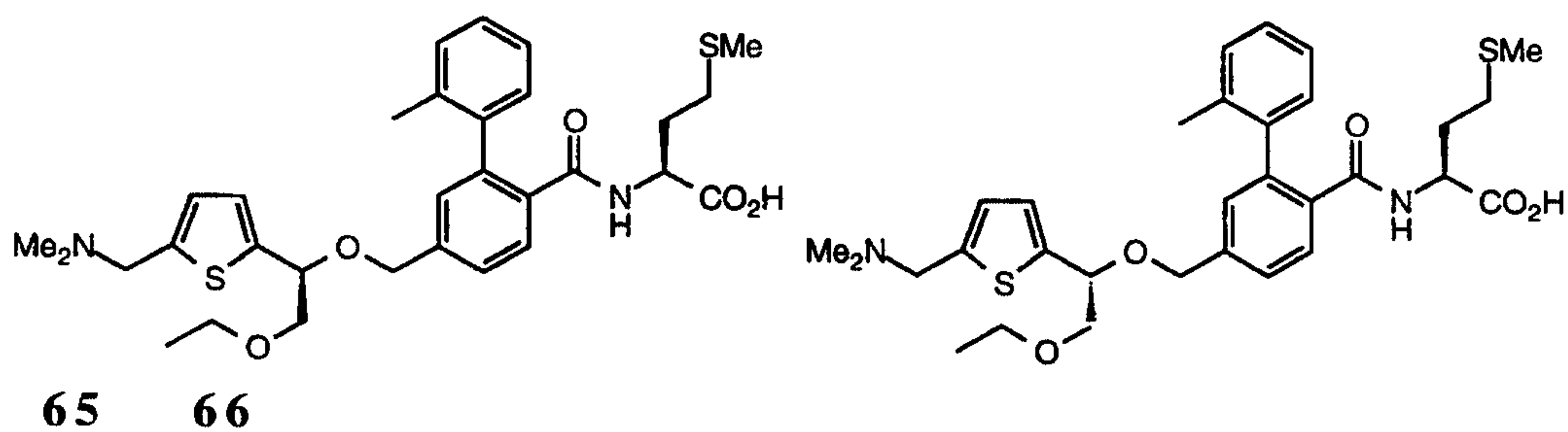




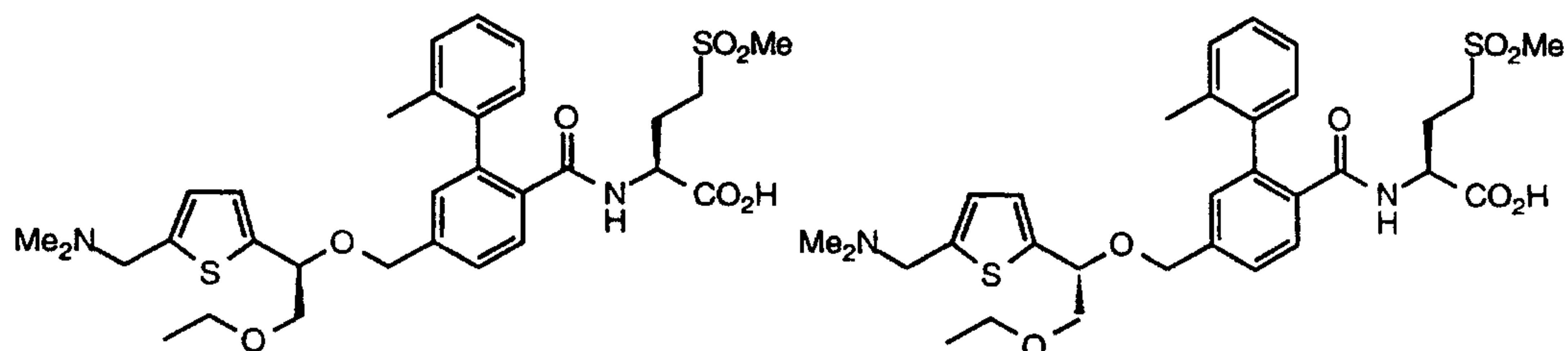
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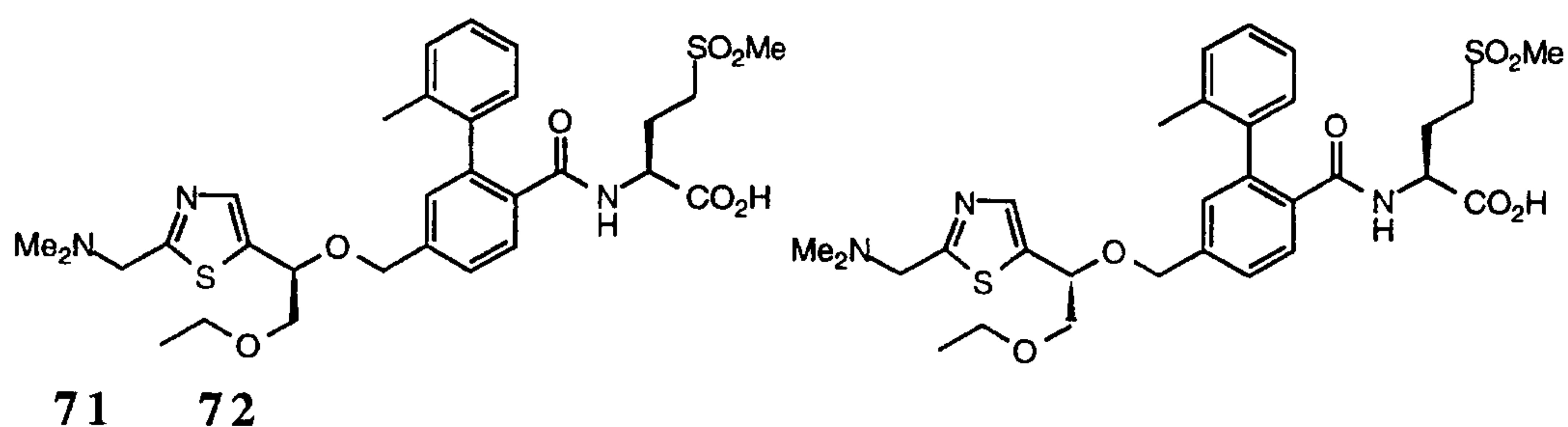


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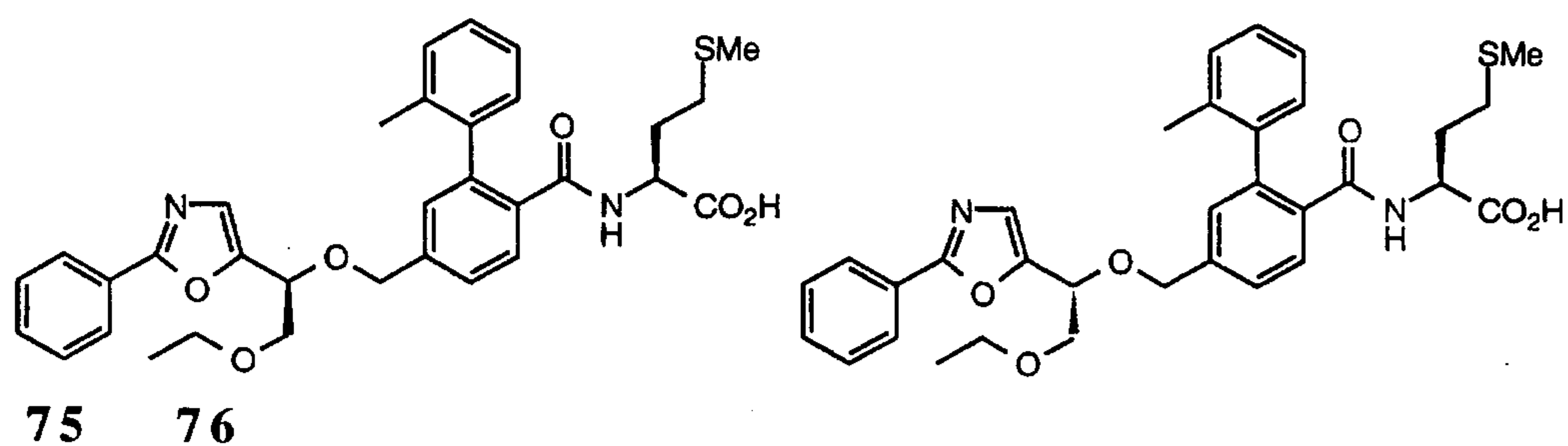
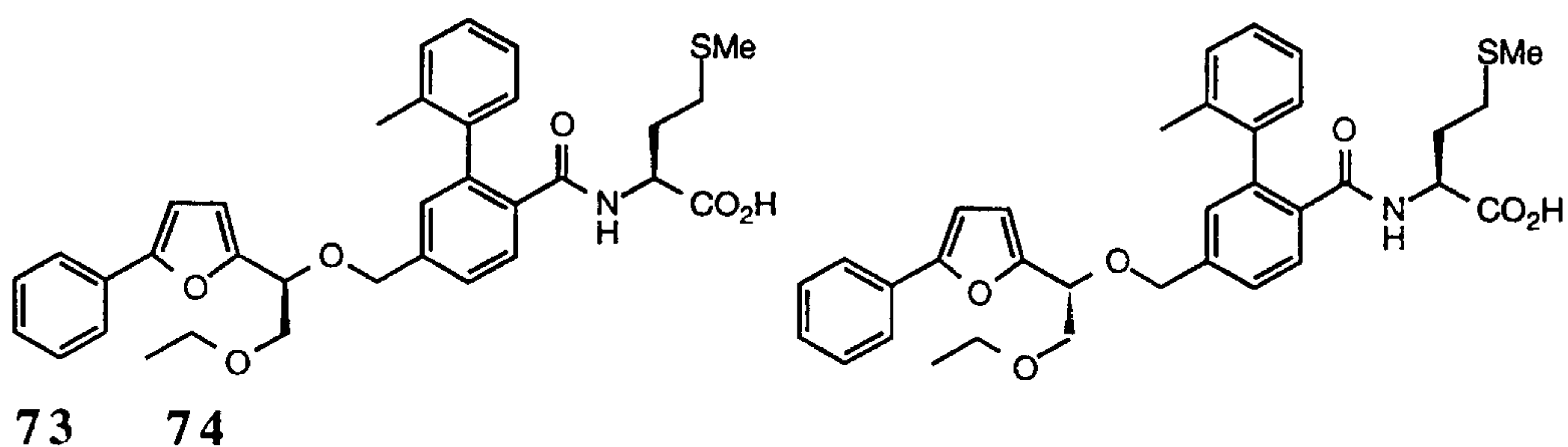
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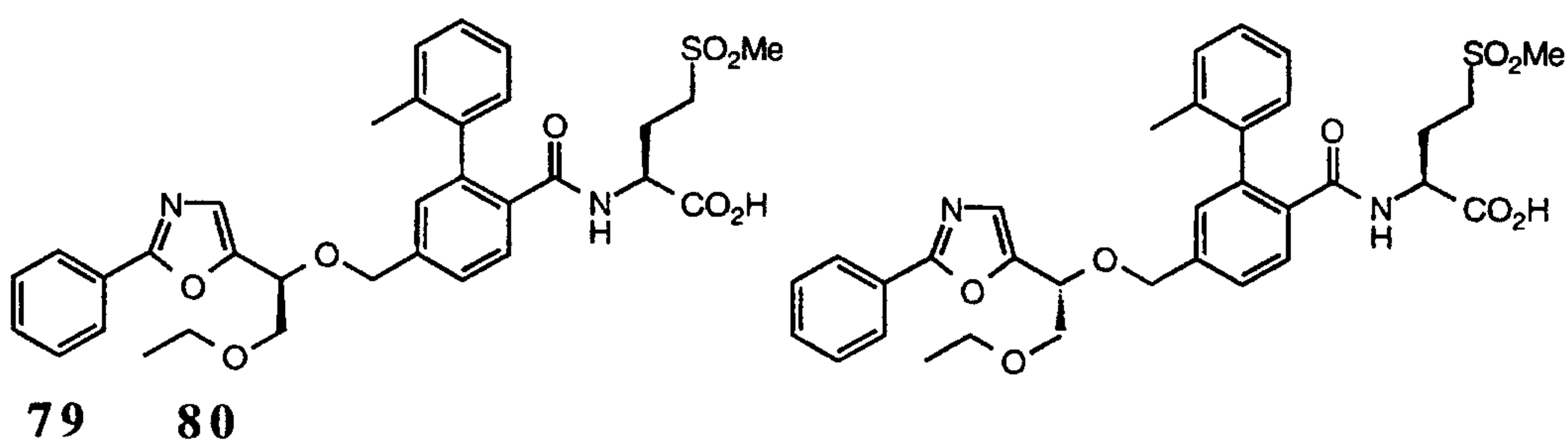
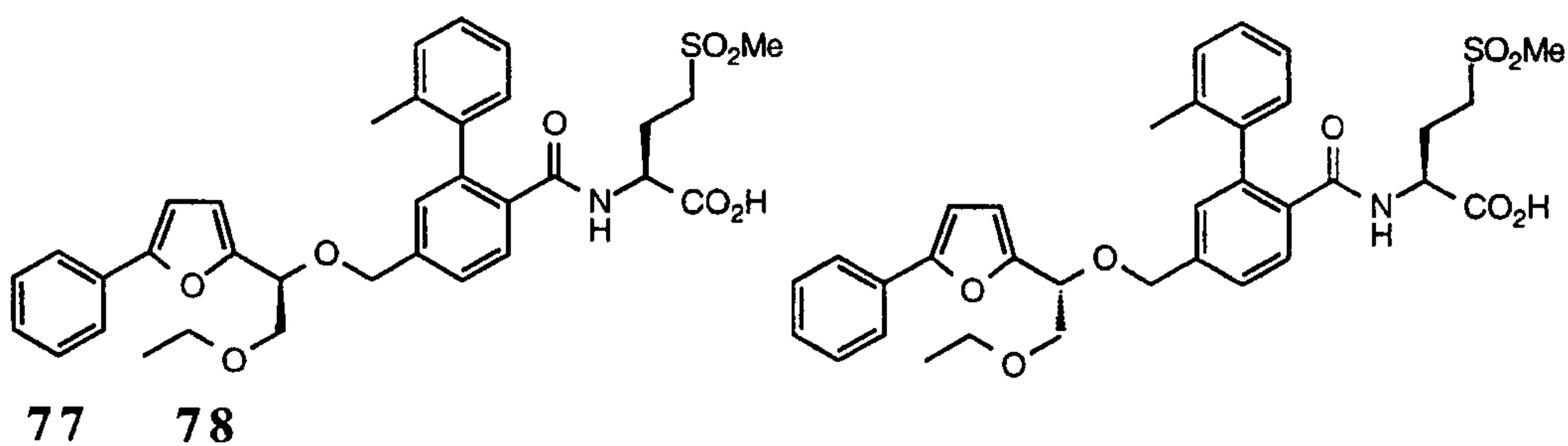
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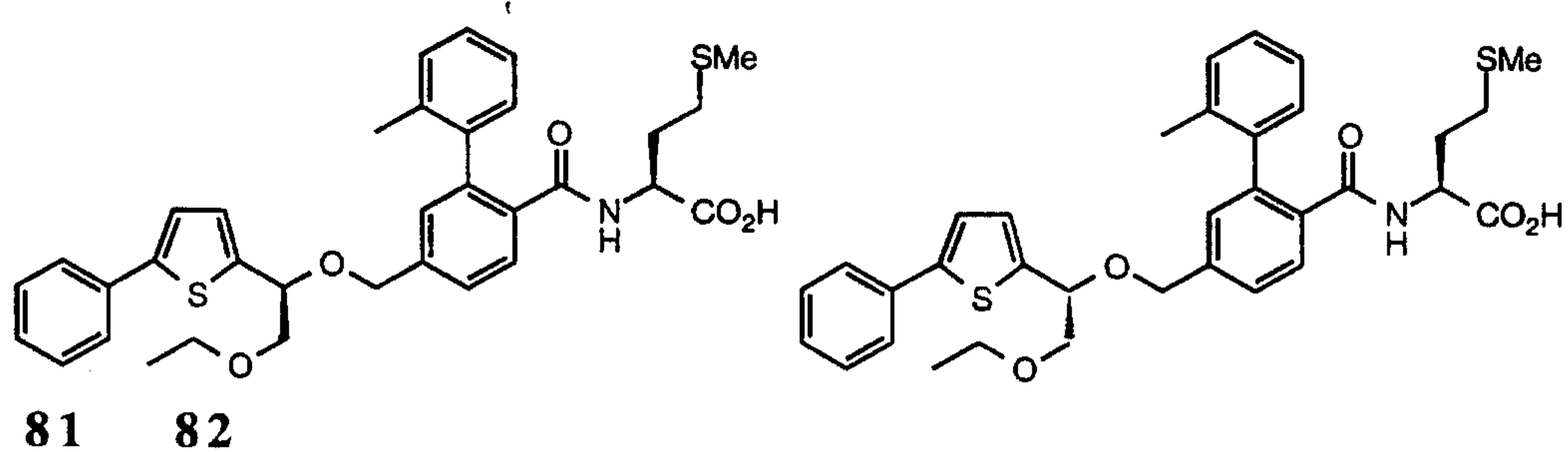
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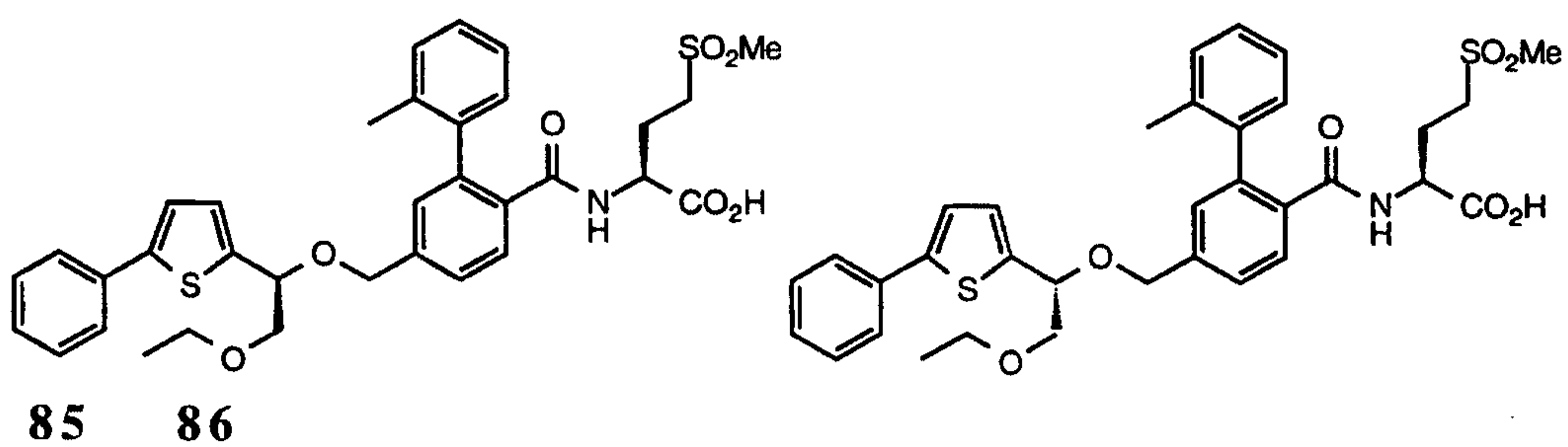
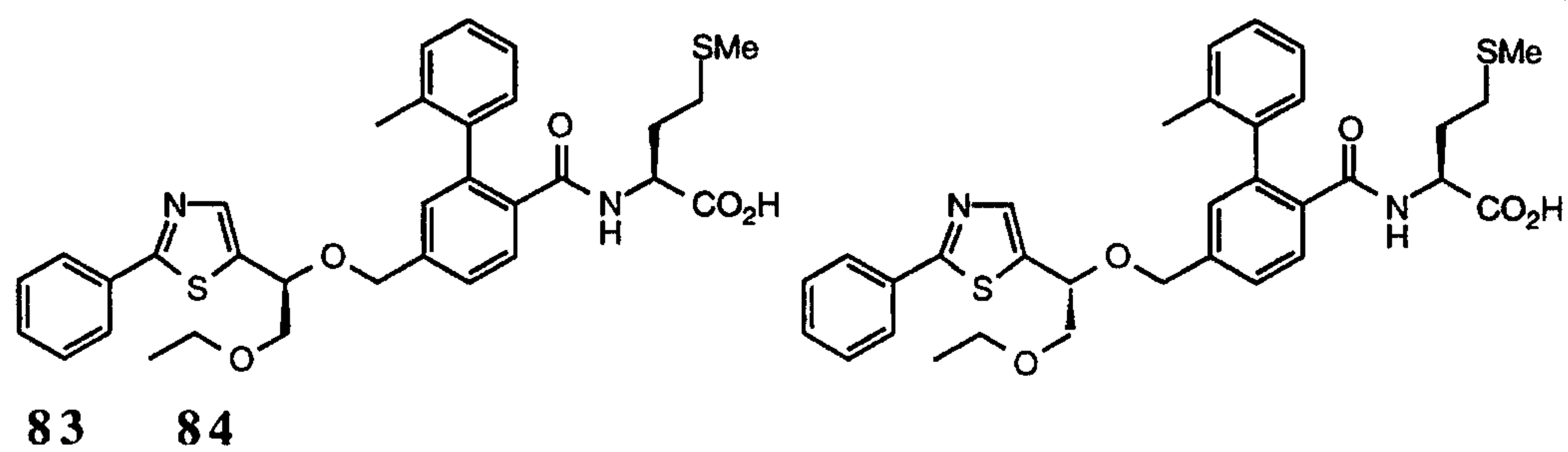
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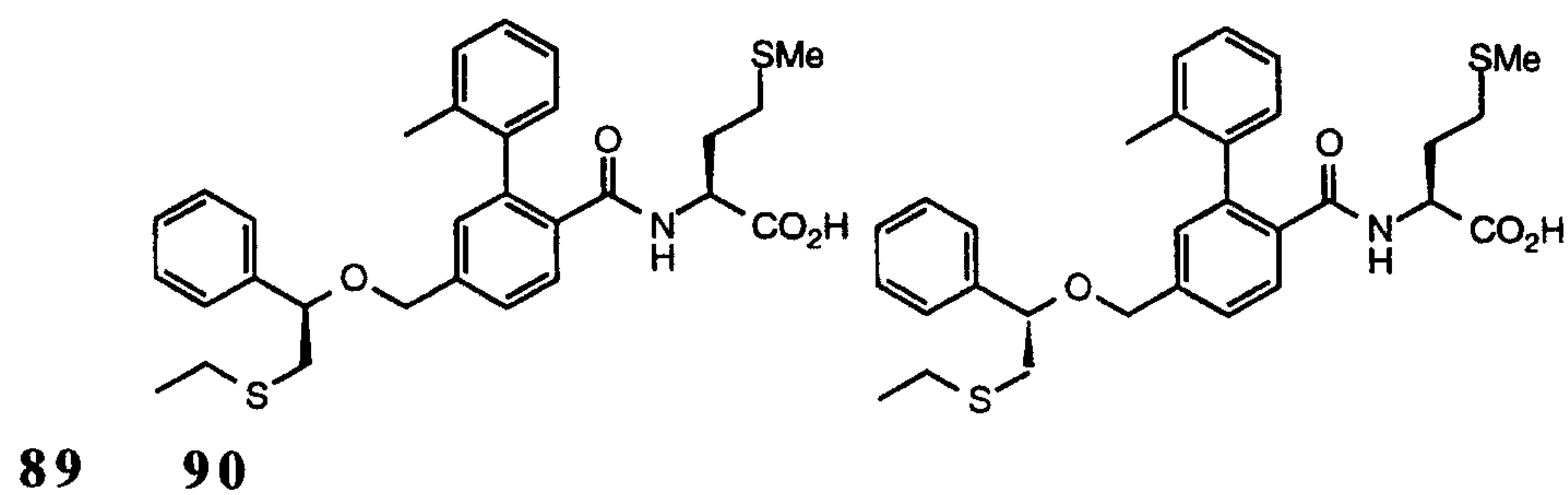
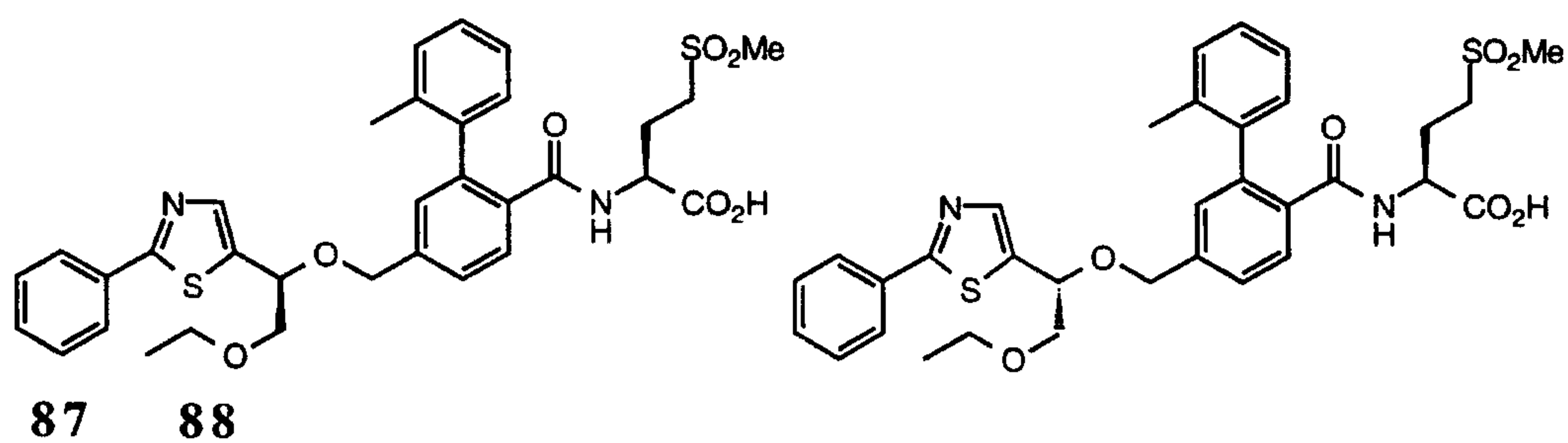
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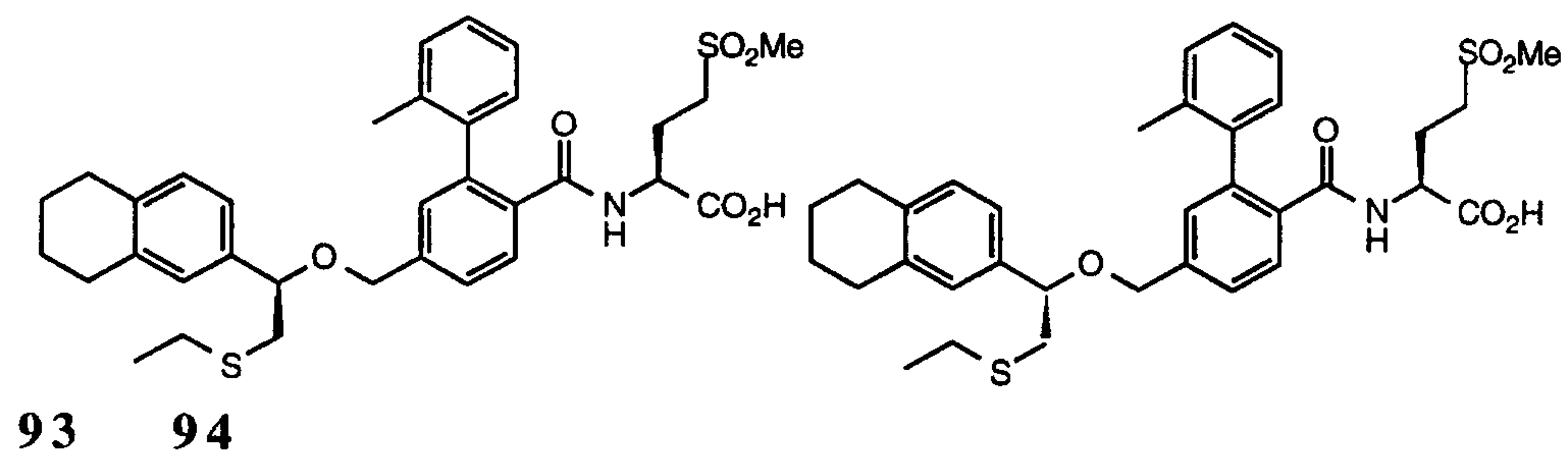
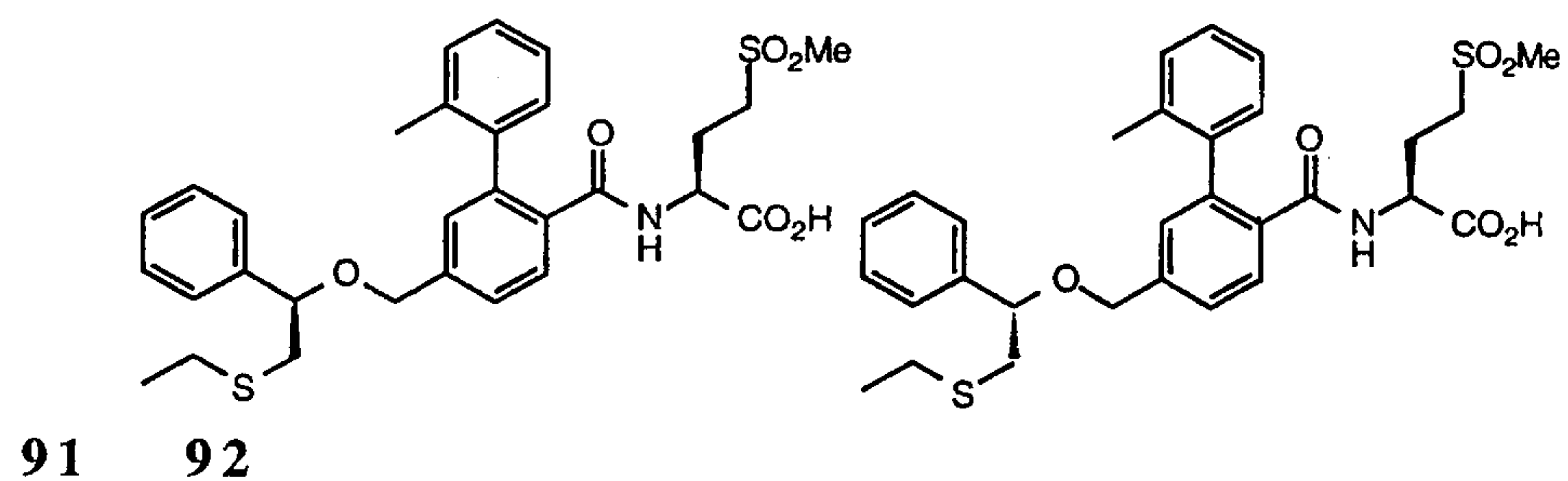
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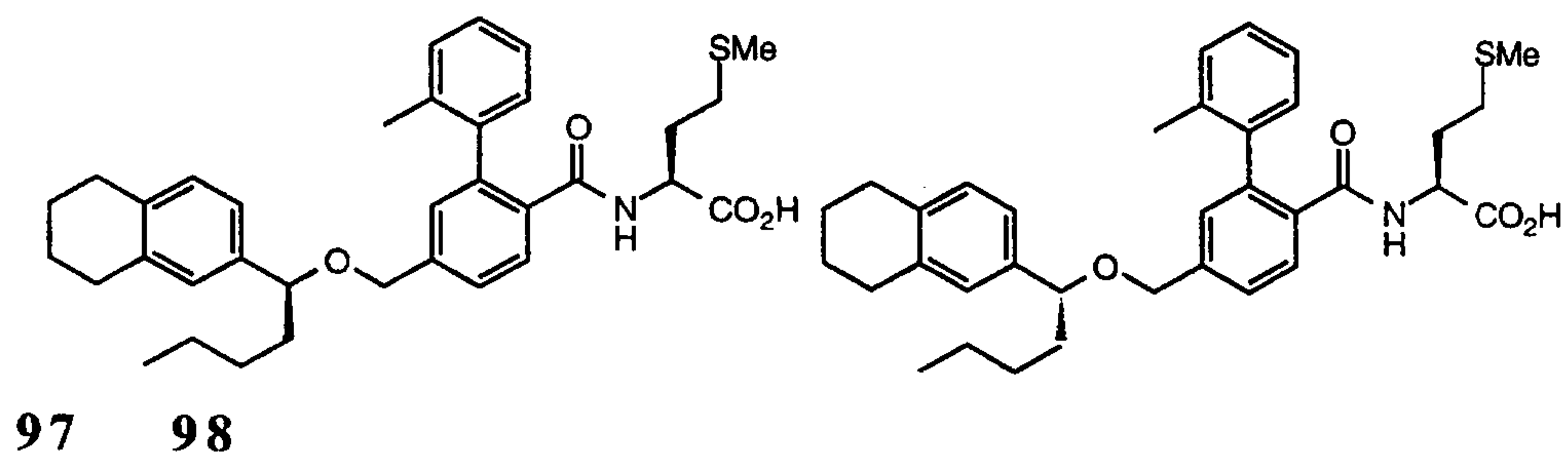
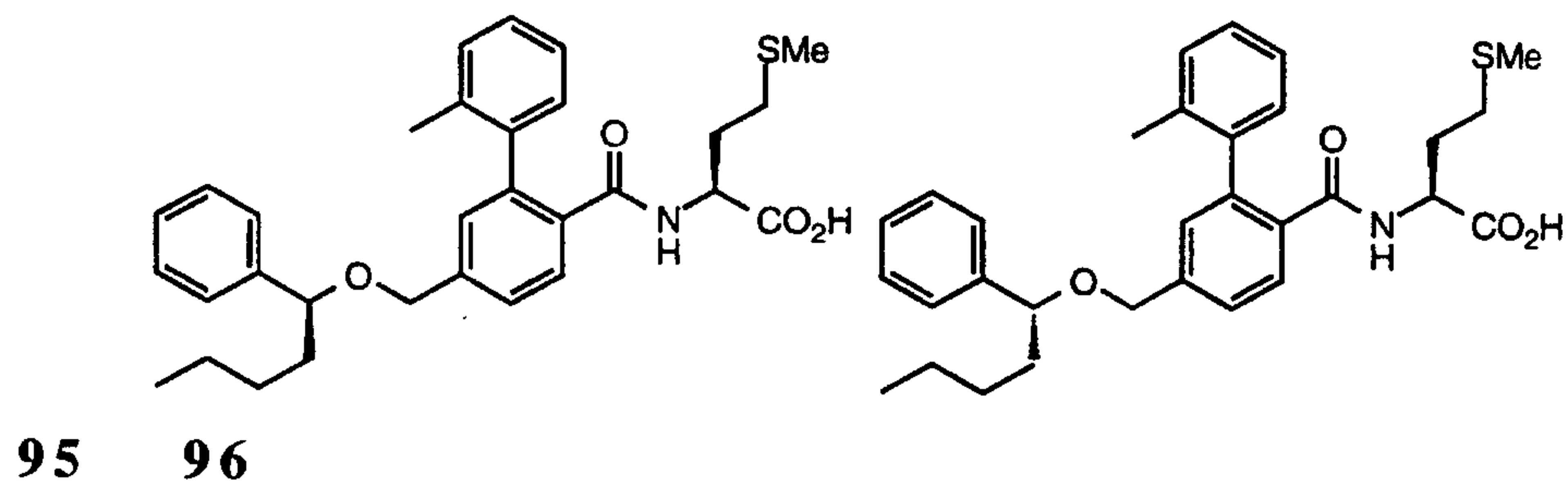
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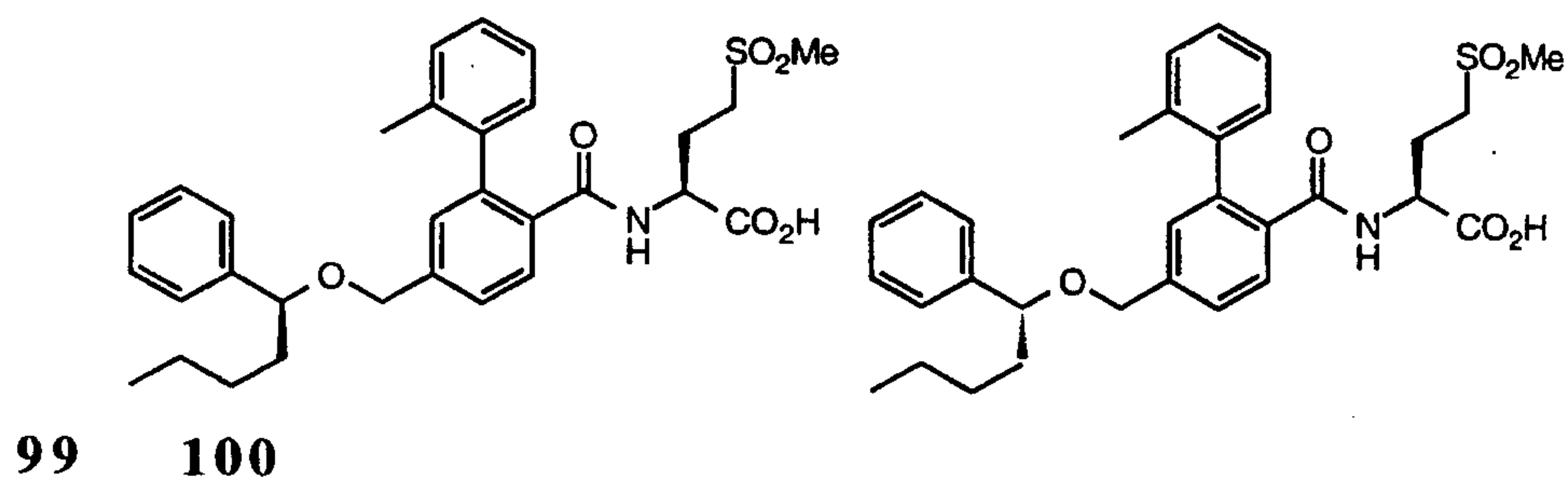
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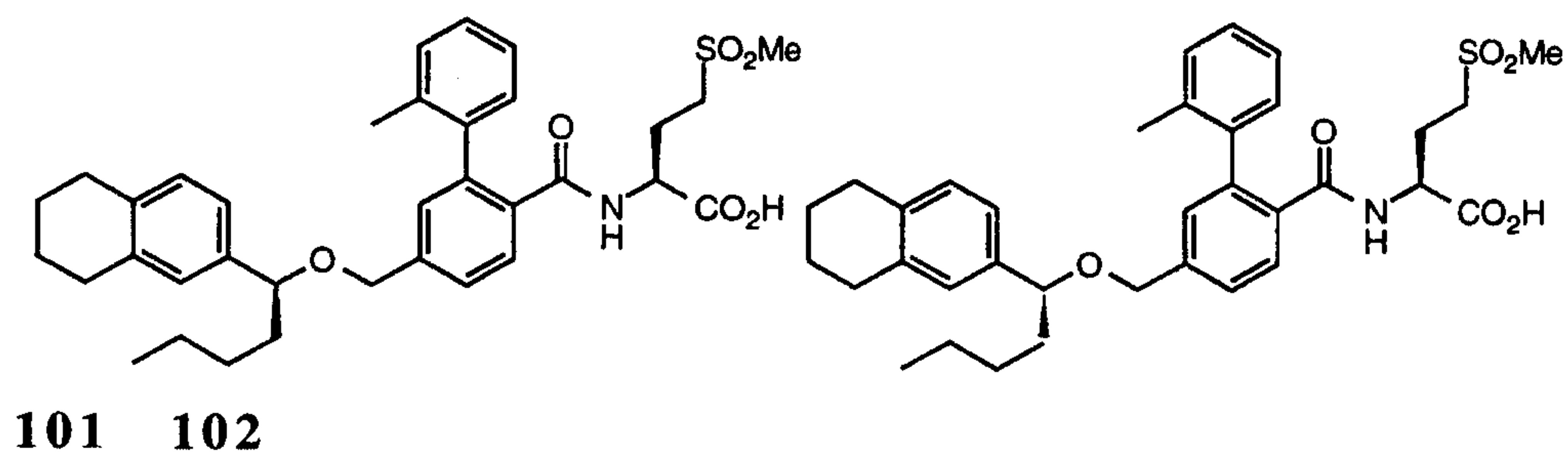
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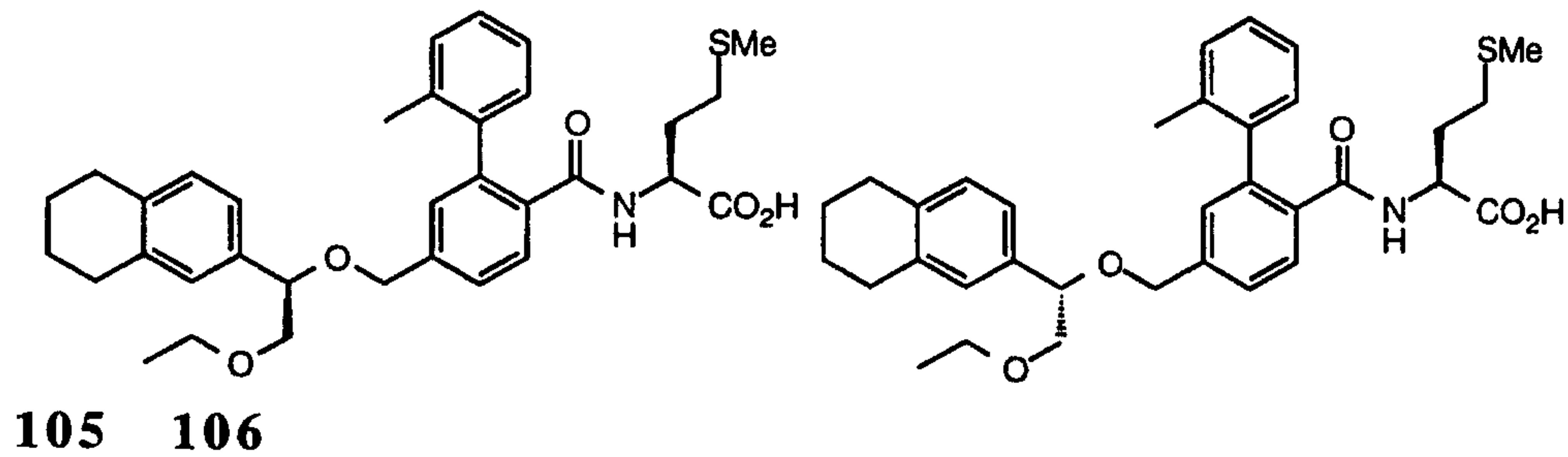
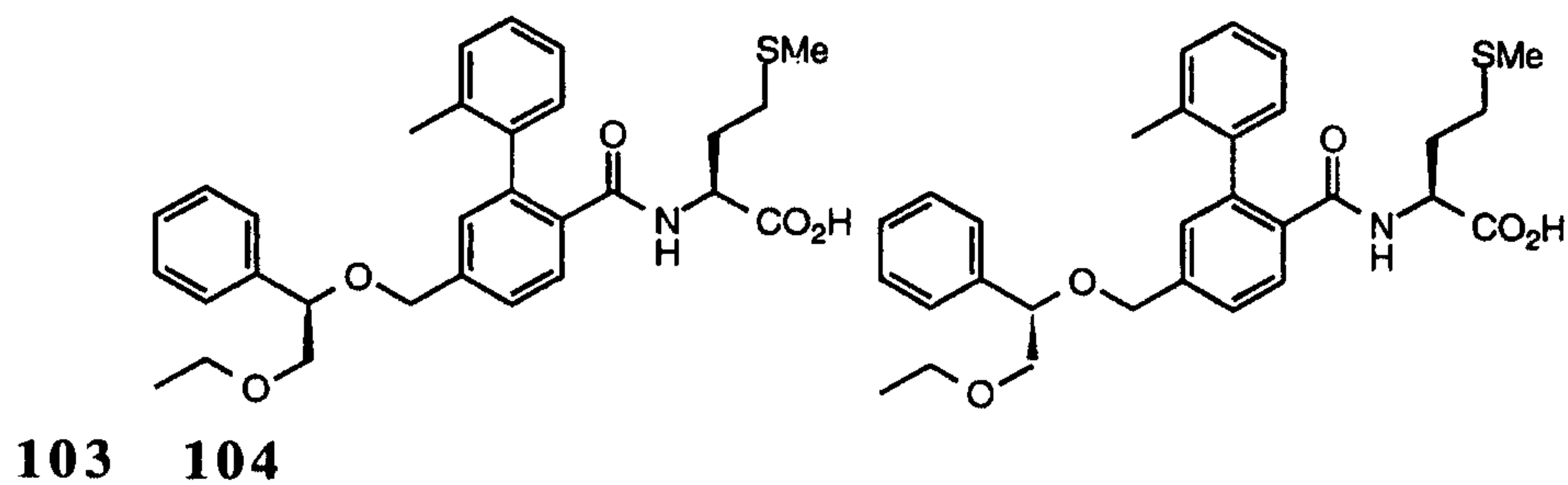
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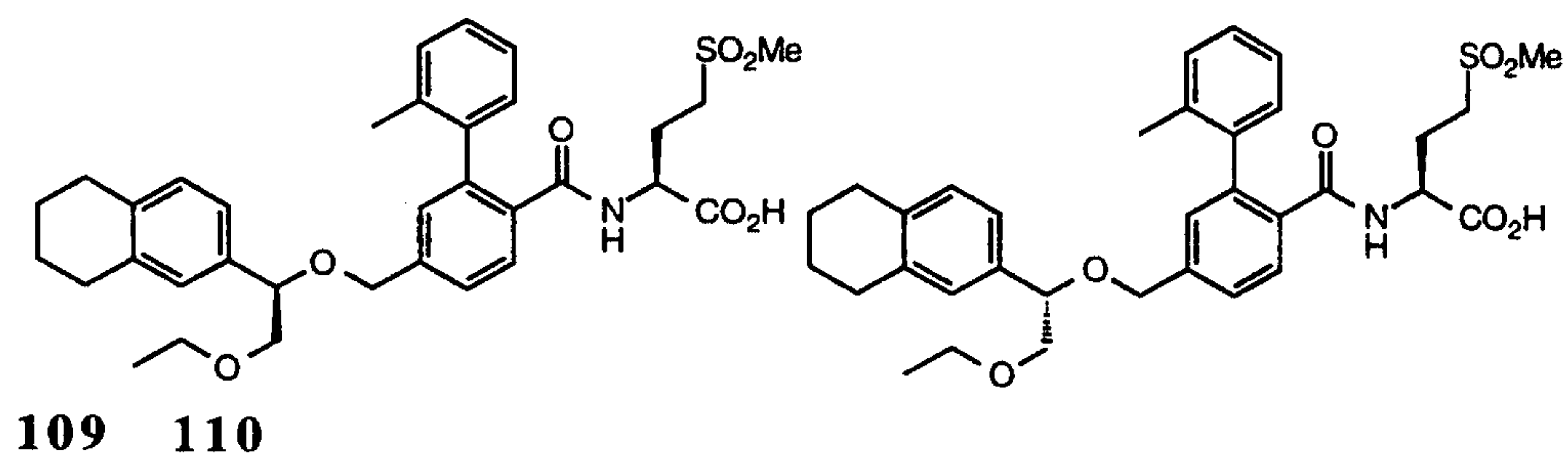
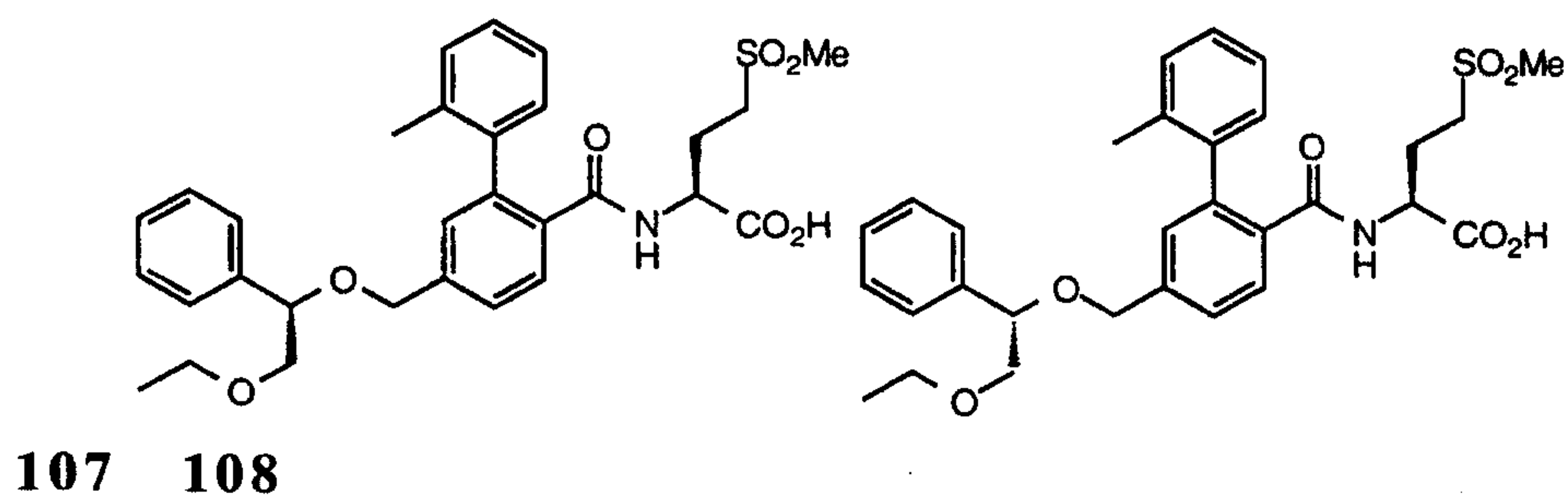
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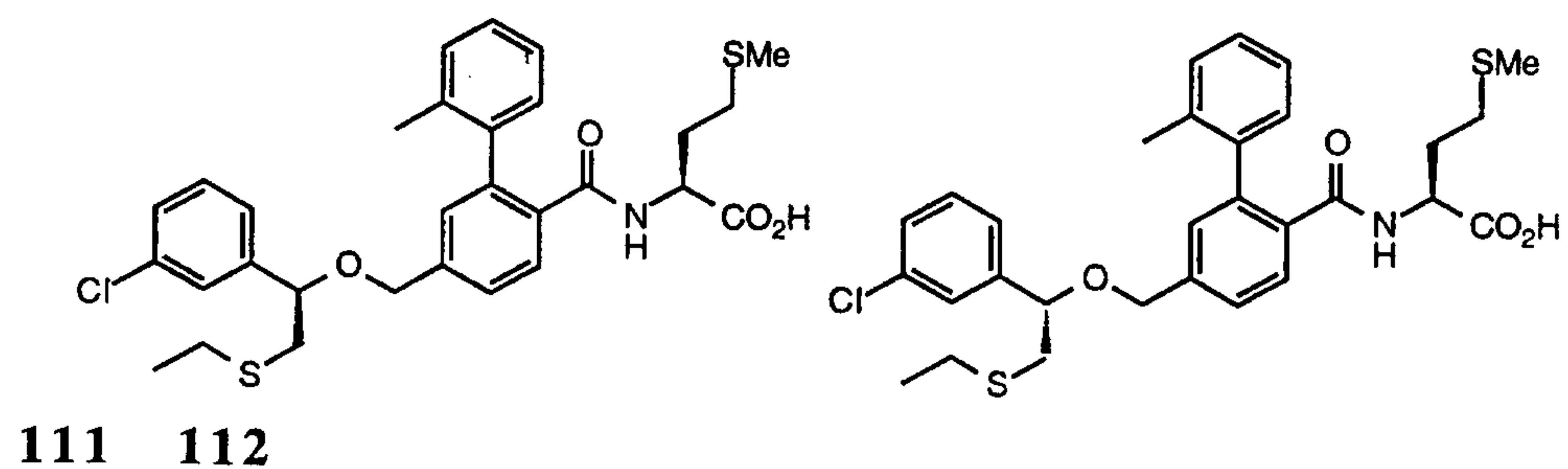
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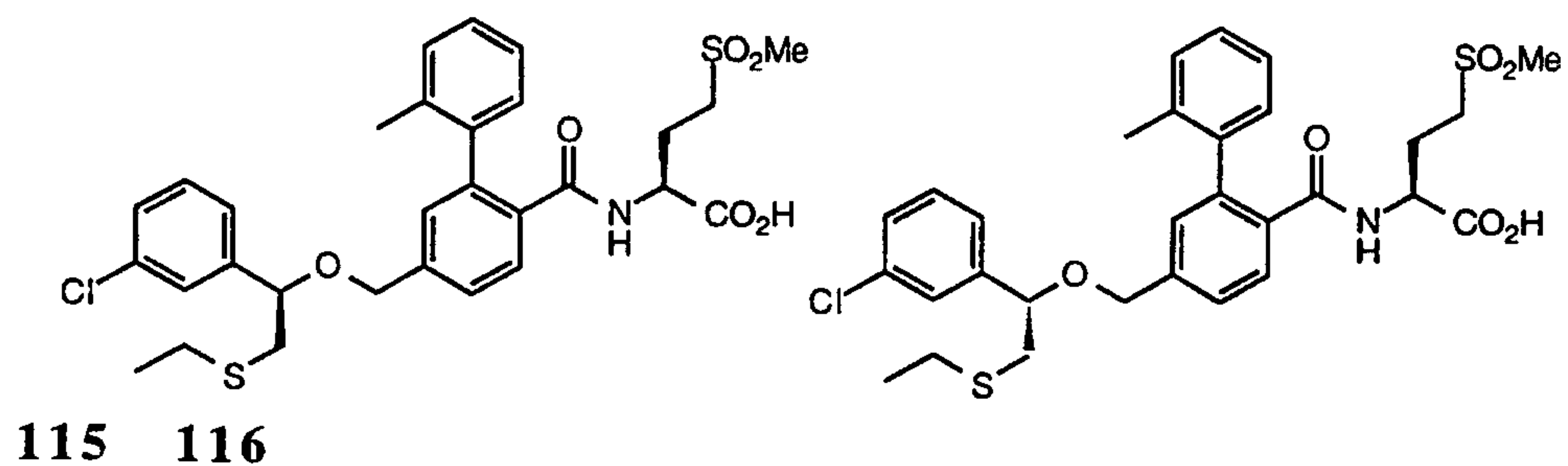
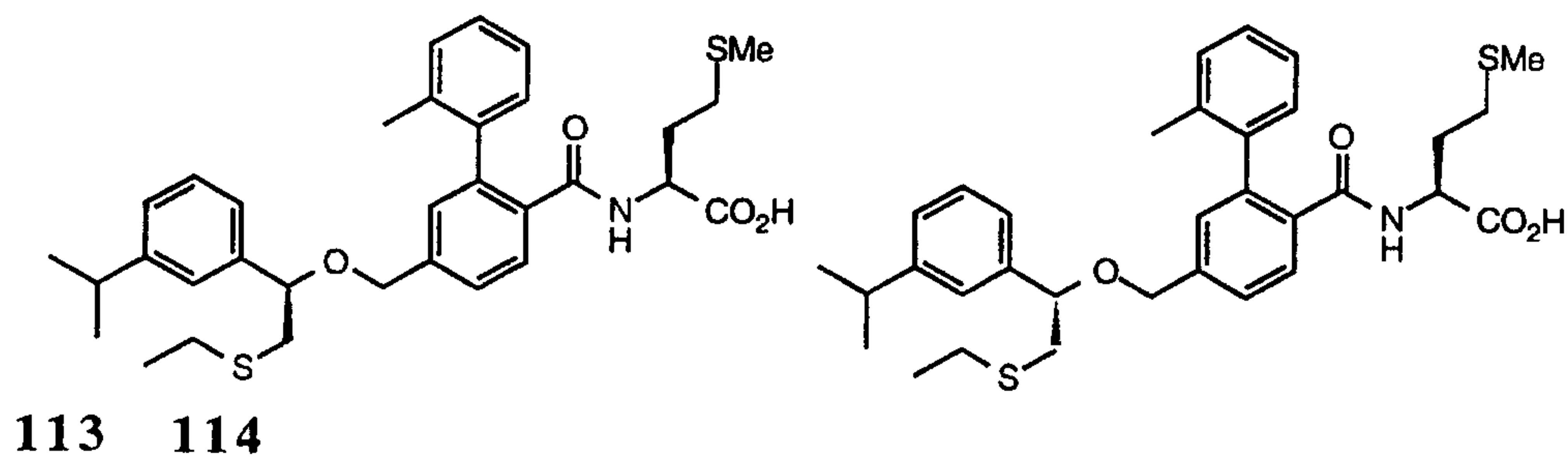
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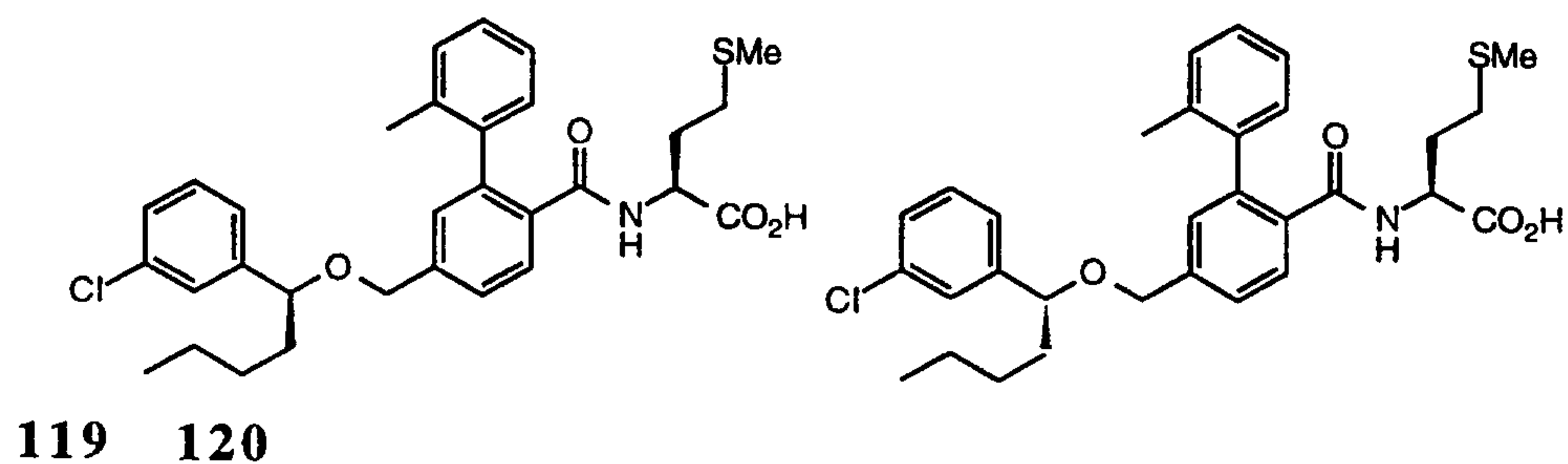
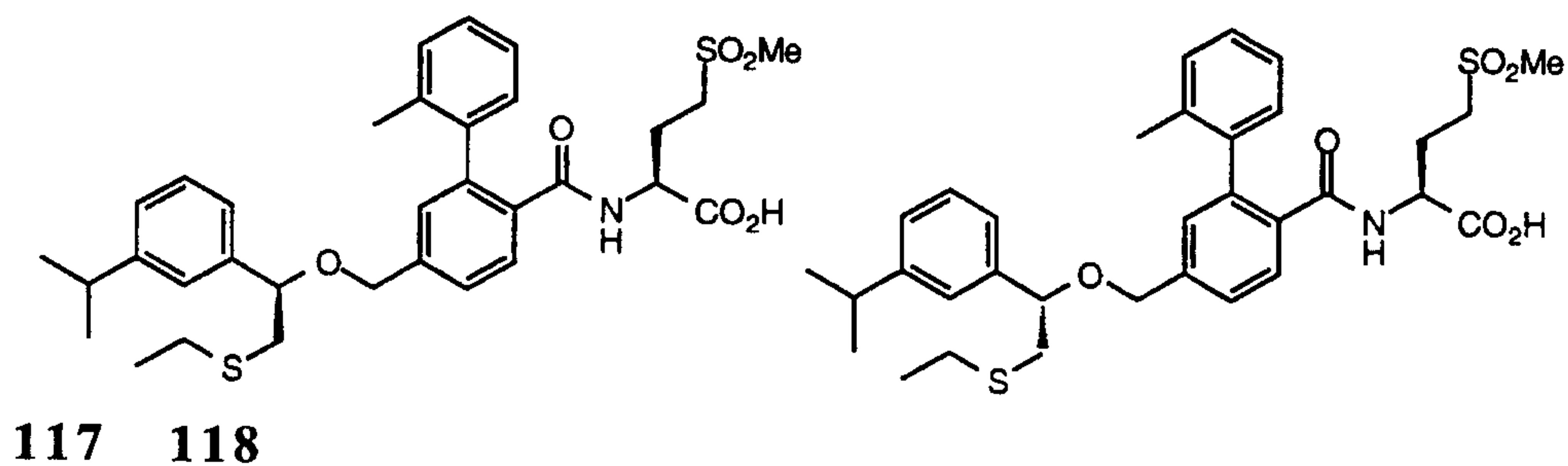
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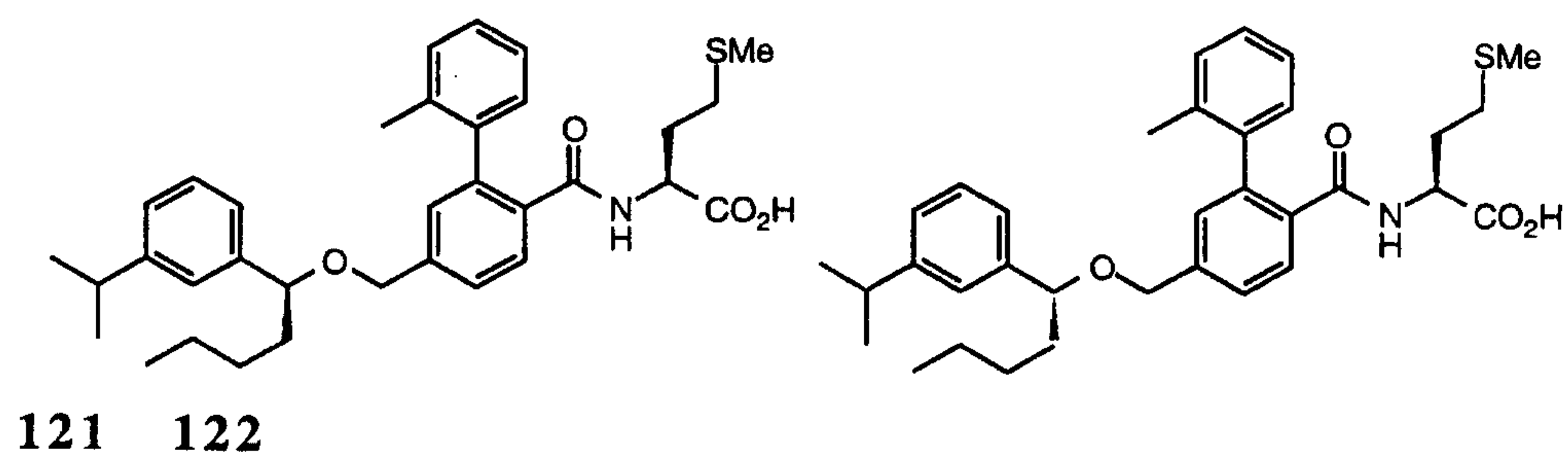
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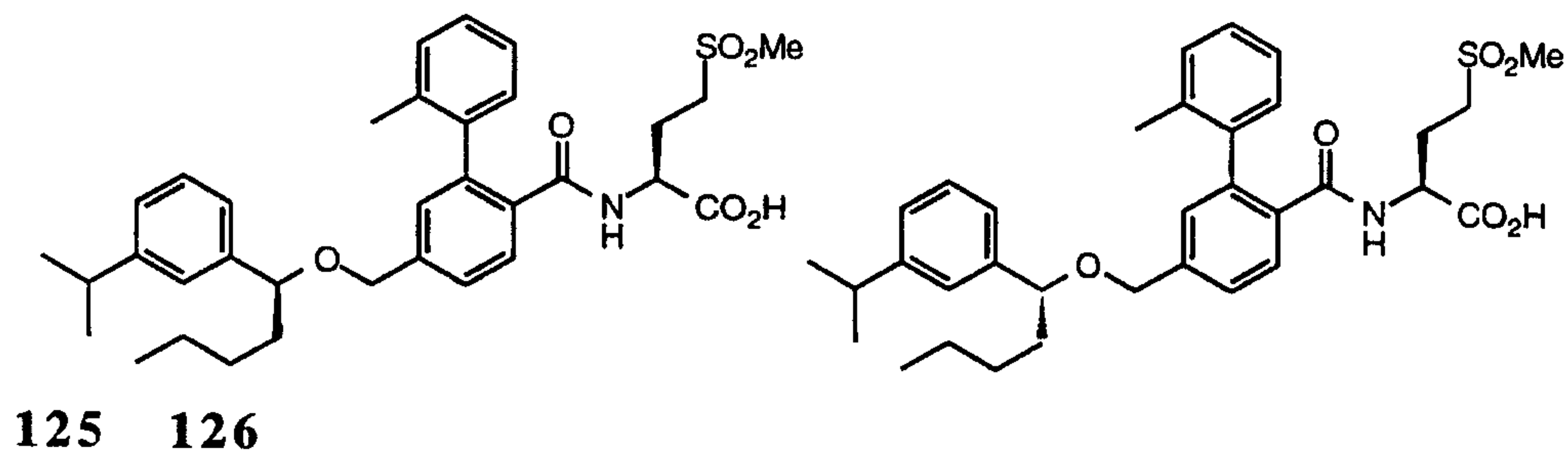
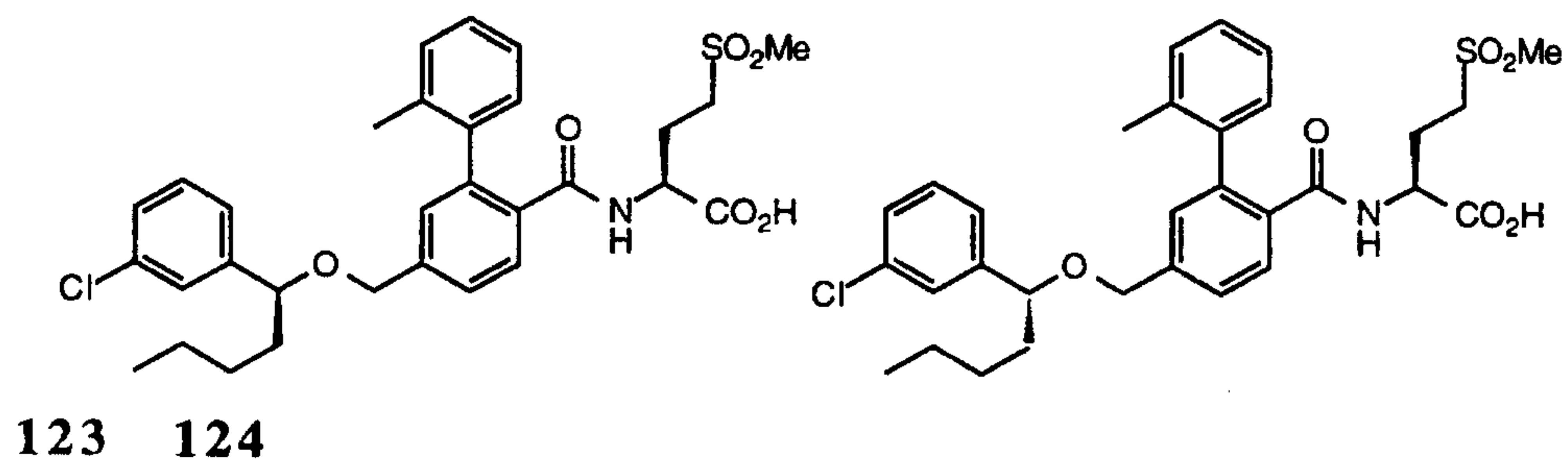
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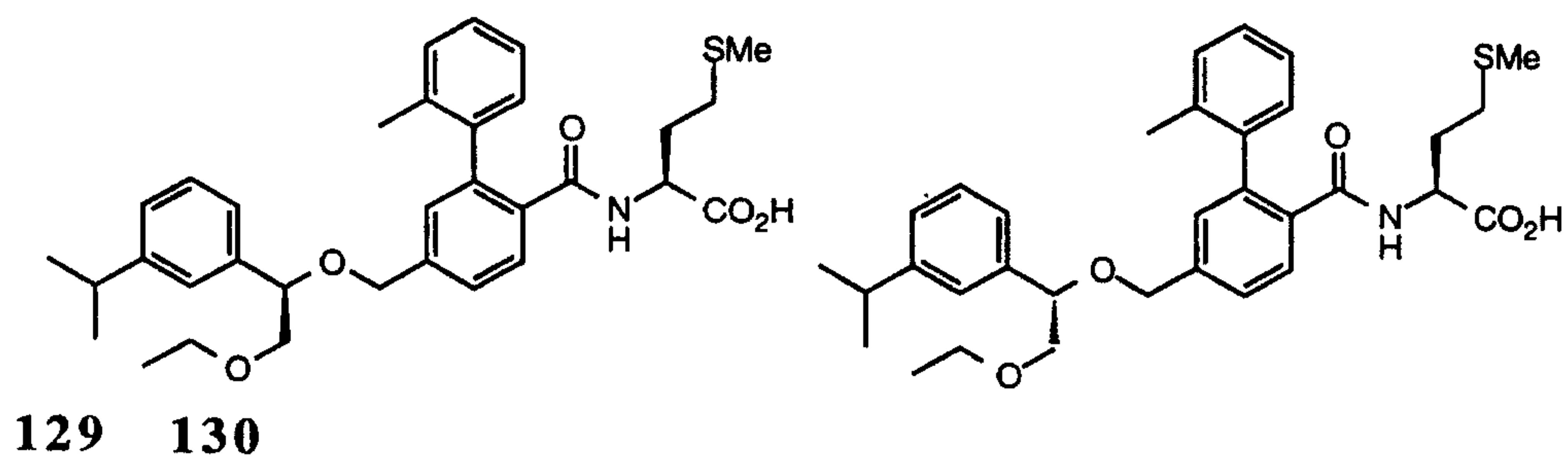
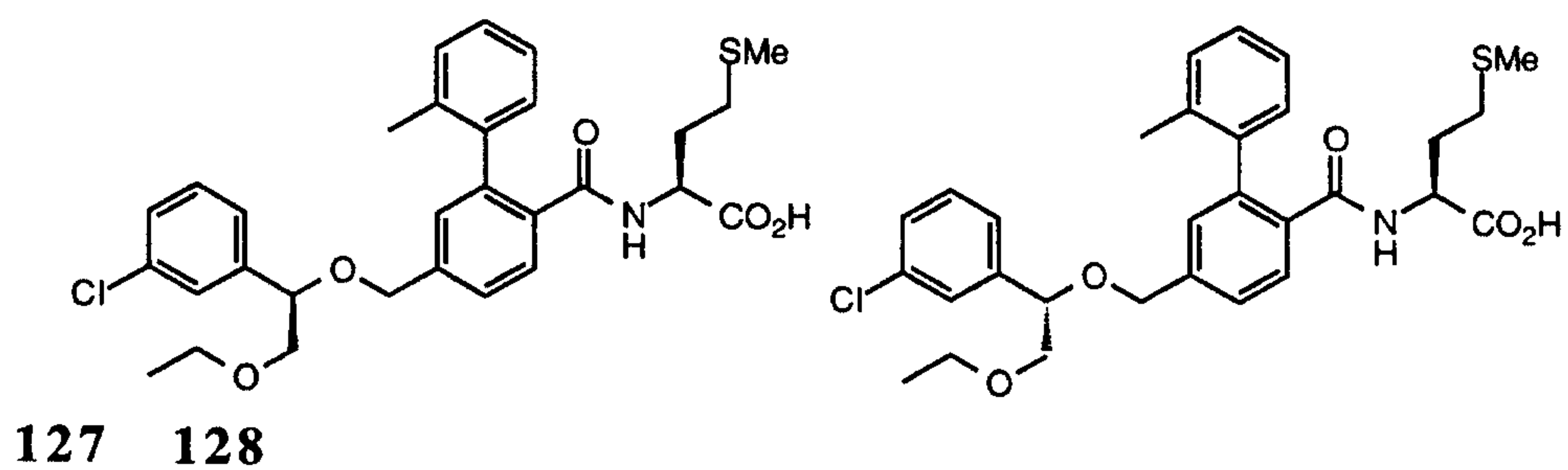
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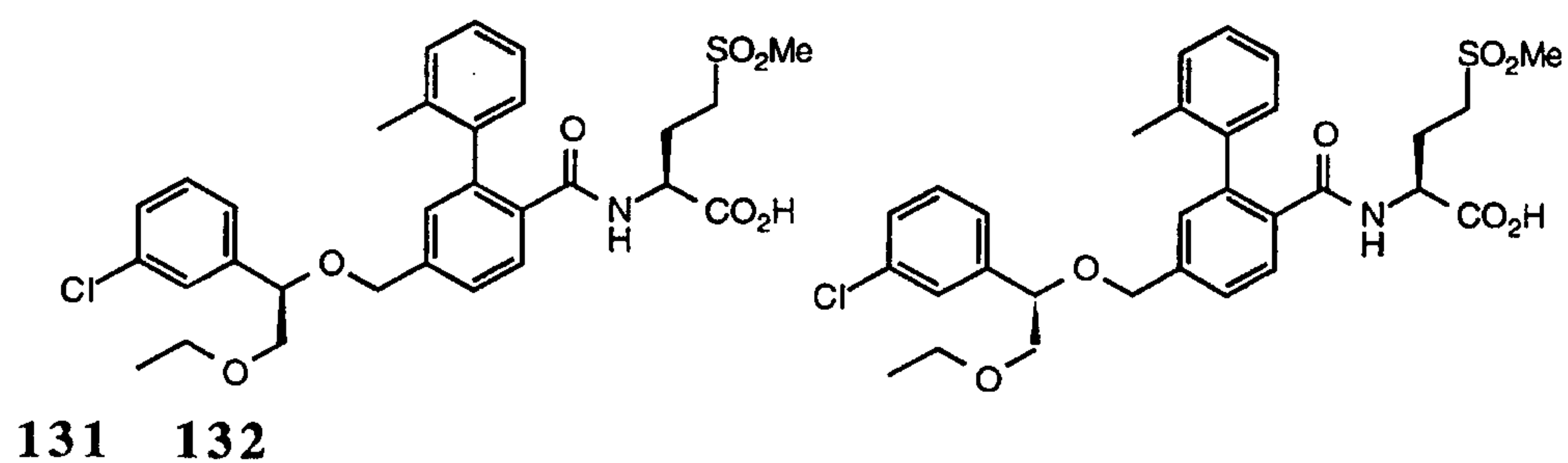
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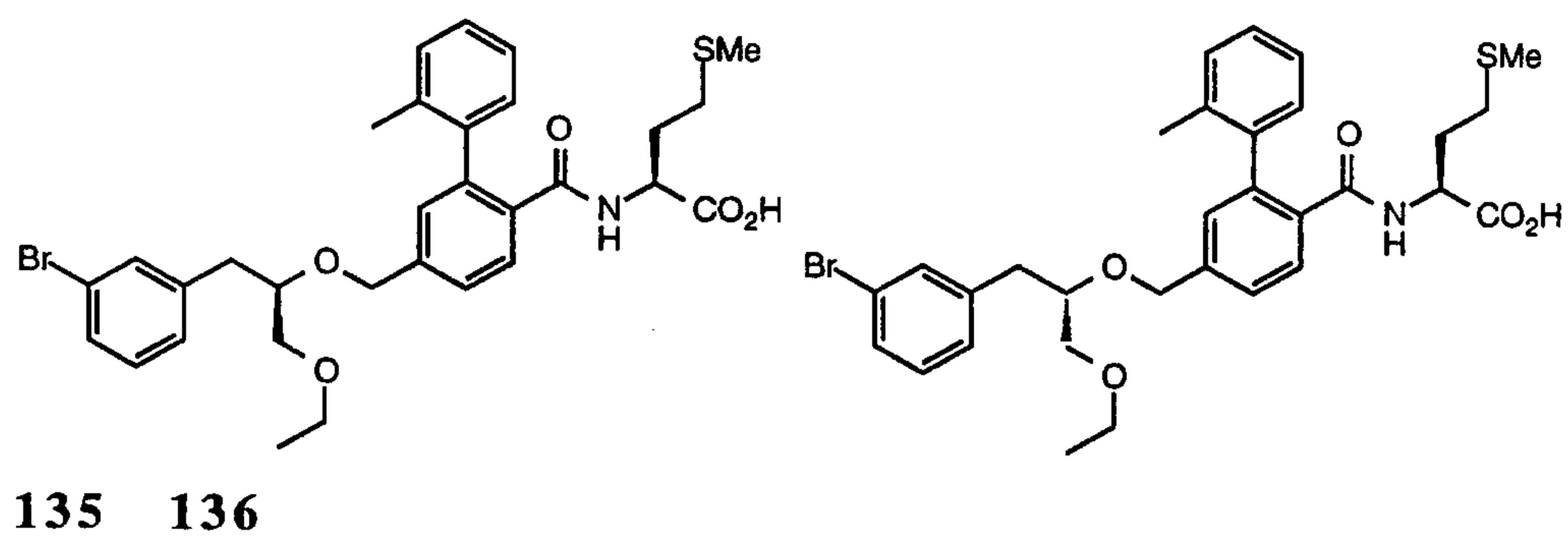
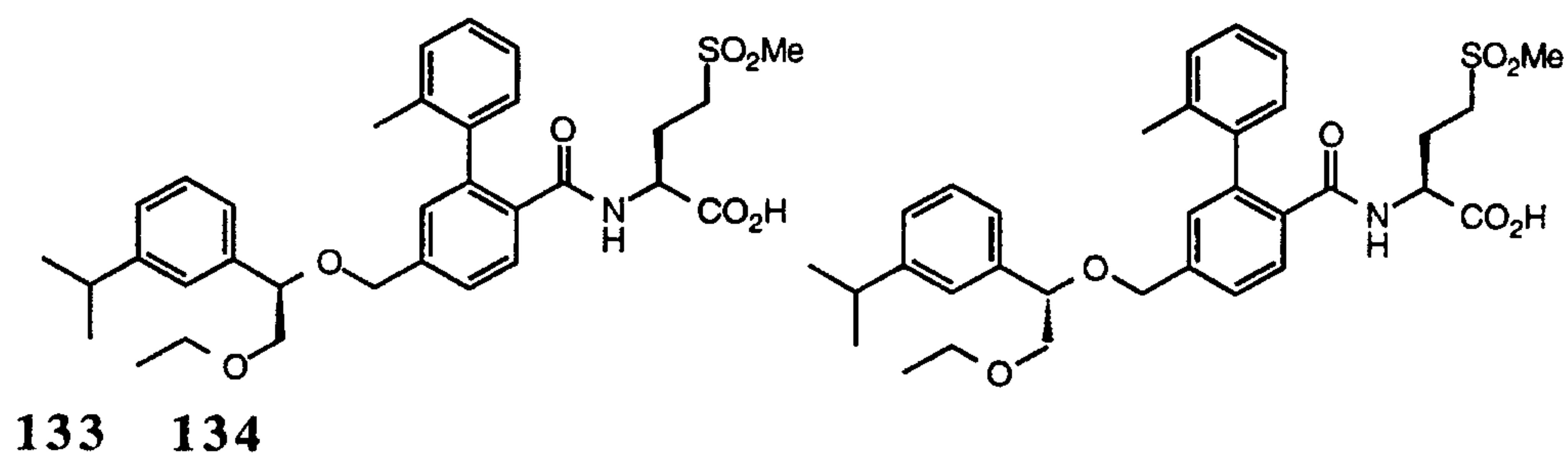
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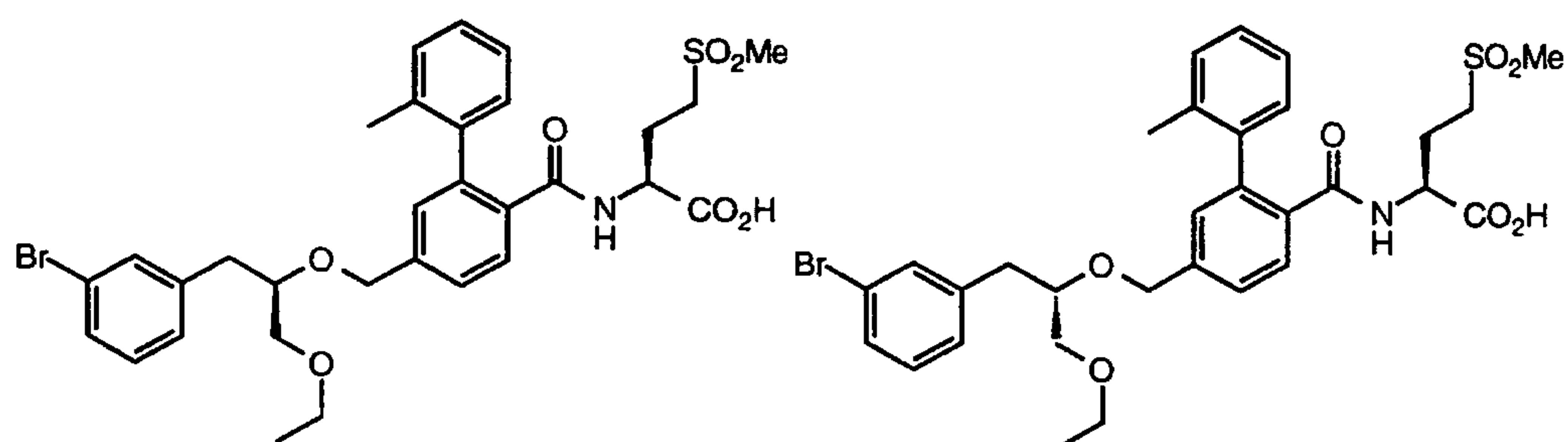
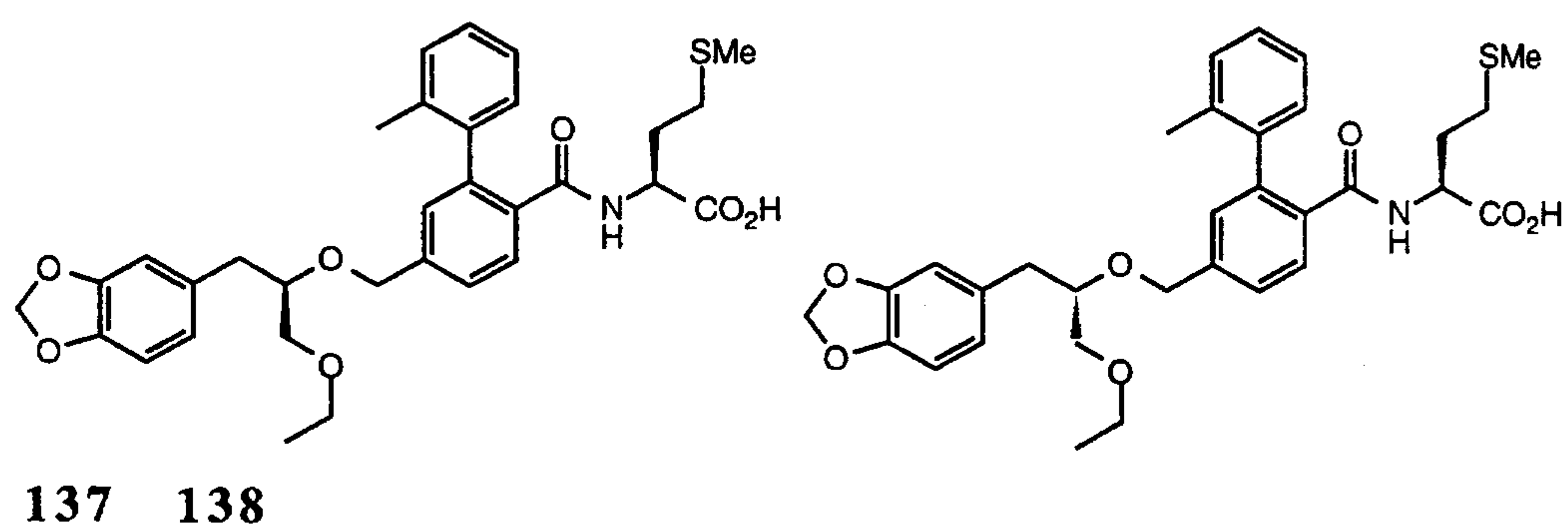
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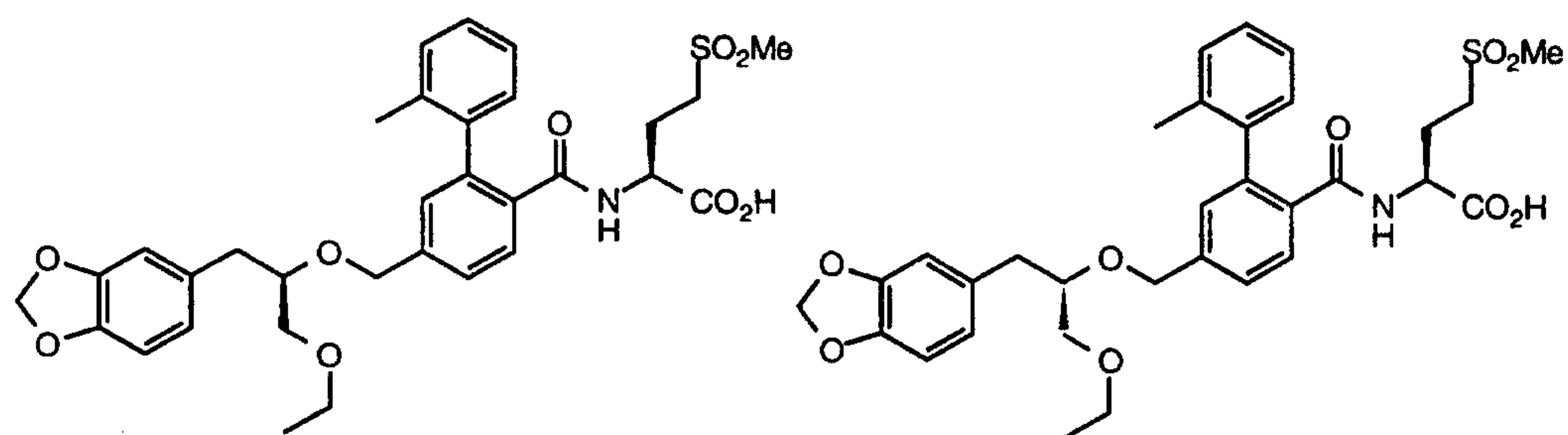
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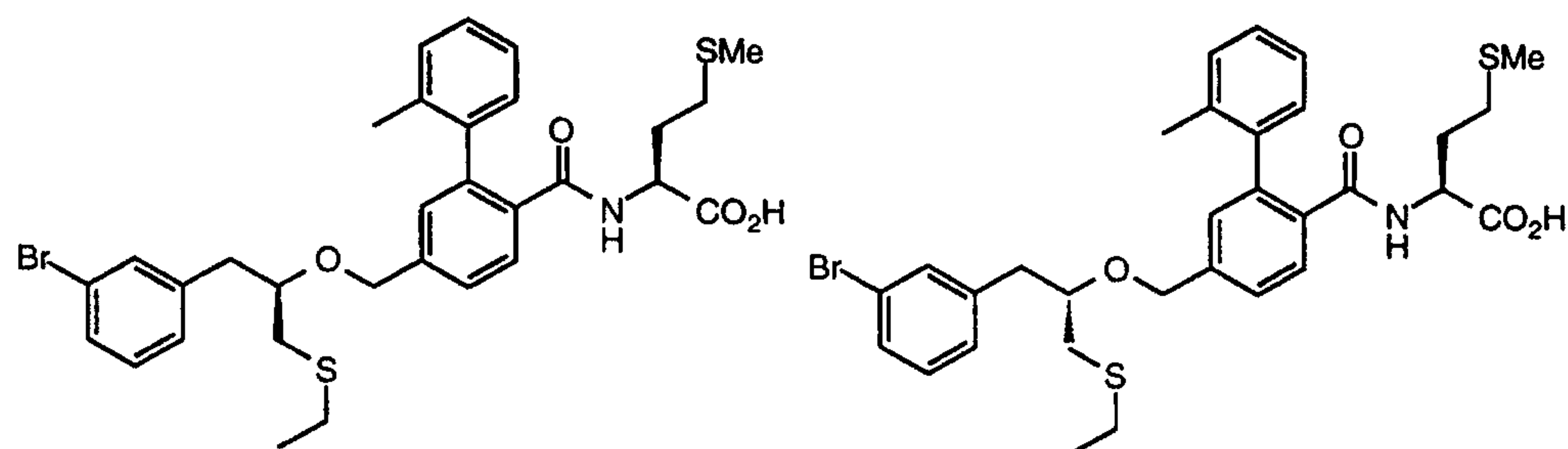
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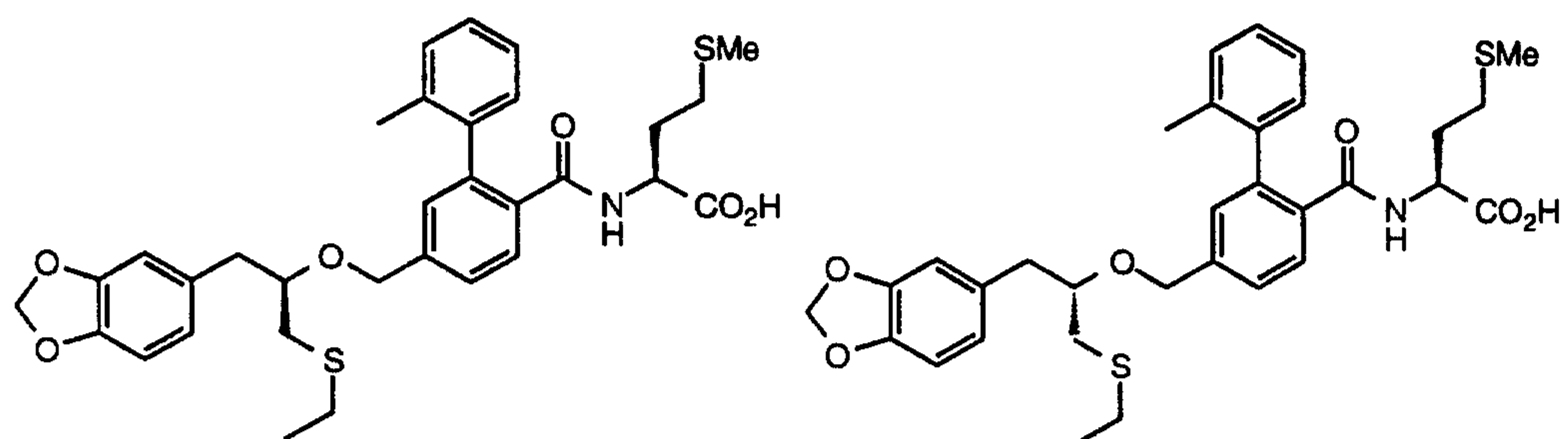


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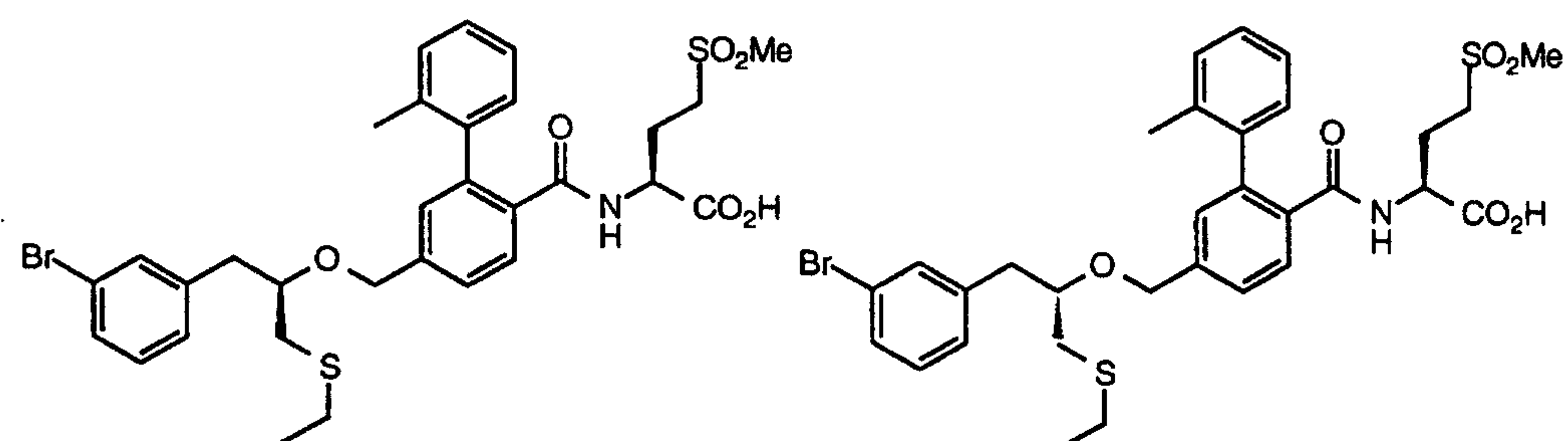


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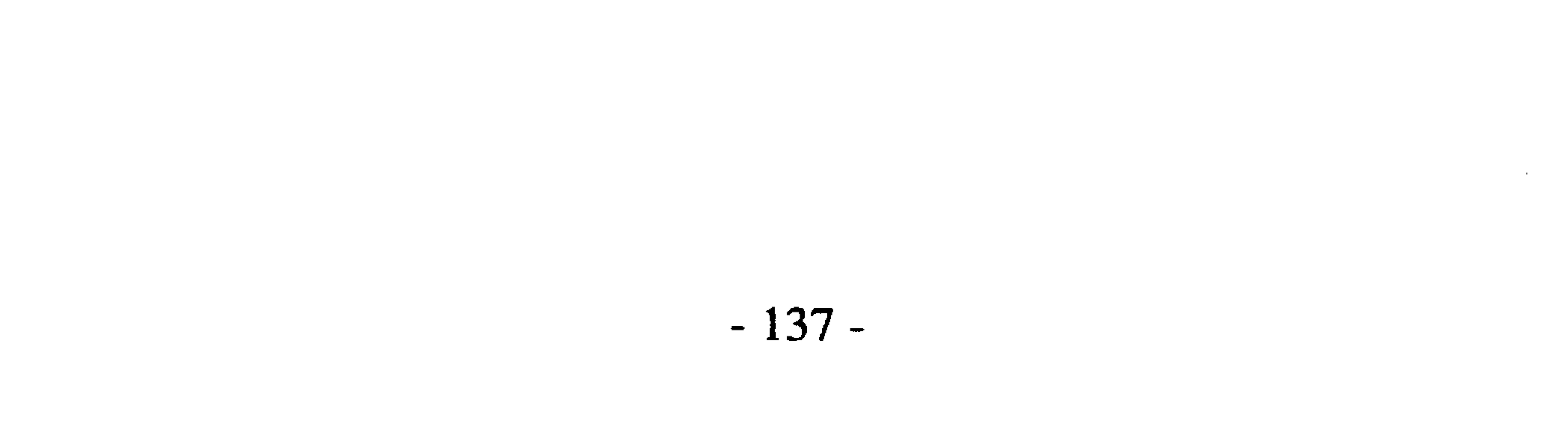
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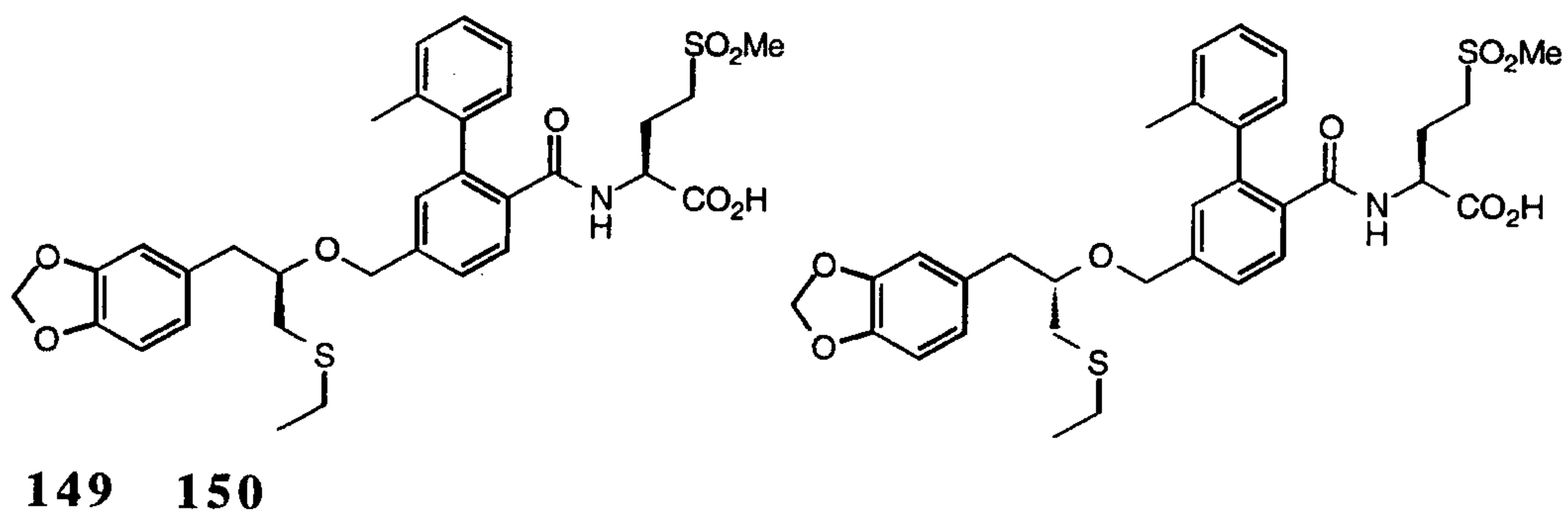
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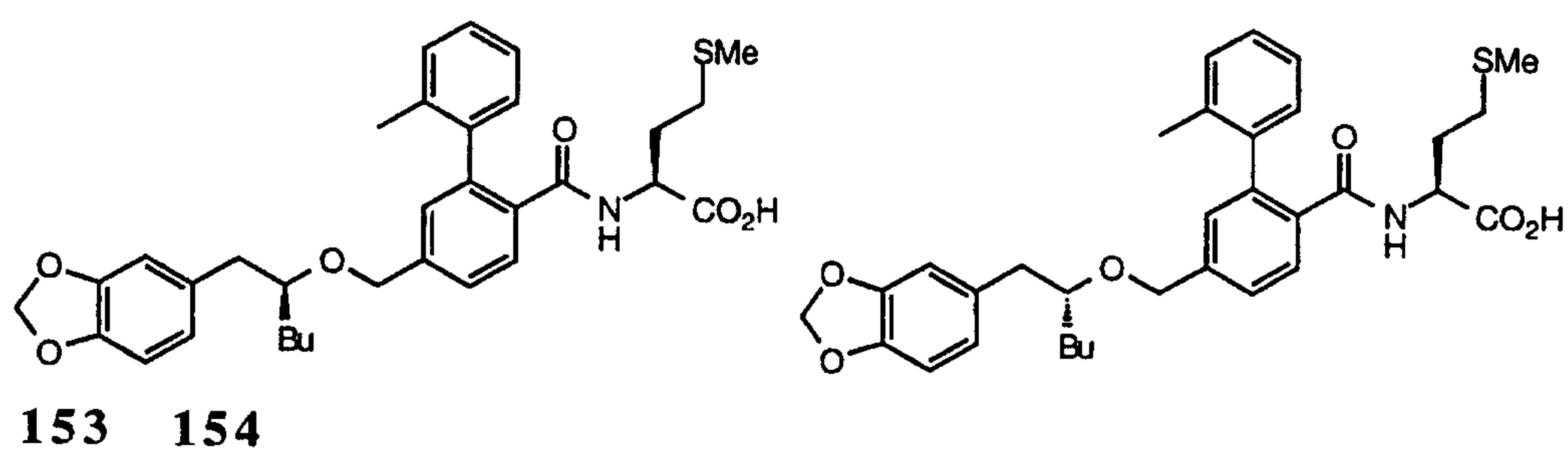
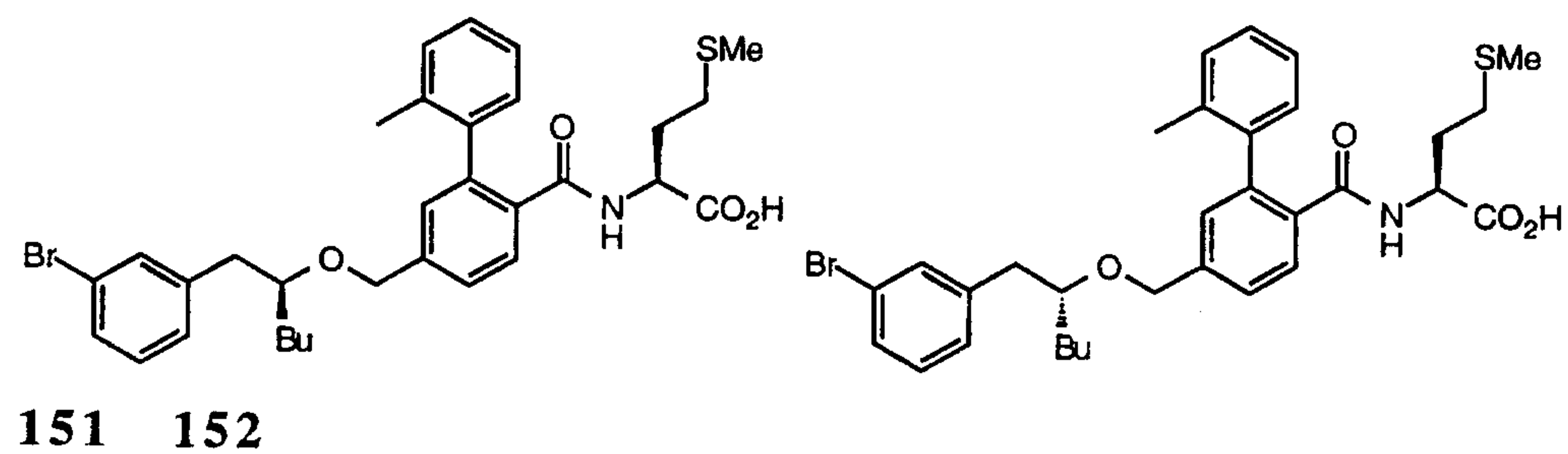
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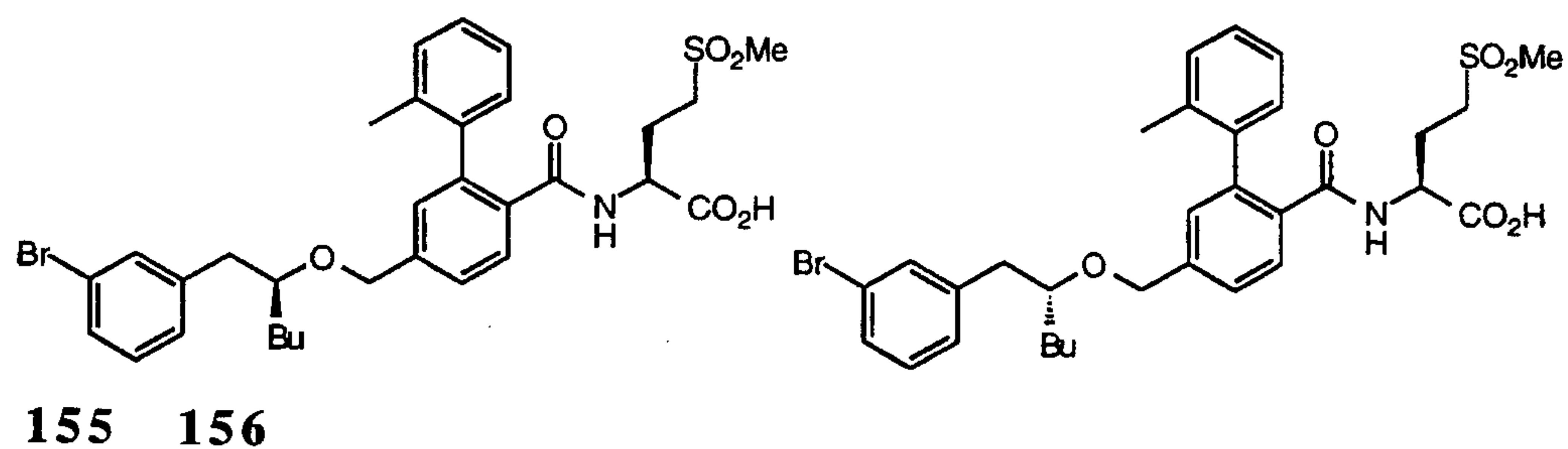




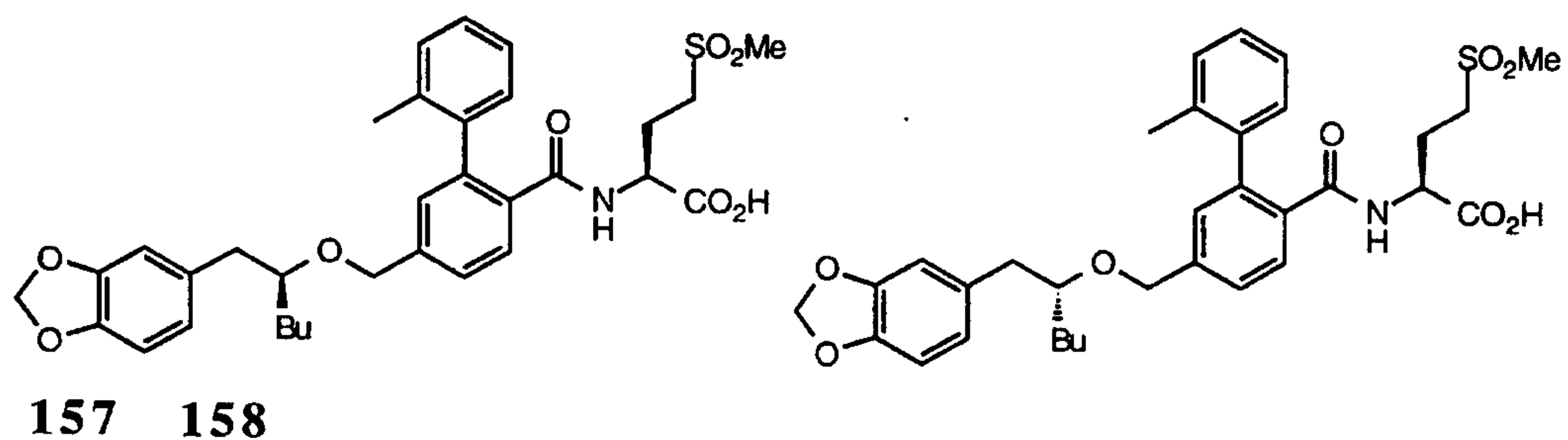
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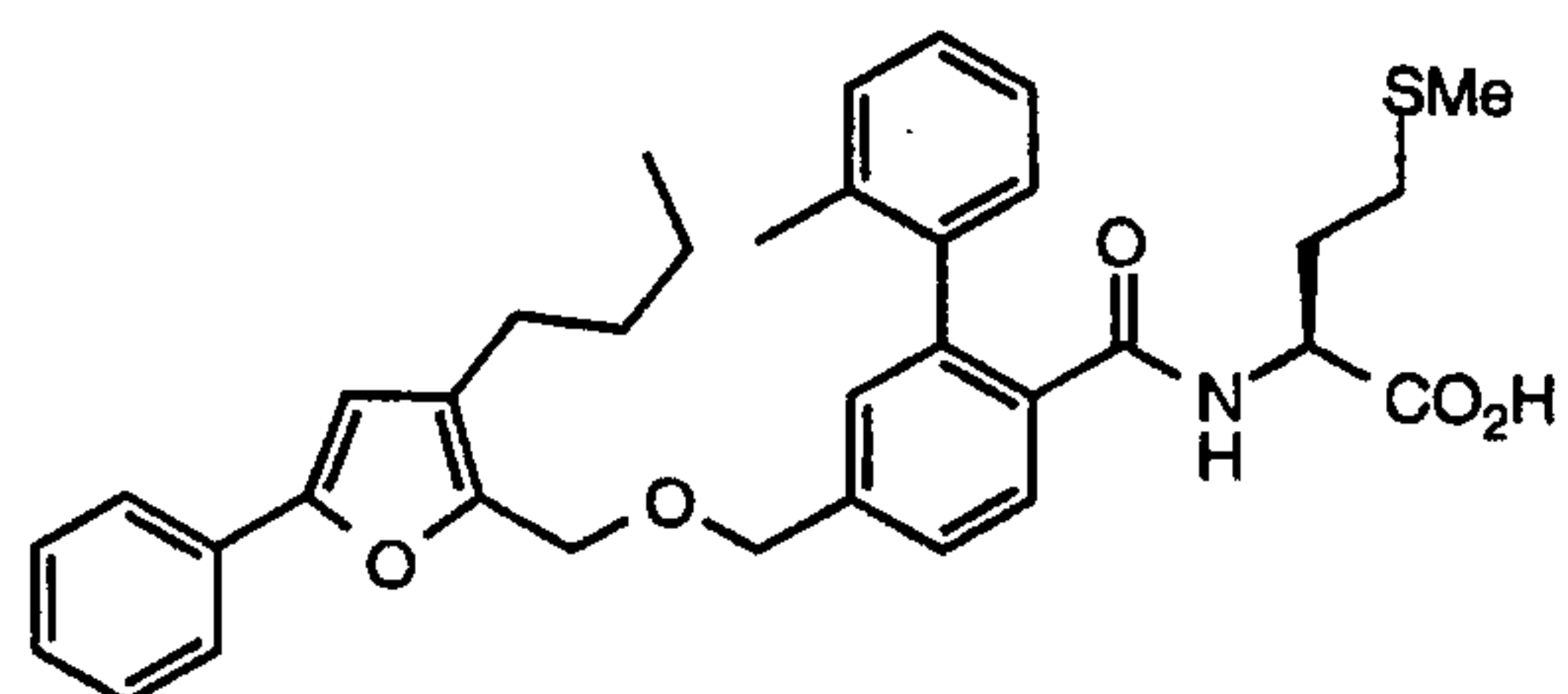
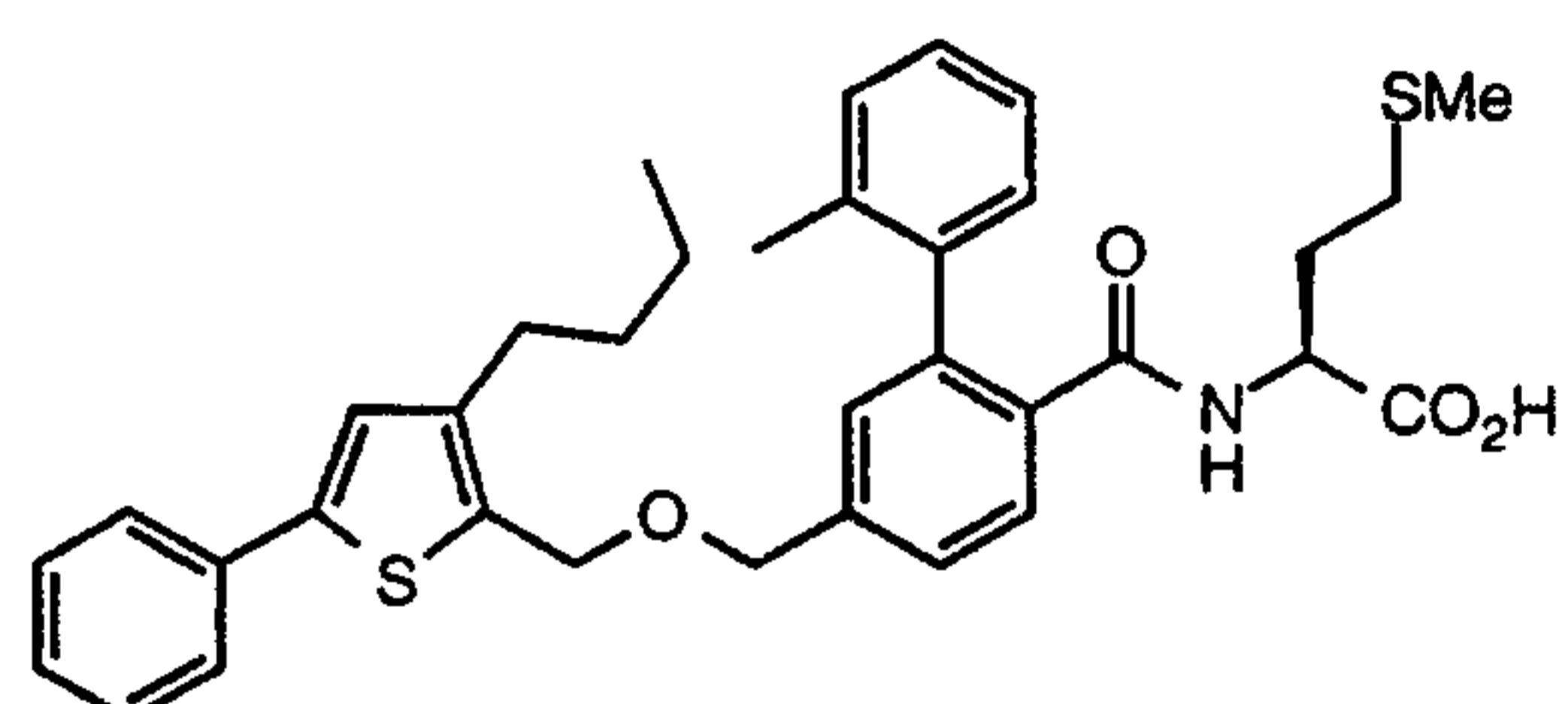


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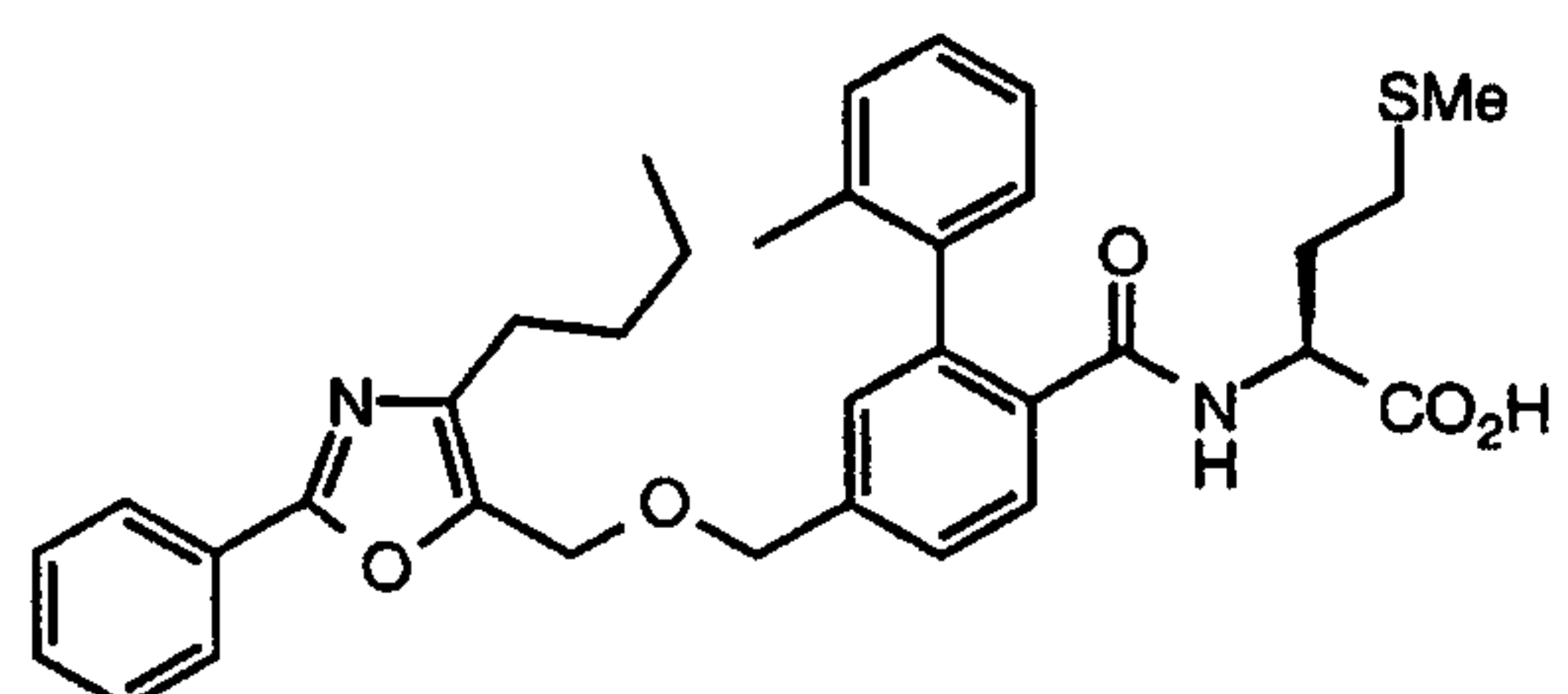
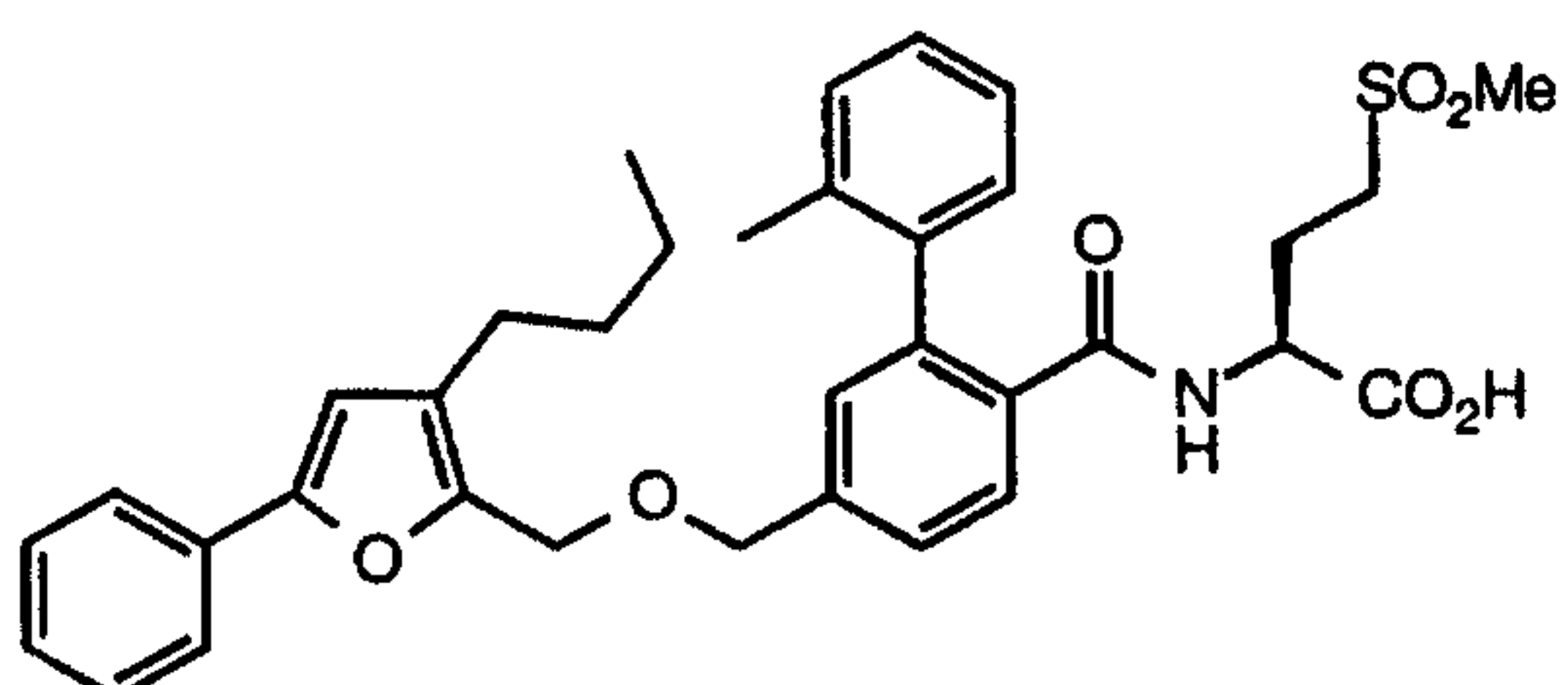
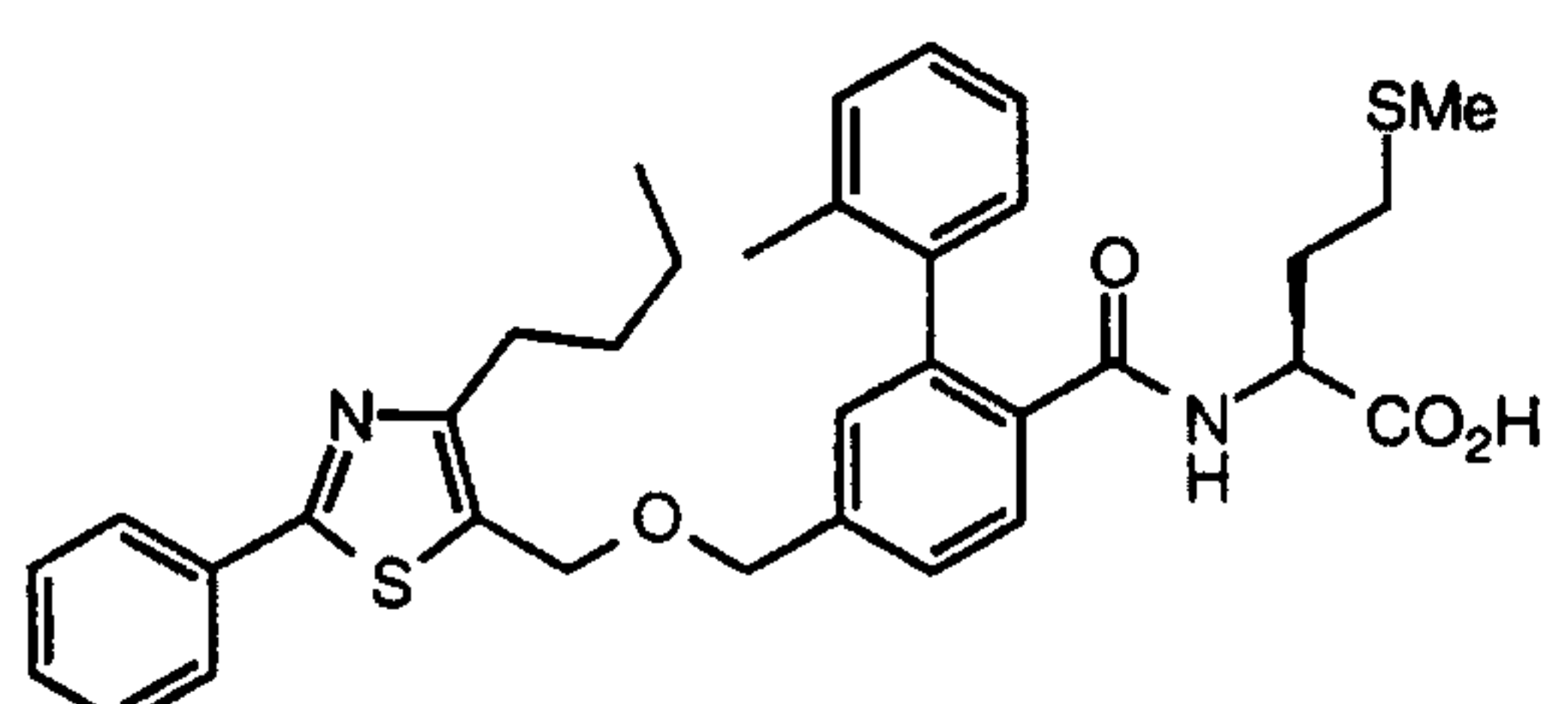
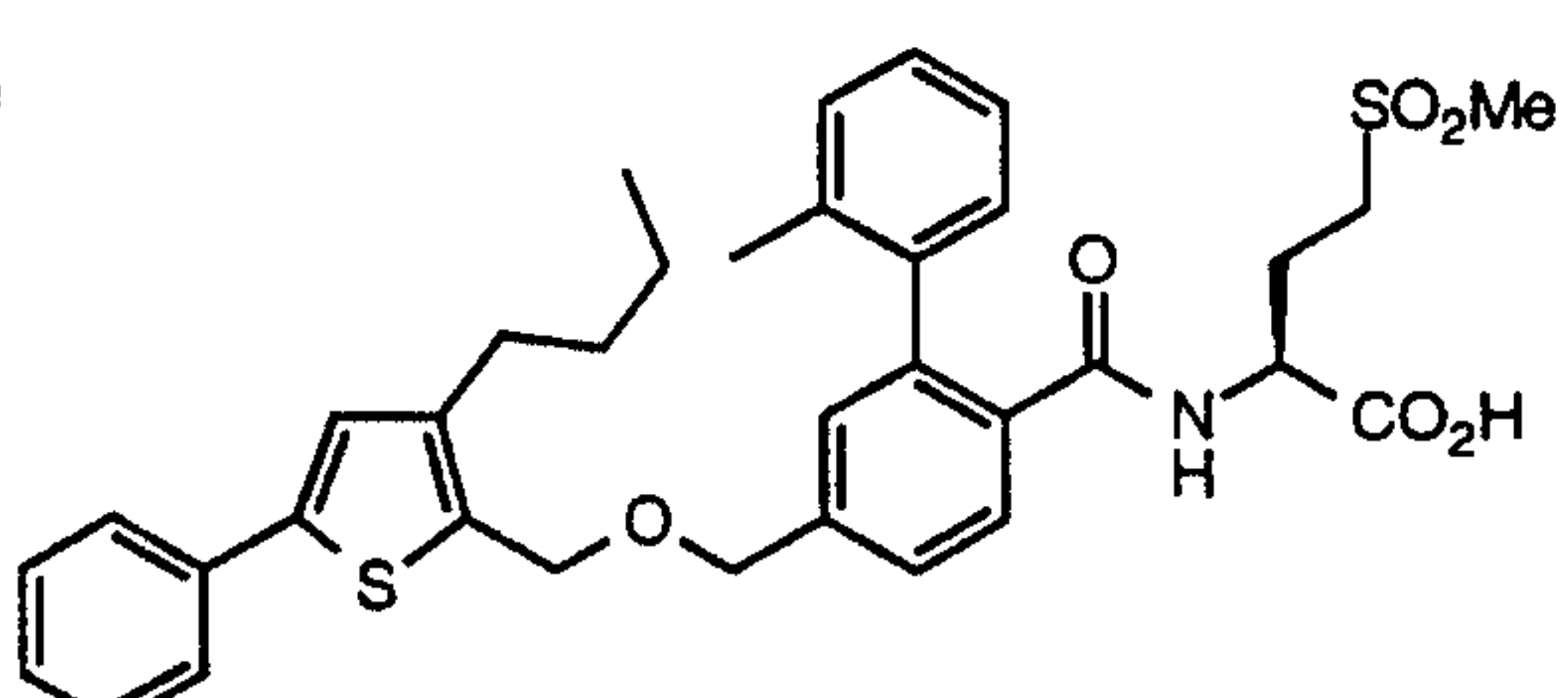


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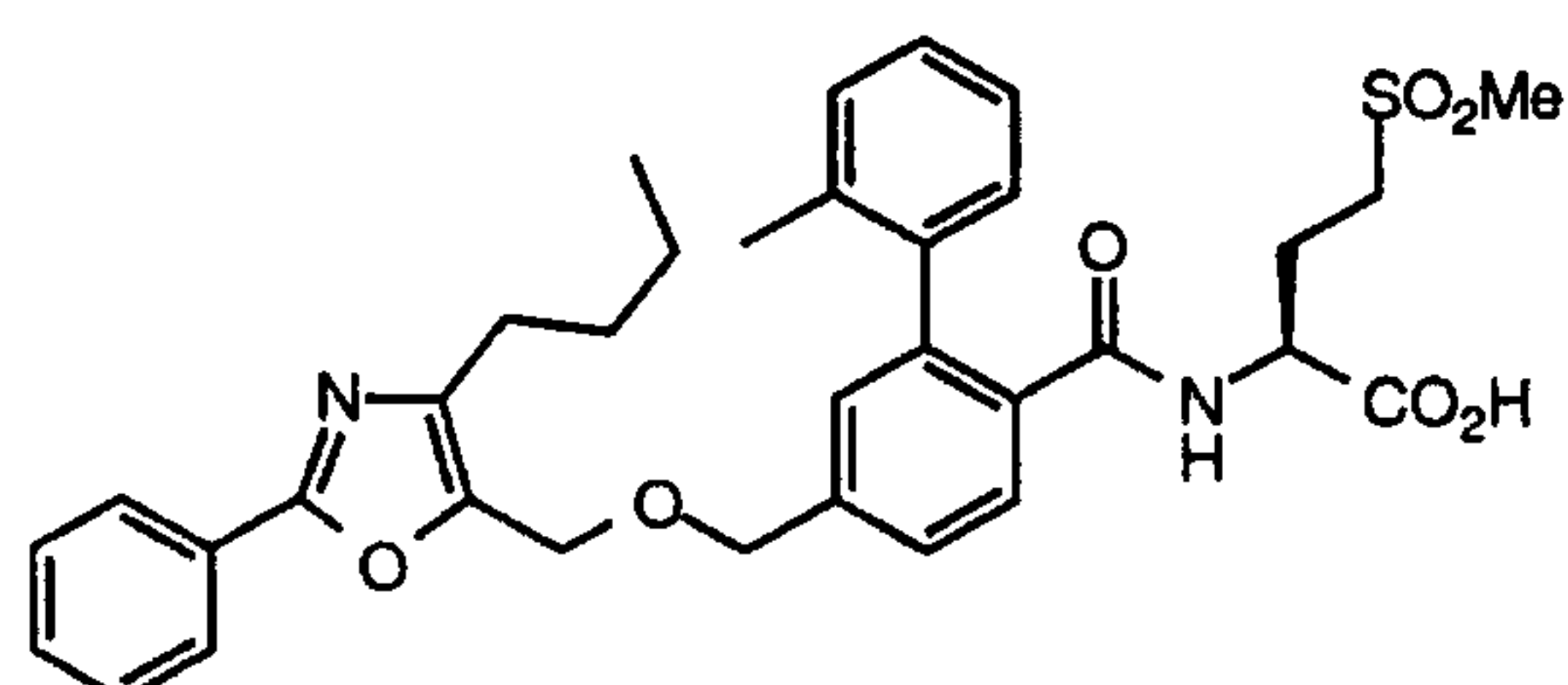
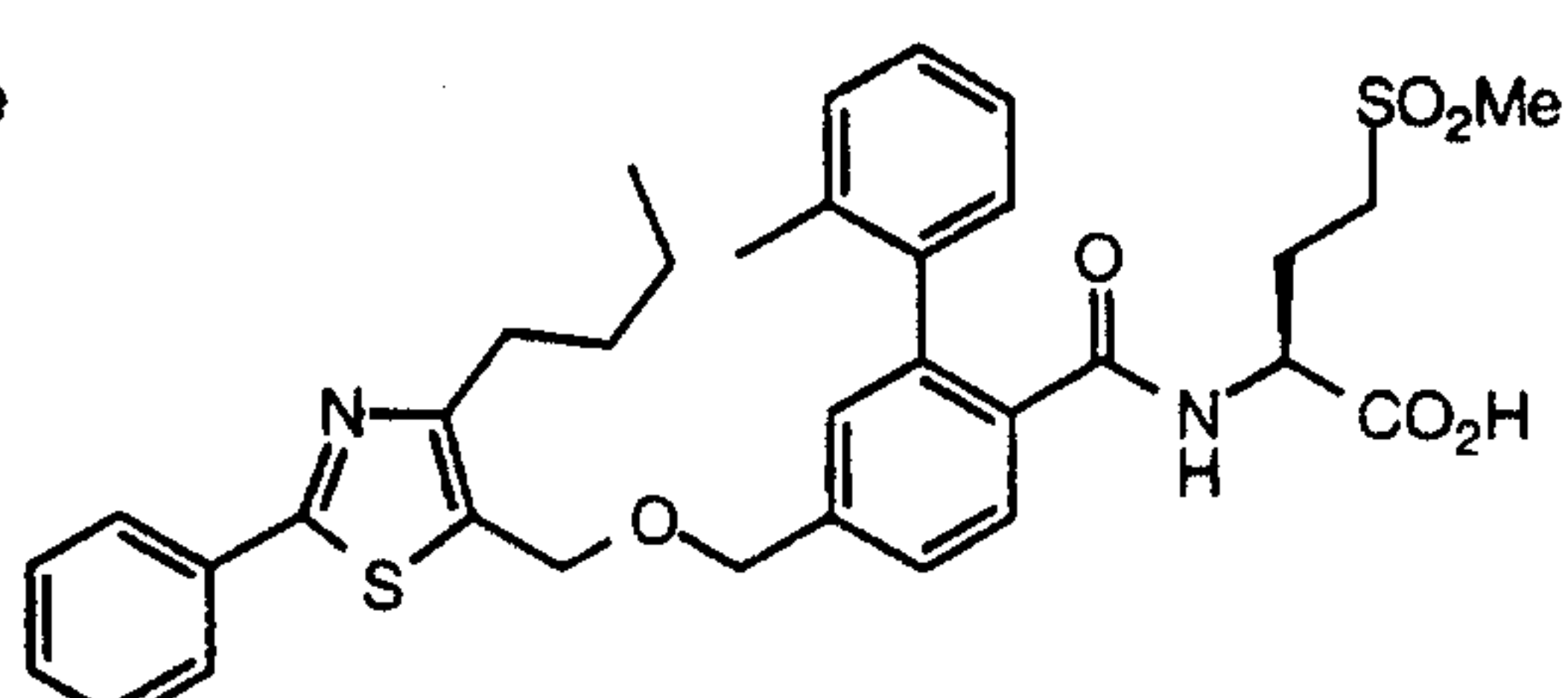


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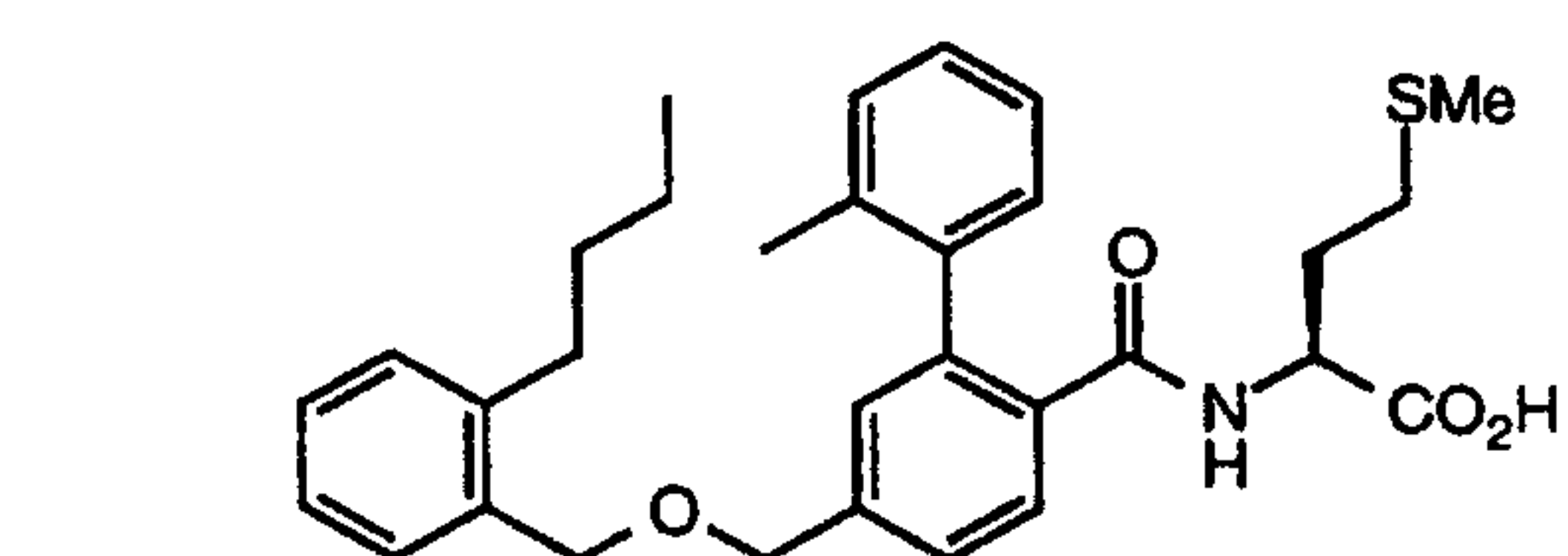
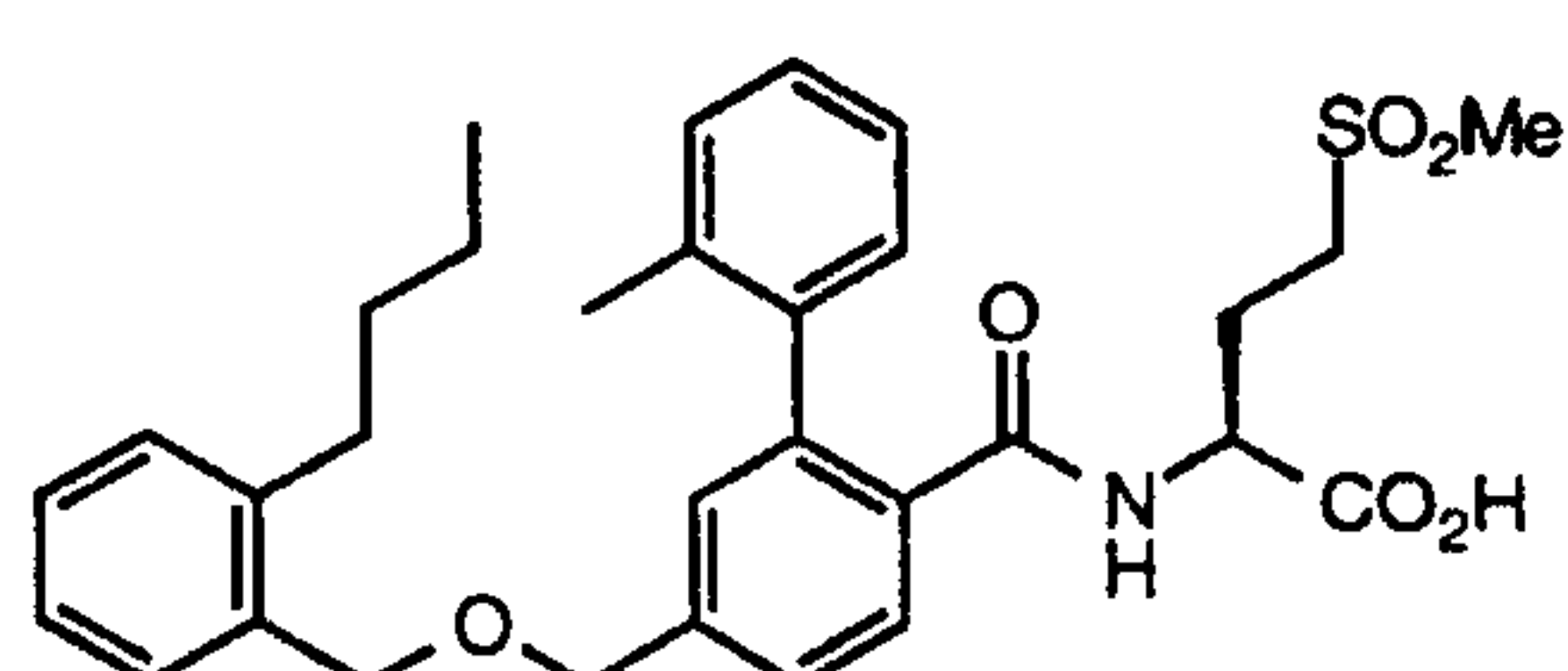
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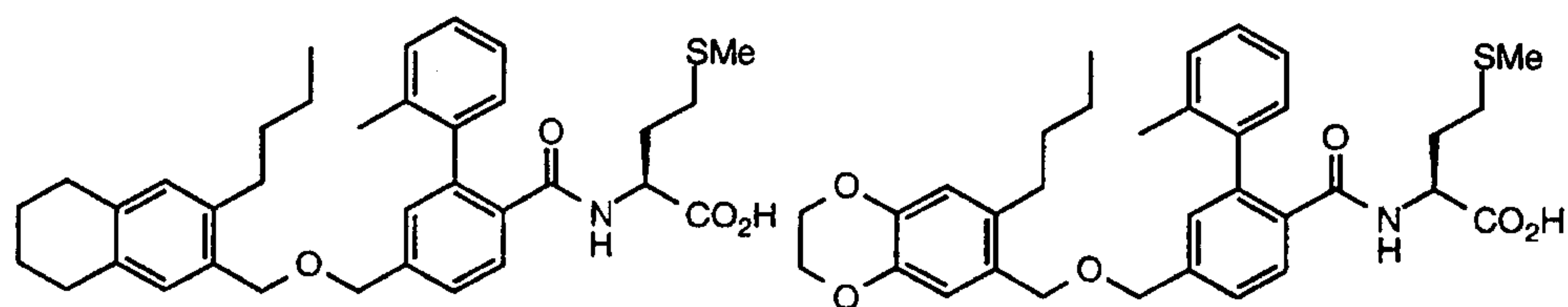
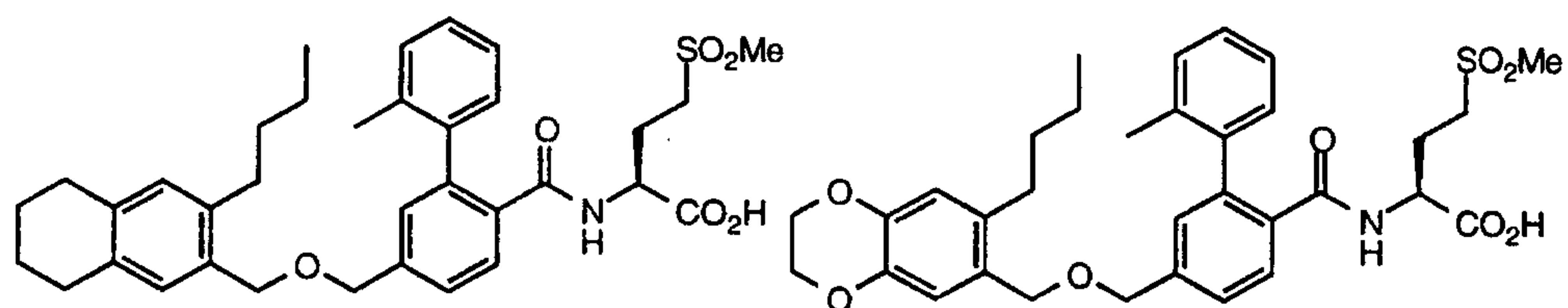
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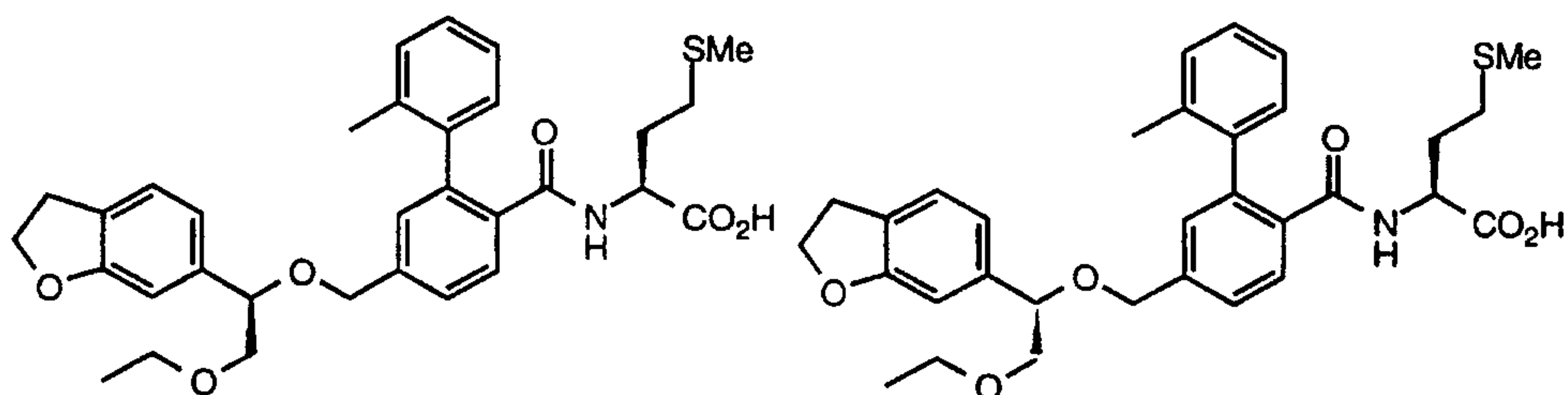
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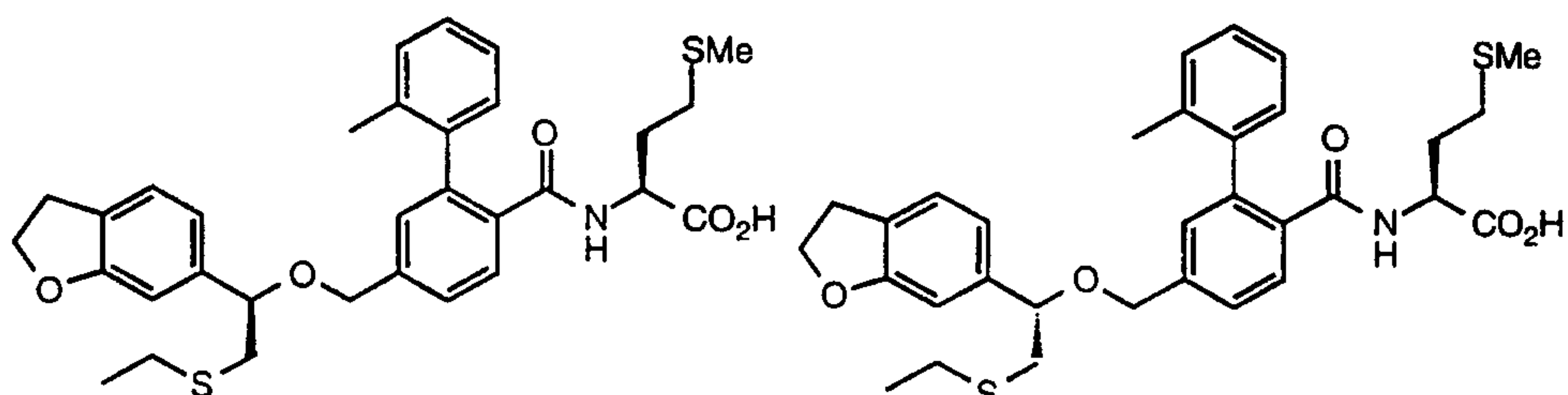
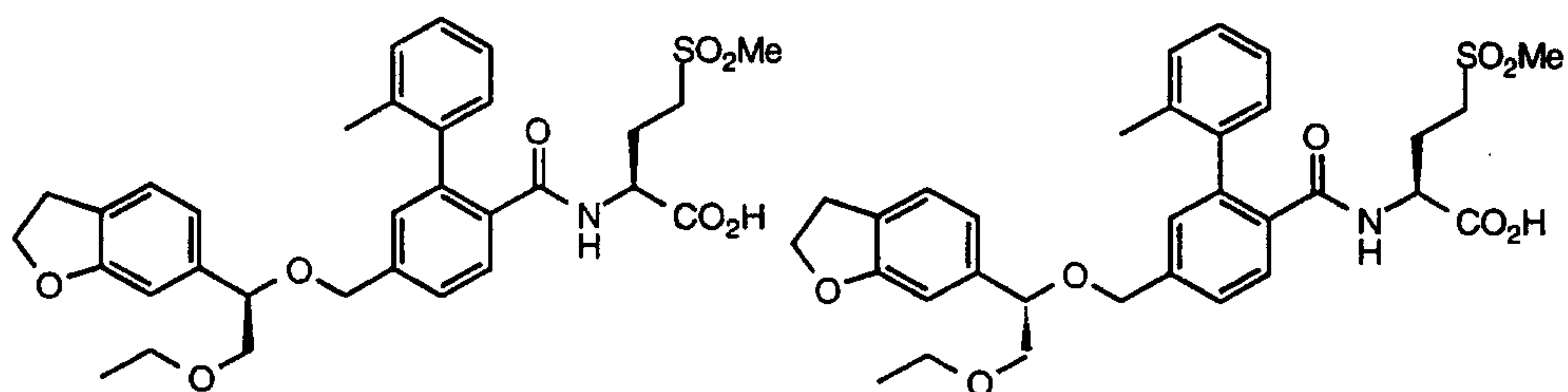
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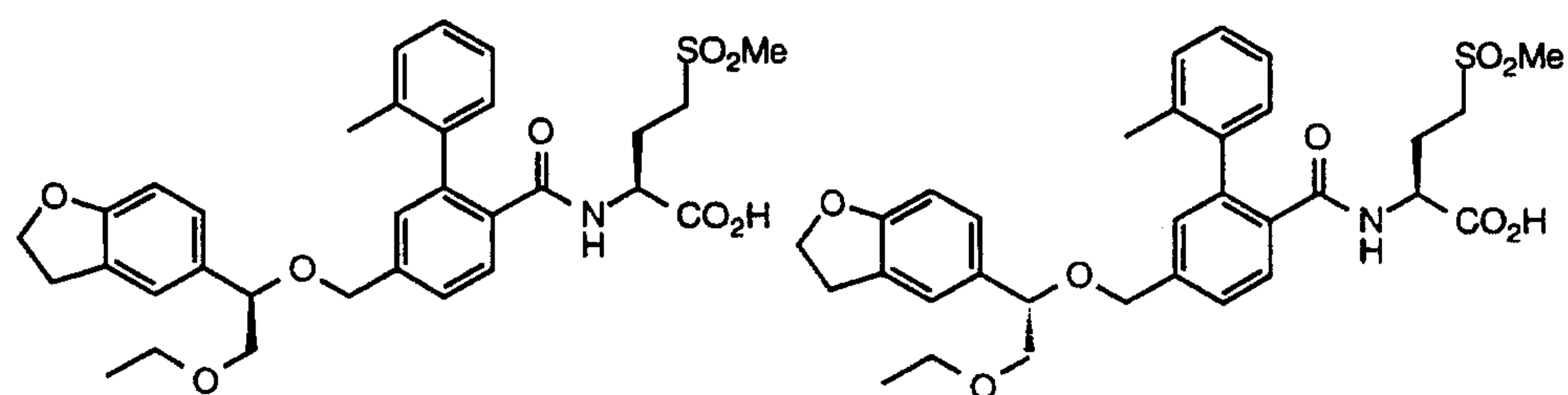
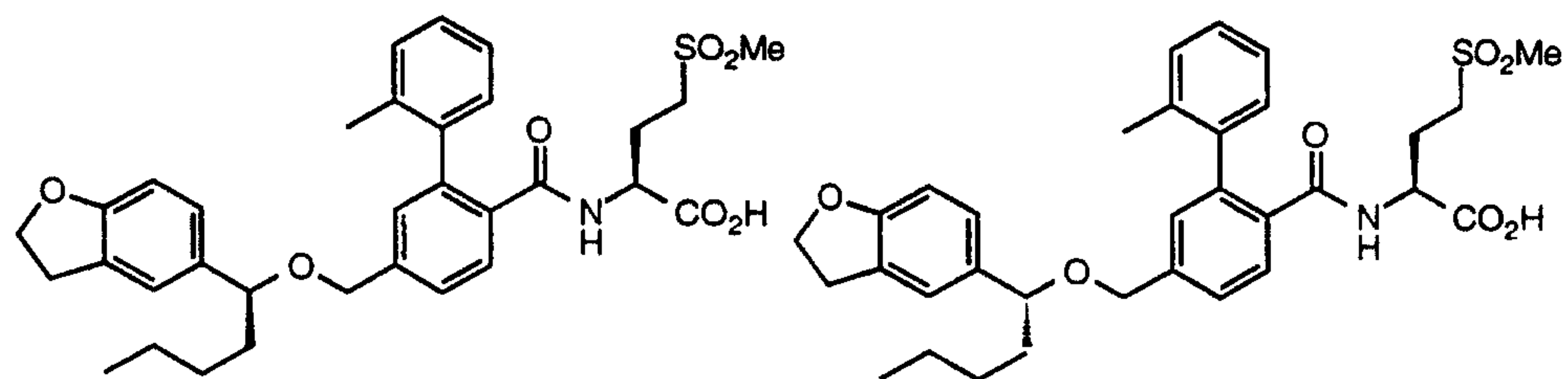
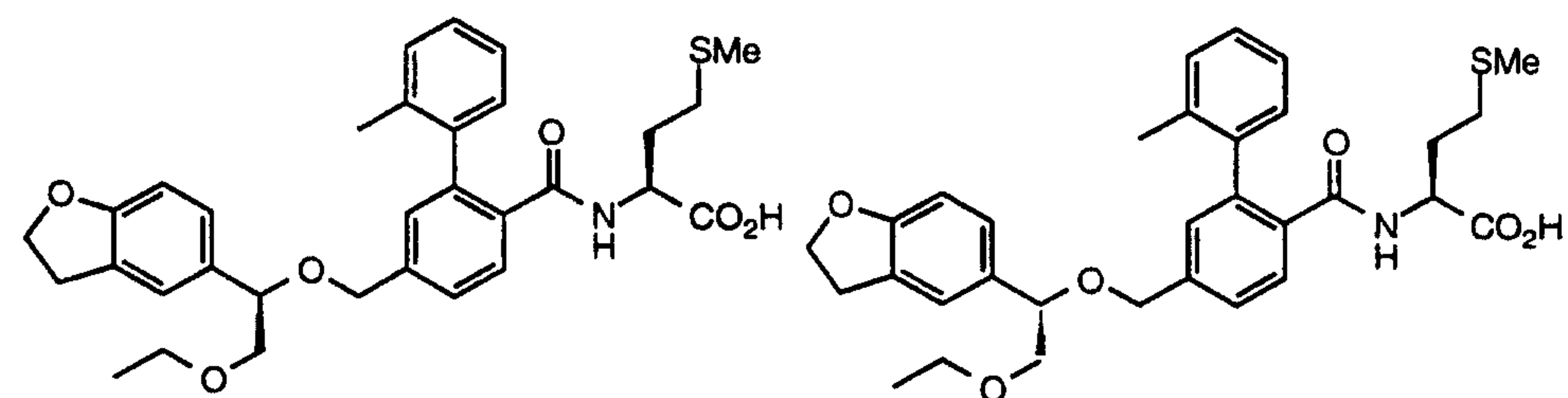
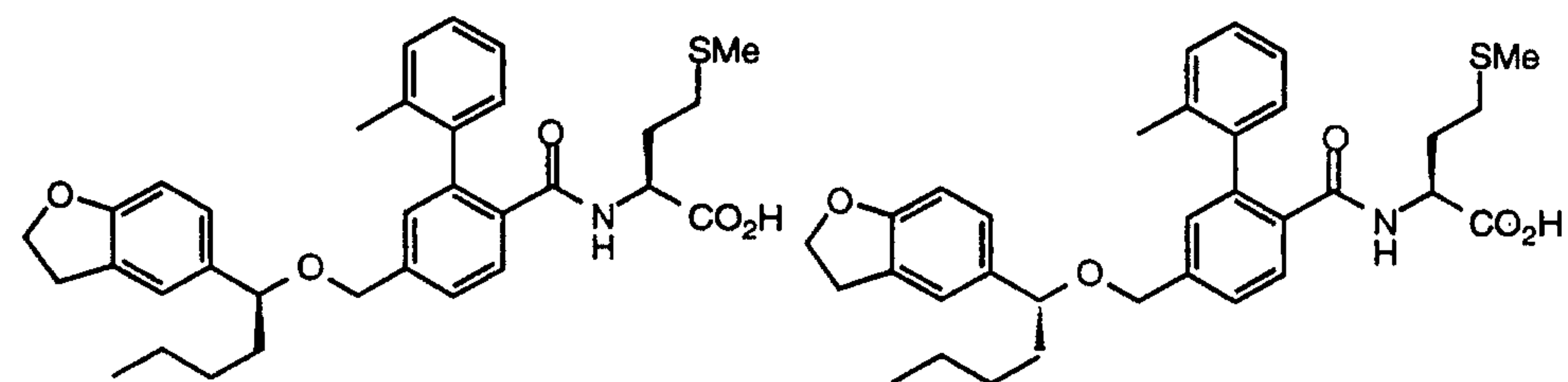
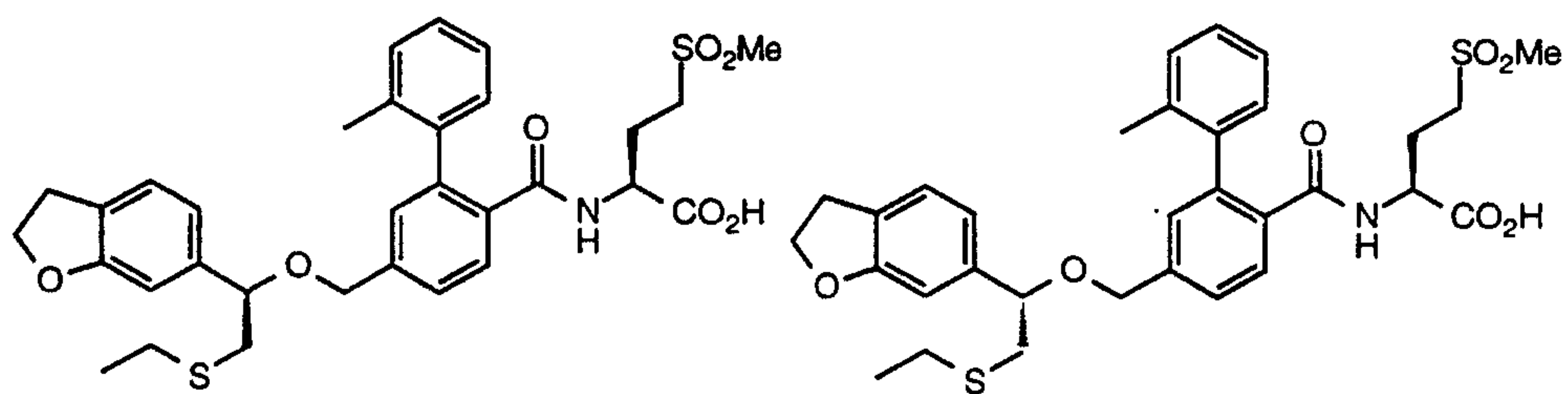
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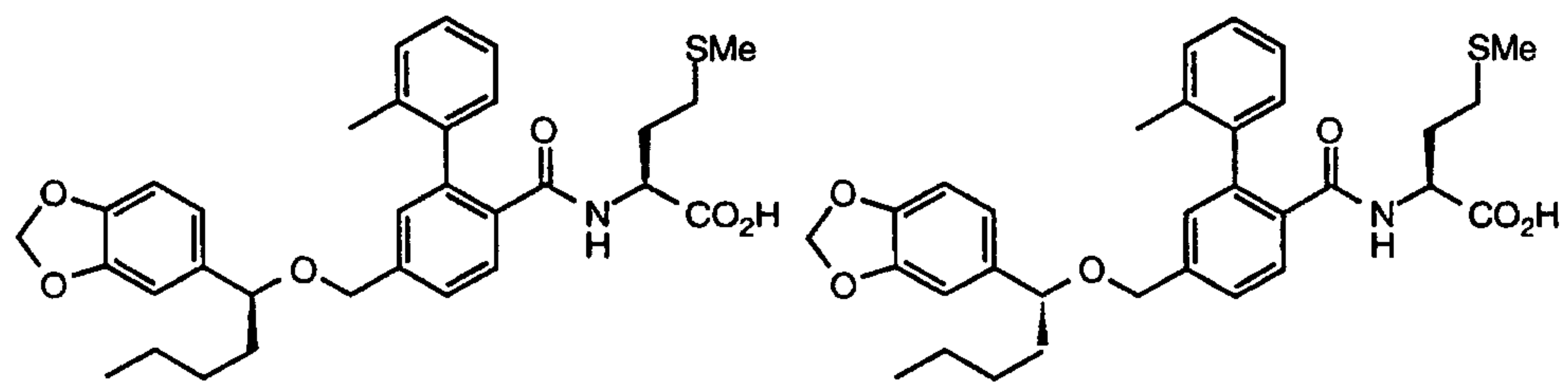
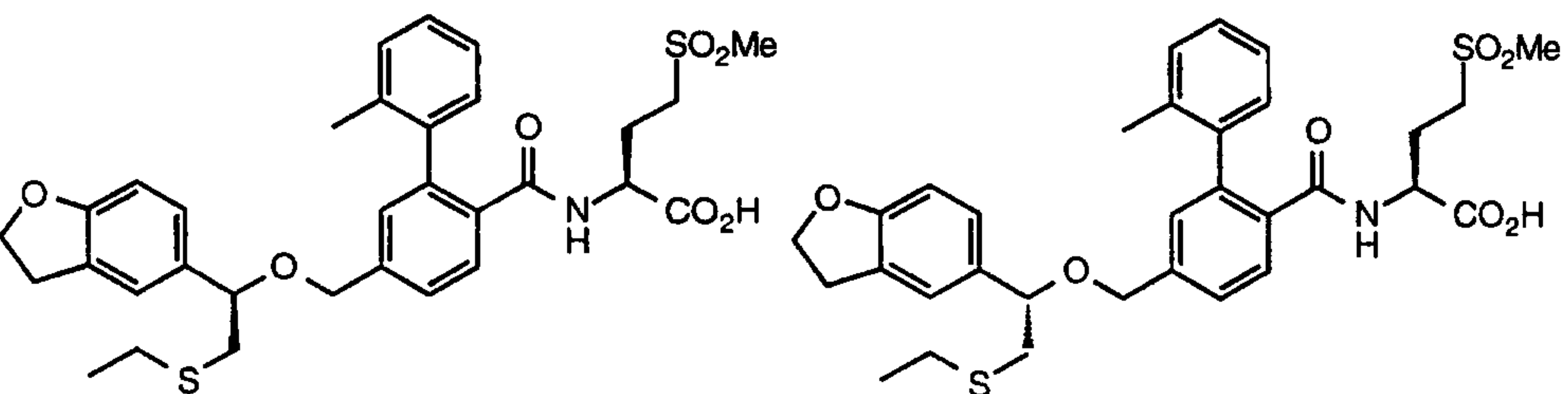
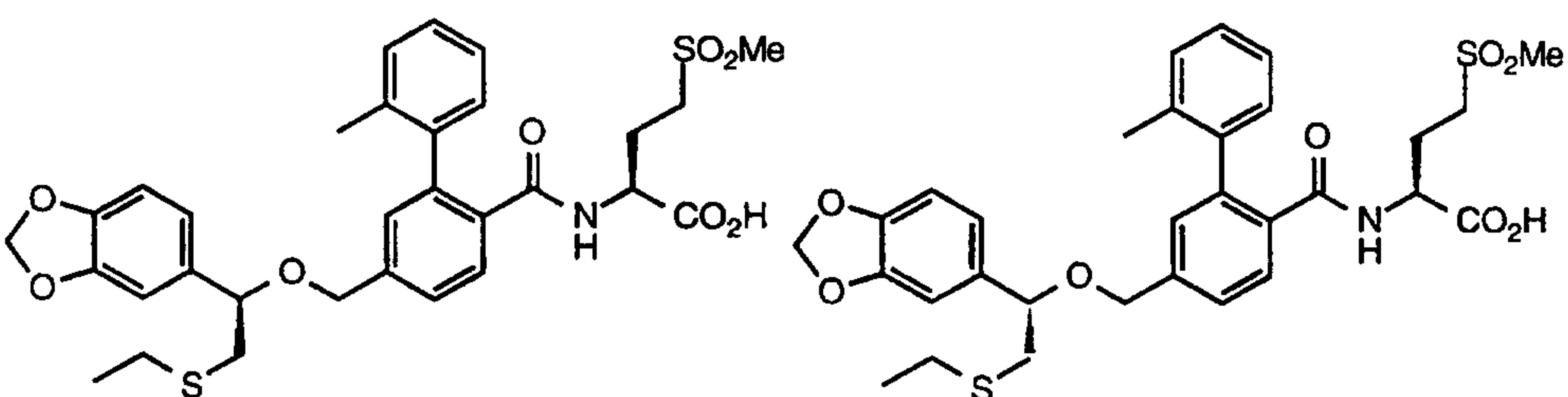
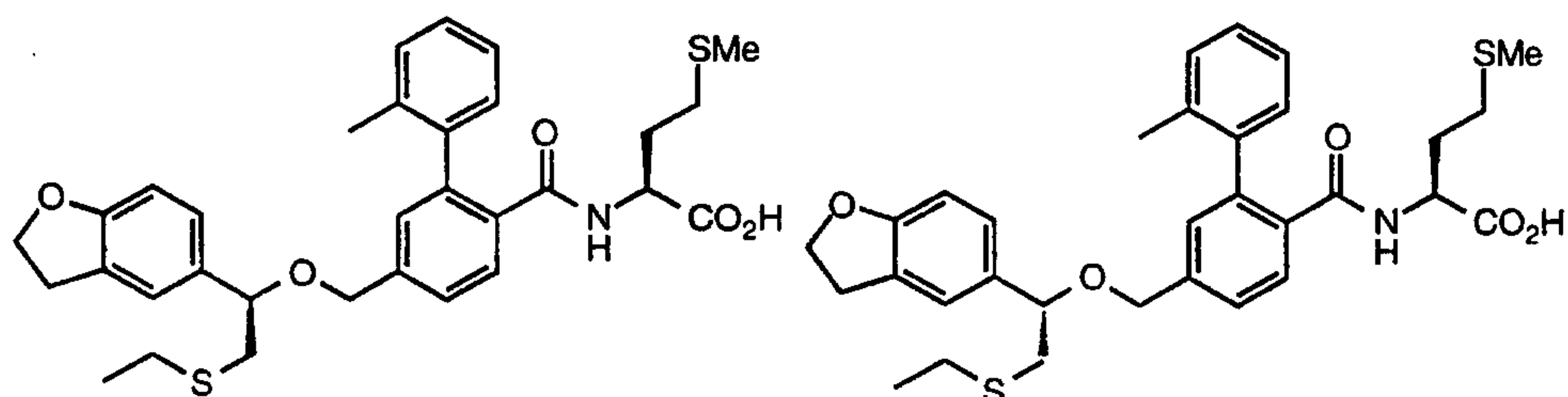
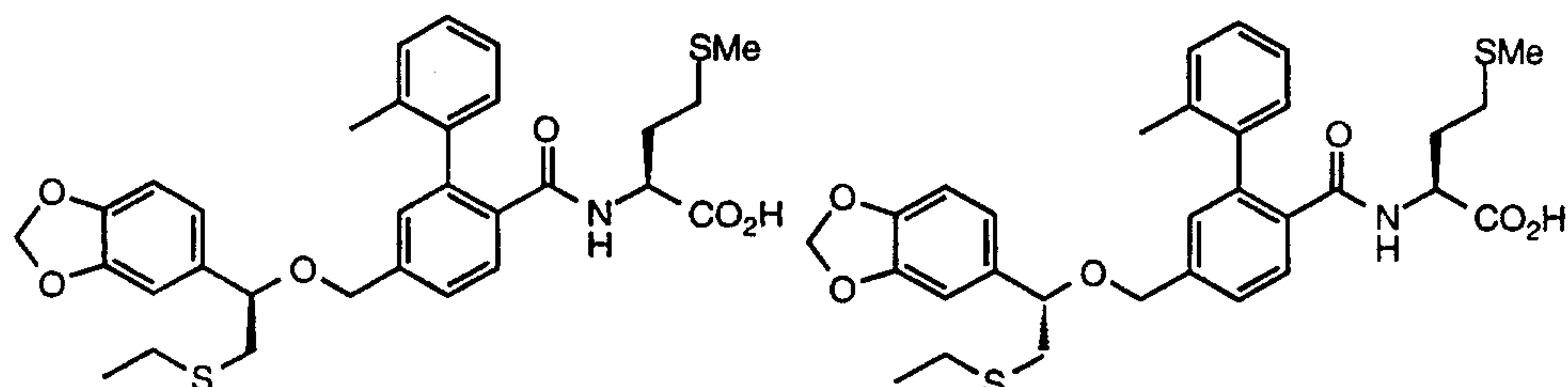
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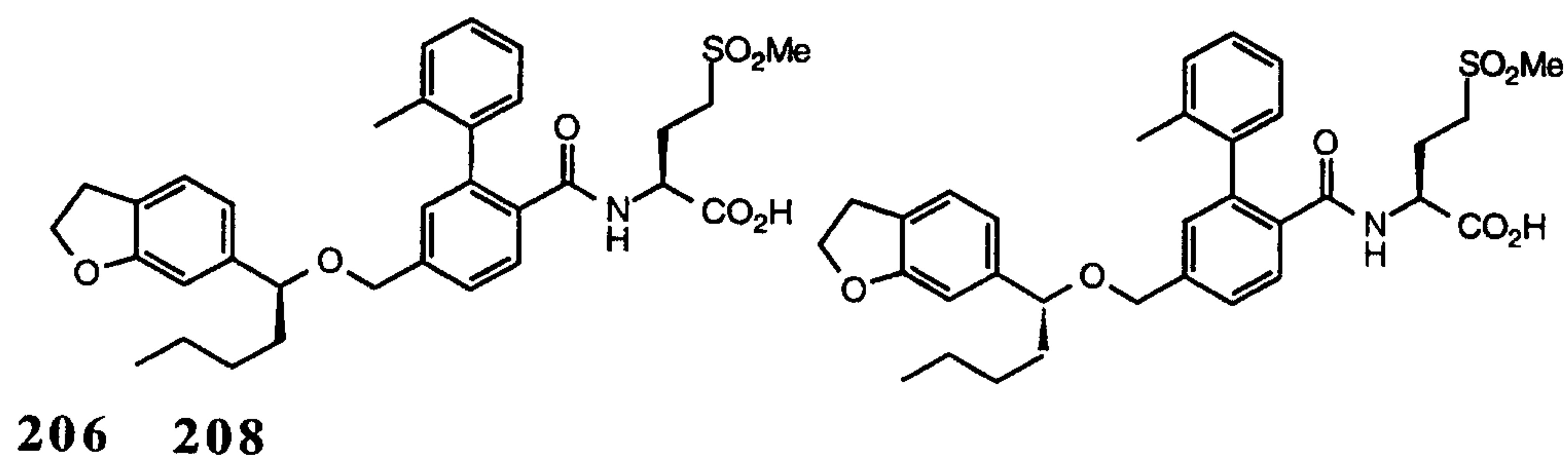
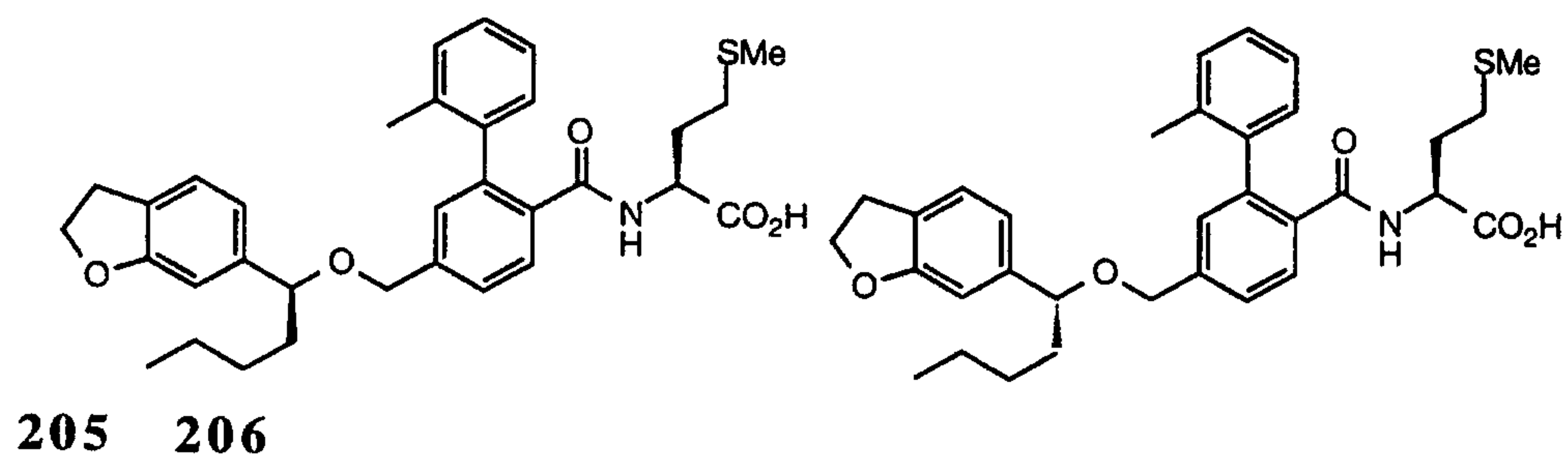
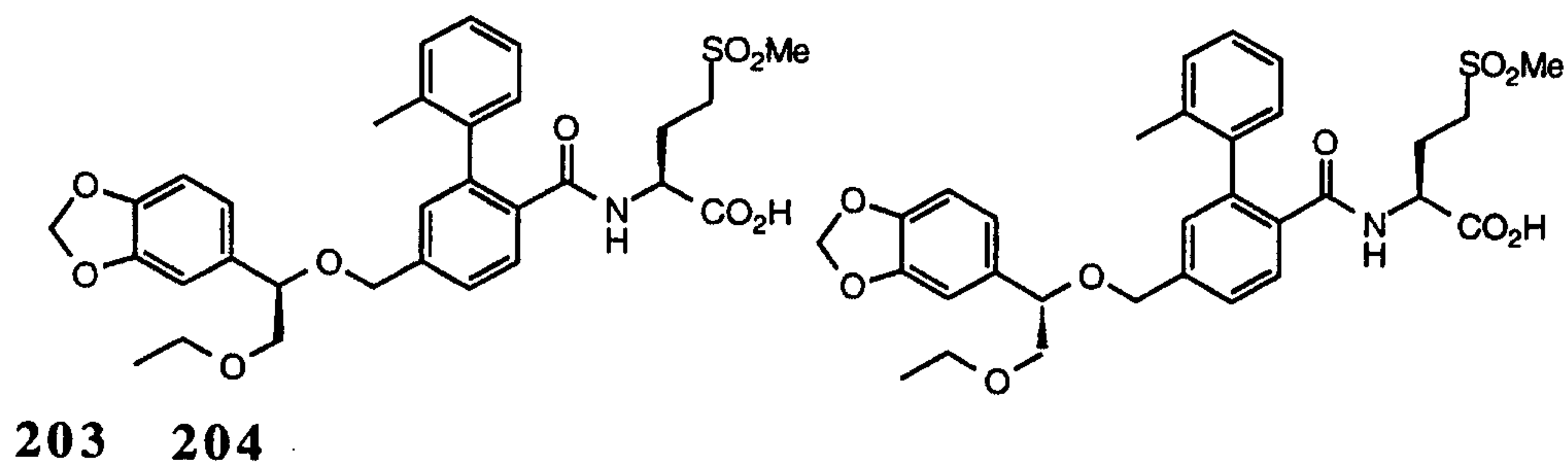
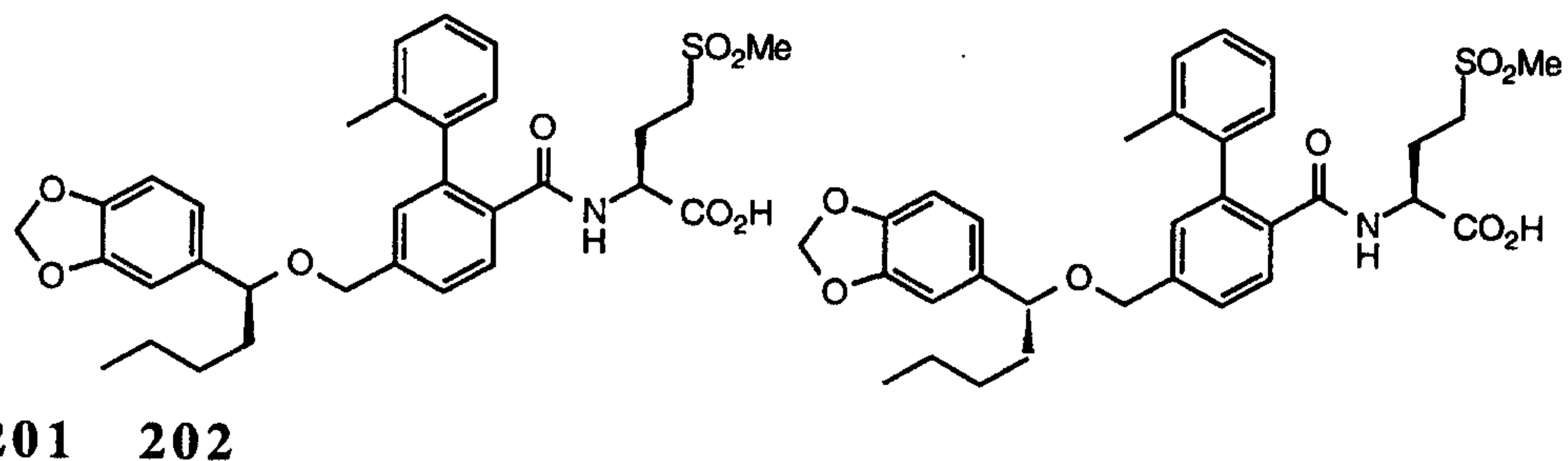
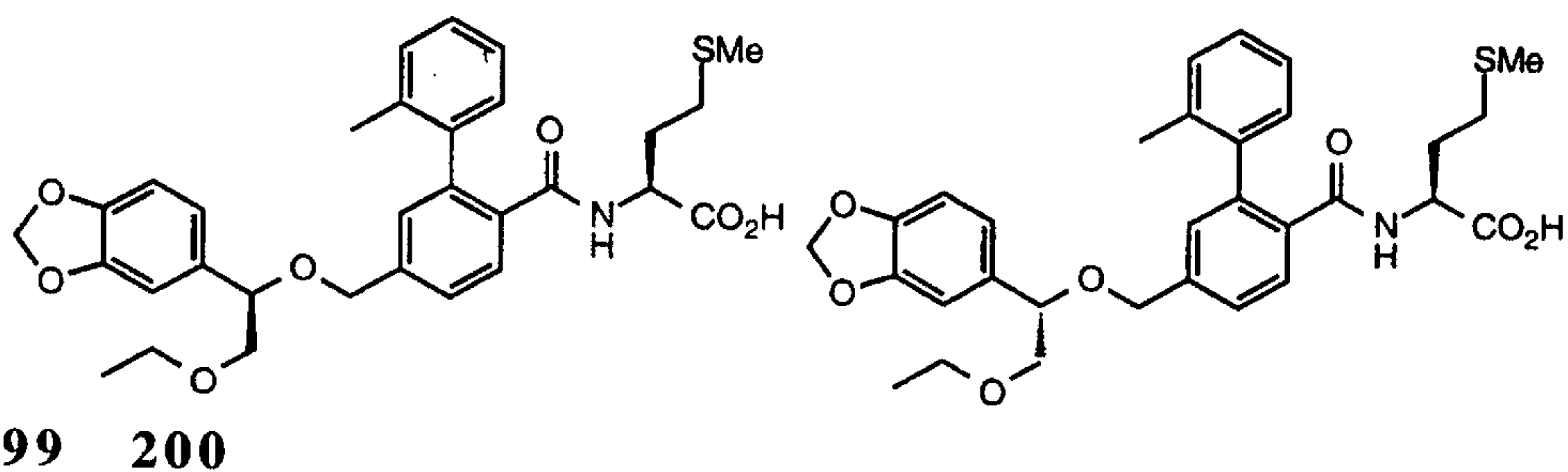
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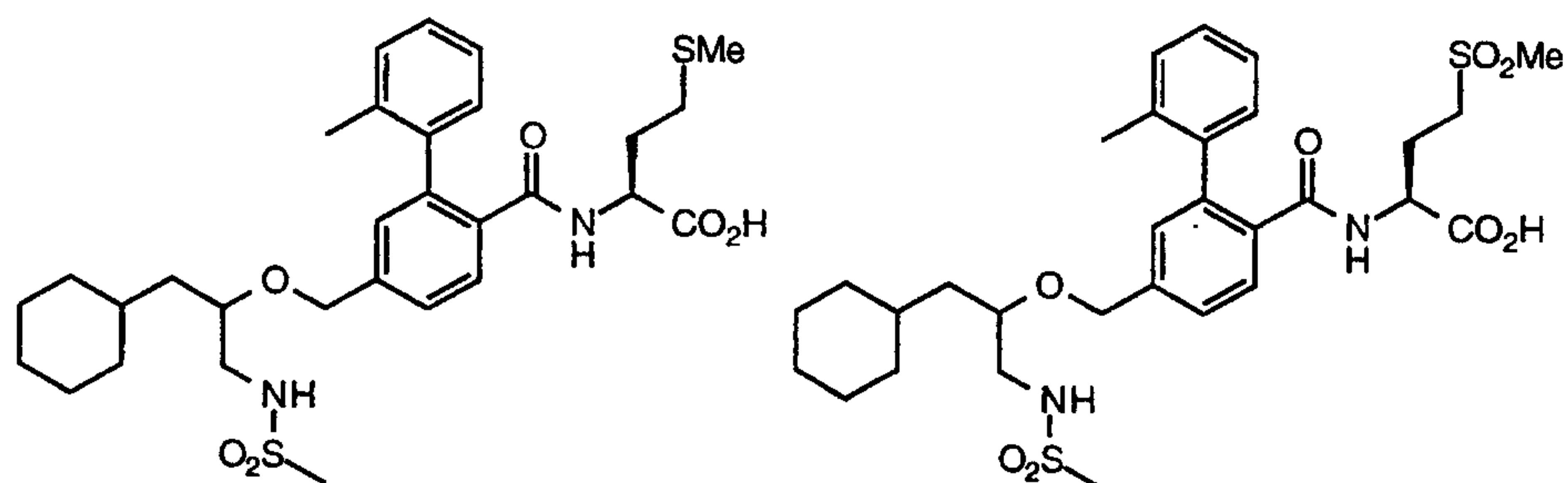
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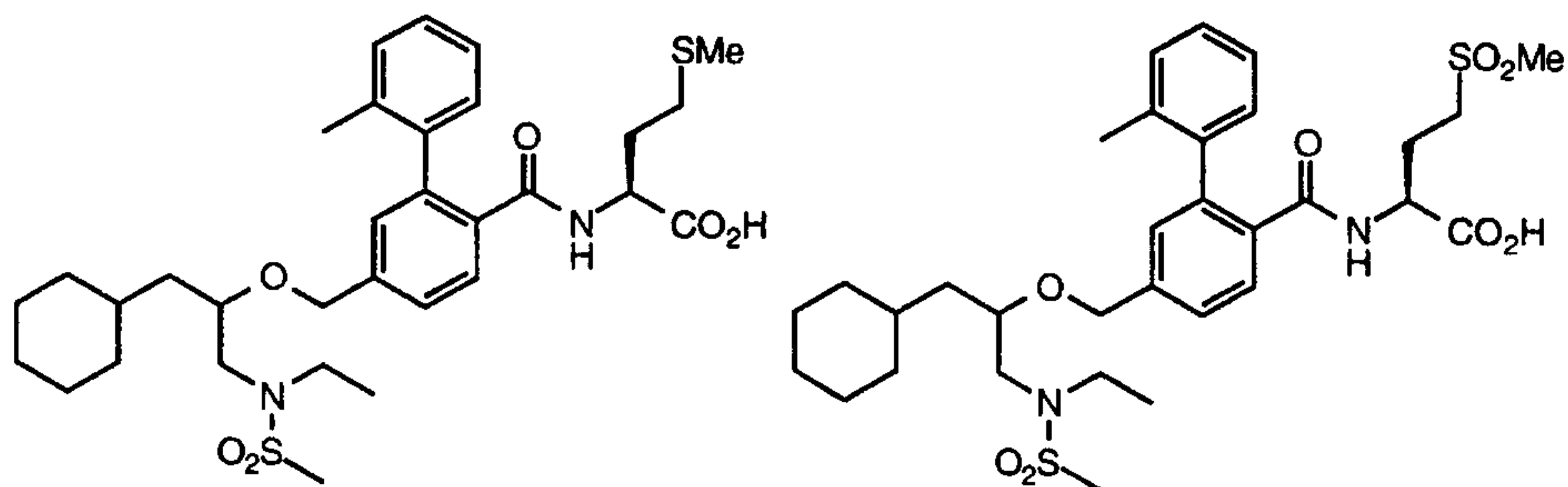






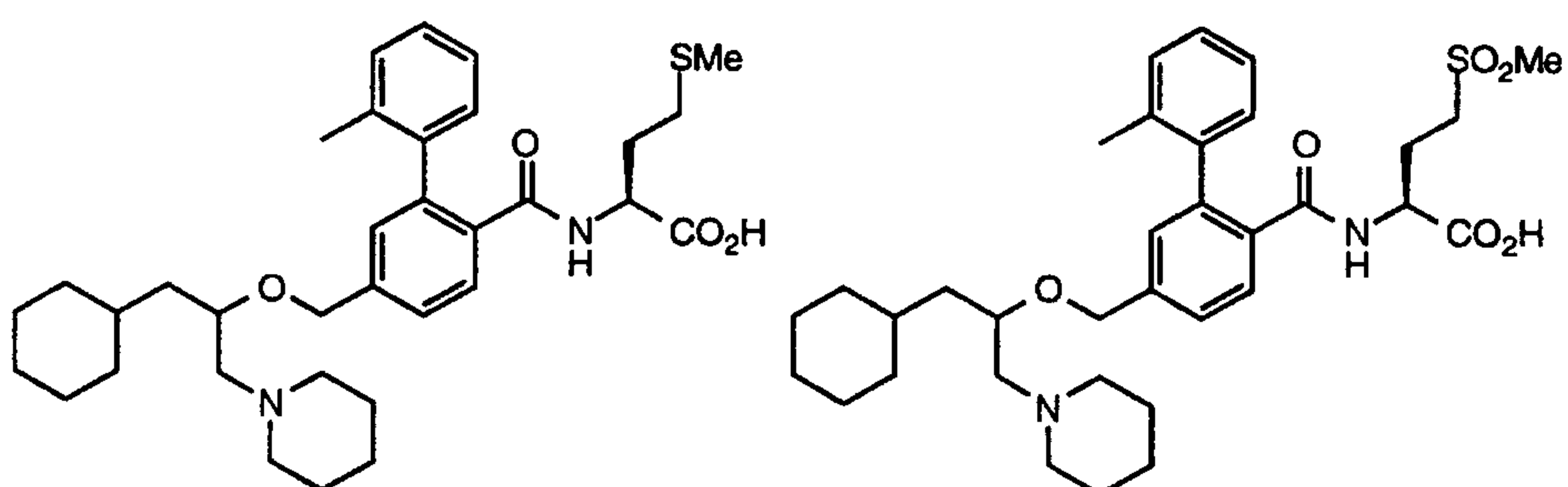


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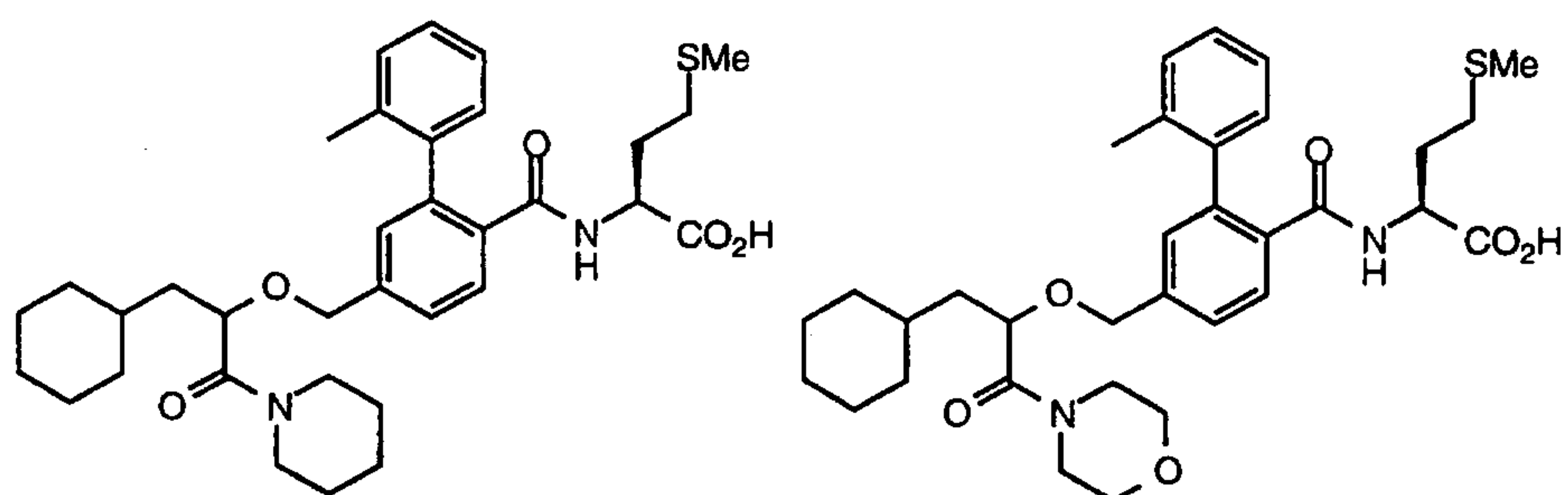
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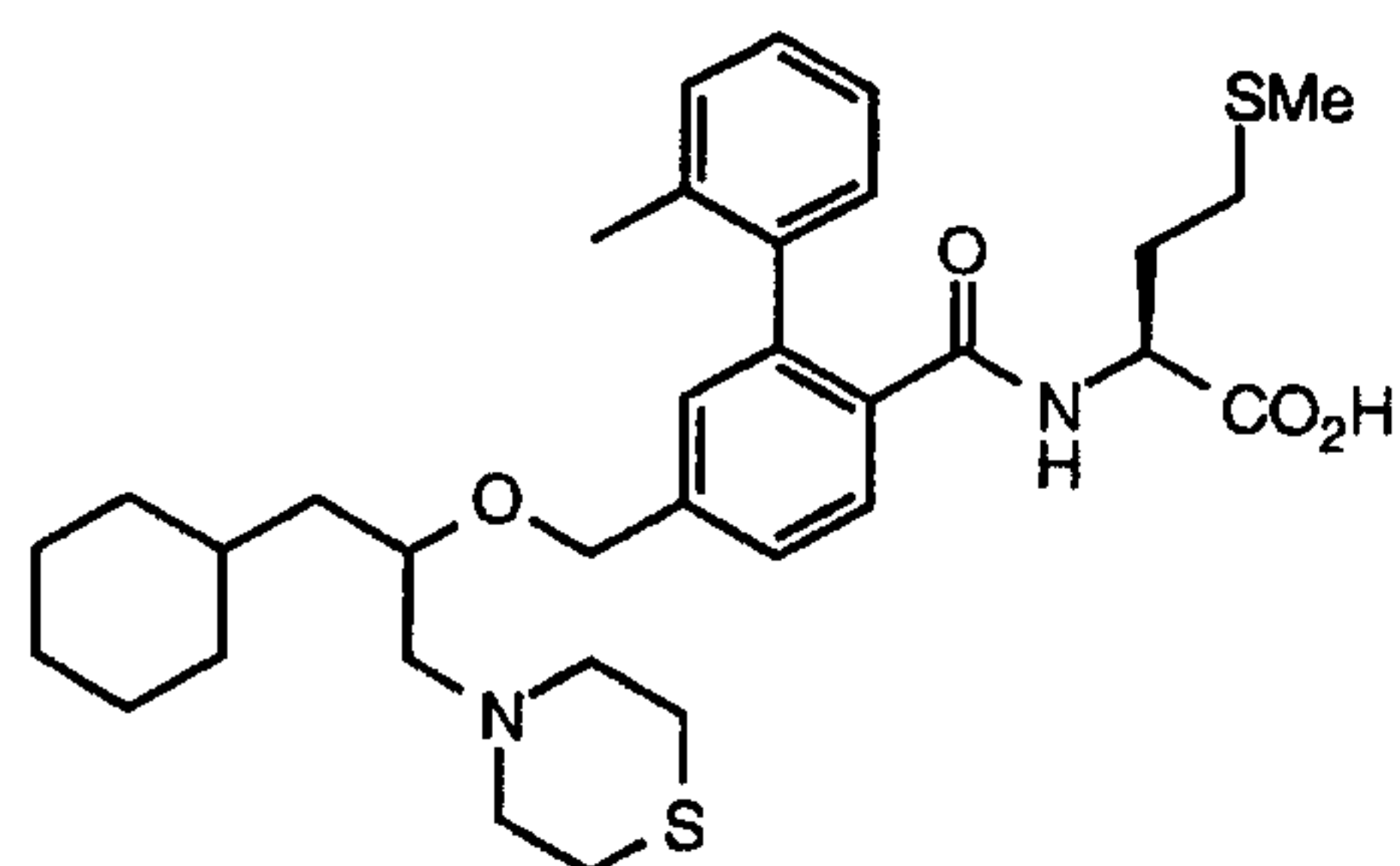
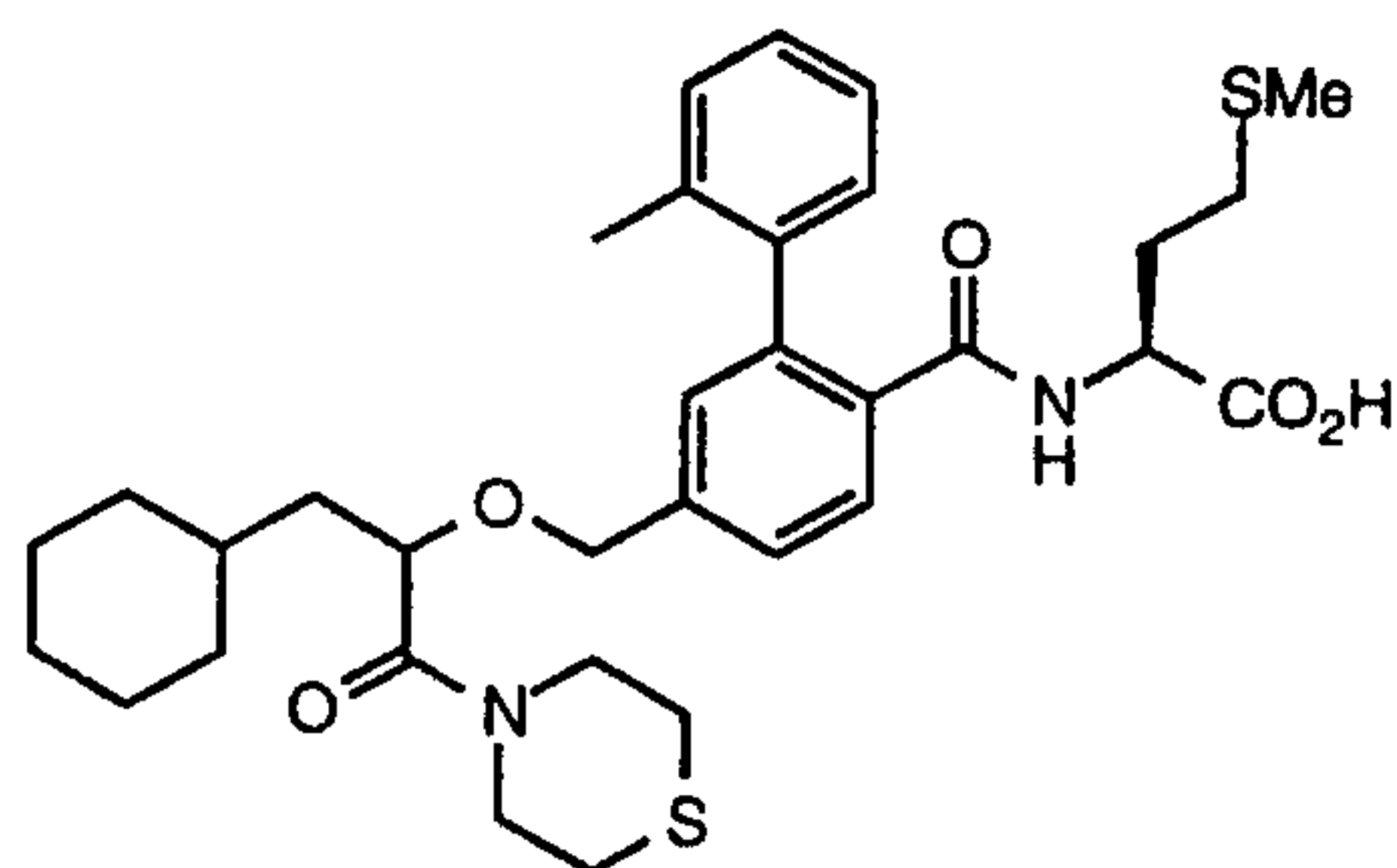
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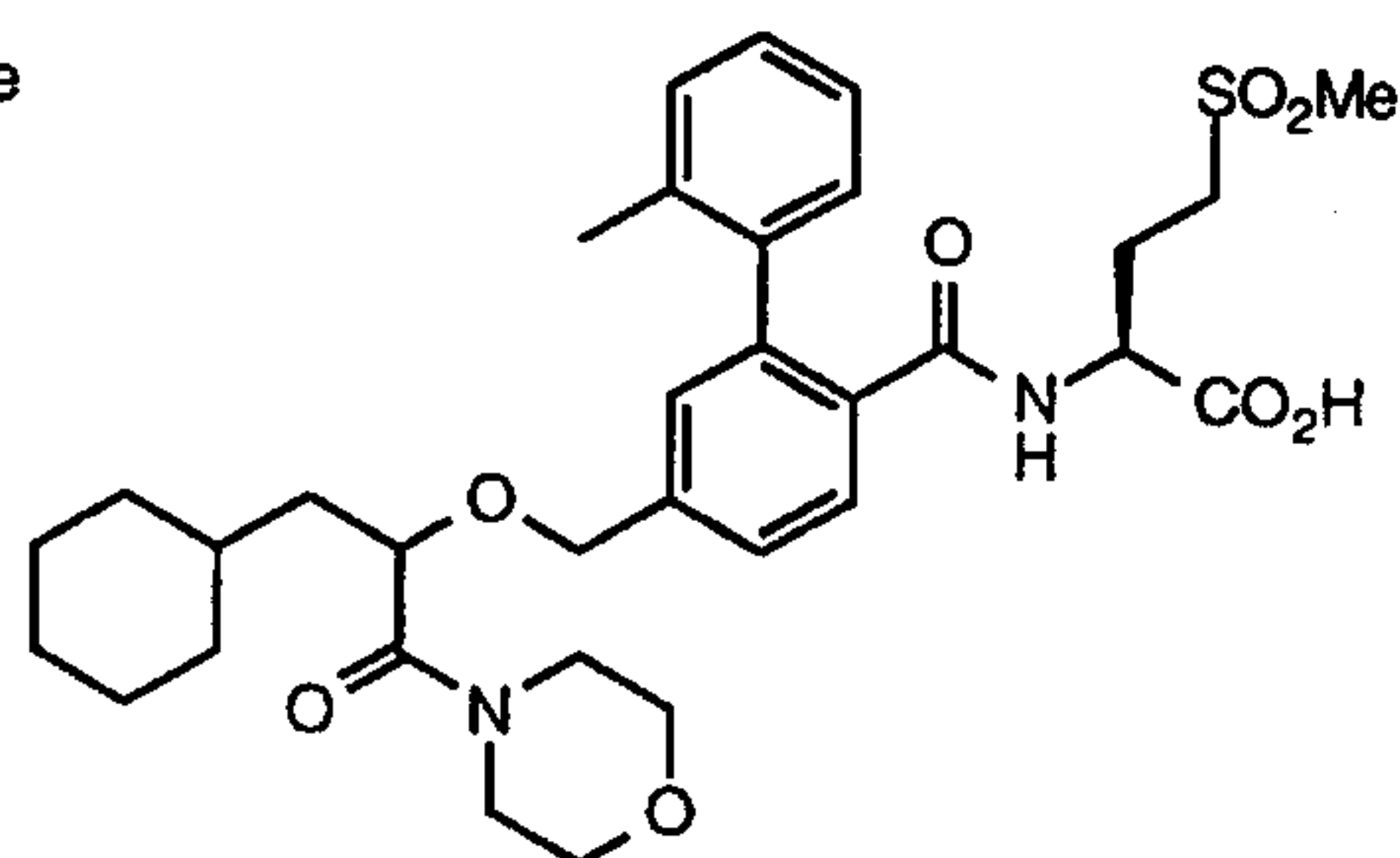
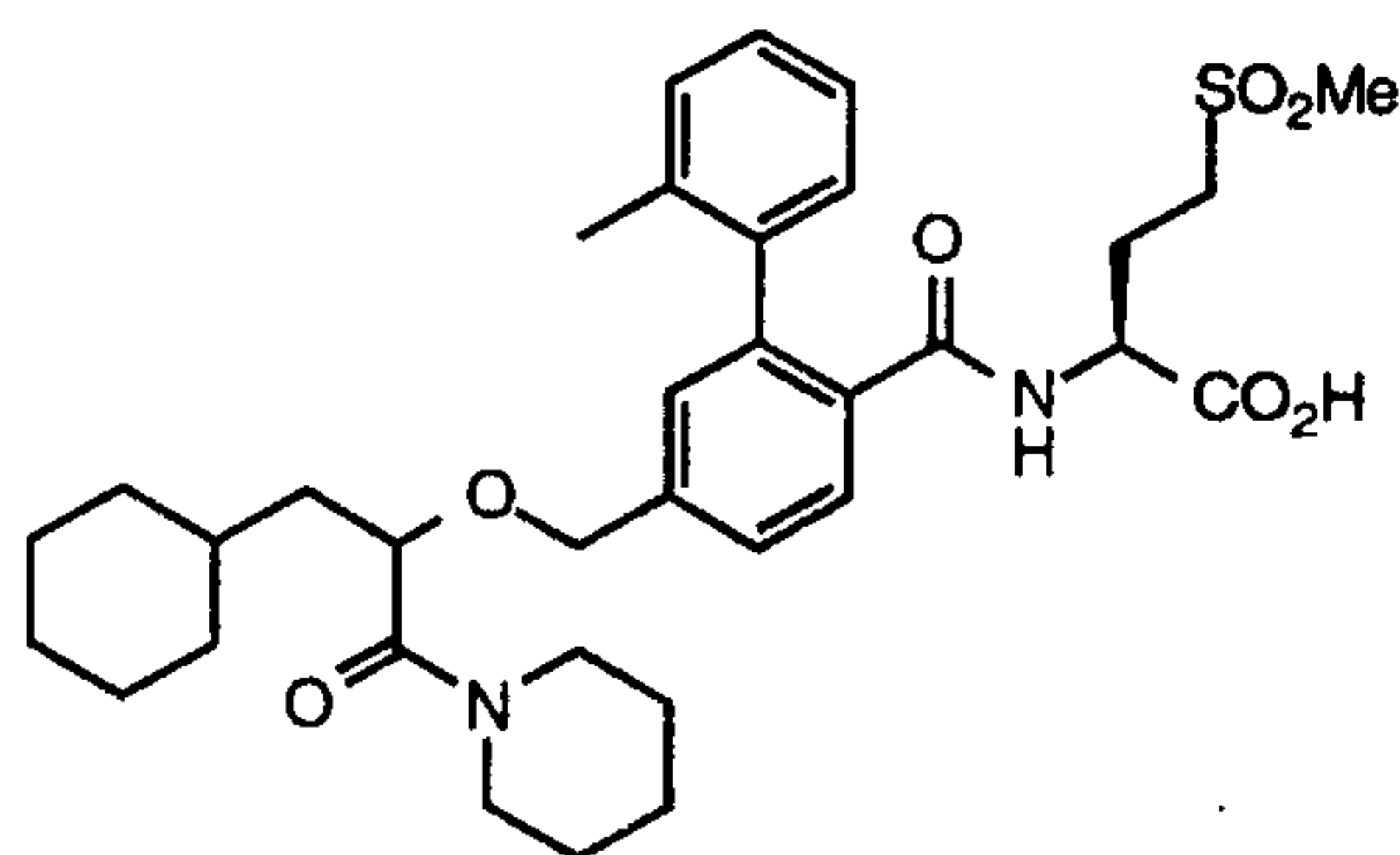
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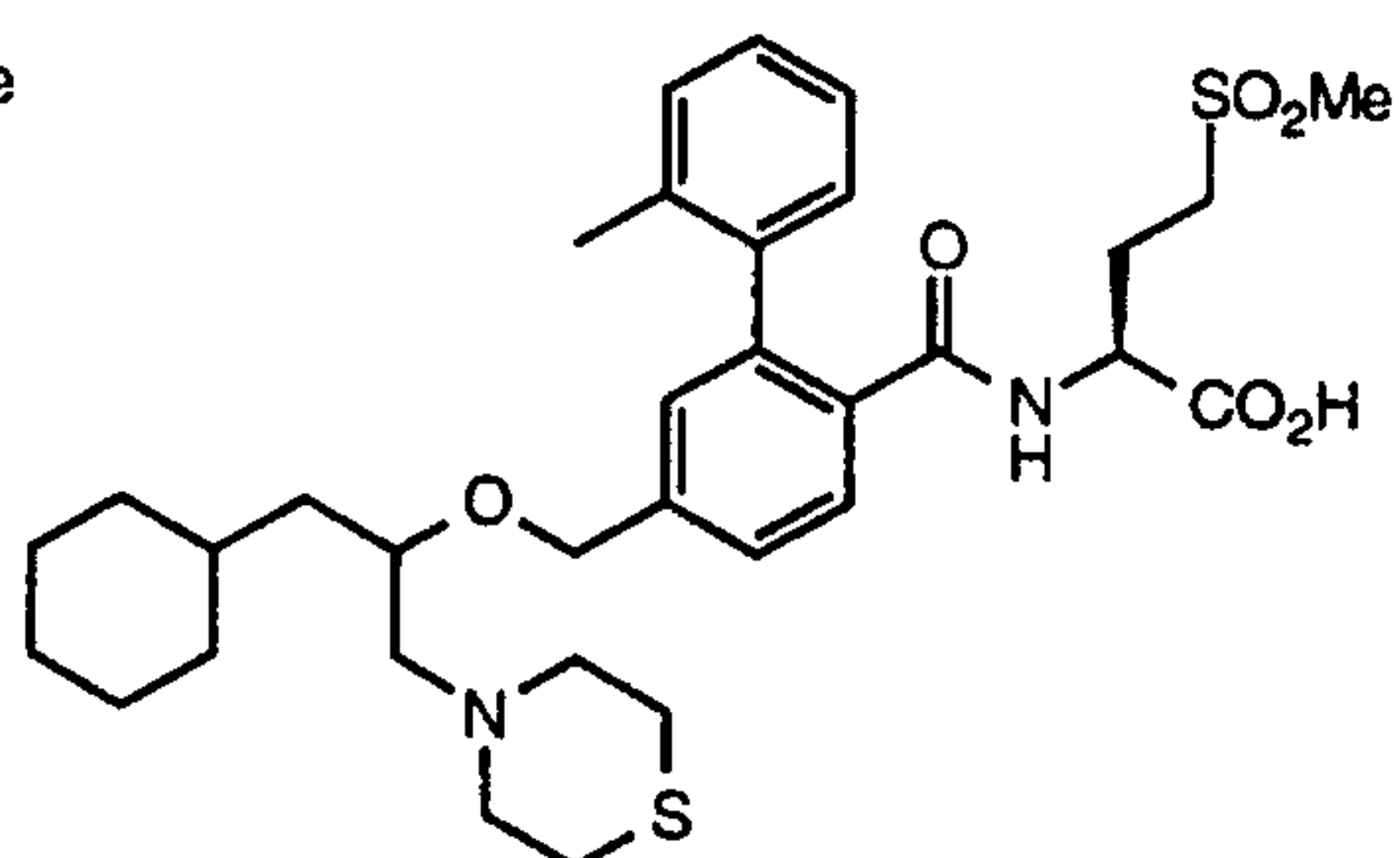
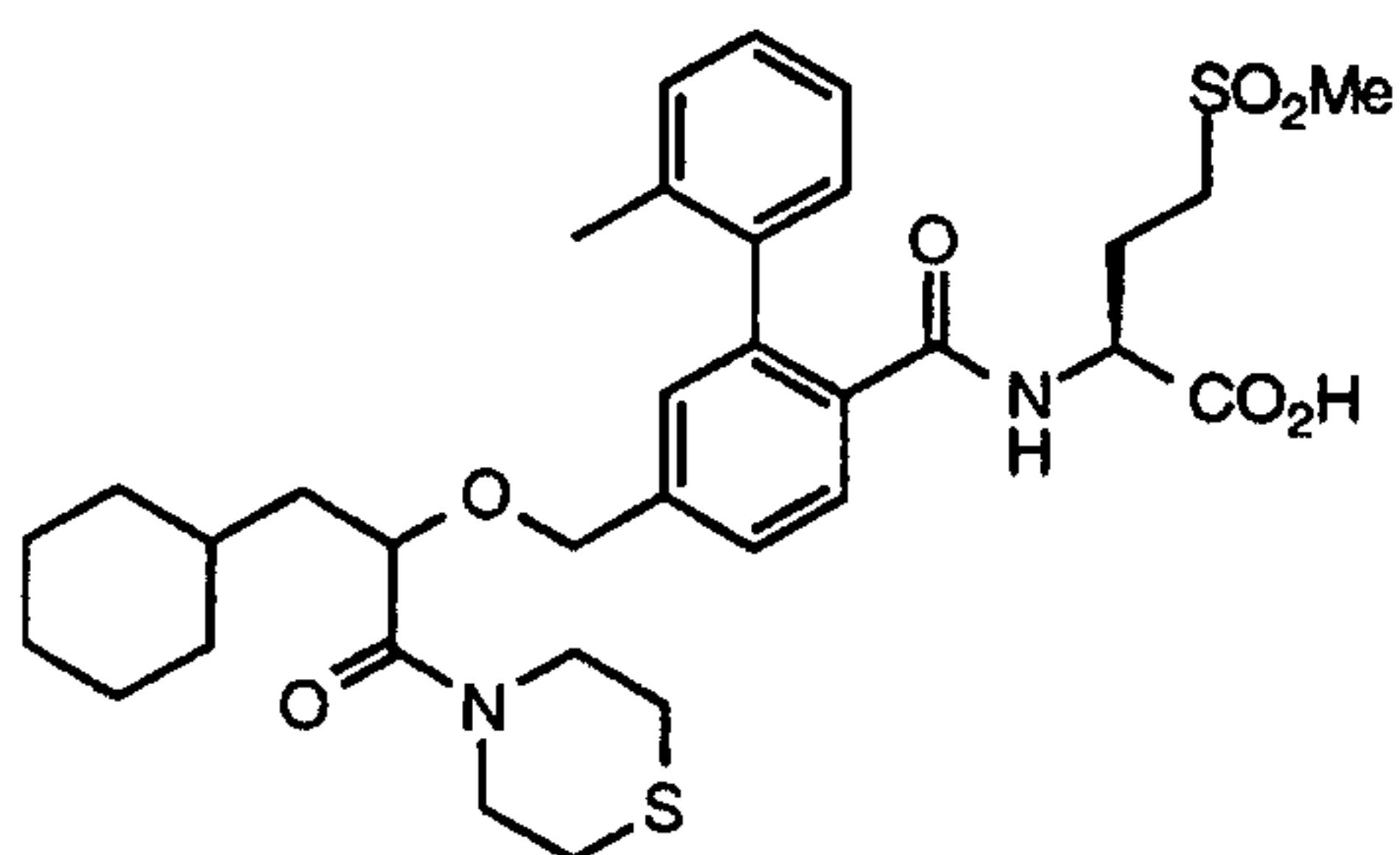


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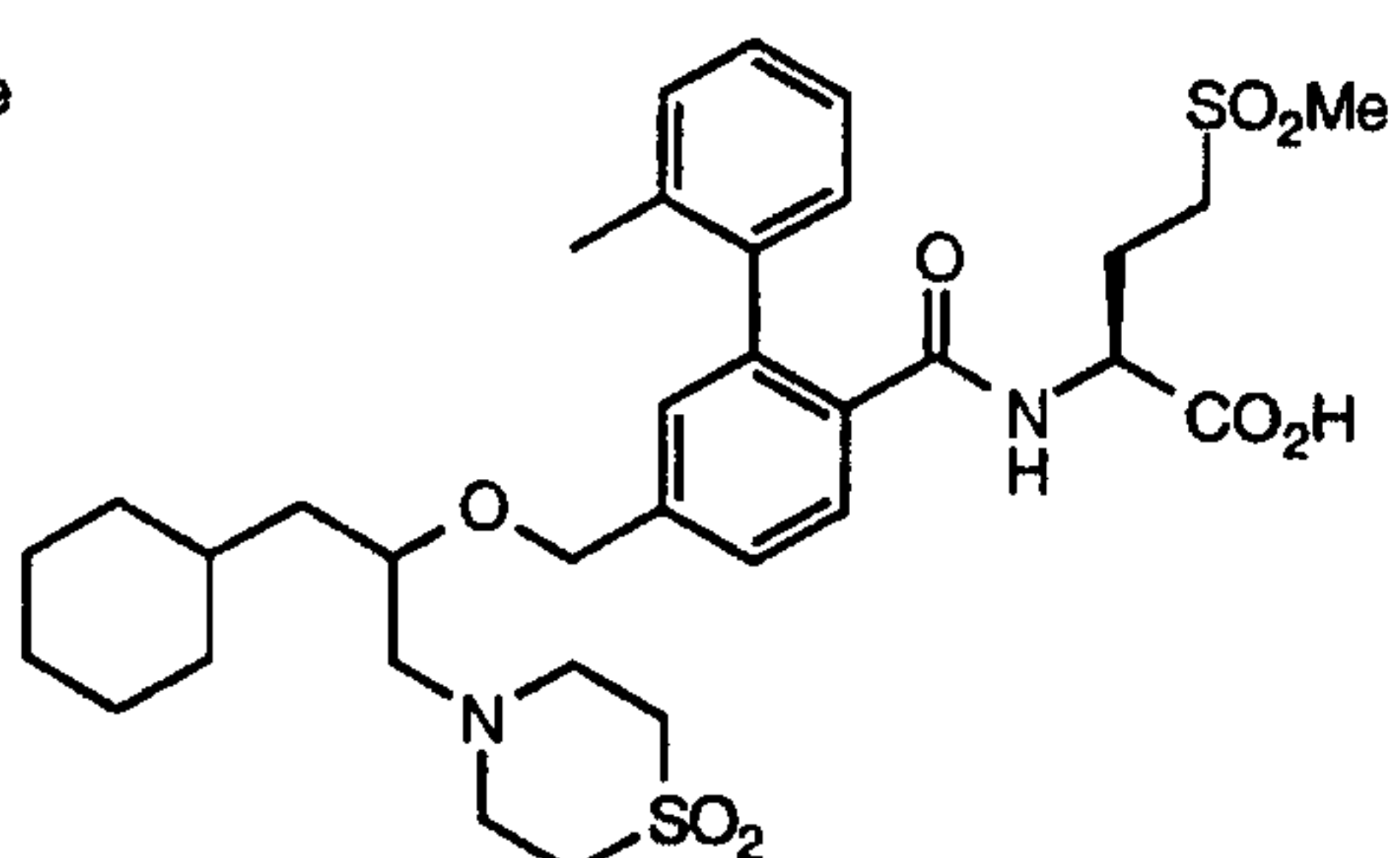
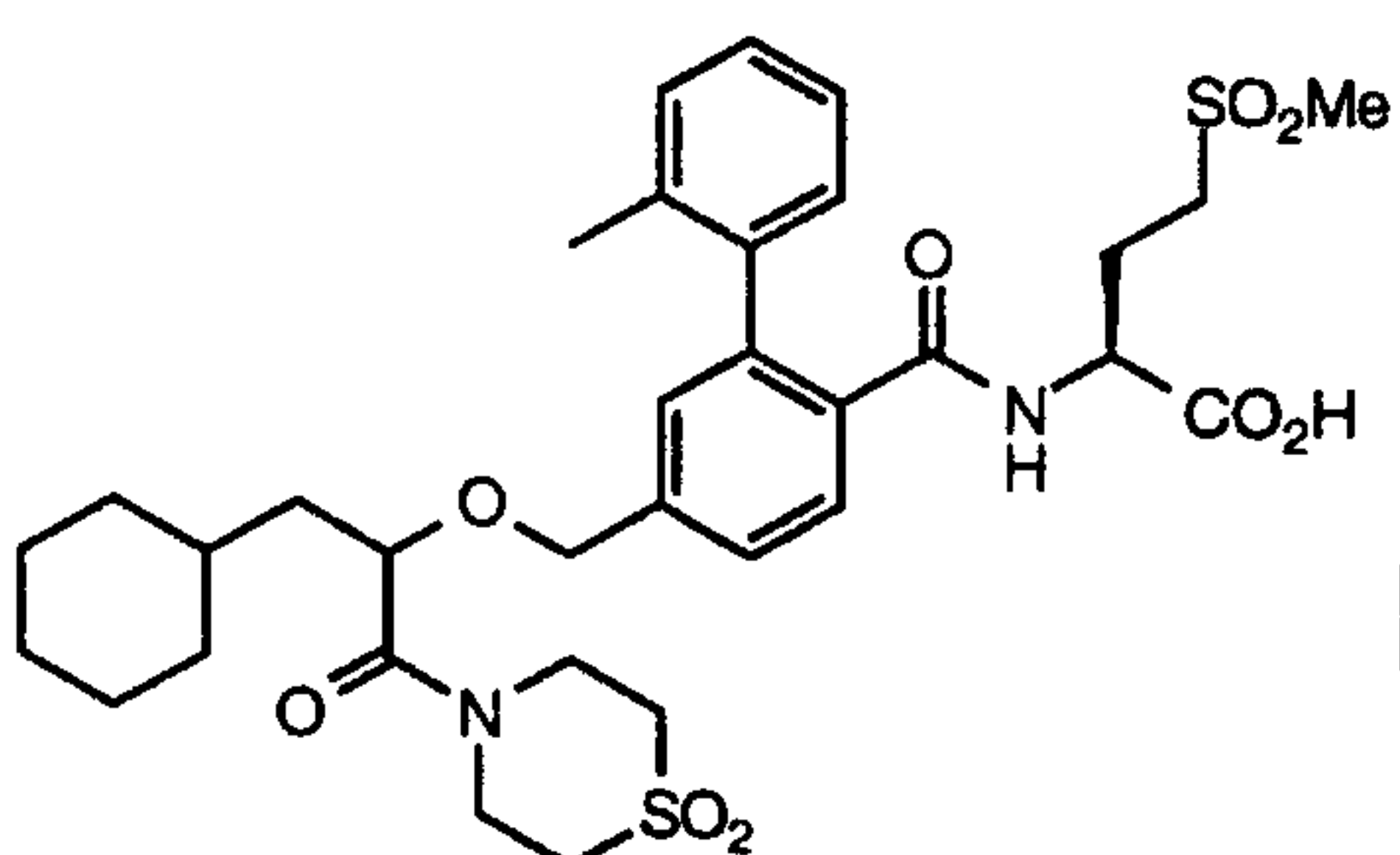


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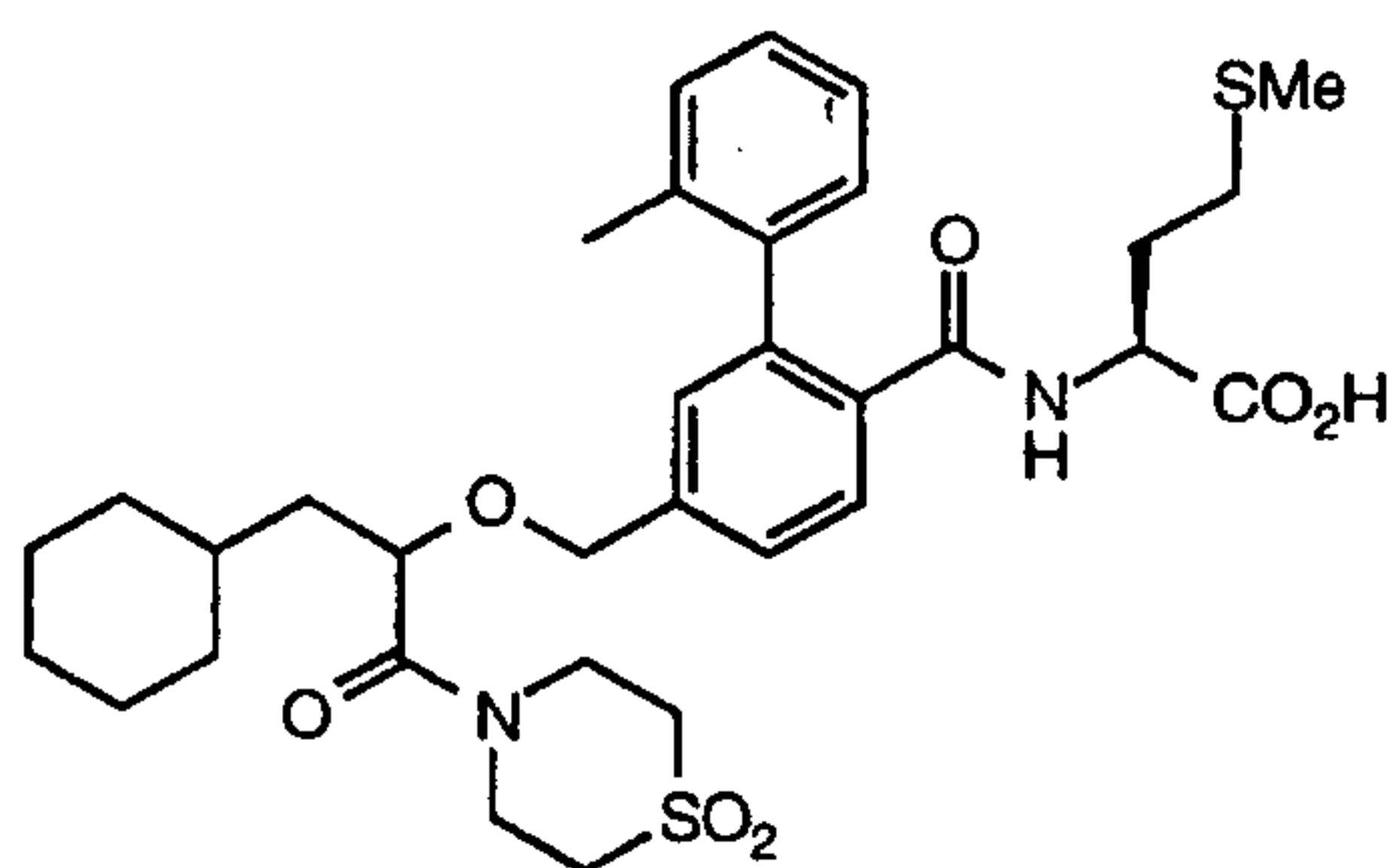


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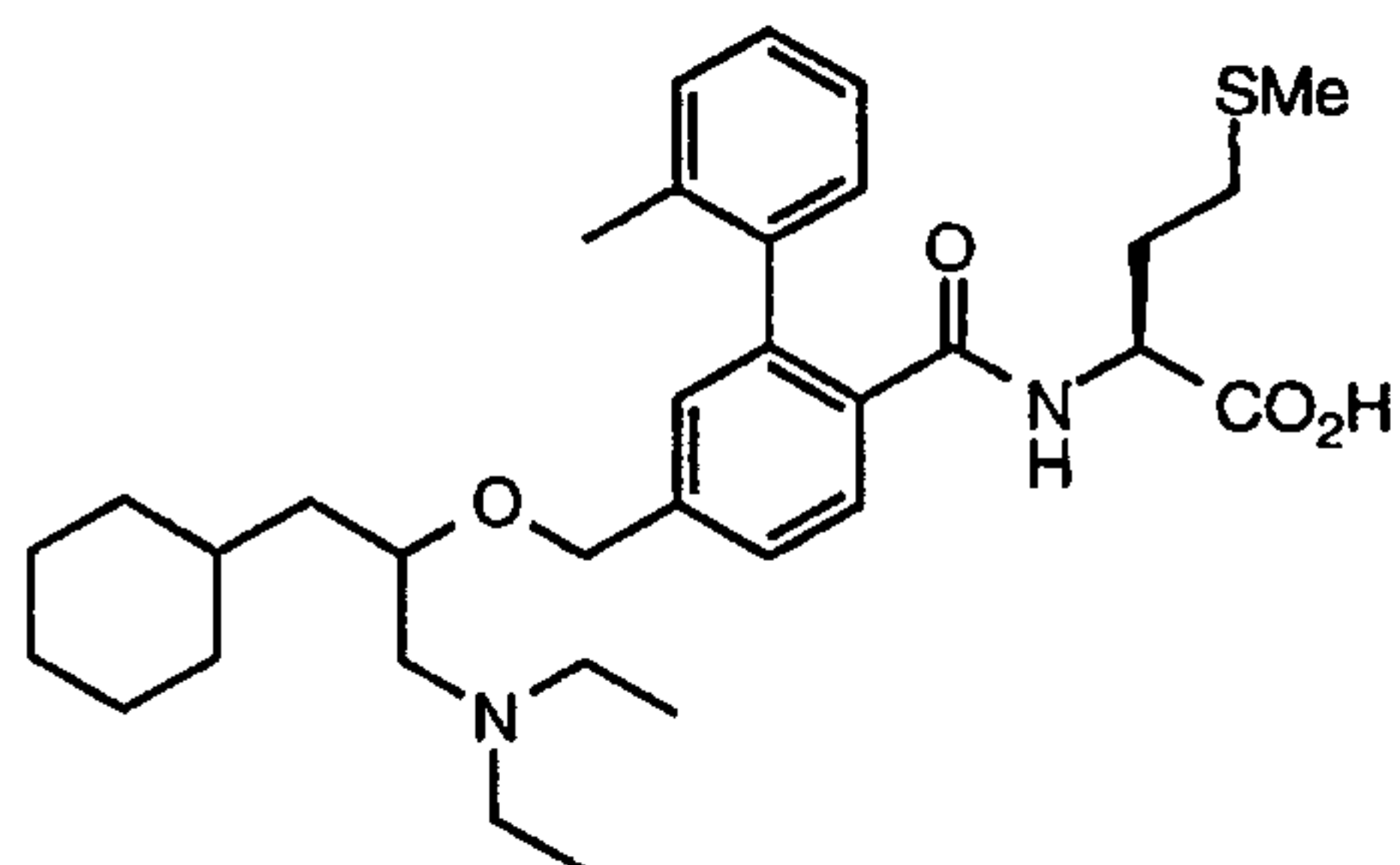
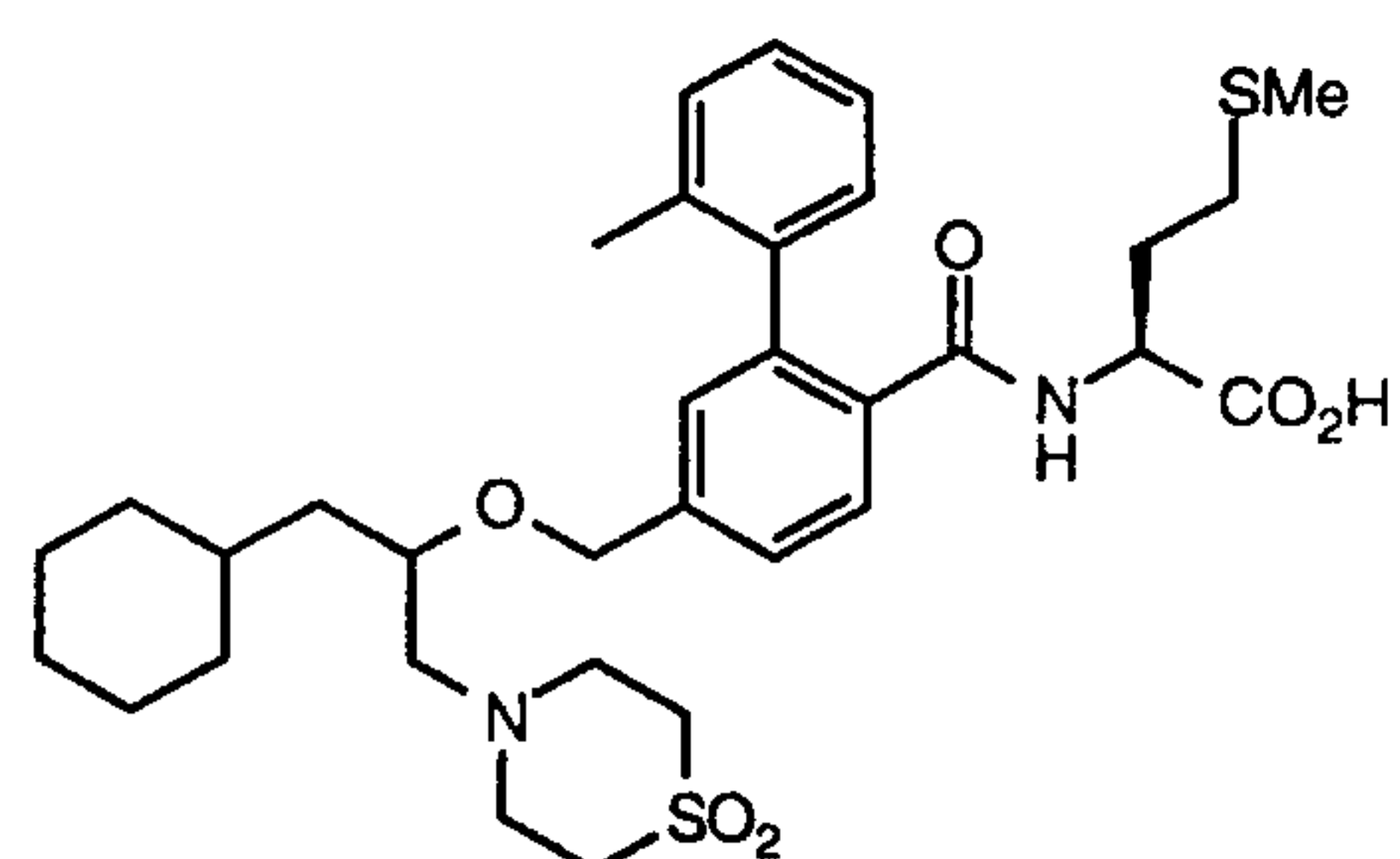
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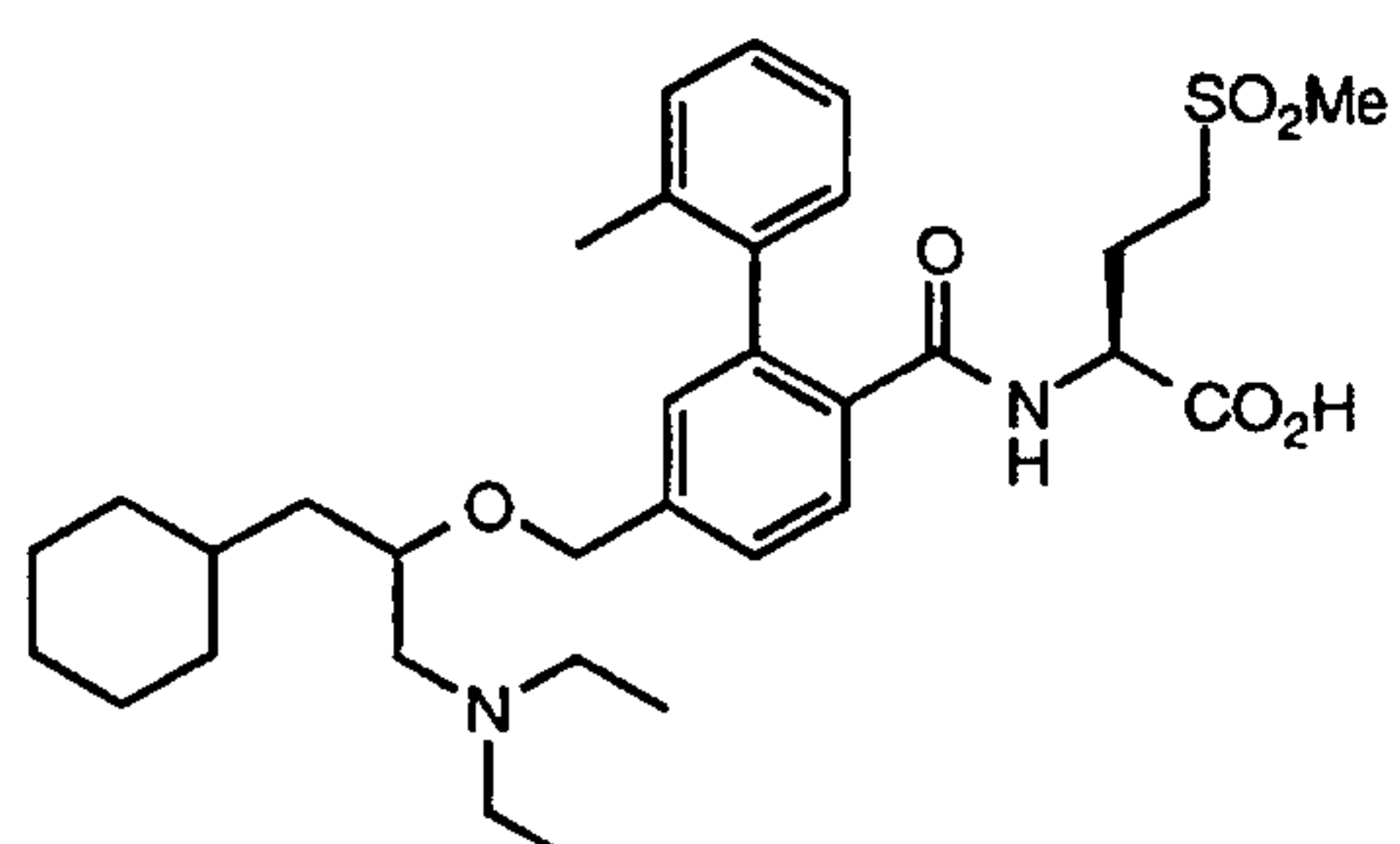
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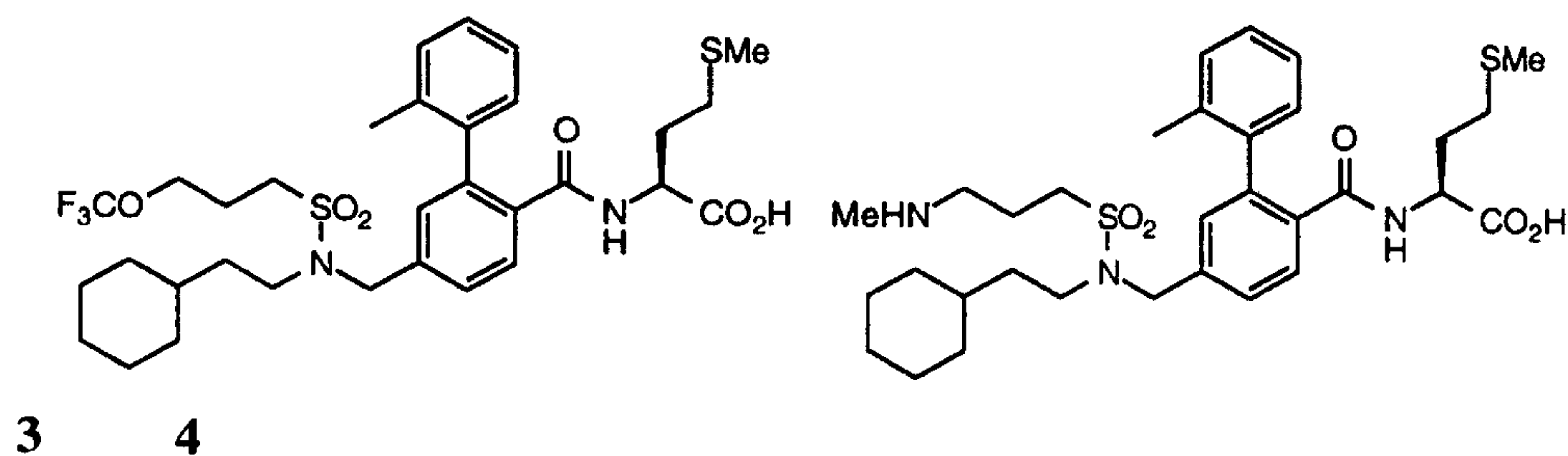
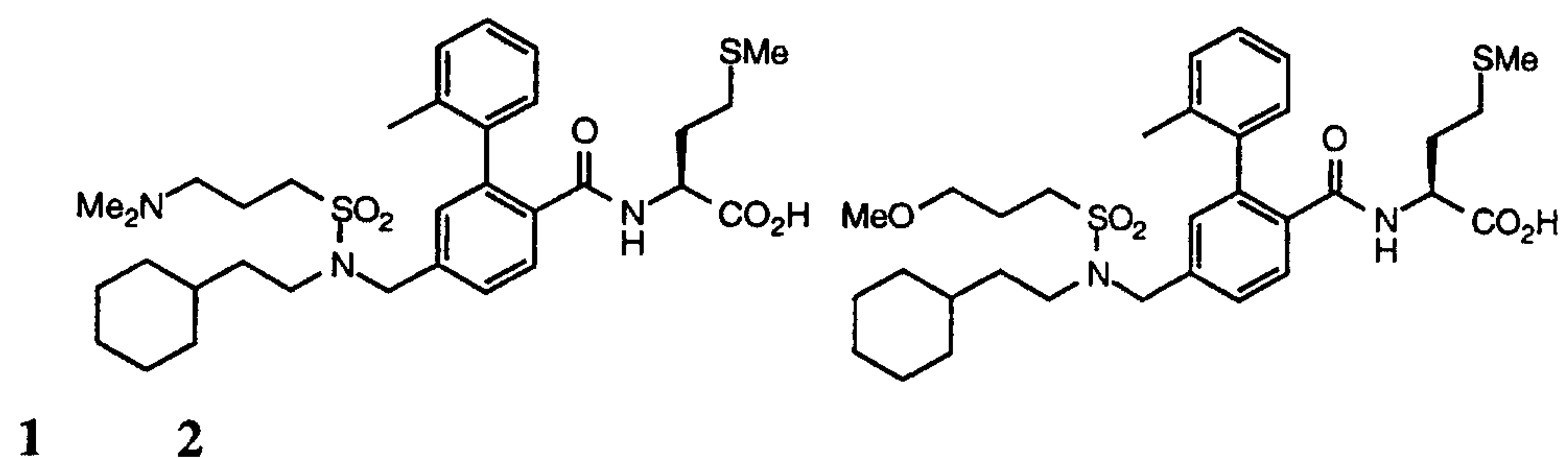
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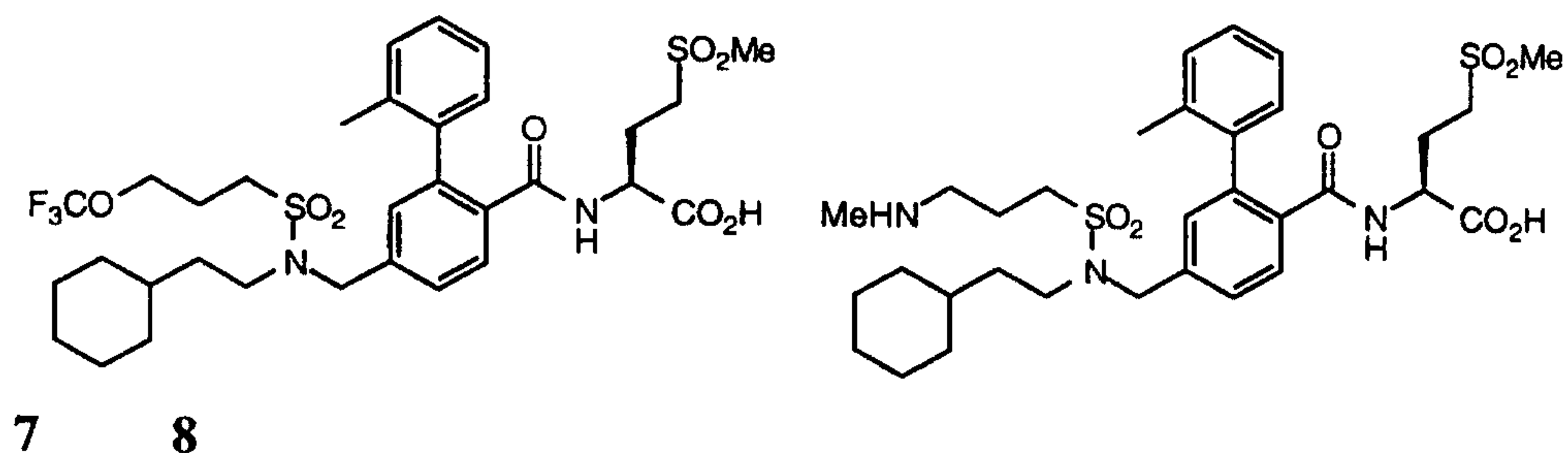
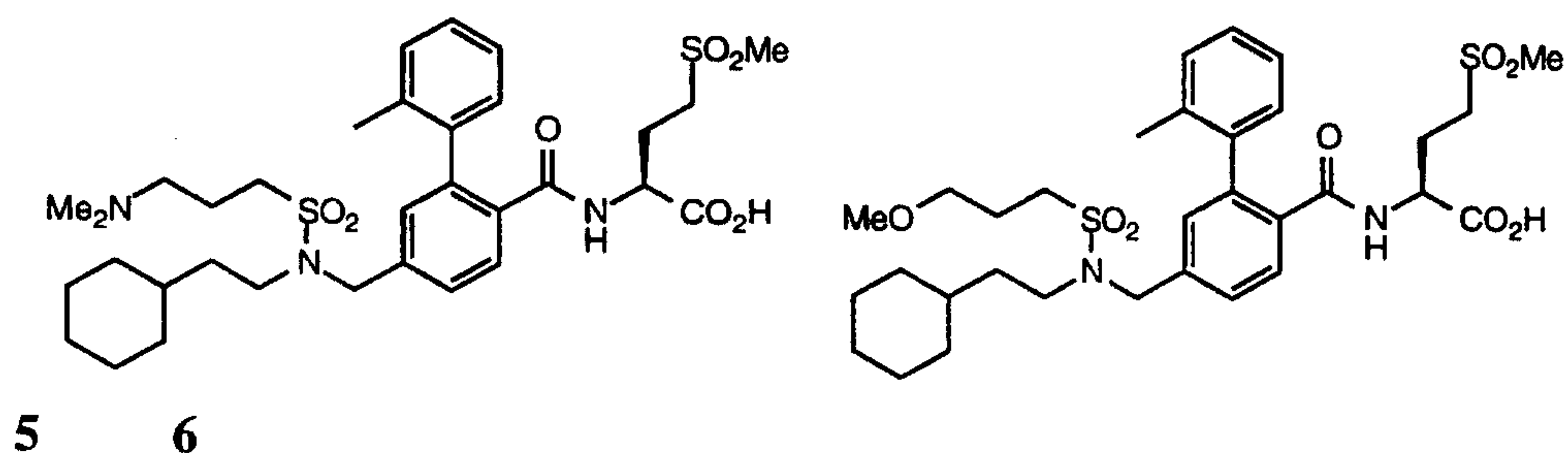
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Table 8. Sulfonamides of the Type ASO₂(B)N-L₁

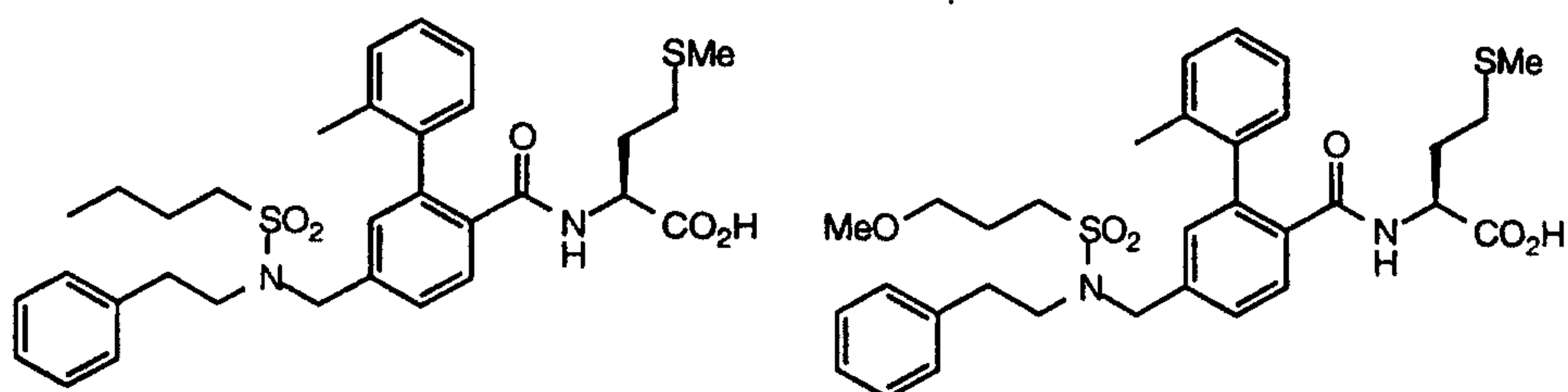
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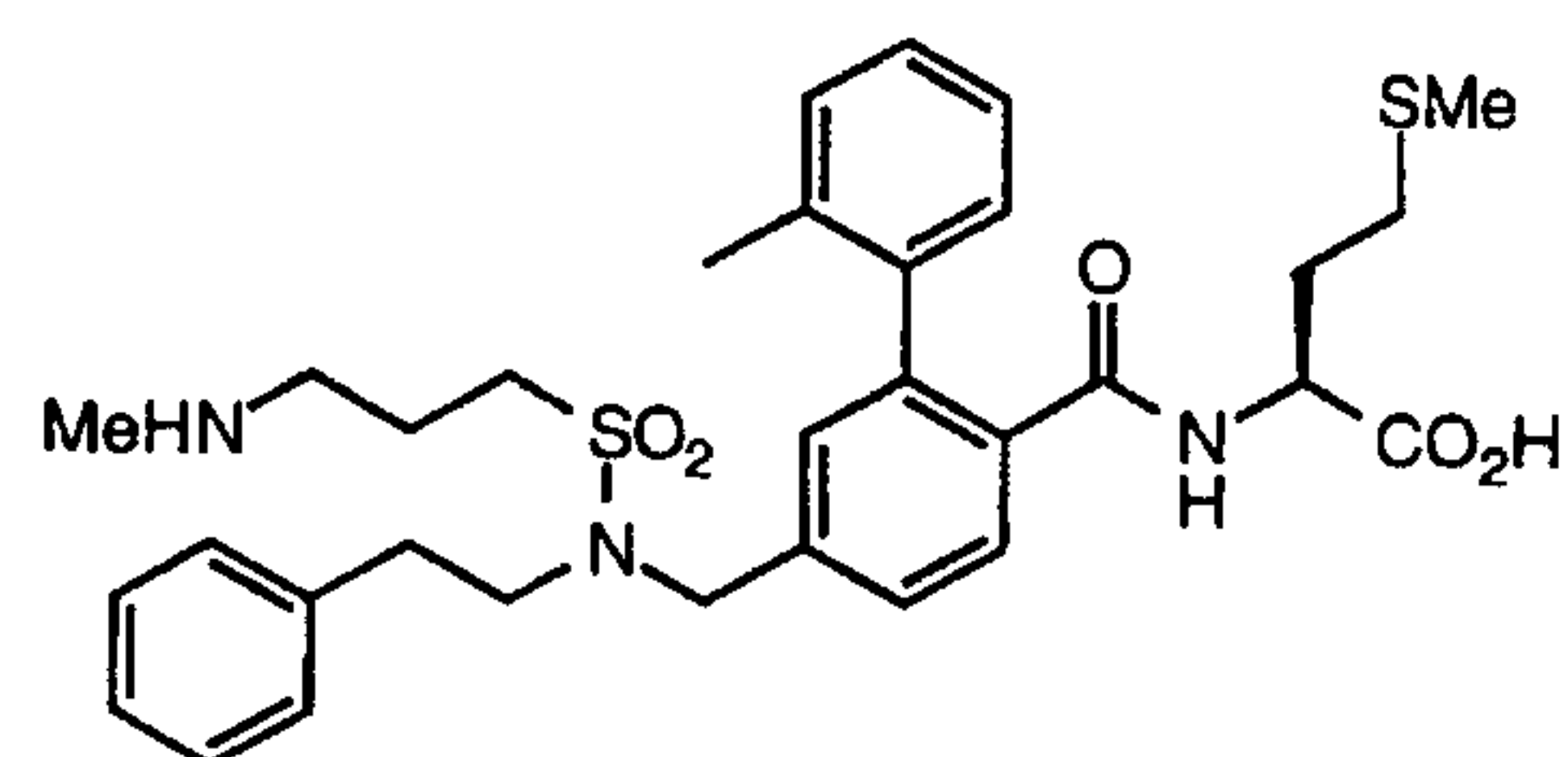
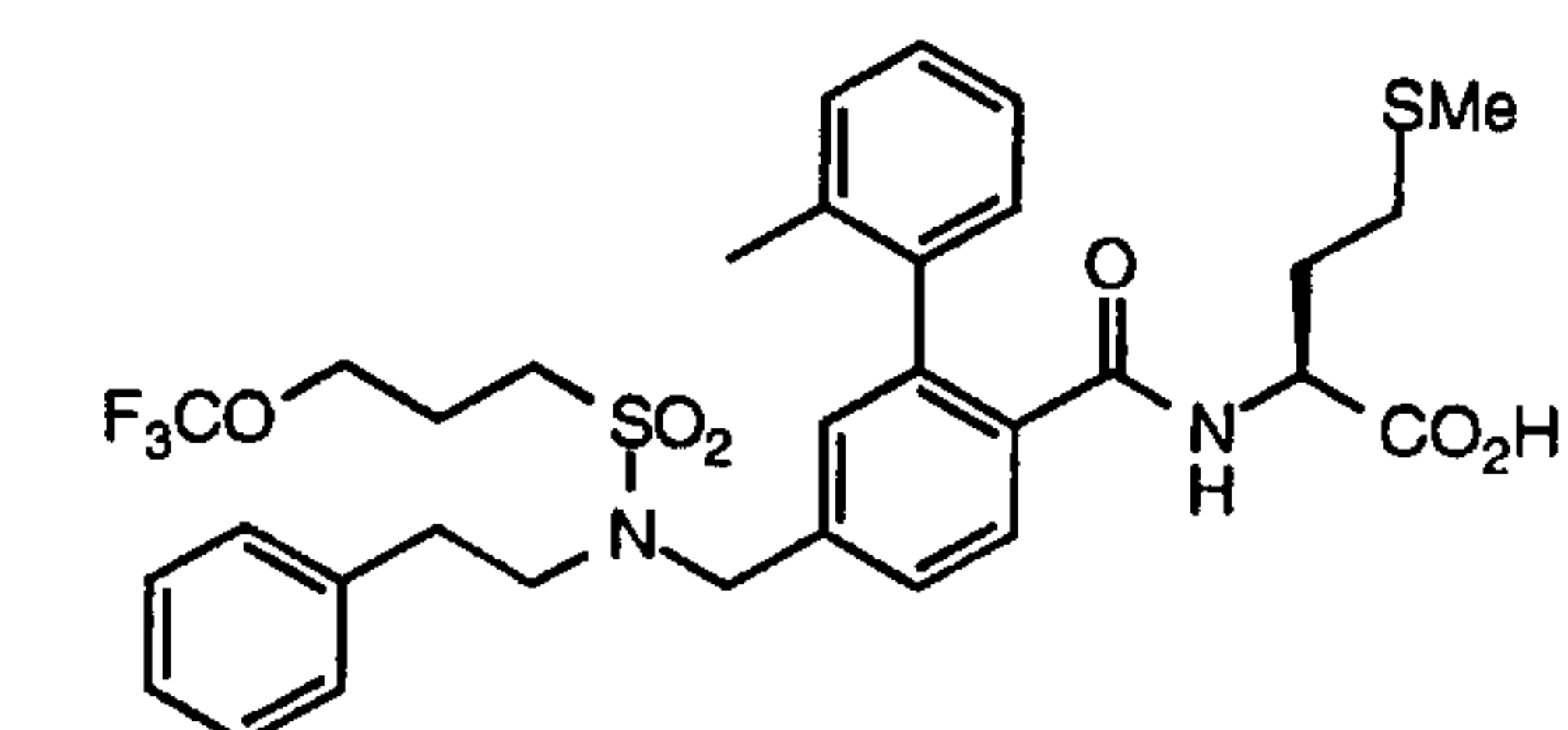
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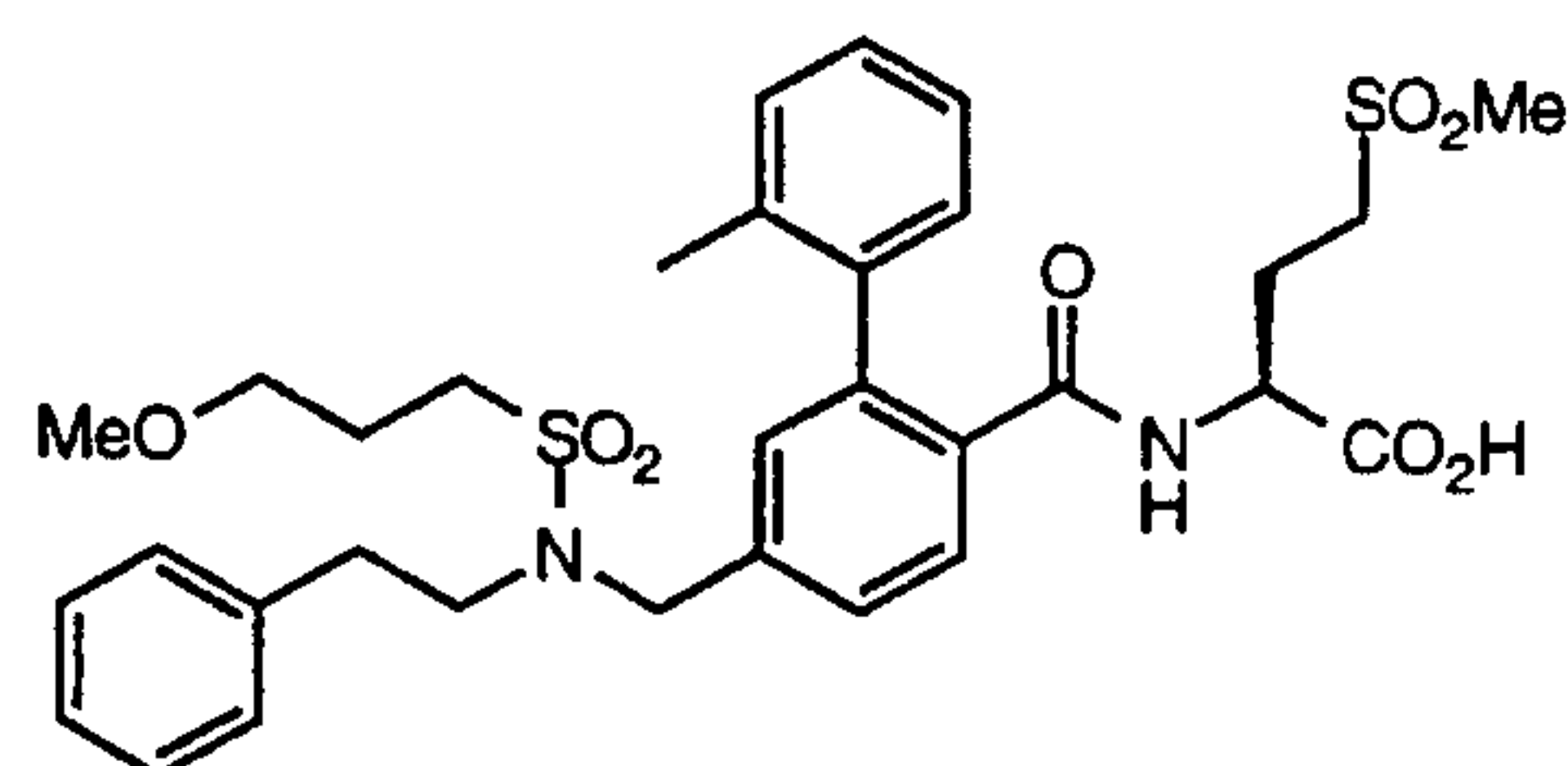
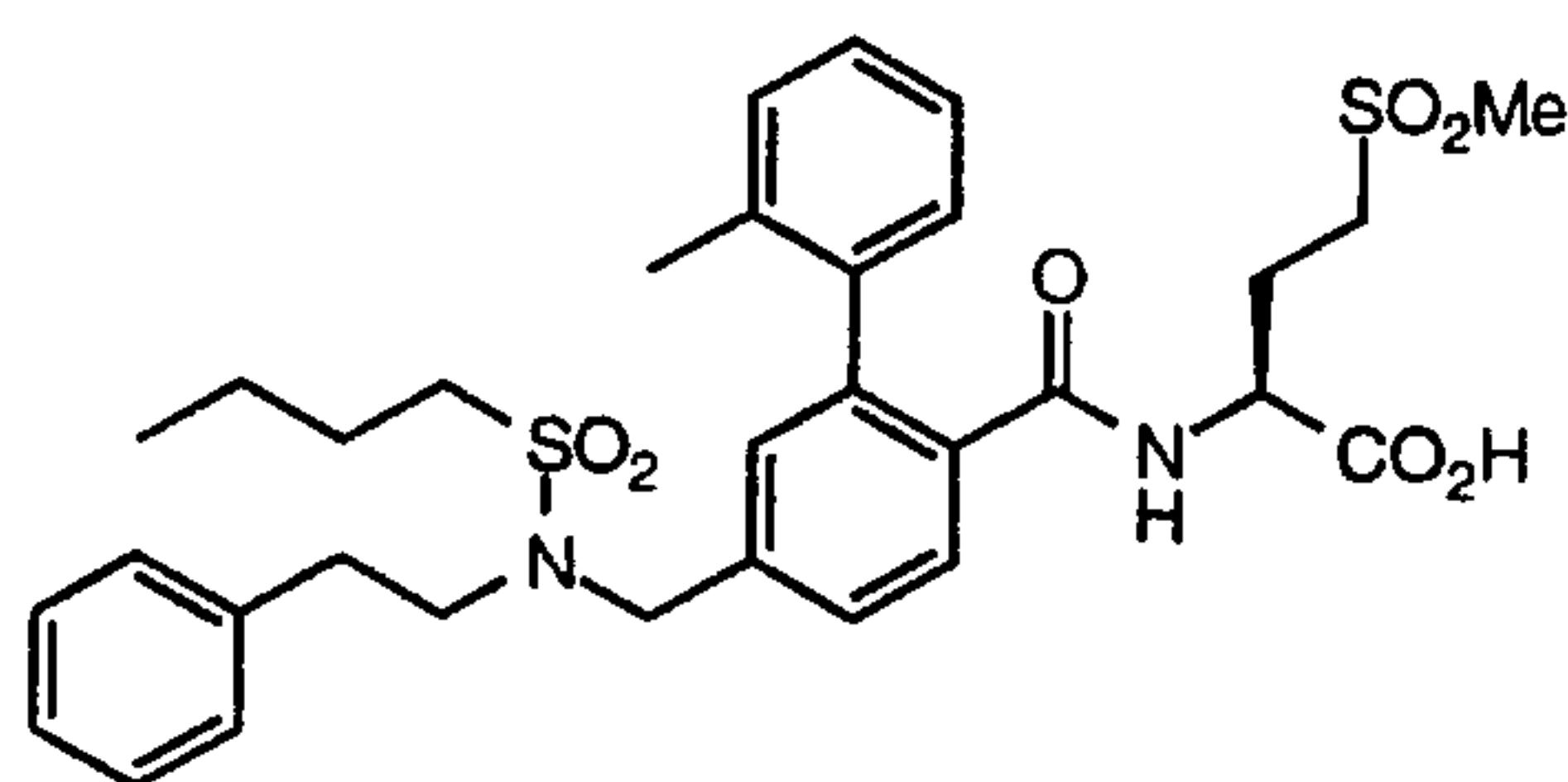
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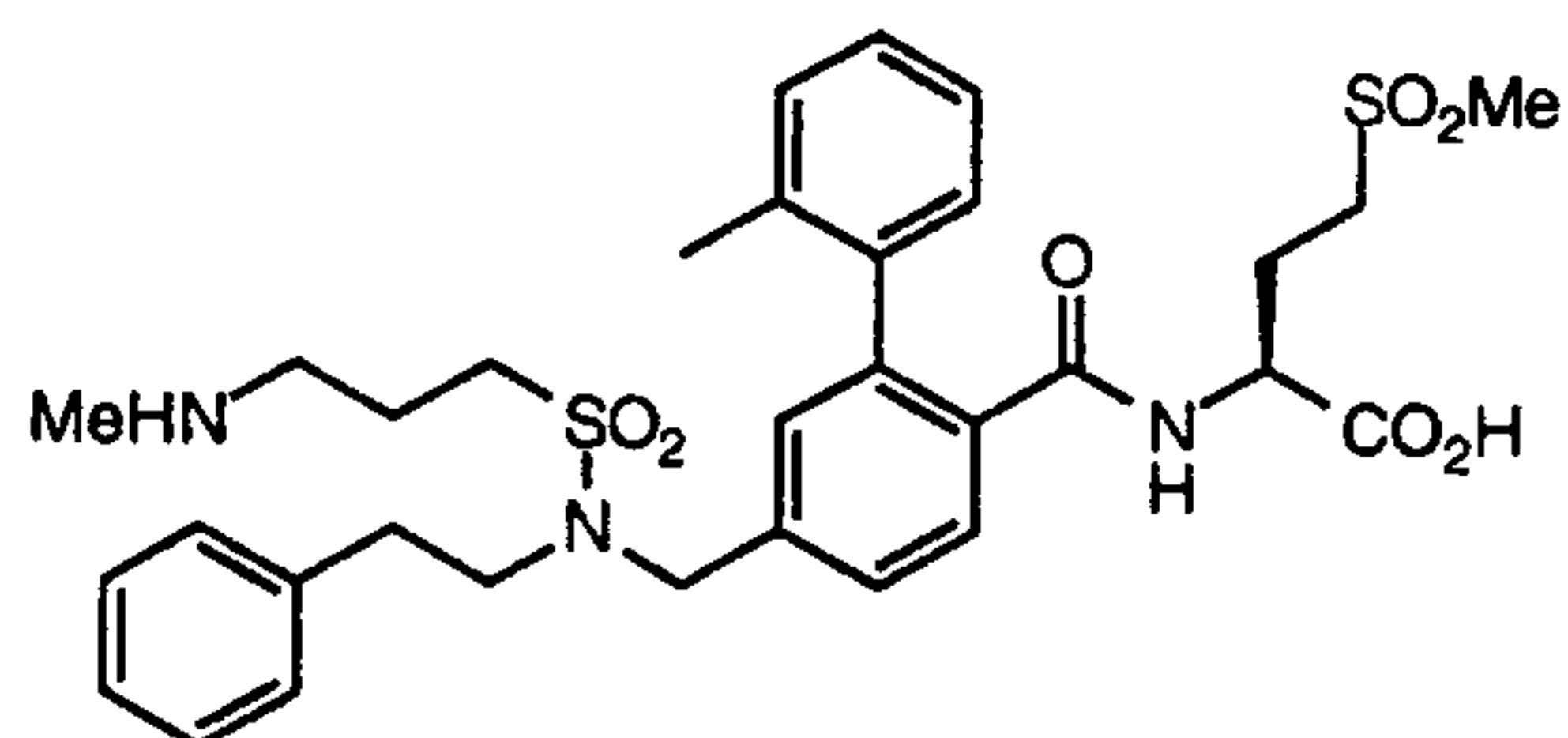
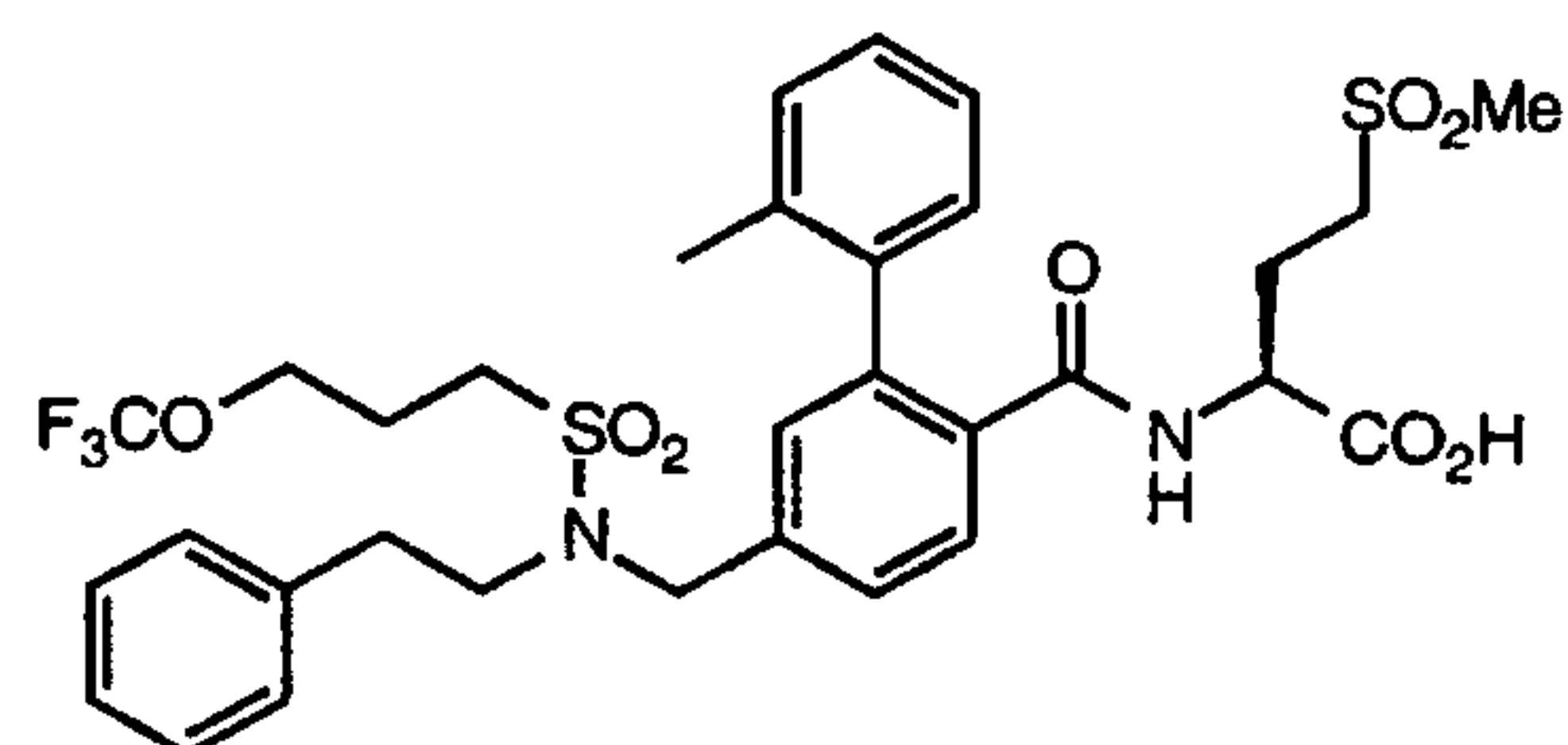


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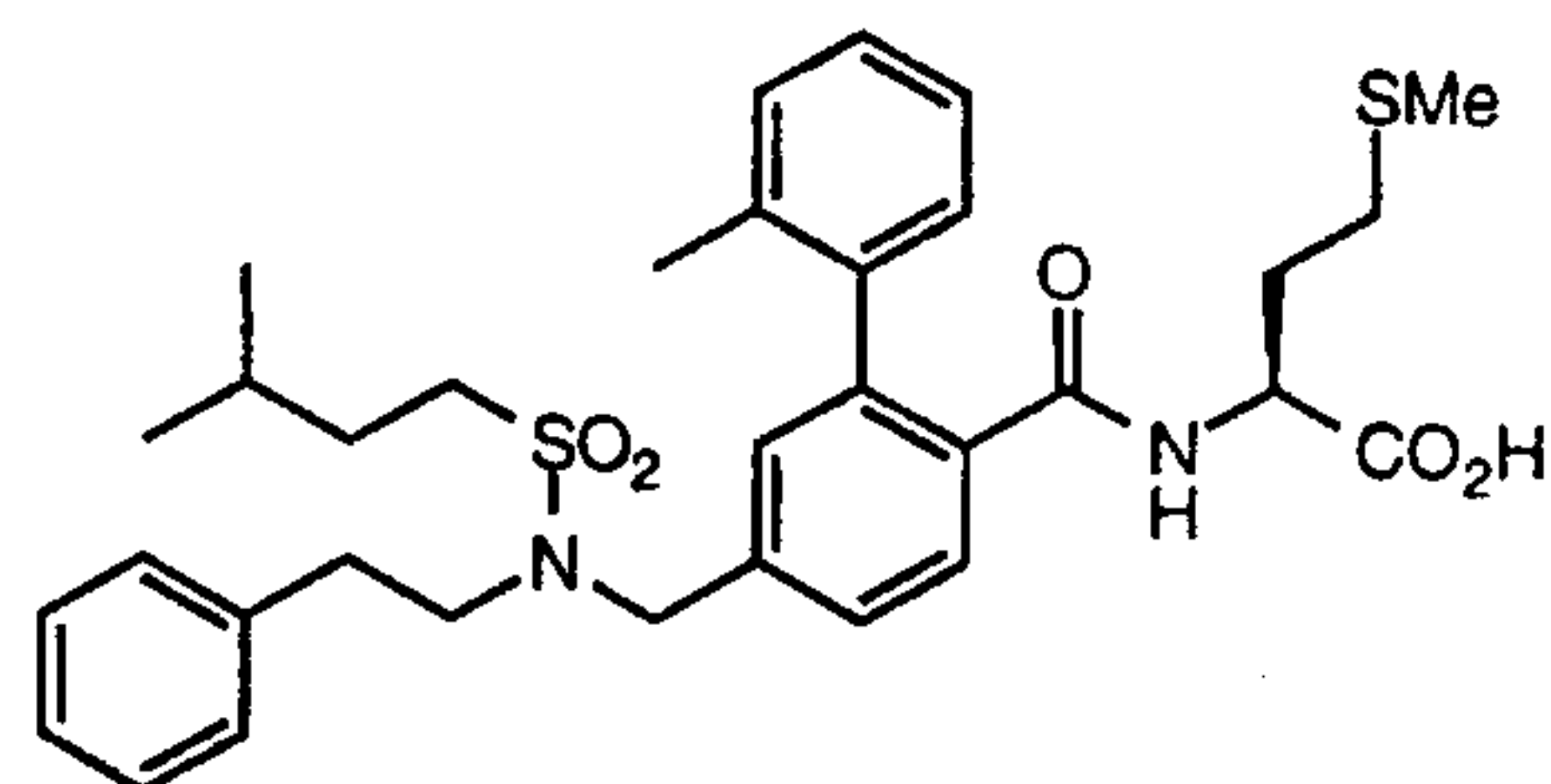
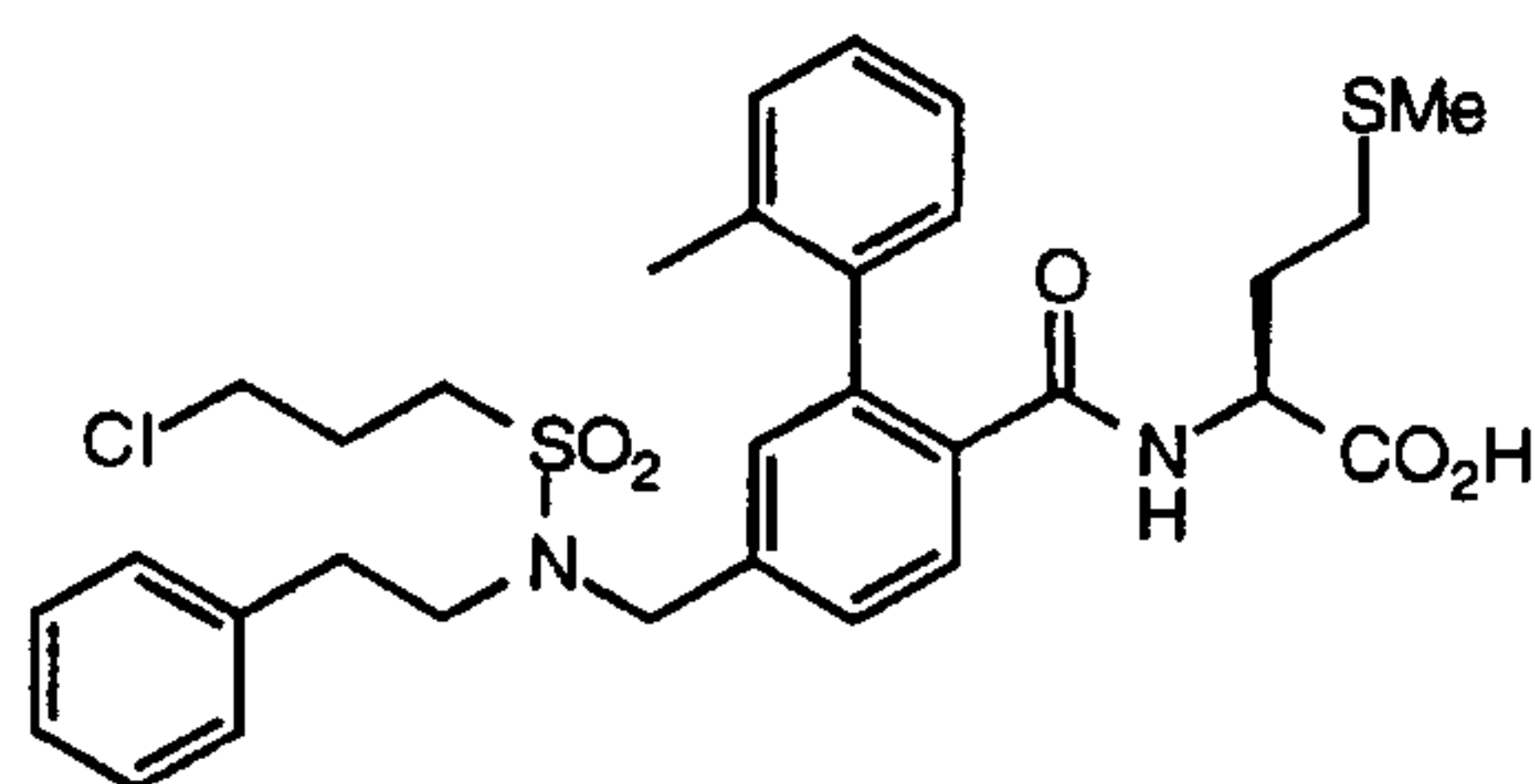


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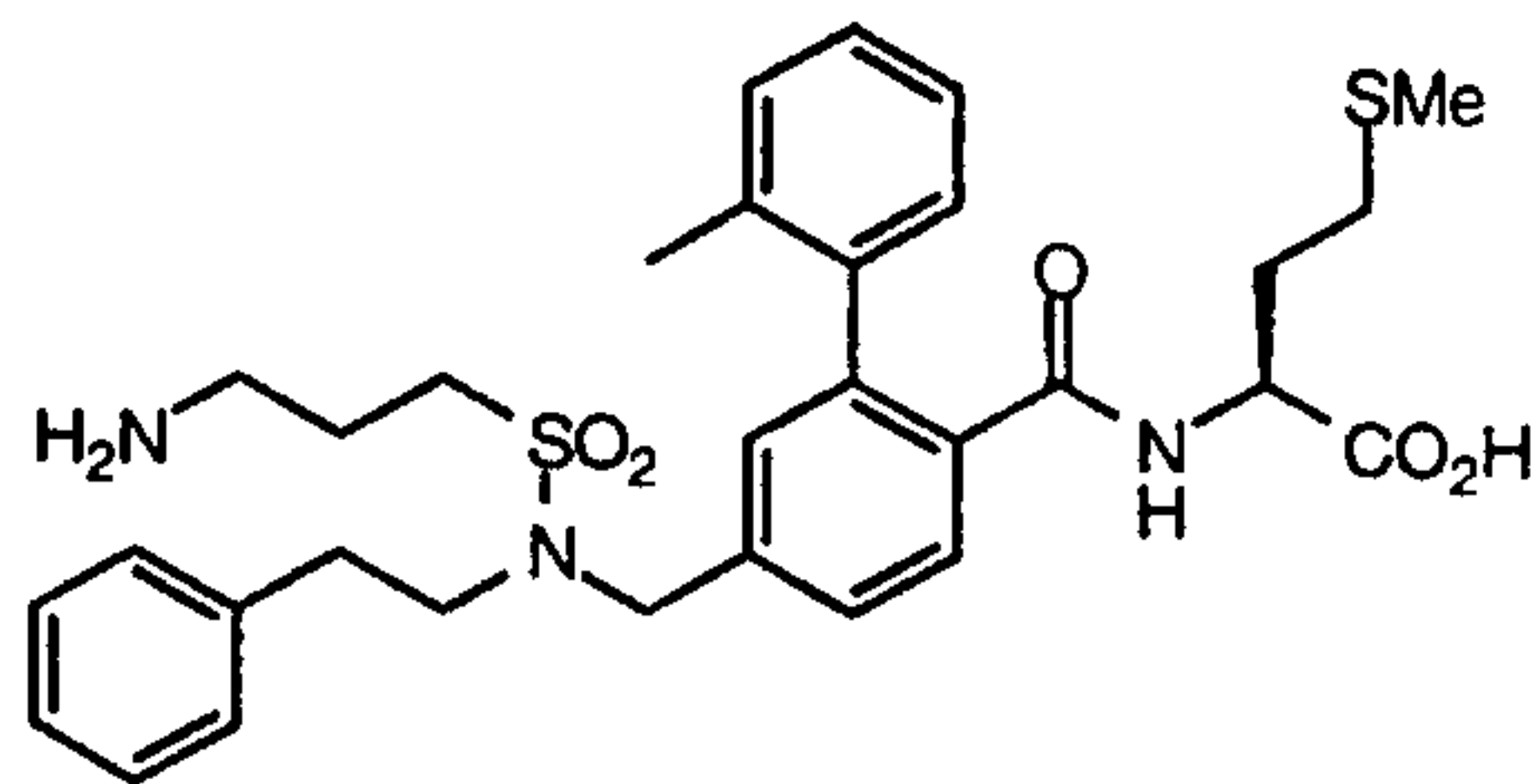
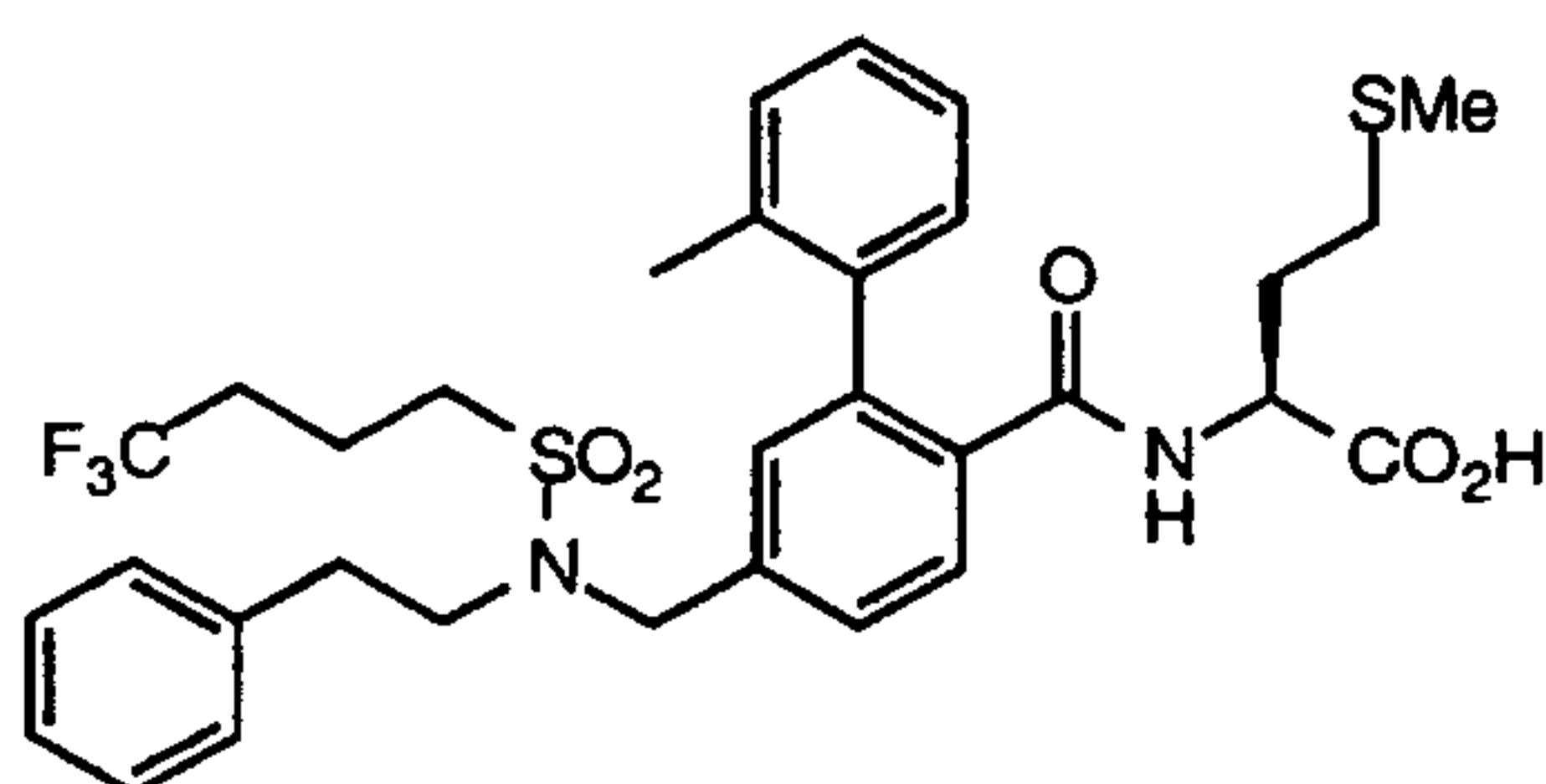
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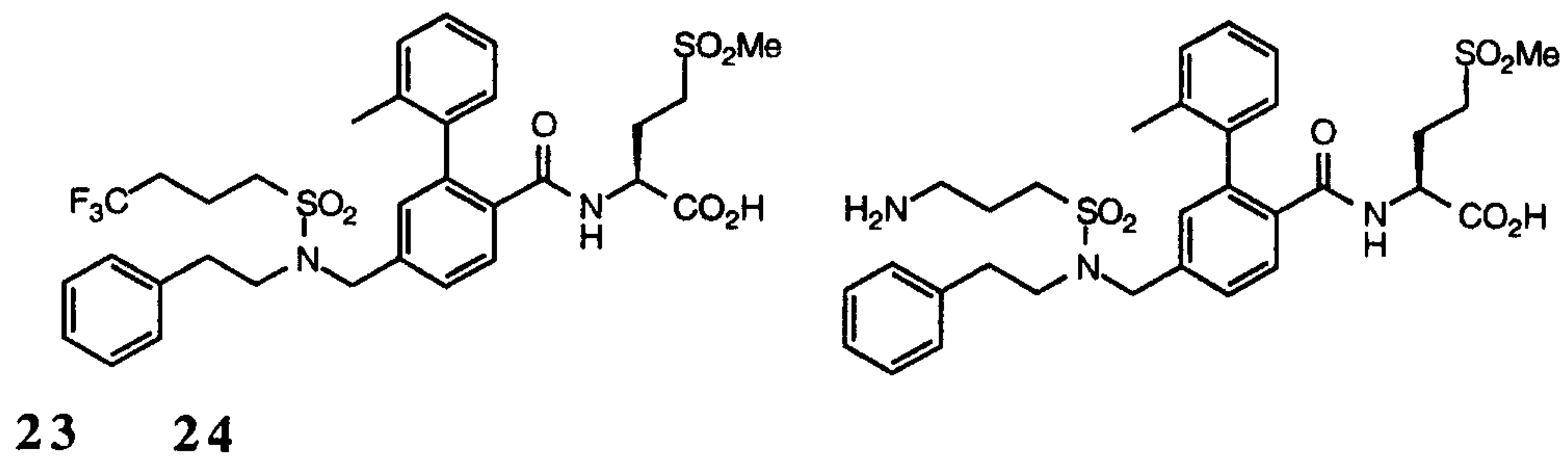
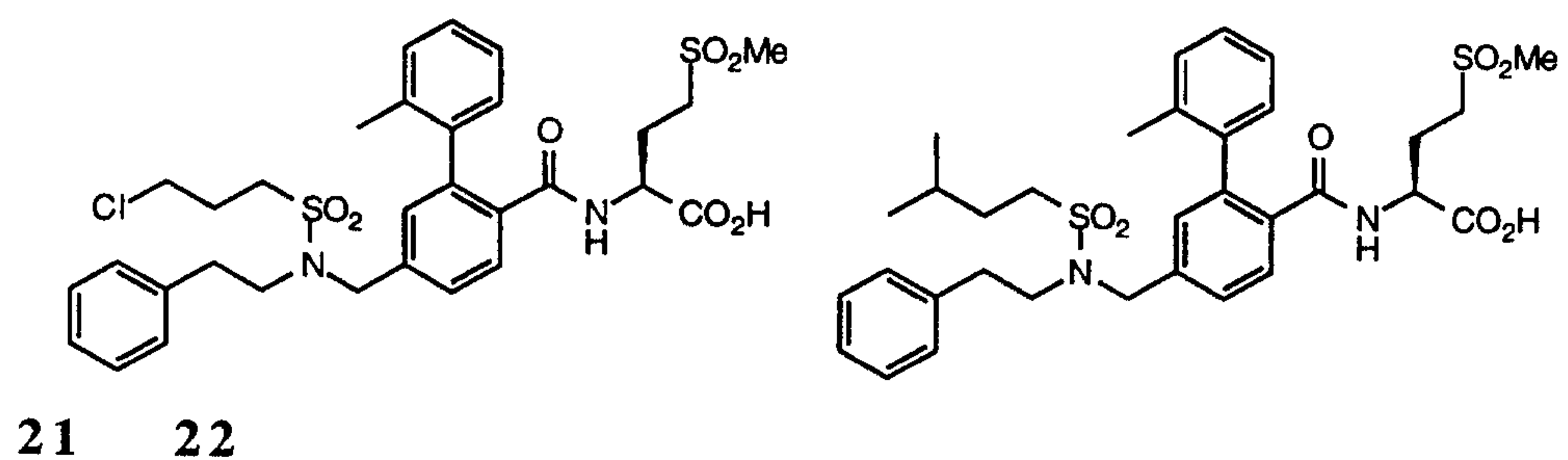
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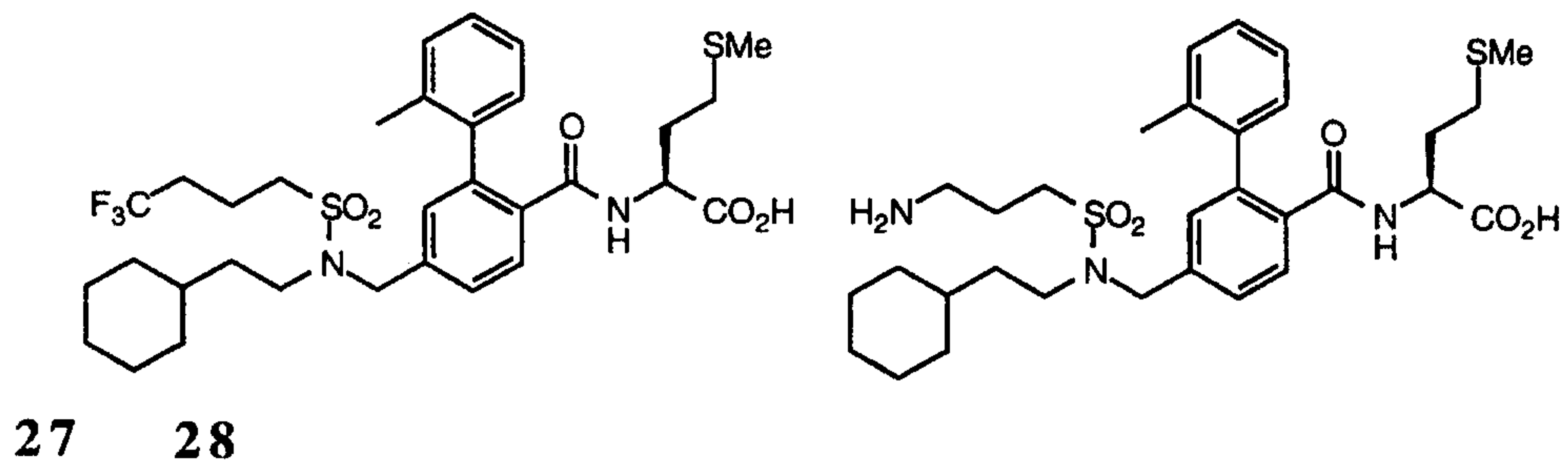
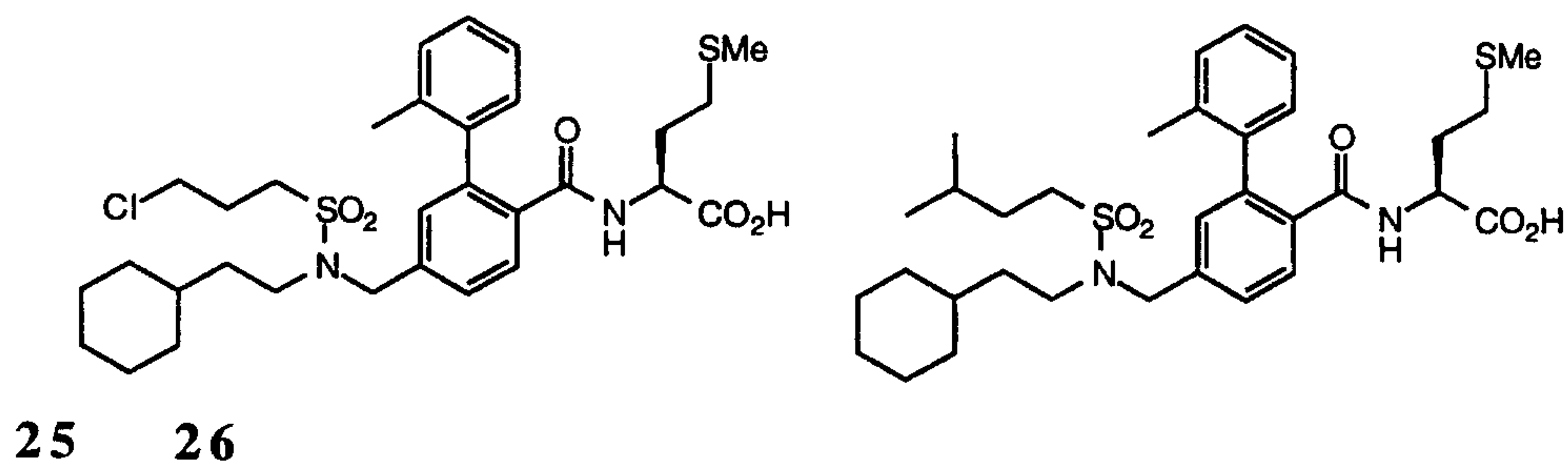


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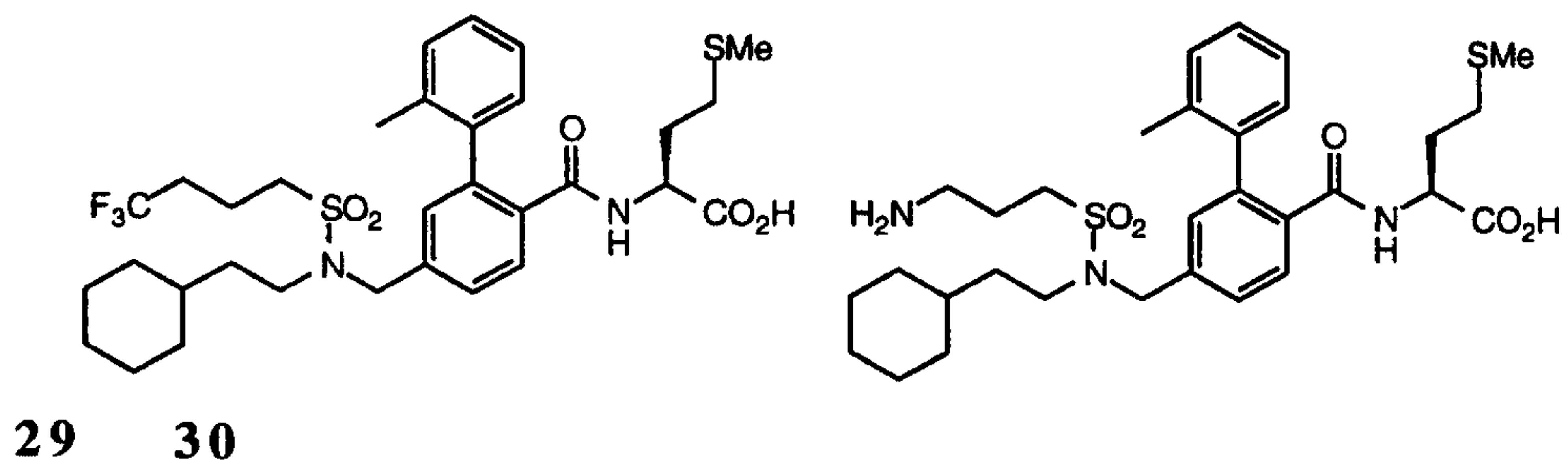
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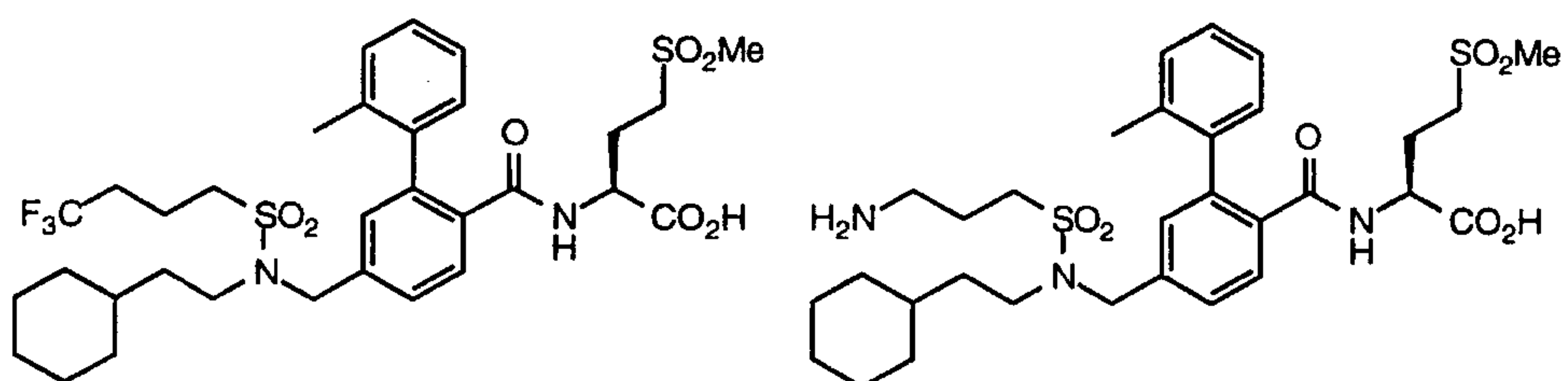


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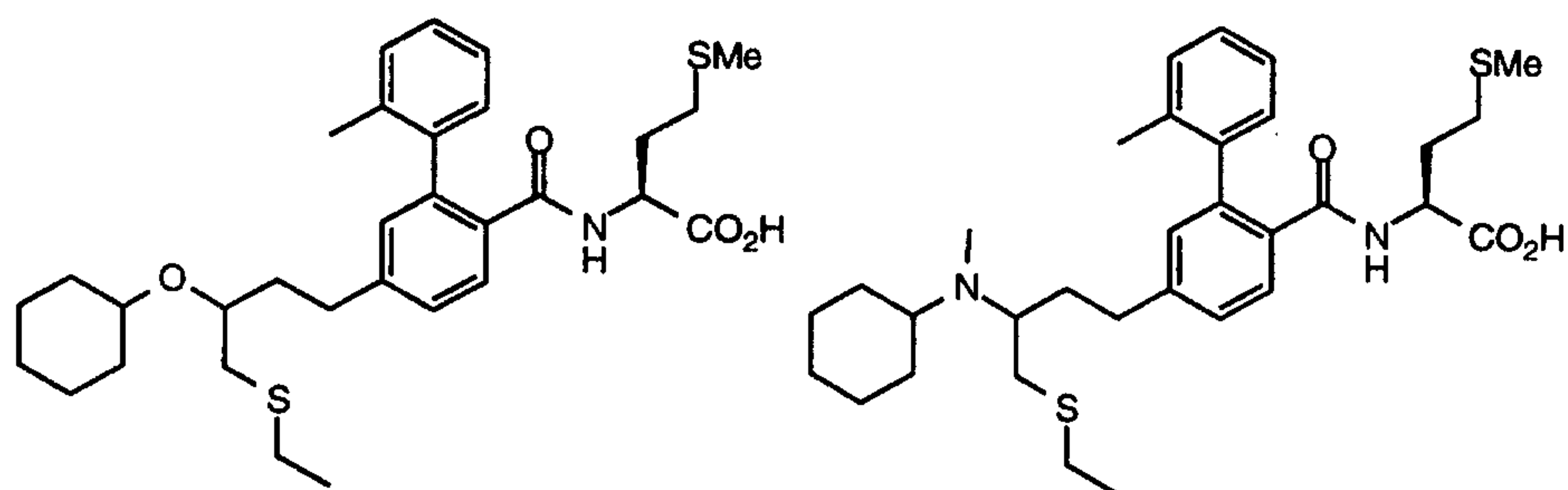
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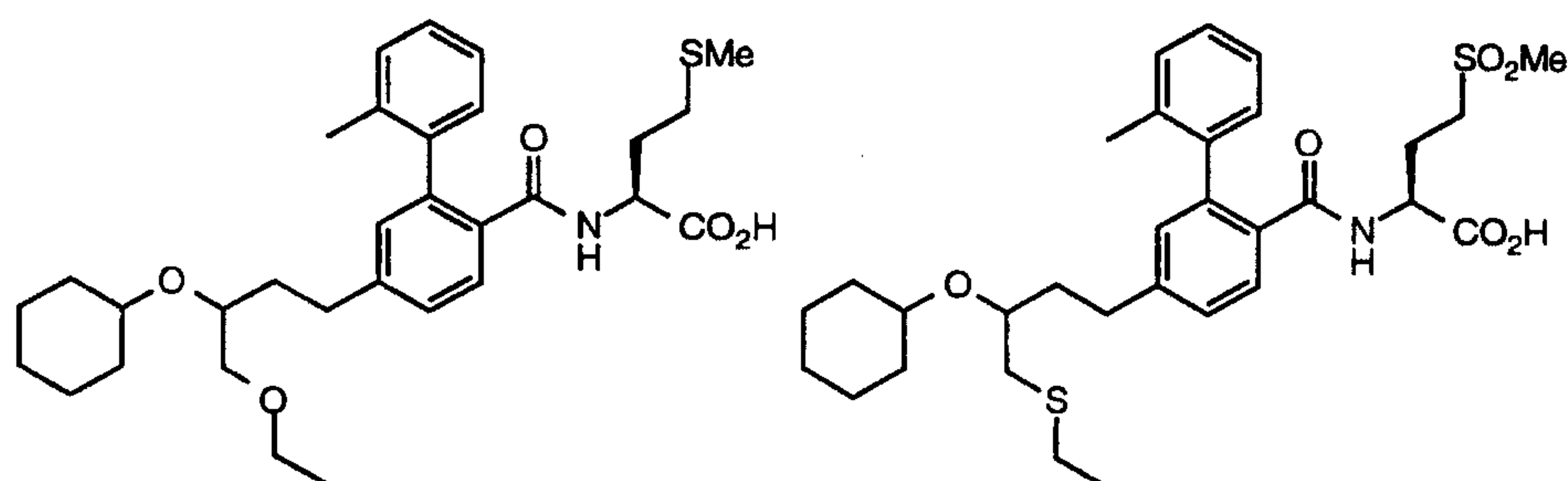
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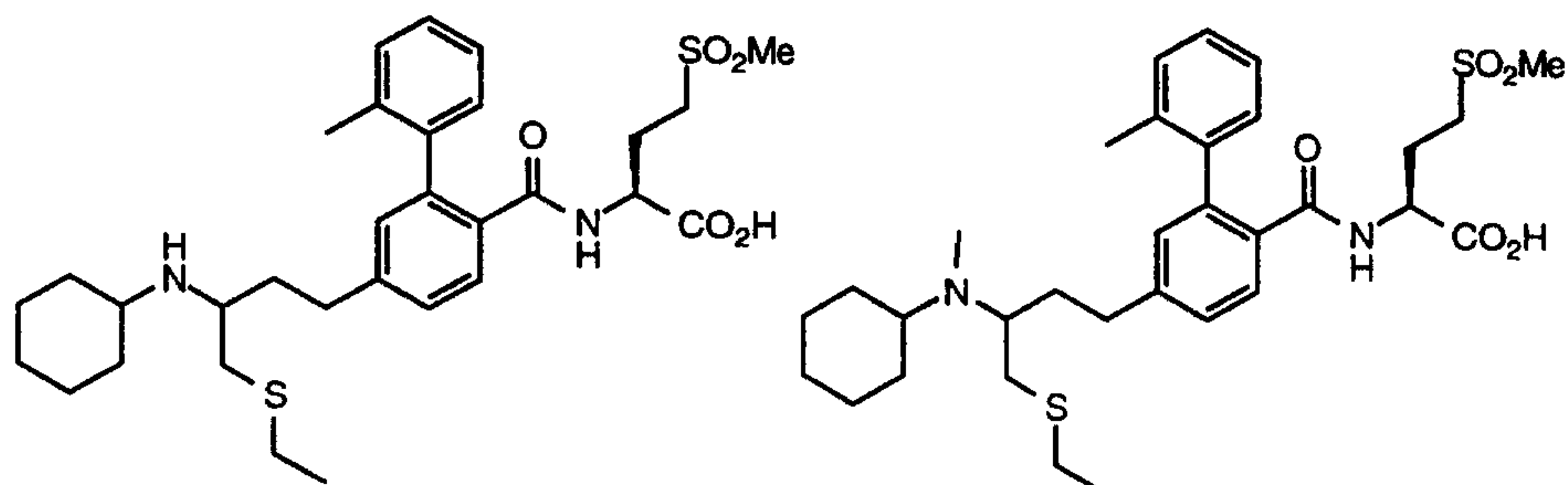
Table 9. Hydrocarbons of the Type A(B)CH₂-L₁

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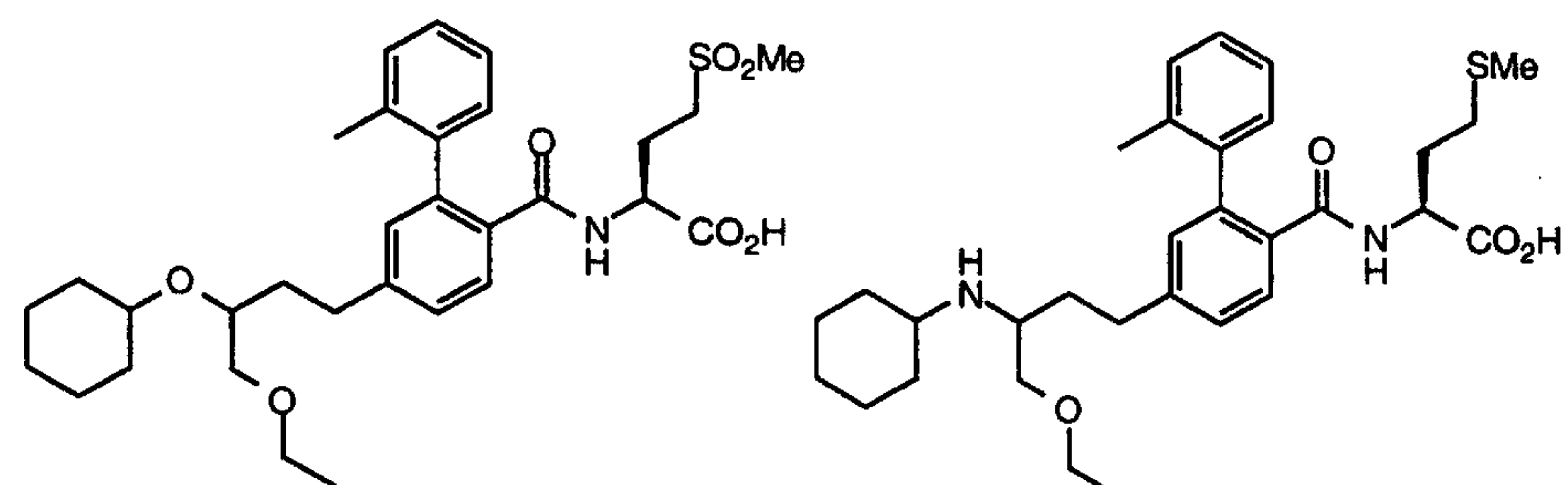


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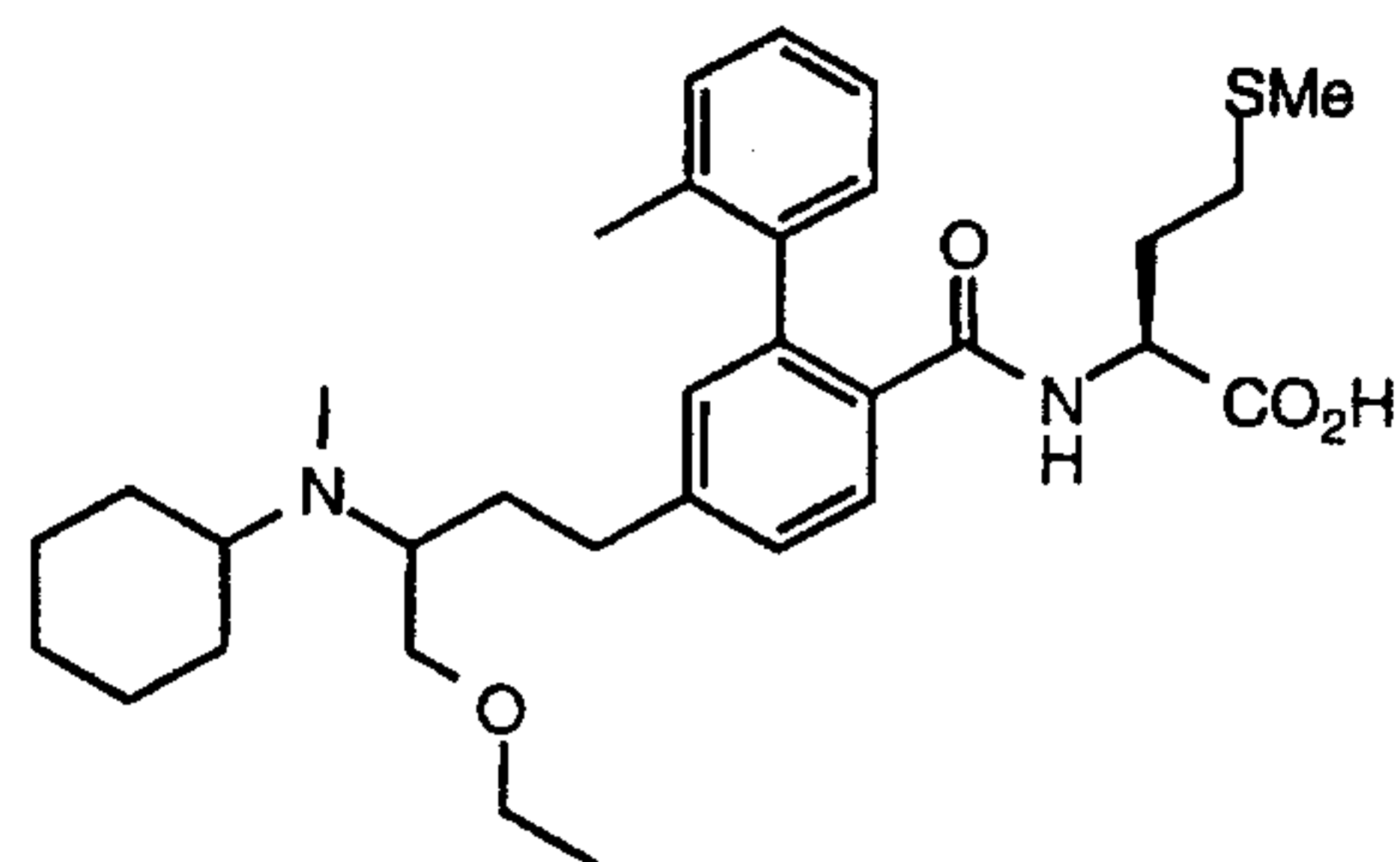


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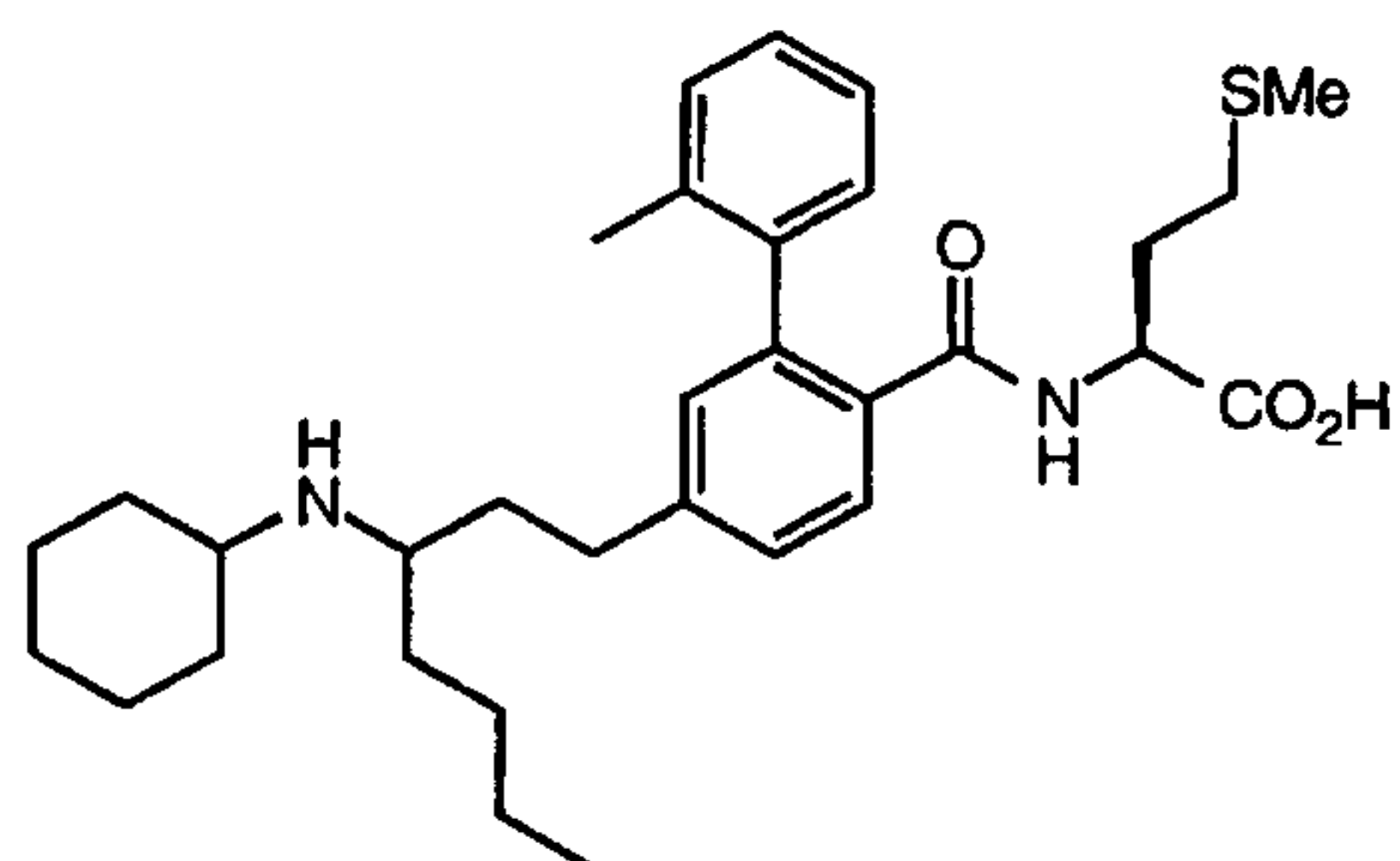
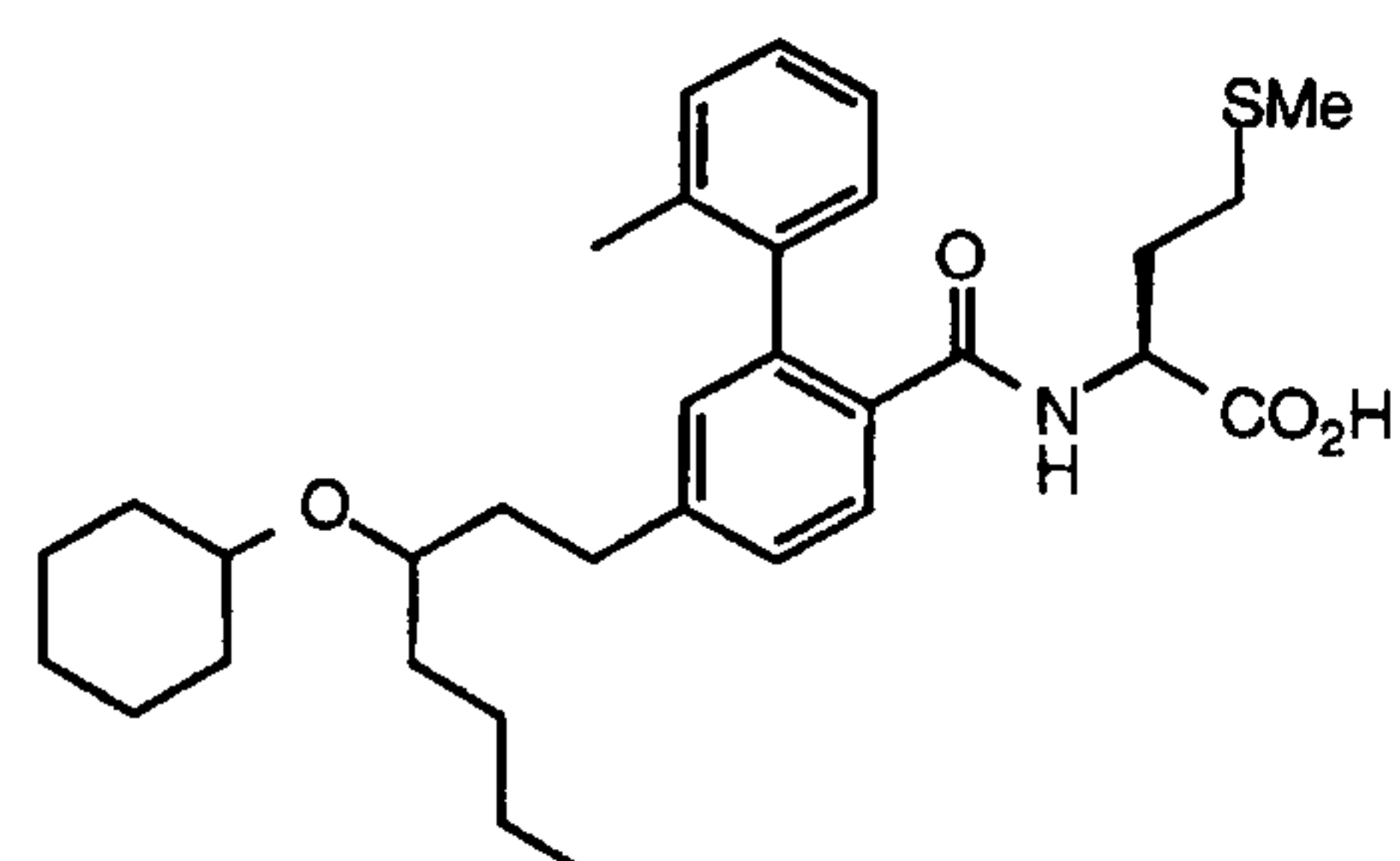
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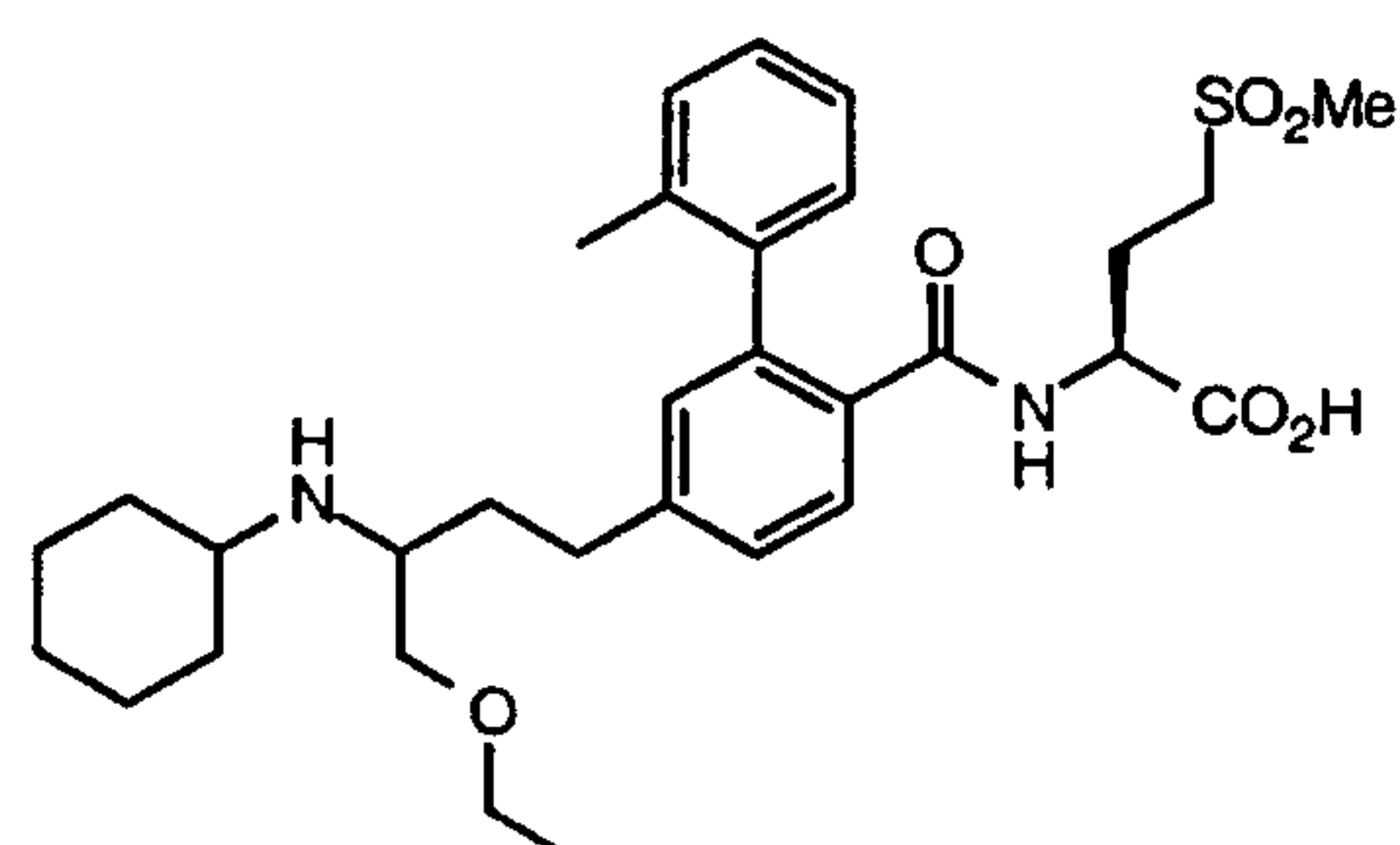
PCT/US98/09296



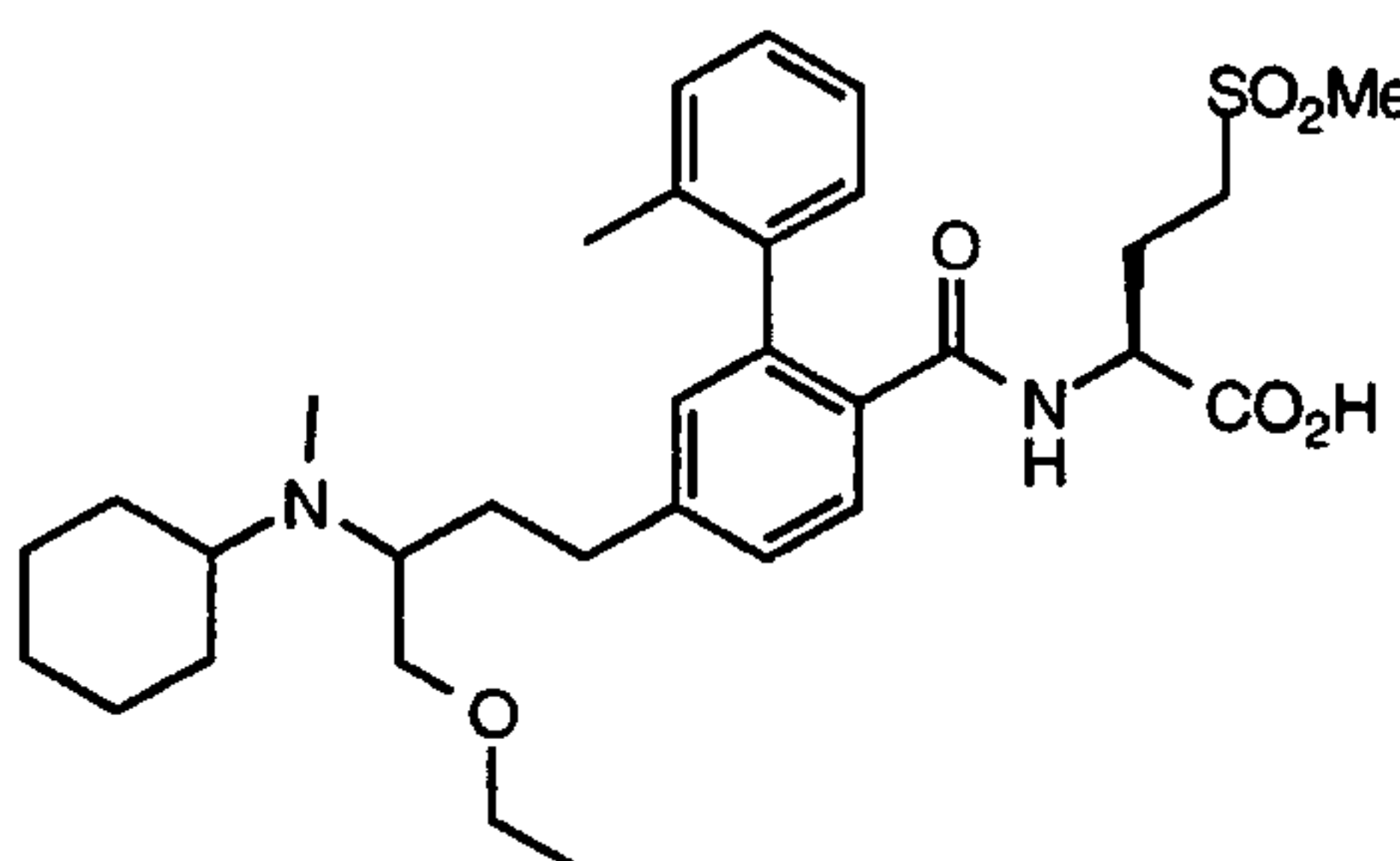
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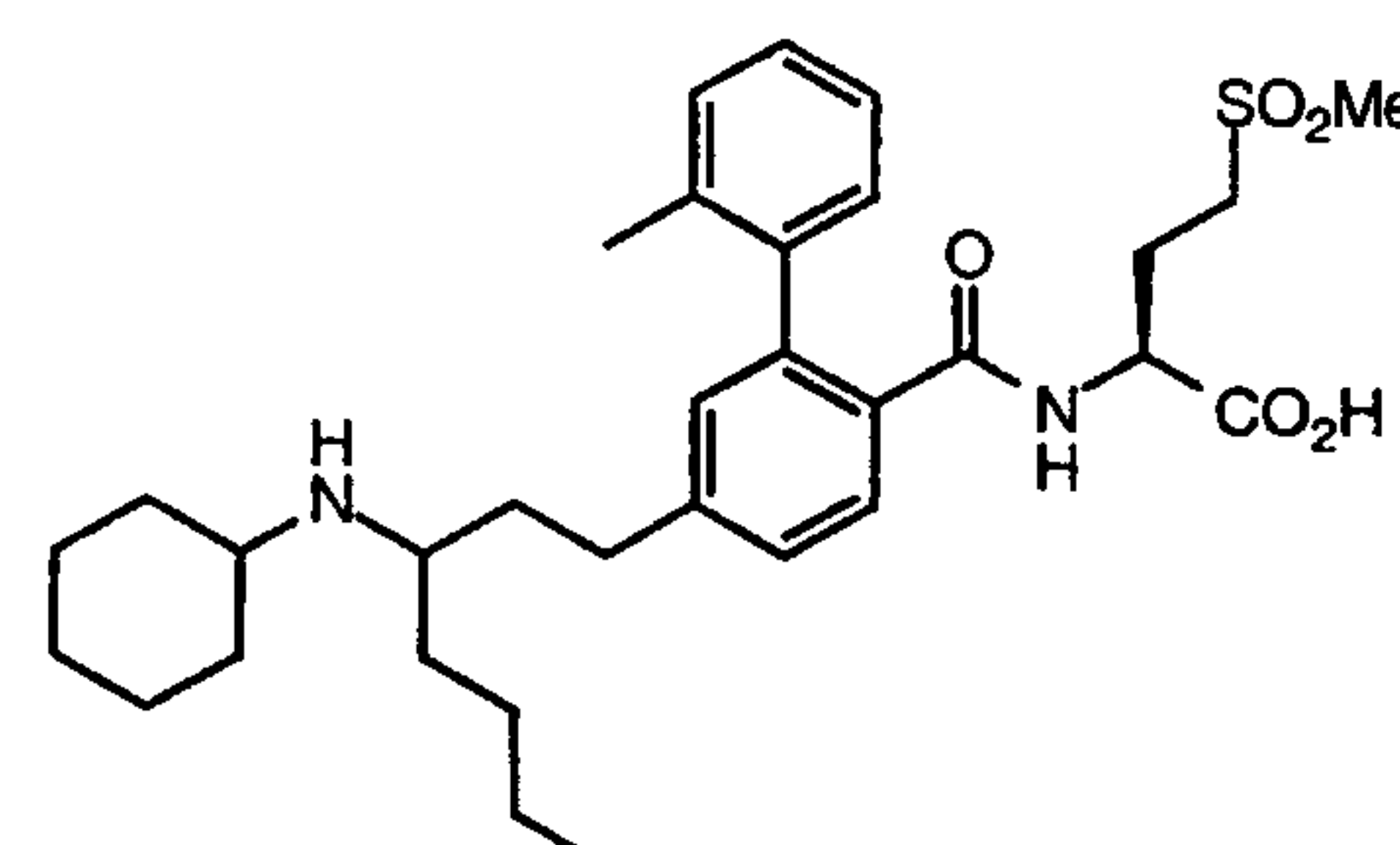
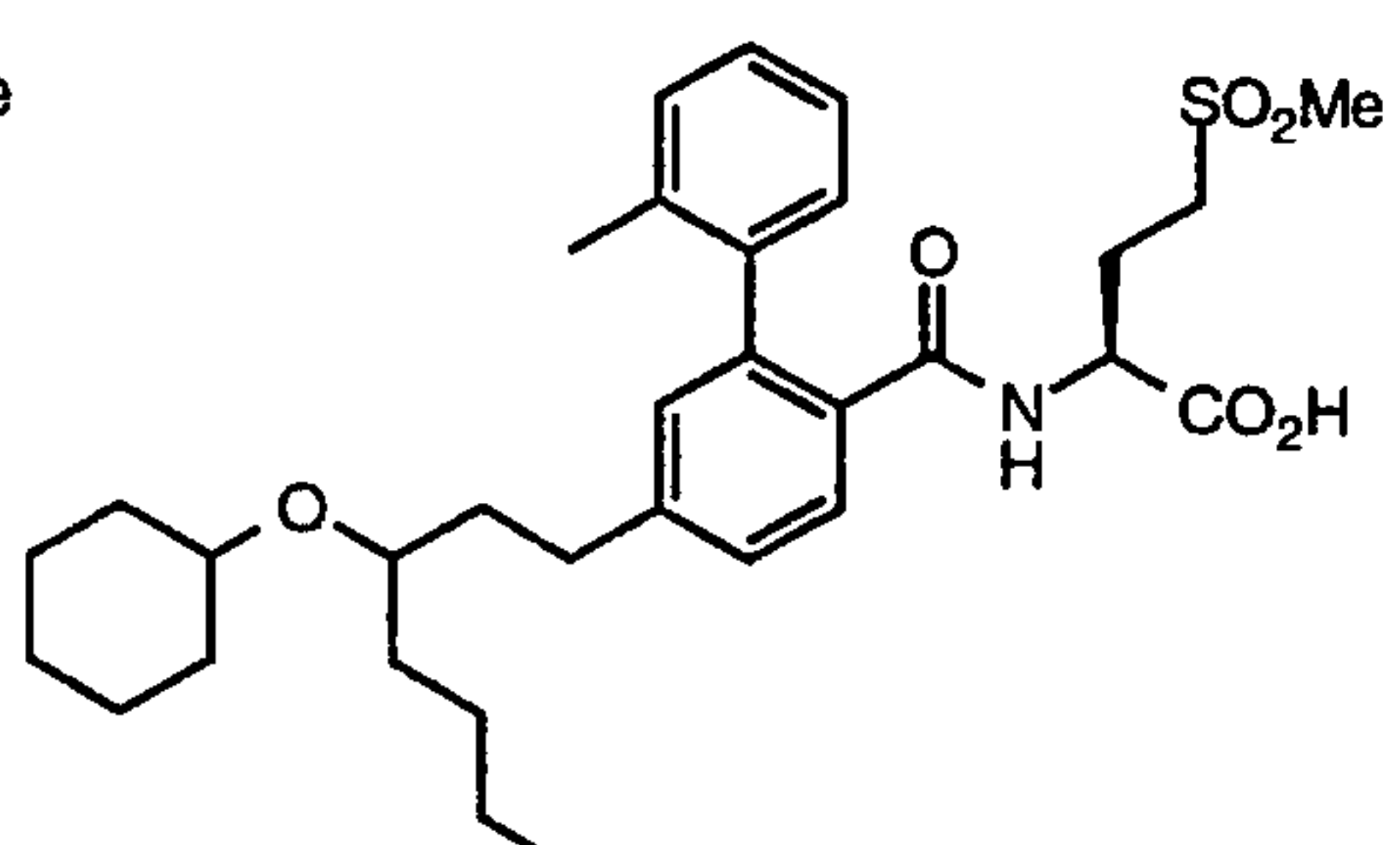
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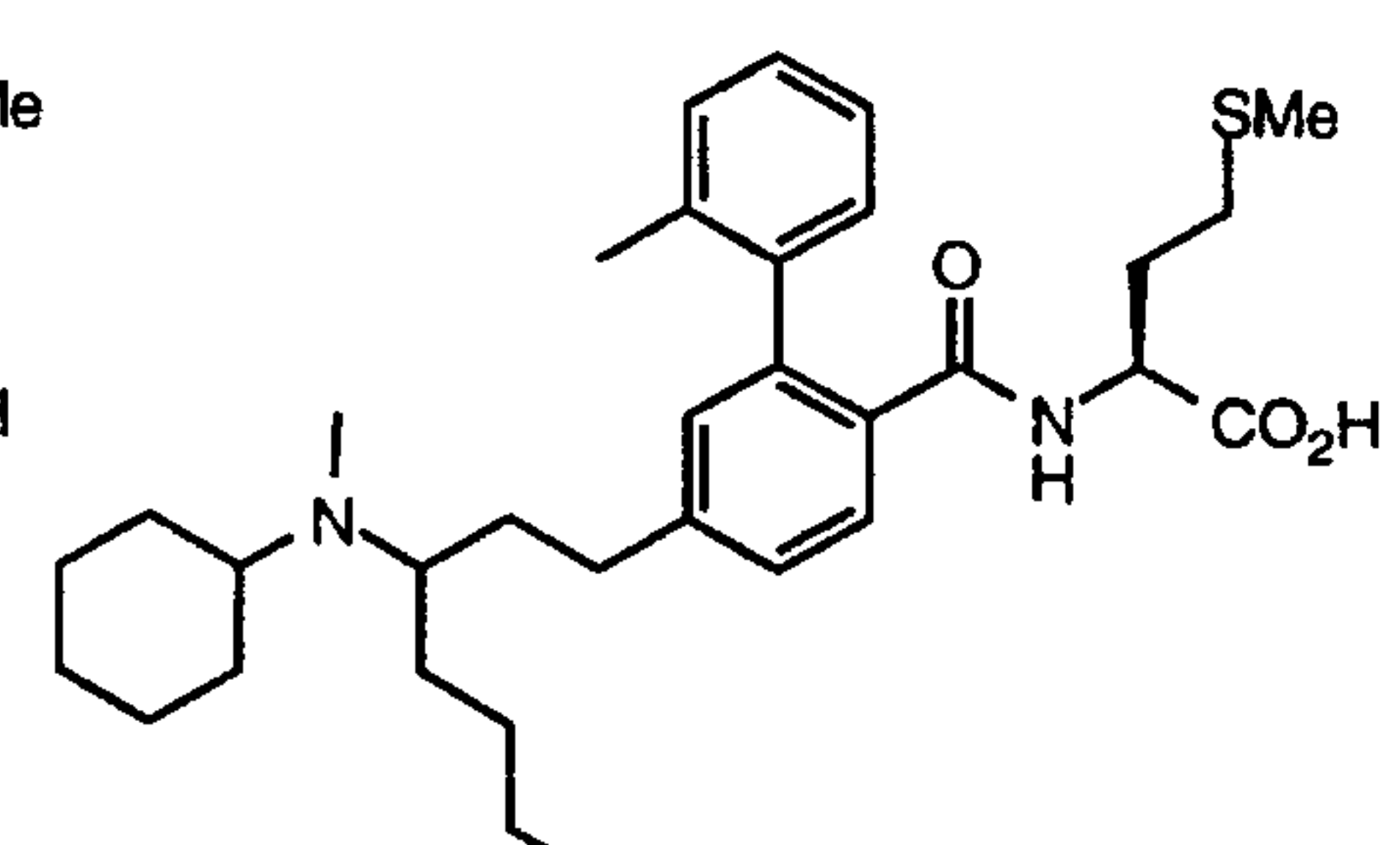
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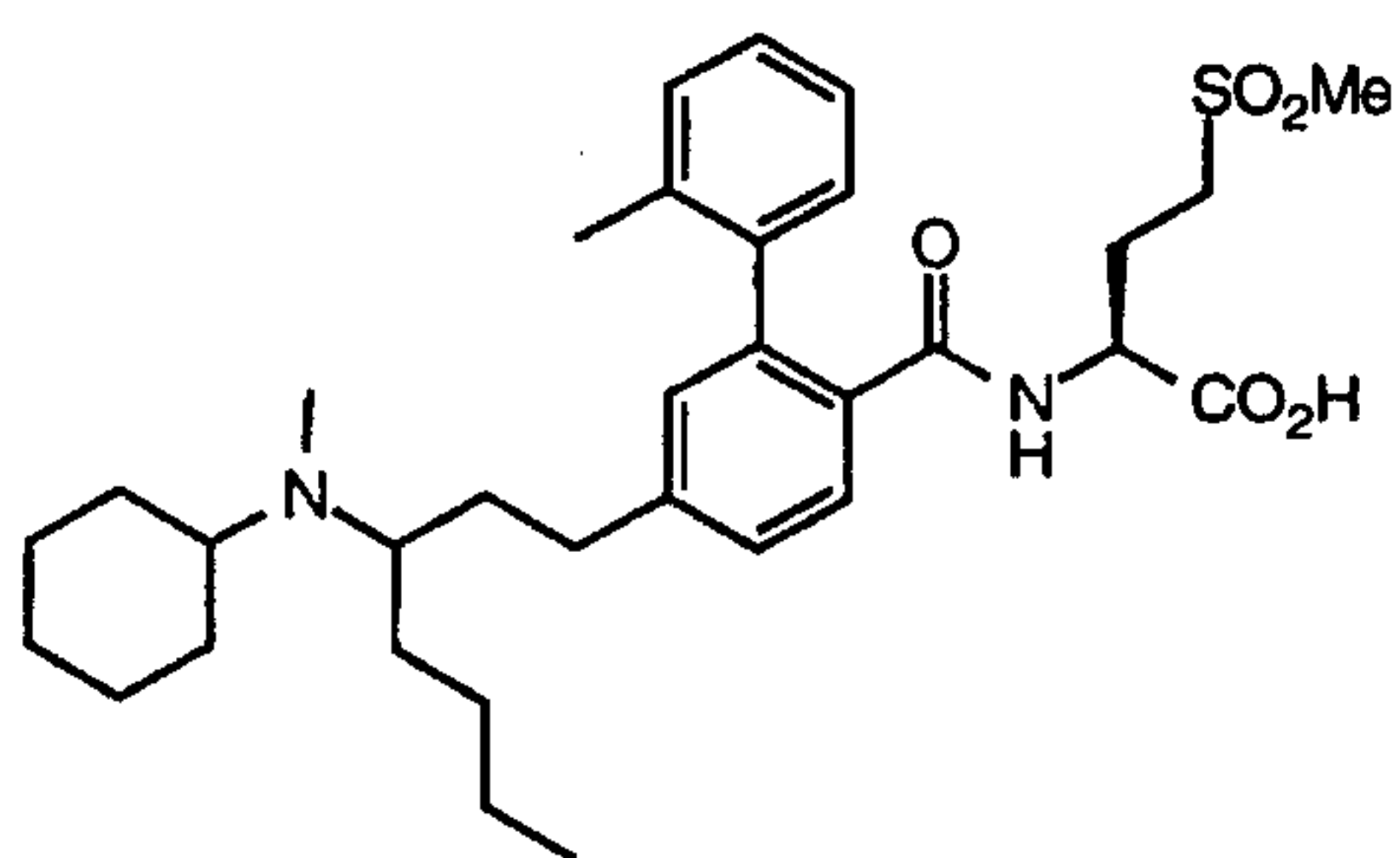
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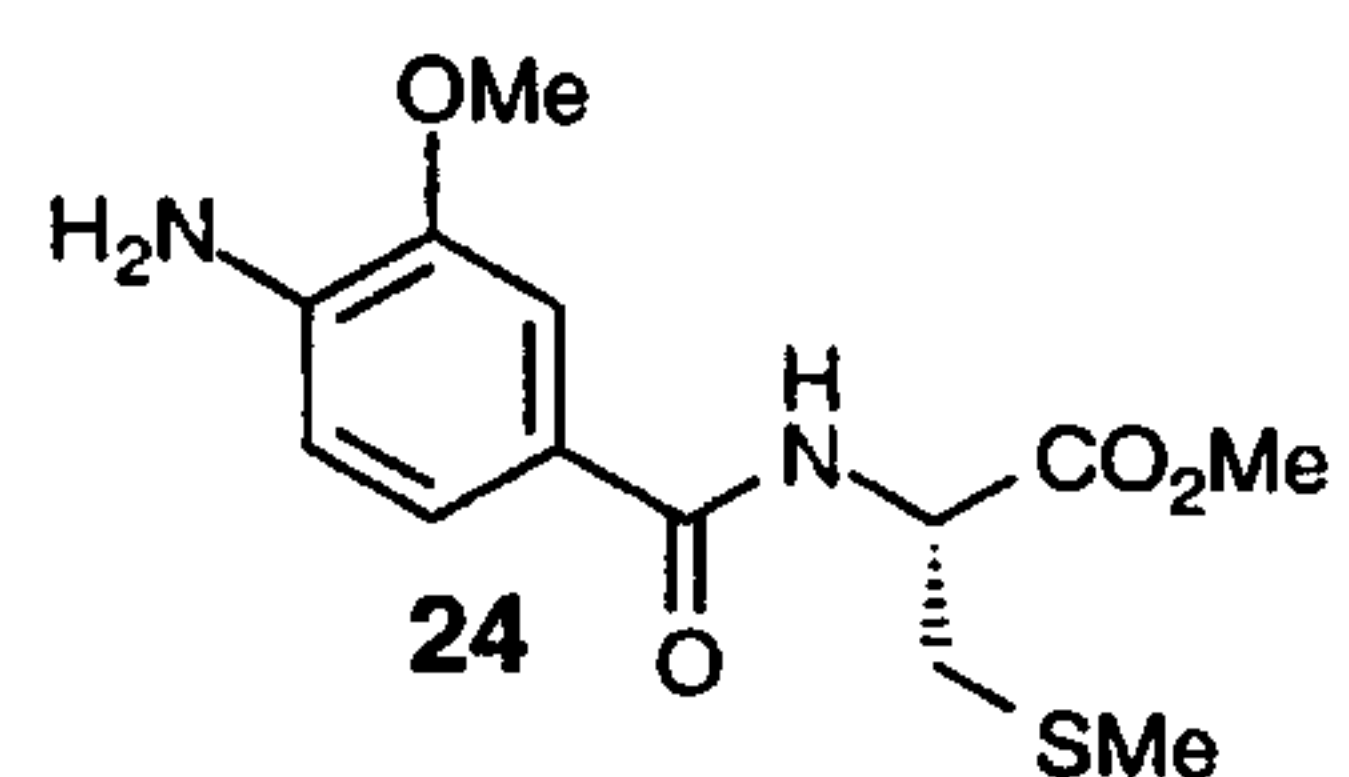
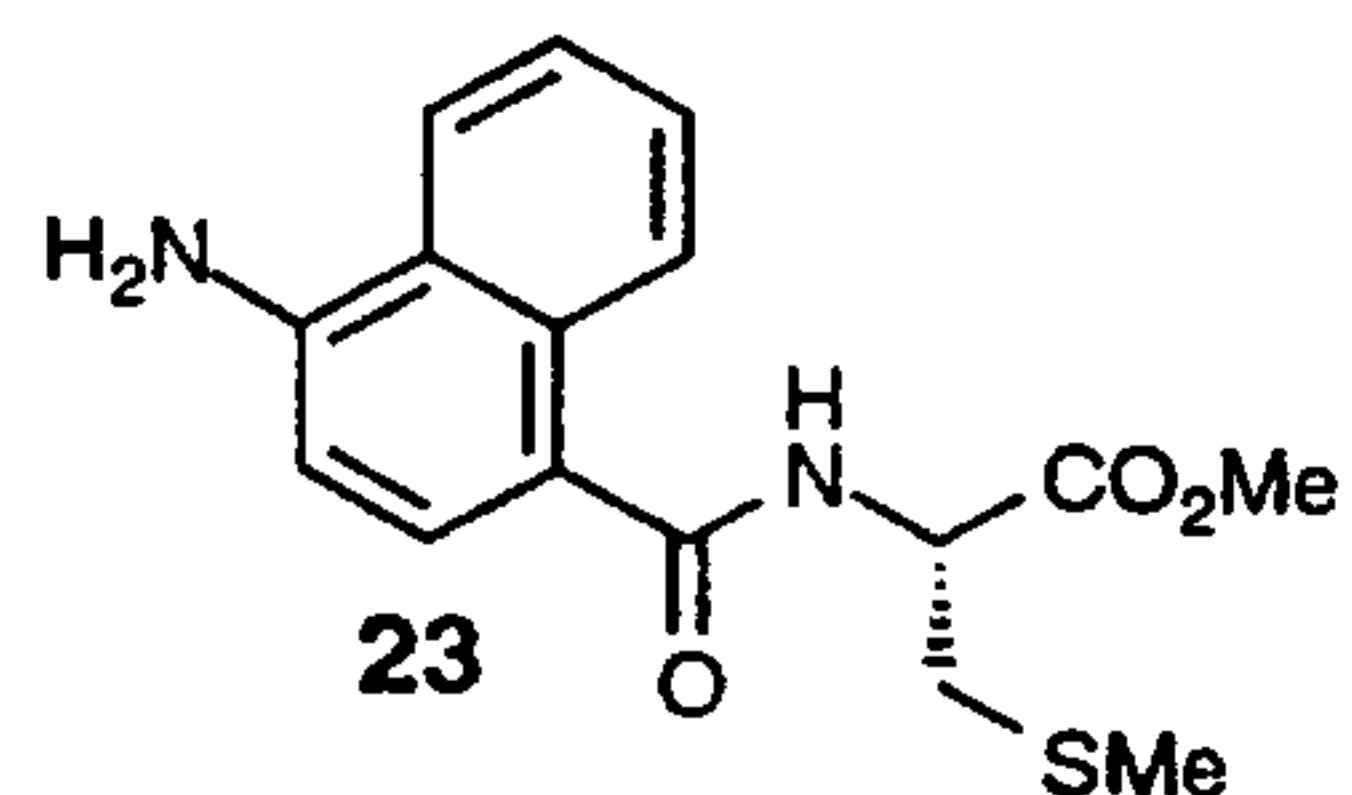
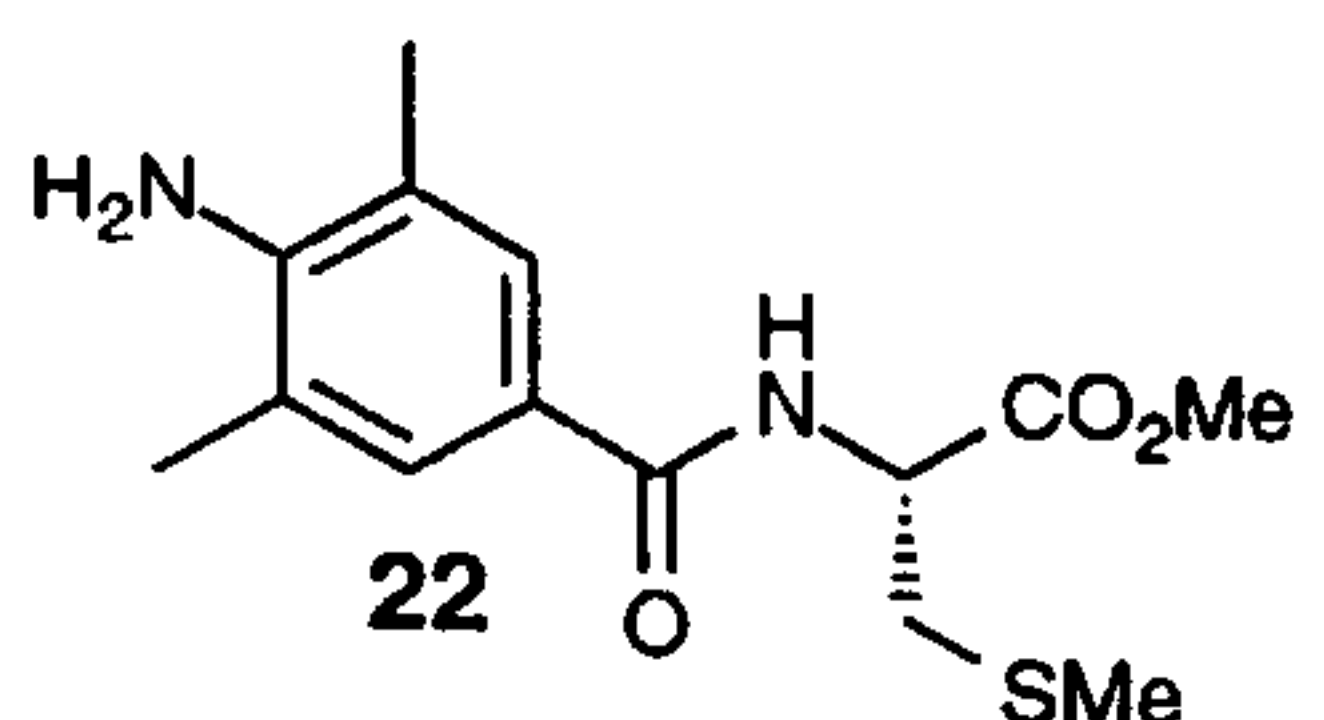
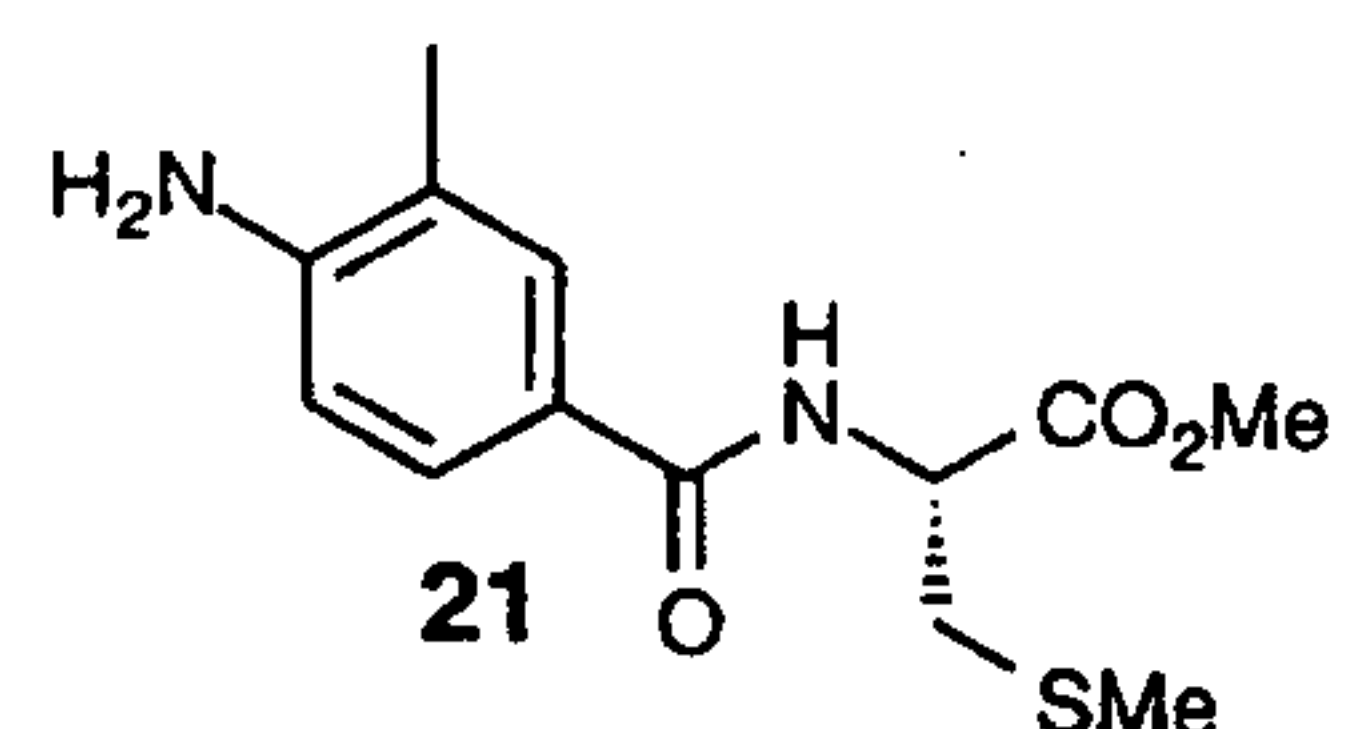
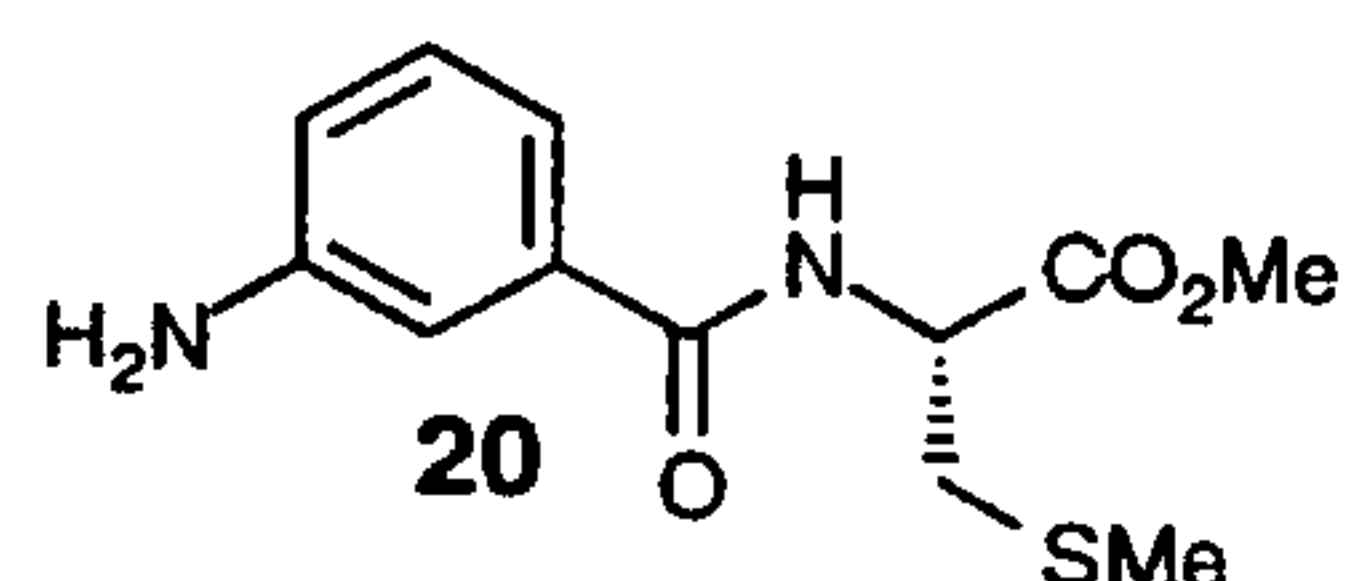
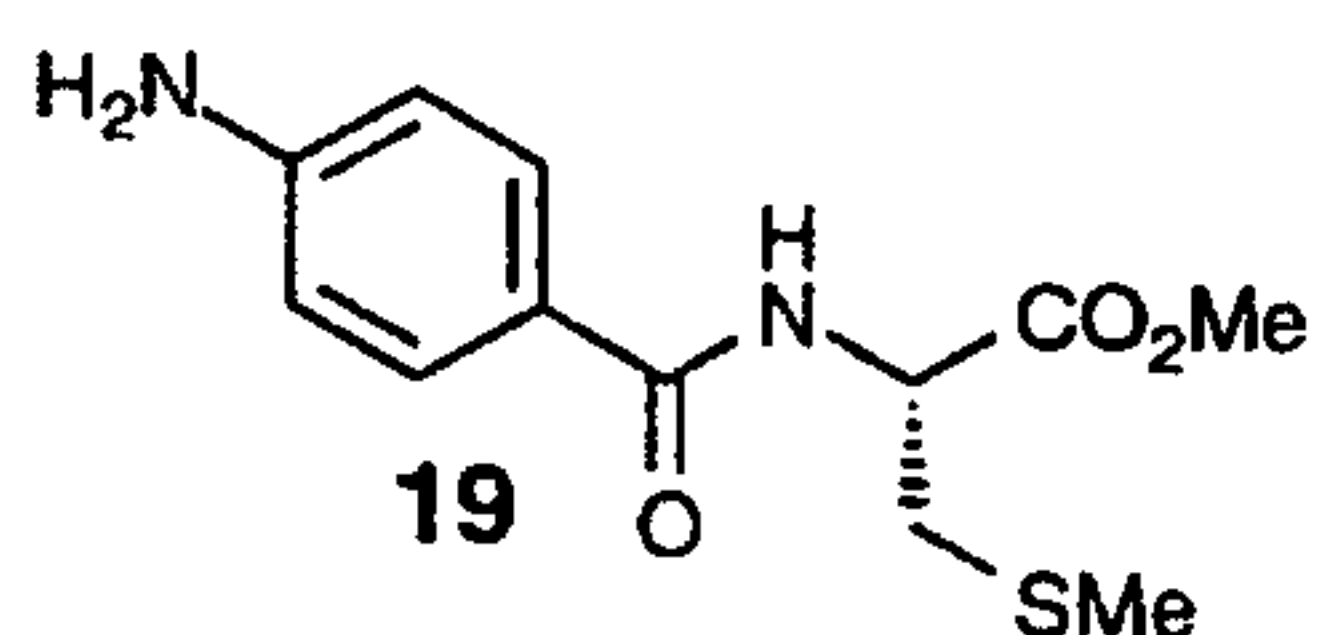
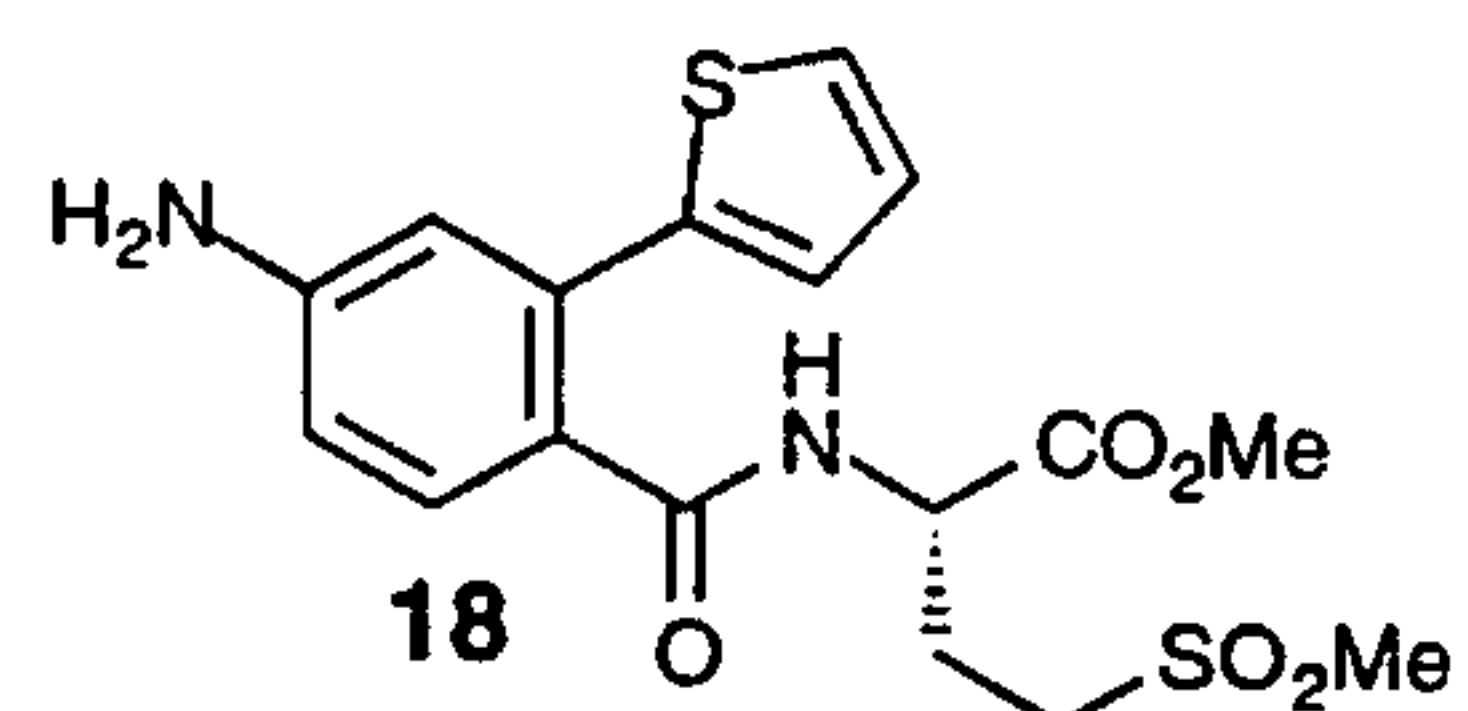
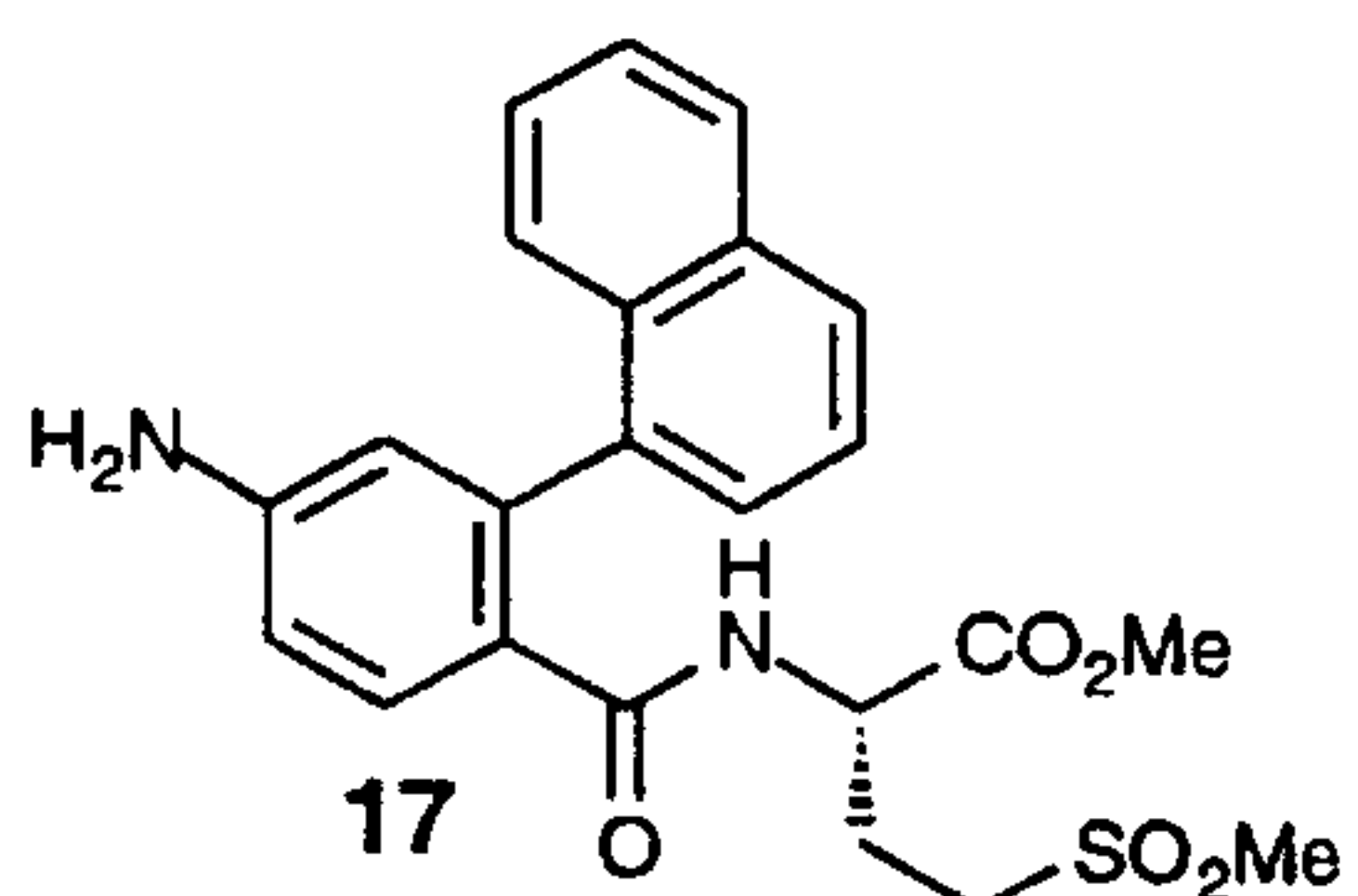
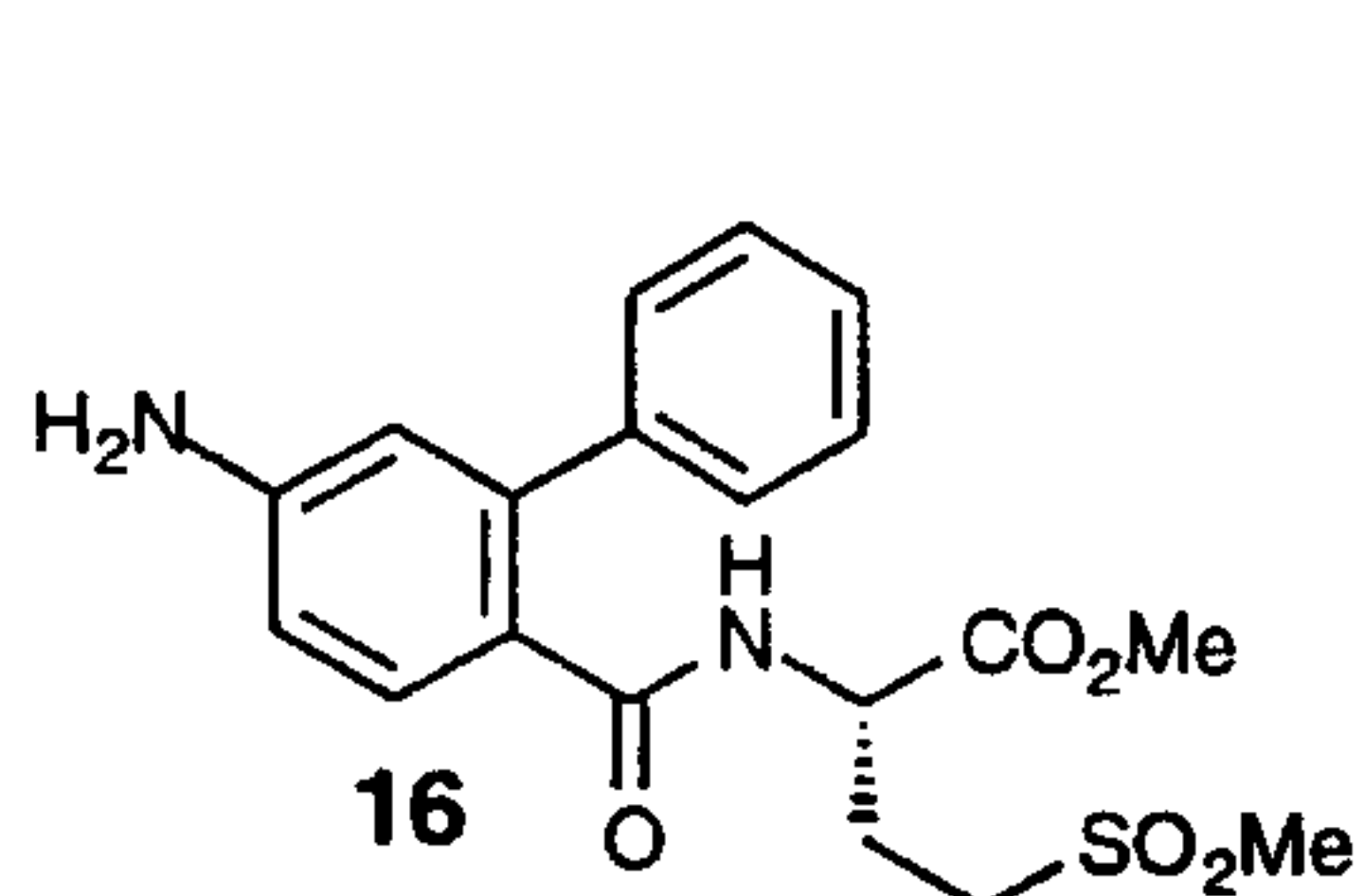
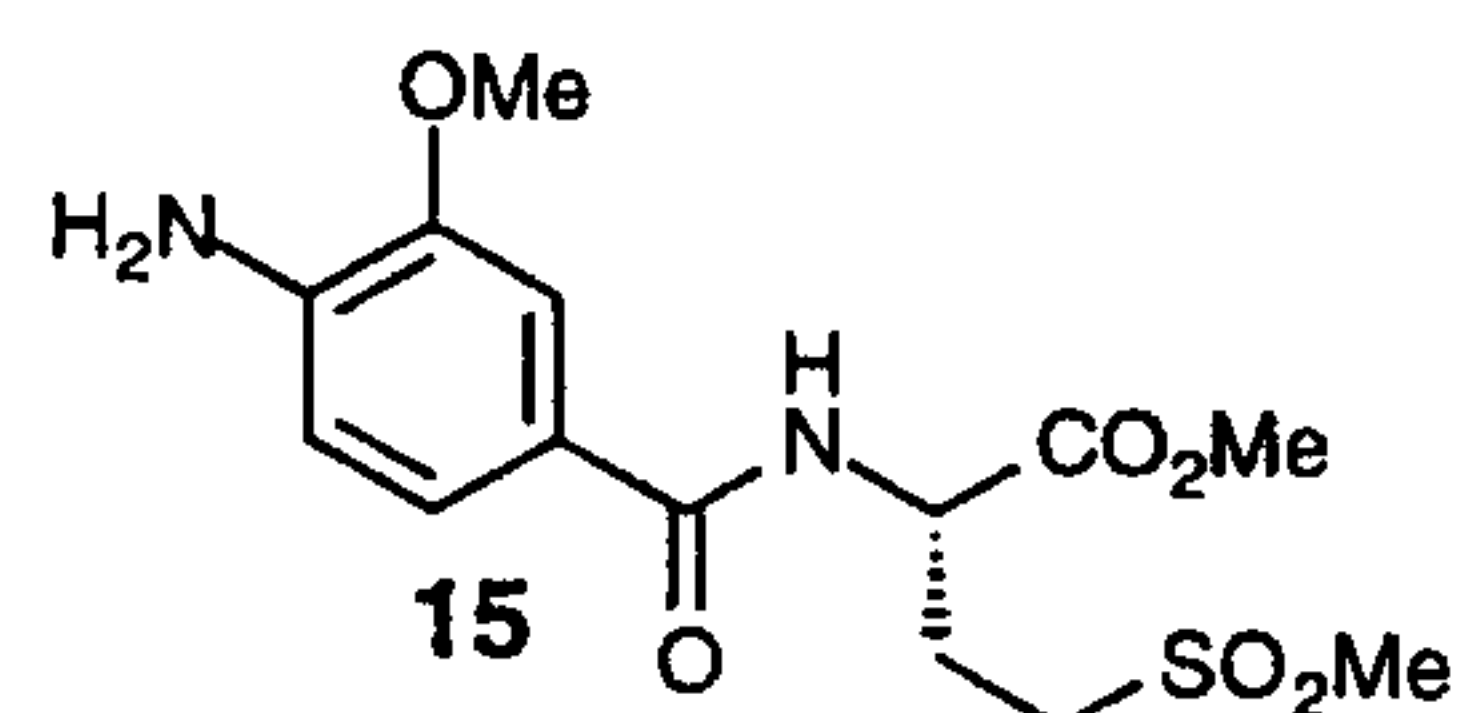
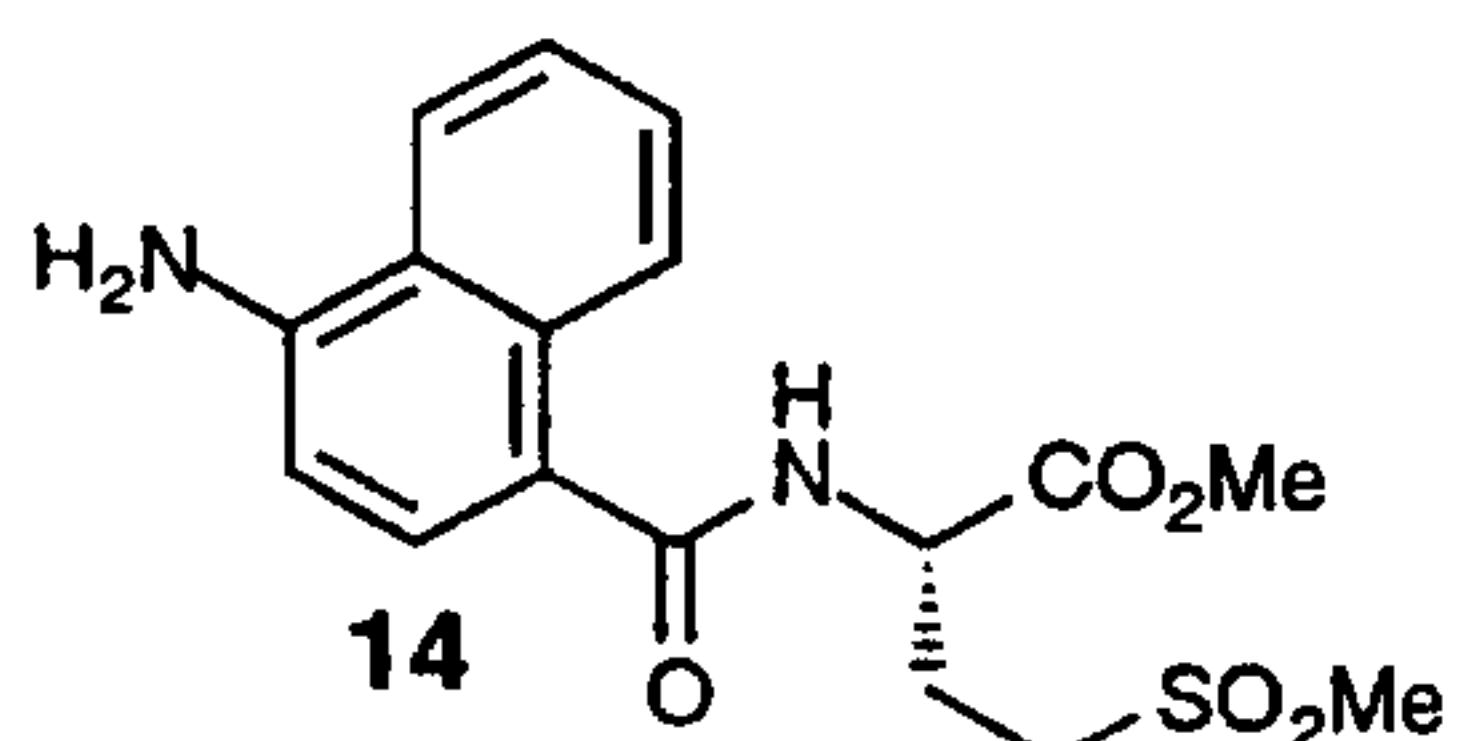
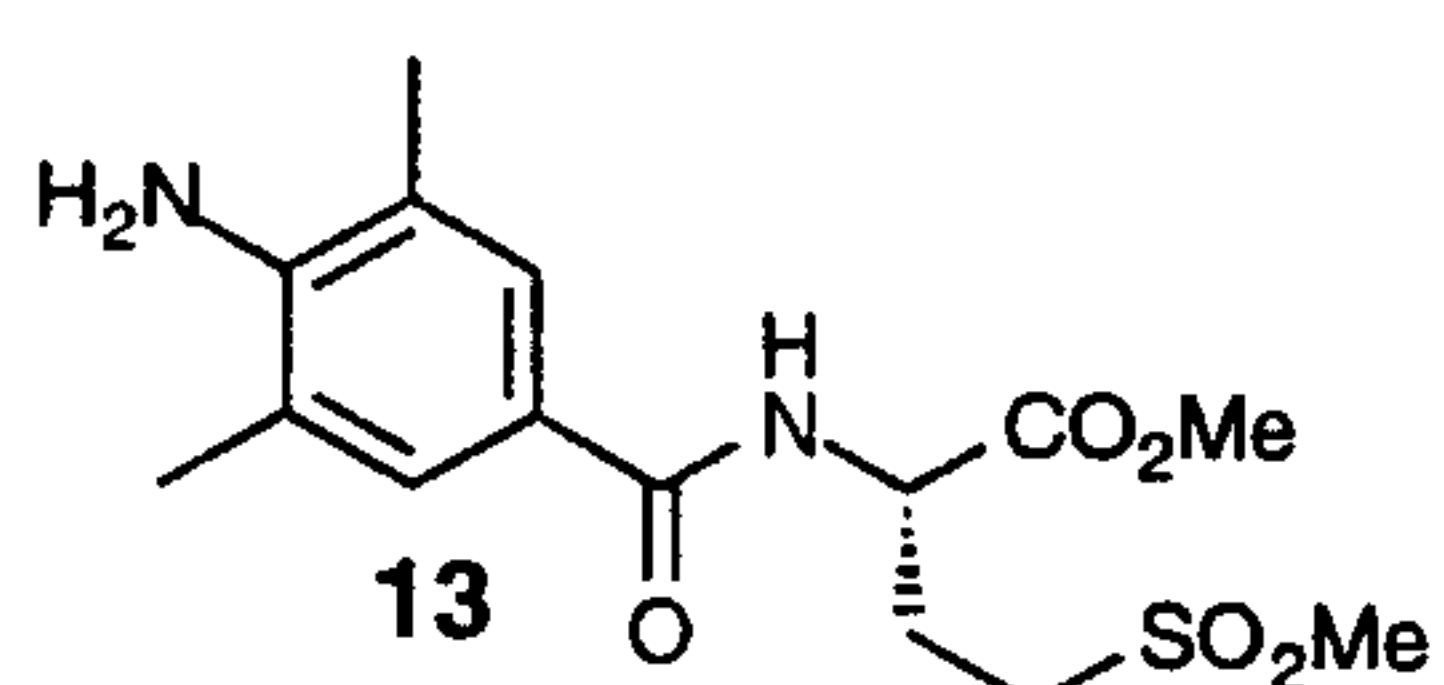
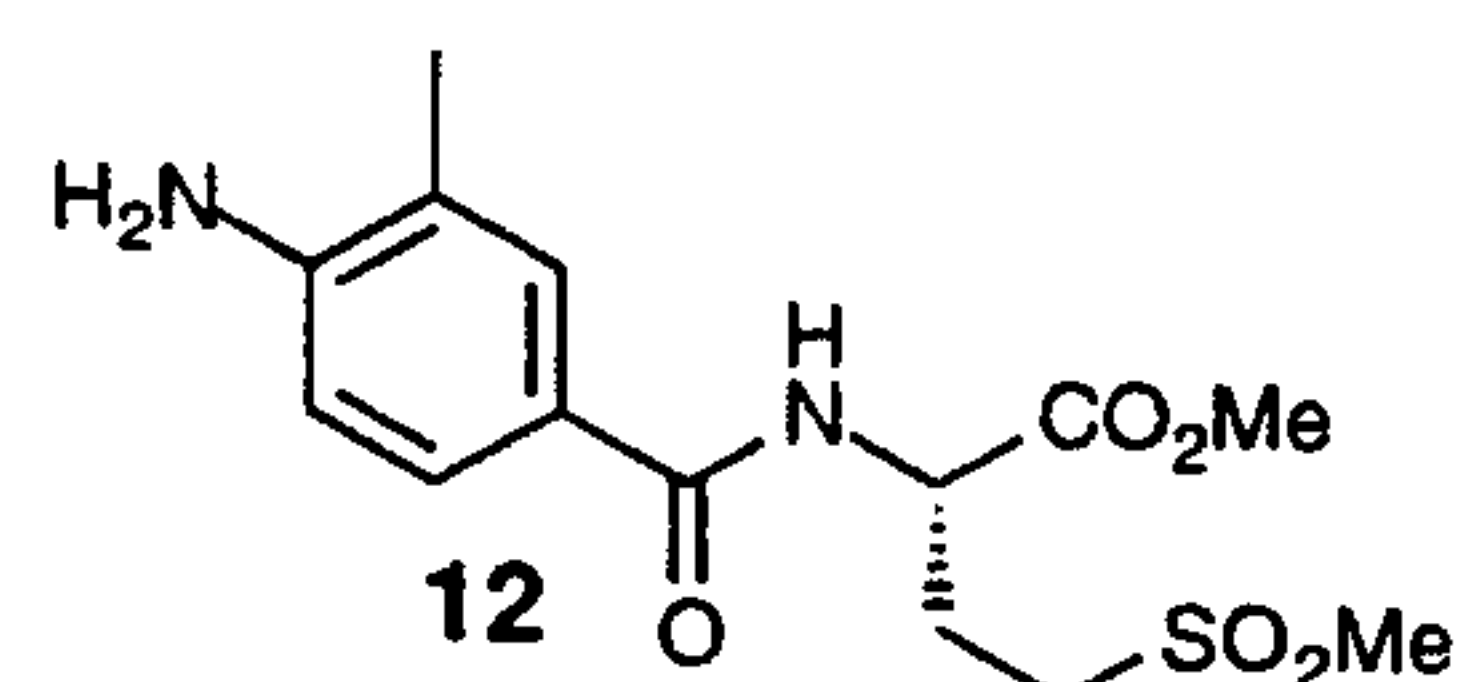
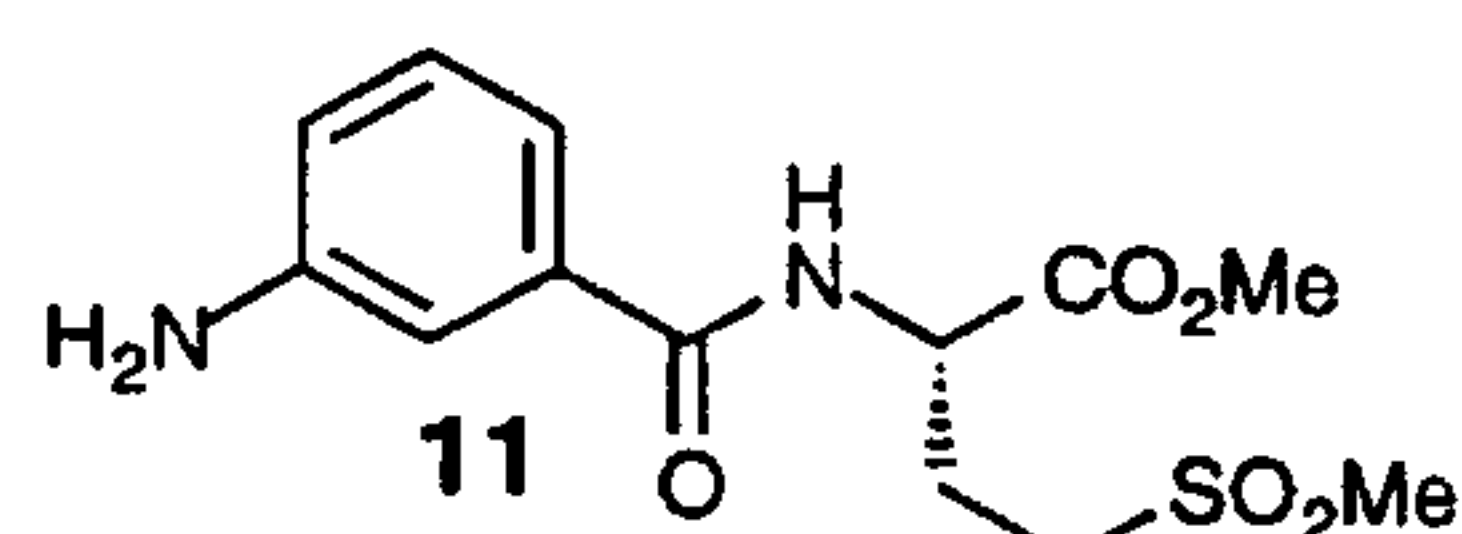
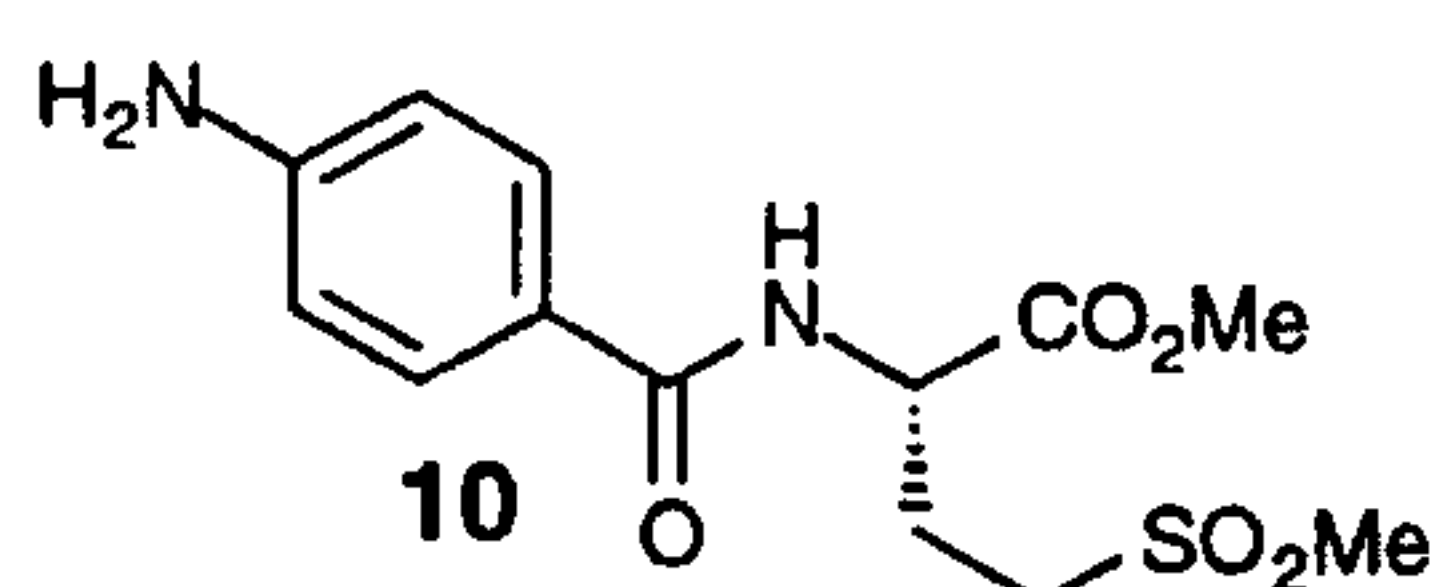
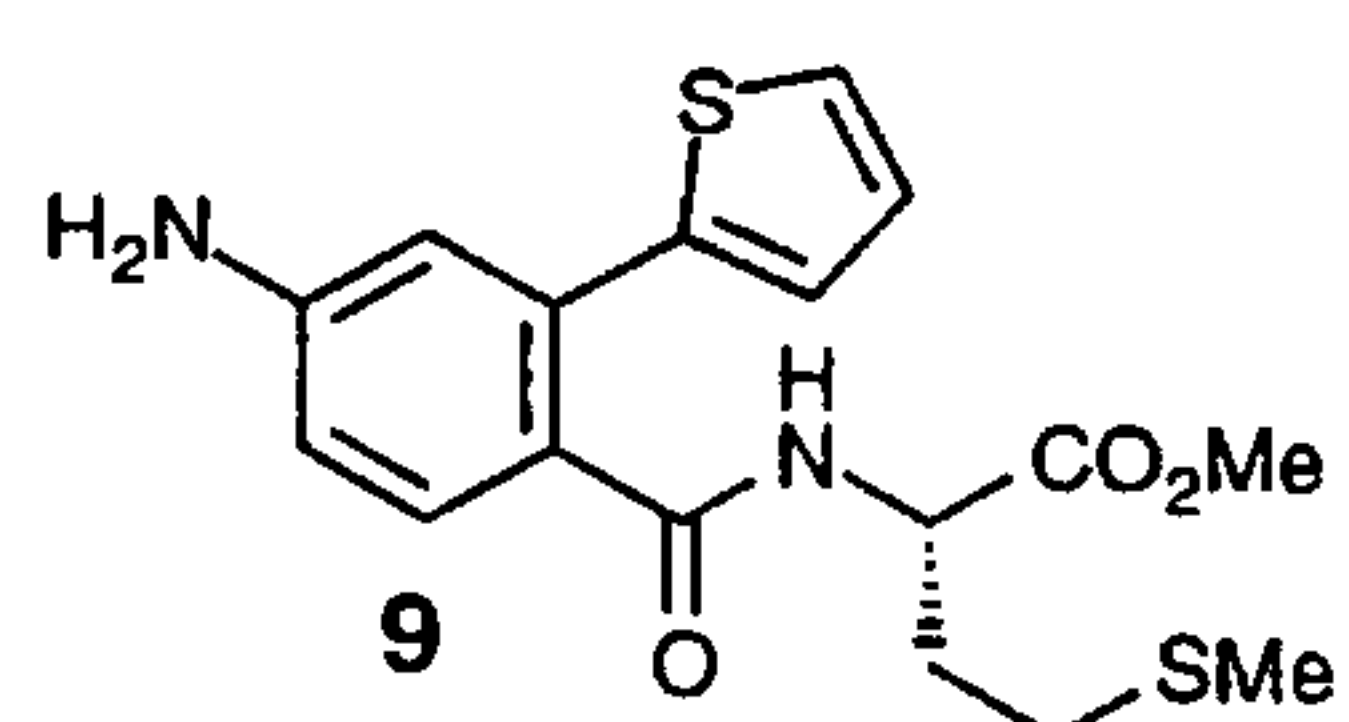
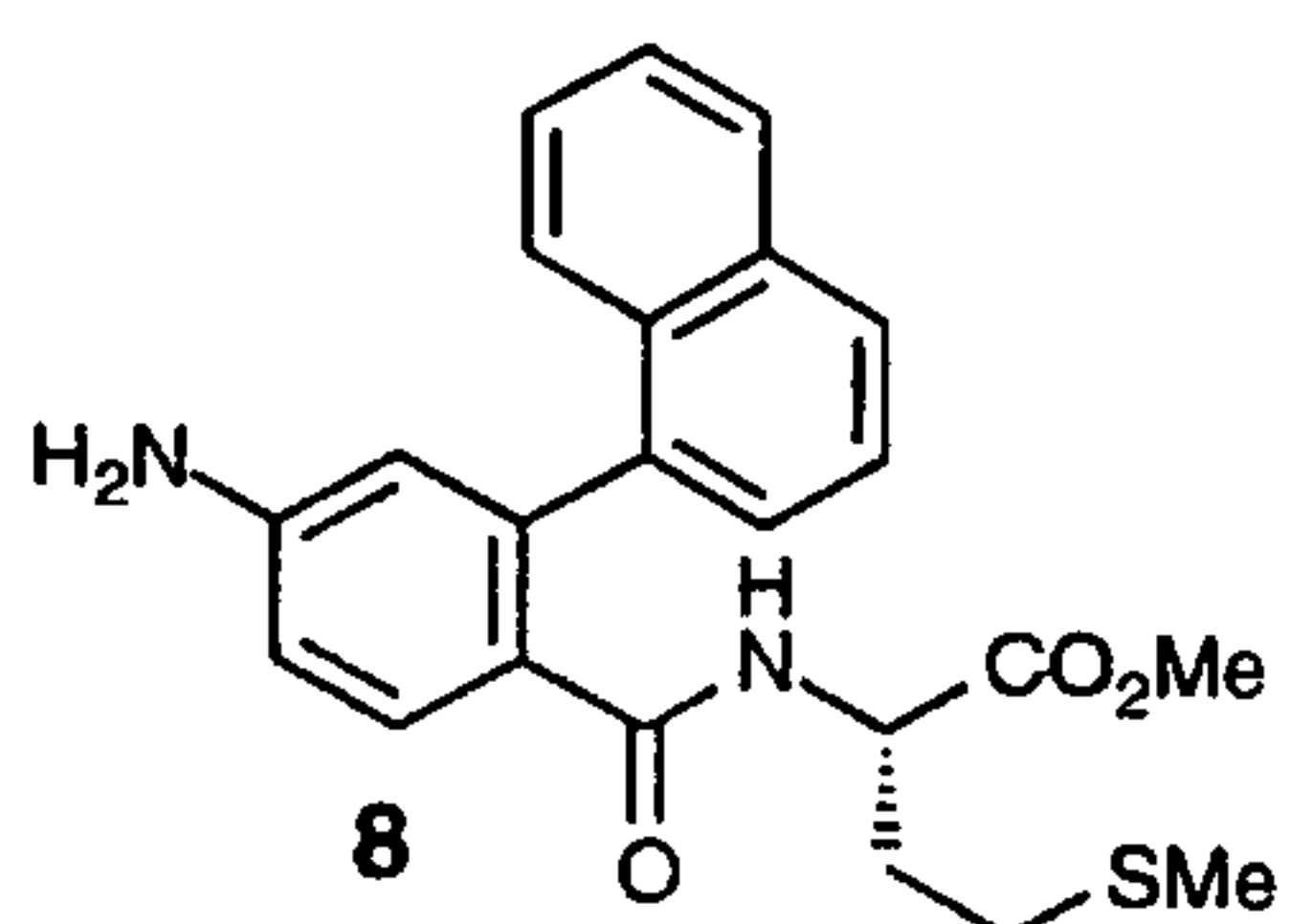
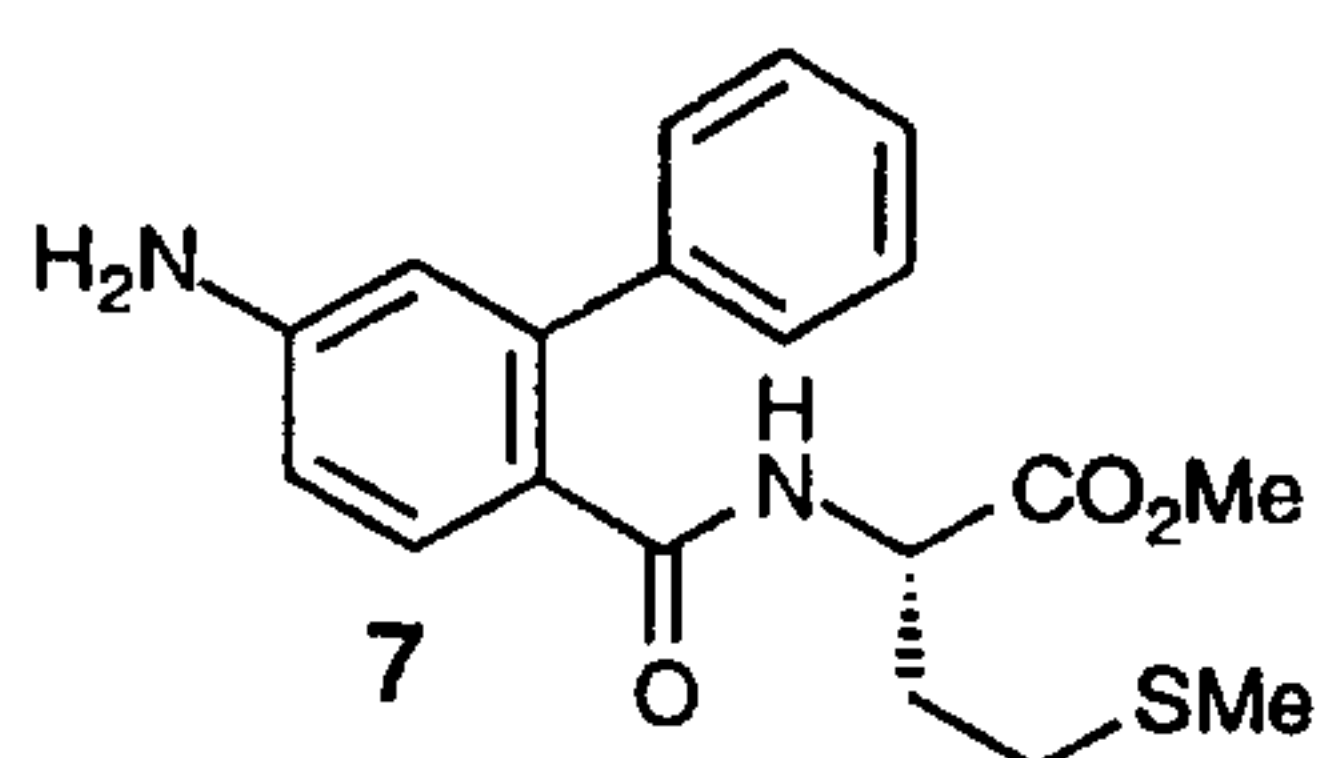
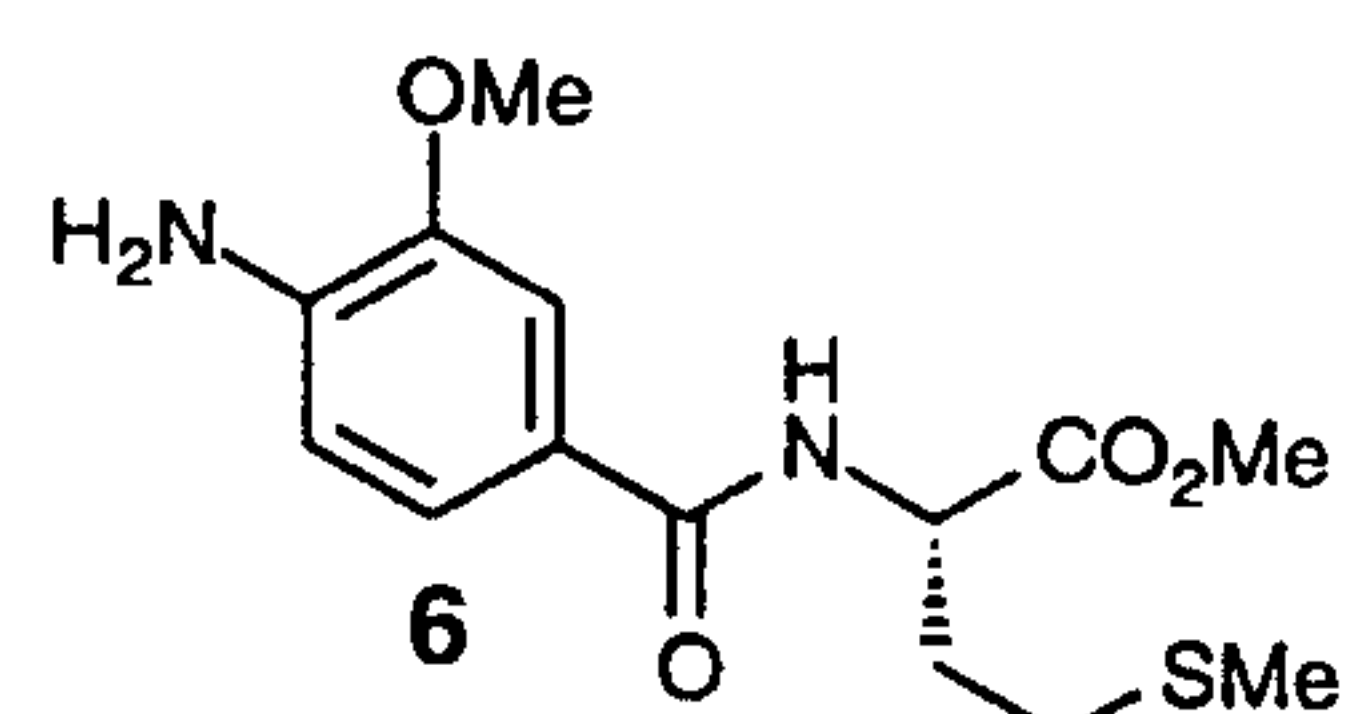
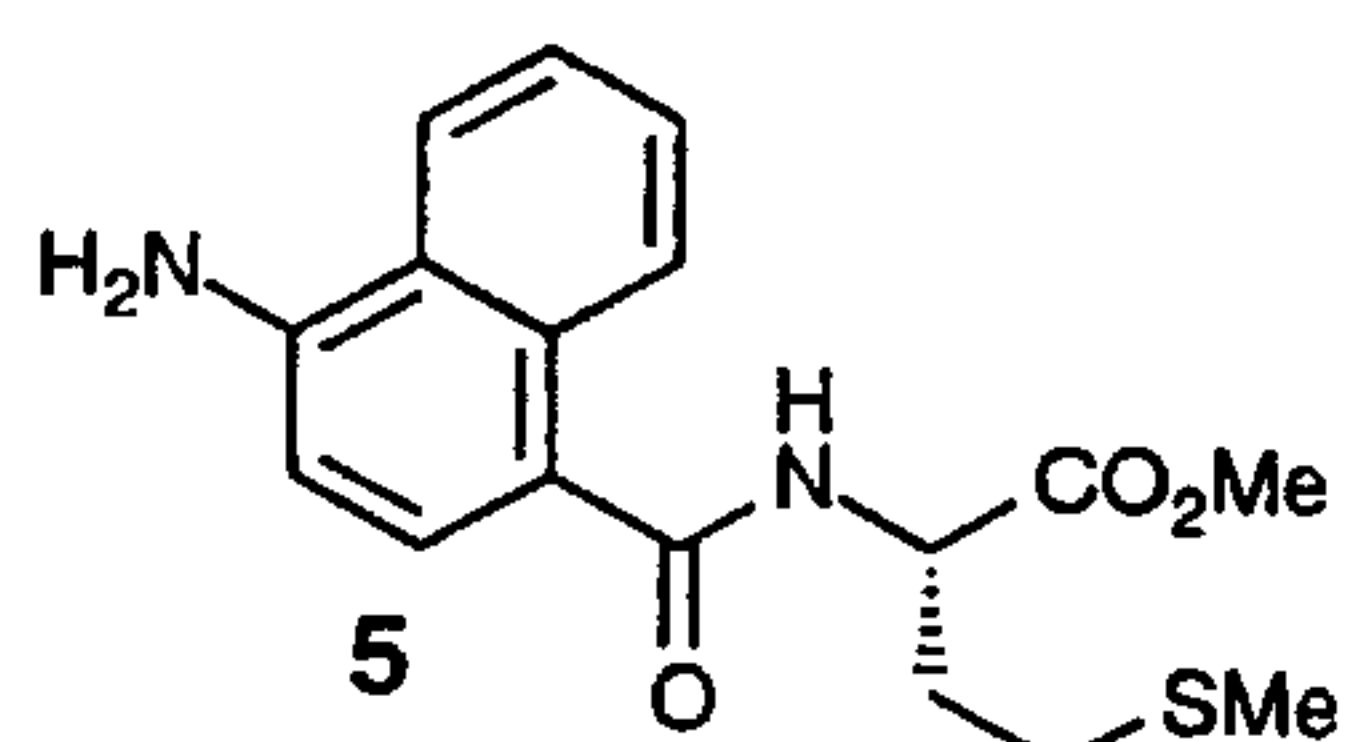
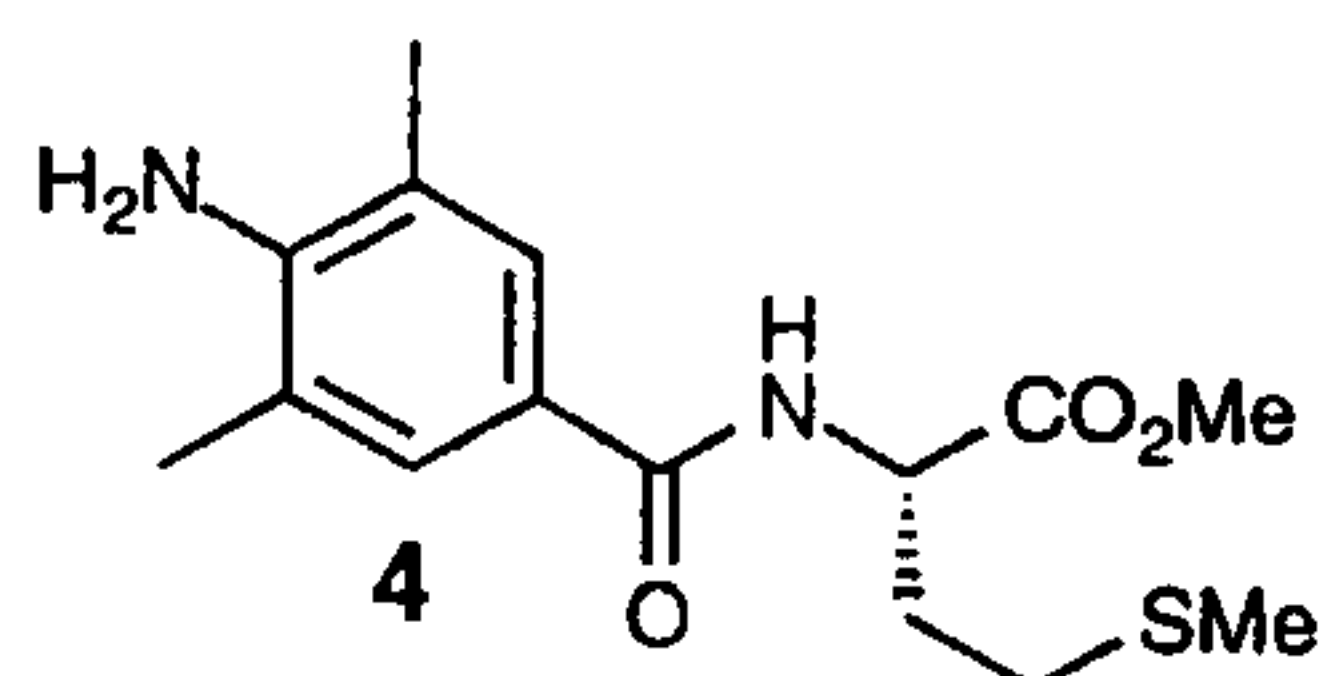
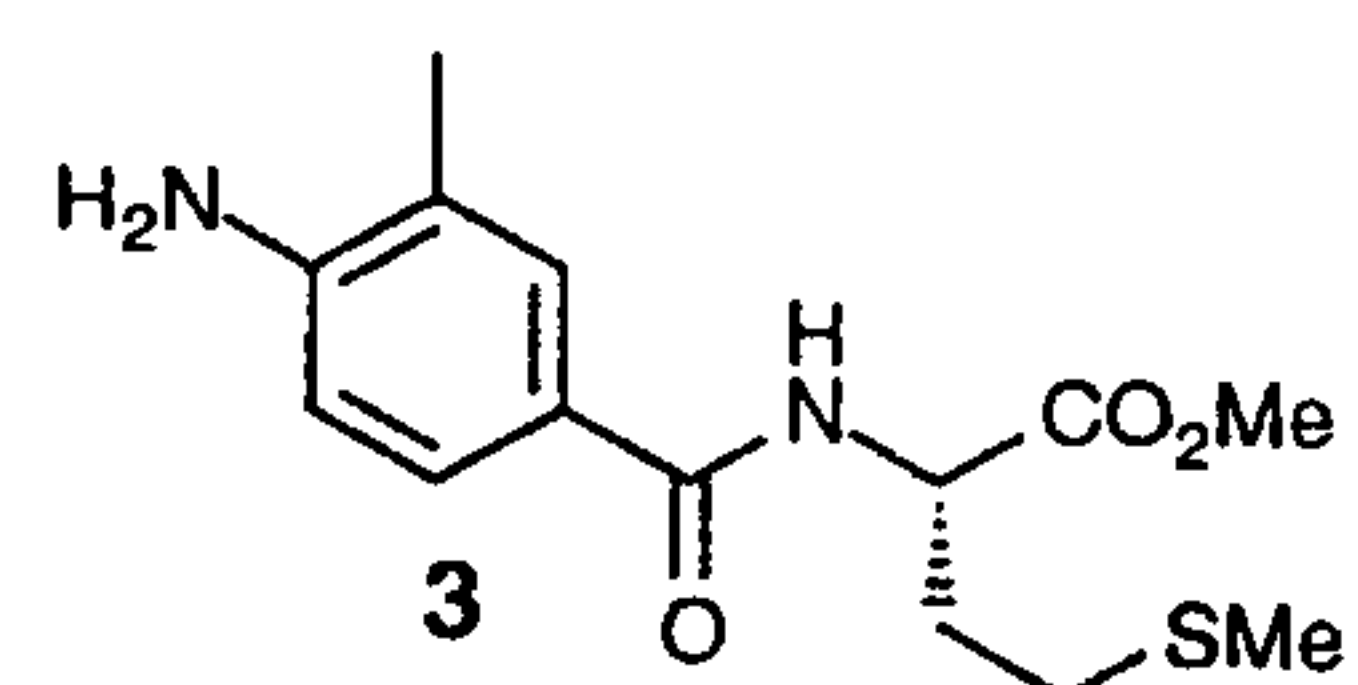
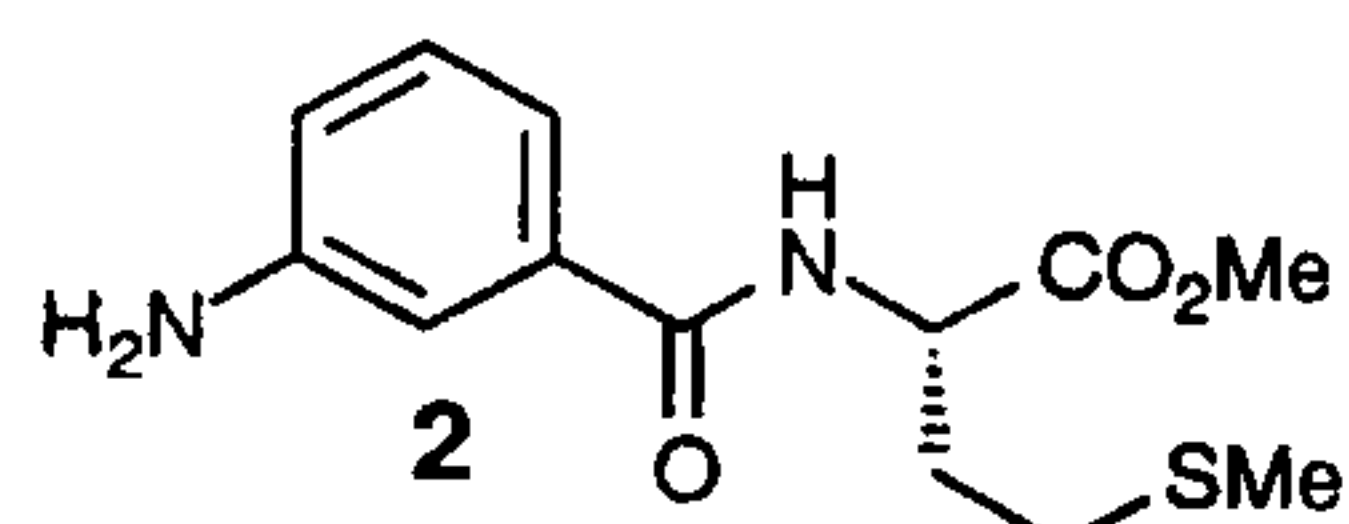
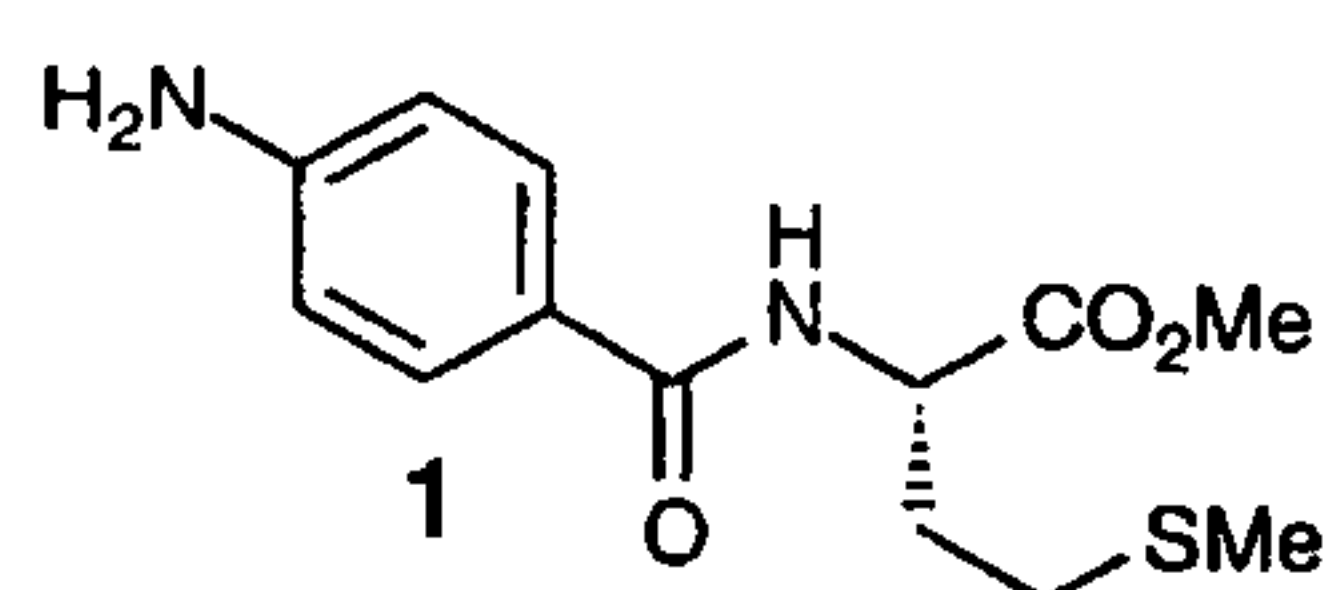
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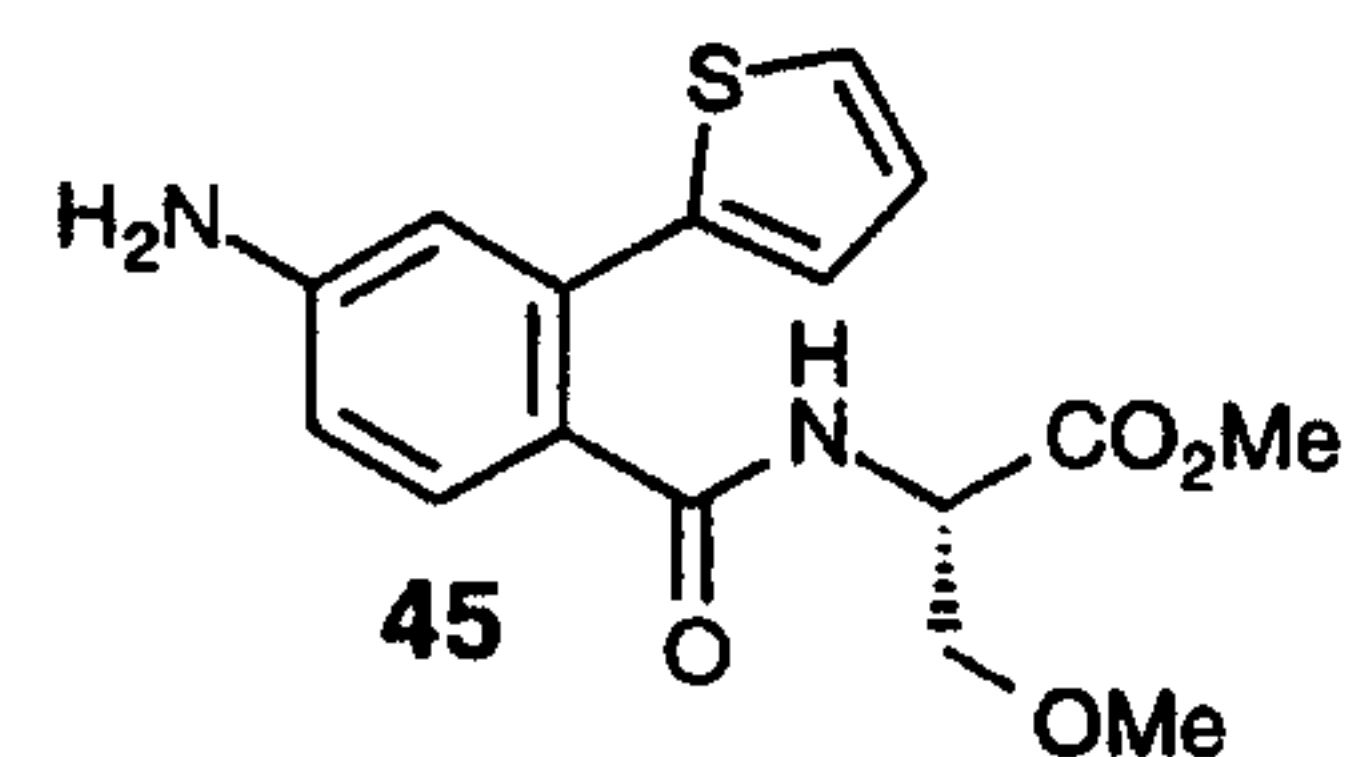
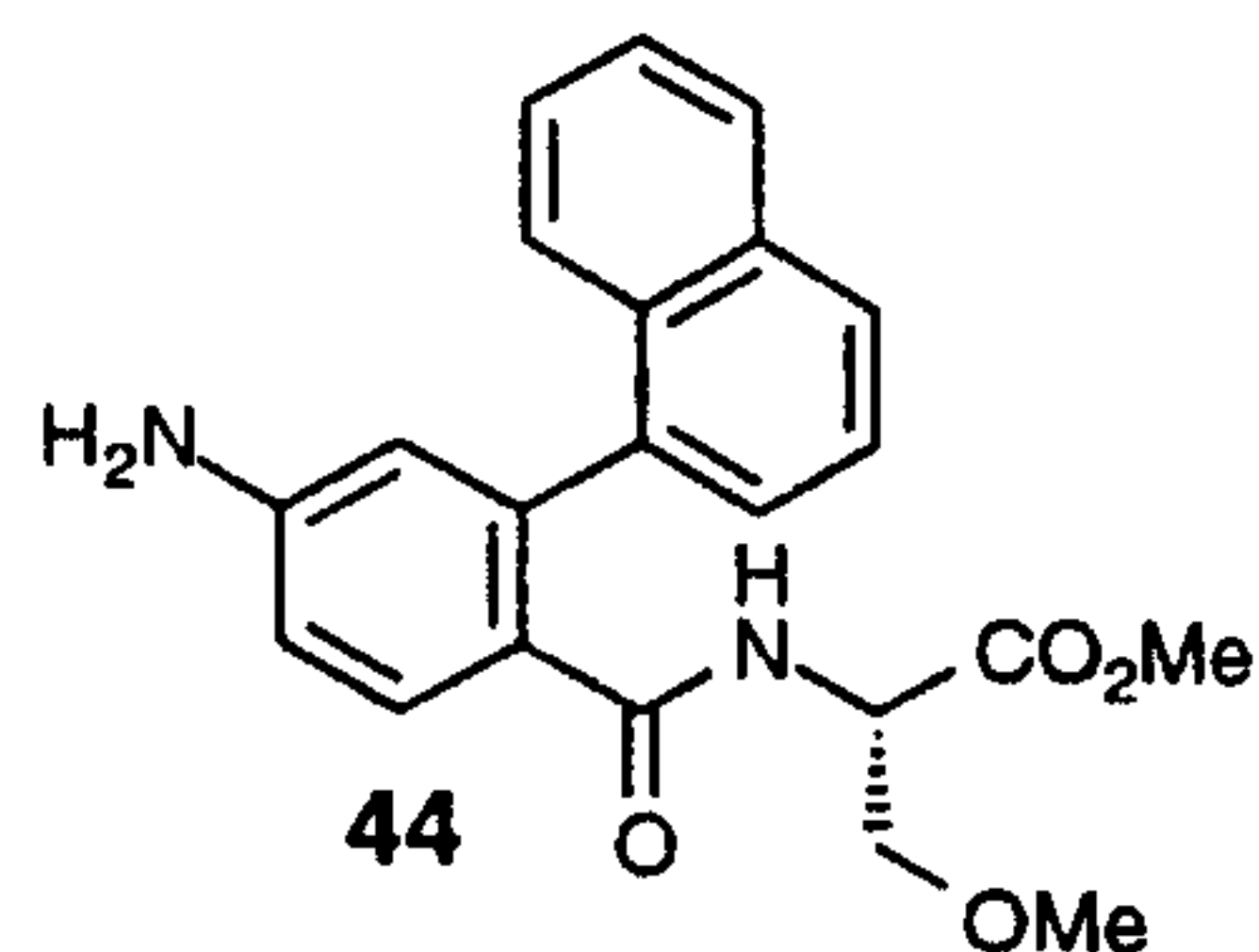
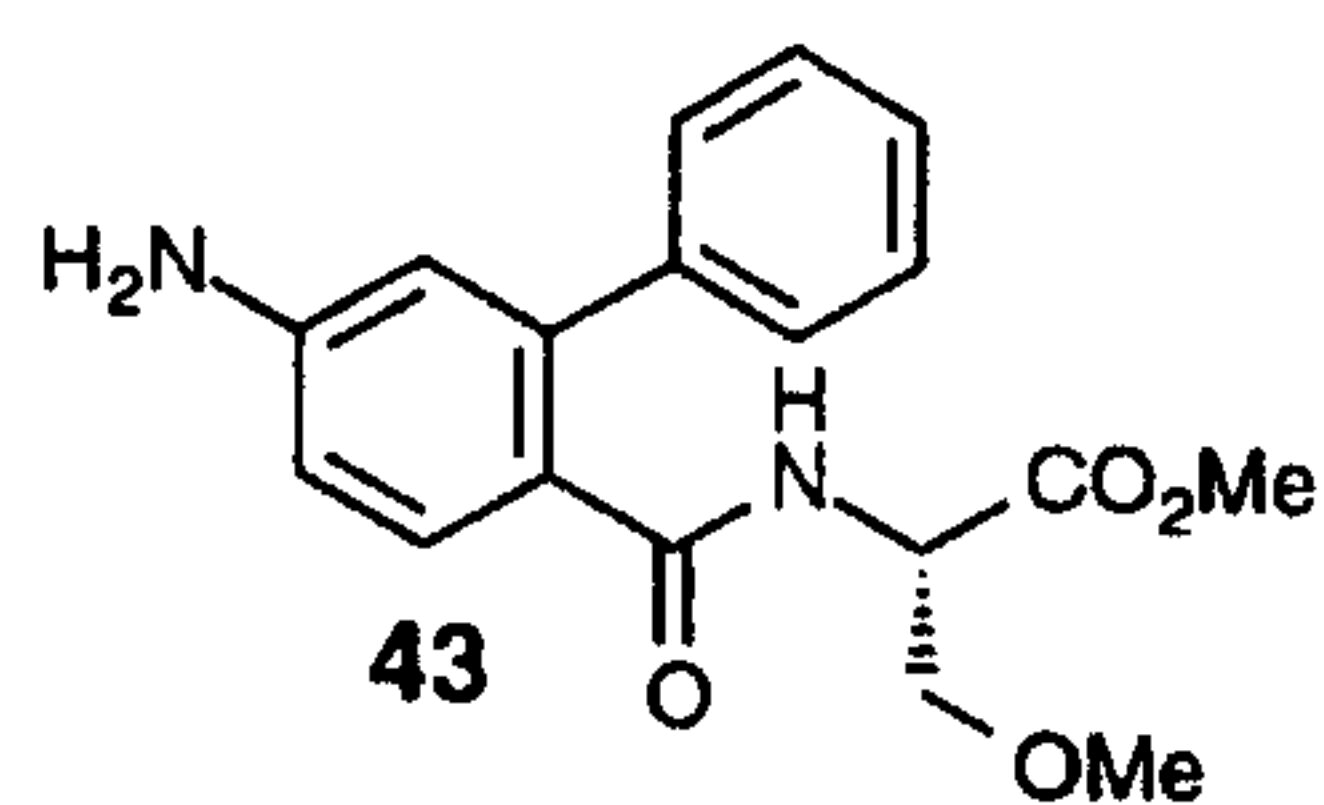
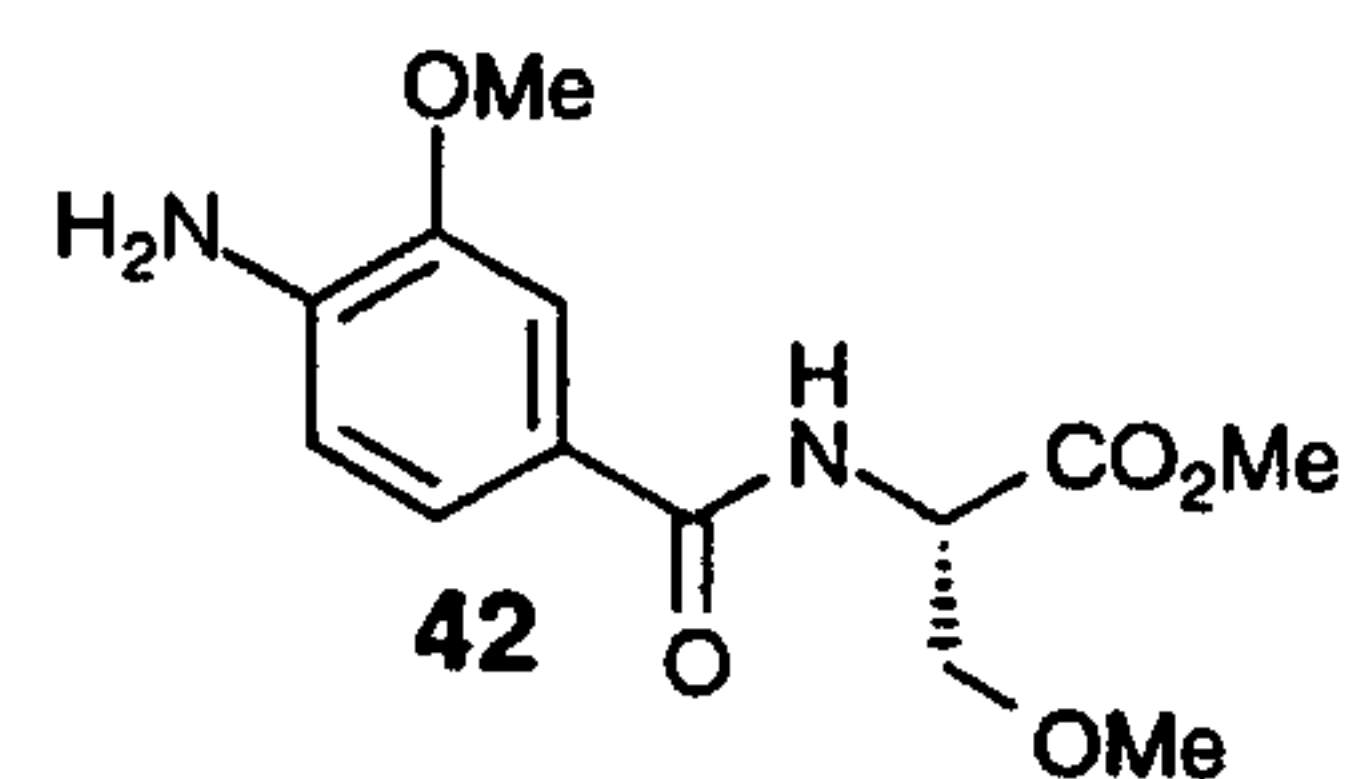
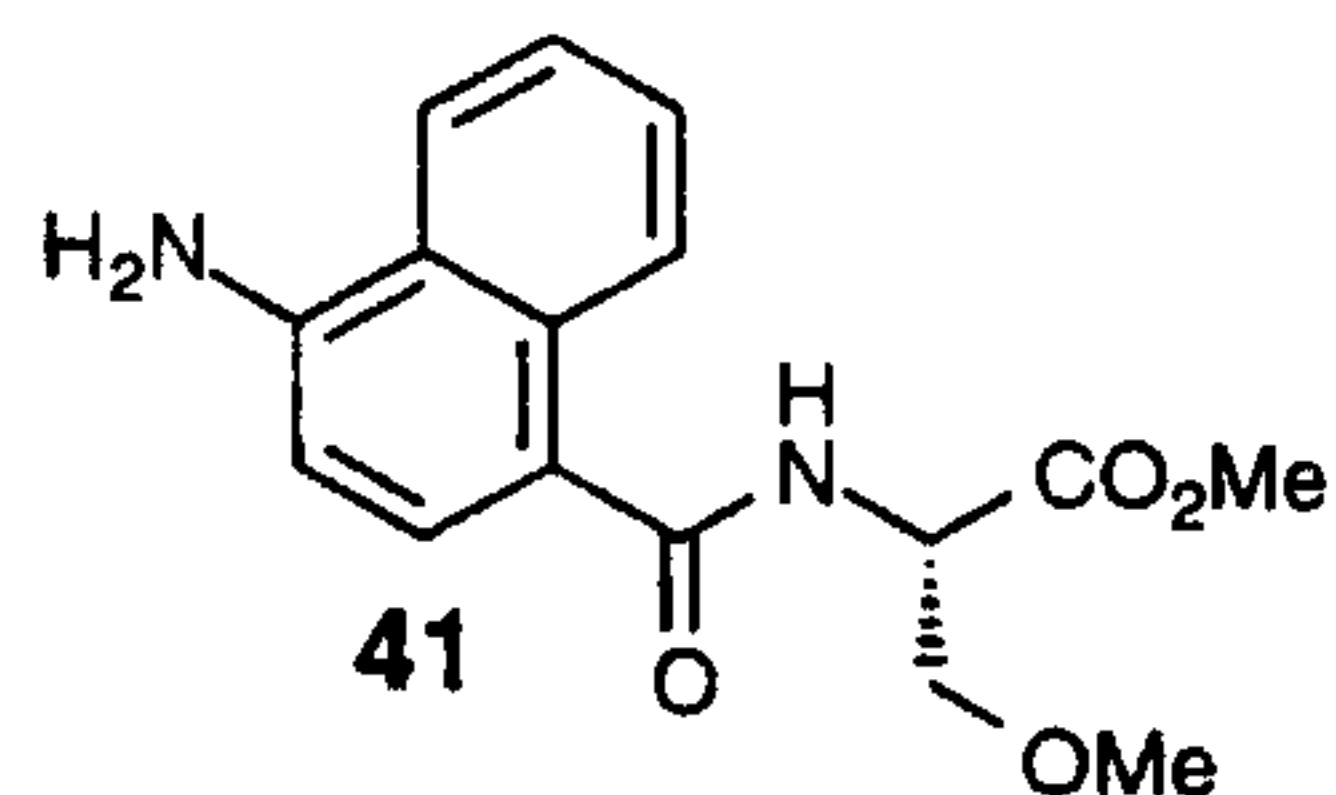
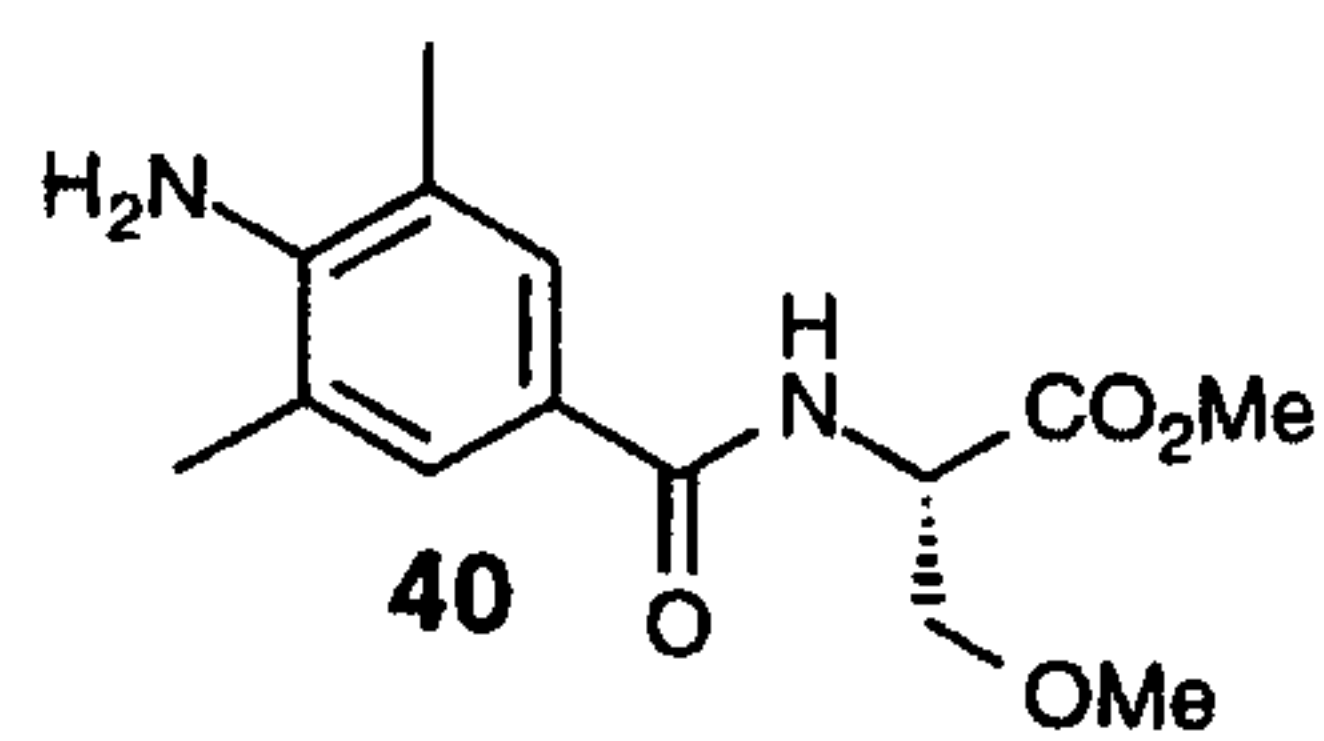
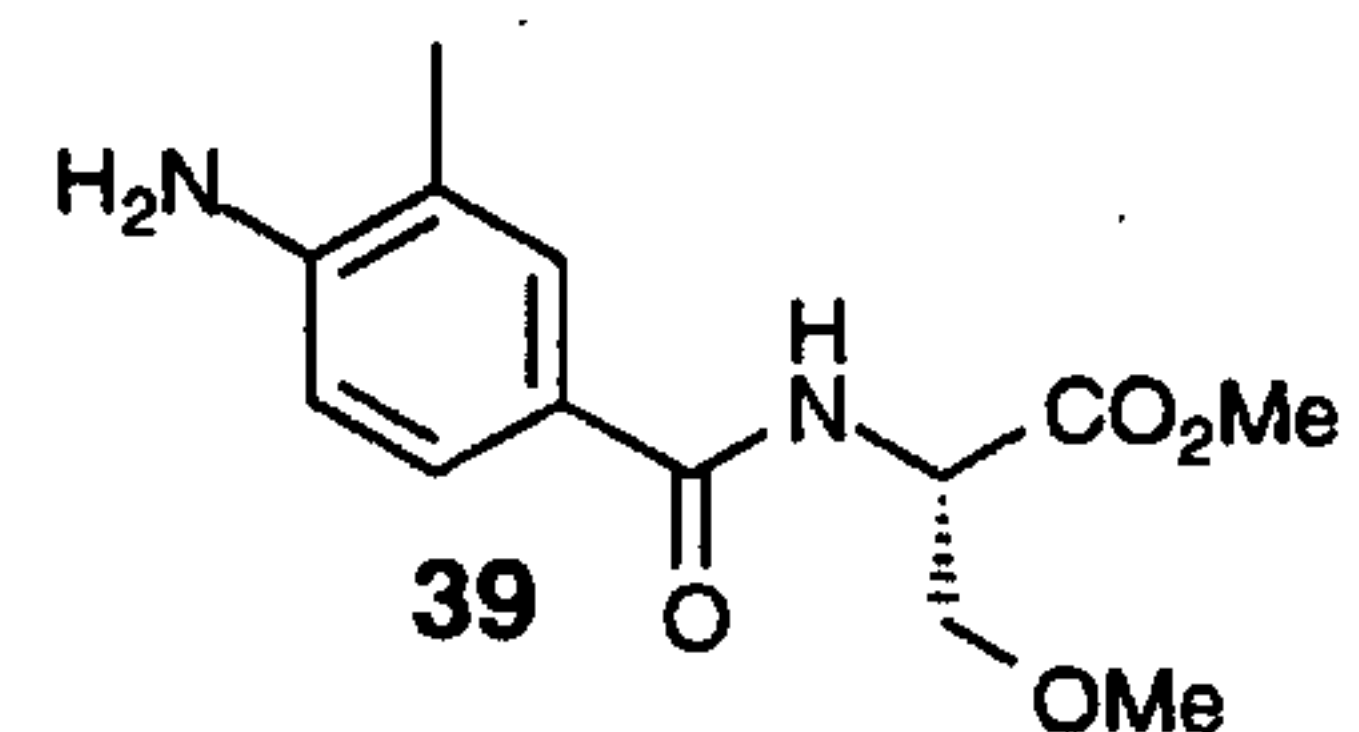
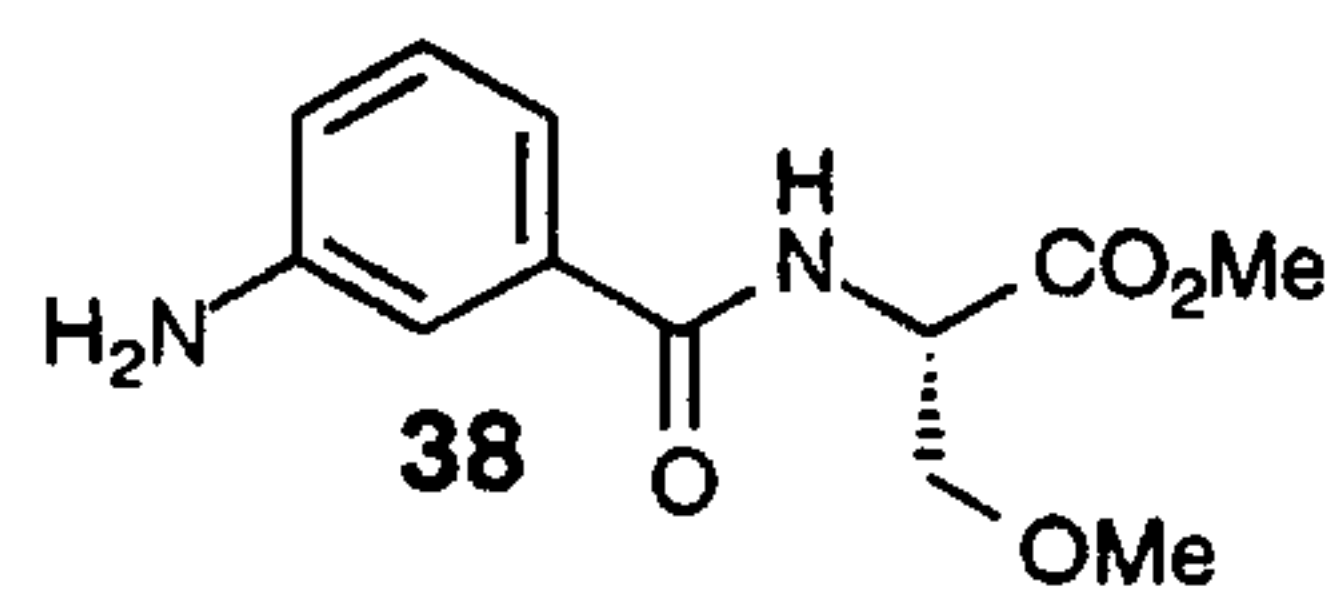
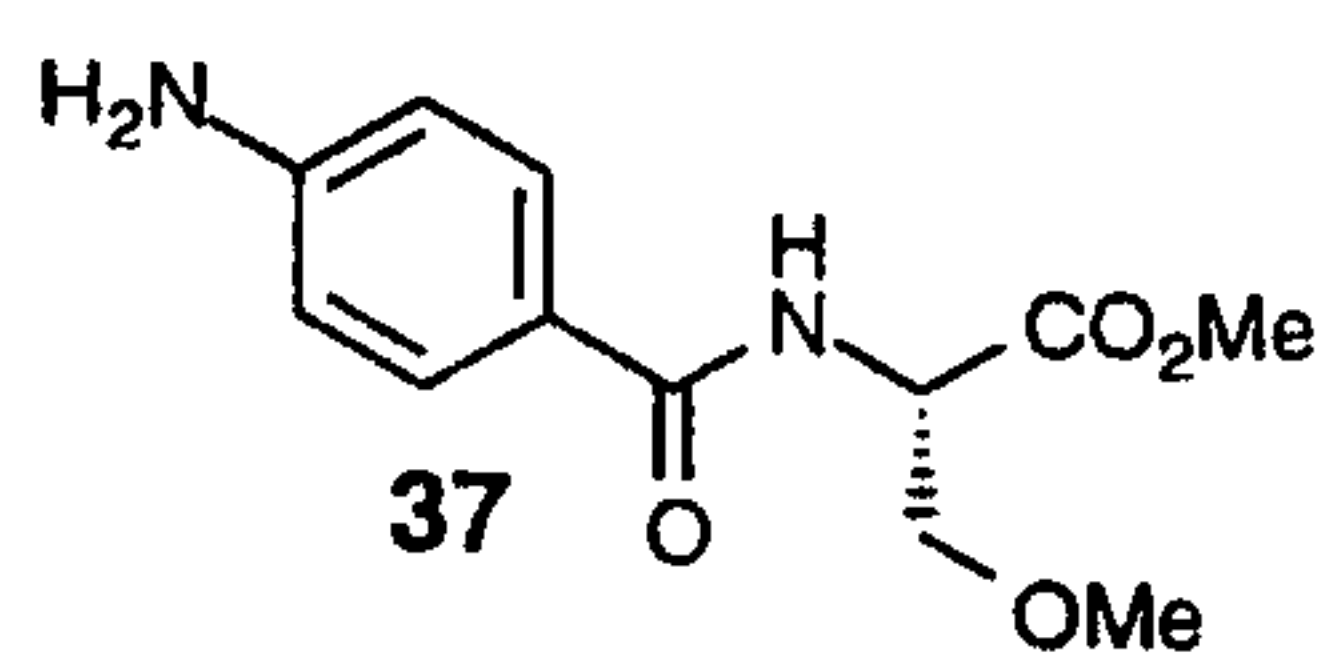
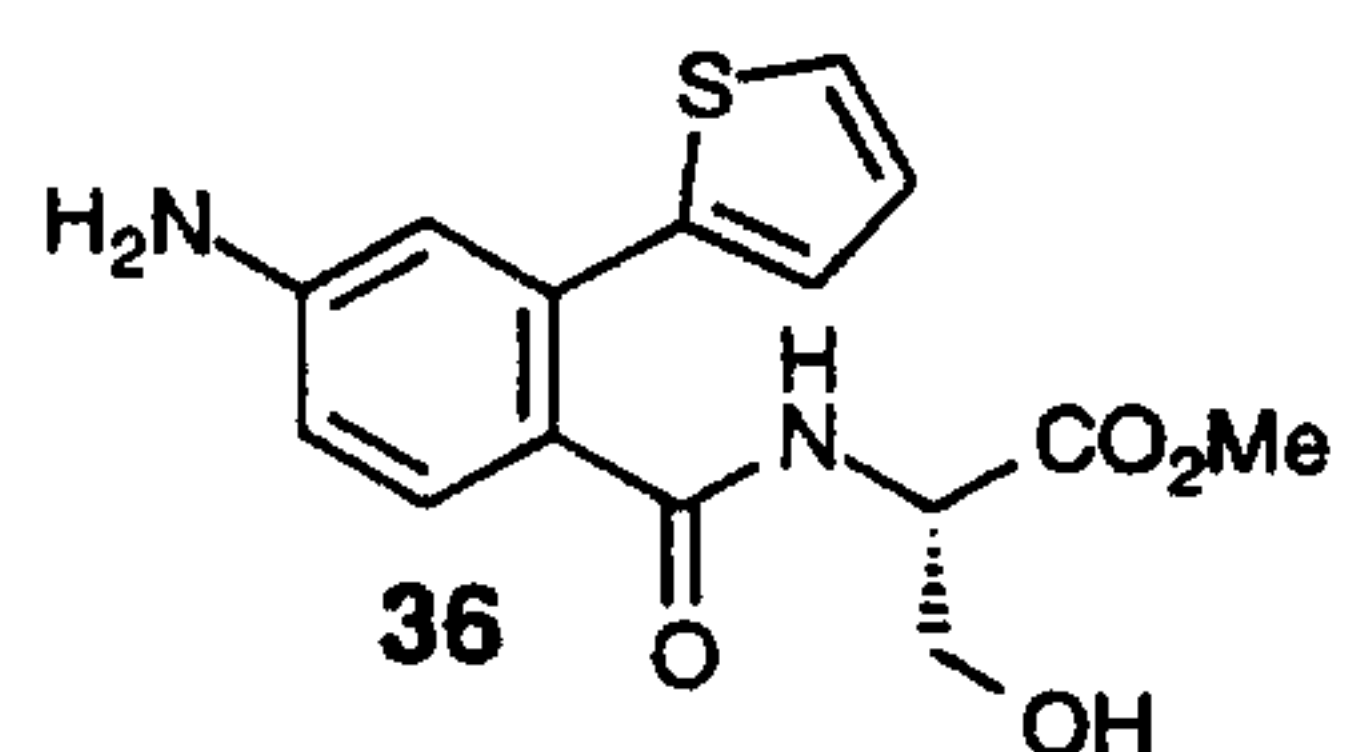
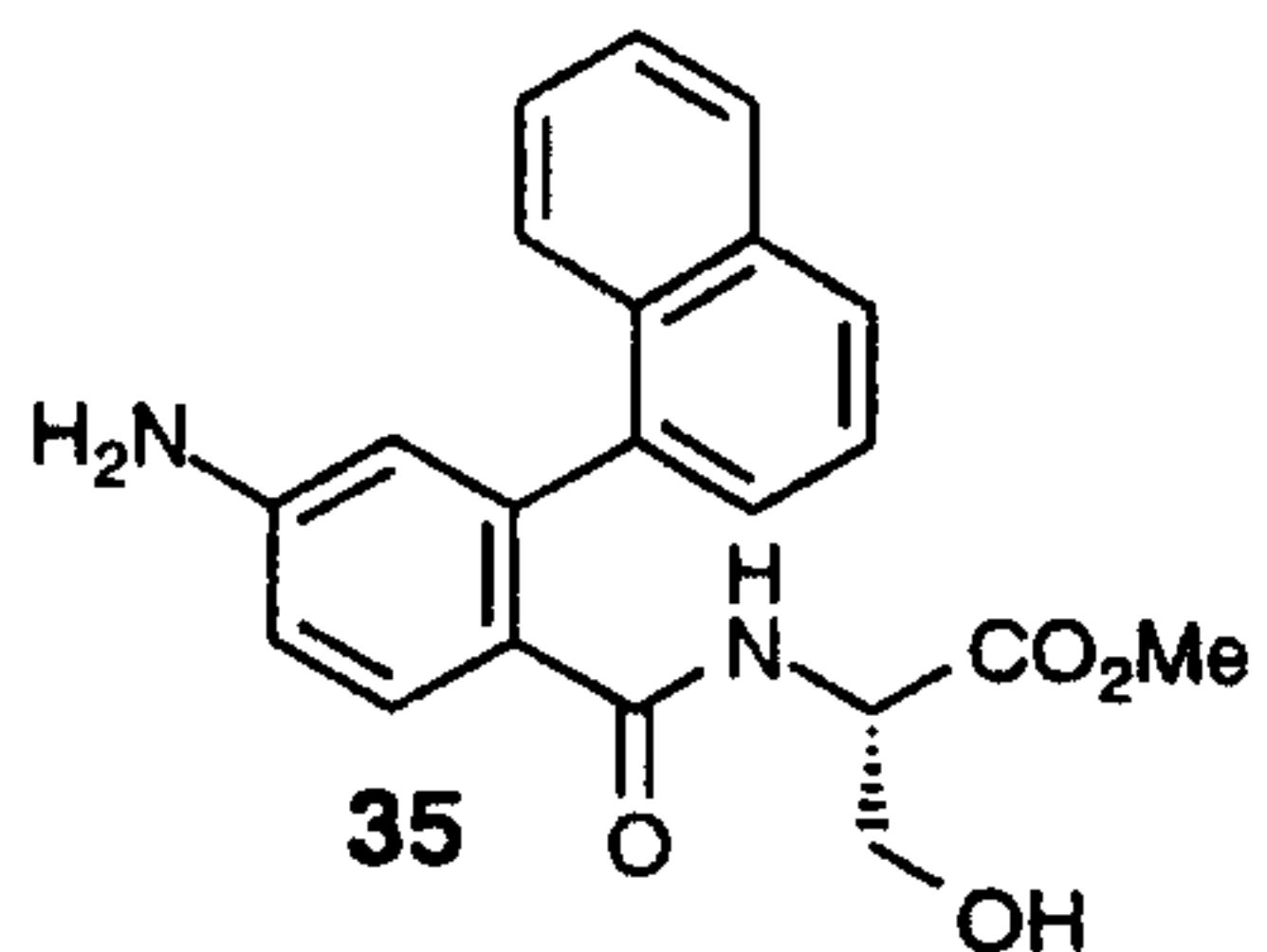
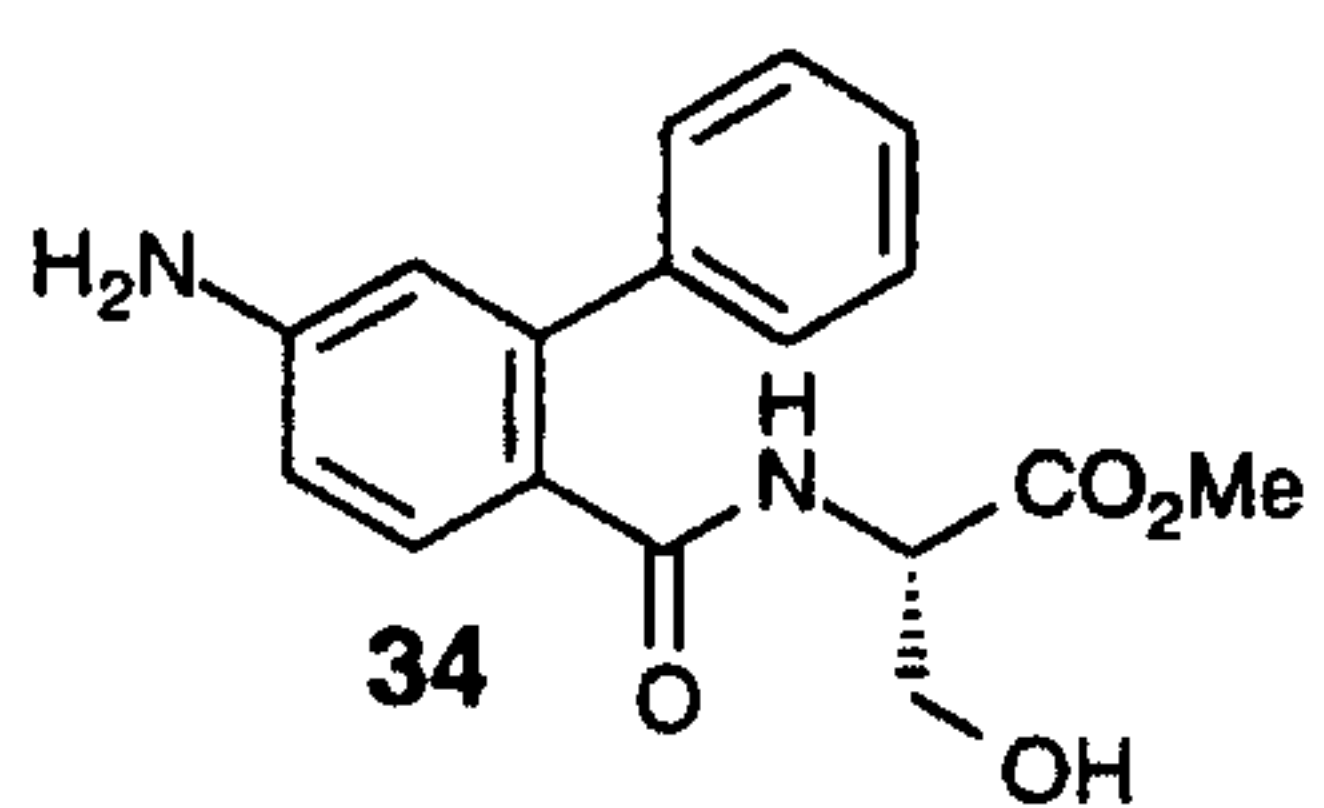
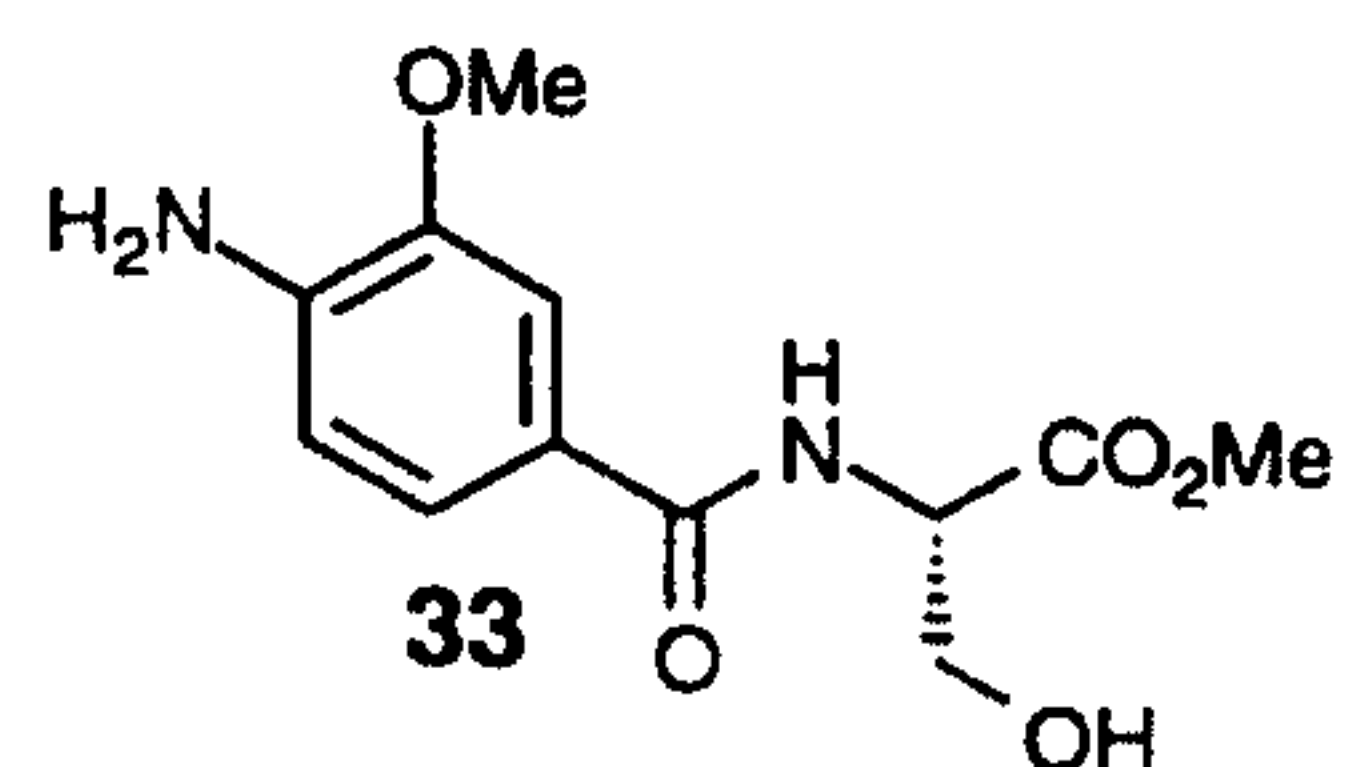
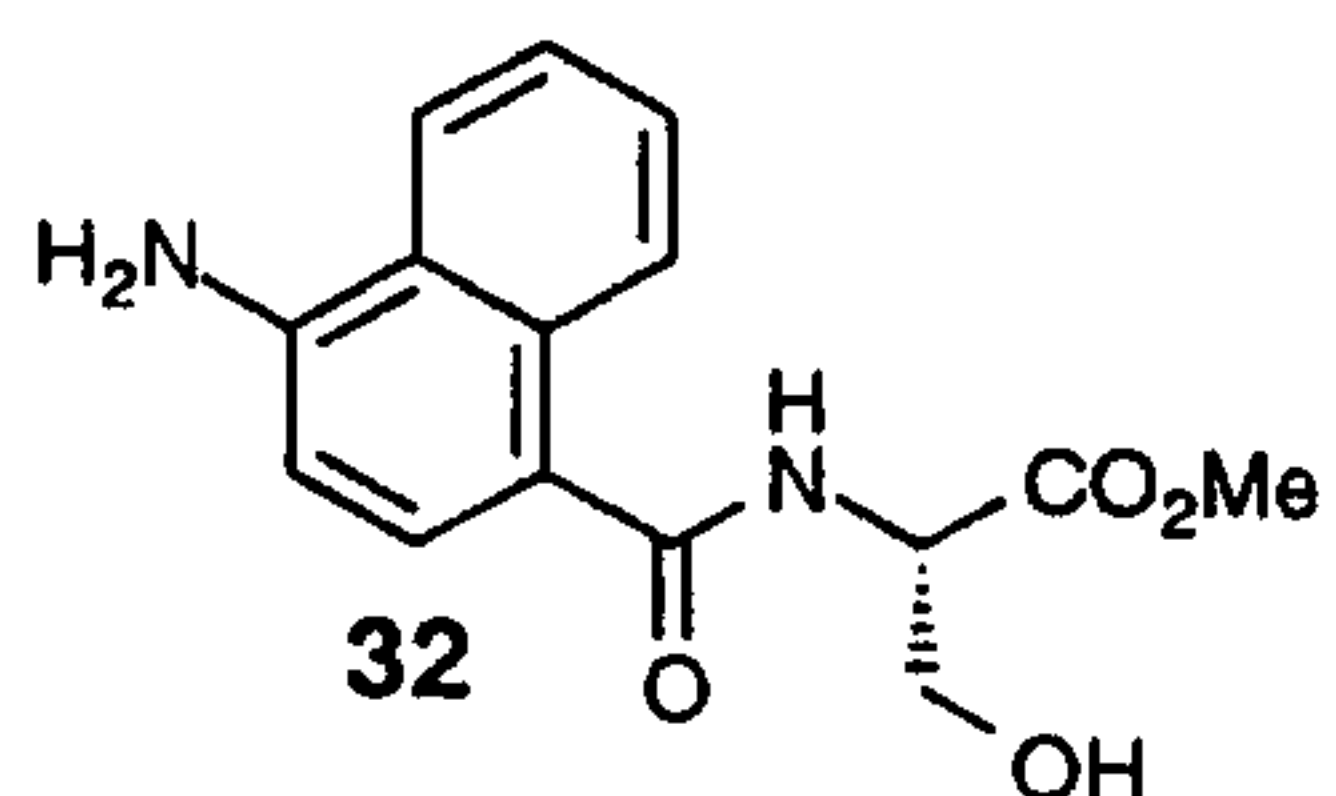
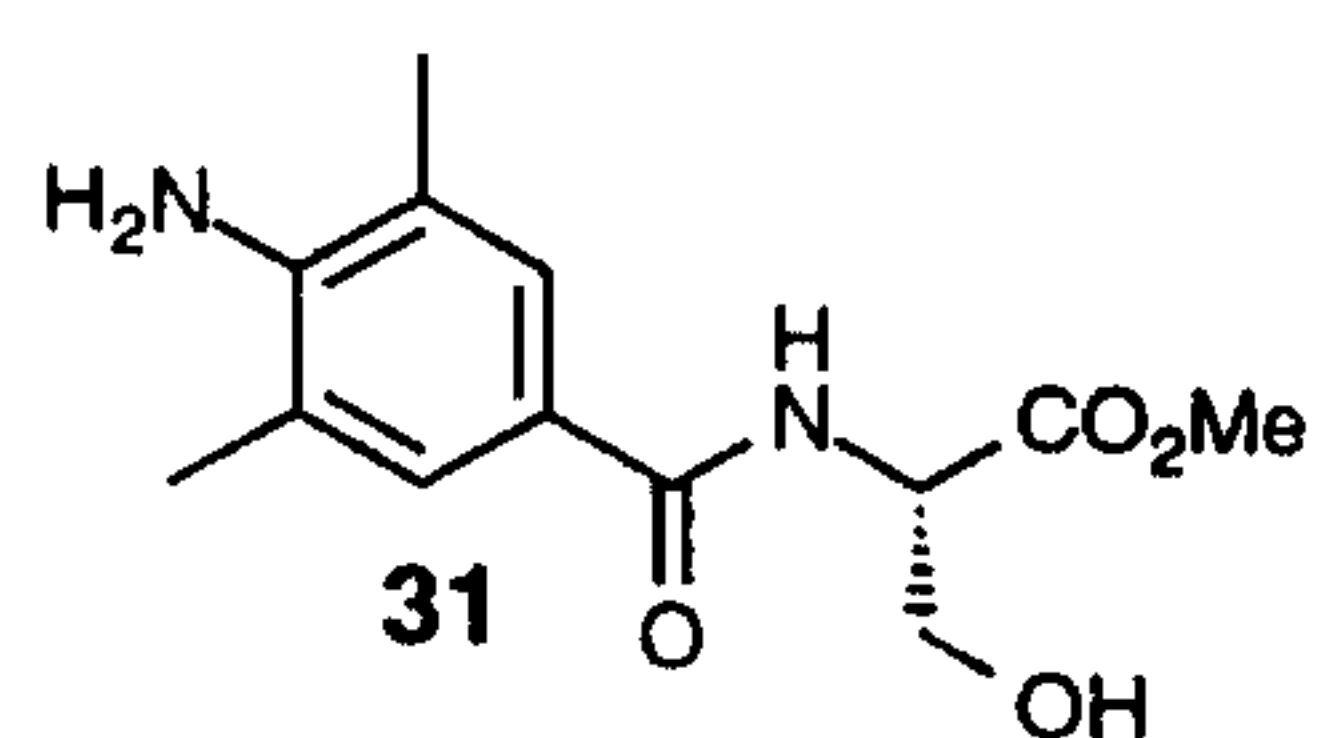
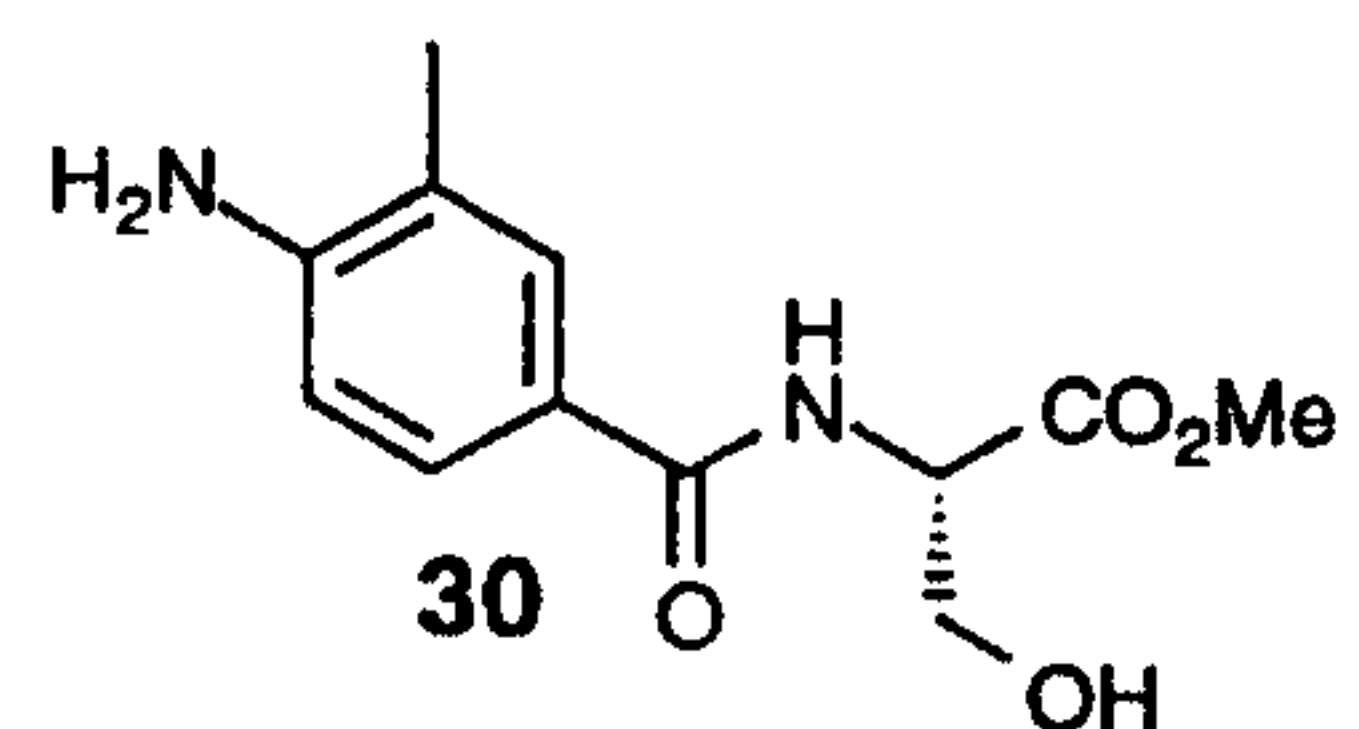
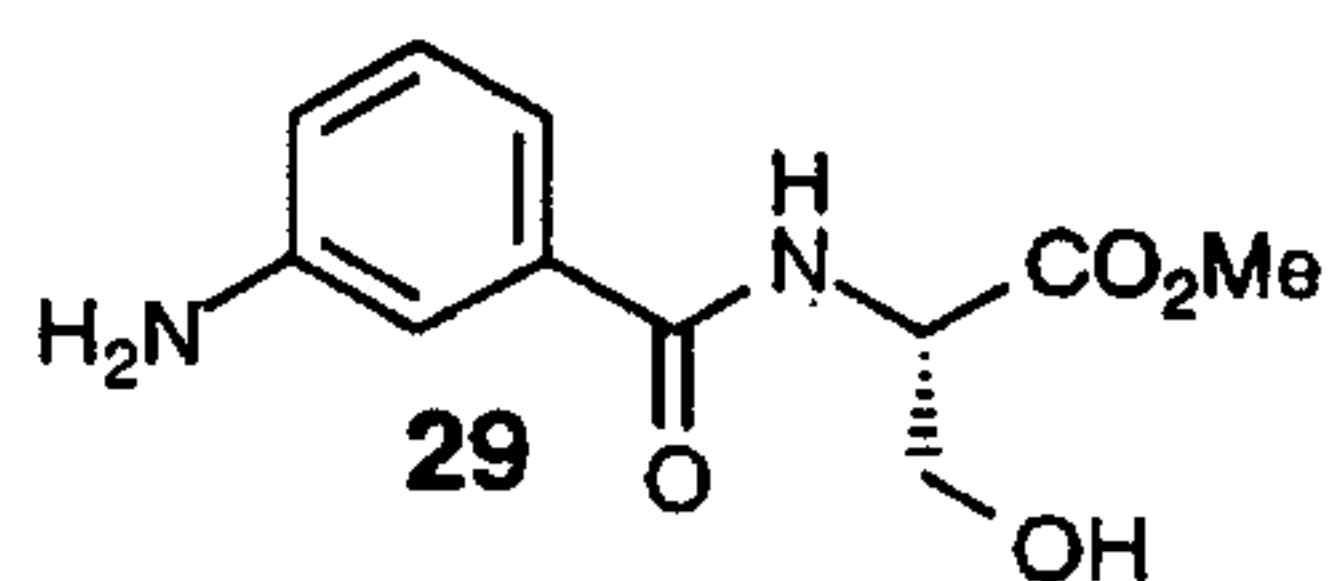
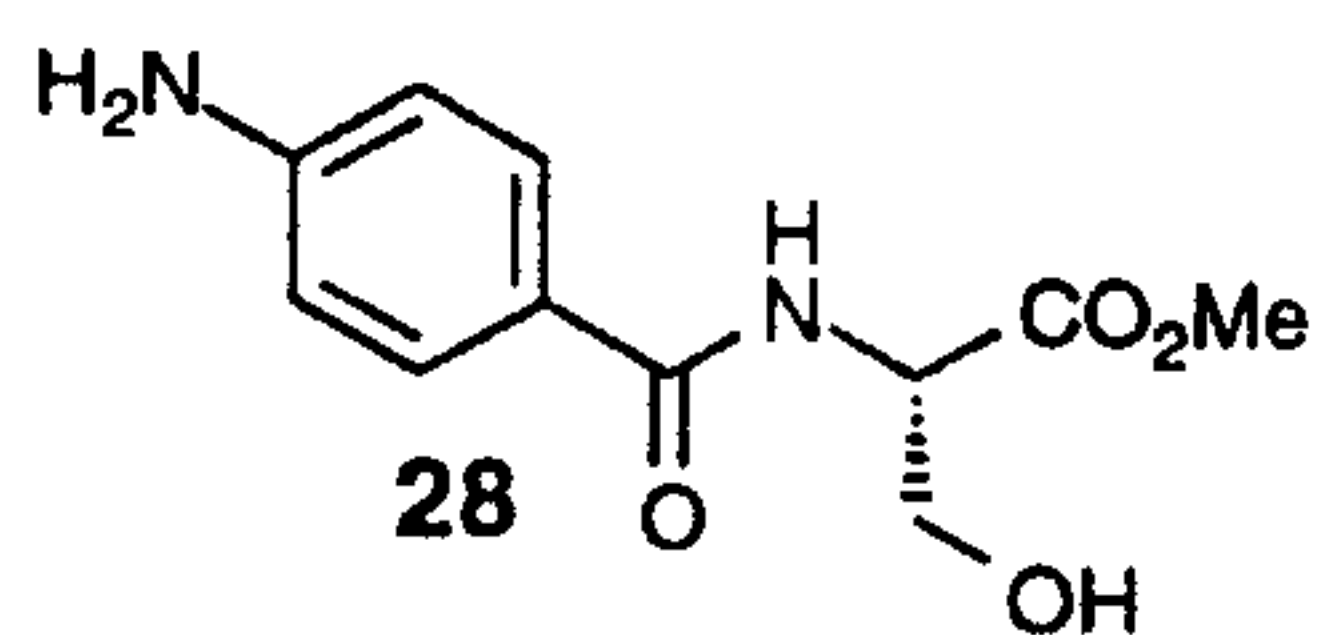
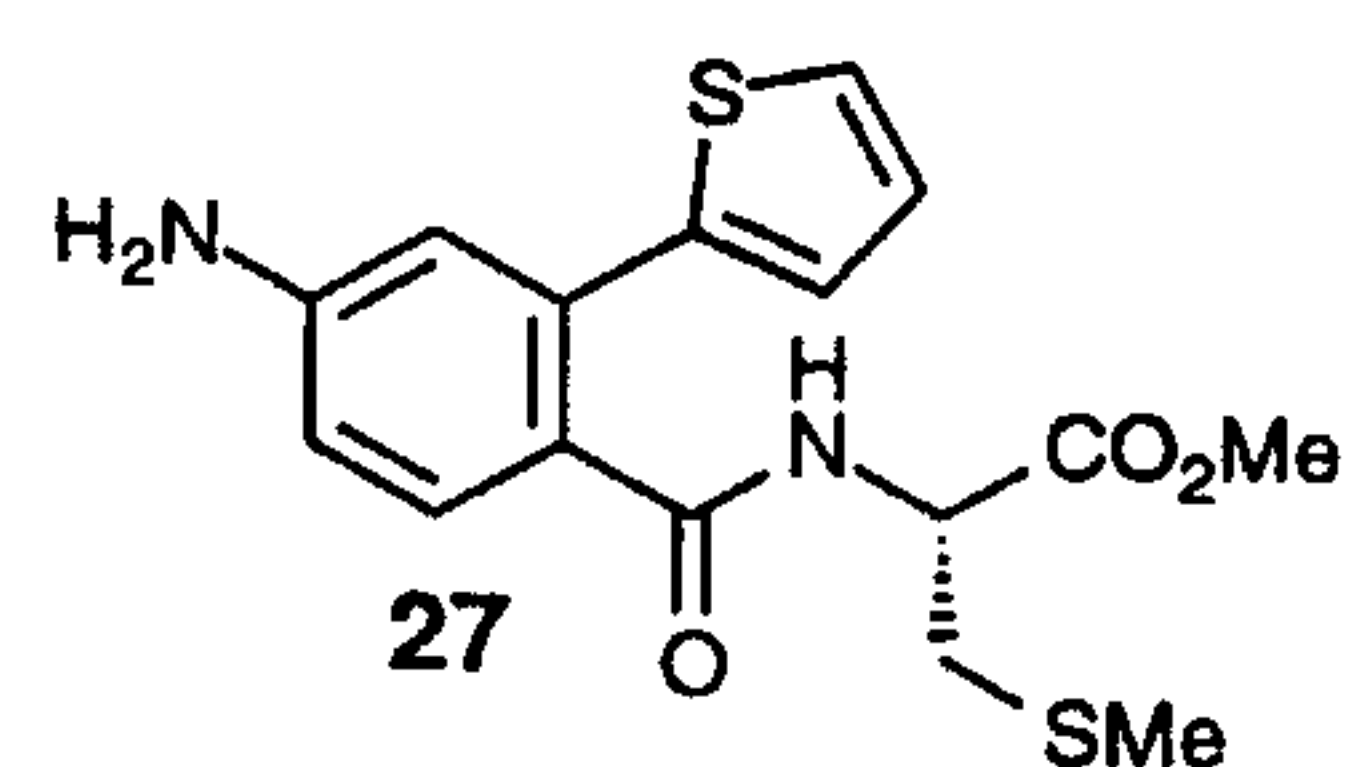
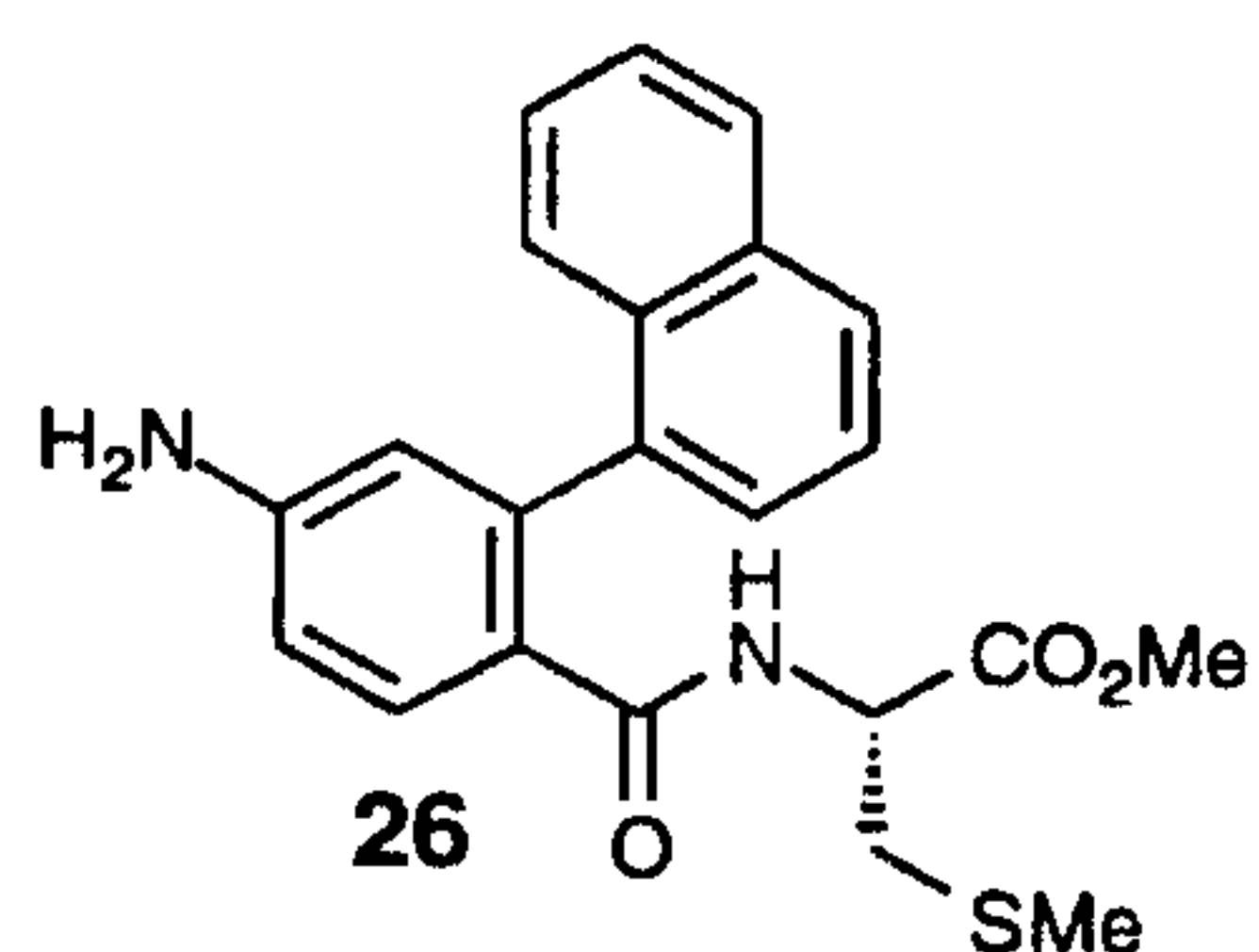
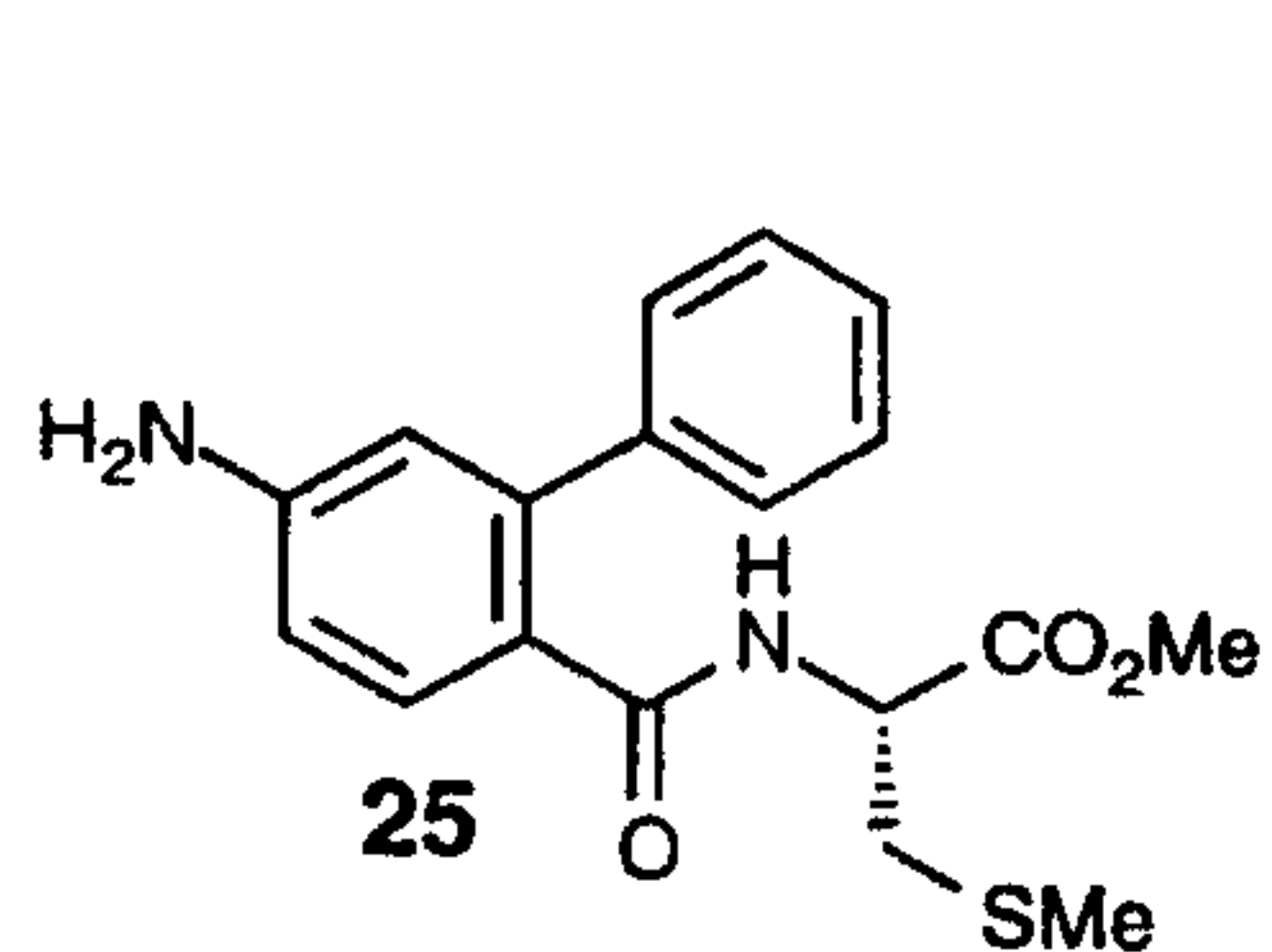
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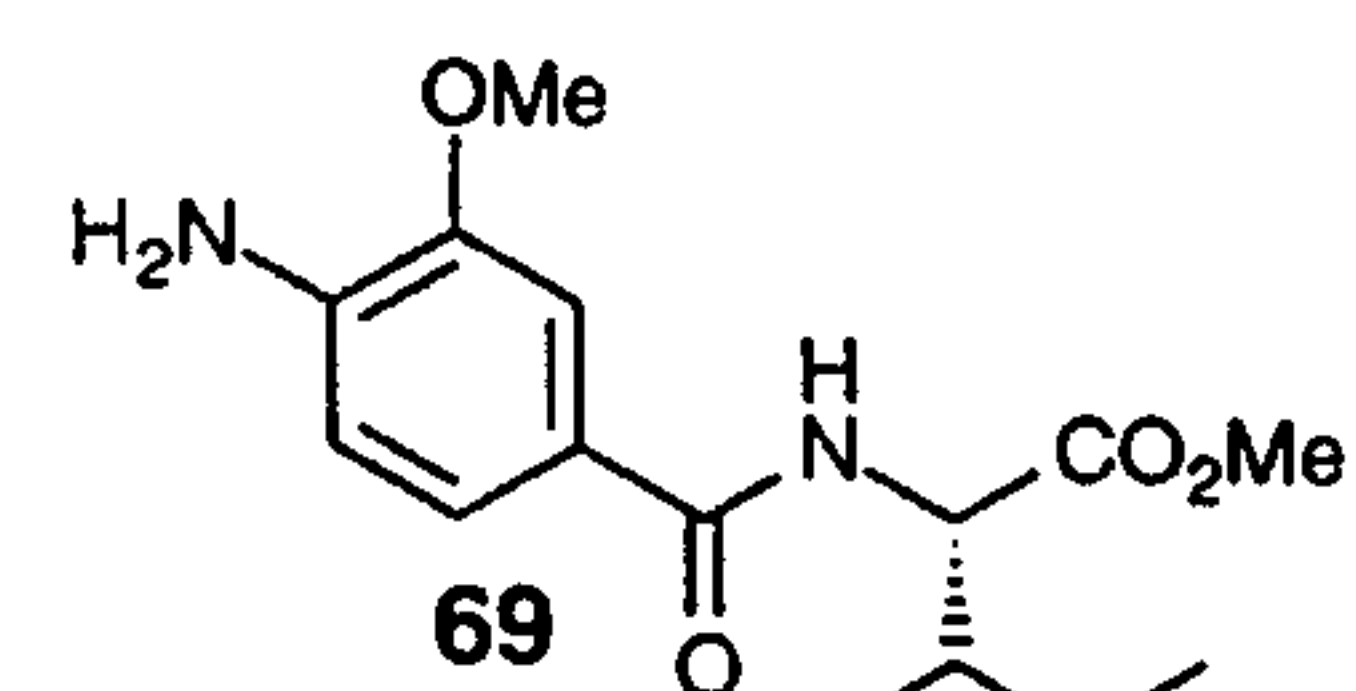
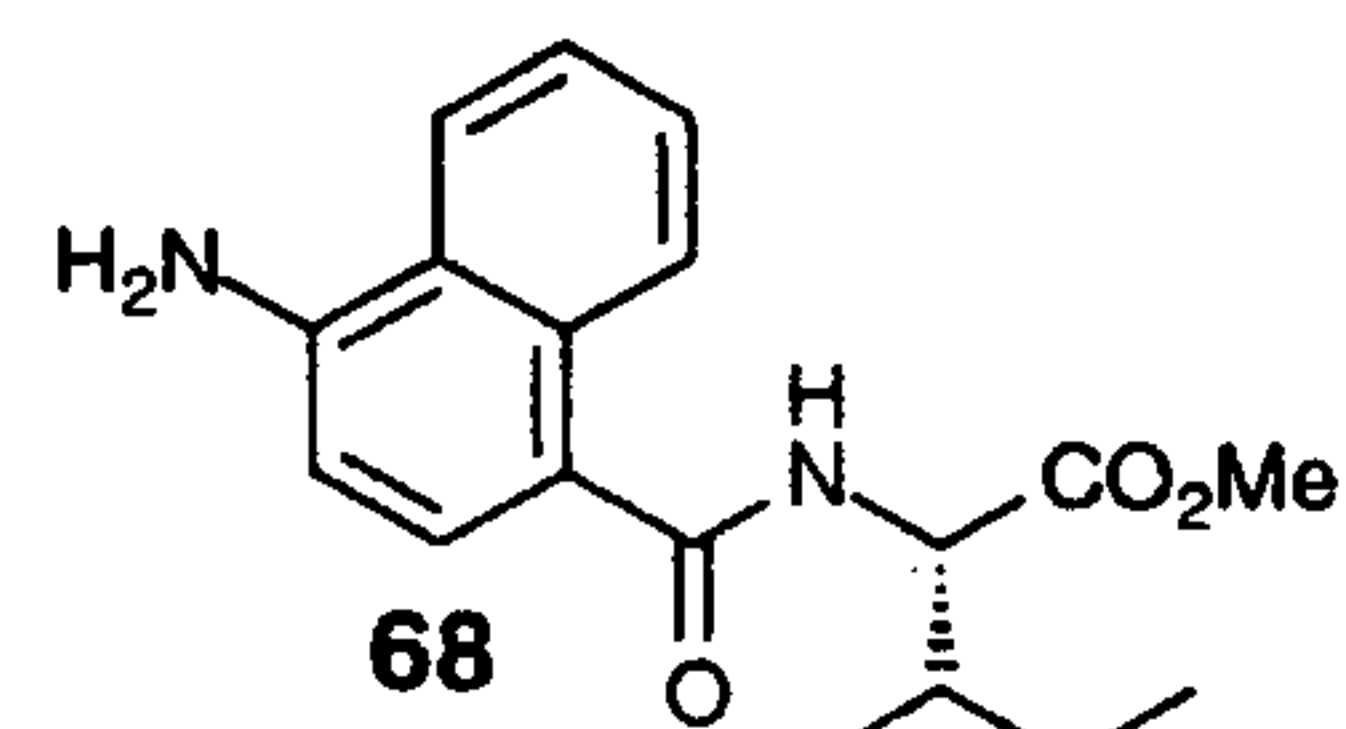
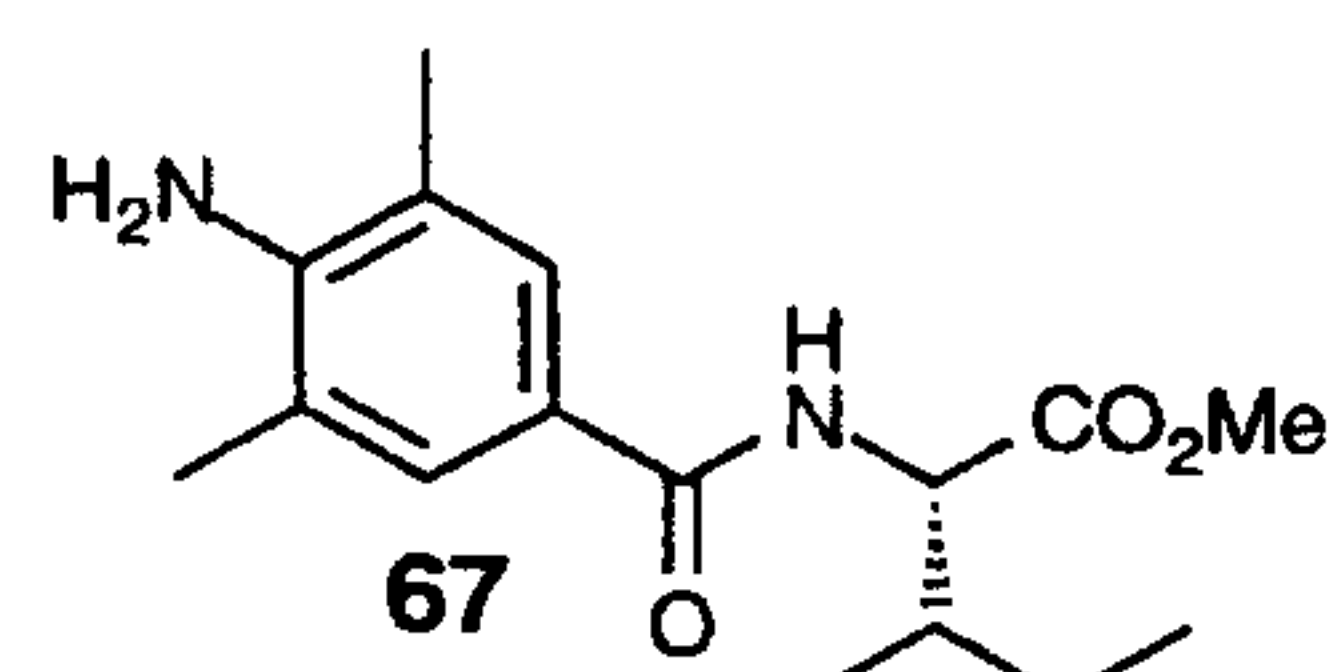
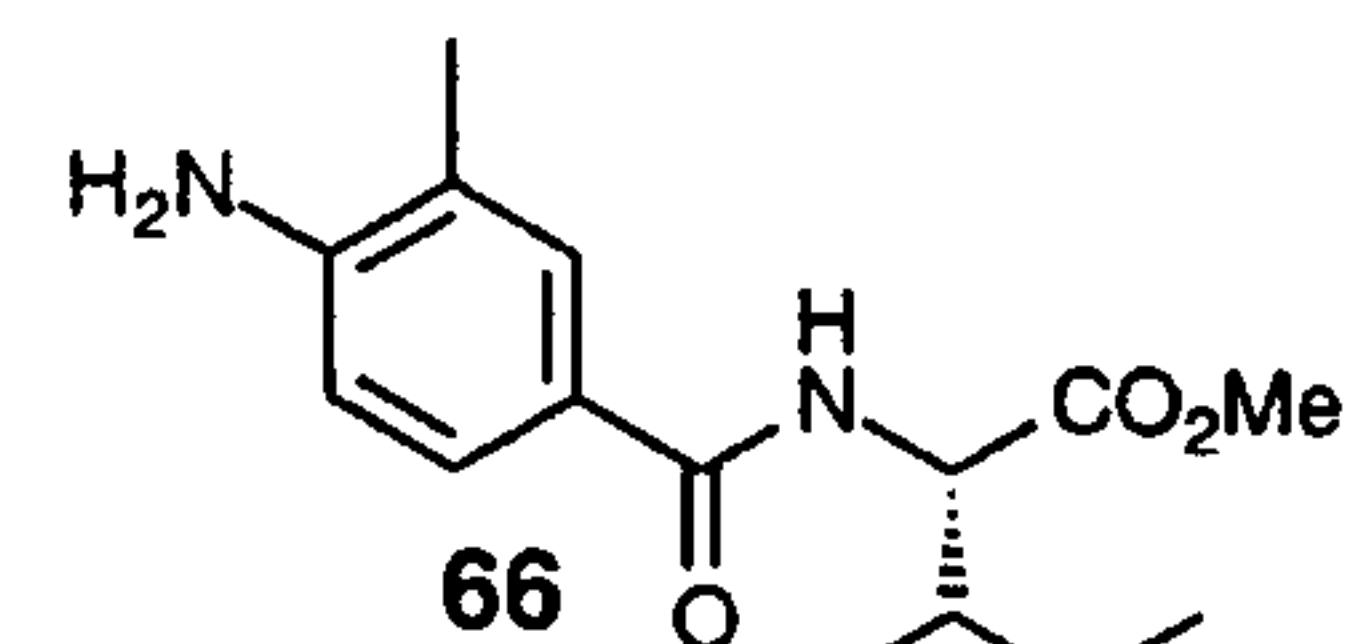
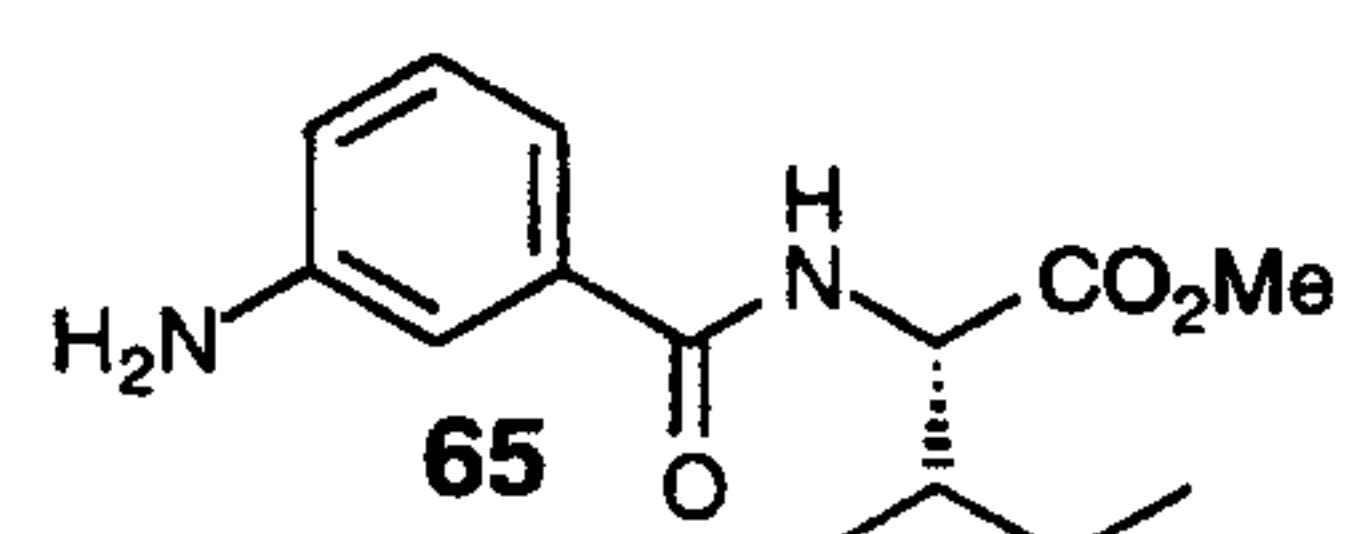
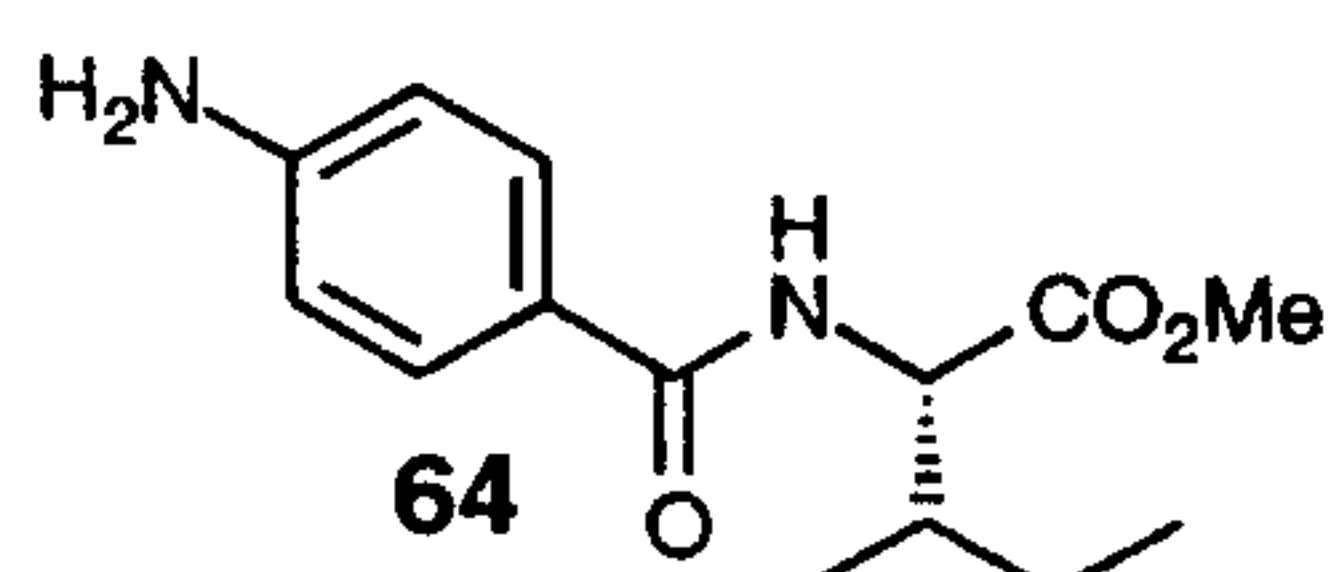
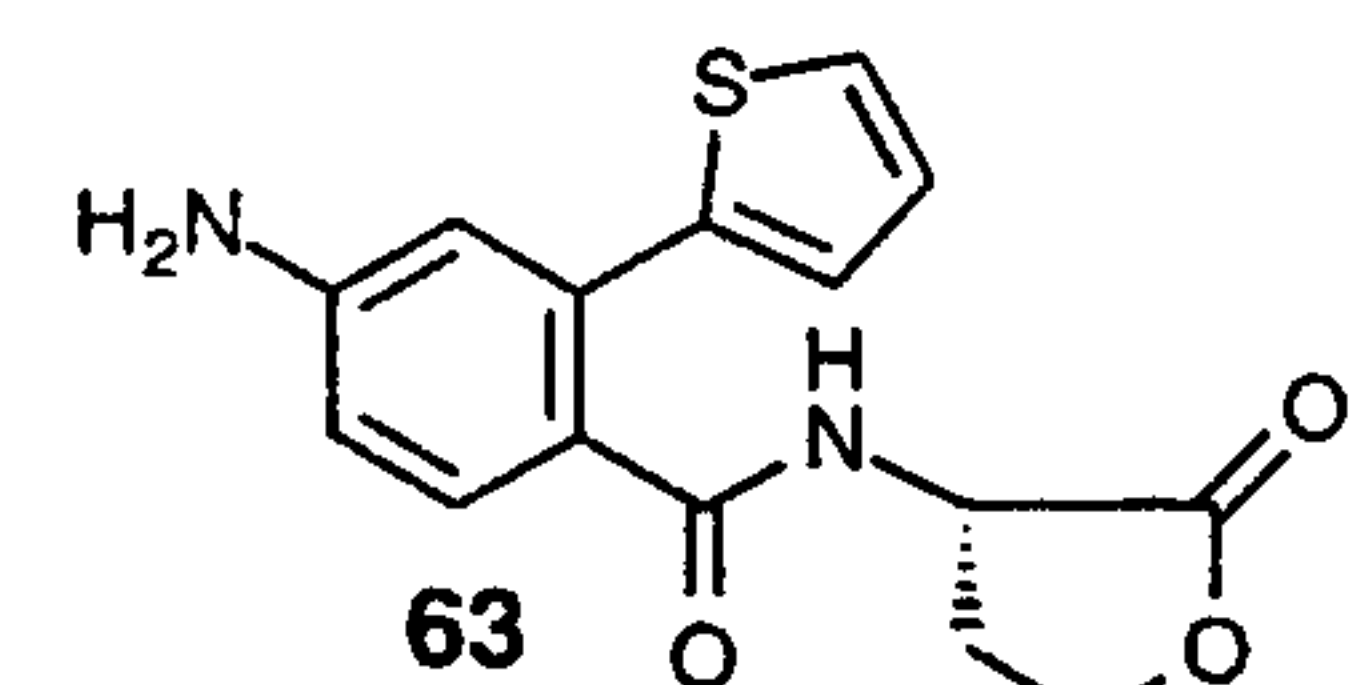
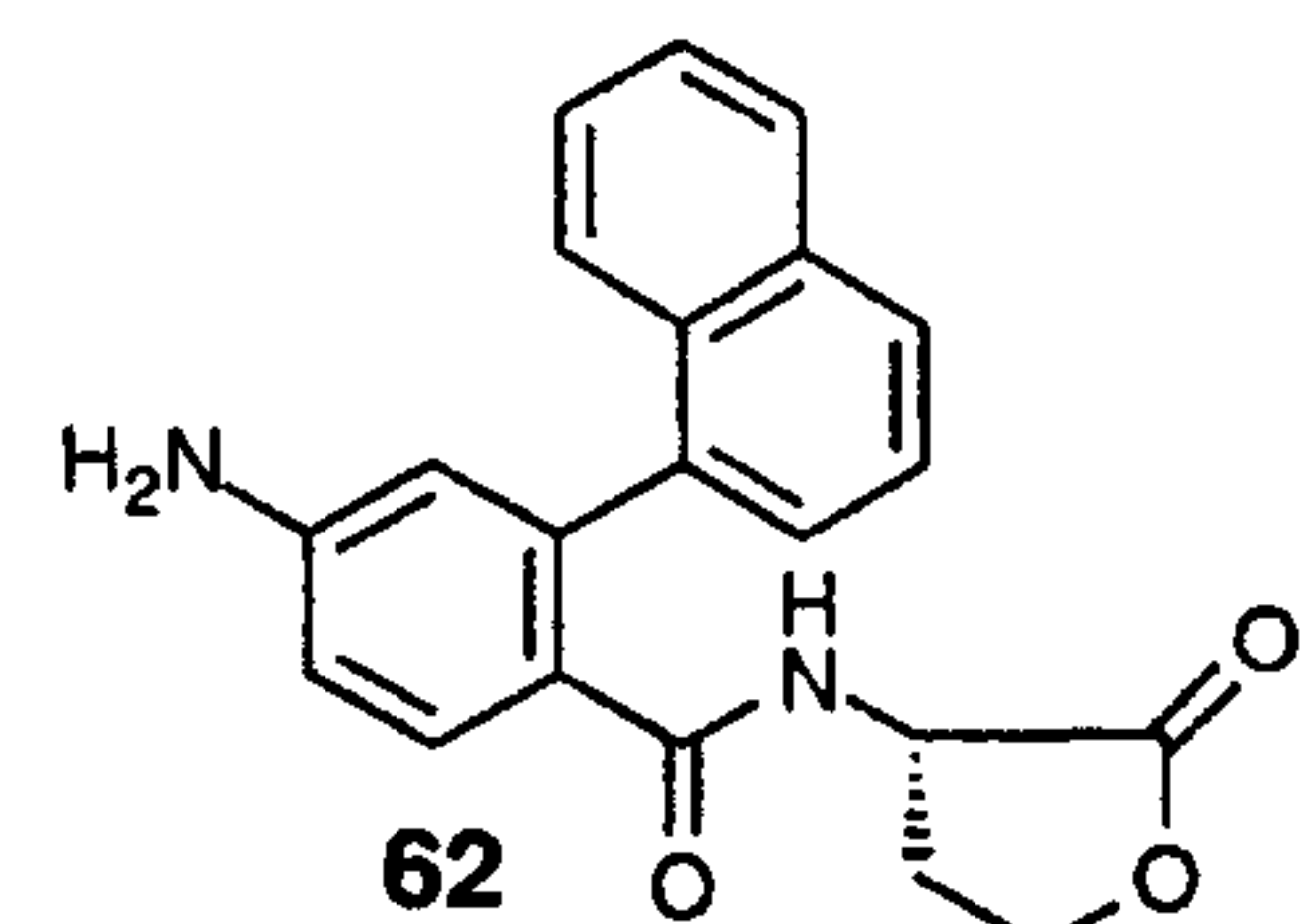
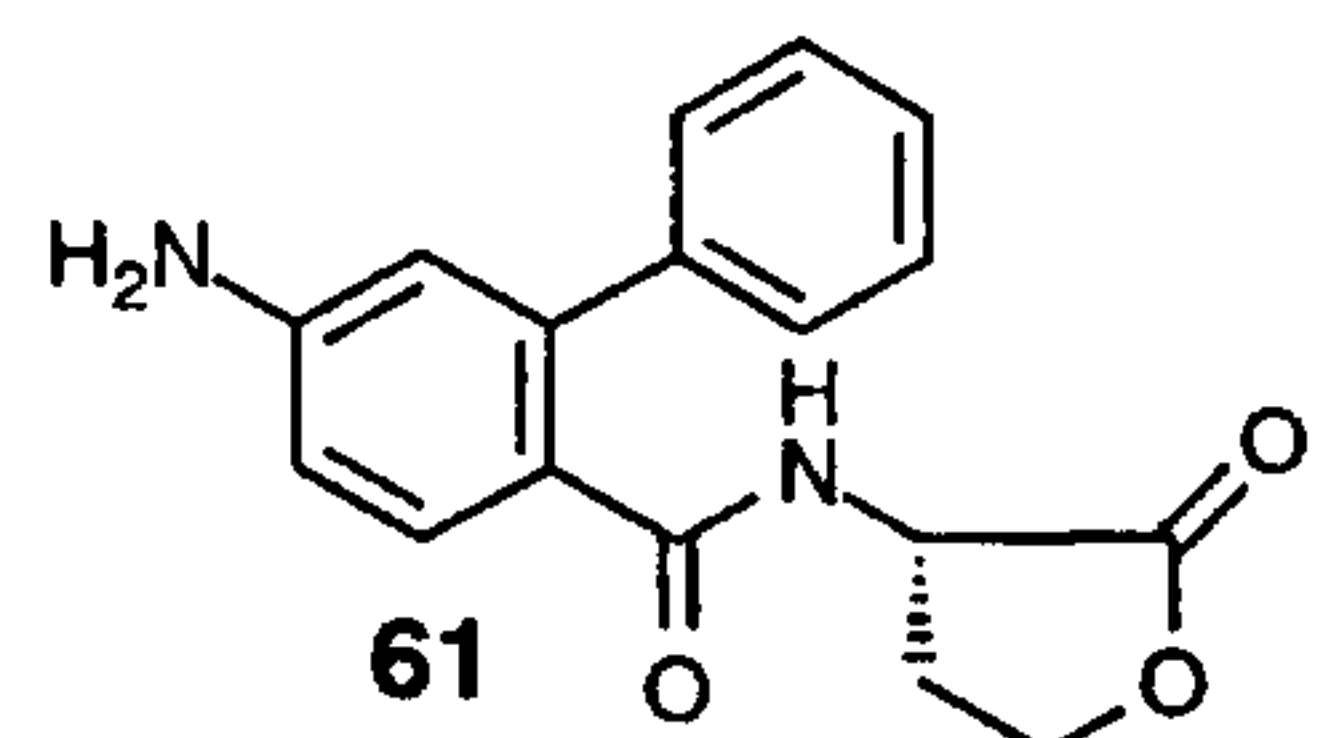
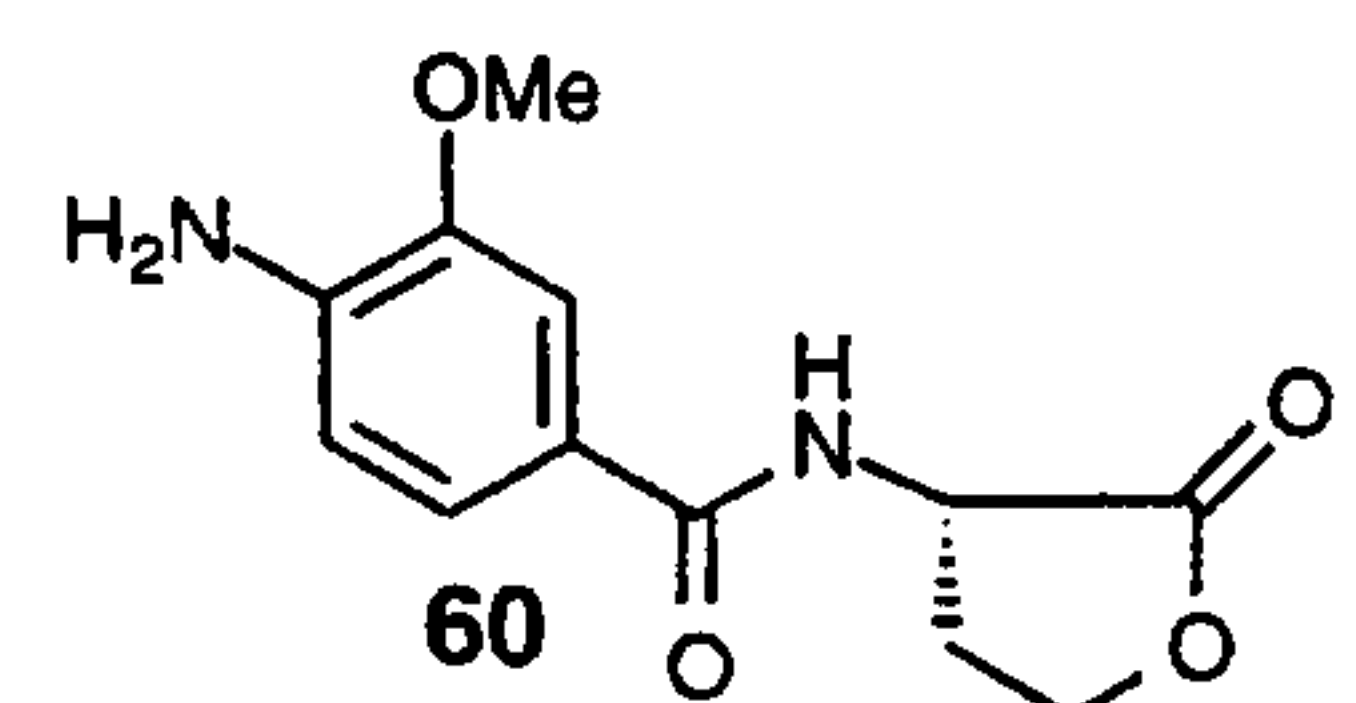
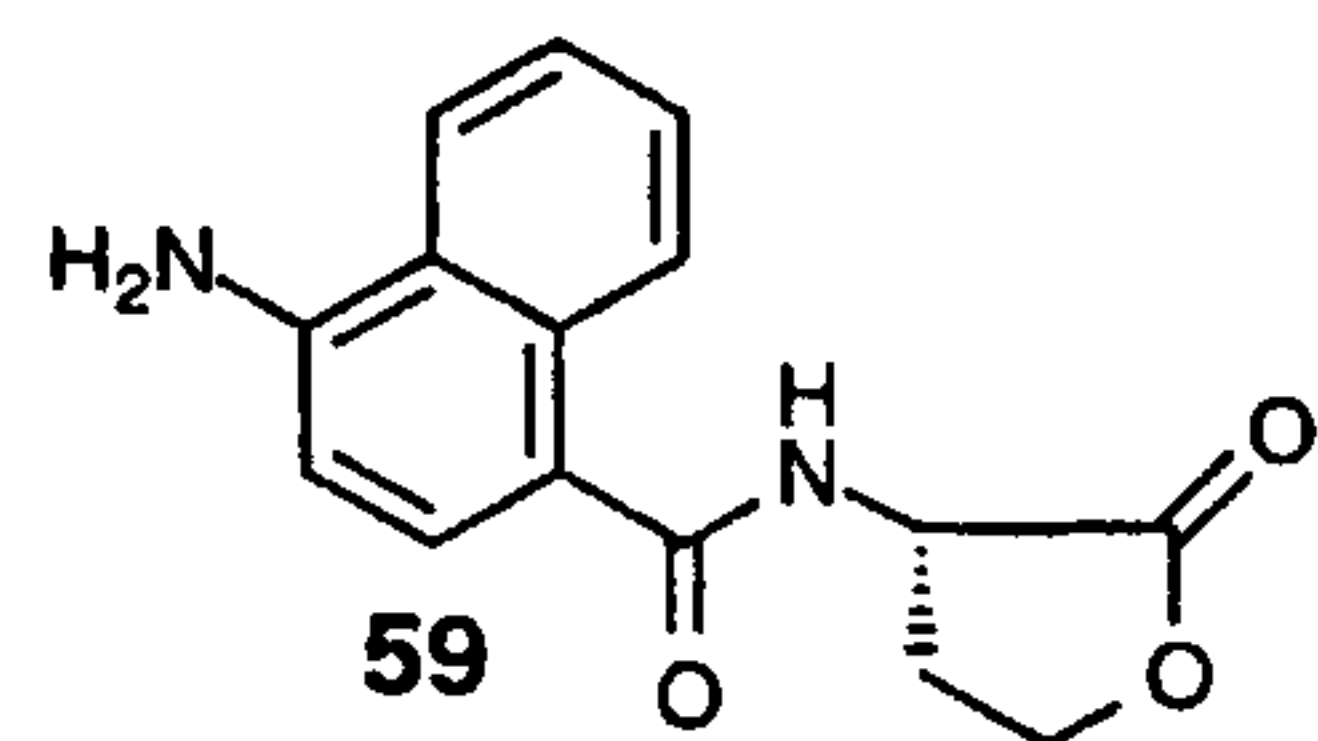
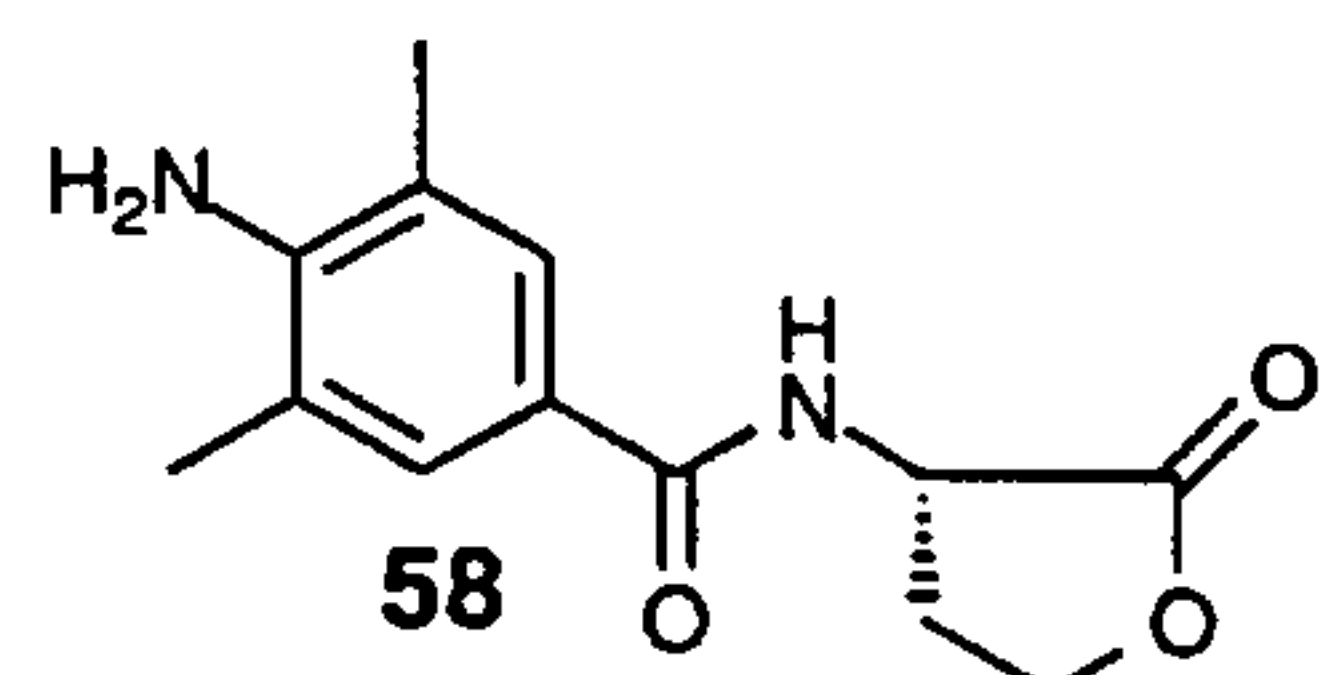
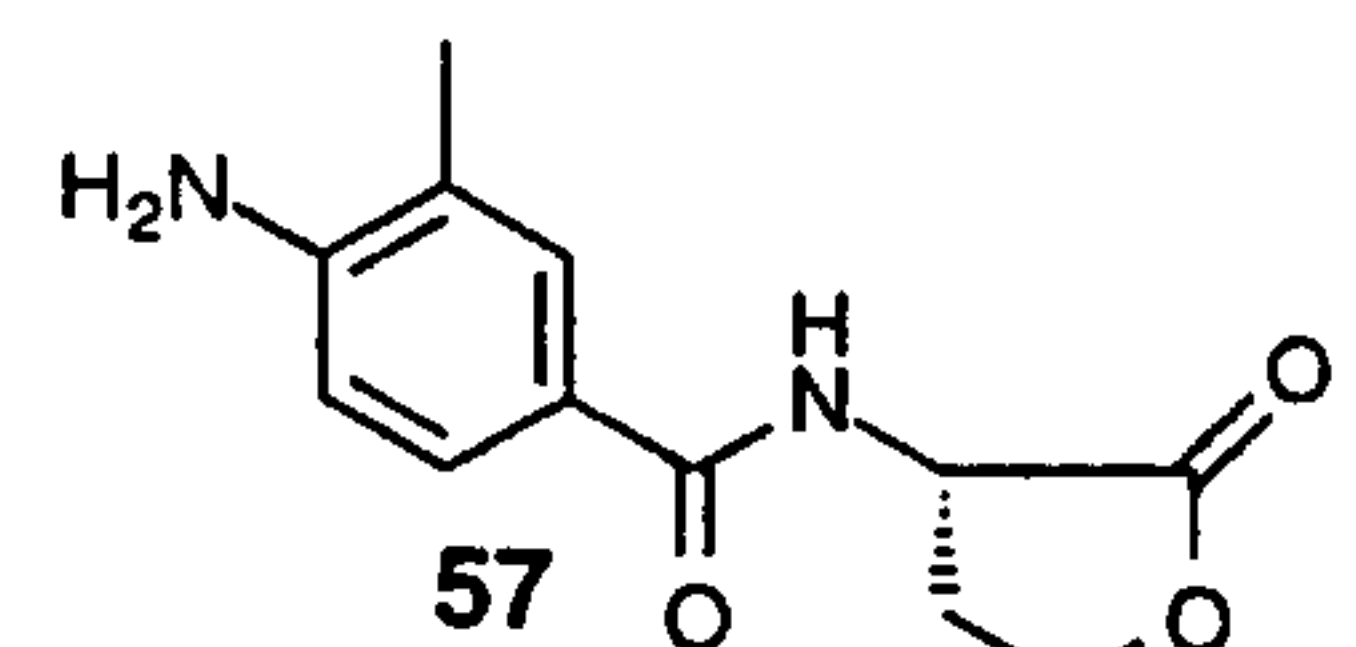
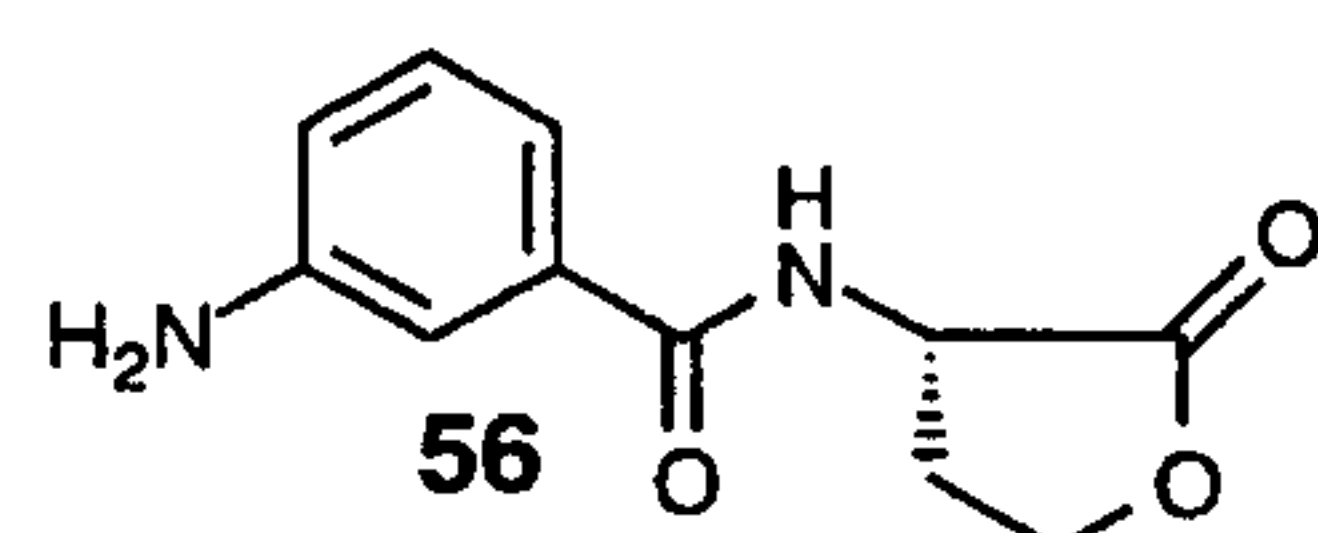
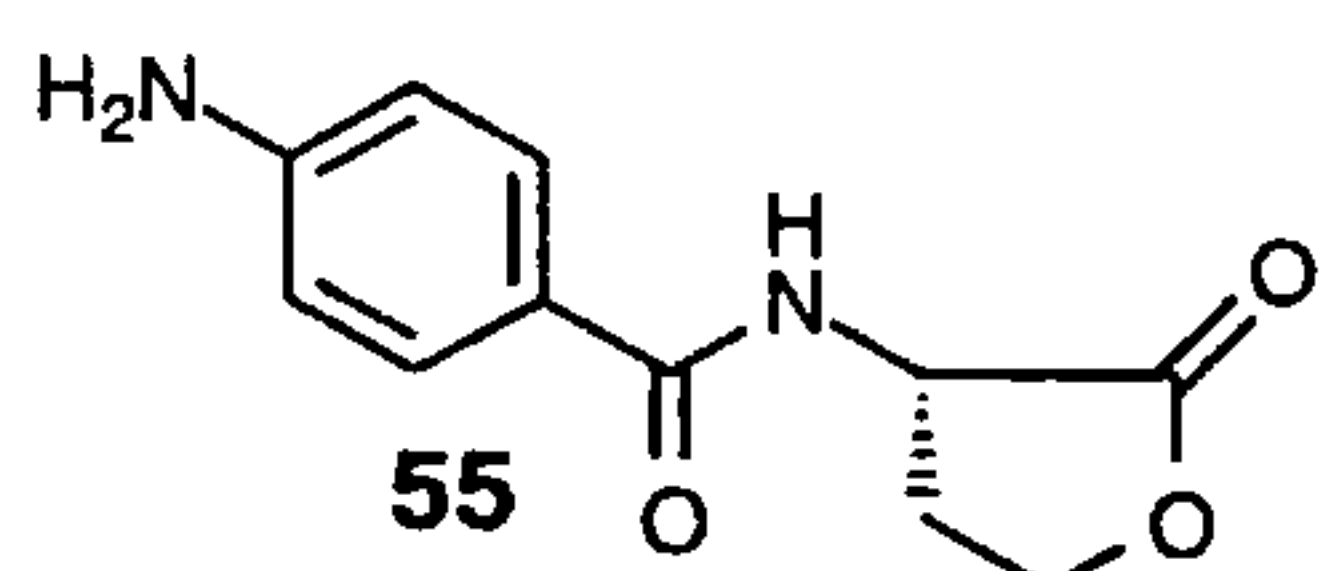
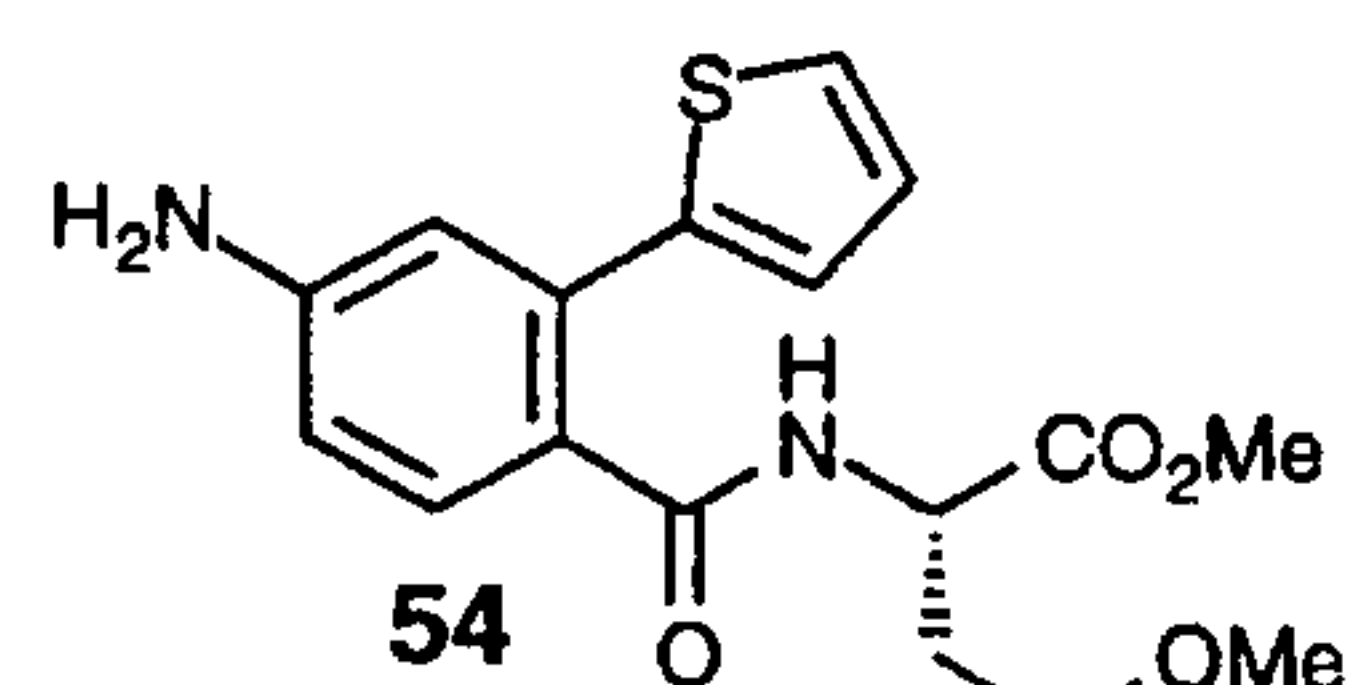
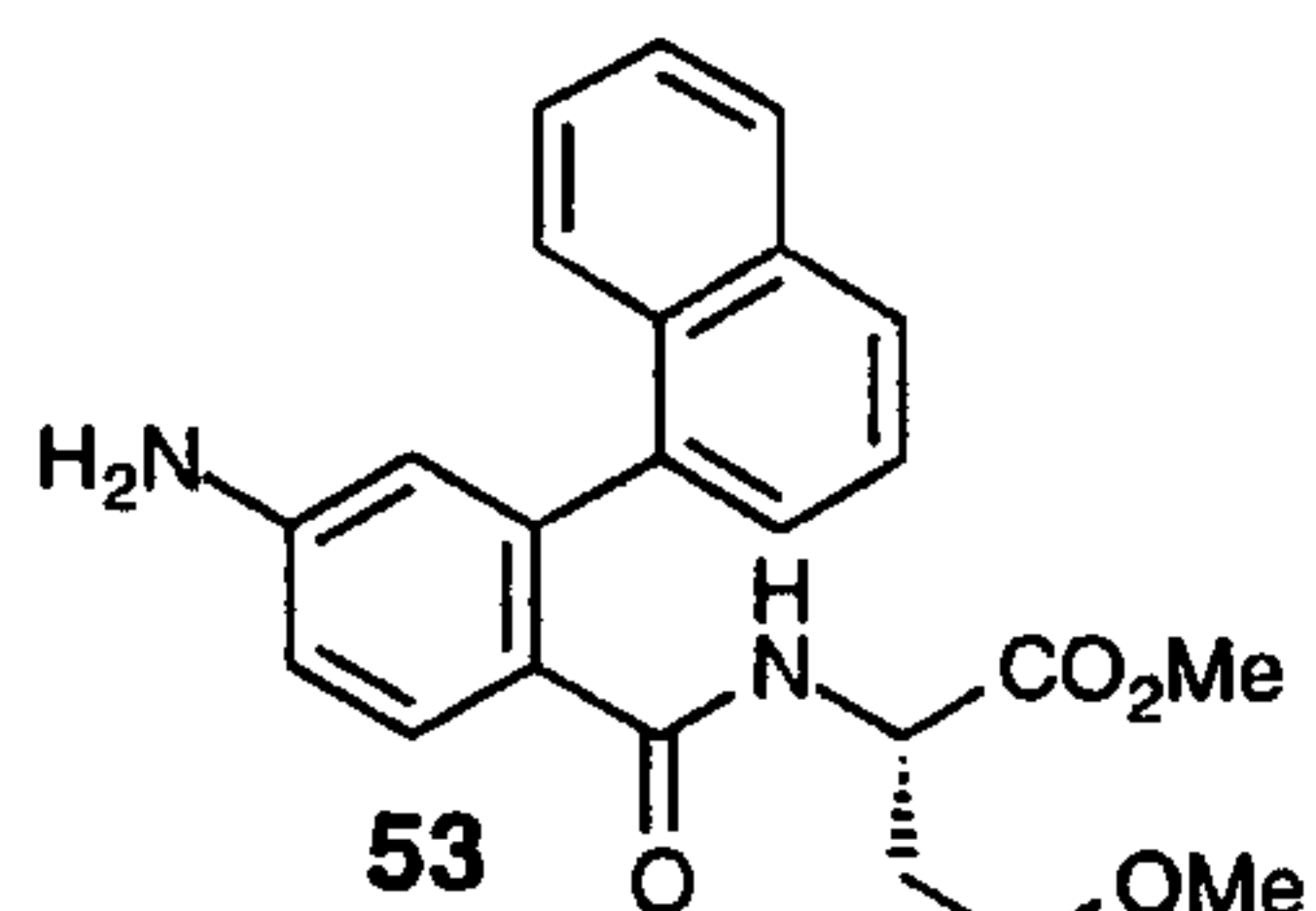
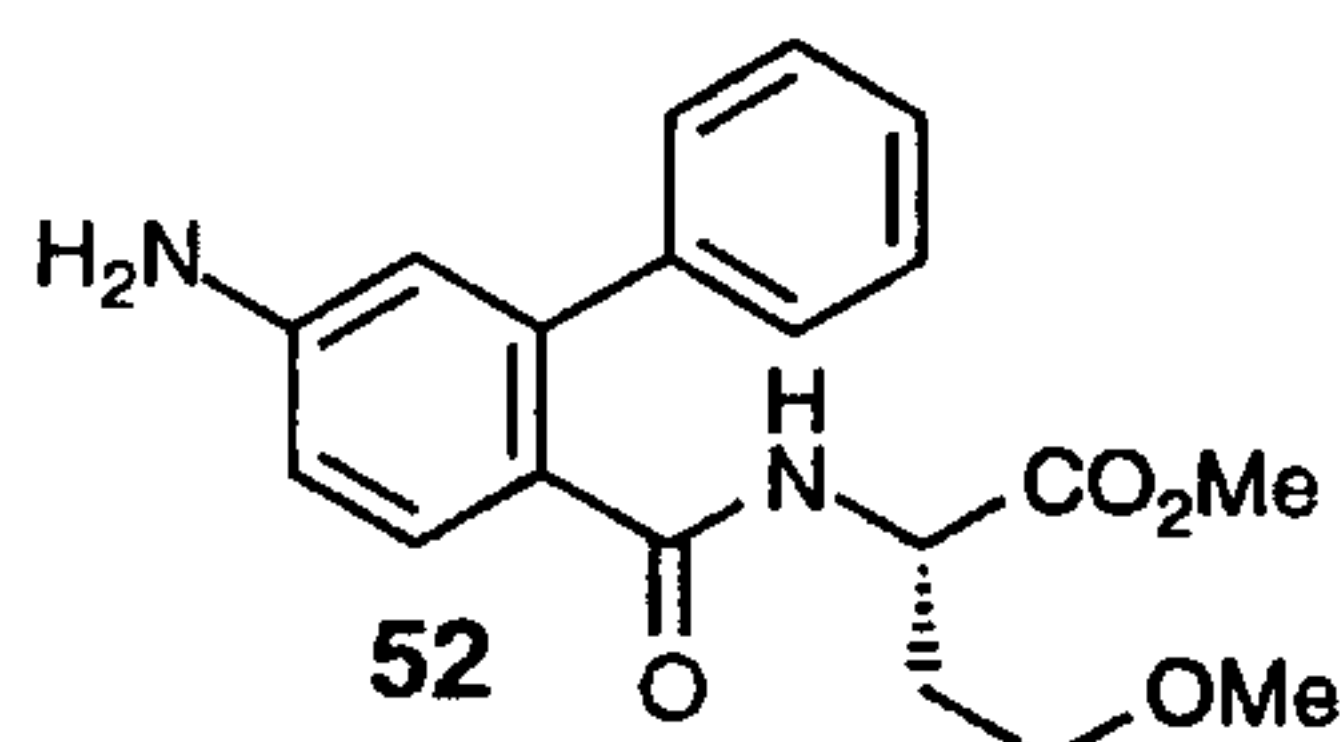
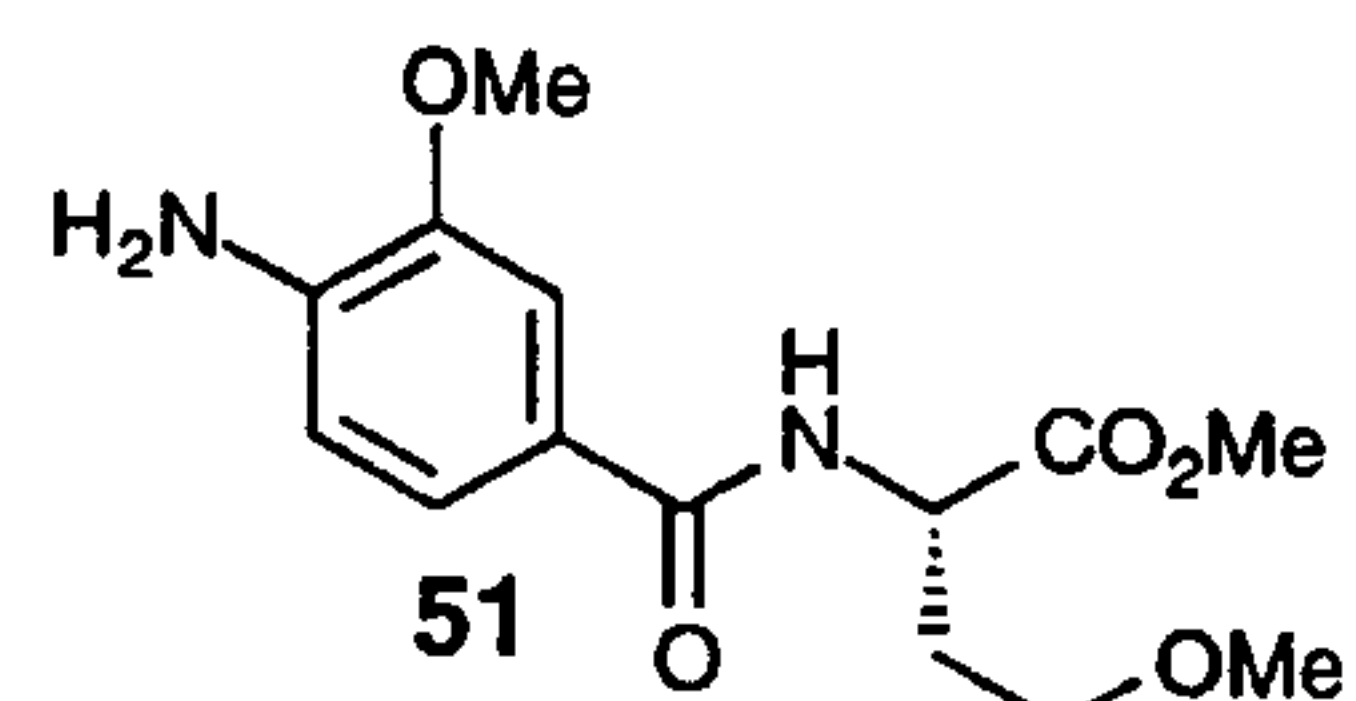
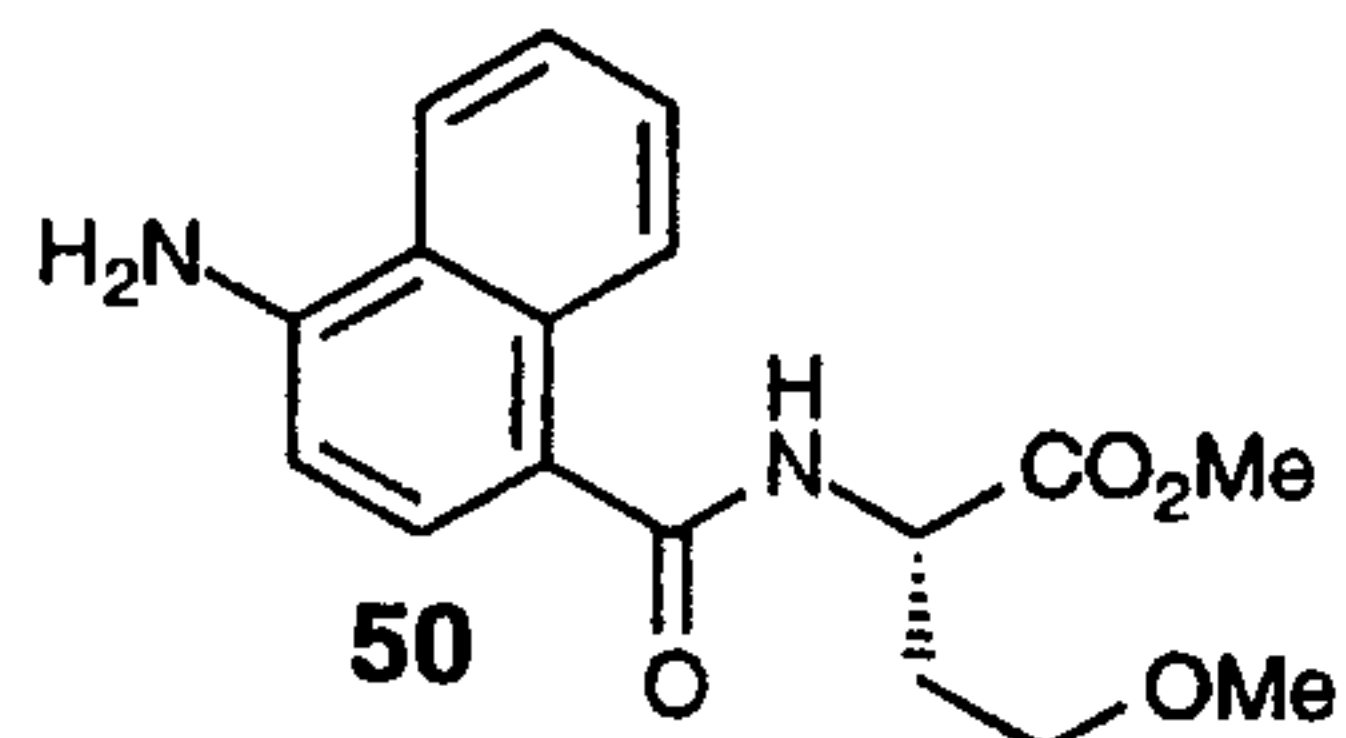
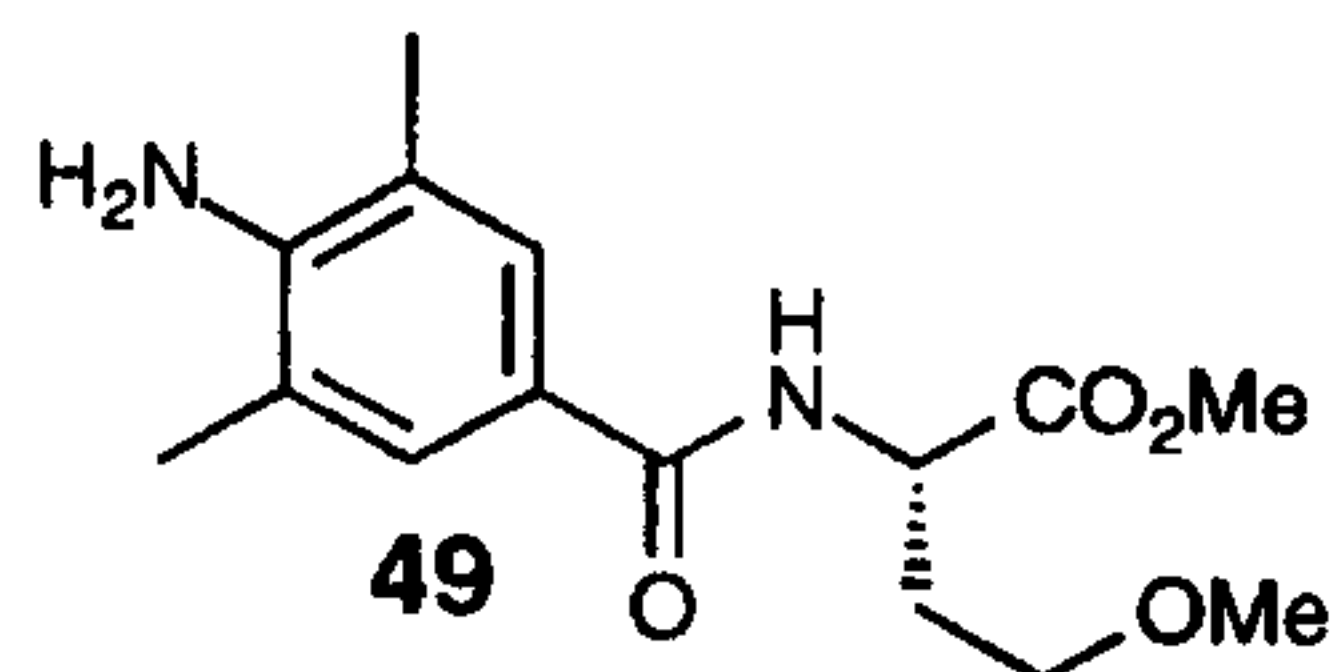
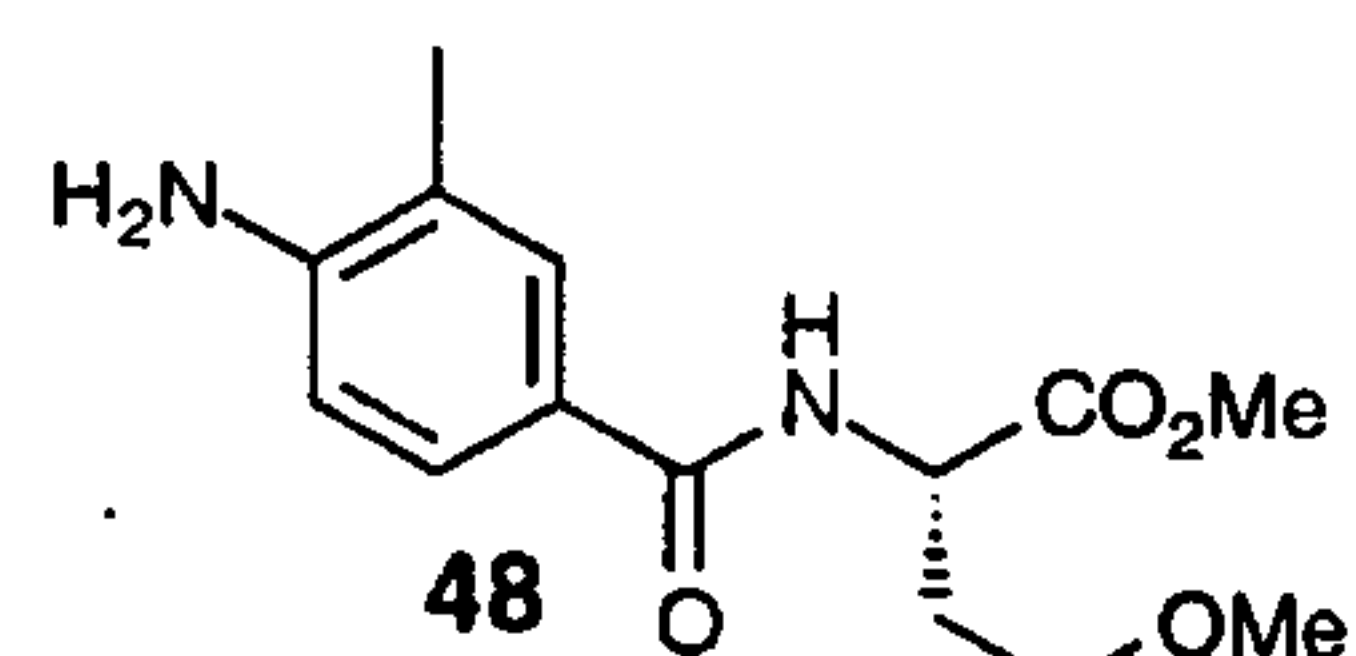
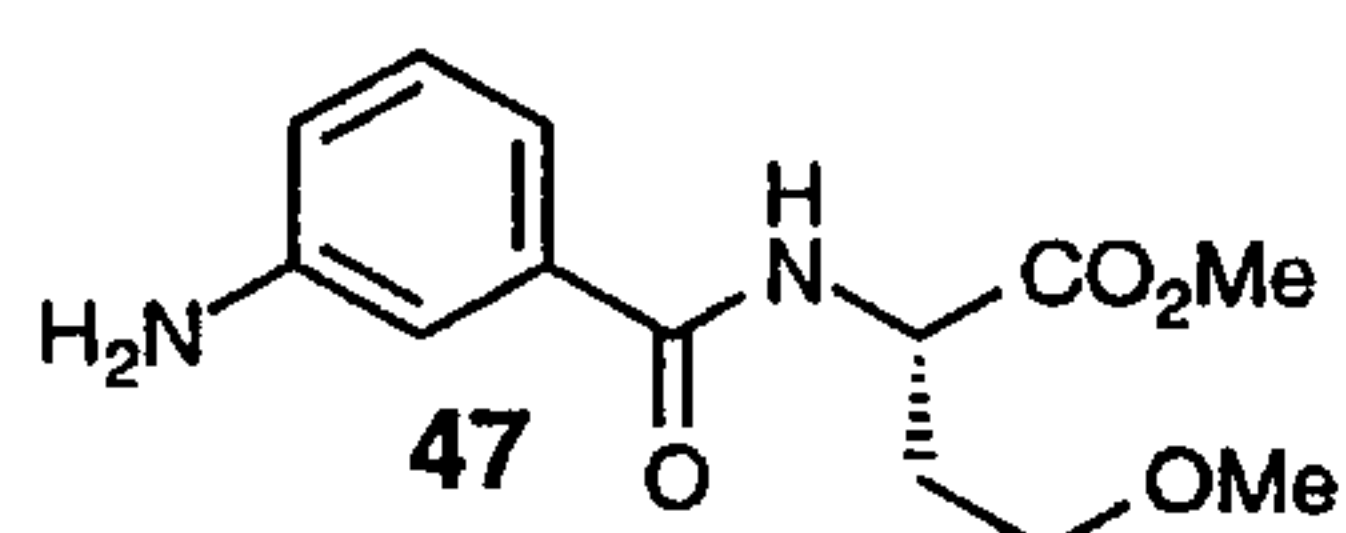
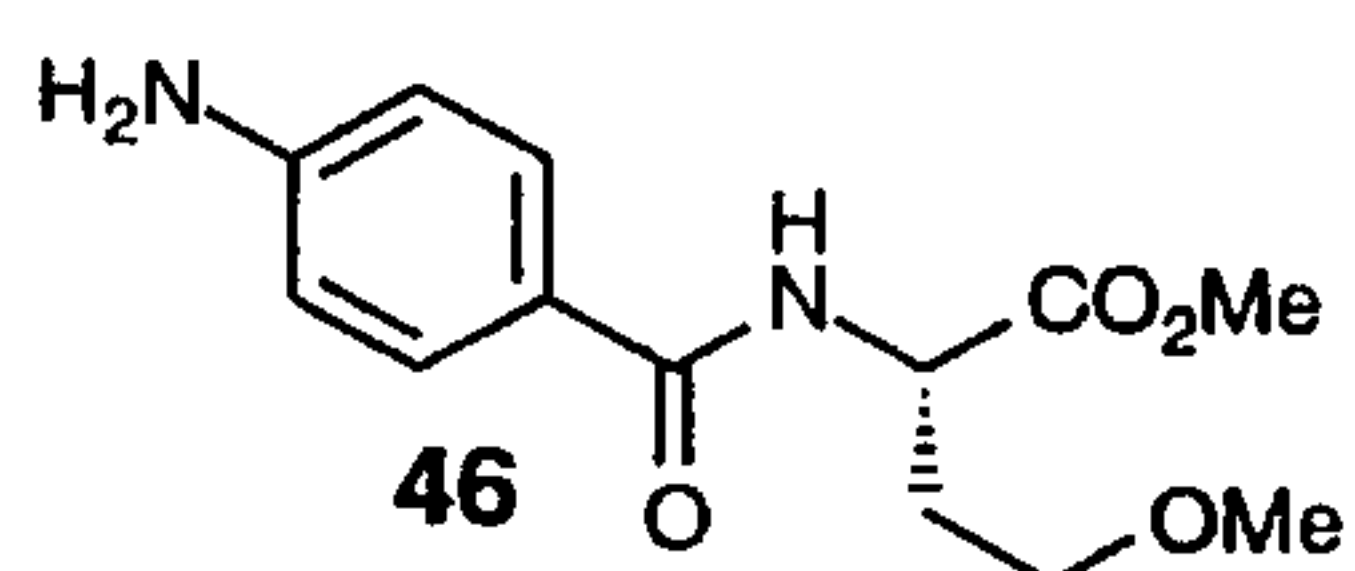
2520 Table 10. Amines of the type B-NH₂

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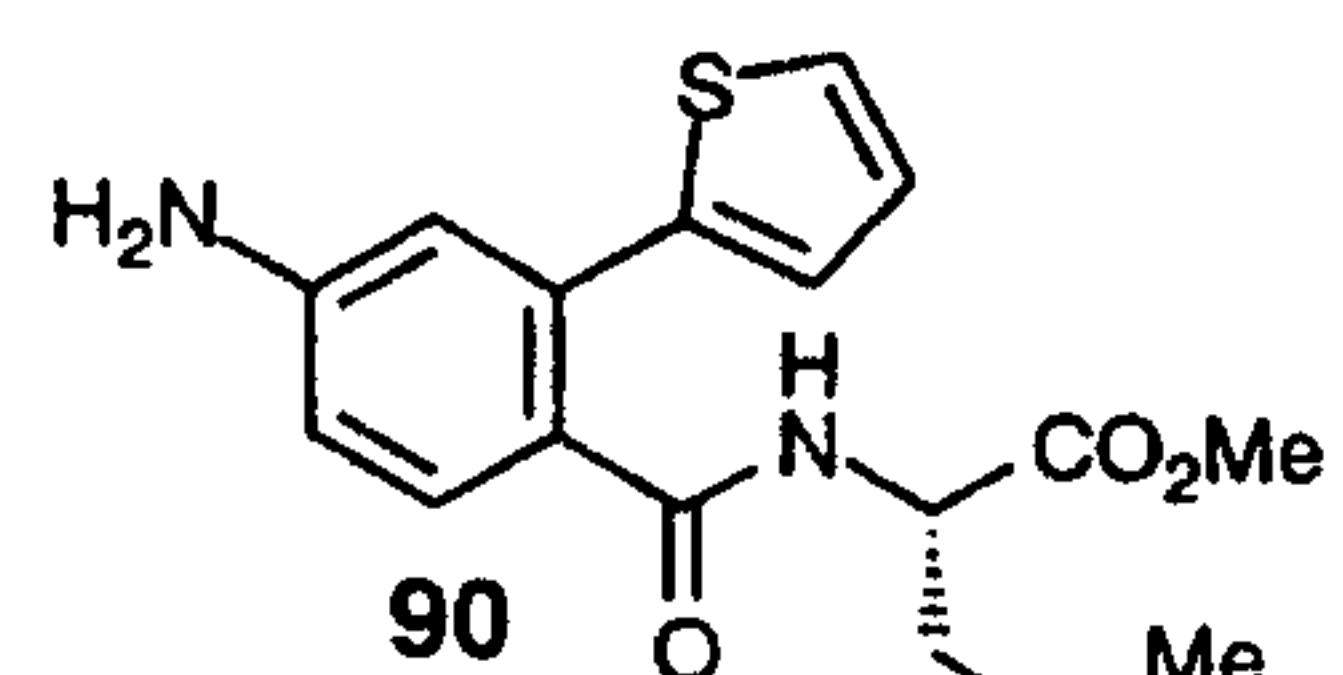
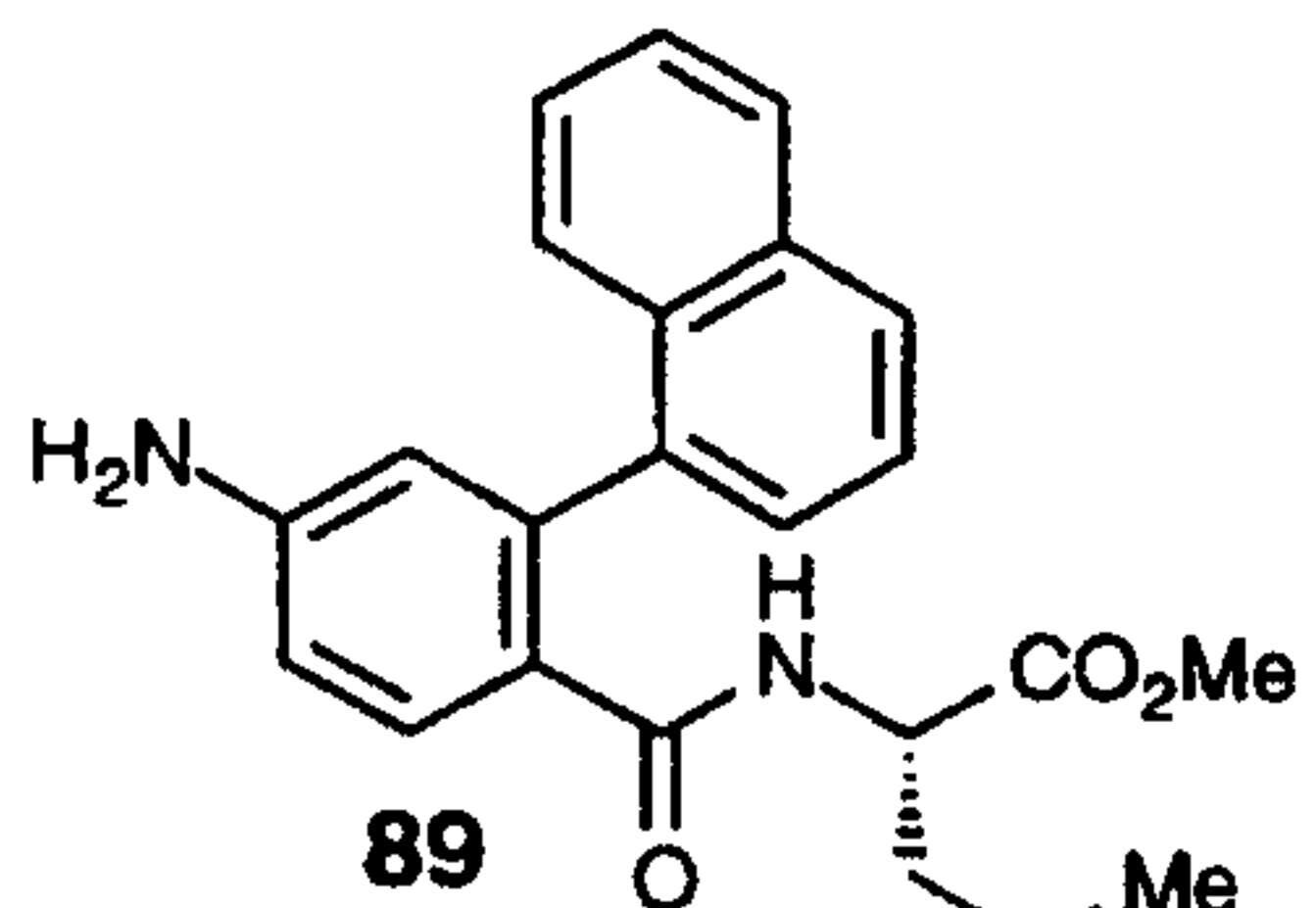
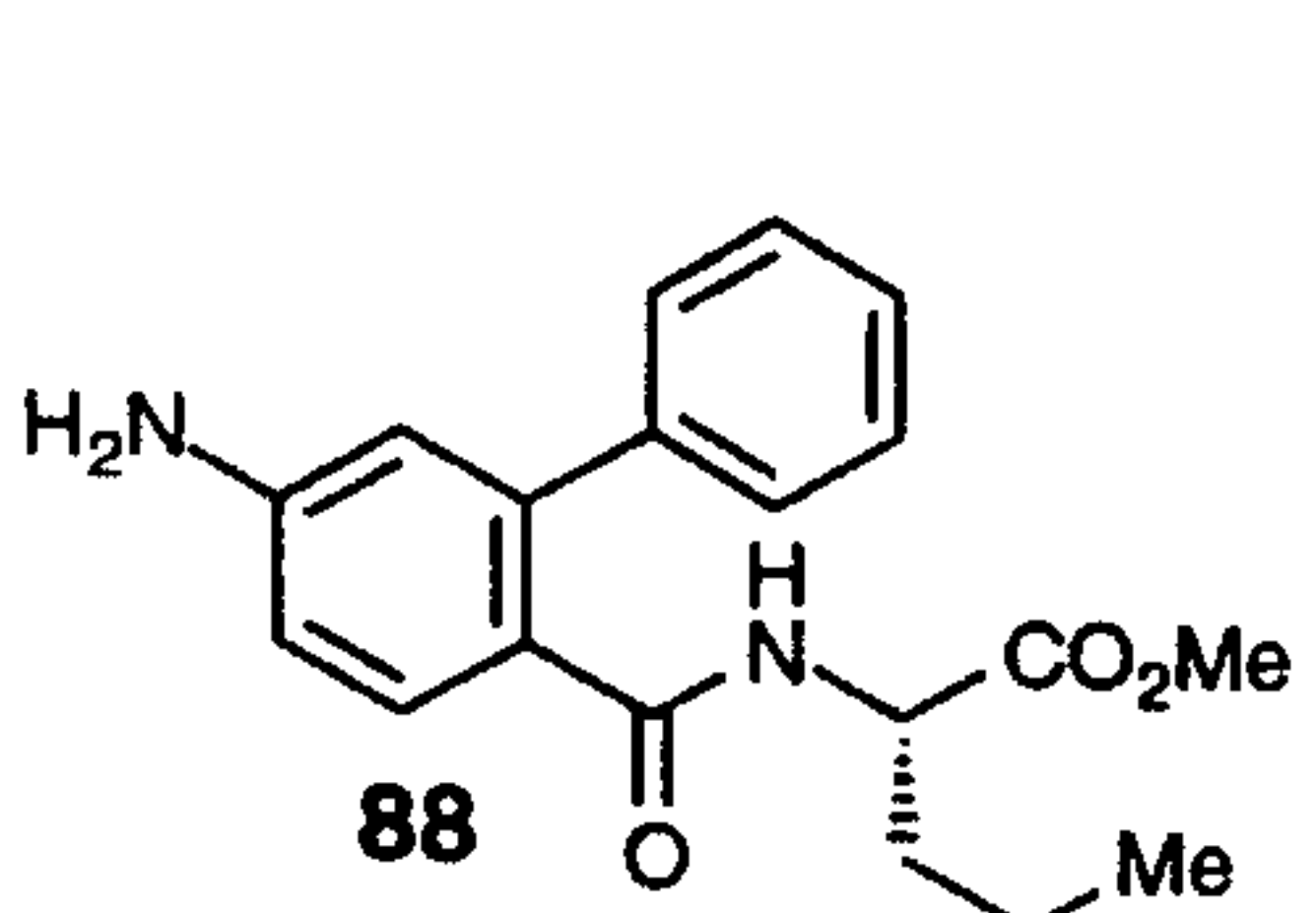
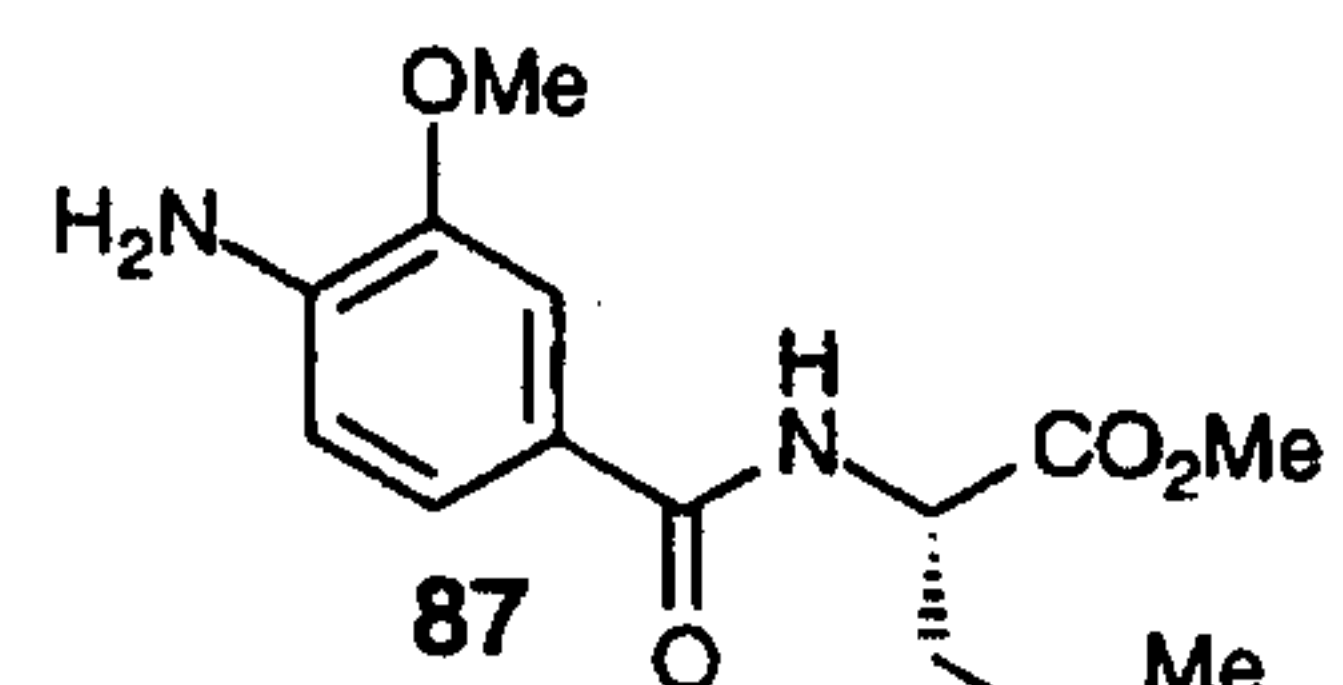
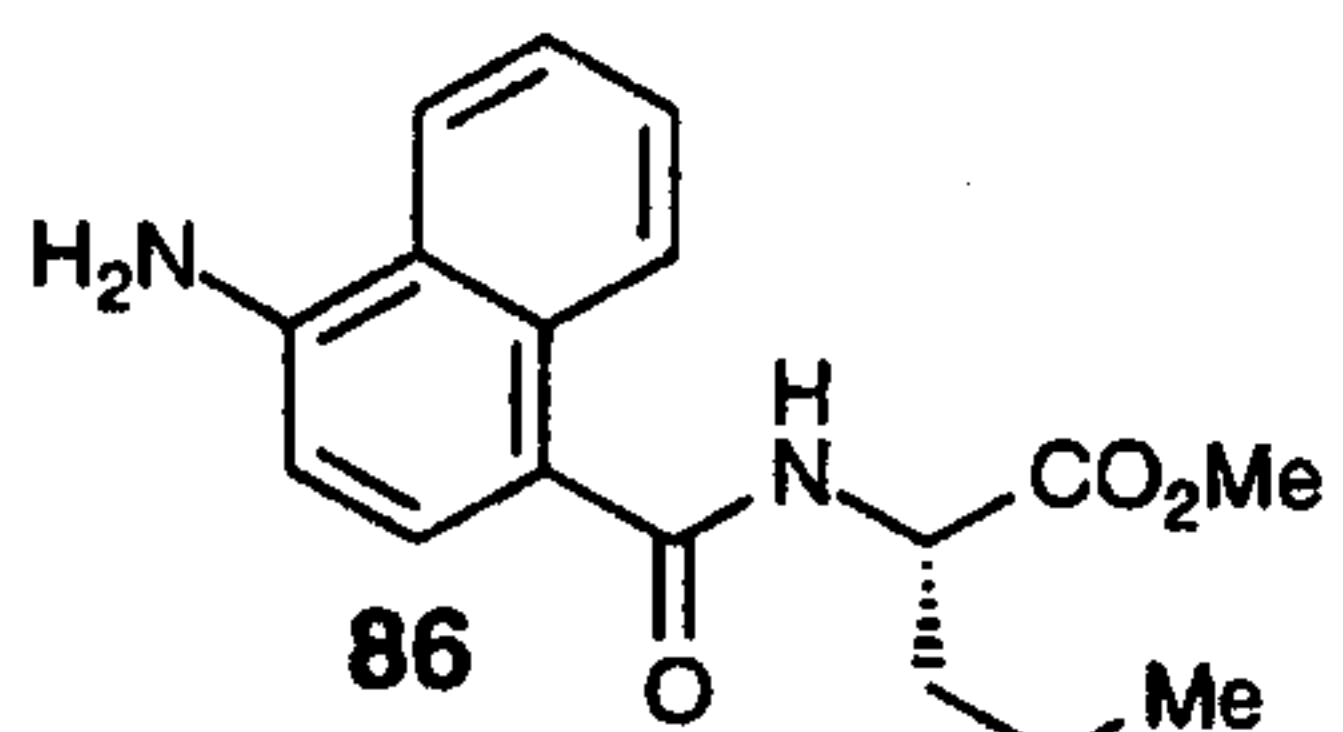
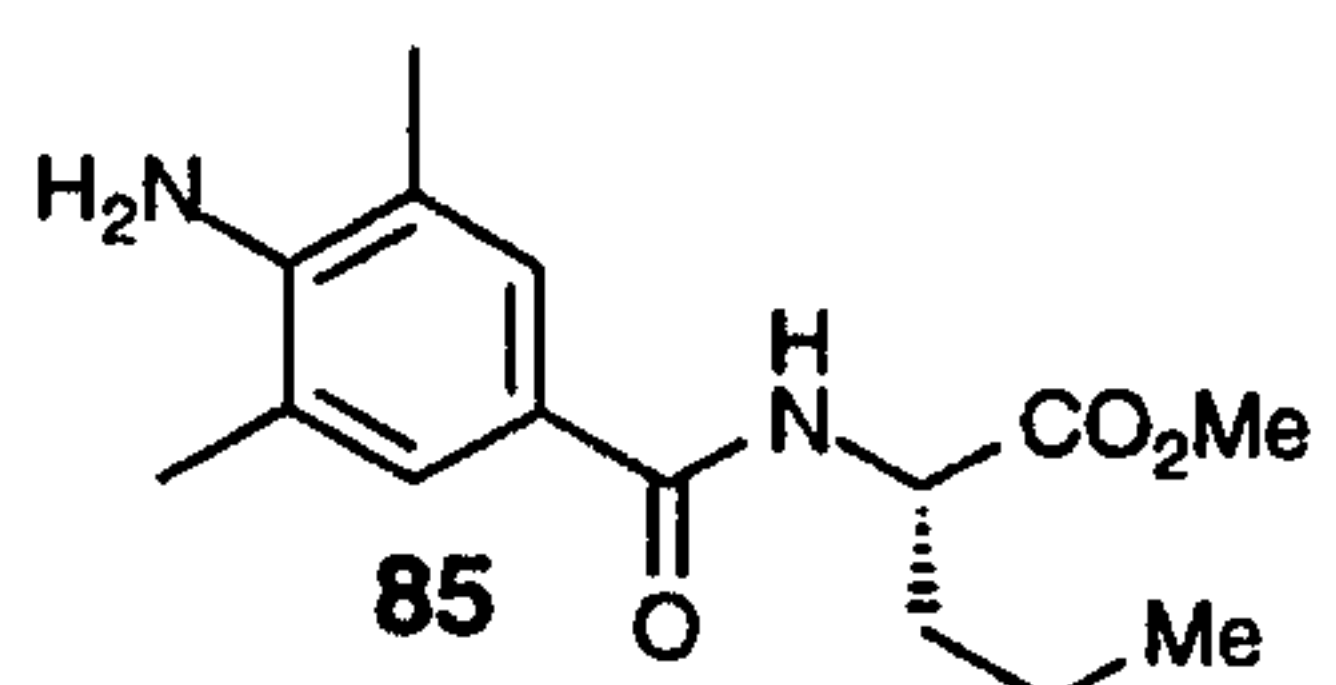
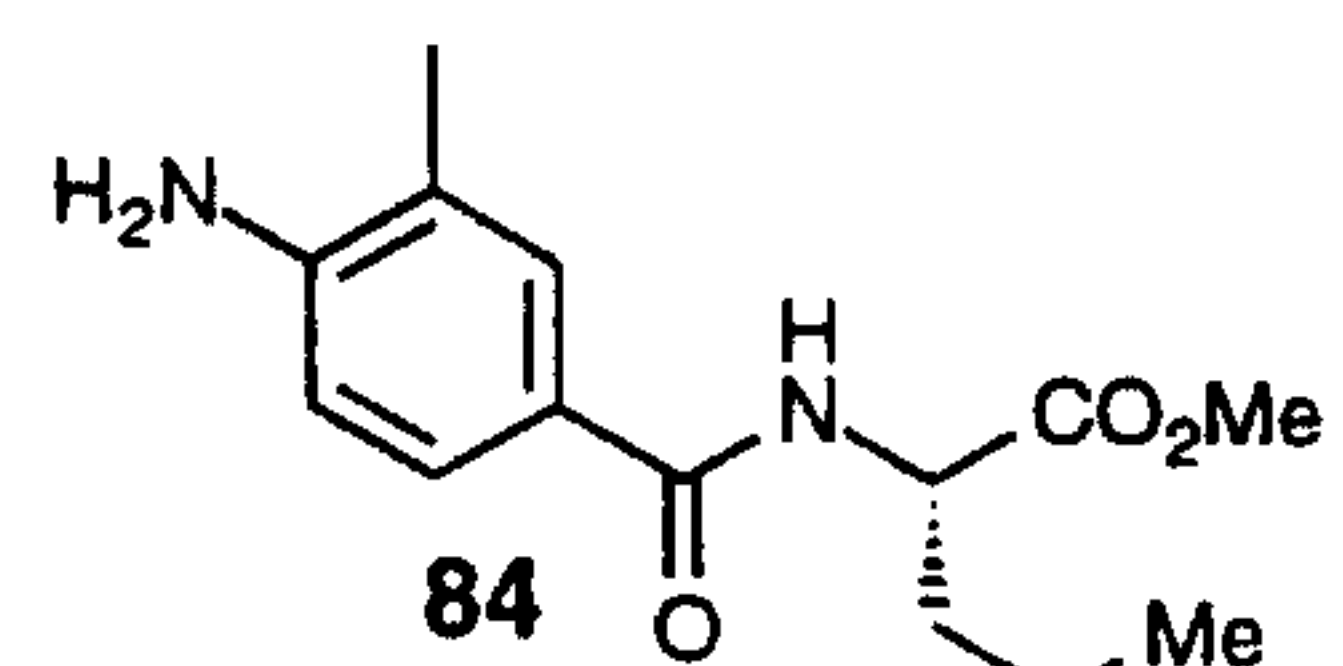
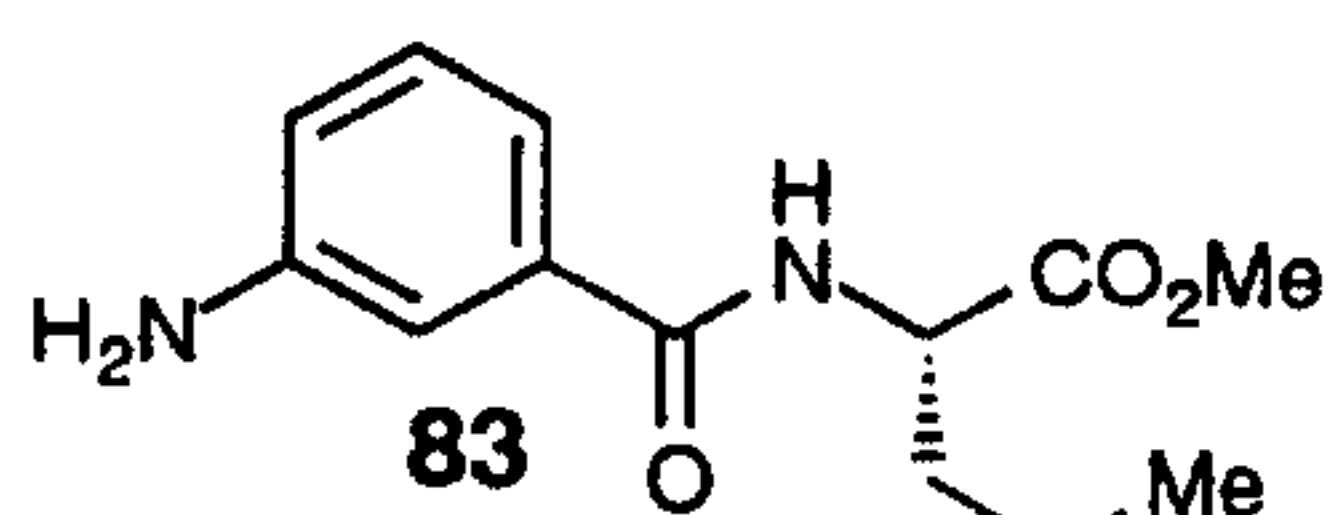
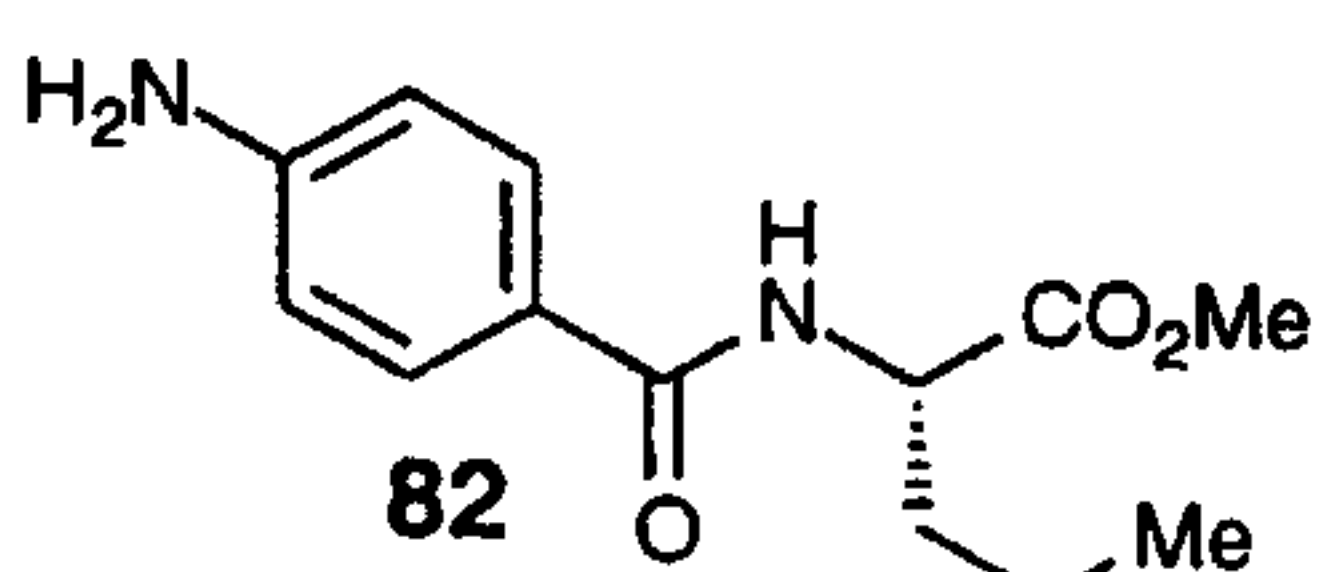
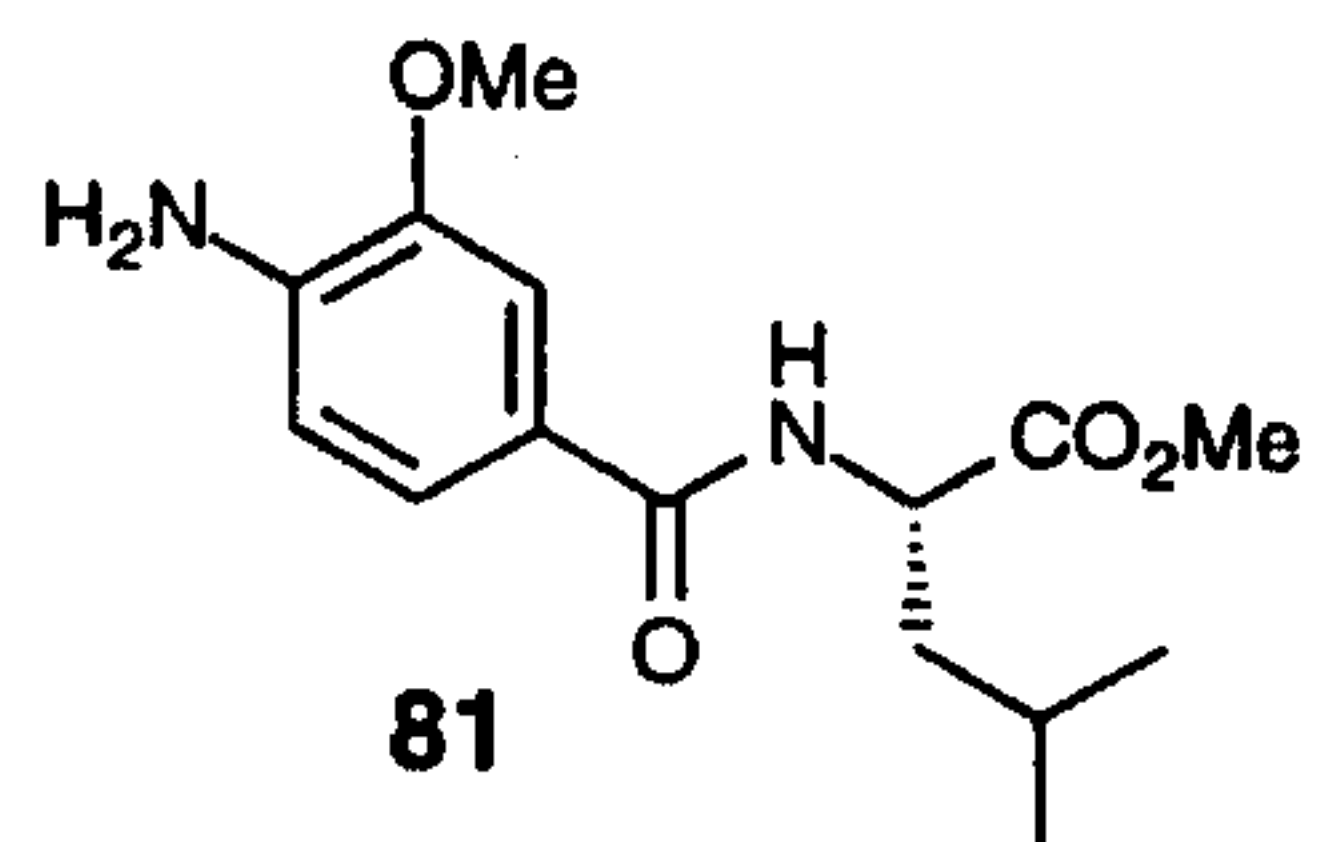
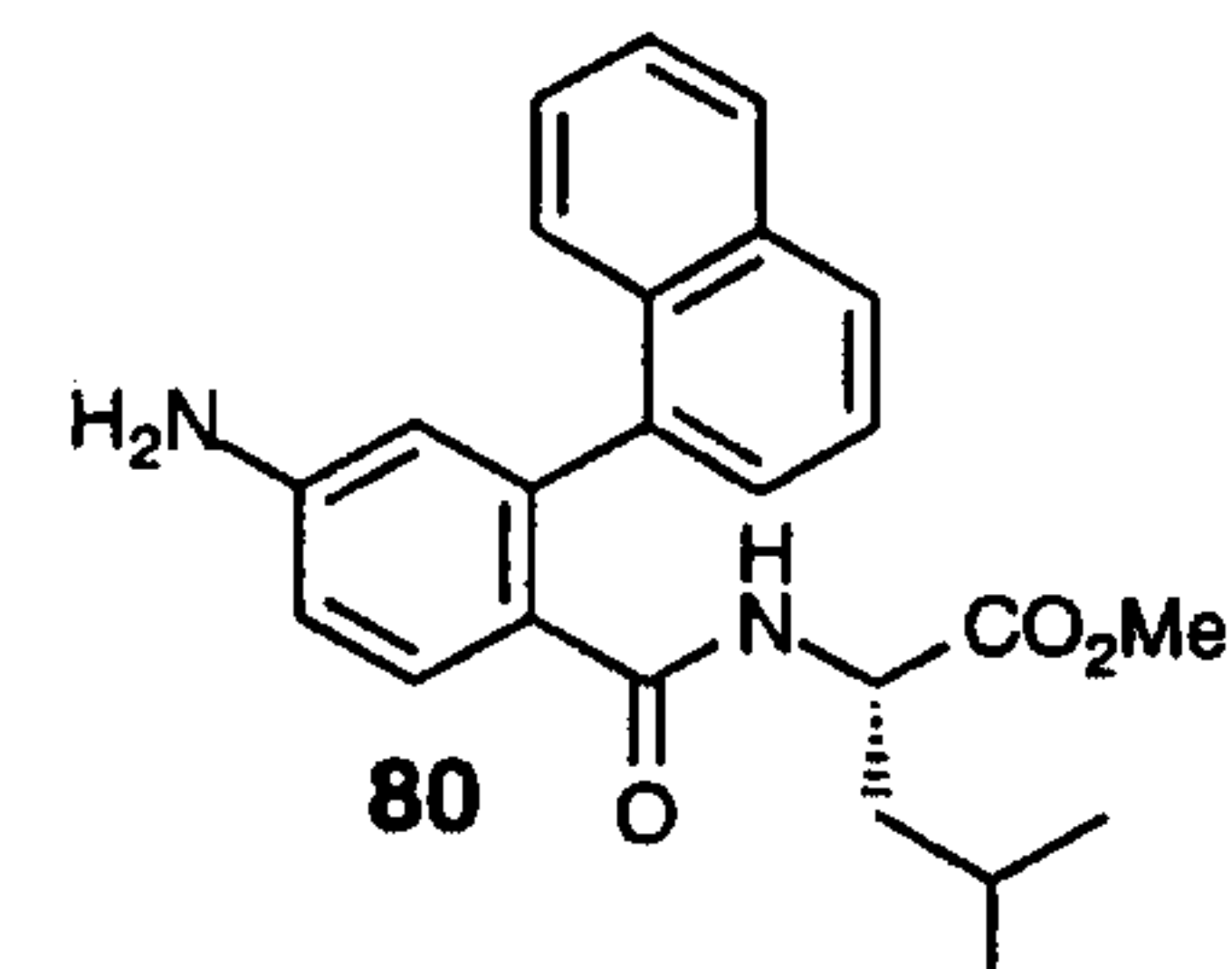
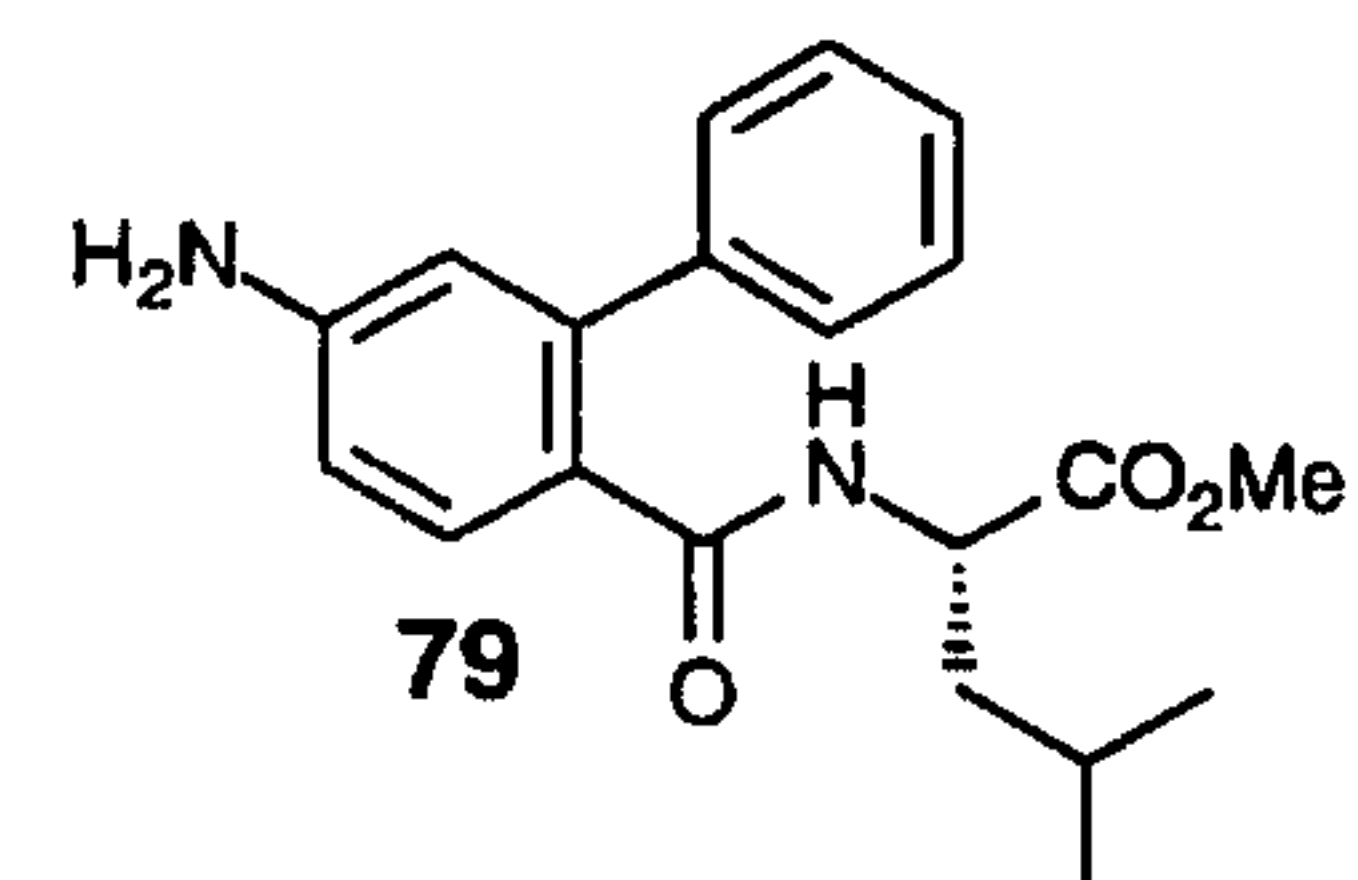
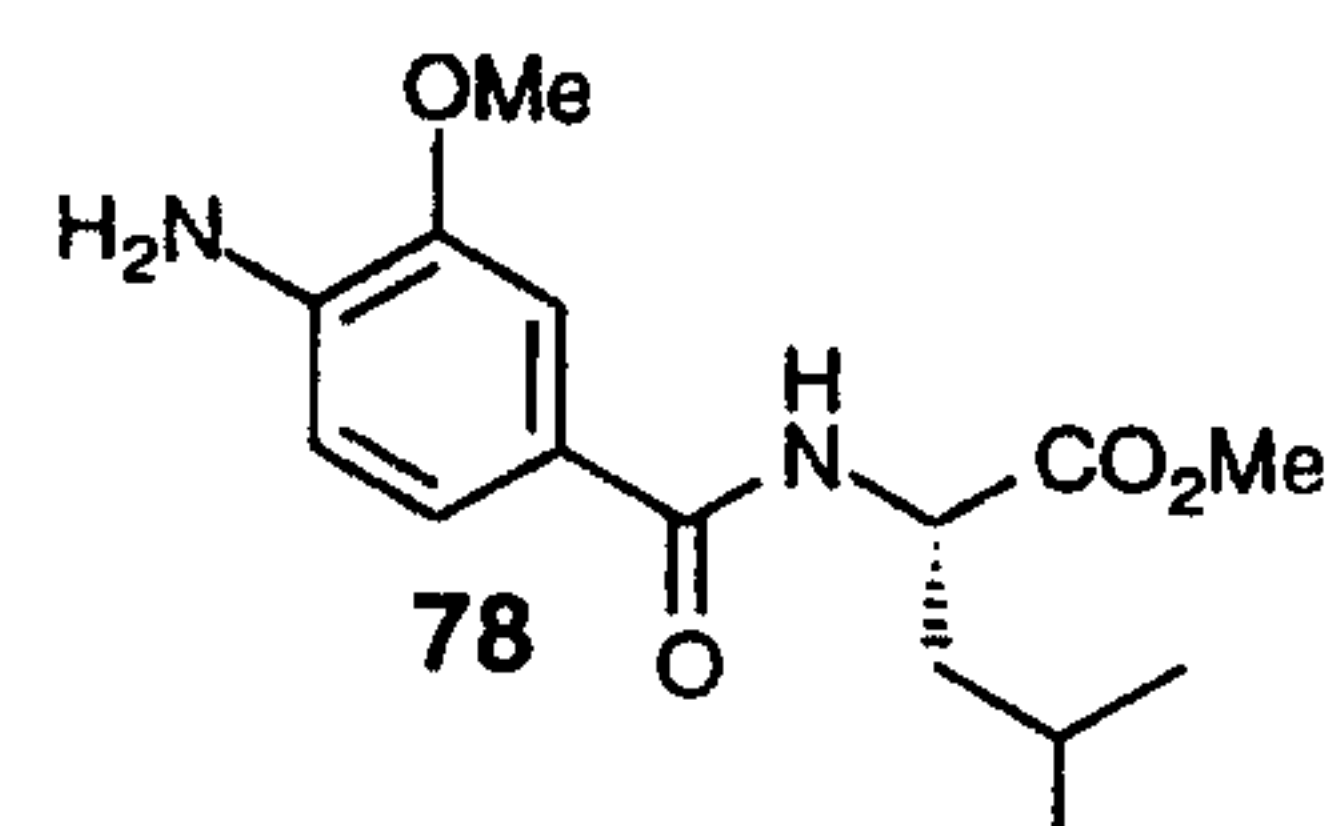
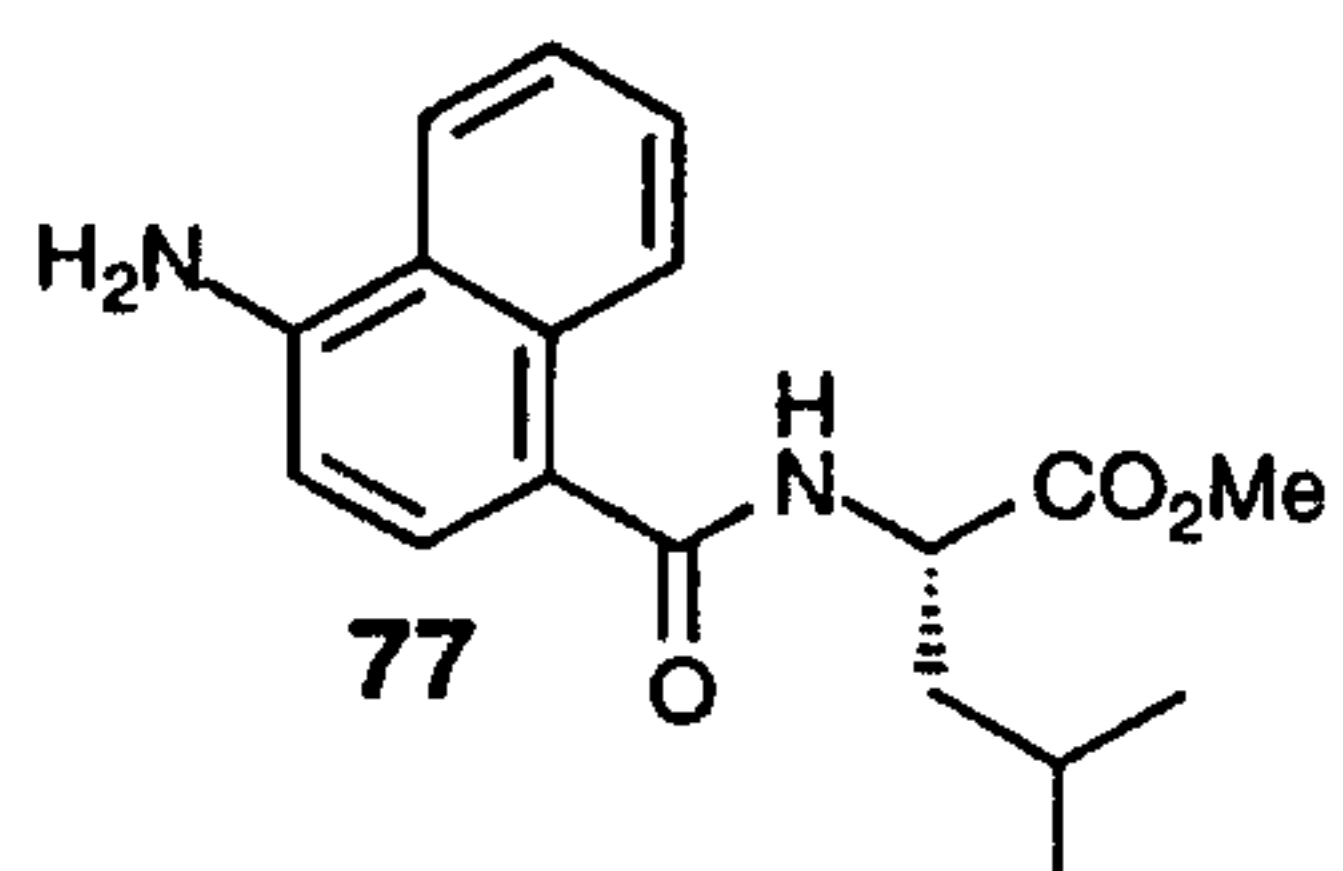
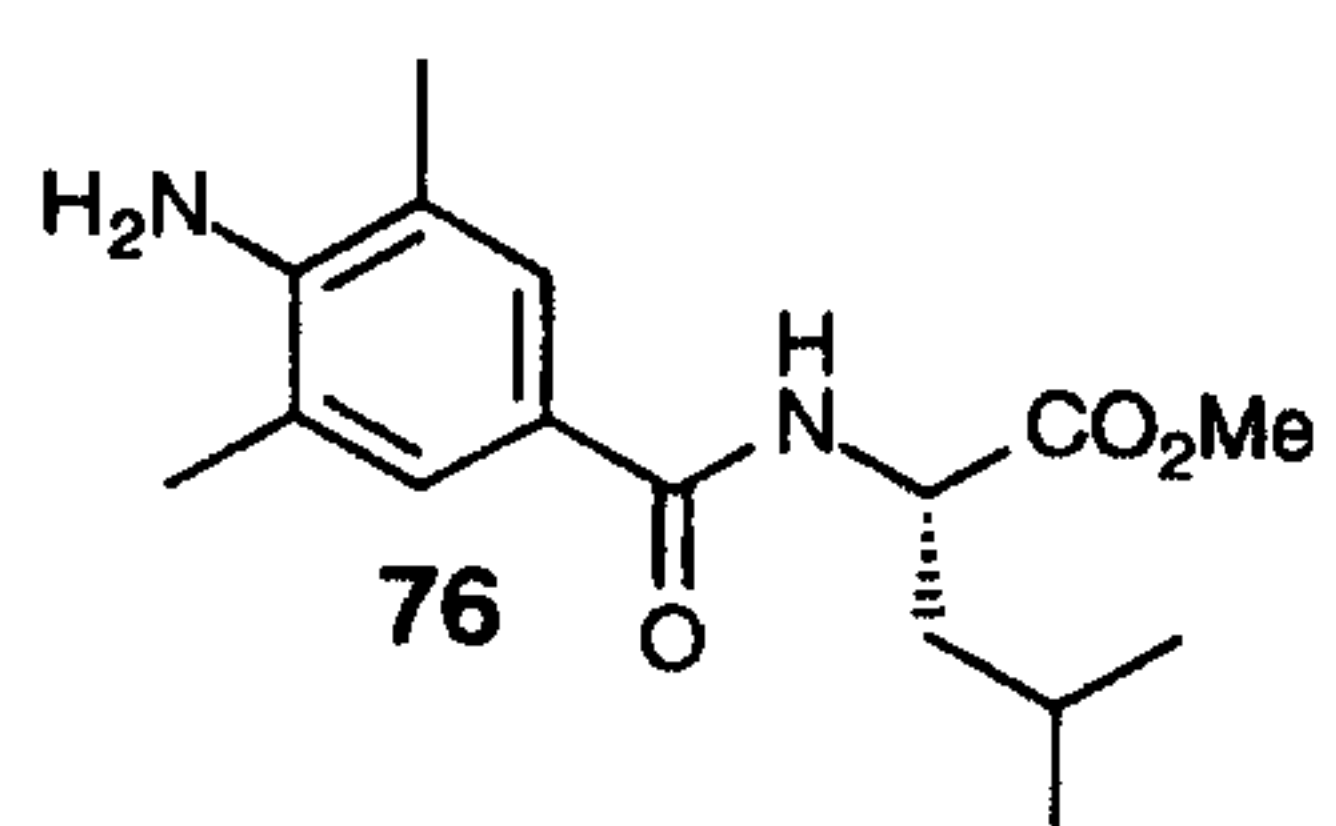
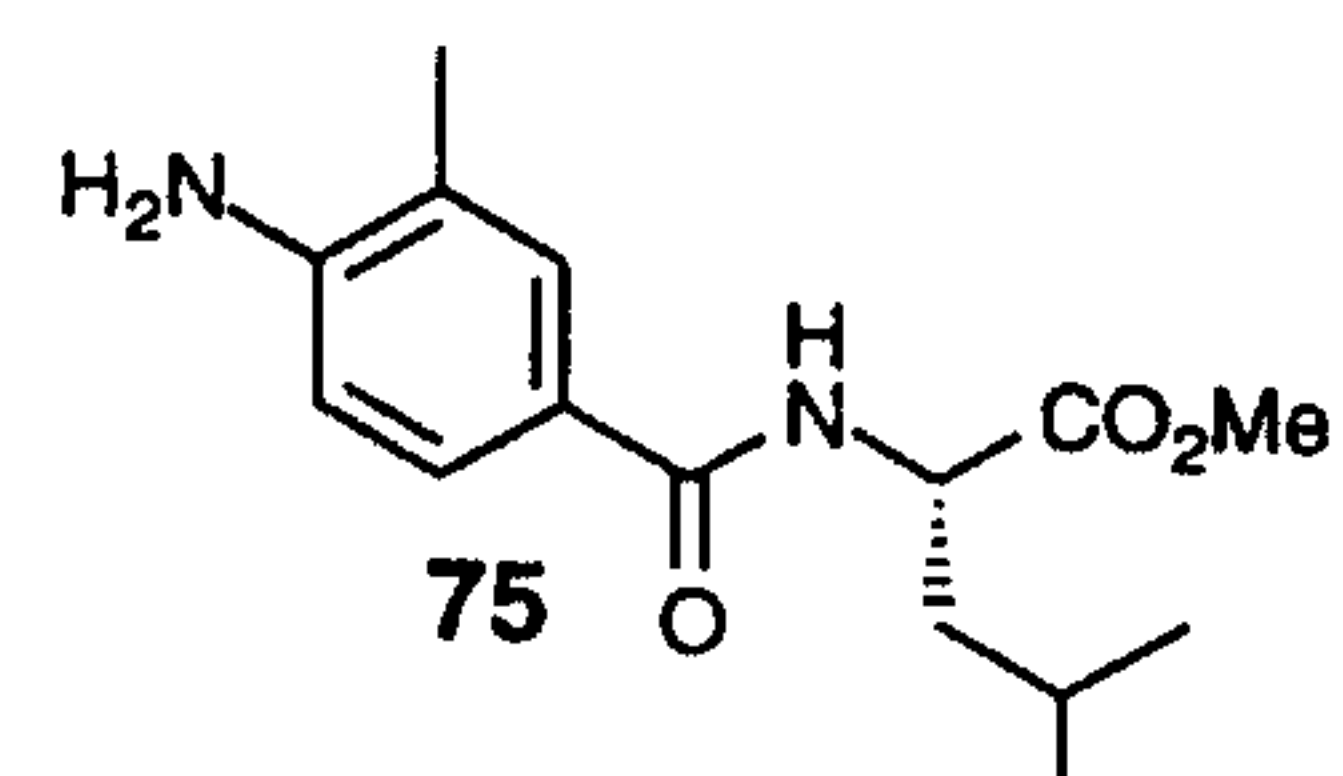
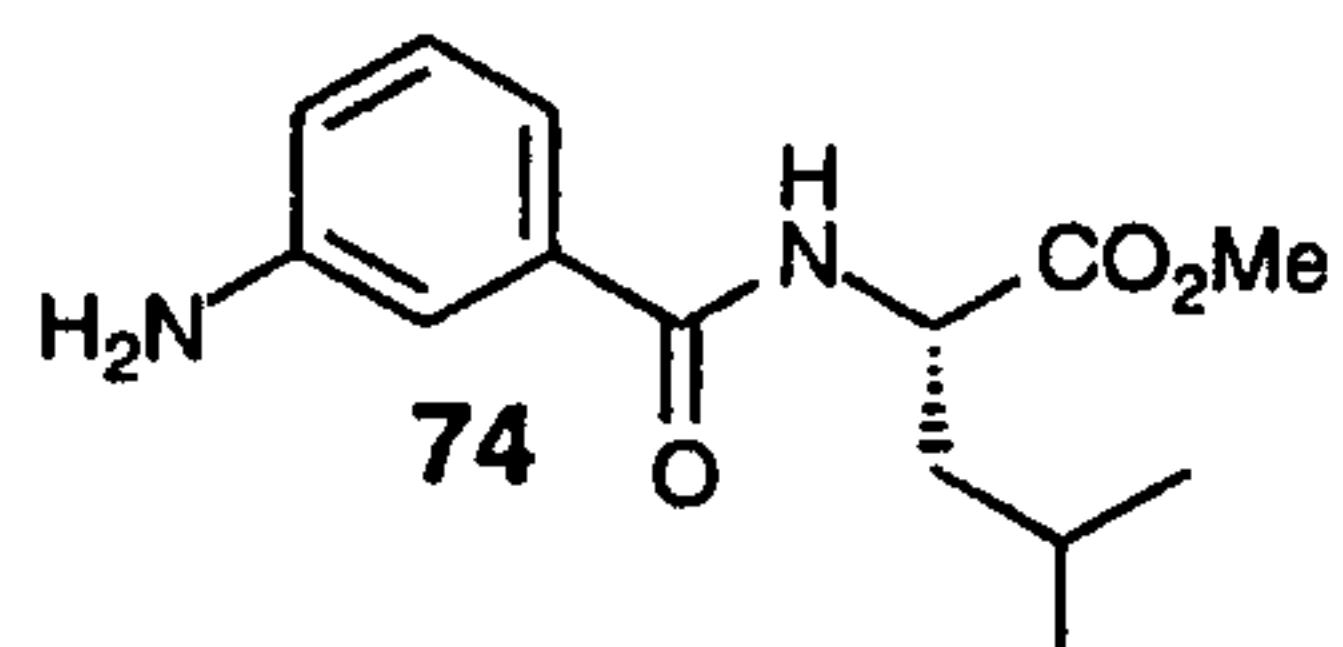
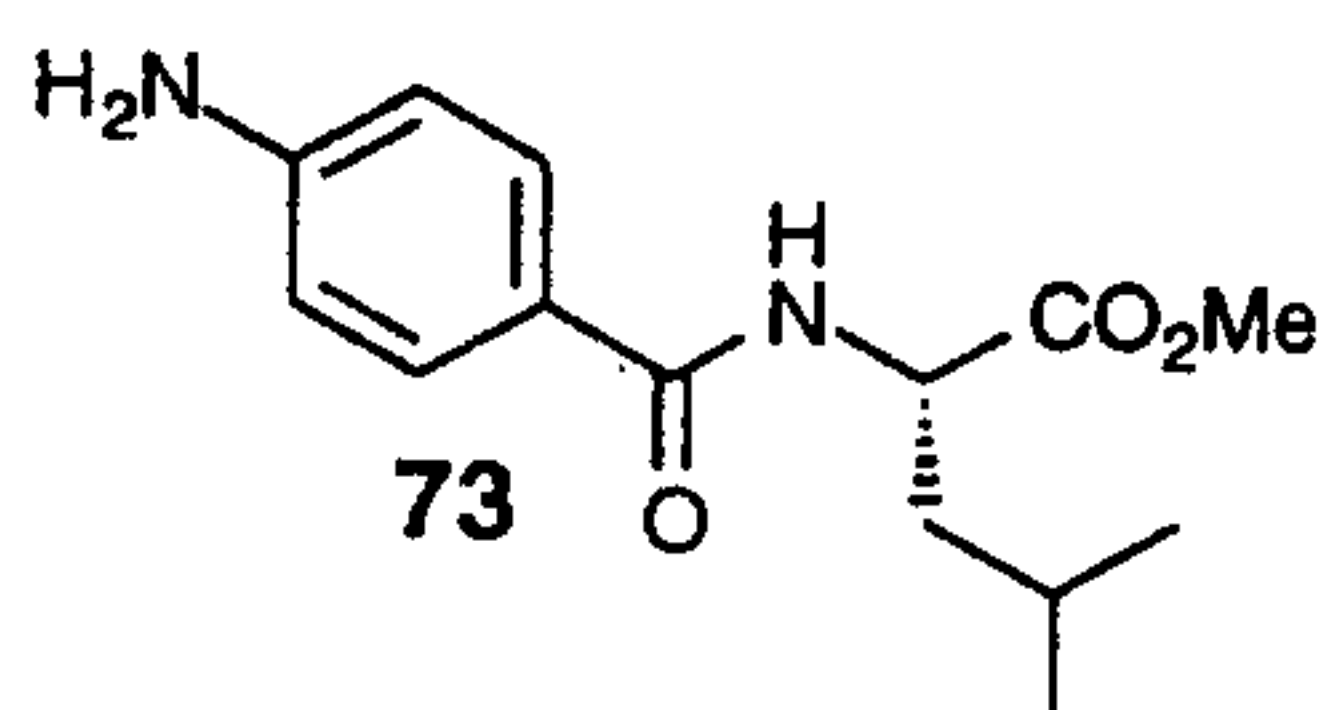
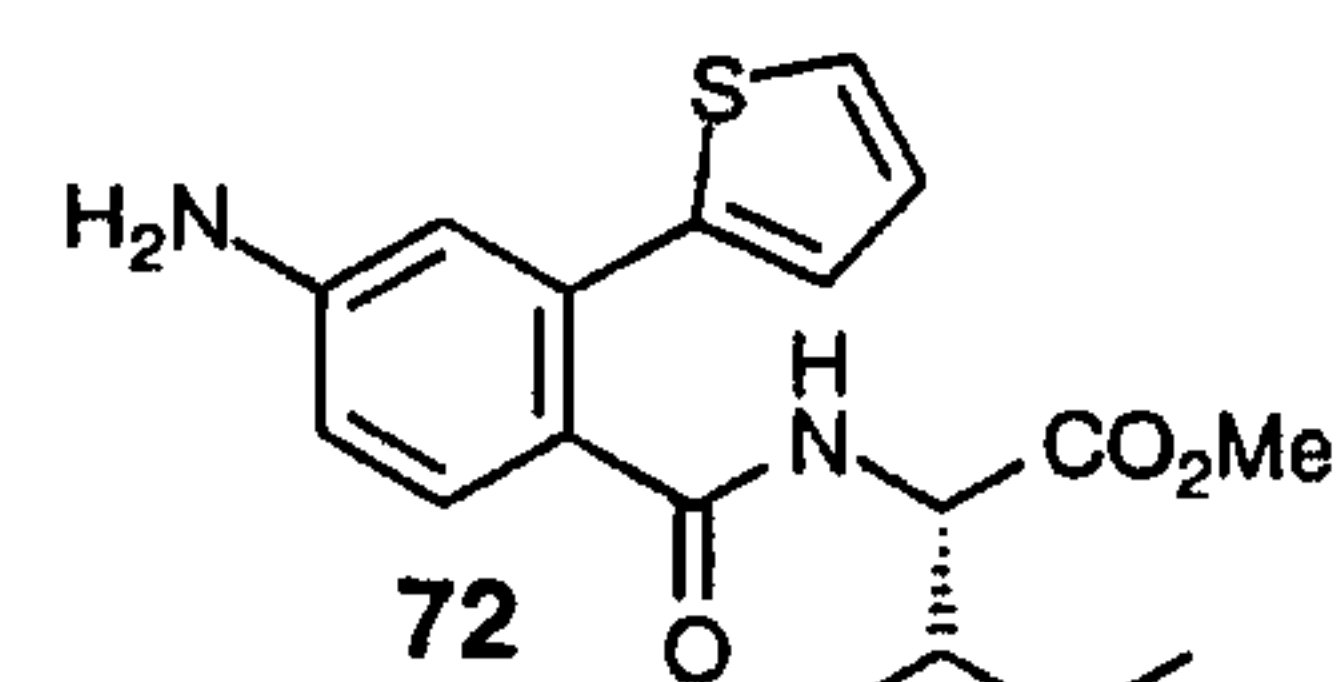
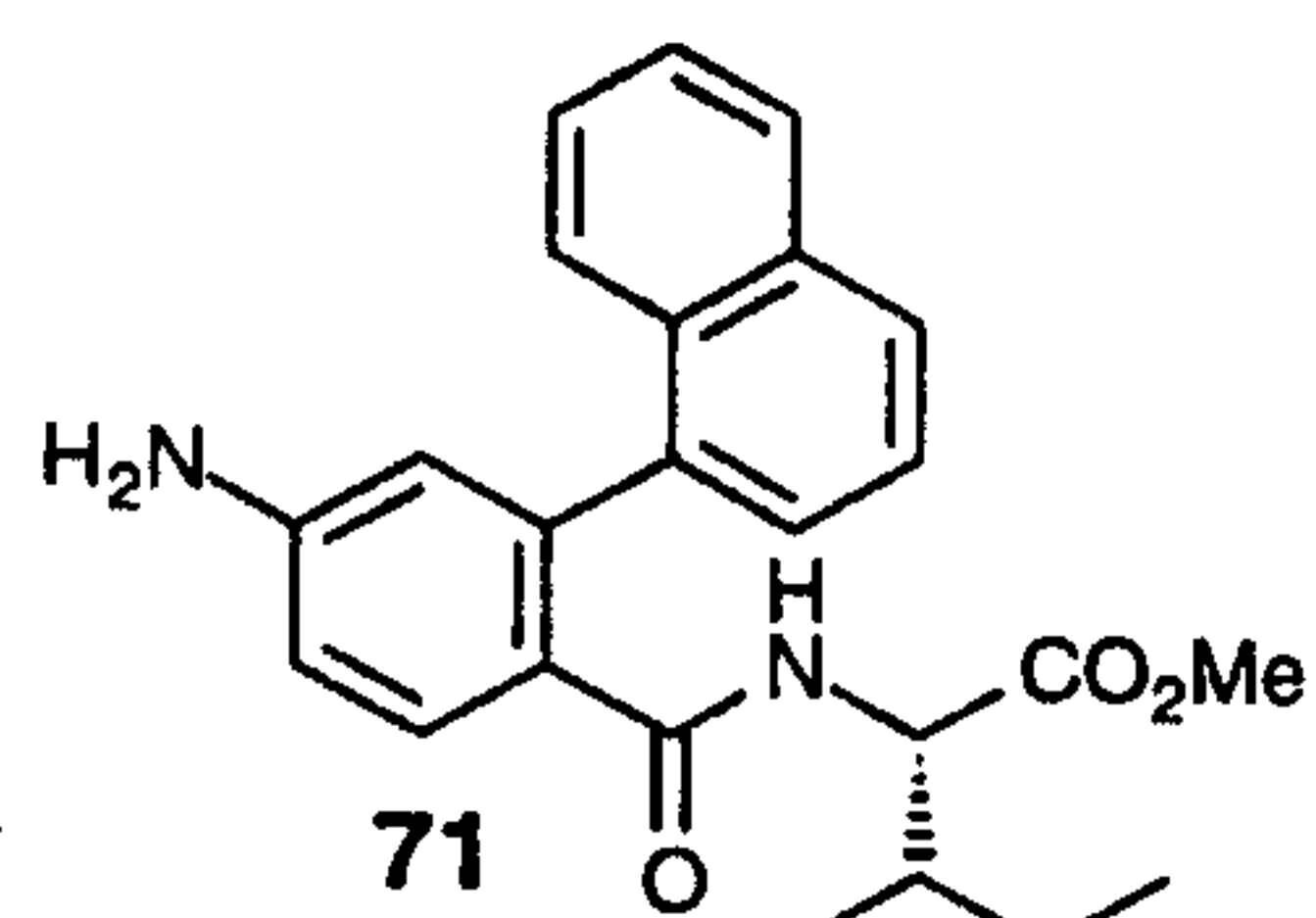
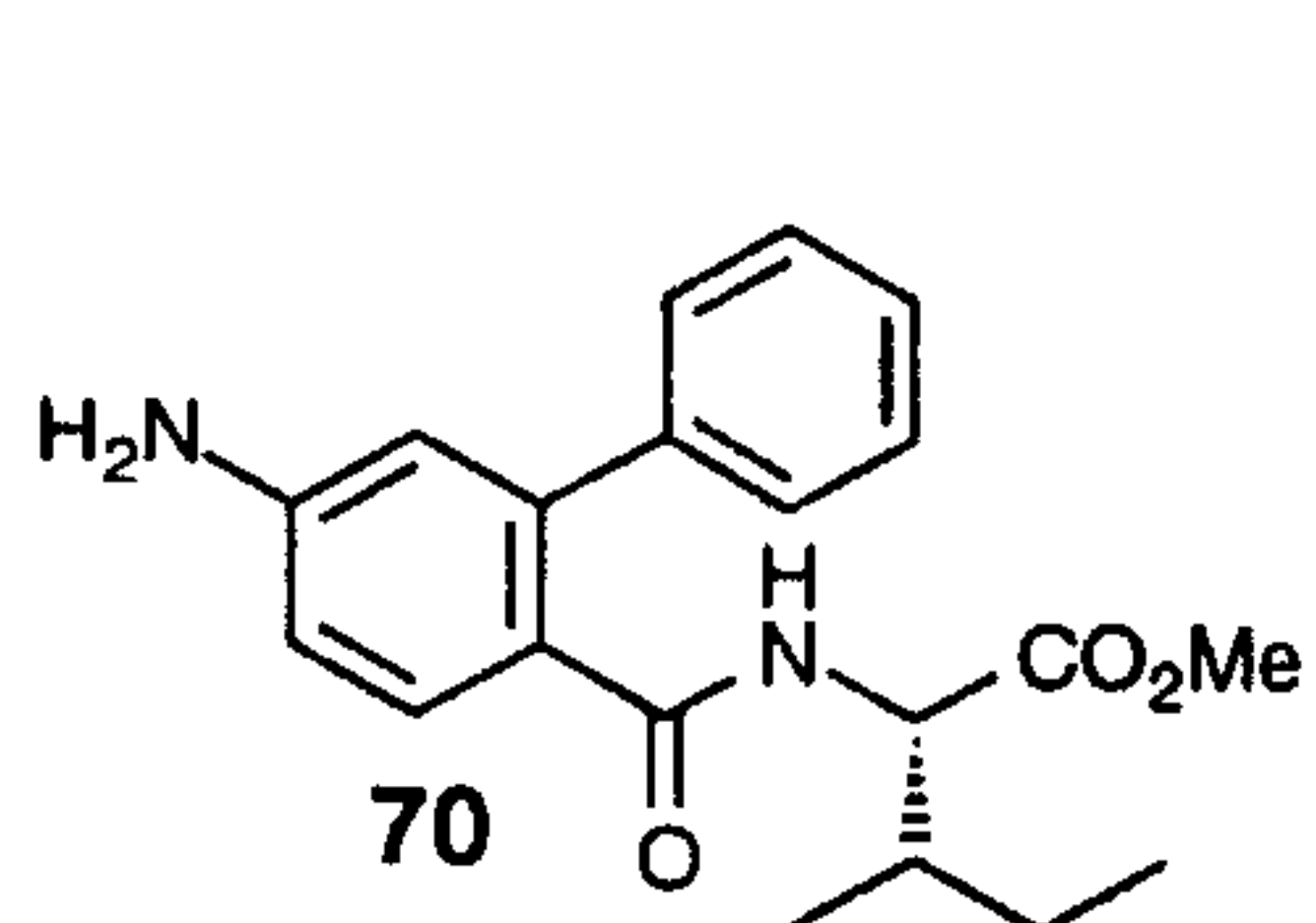




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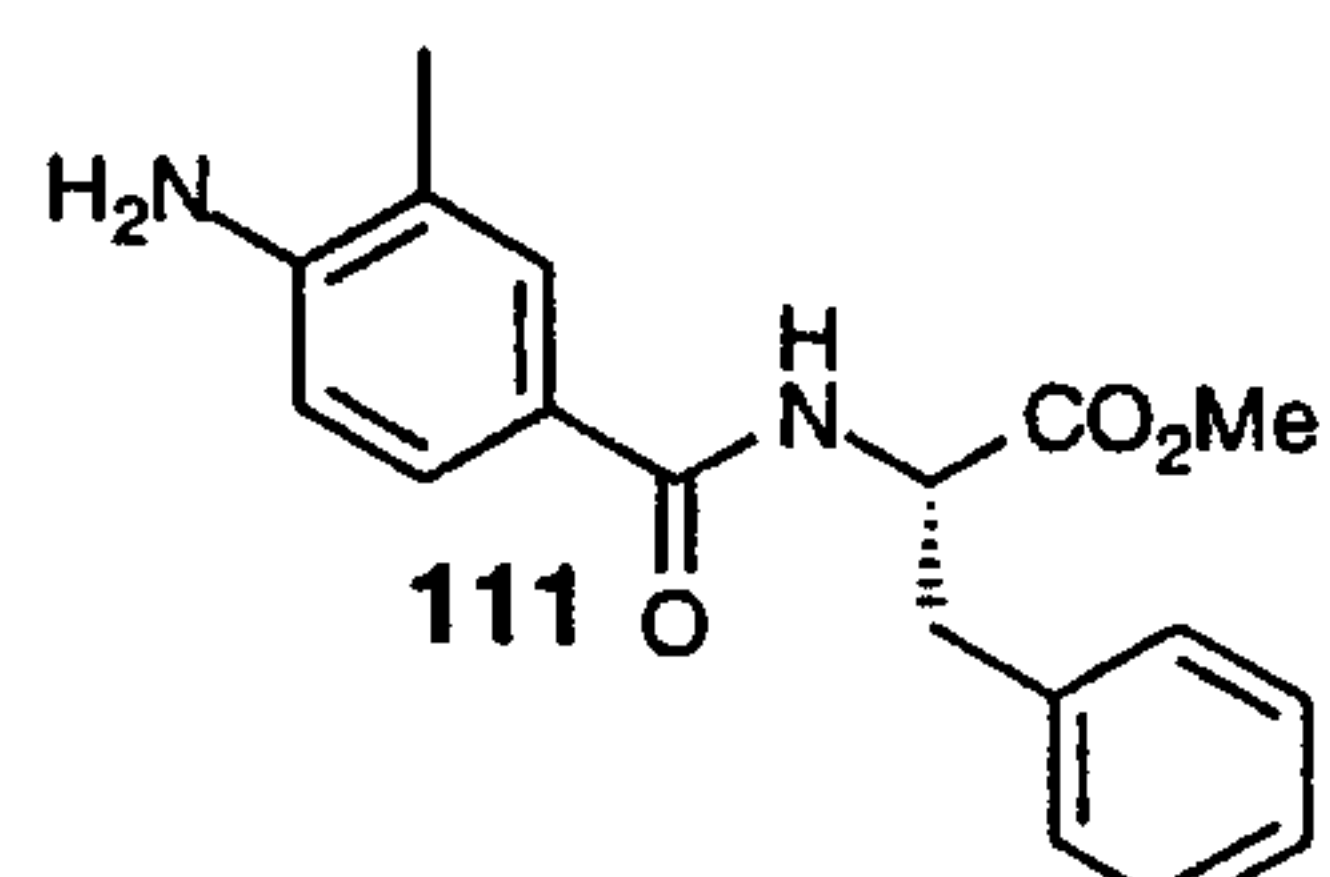
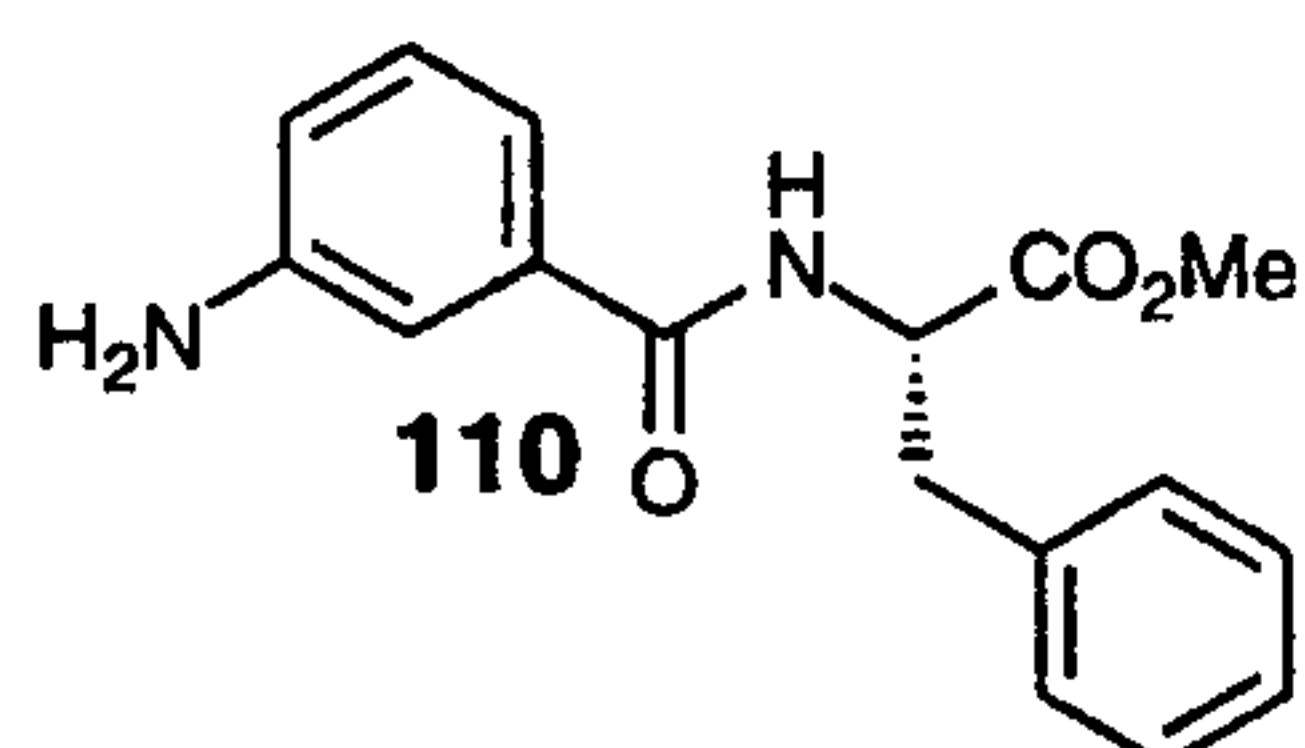
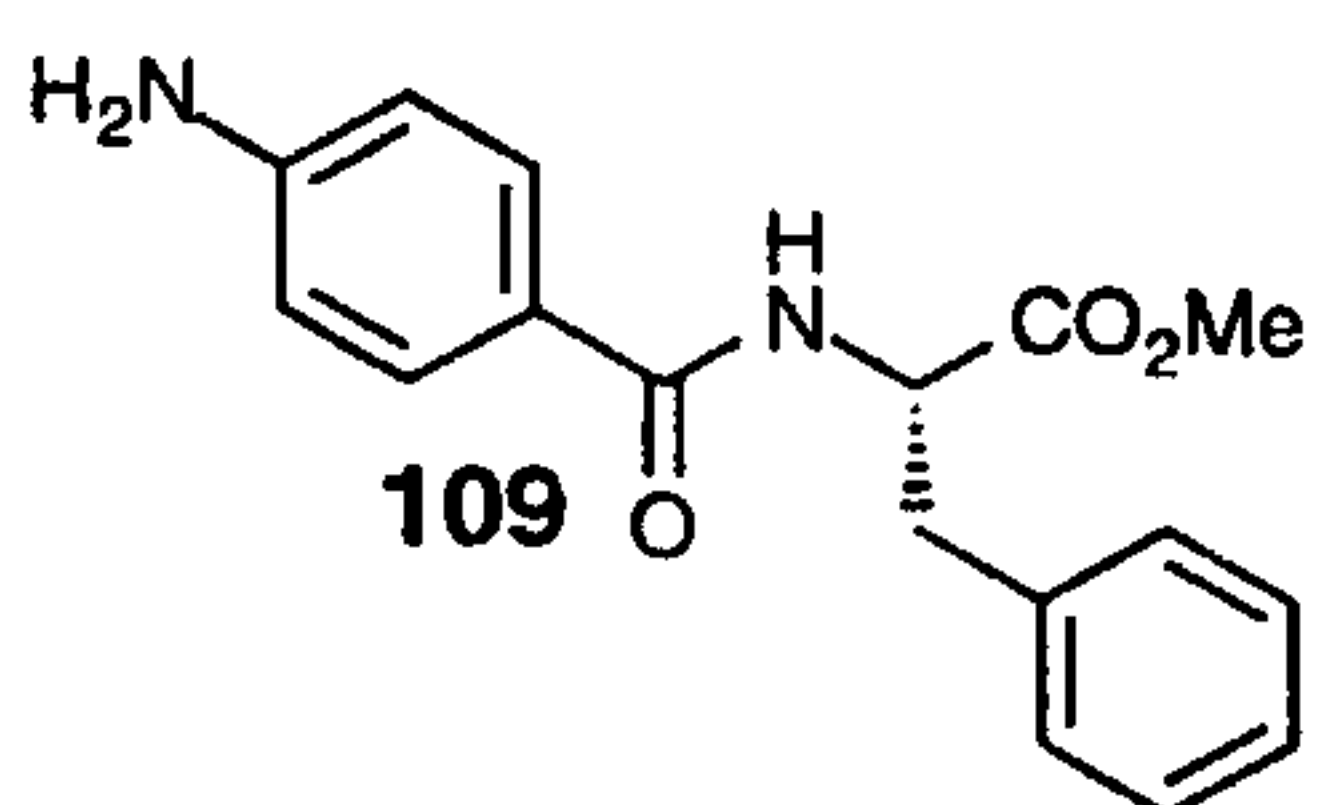
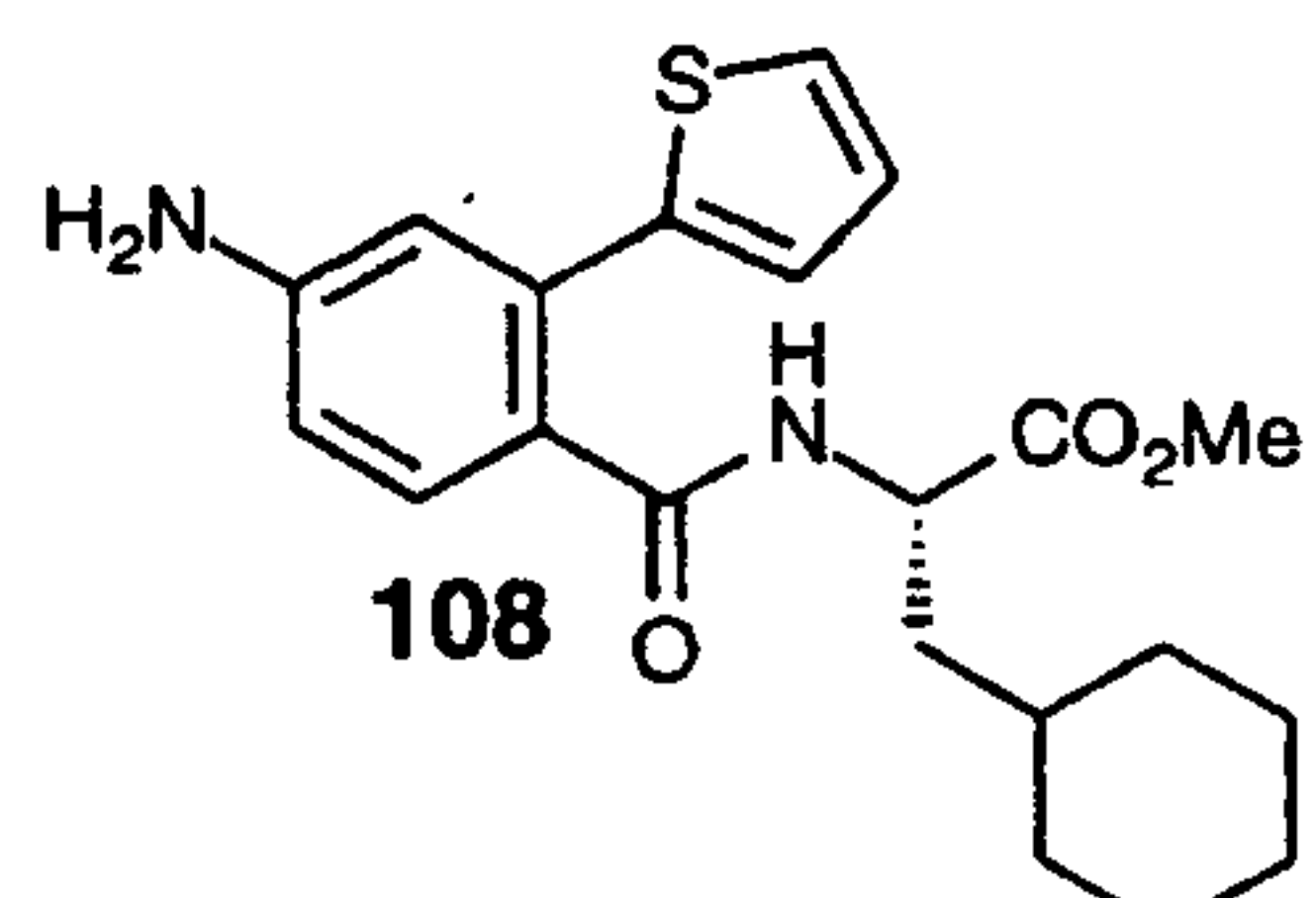
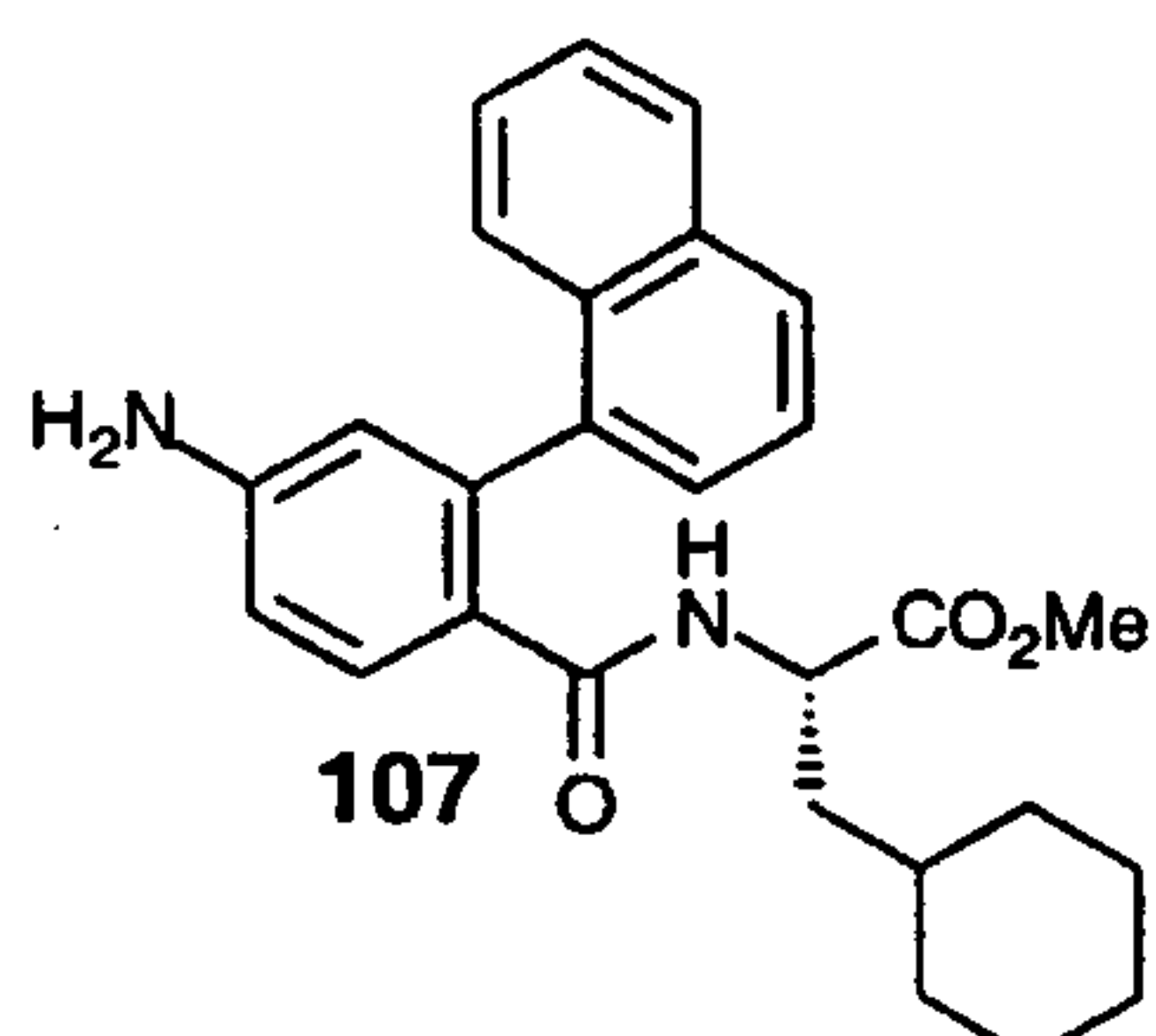
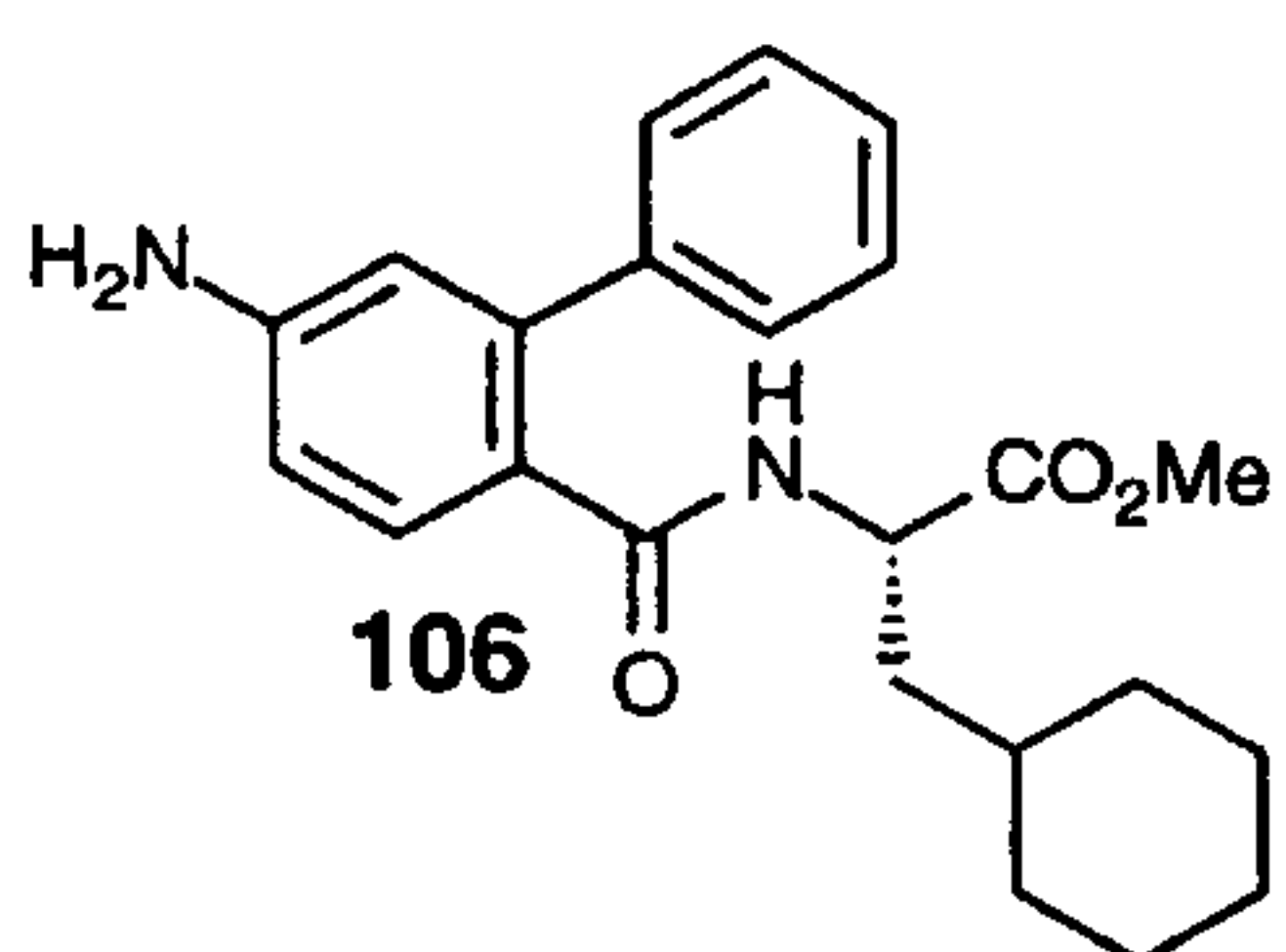
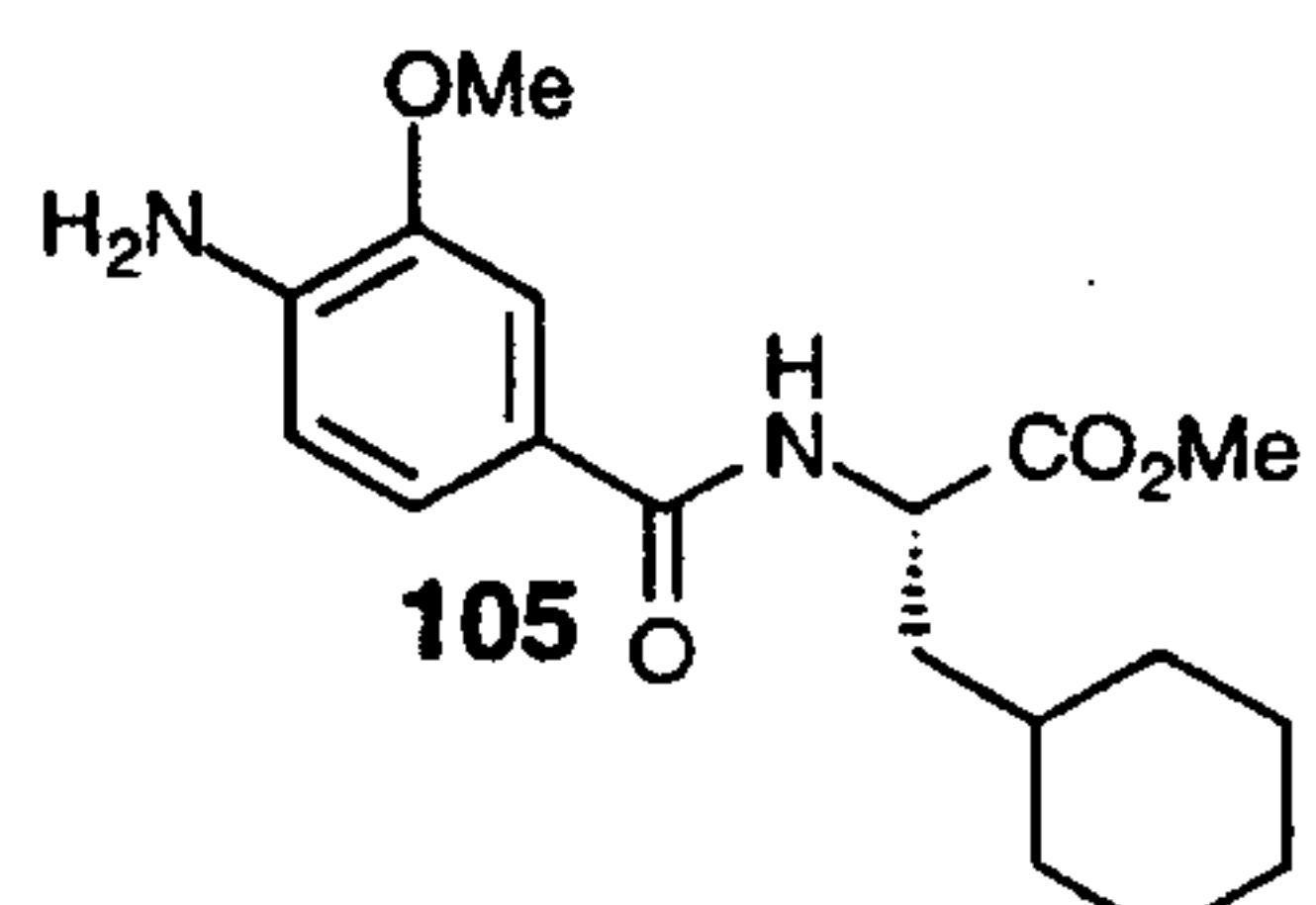
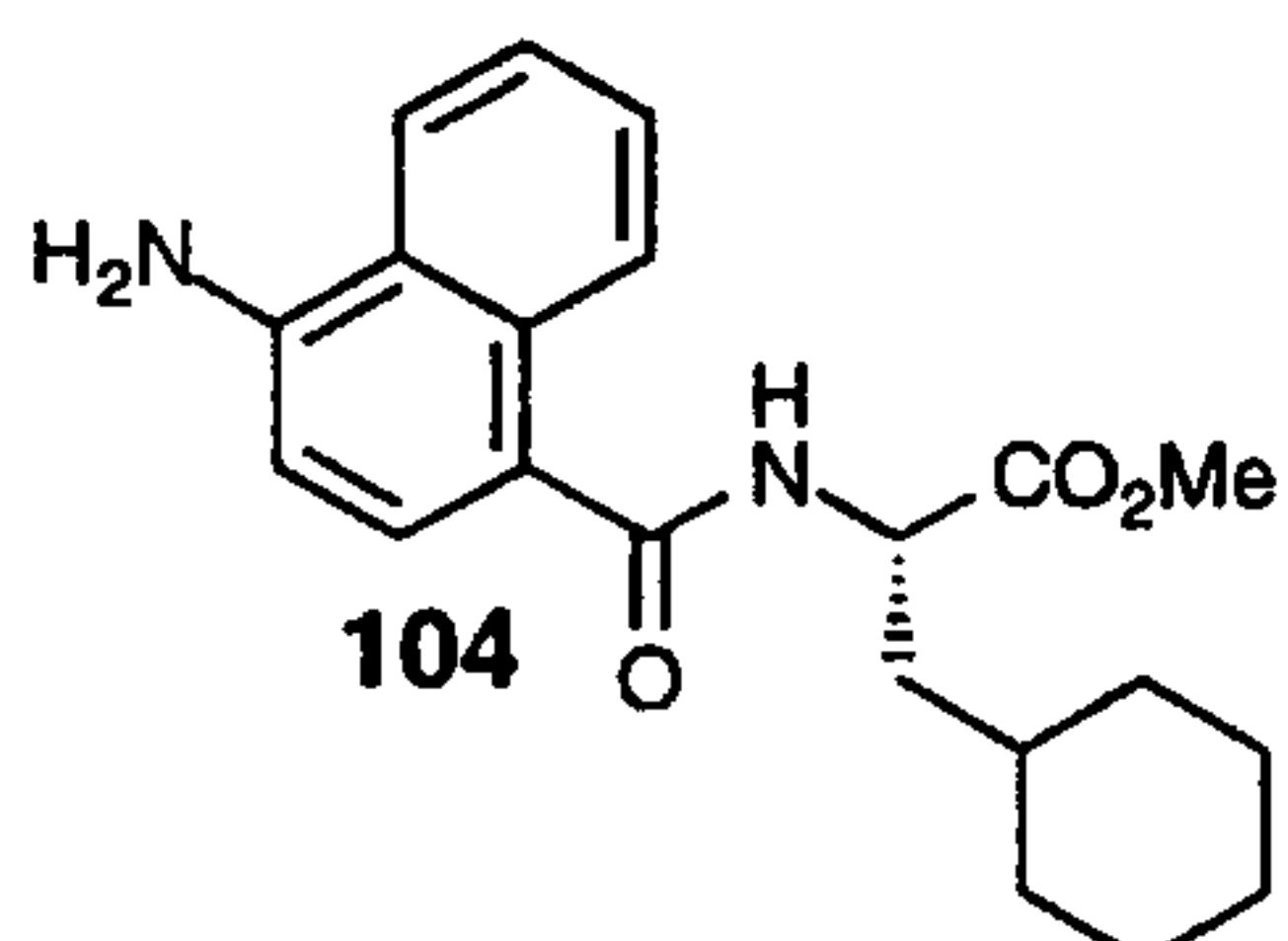
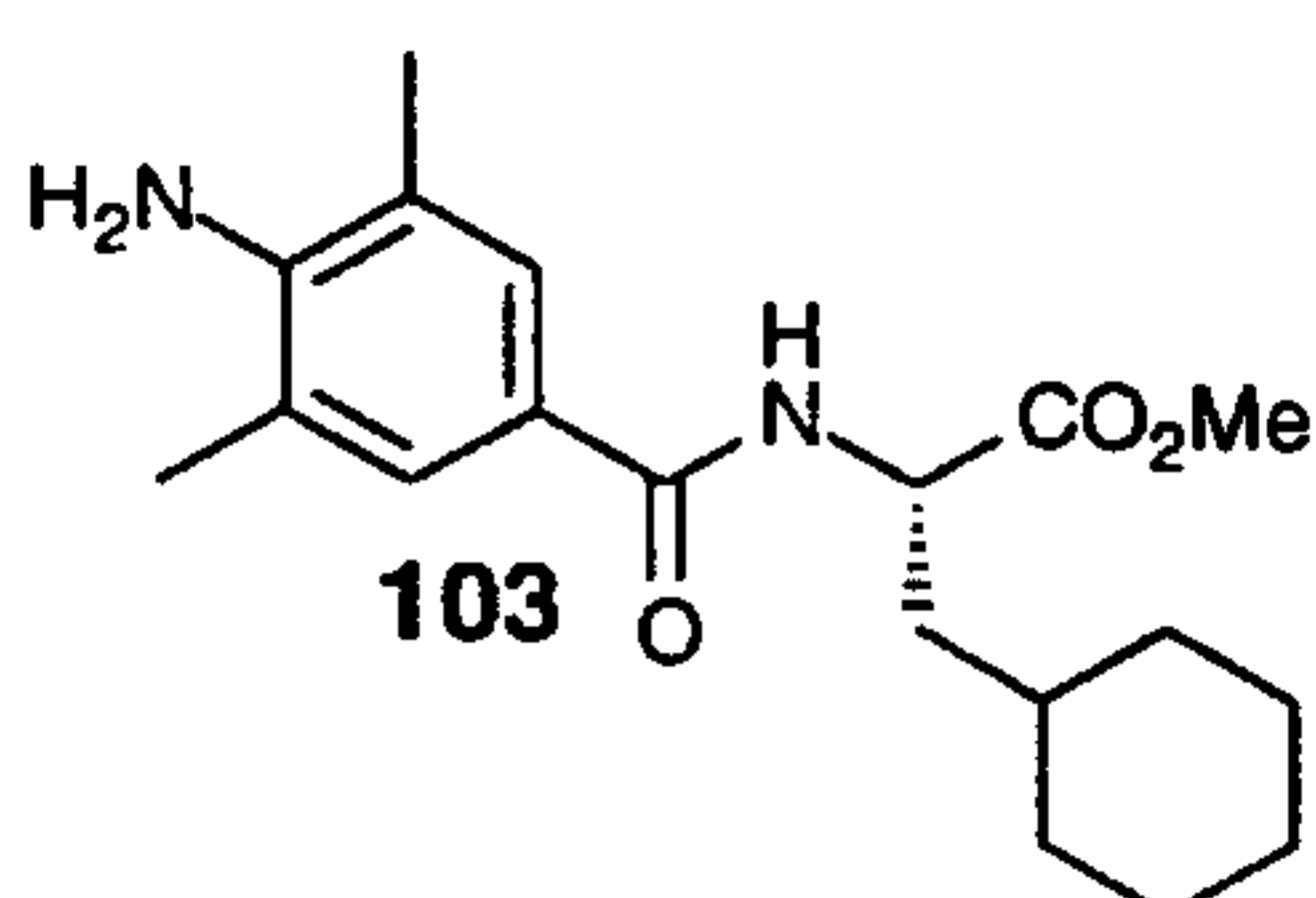
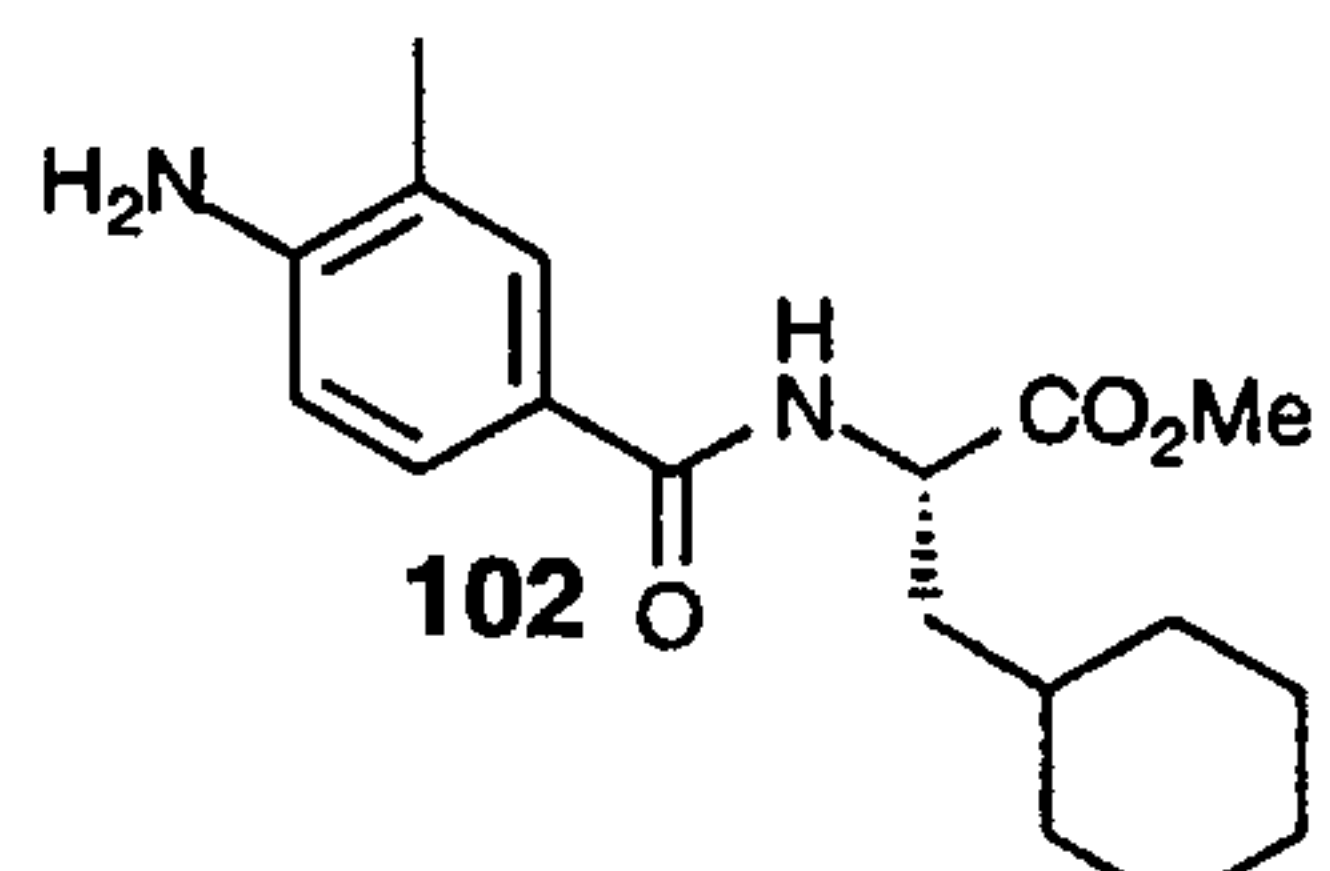
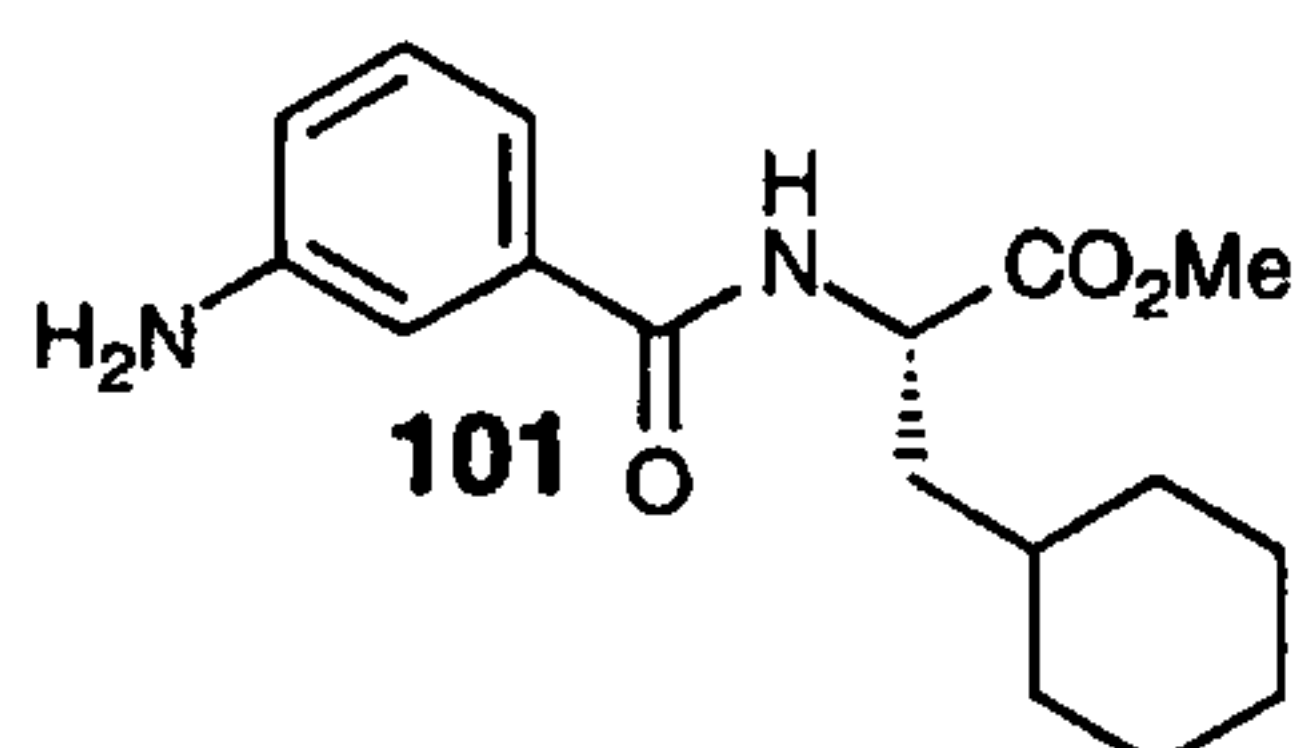
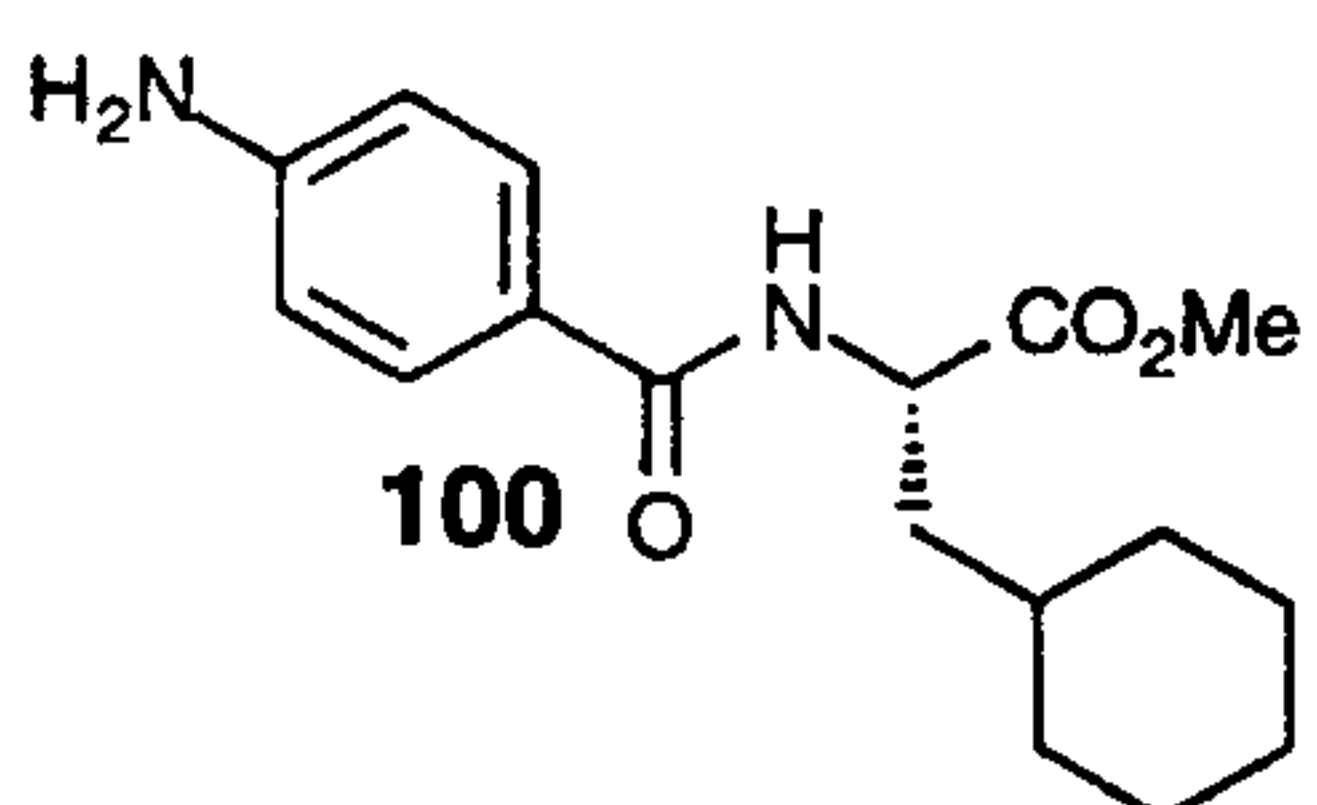
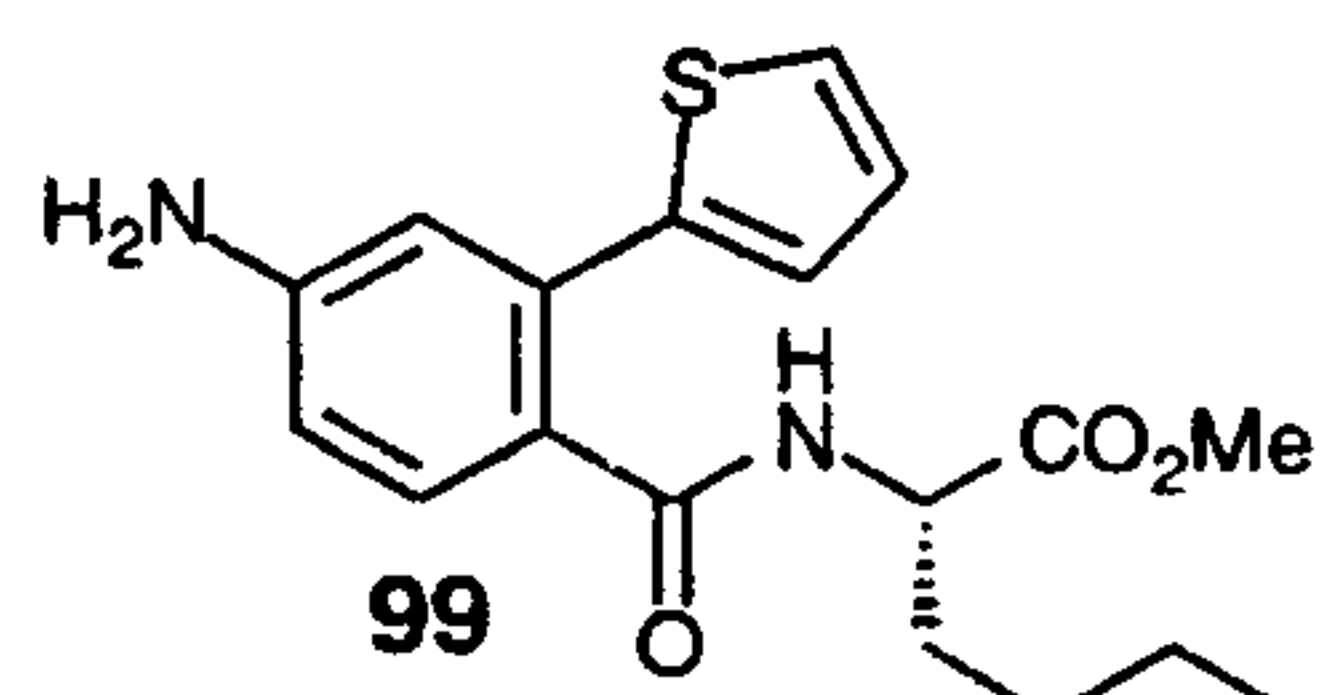
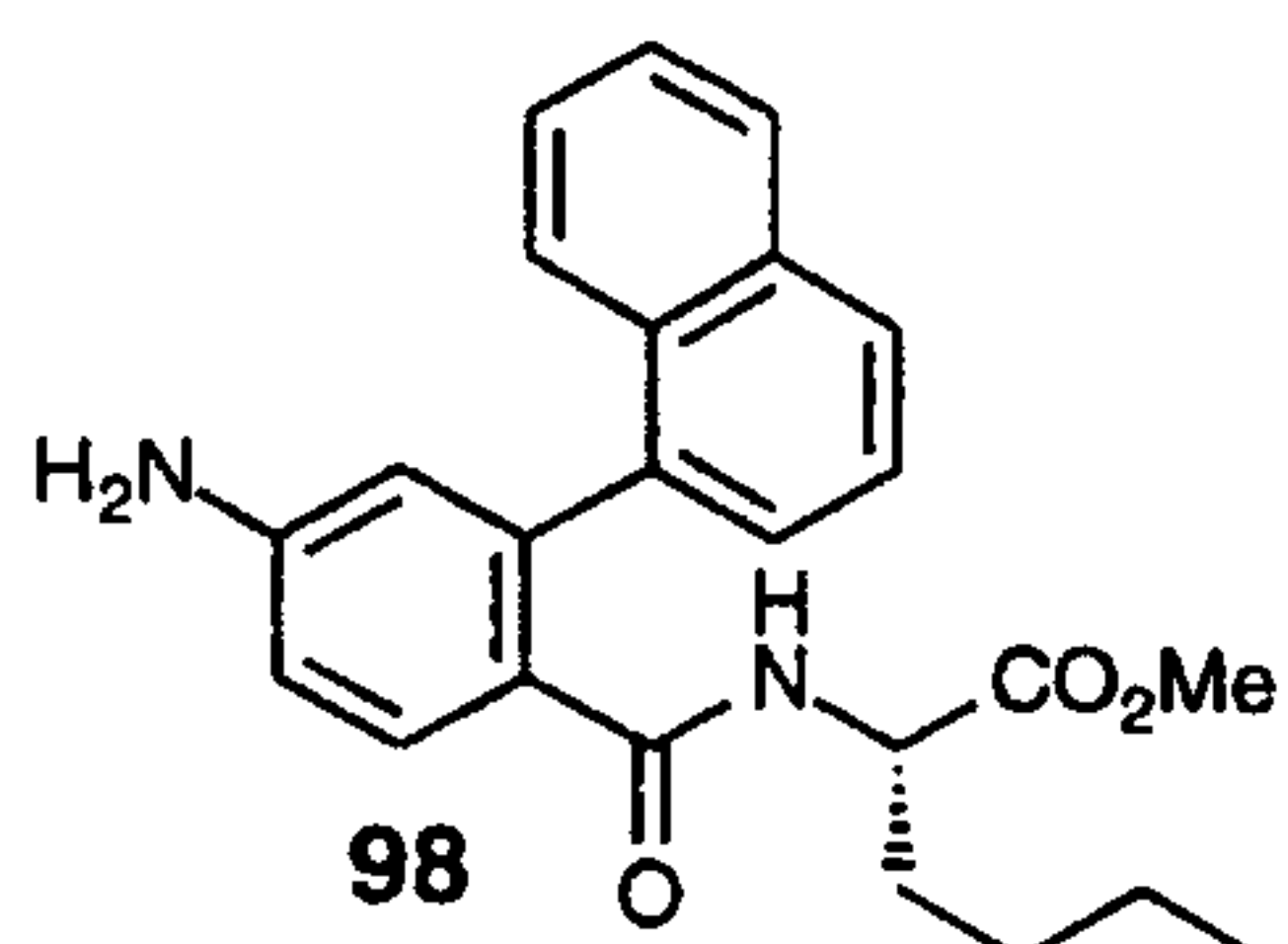
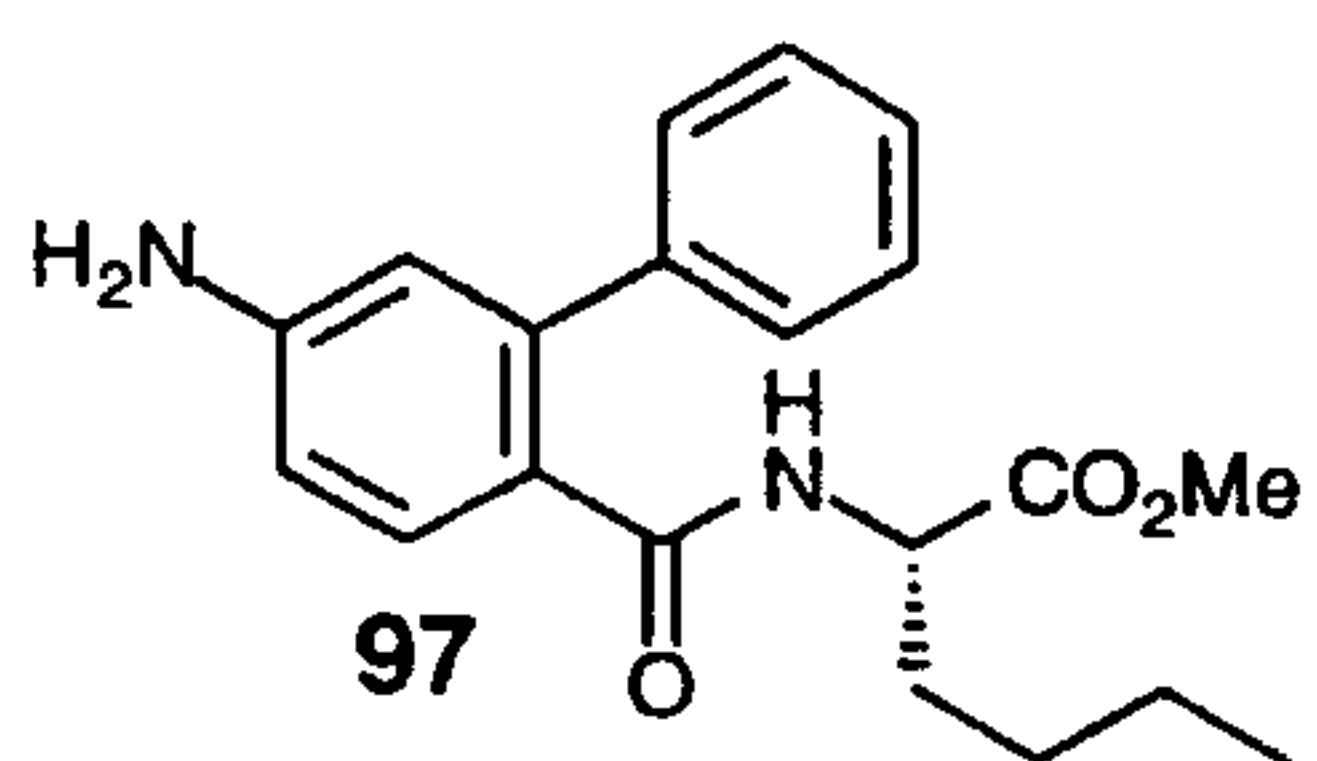
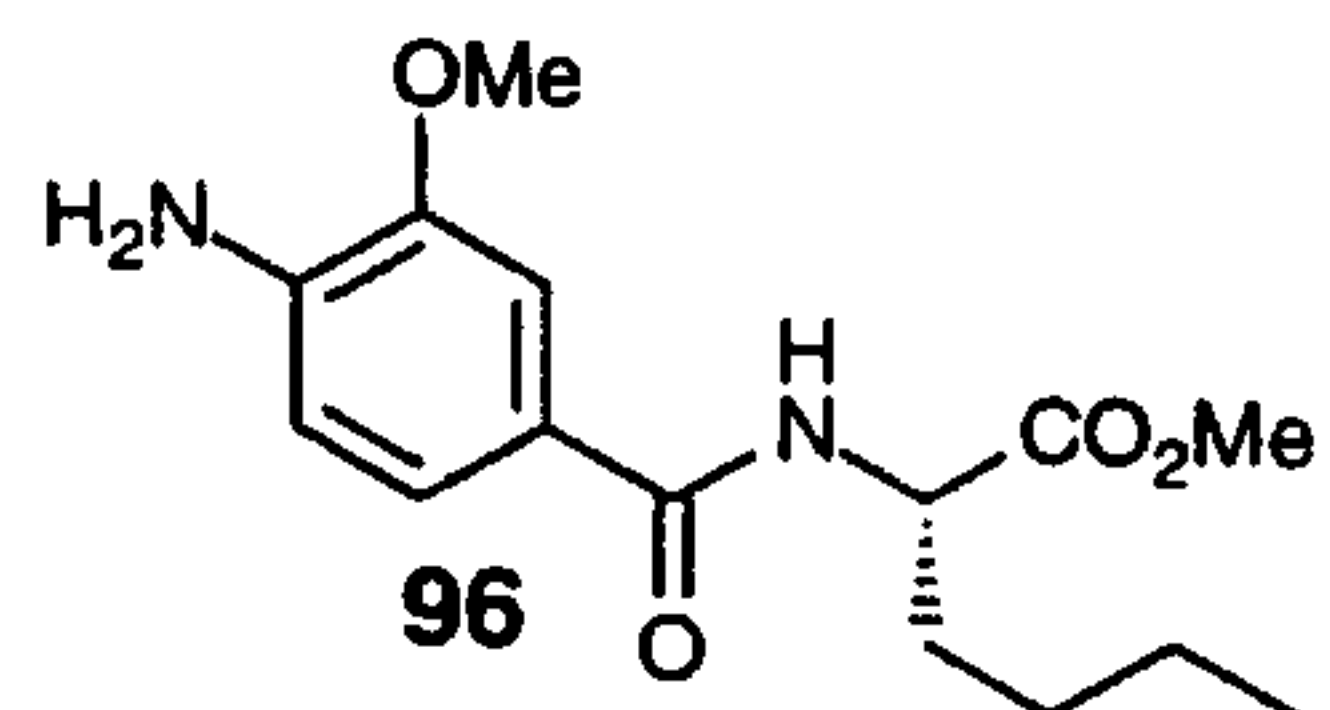
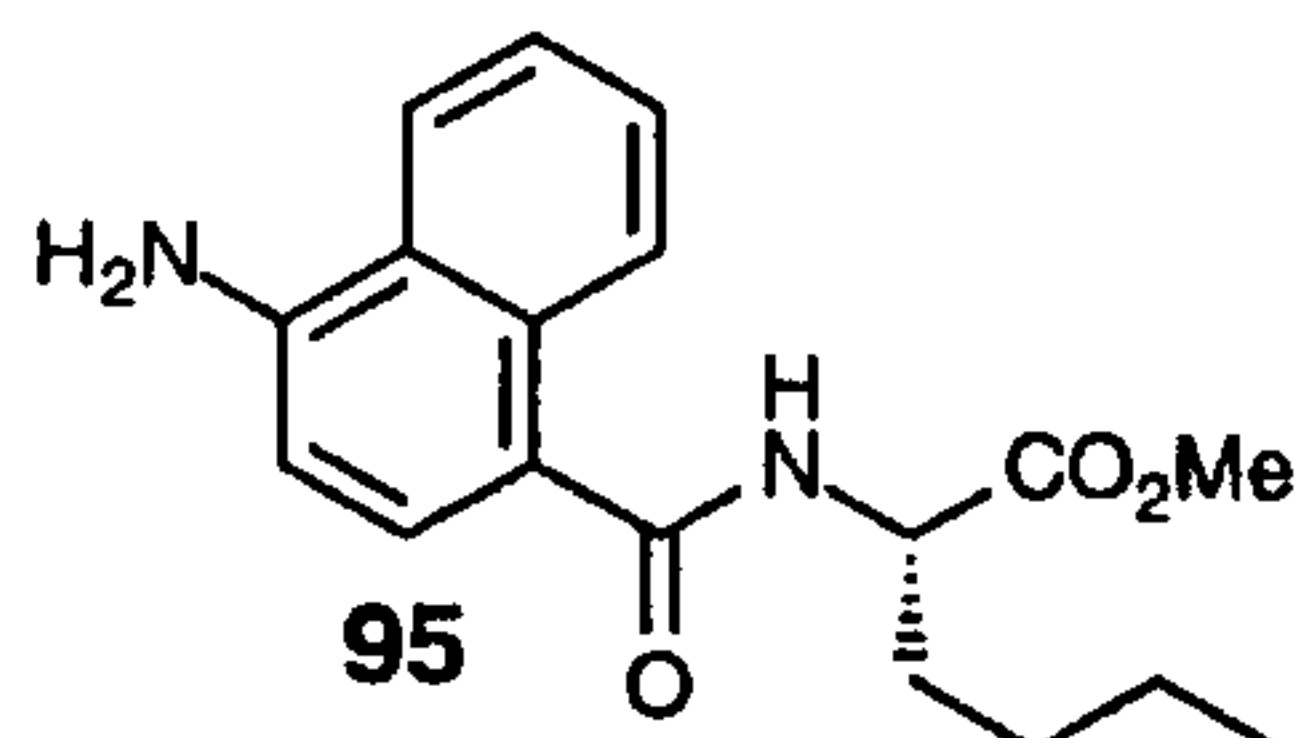
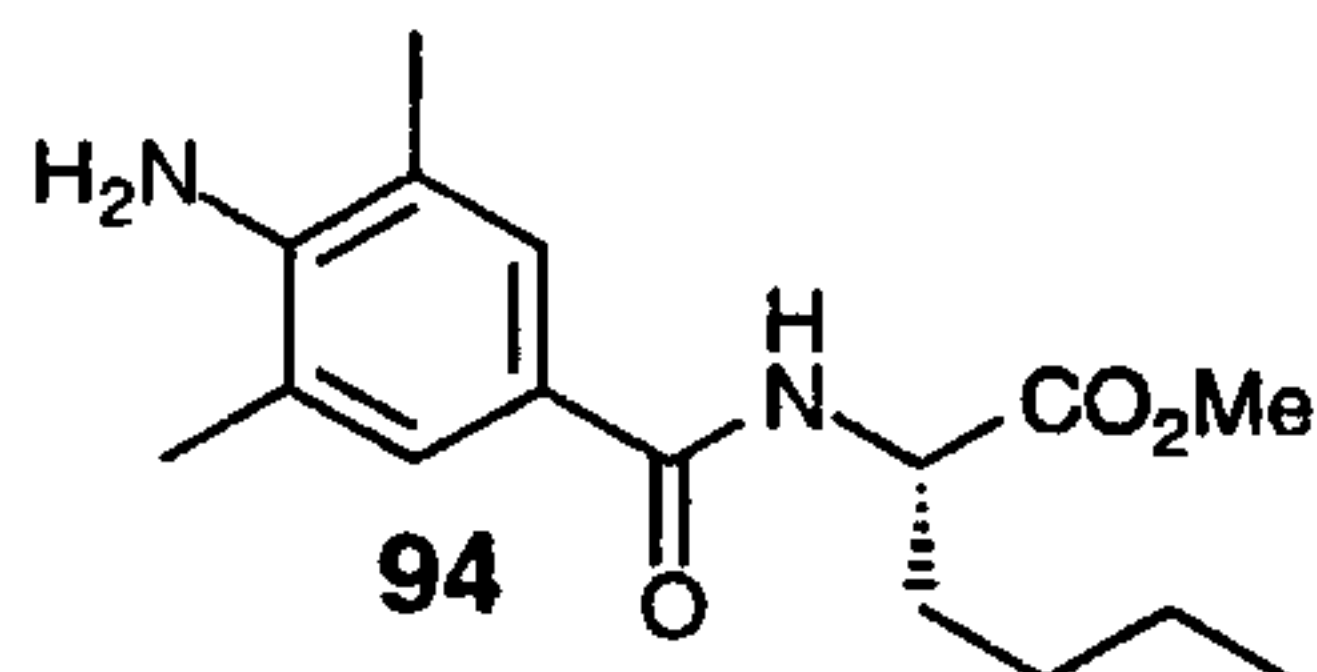
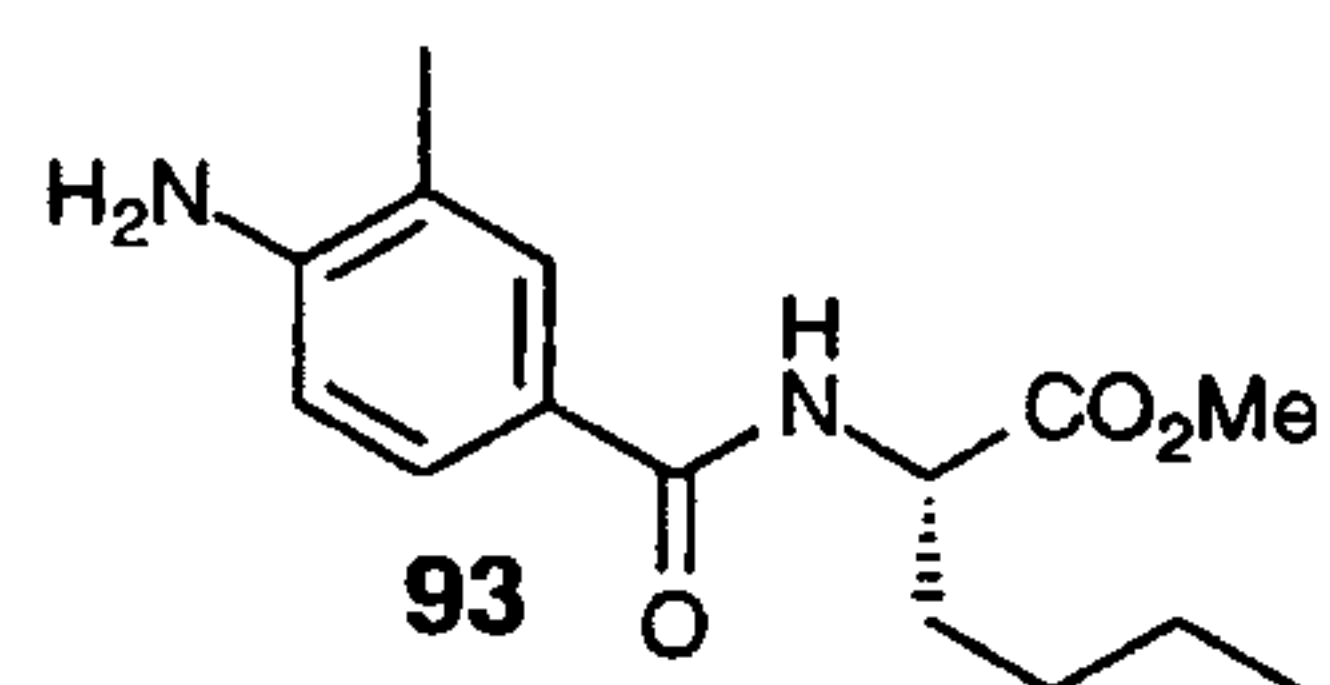
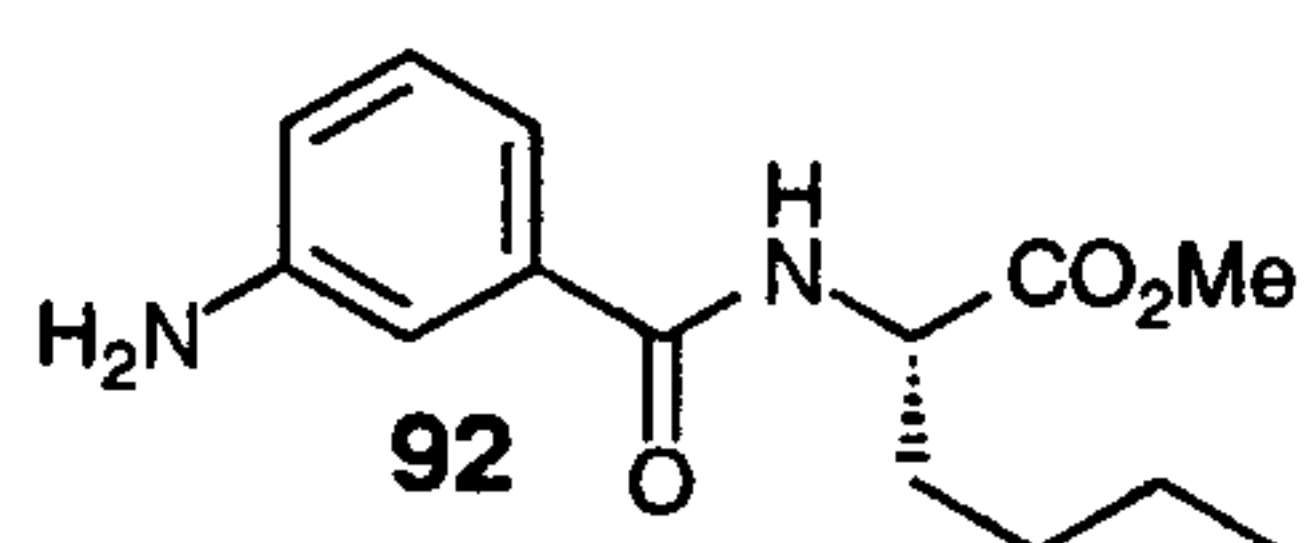
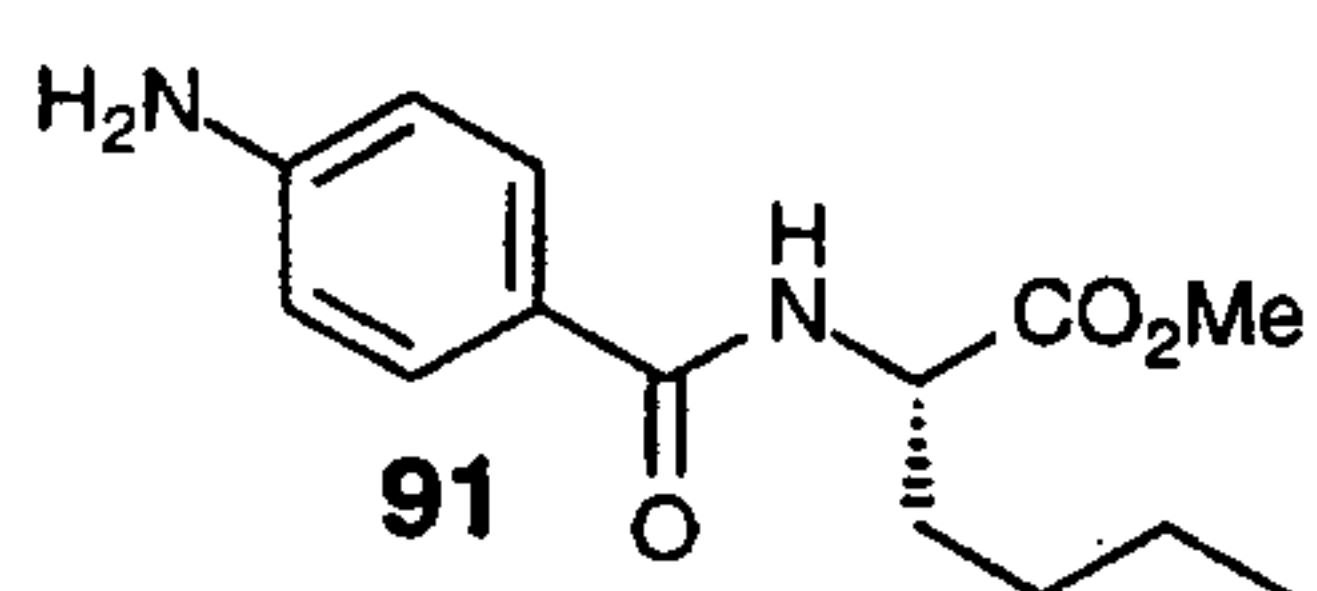
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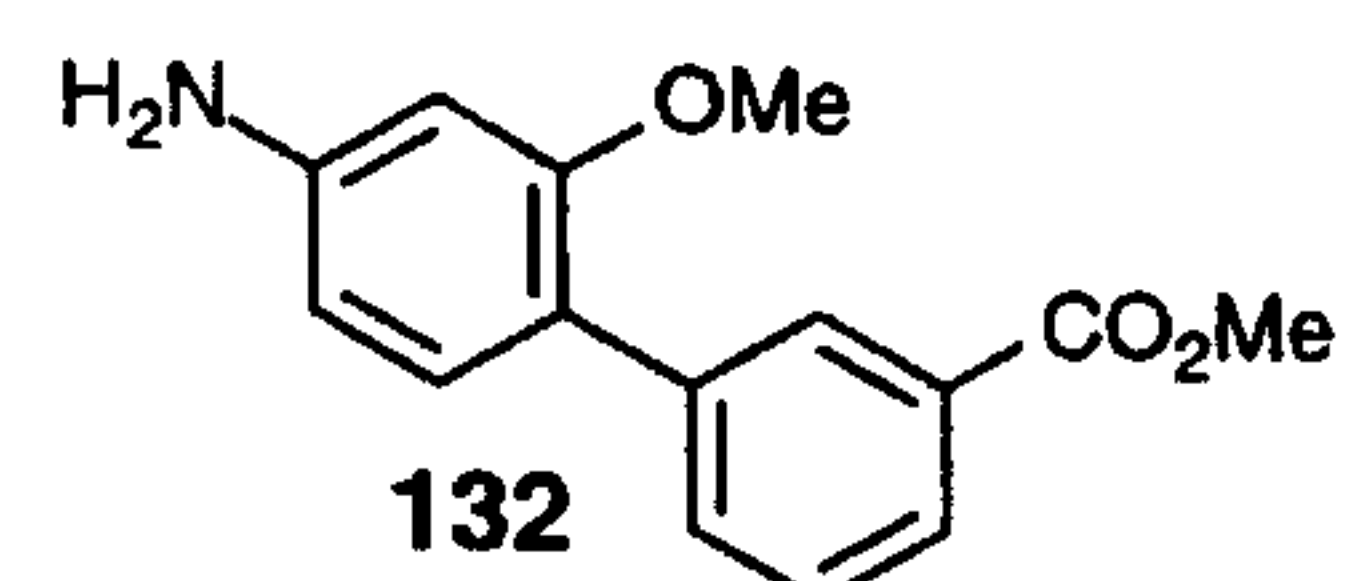
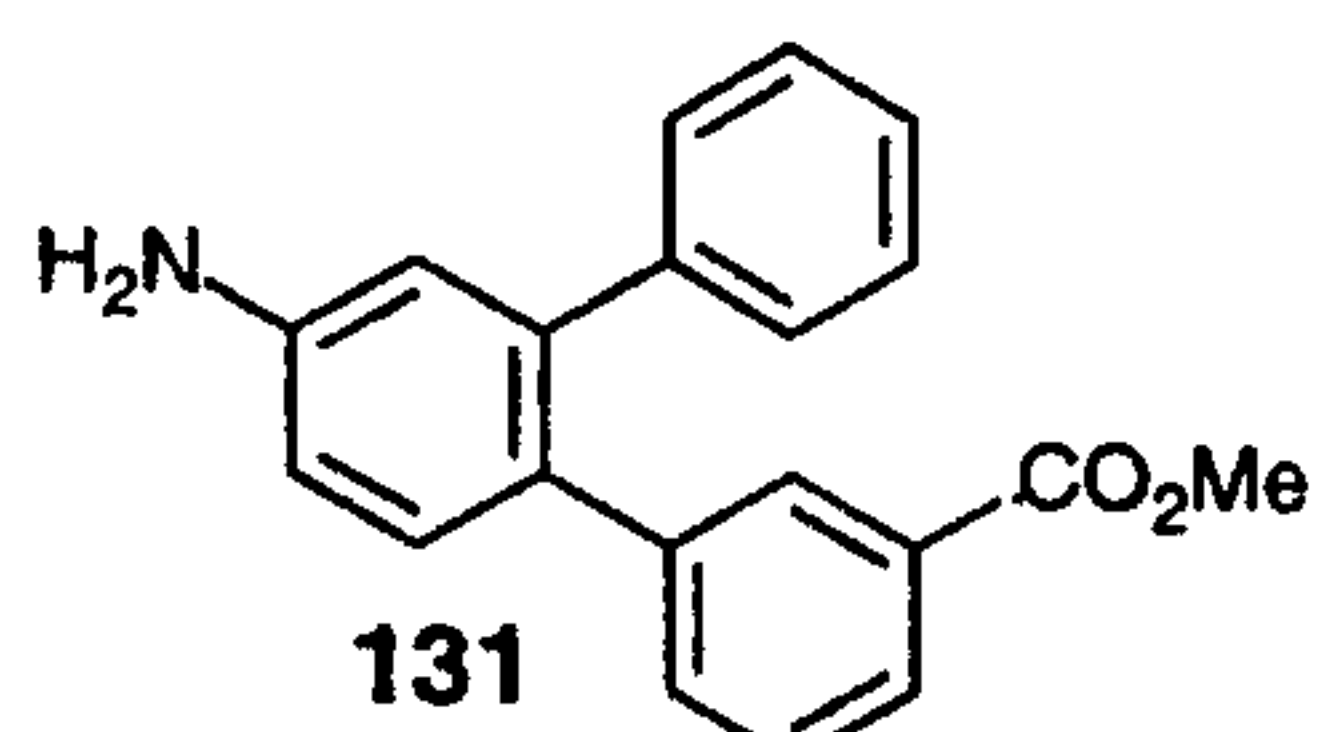
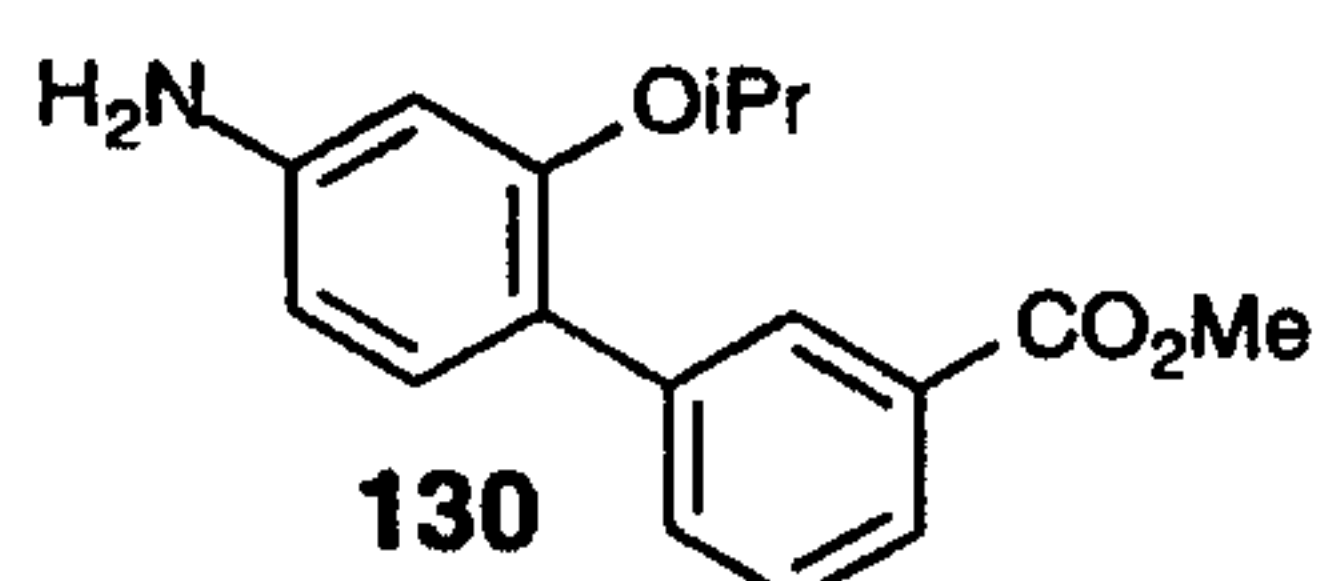
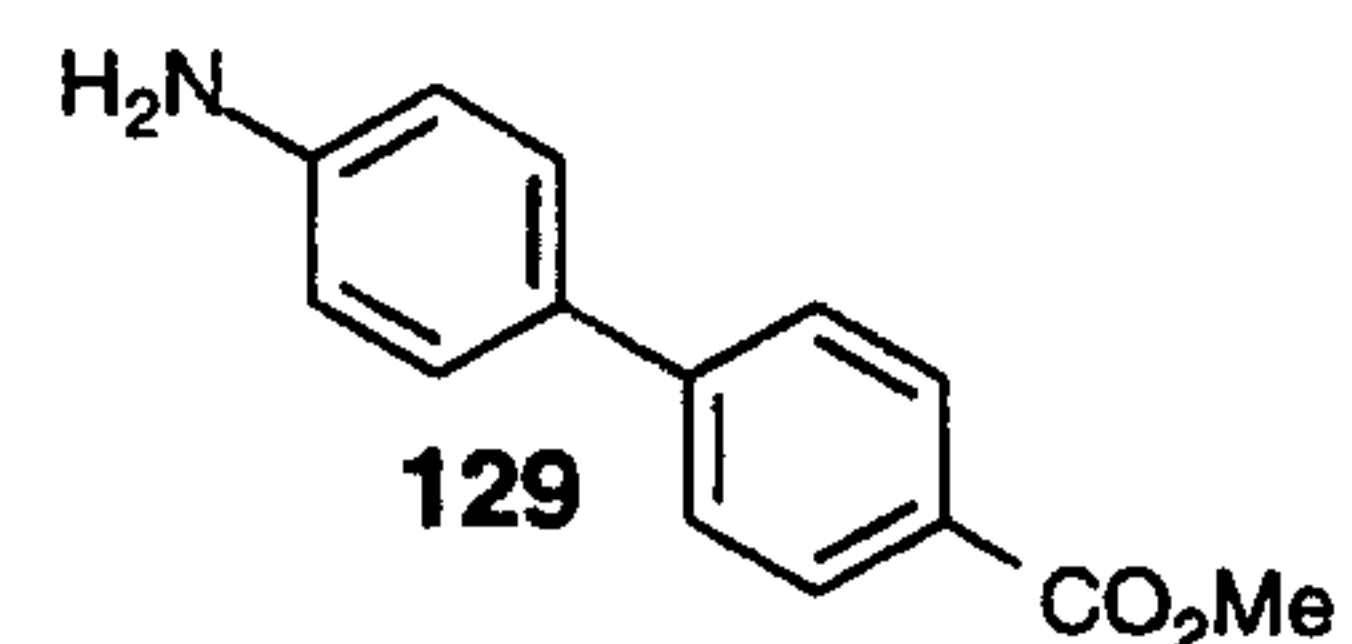
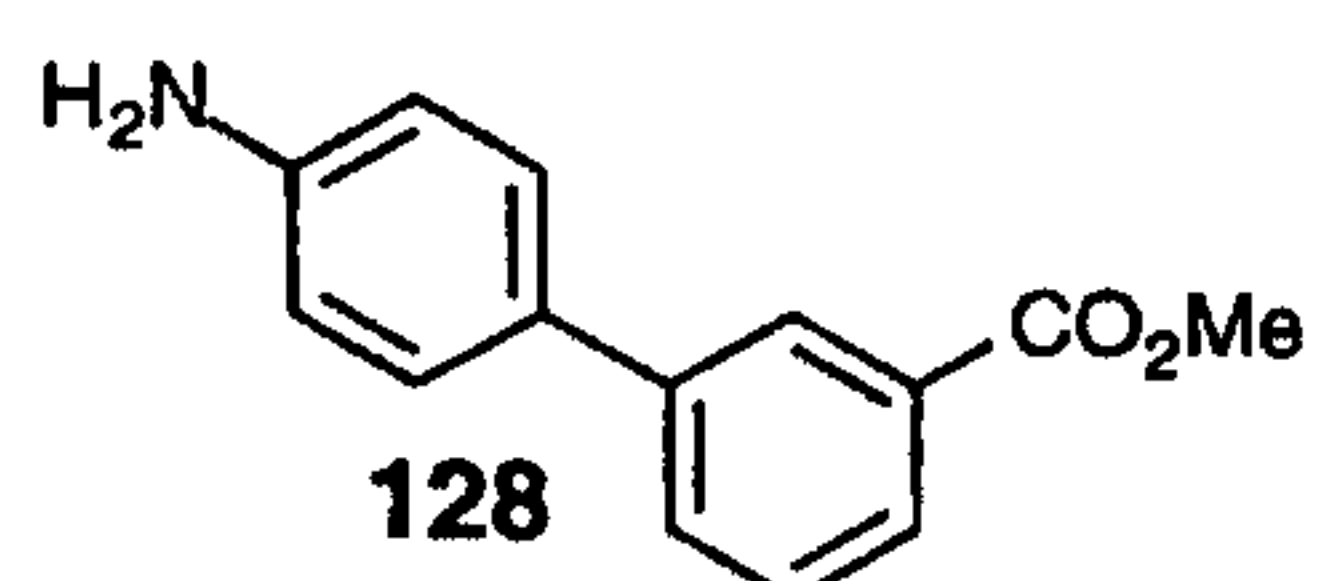
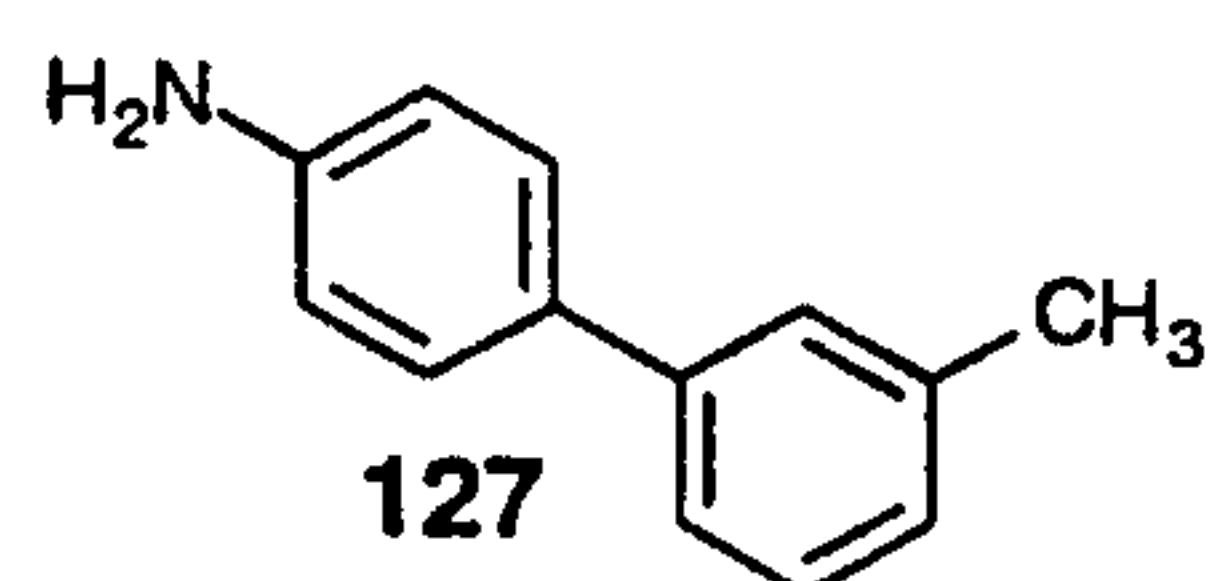
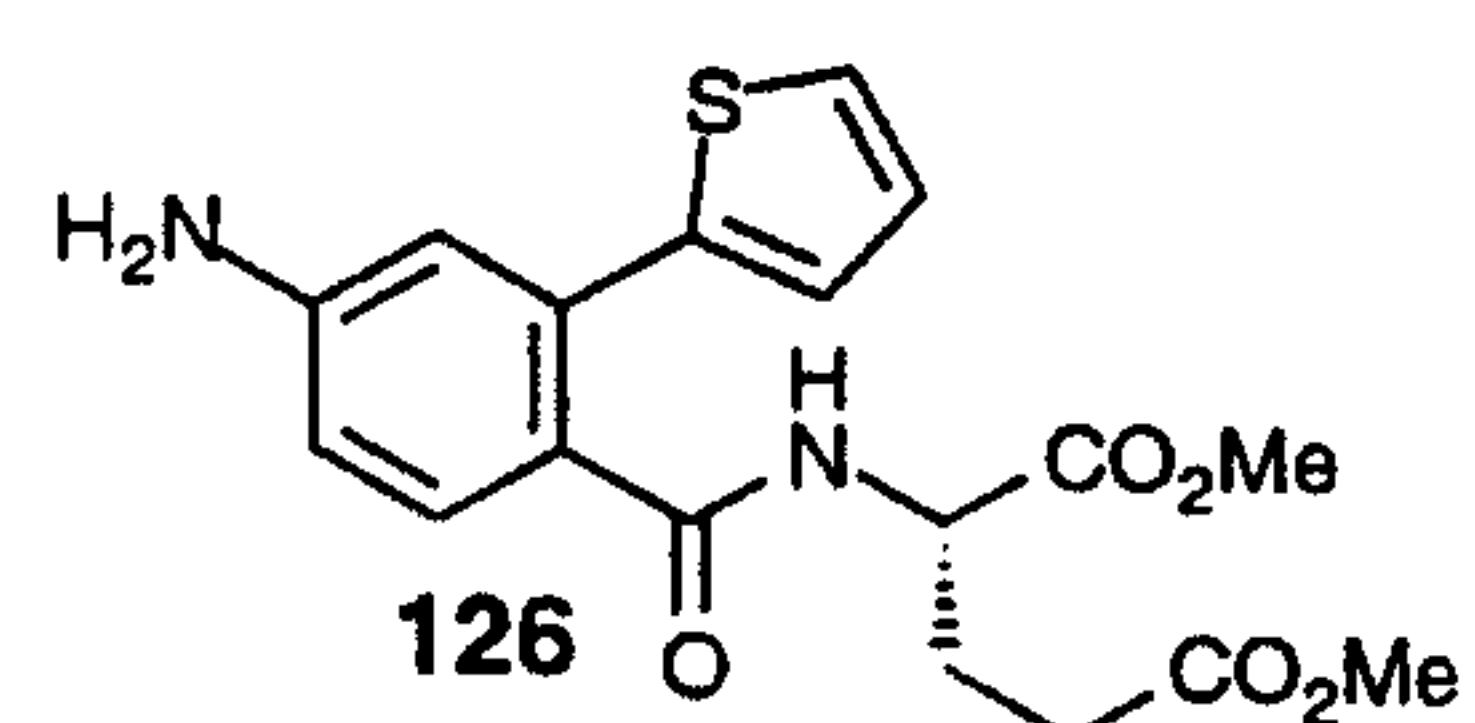
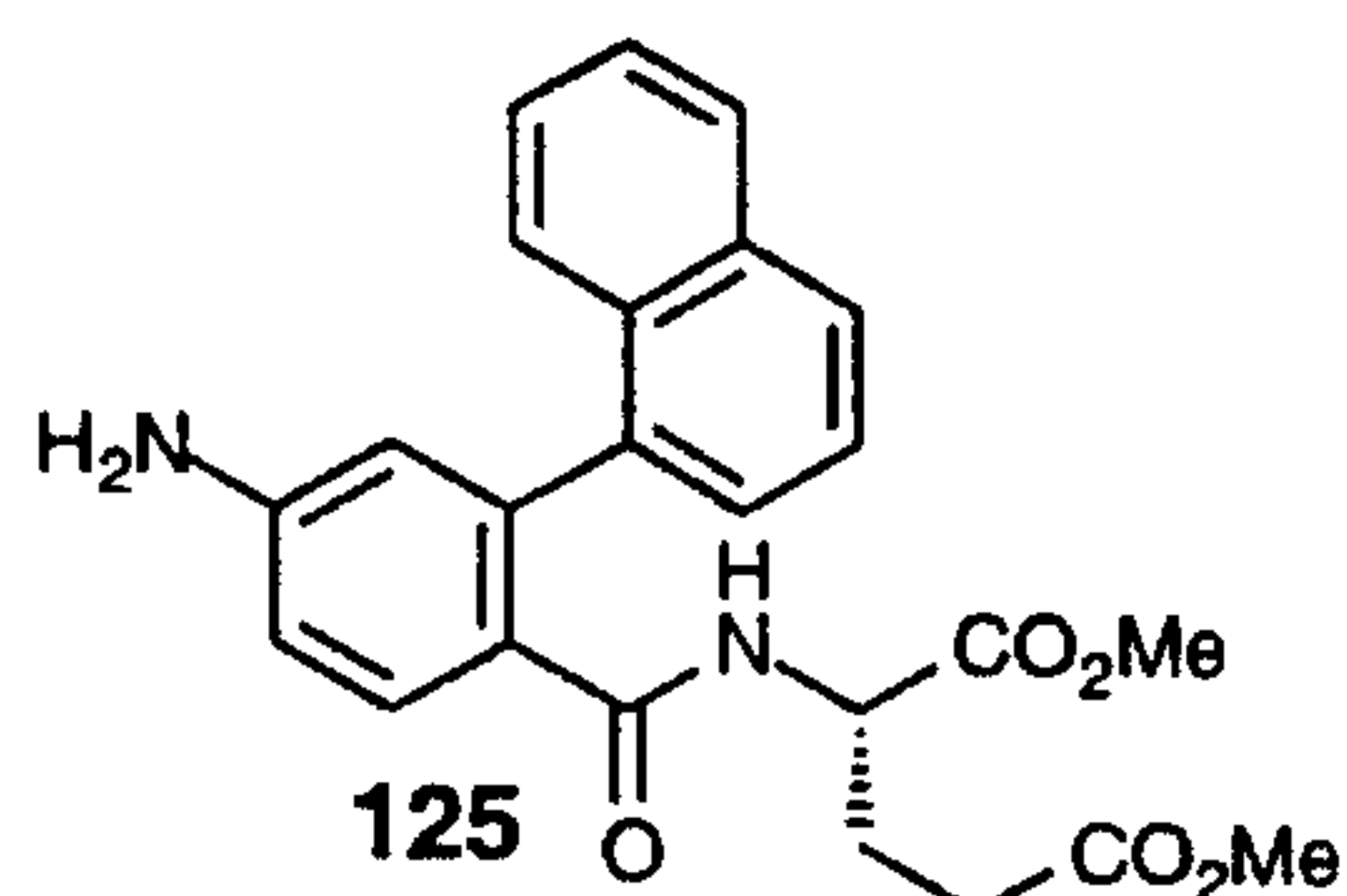
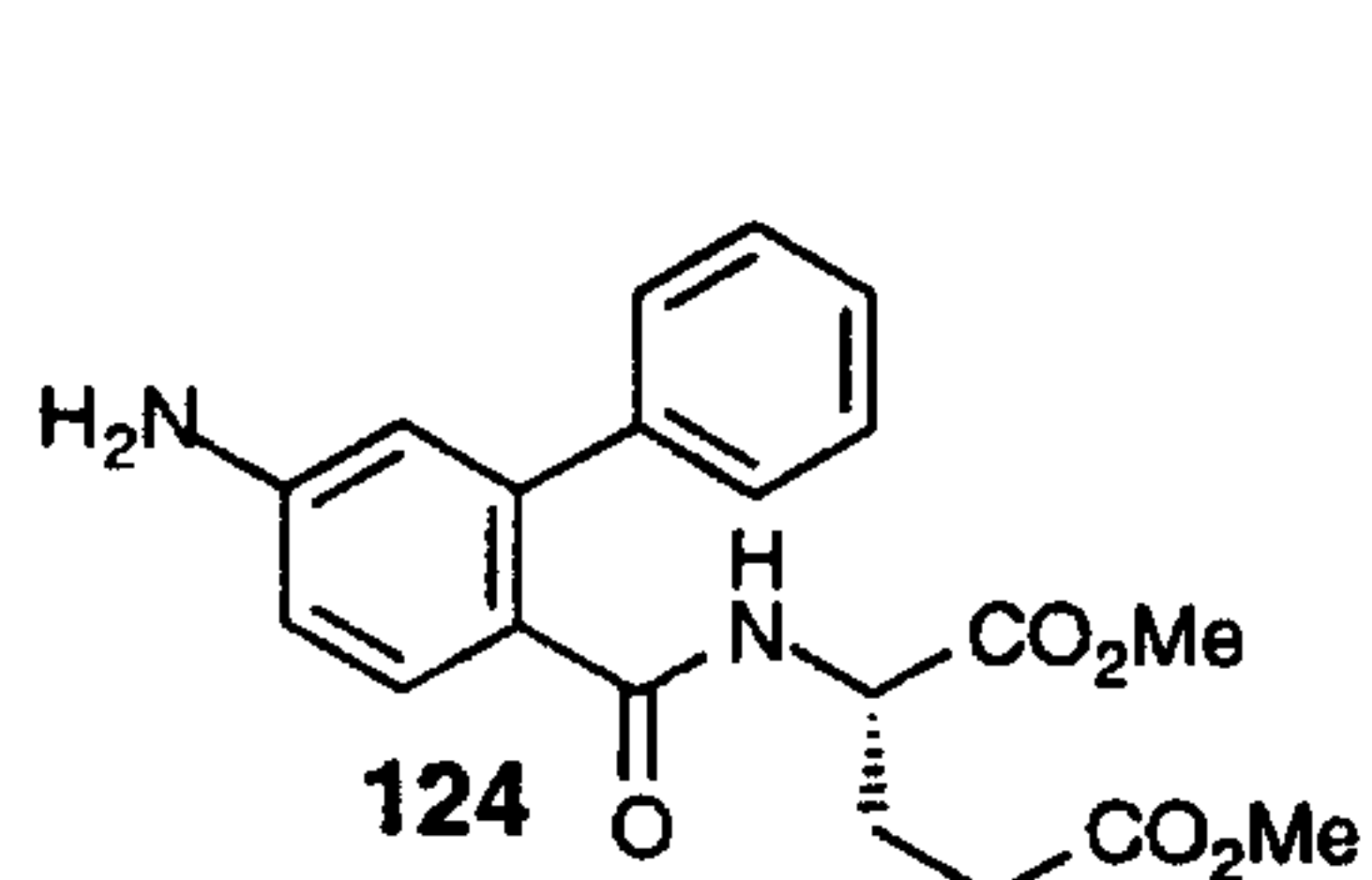
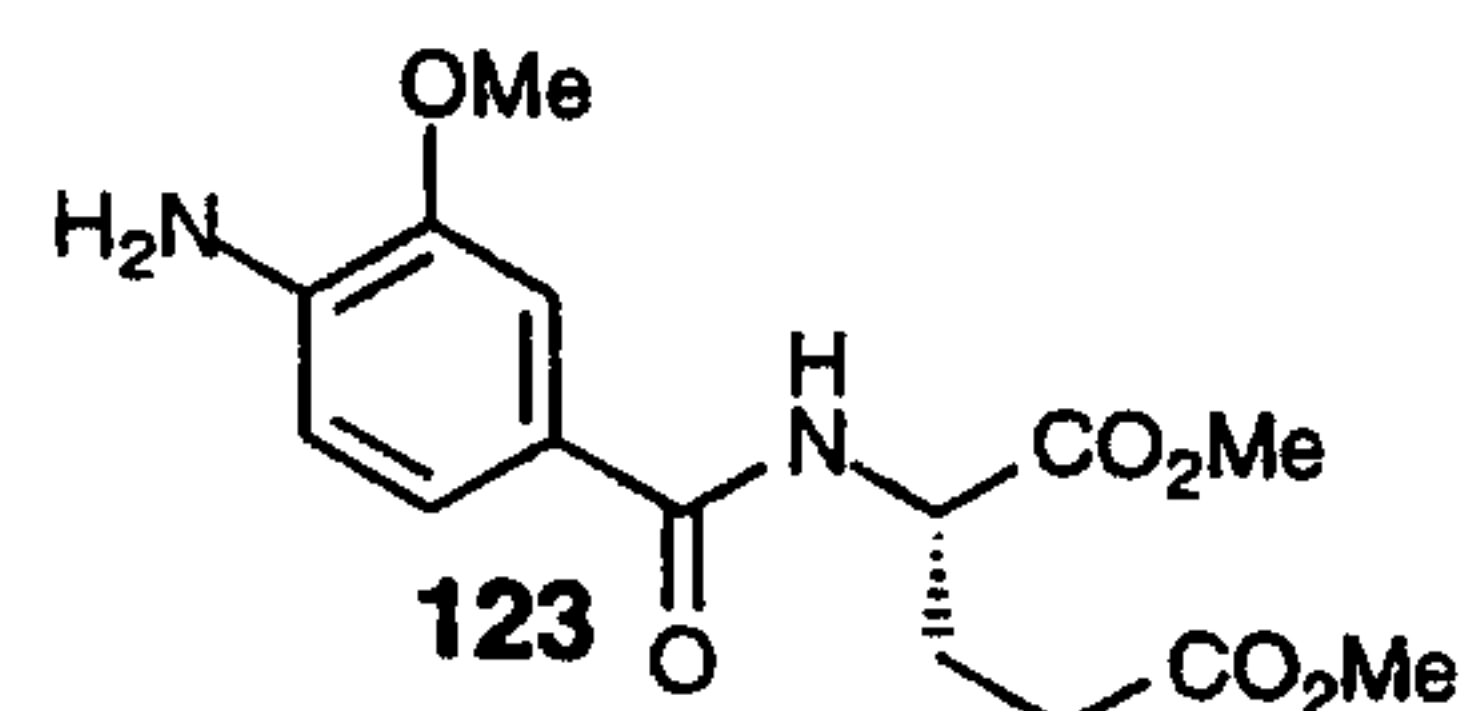
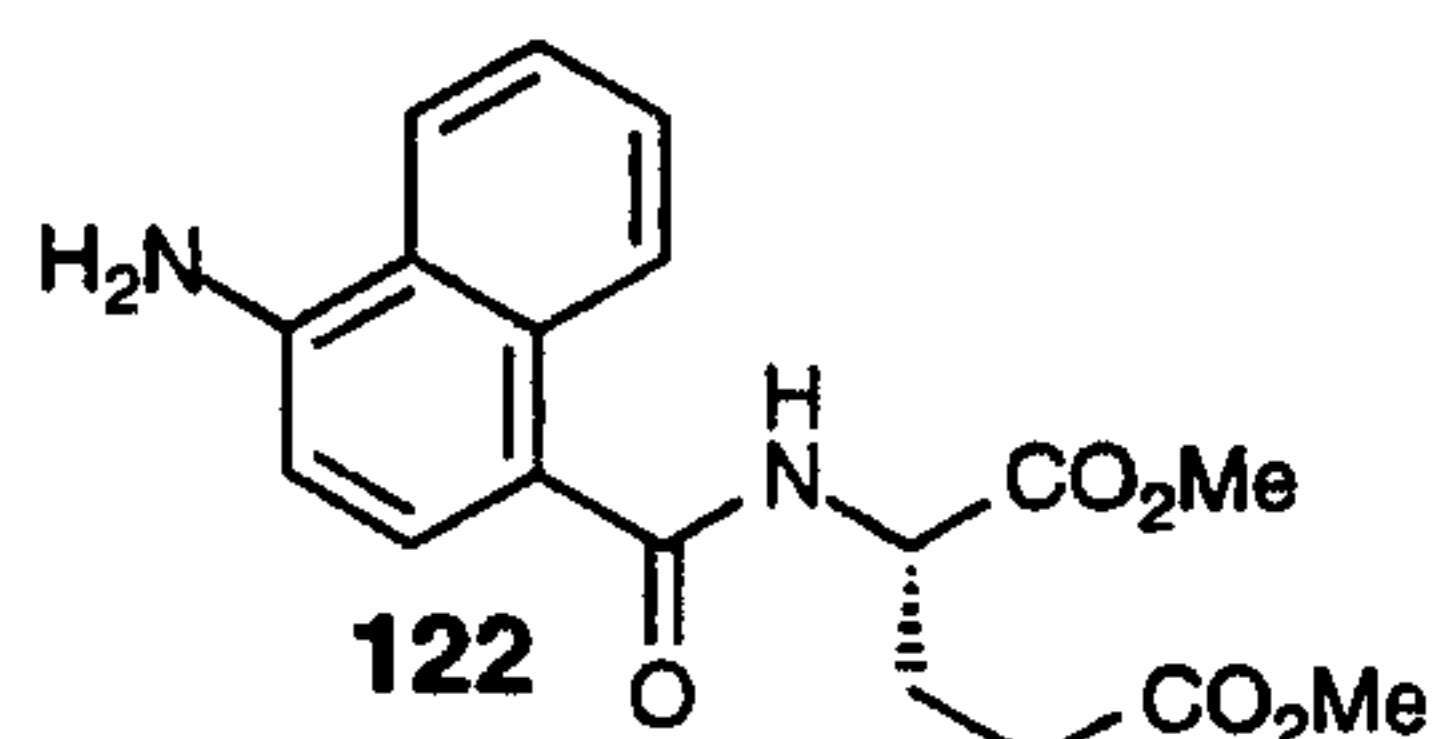
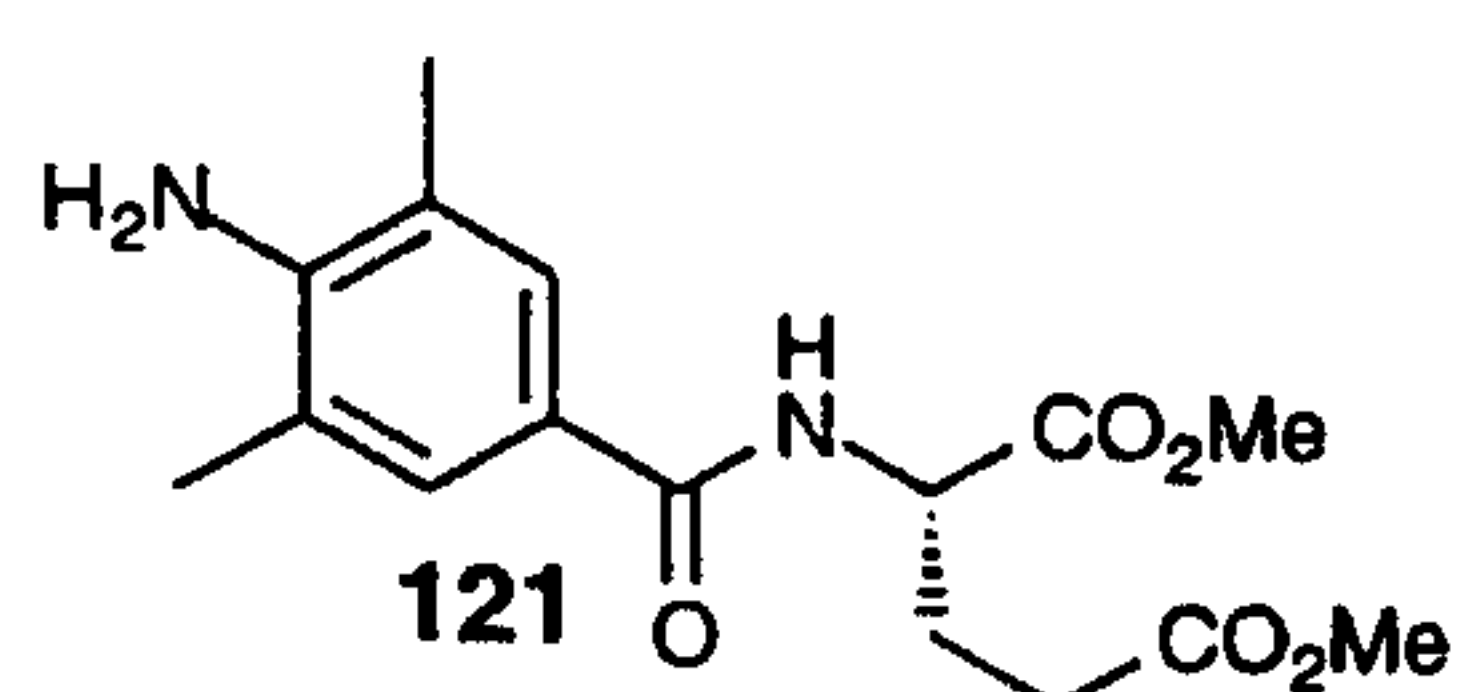
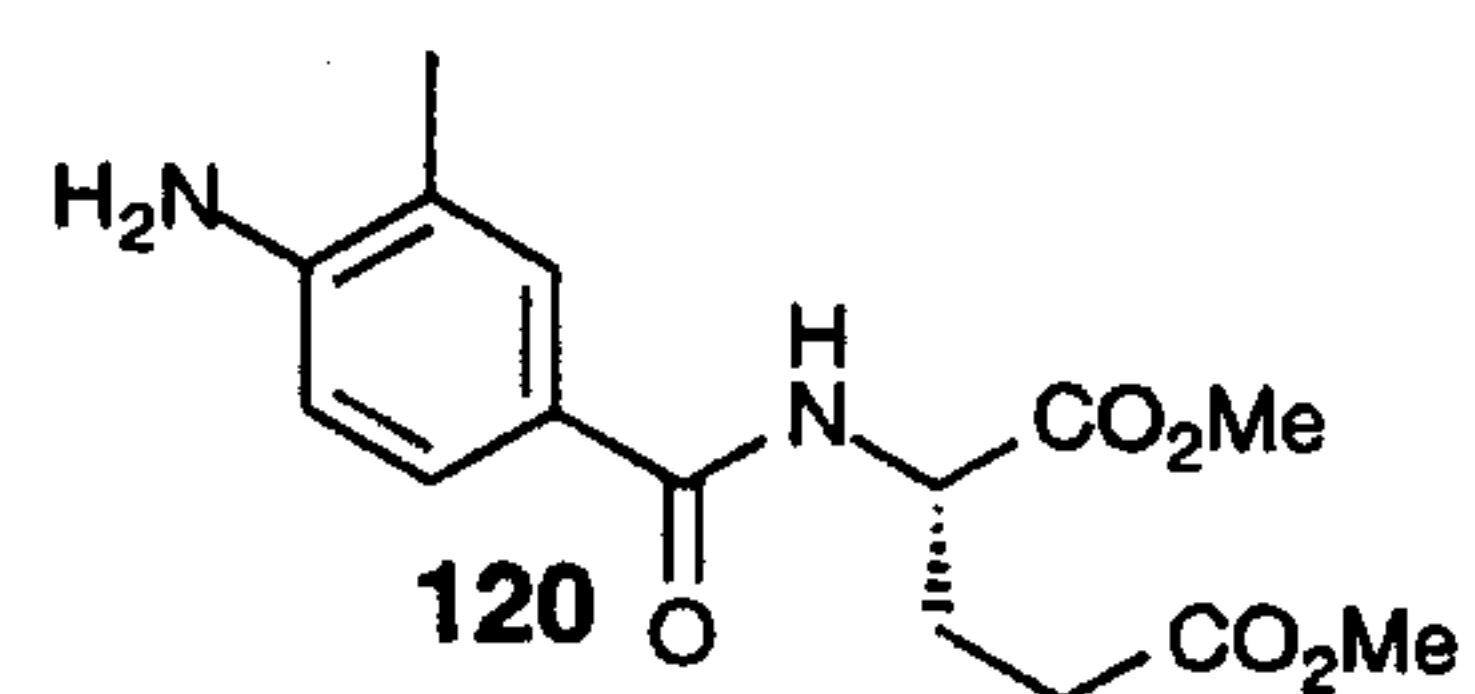
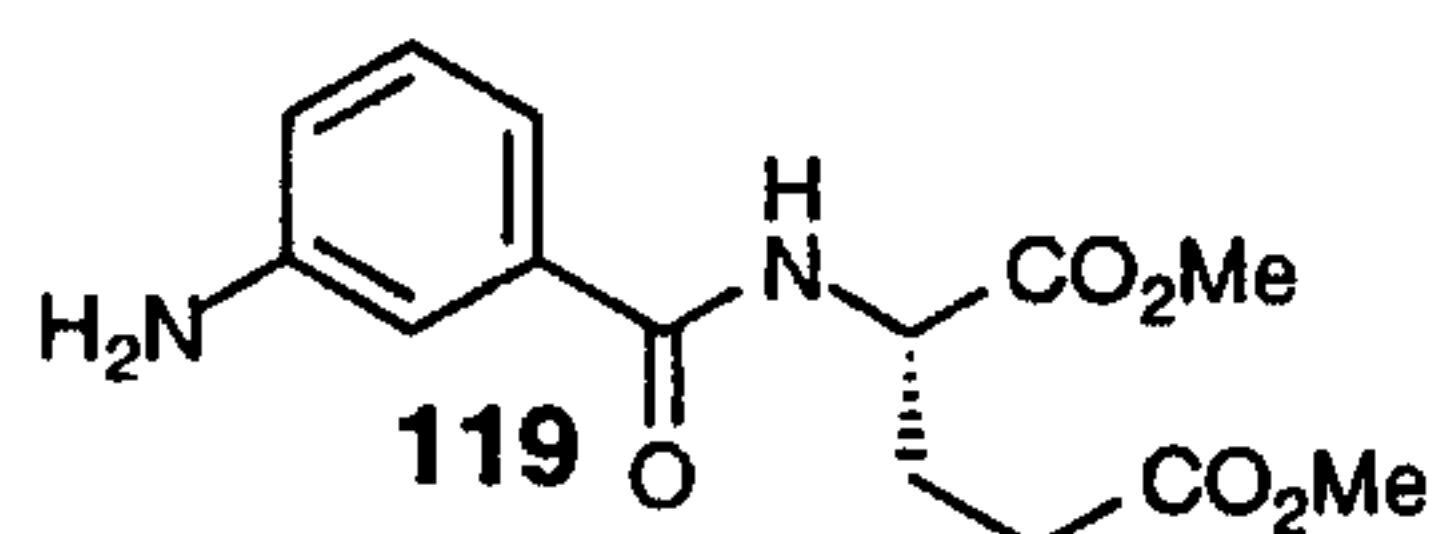
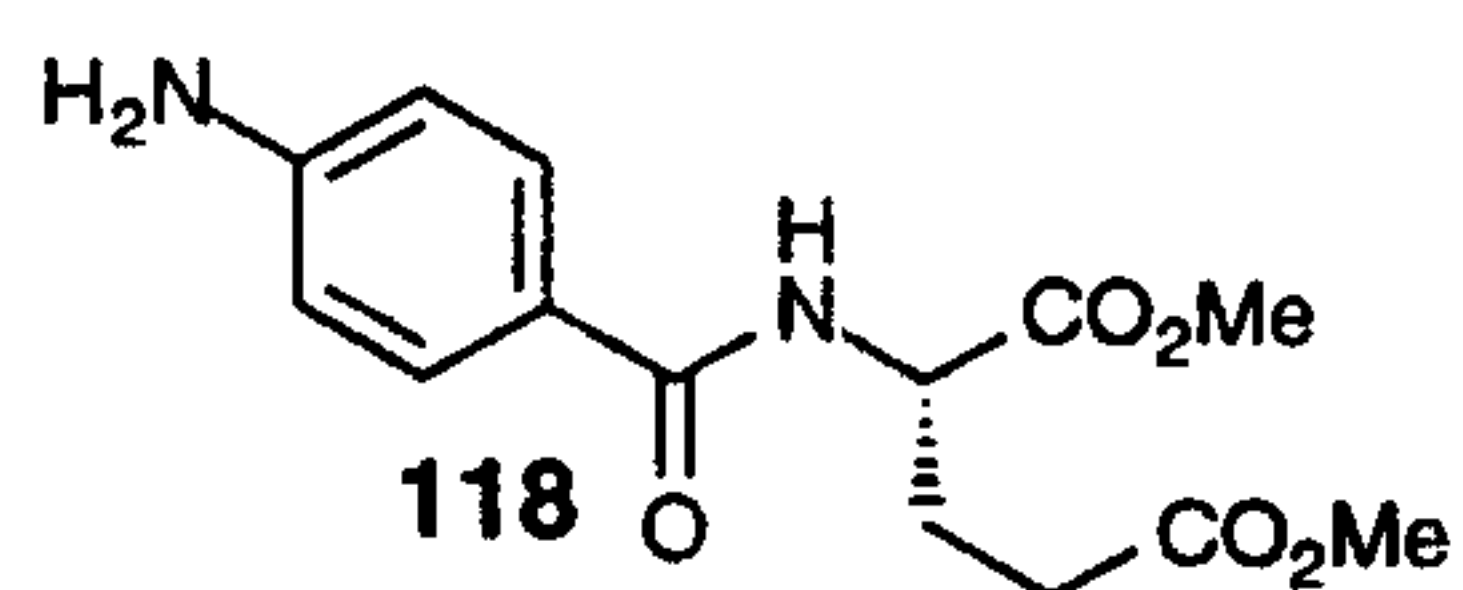
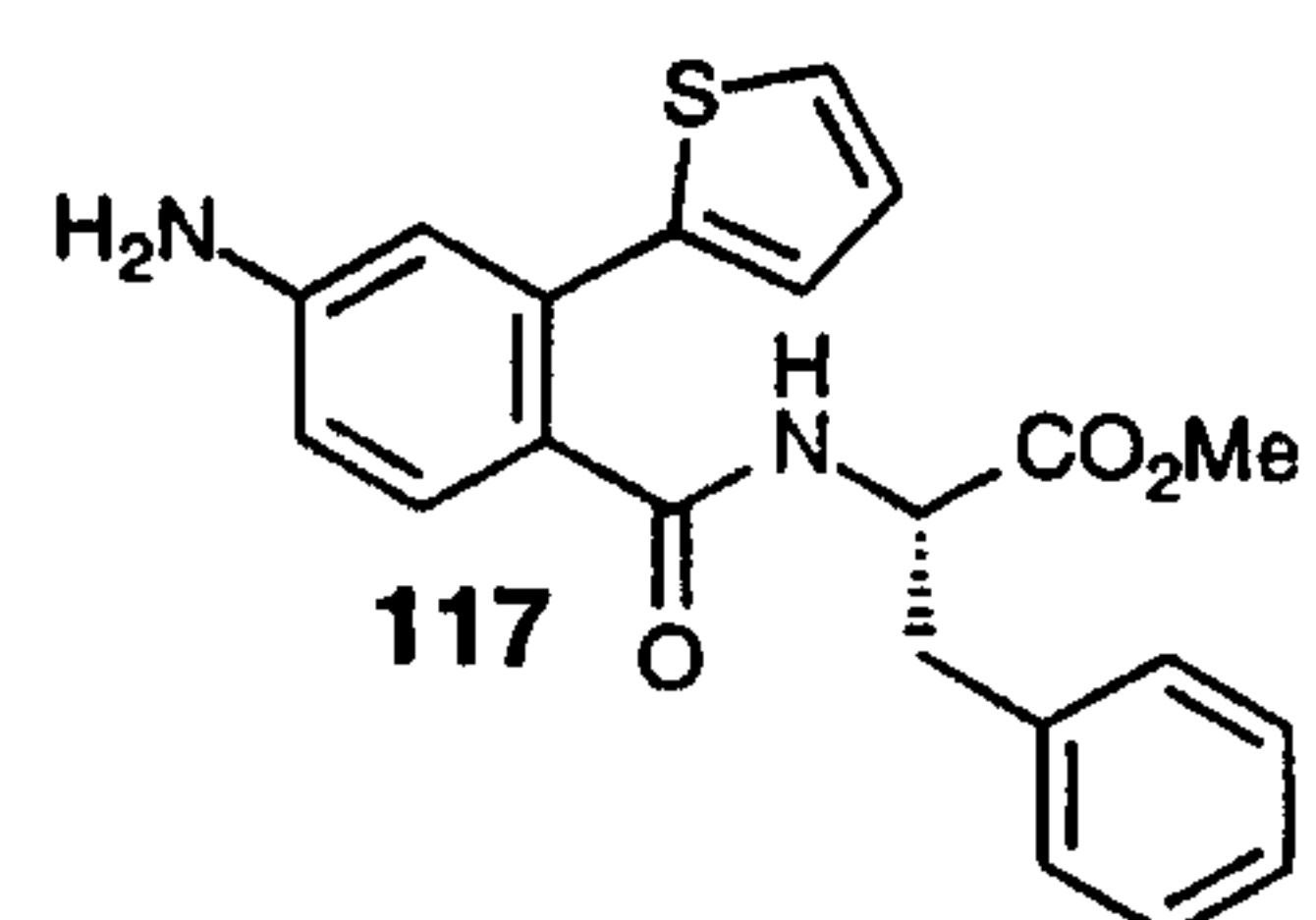
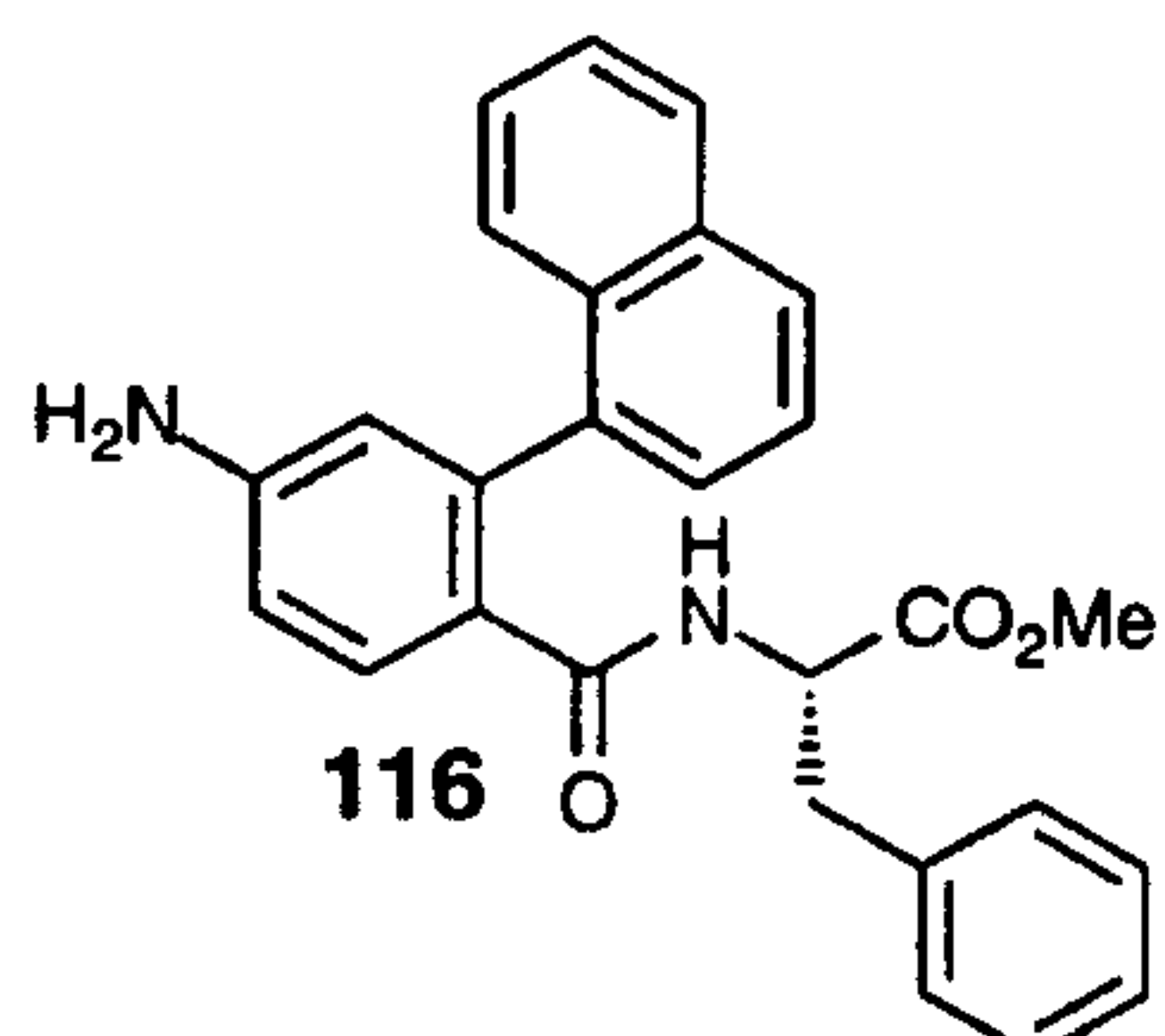
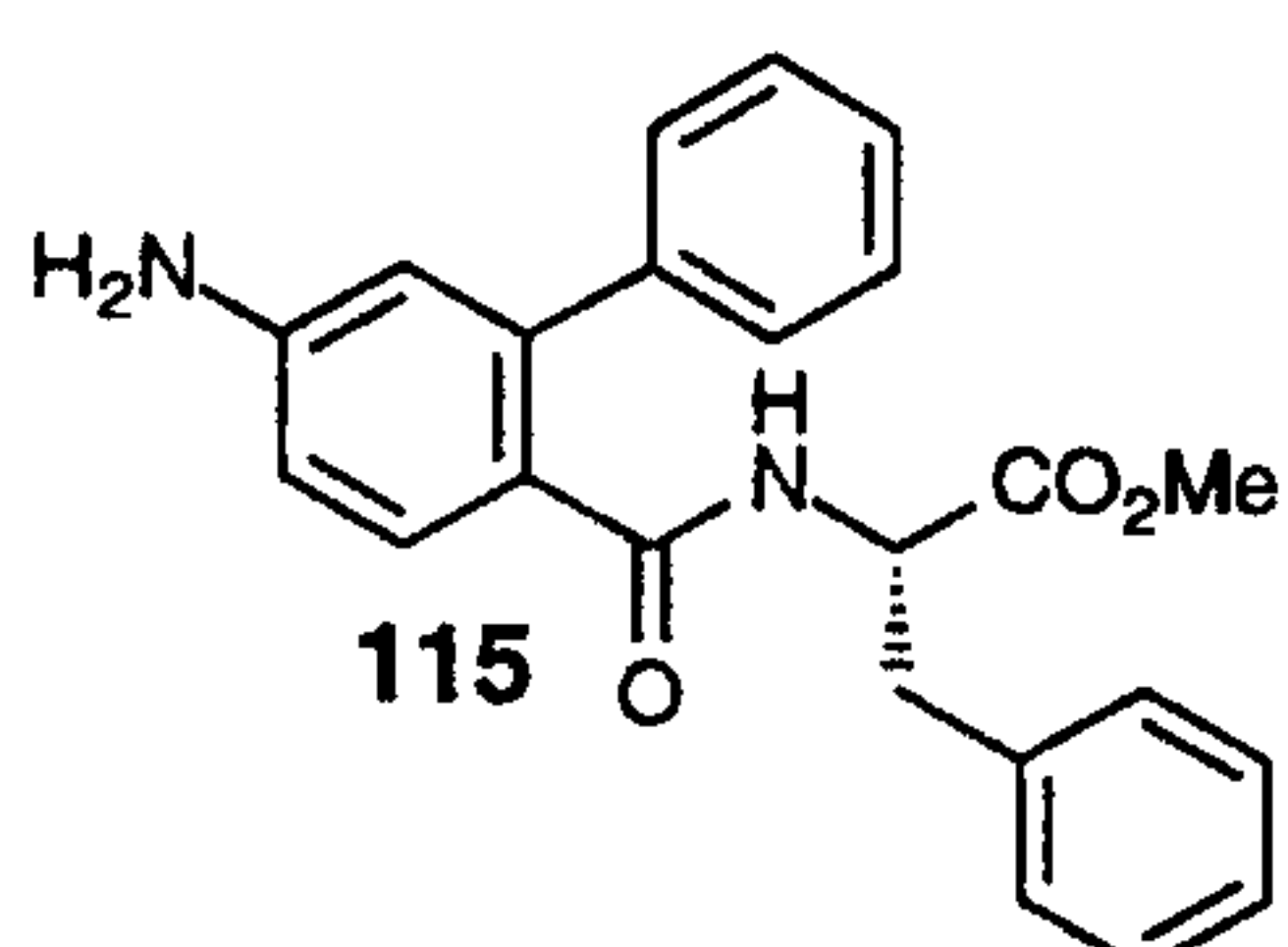
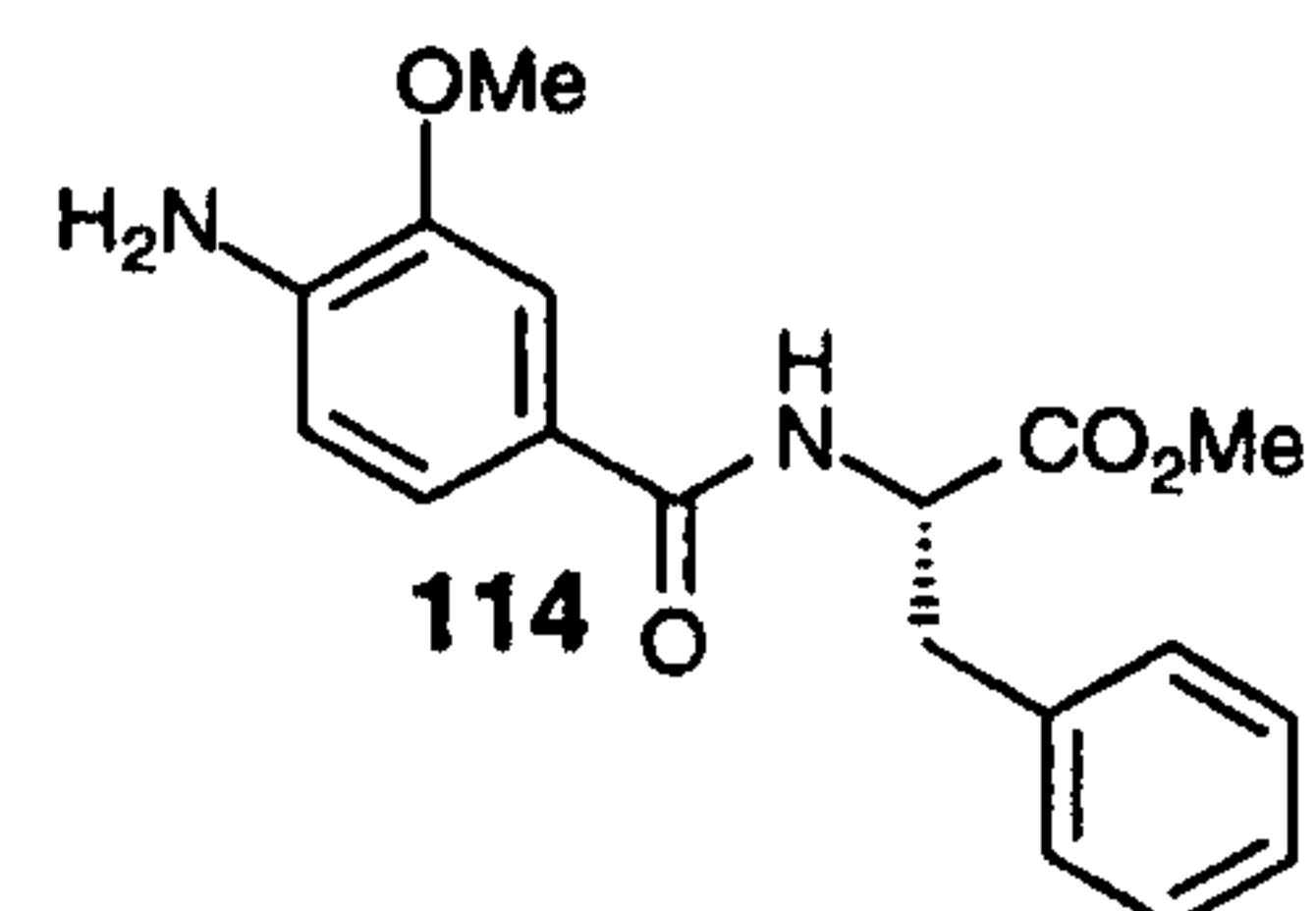
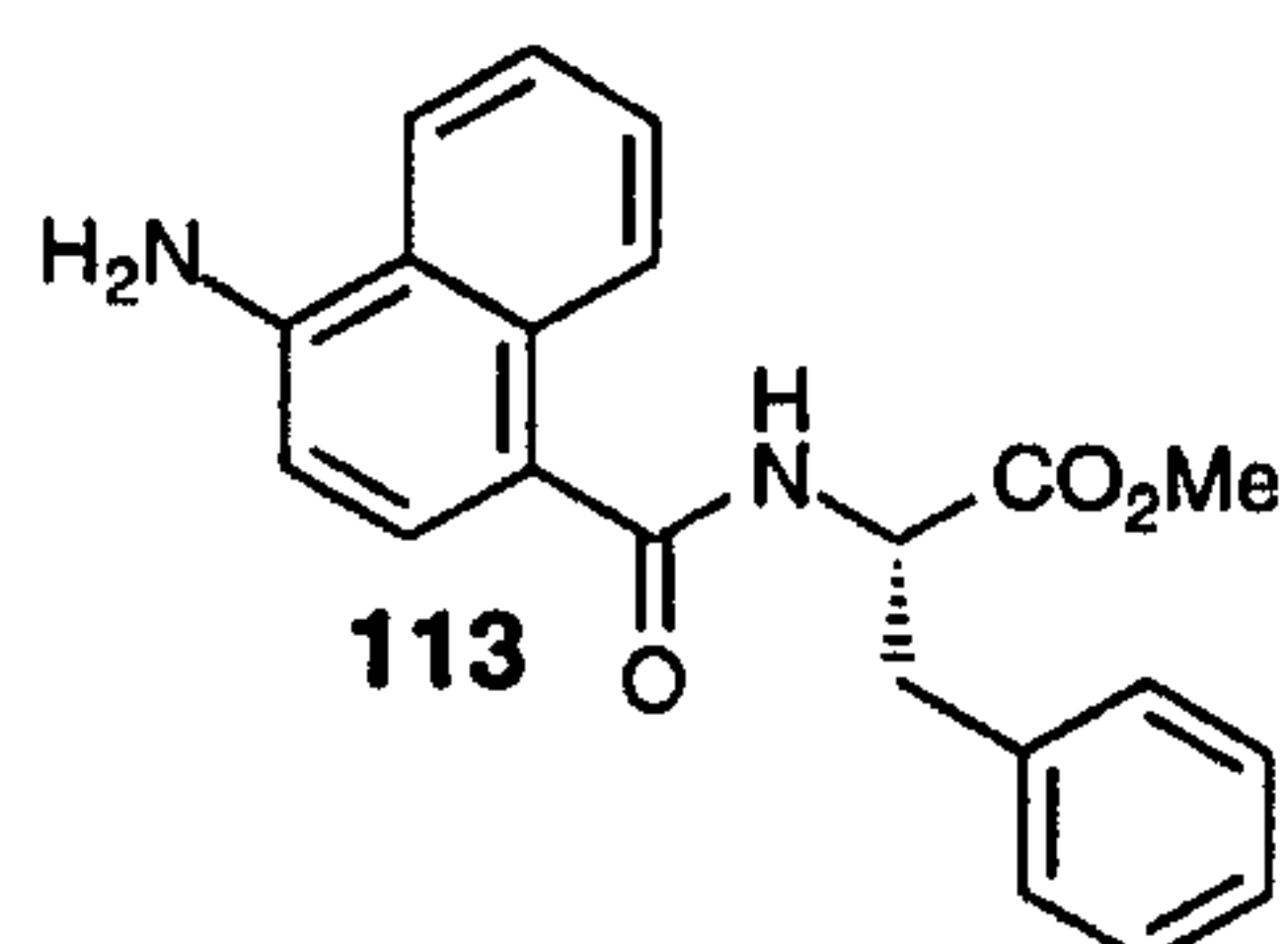
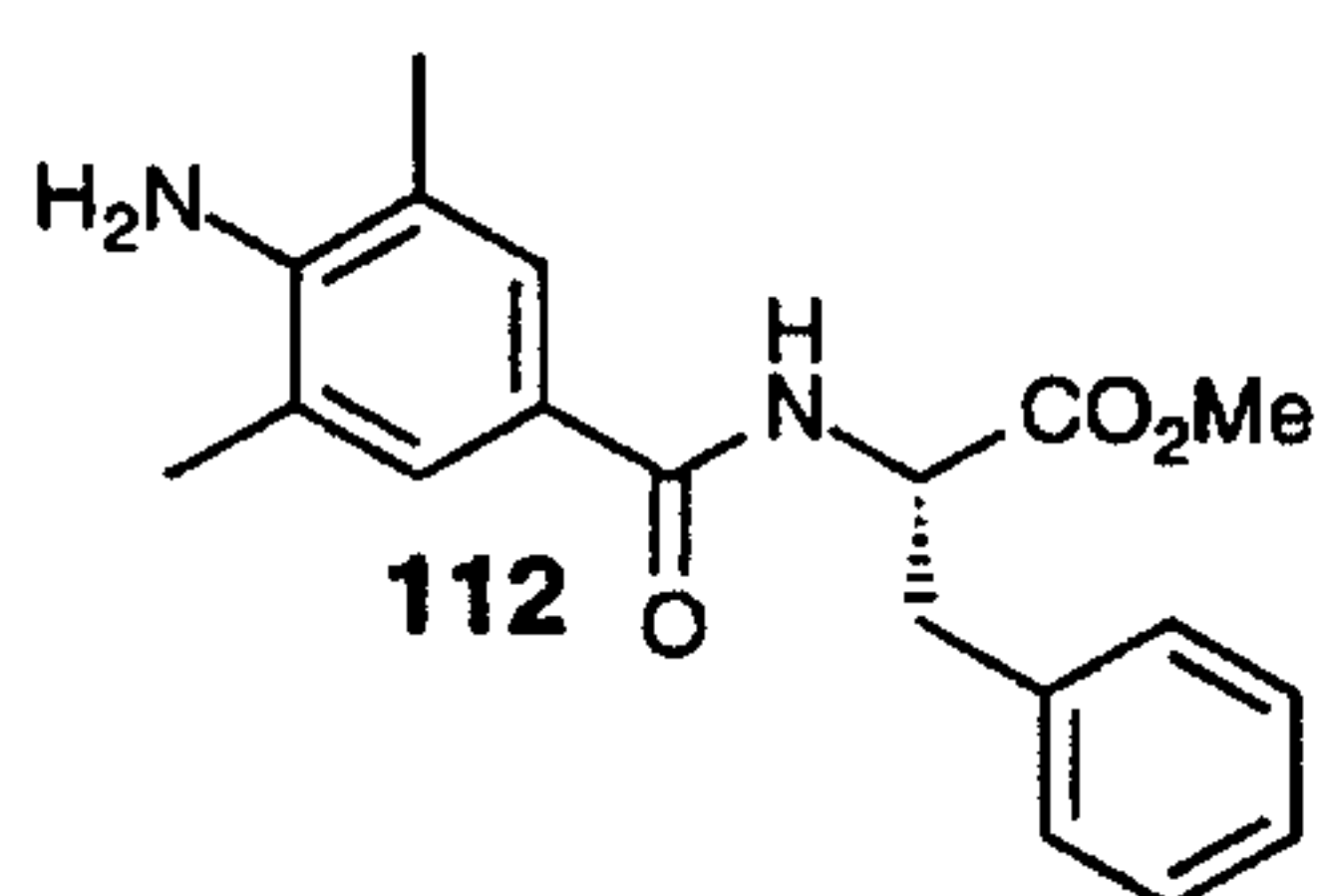
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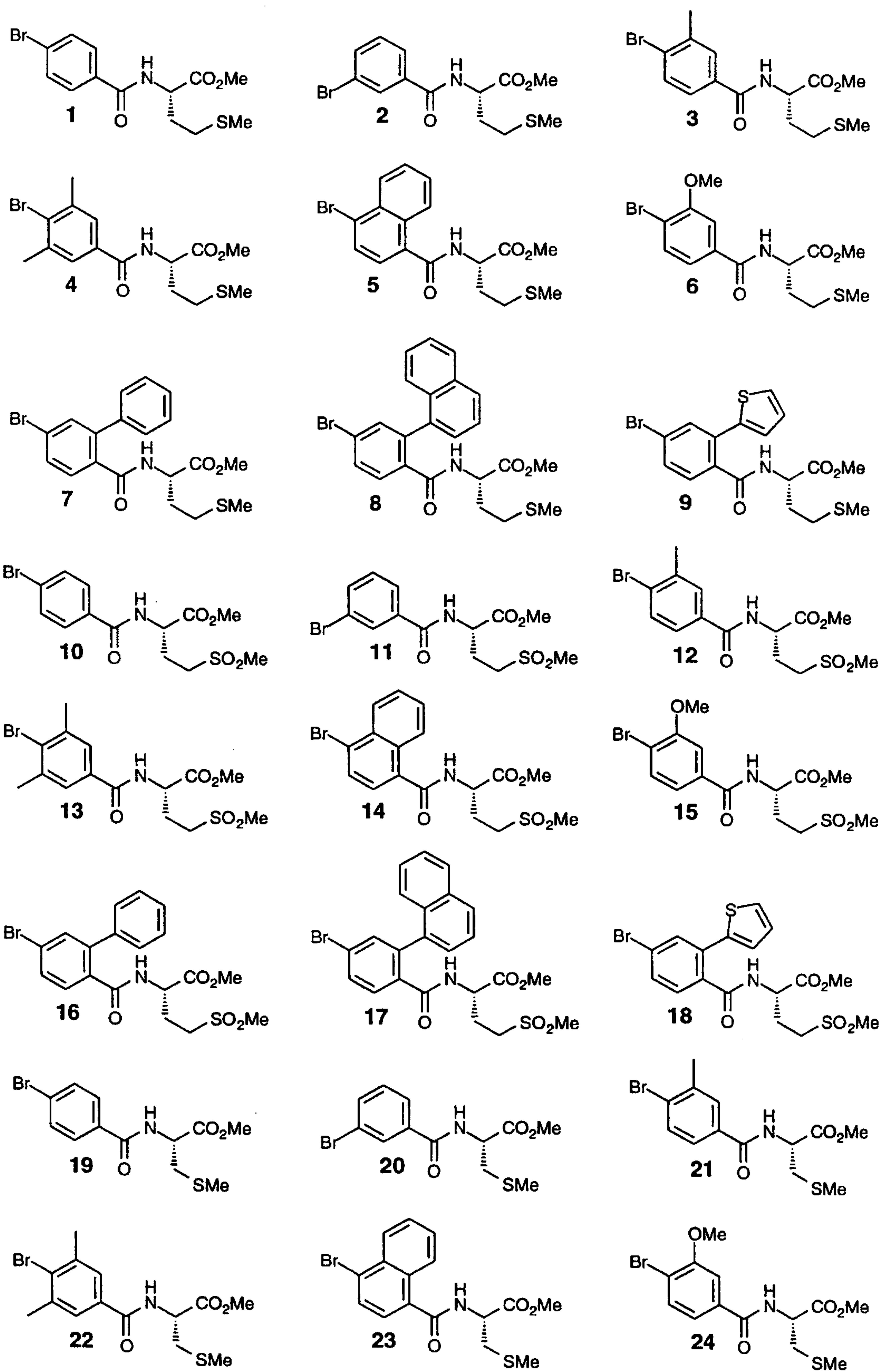




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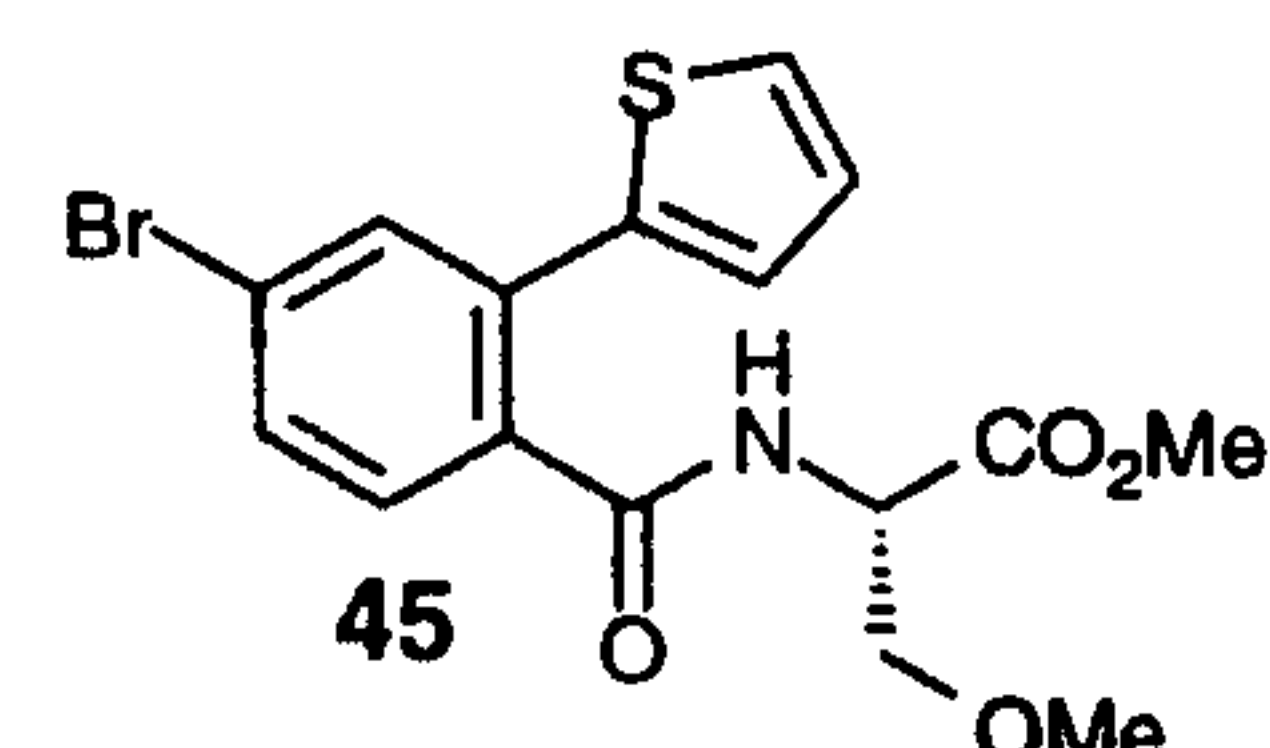
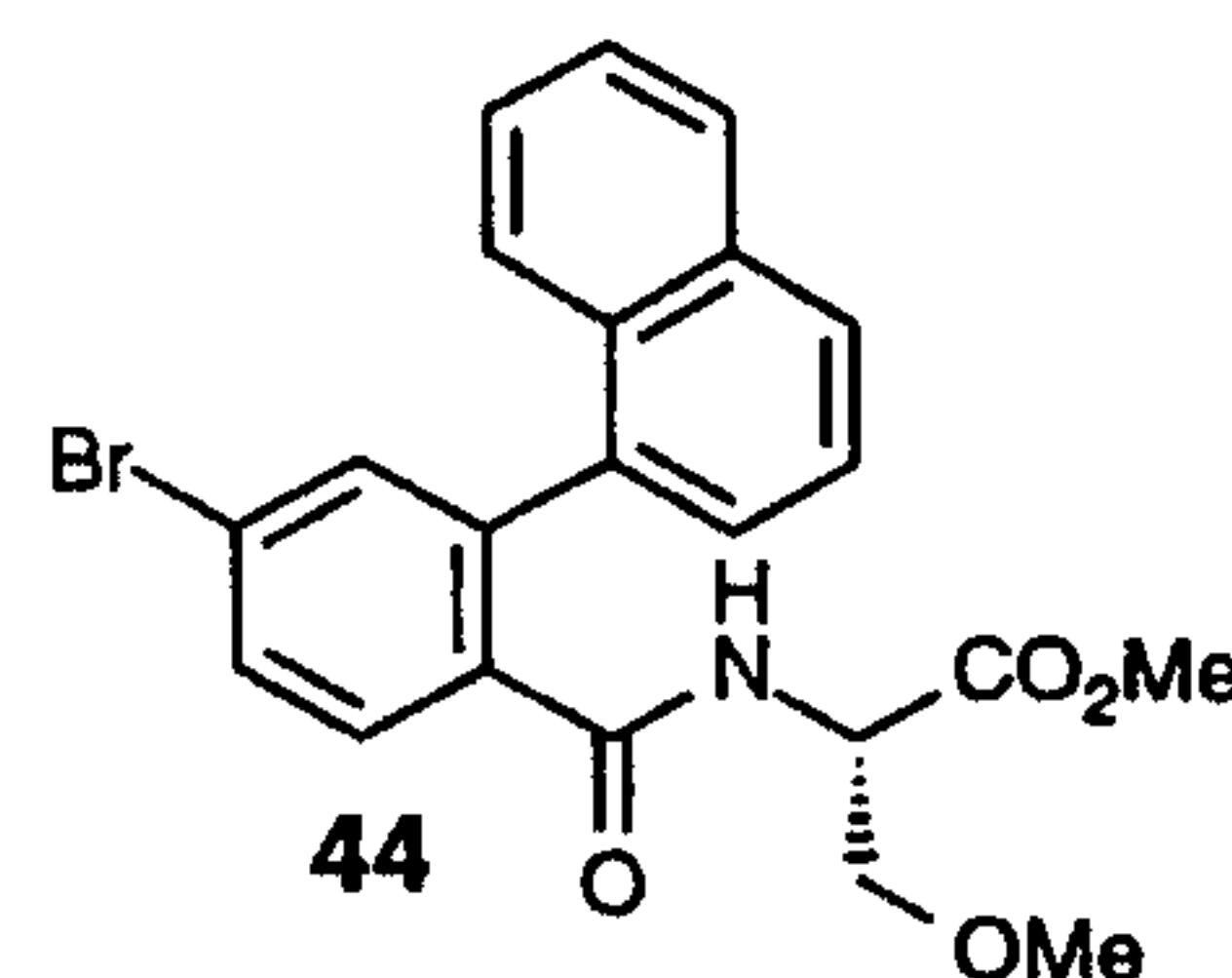
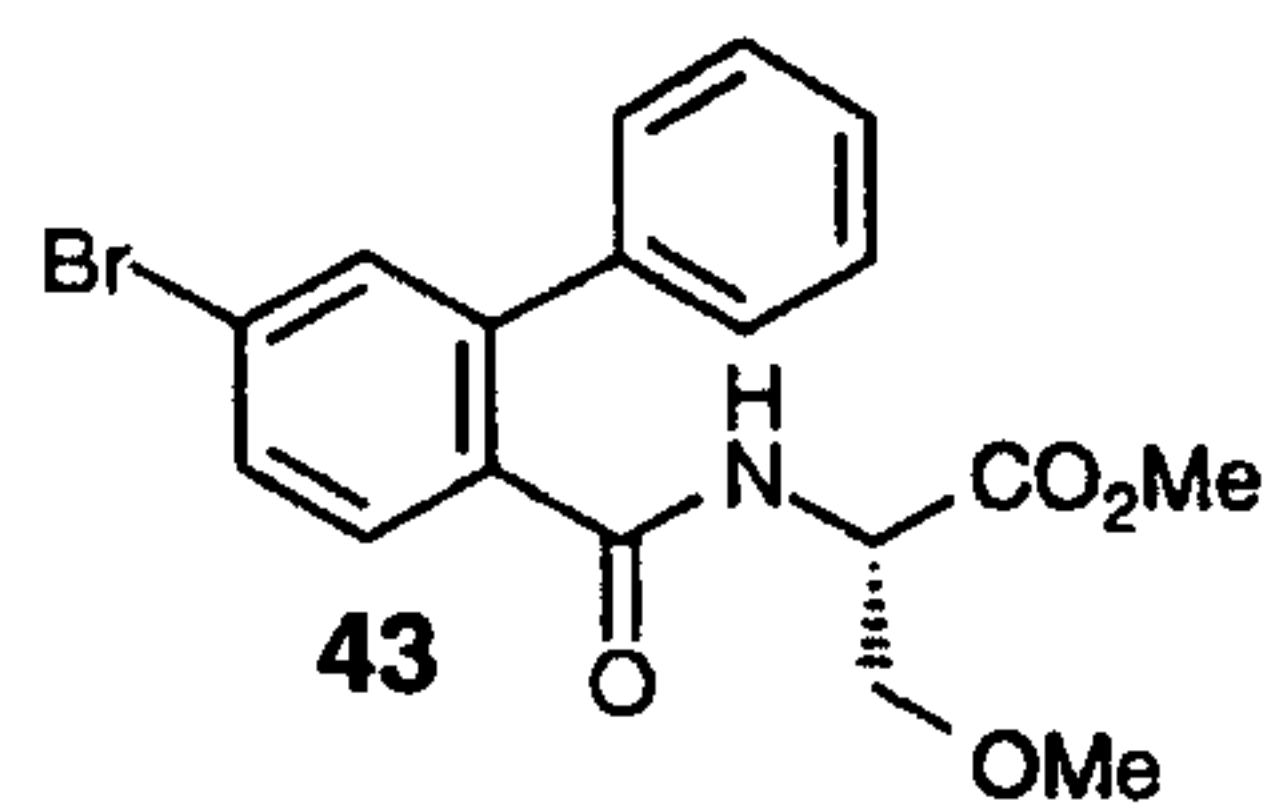
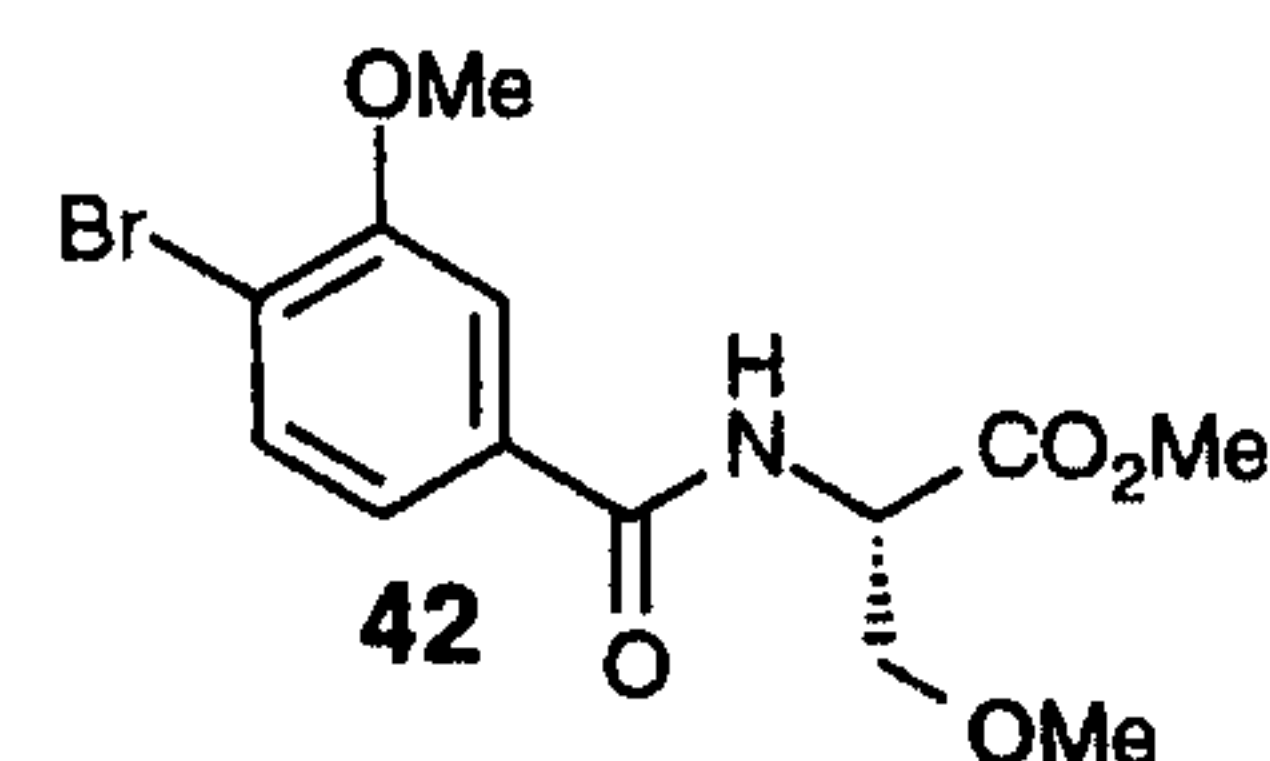
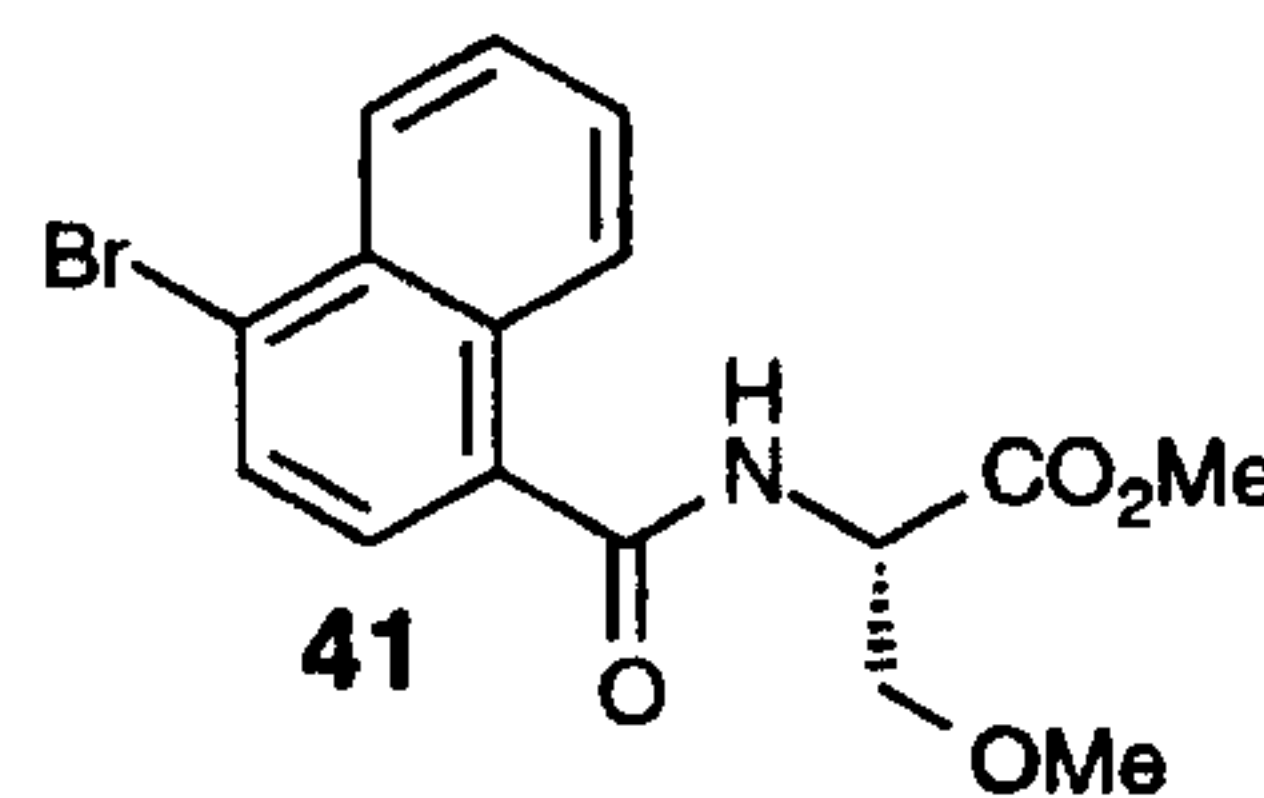
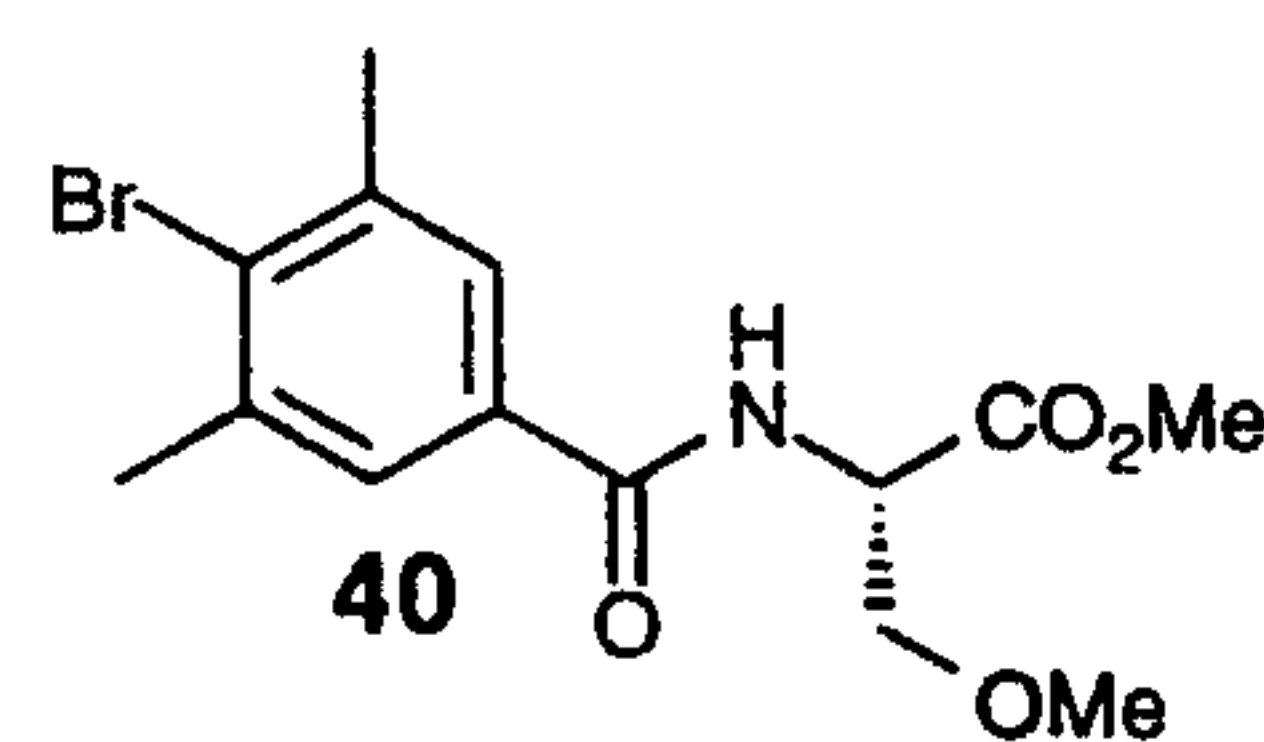
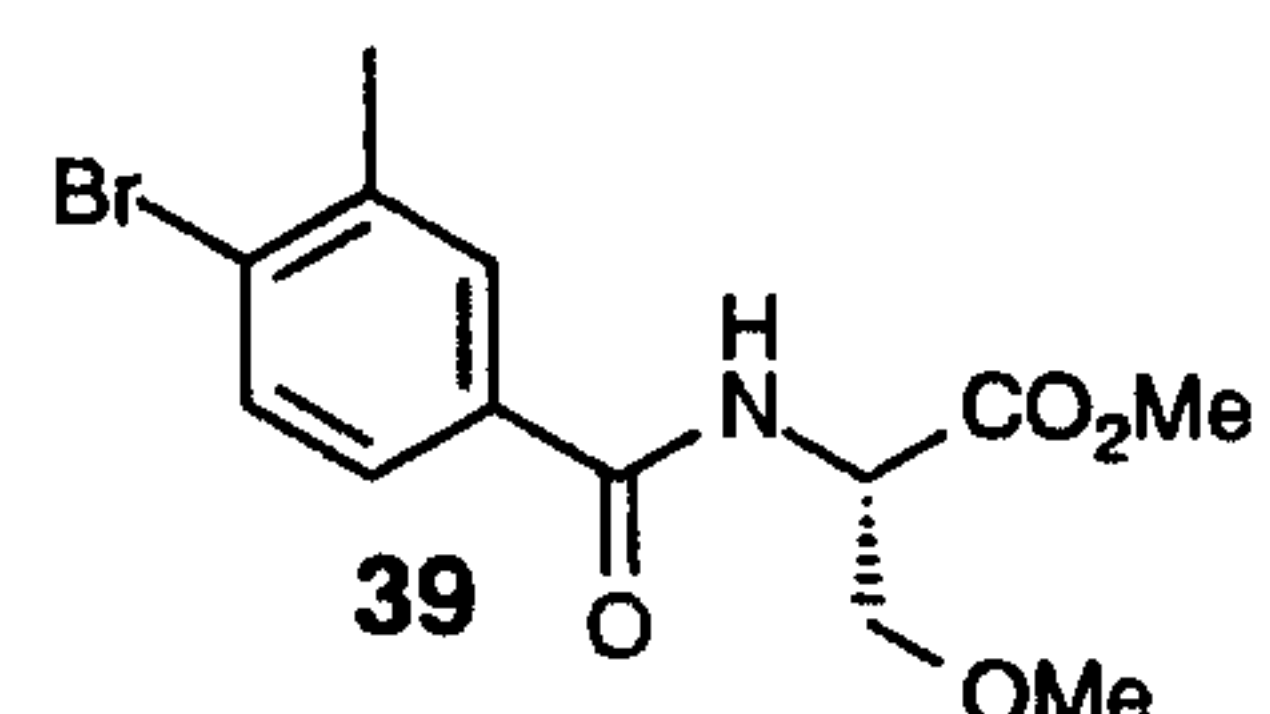
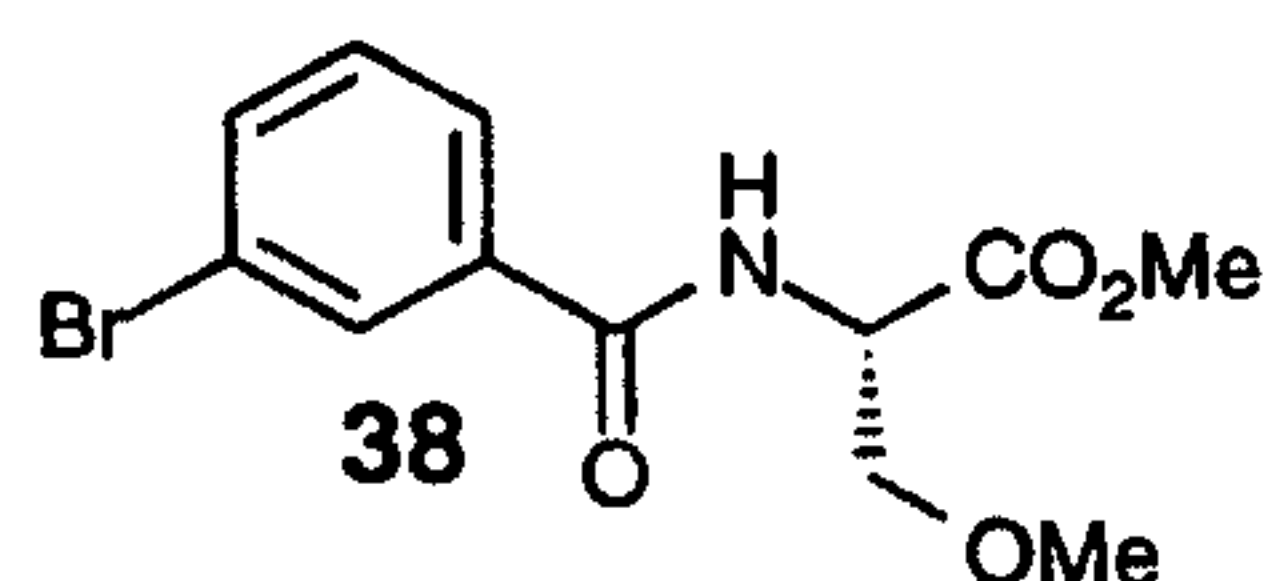
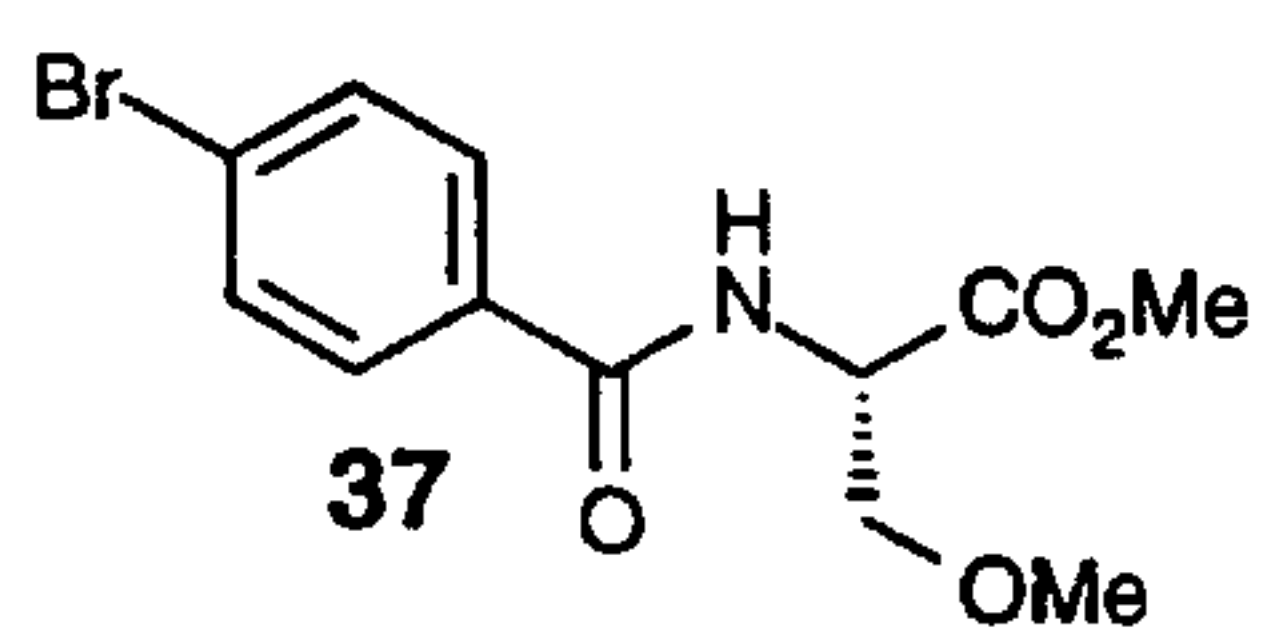
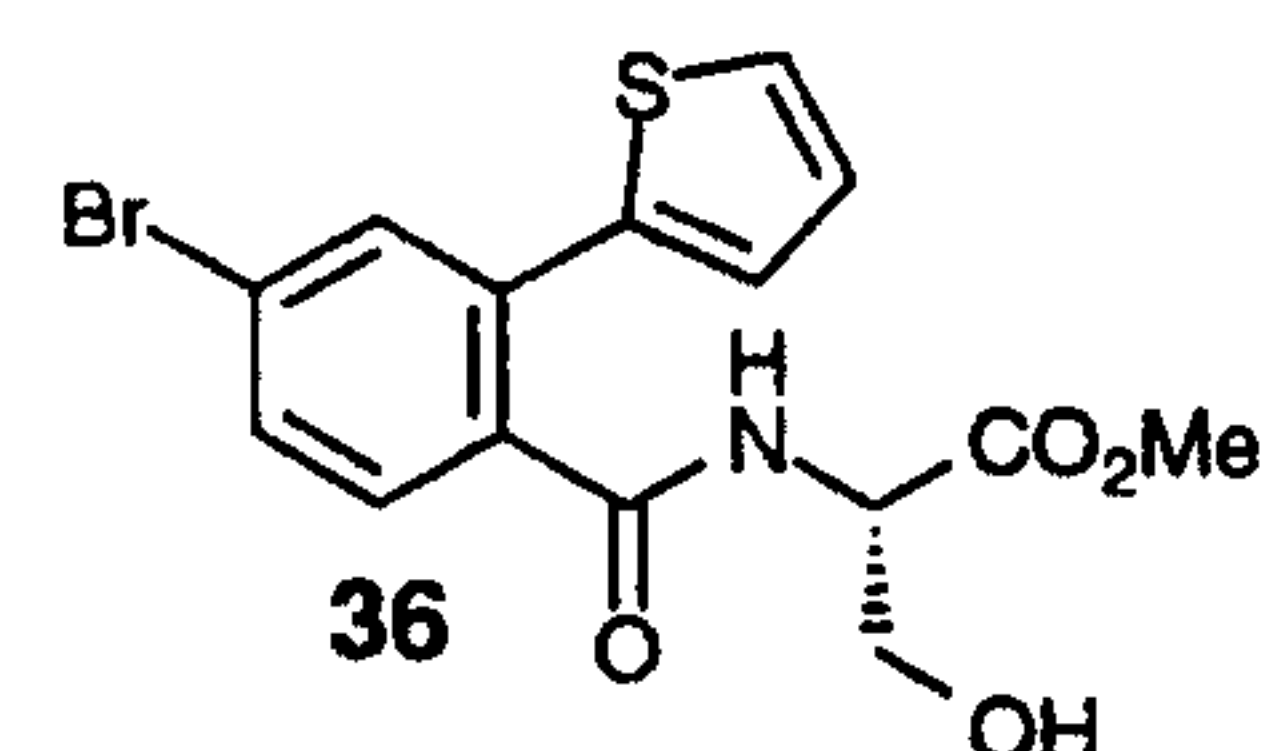
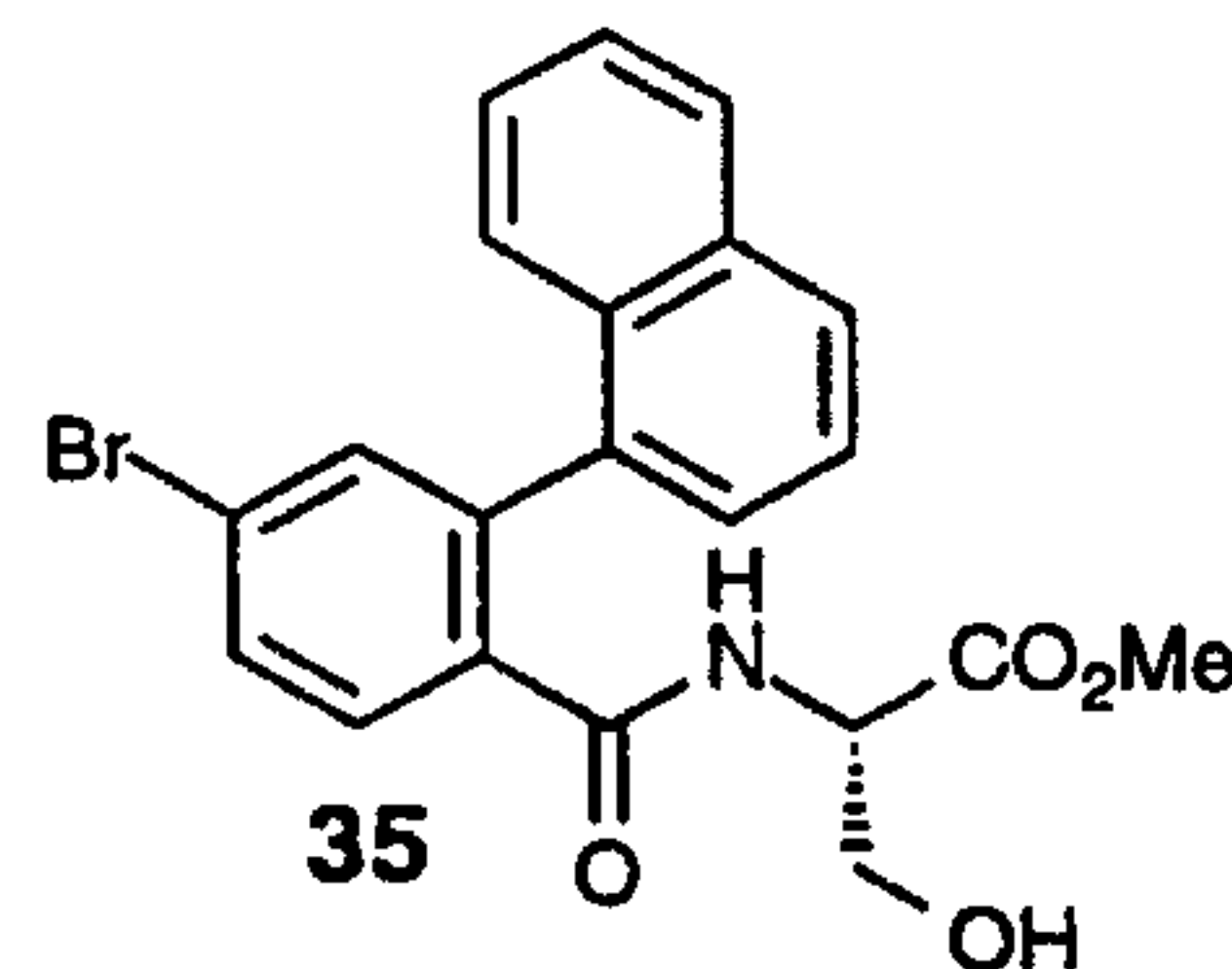
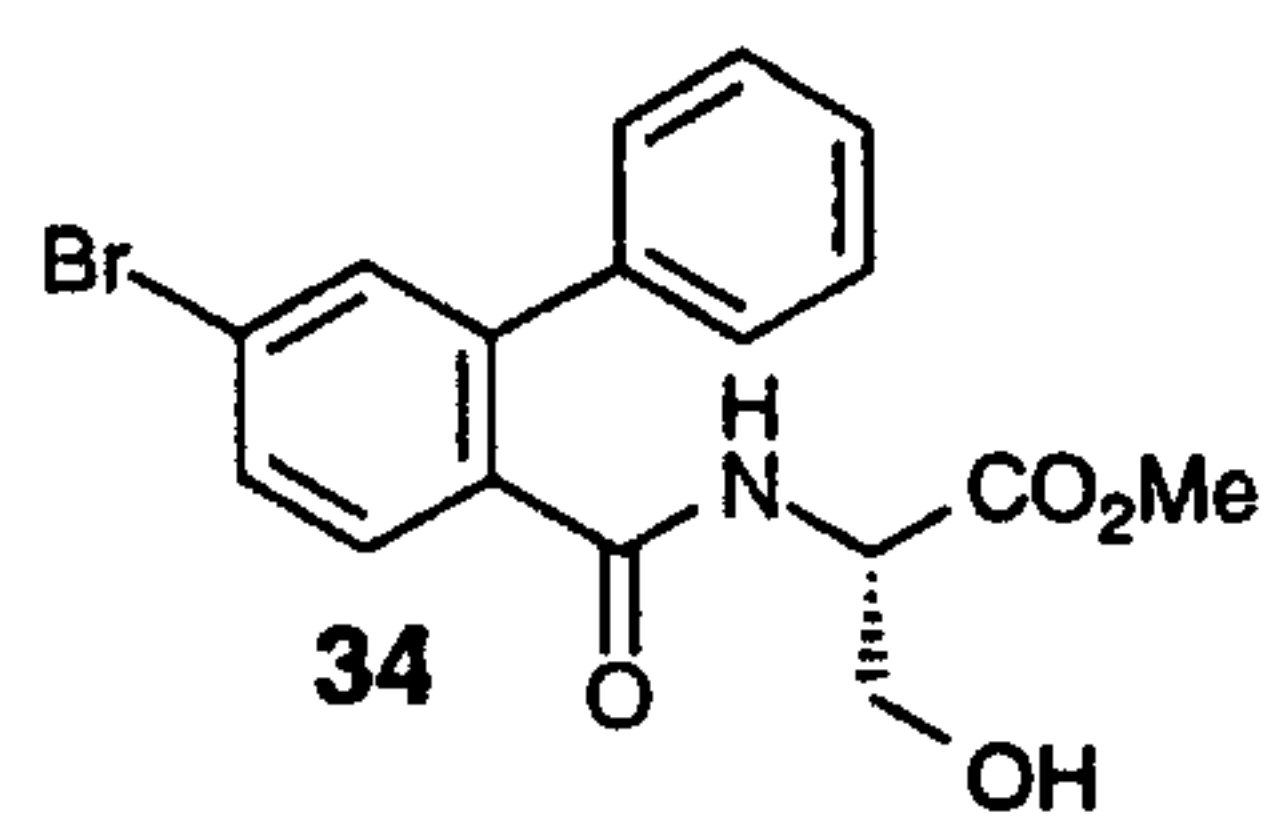
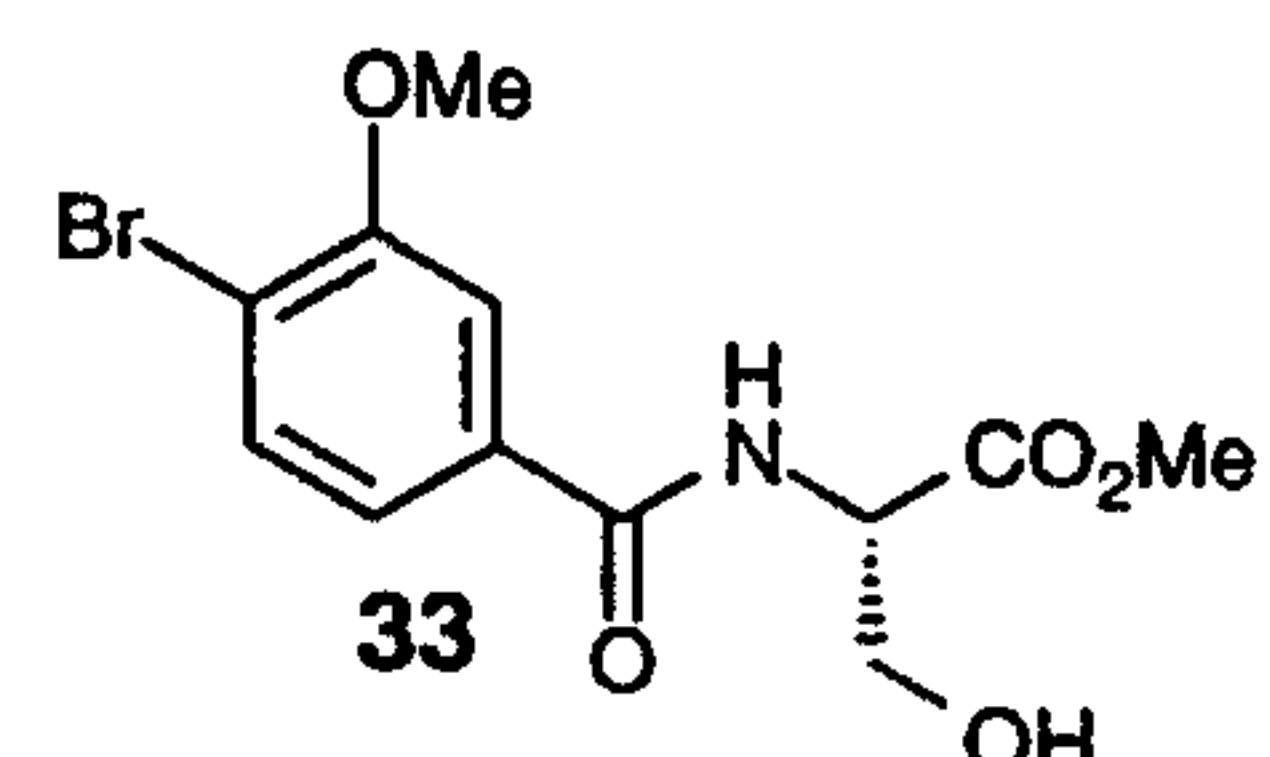
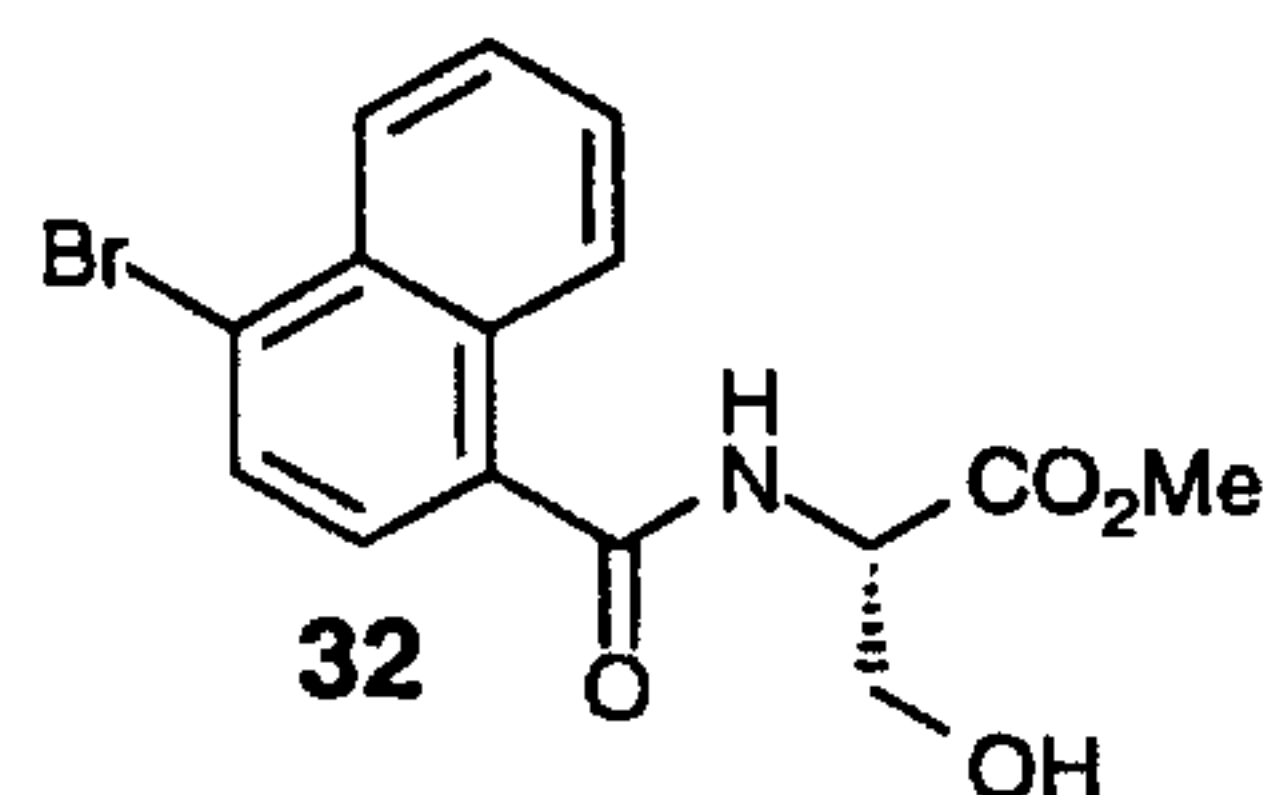
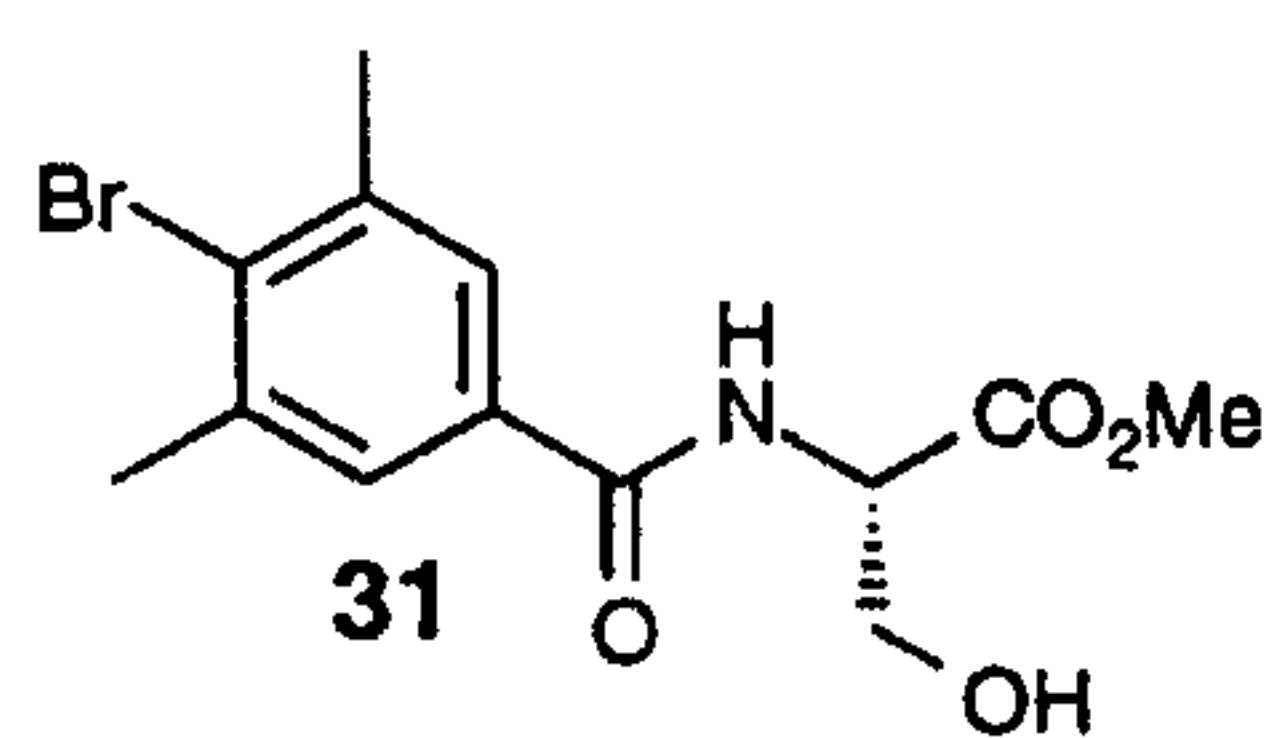
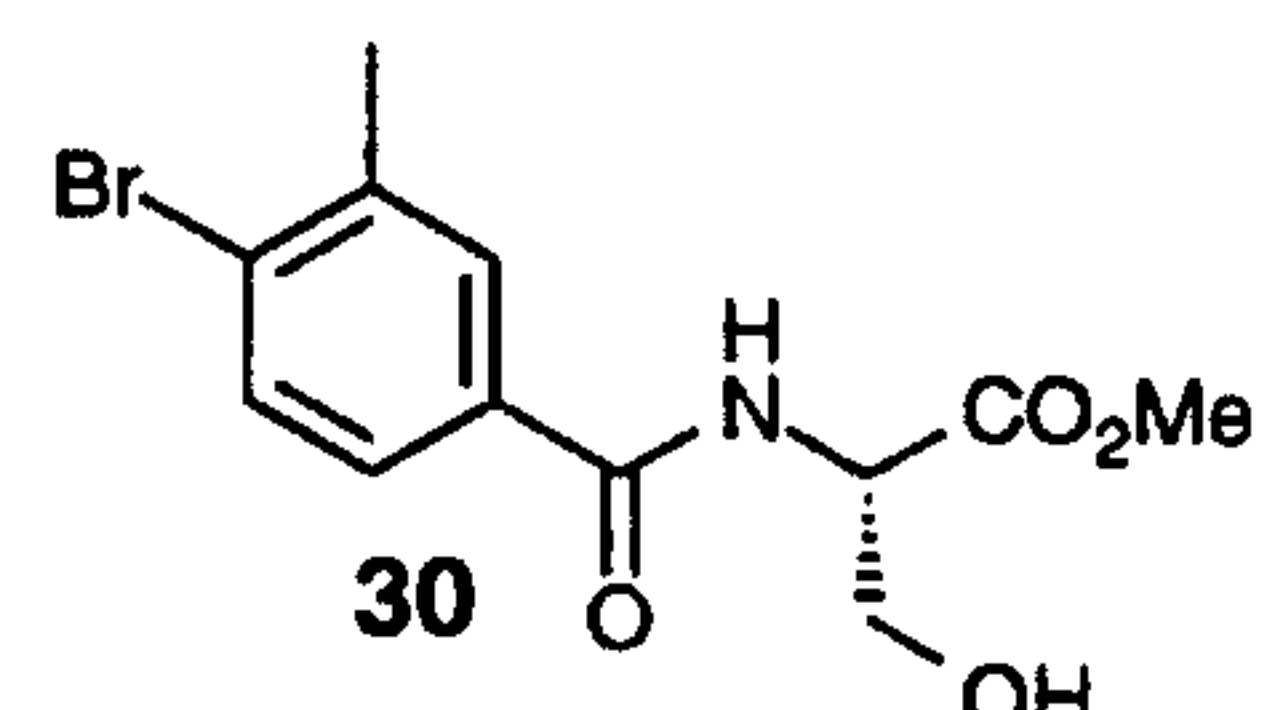
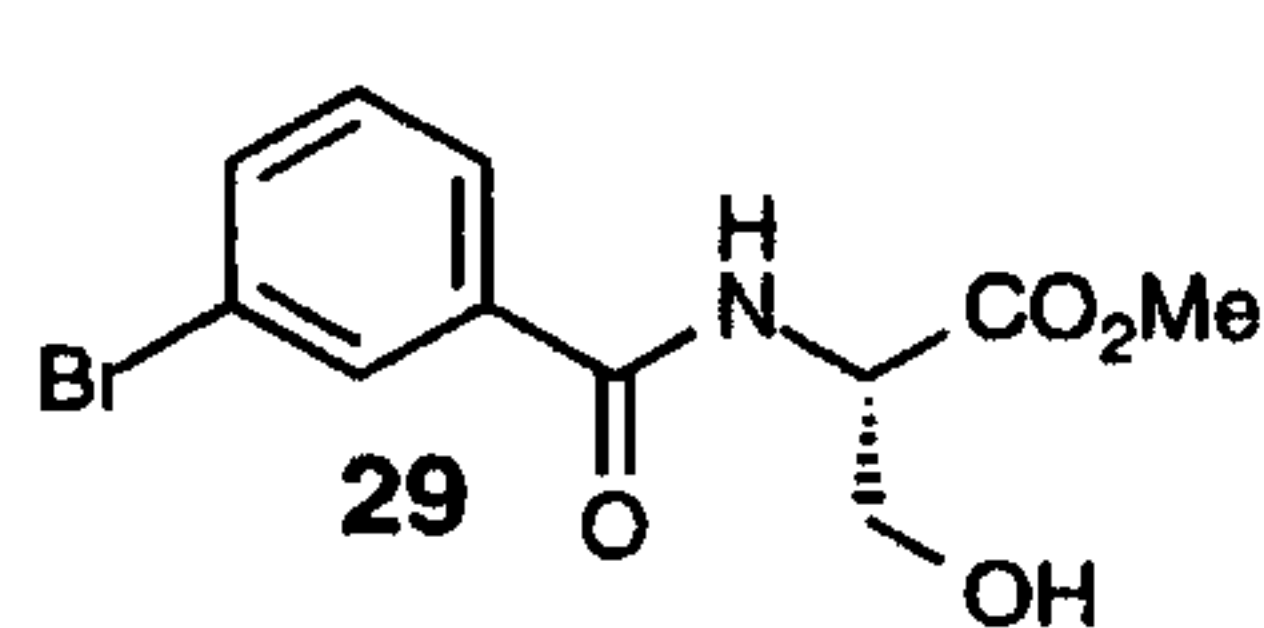
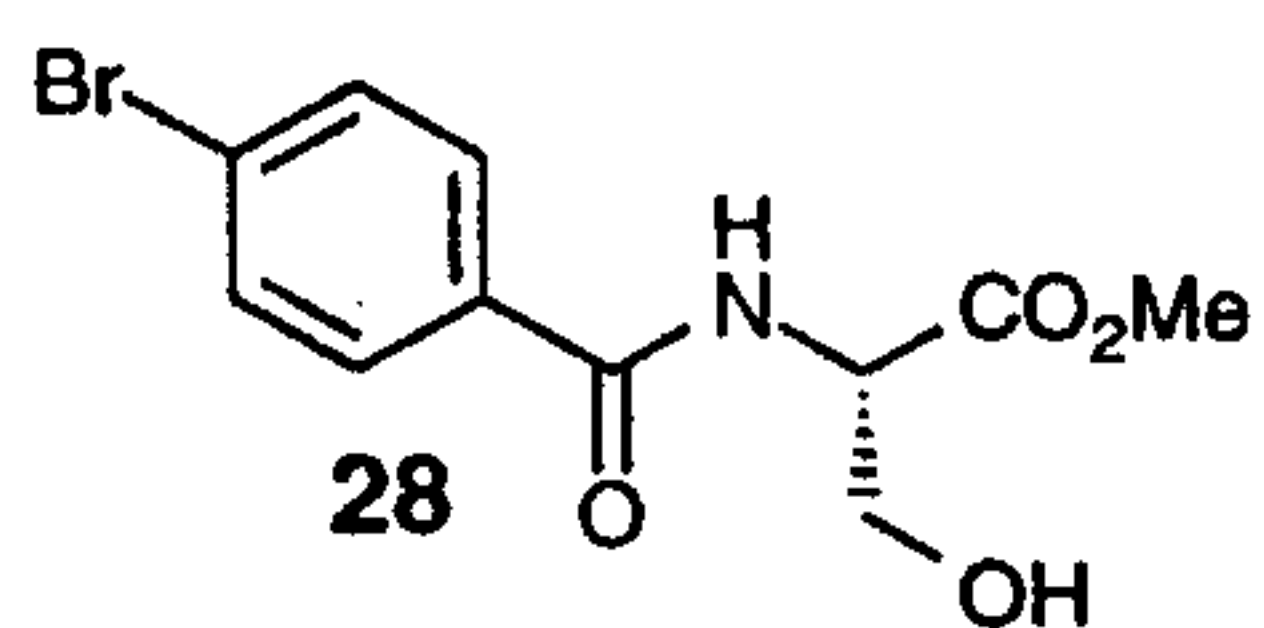
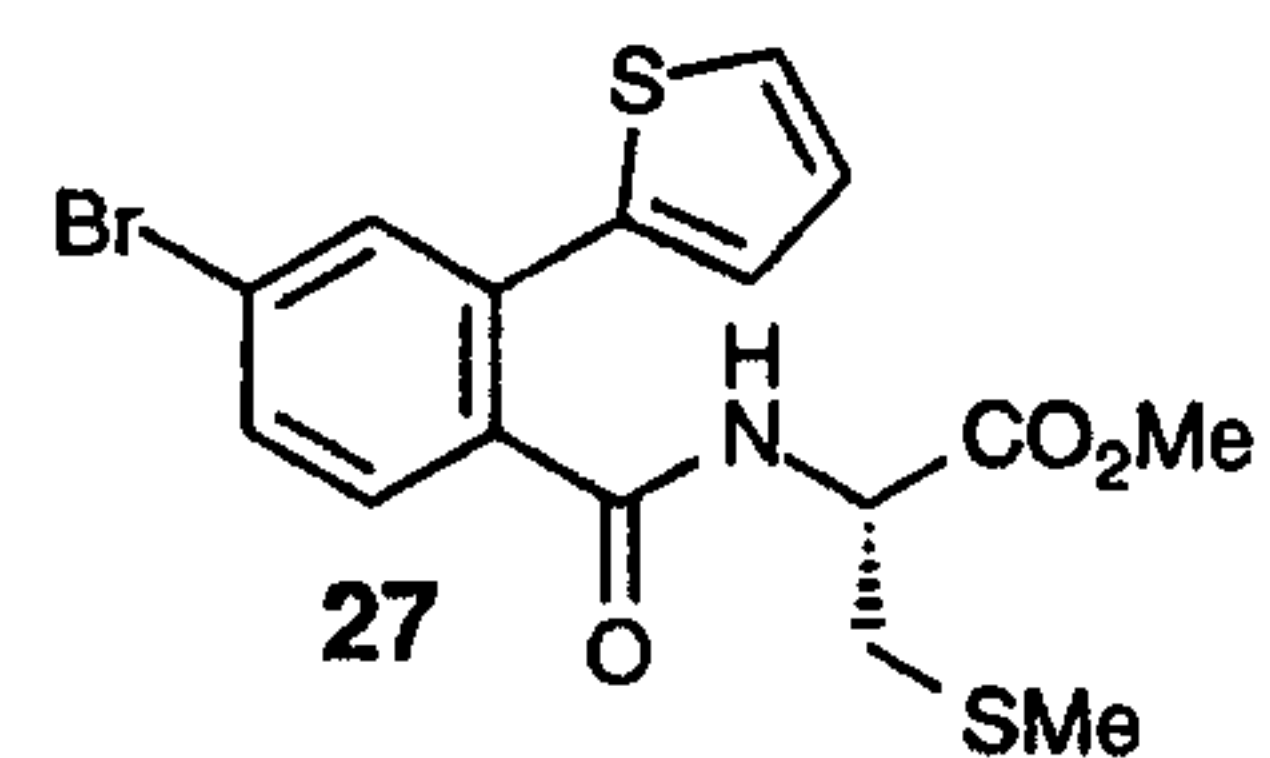
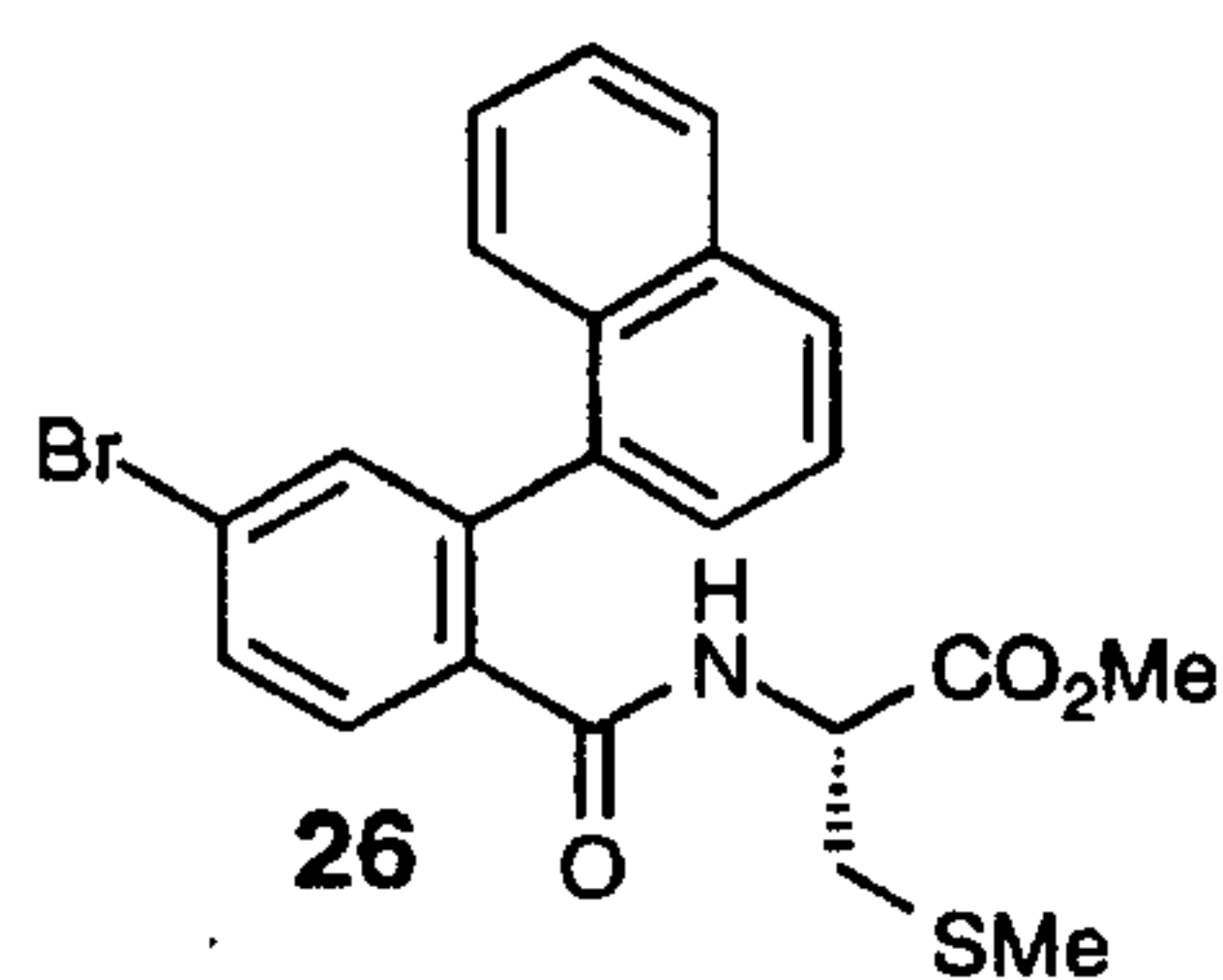
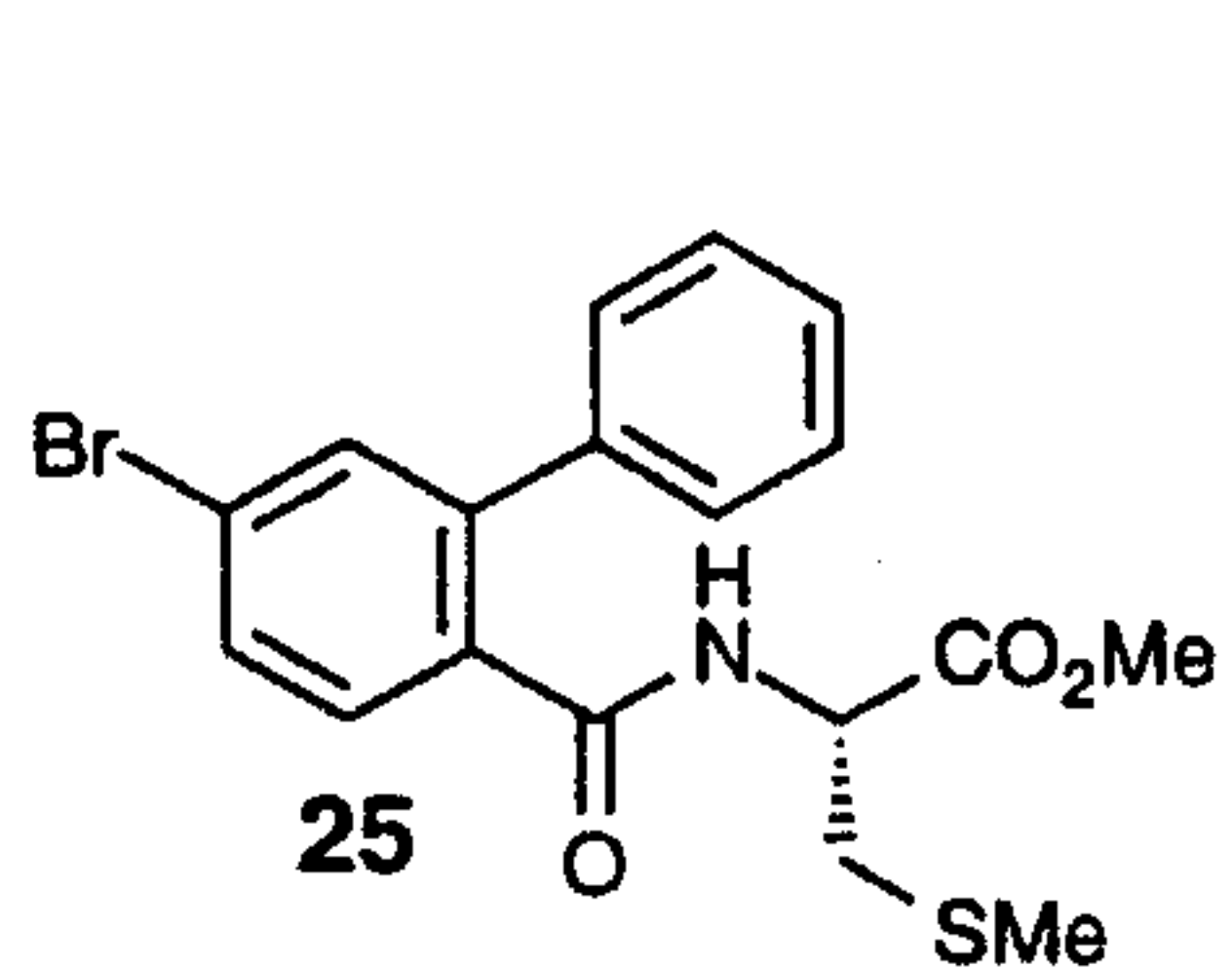
Table 11. Bromides of the type B-Br

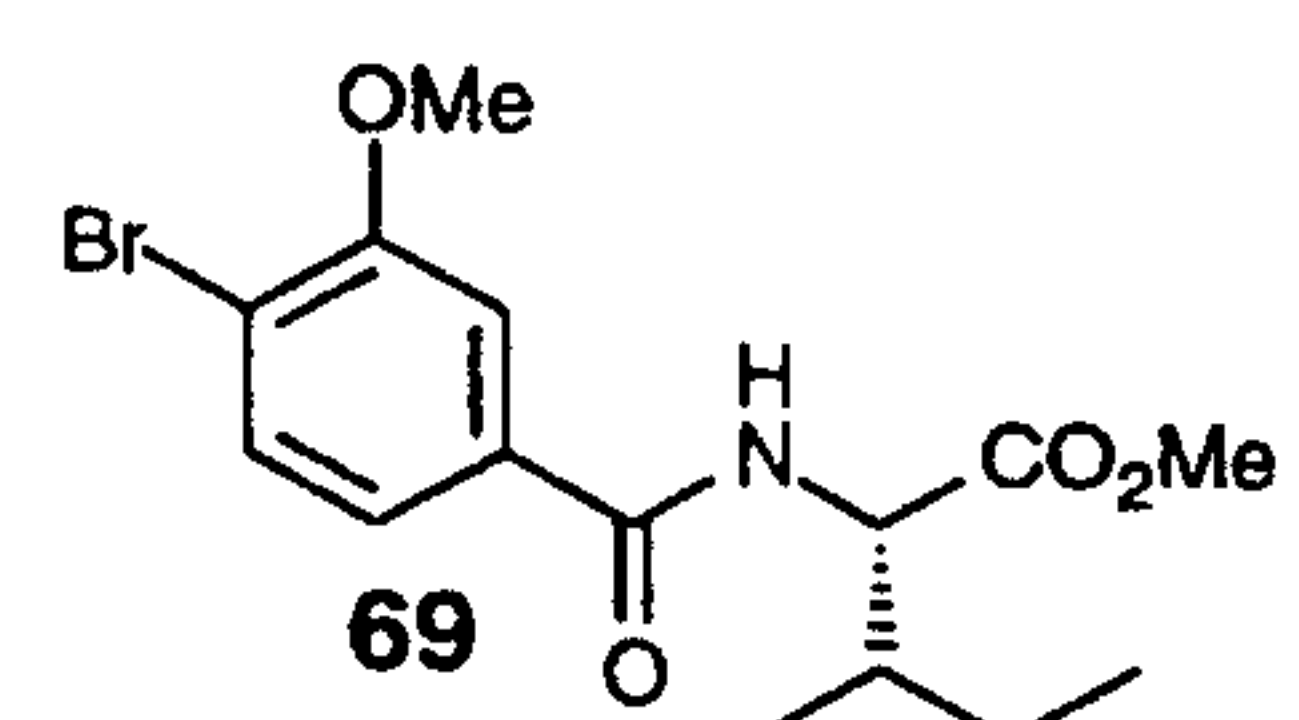
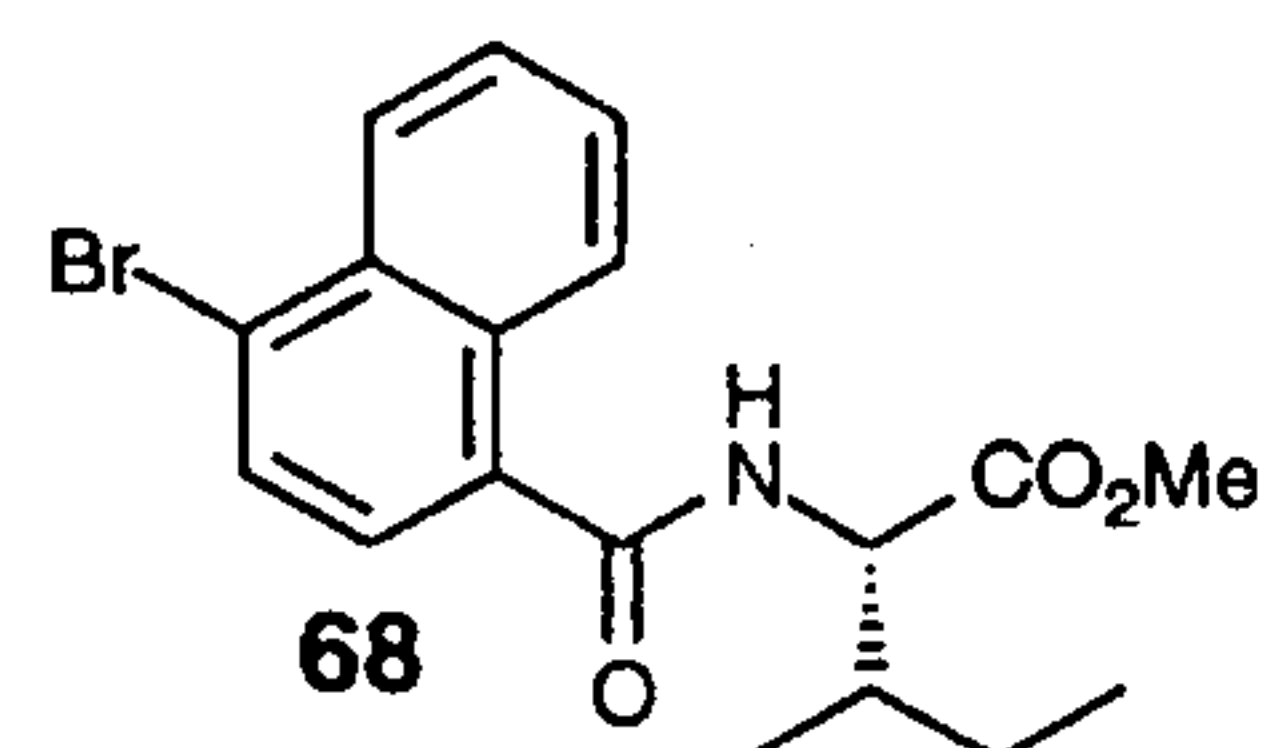
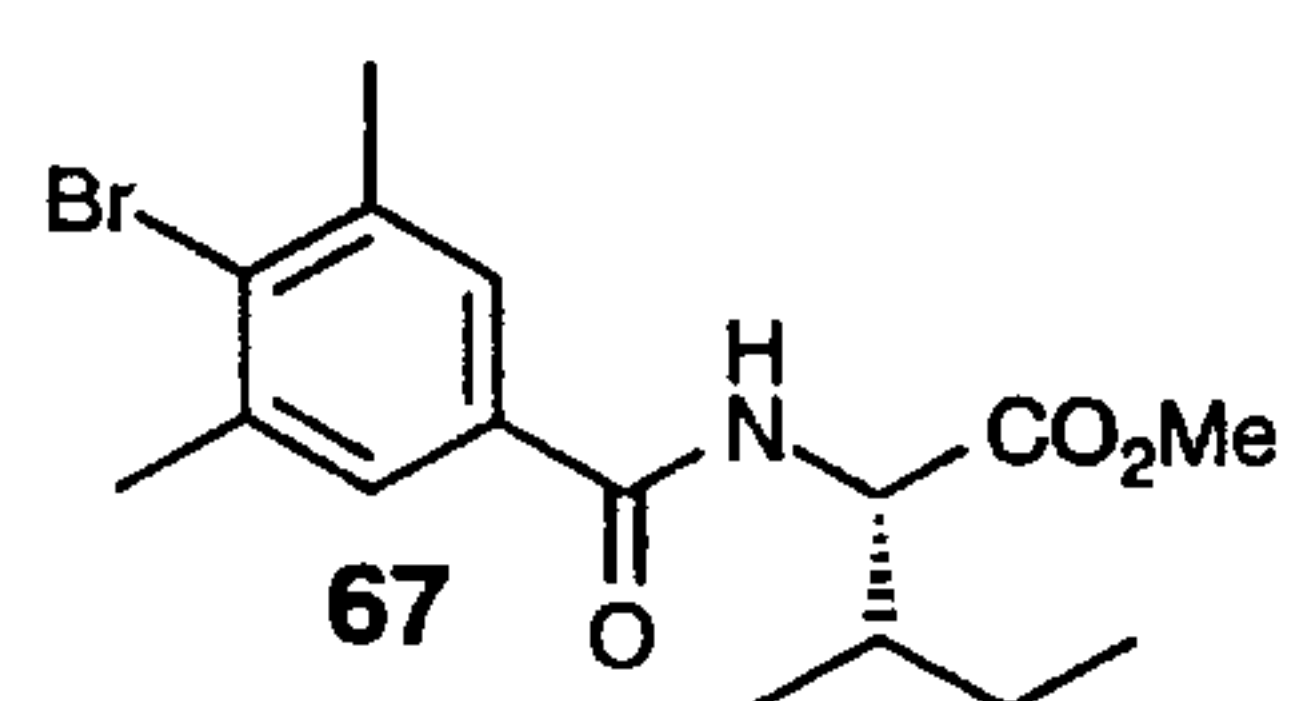
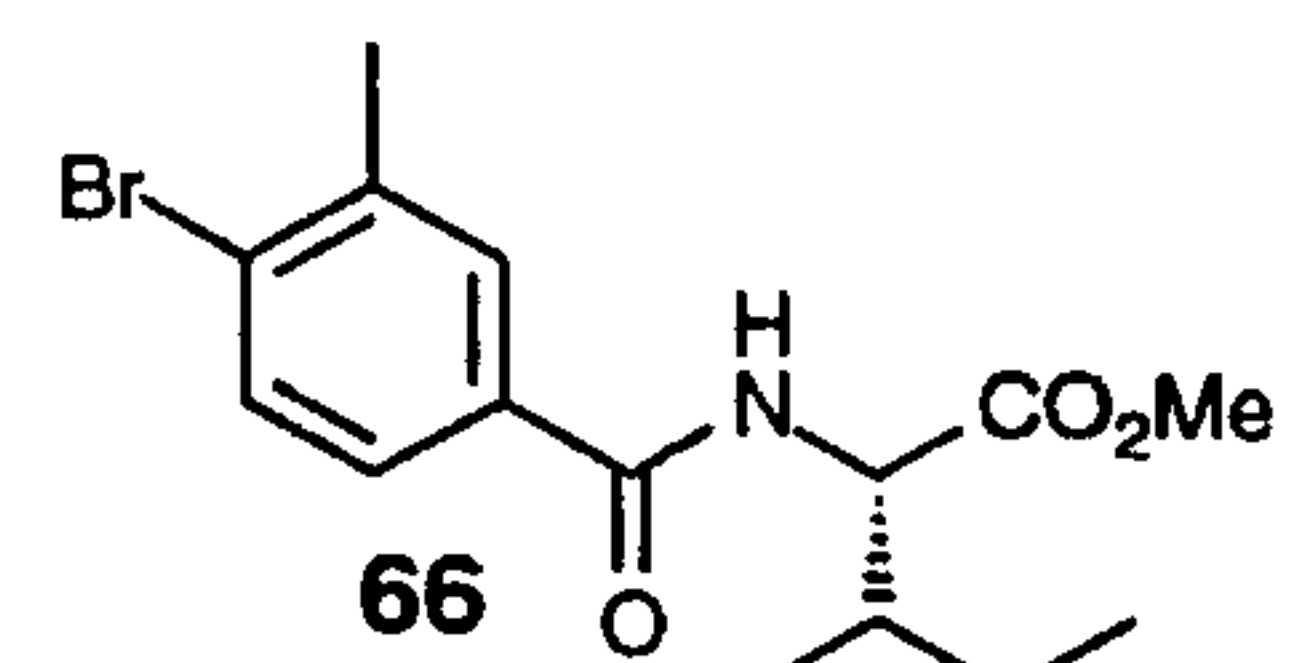
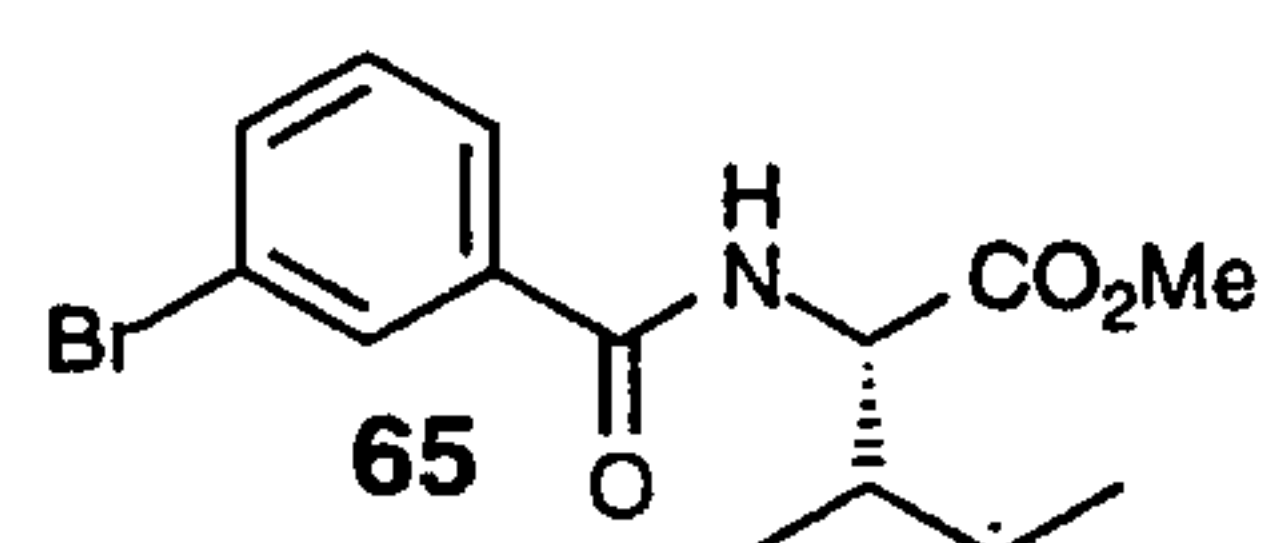
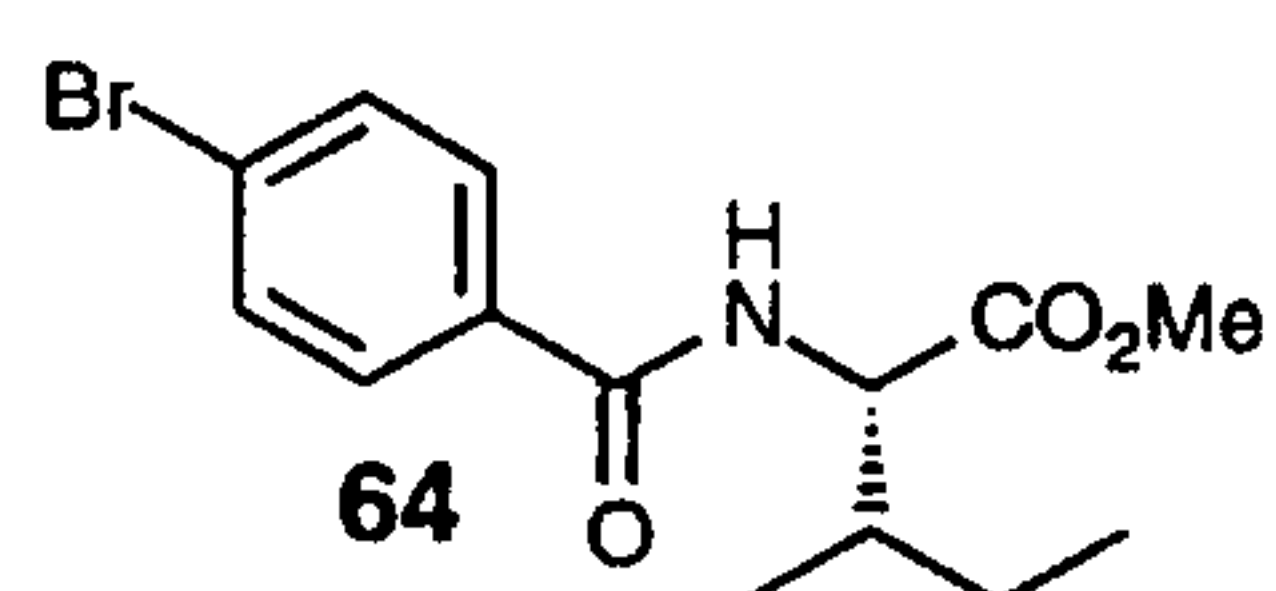
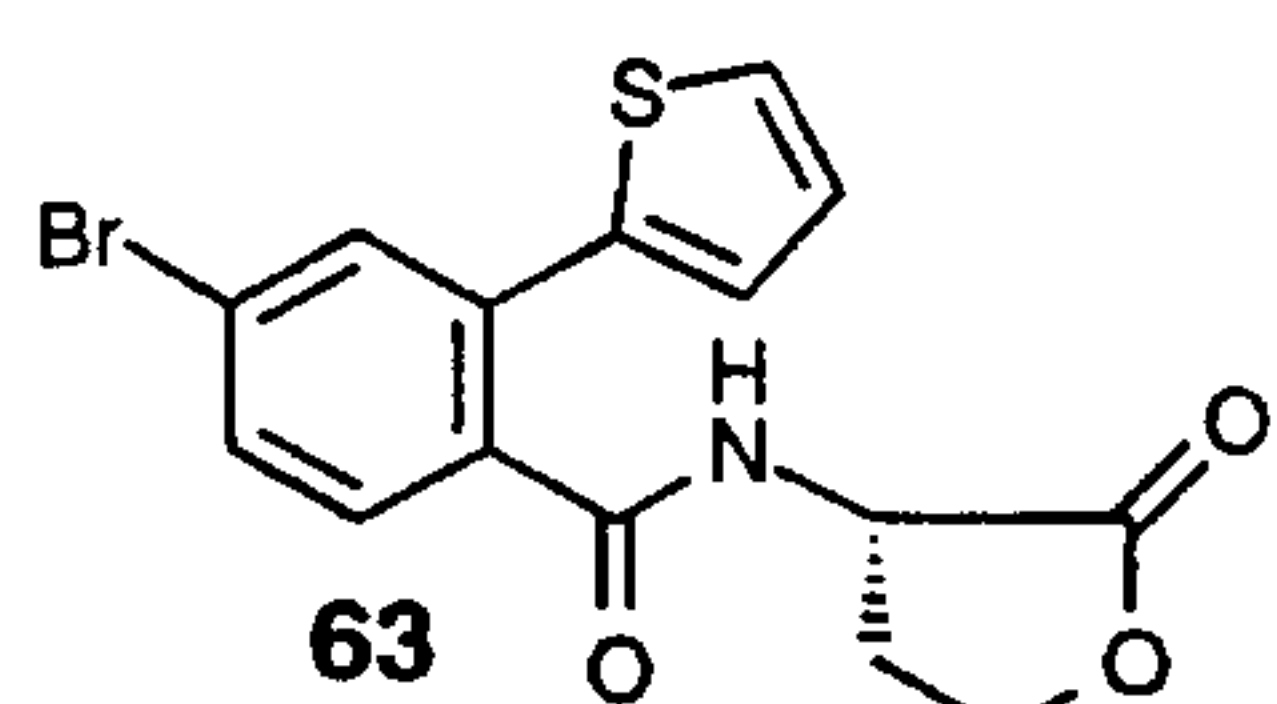
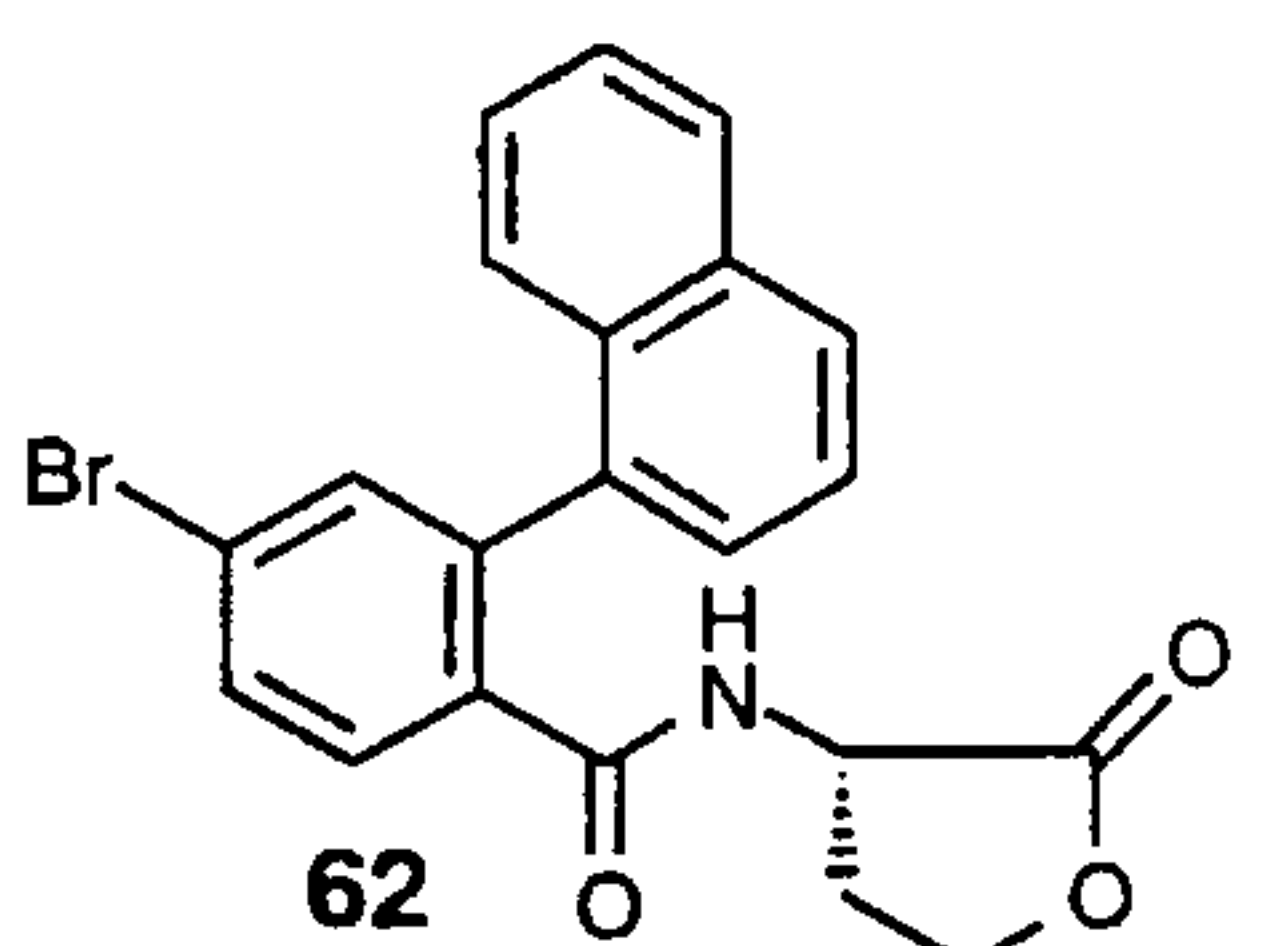
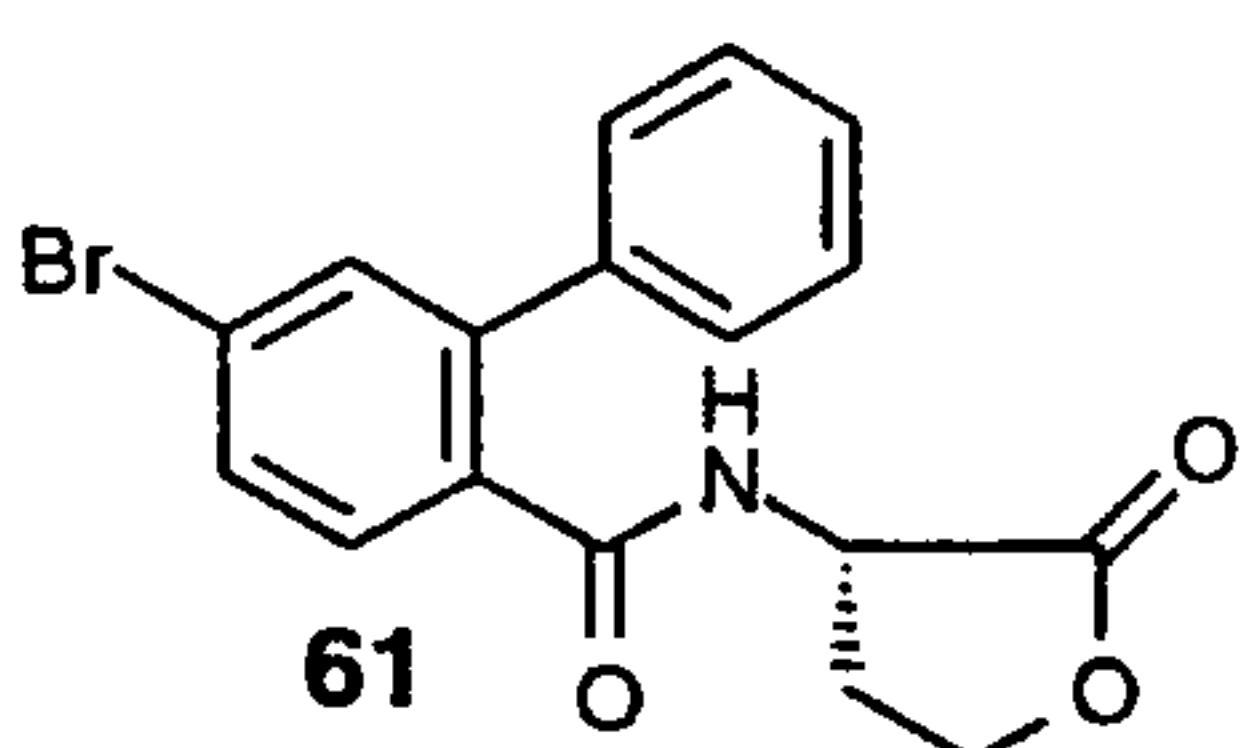
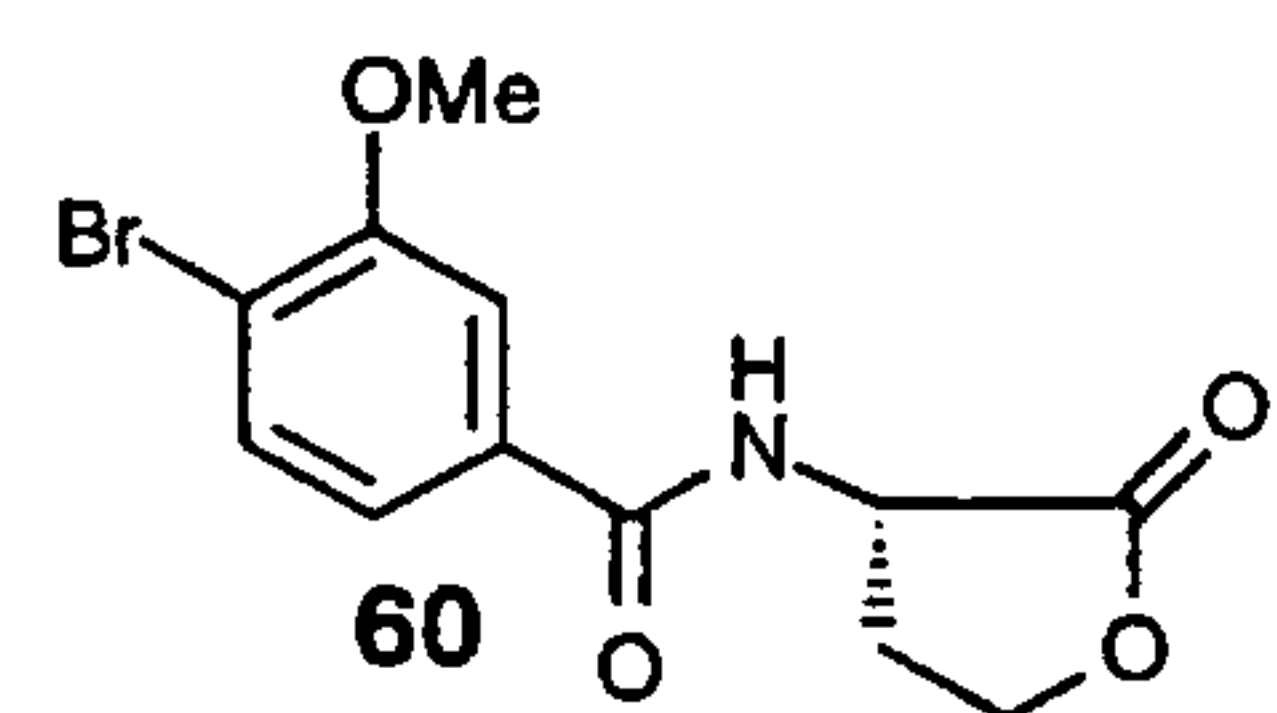
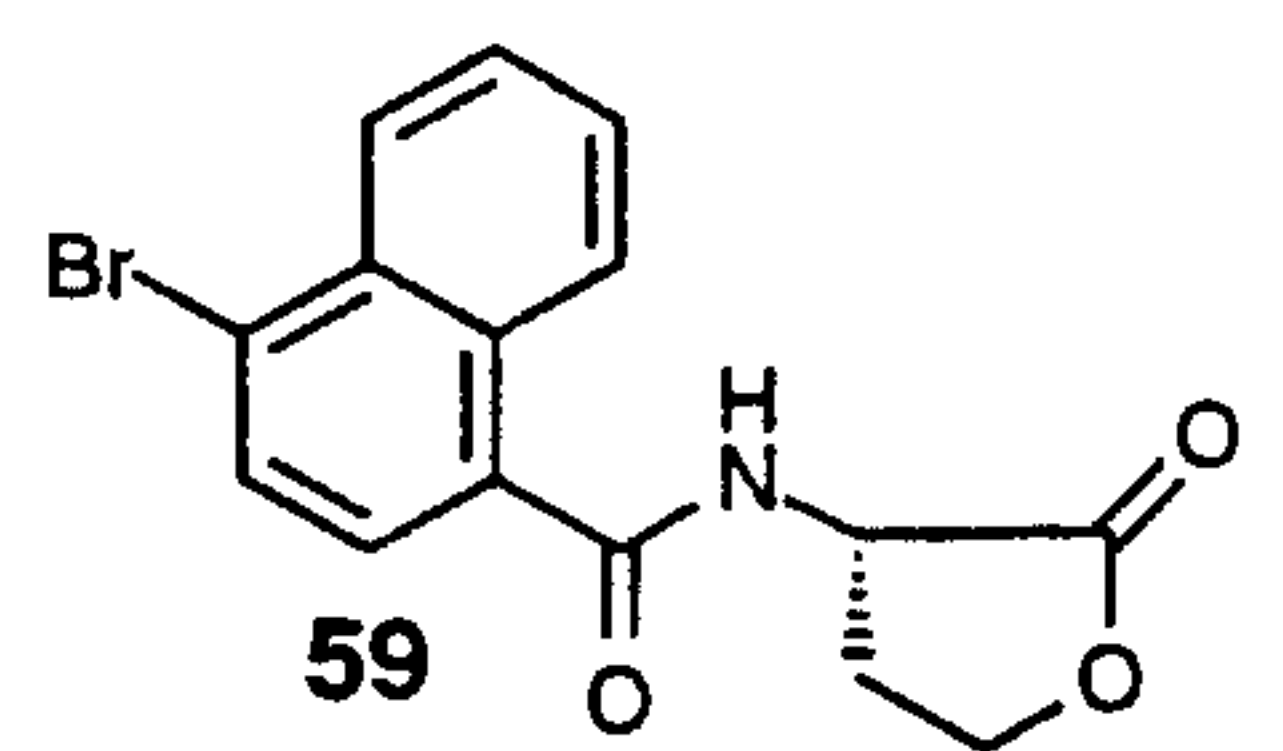
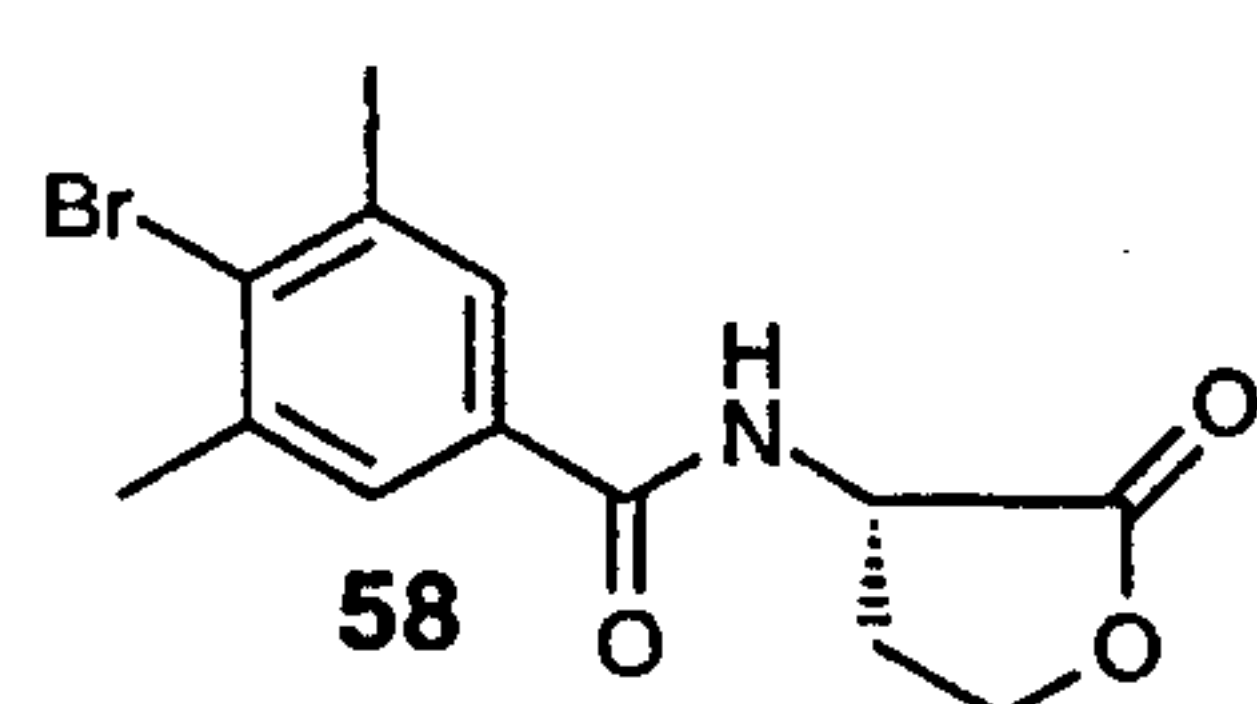
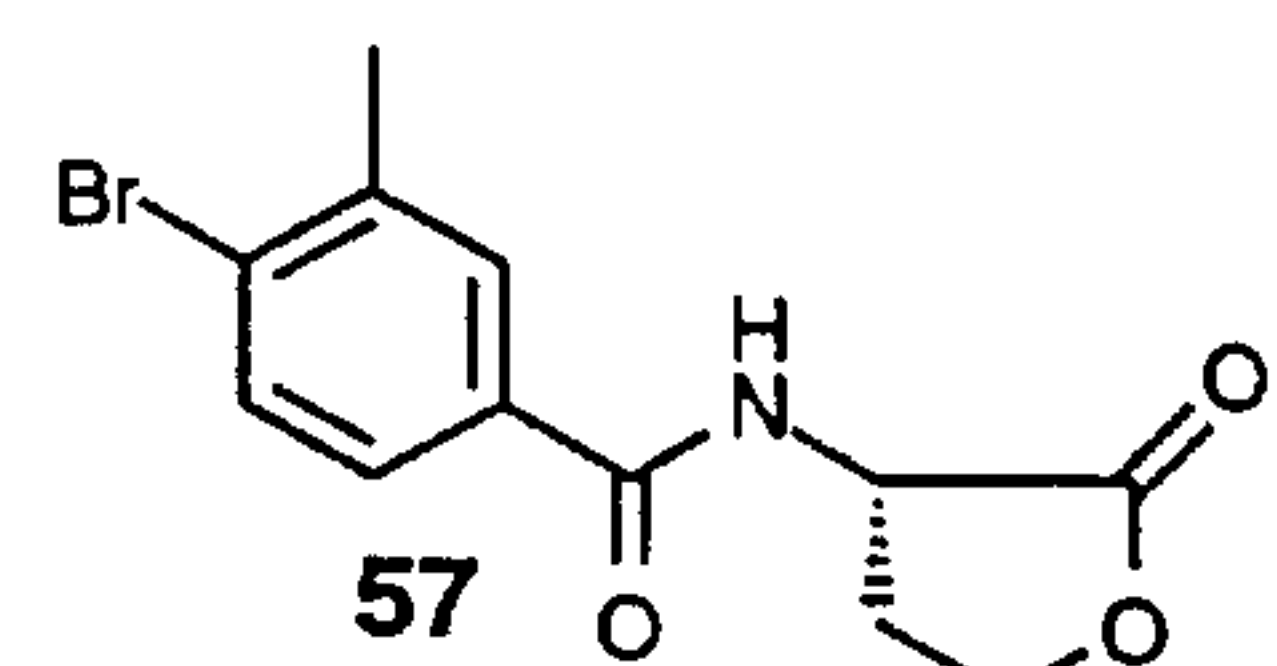
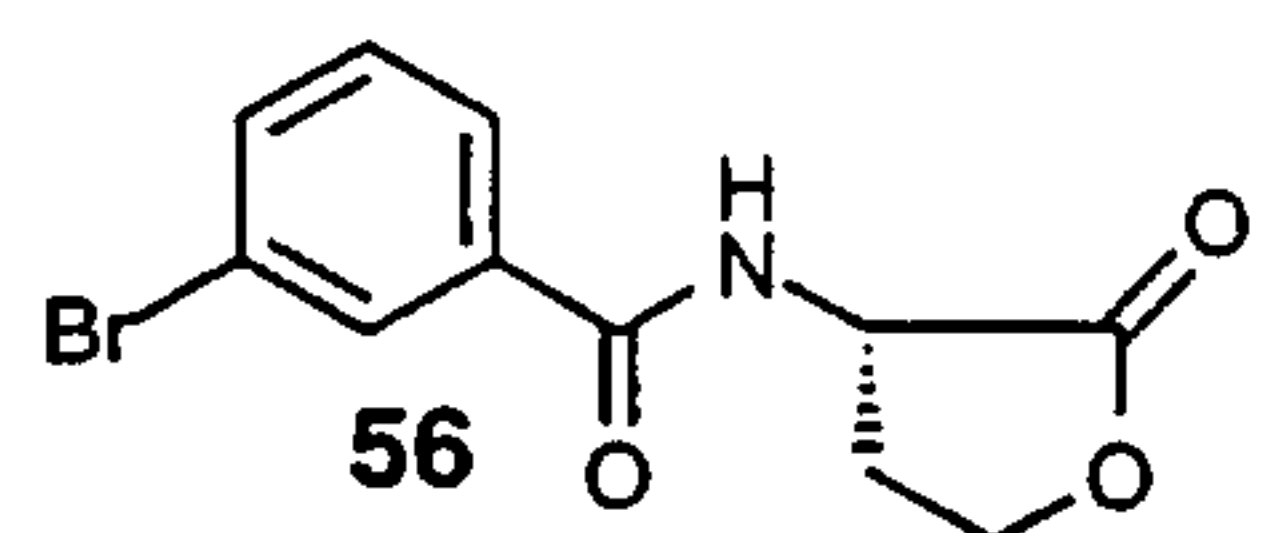
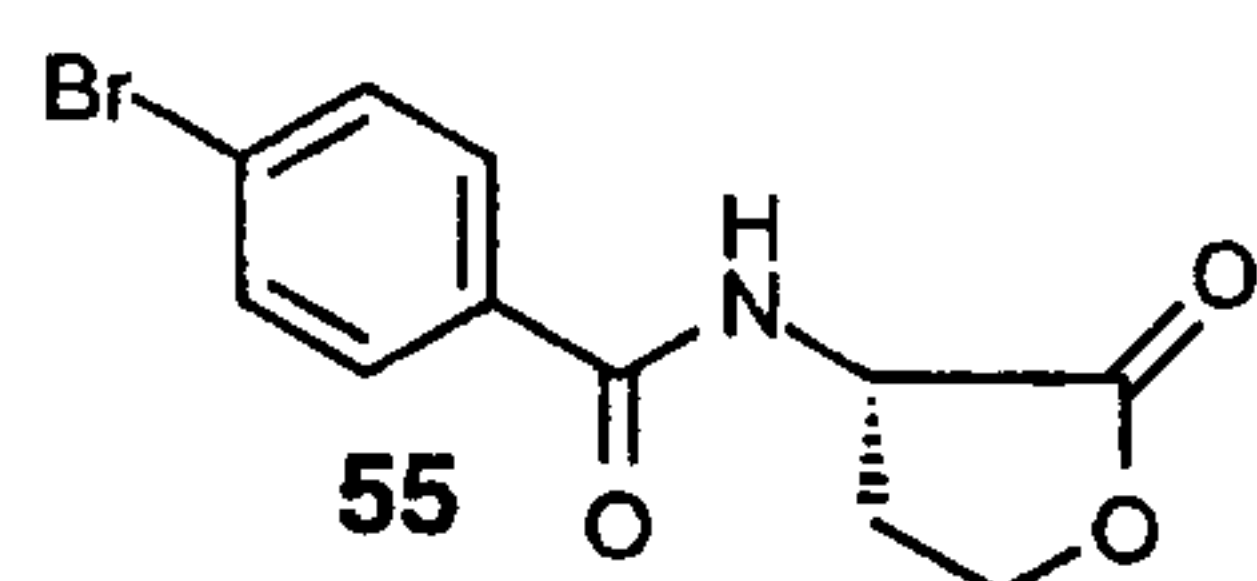
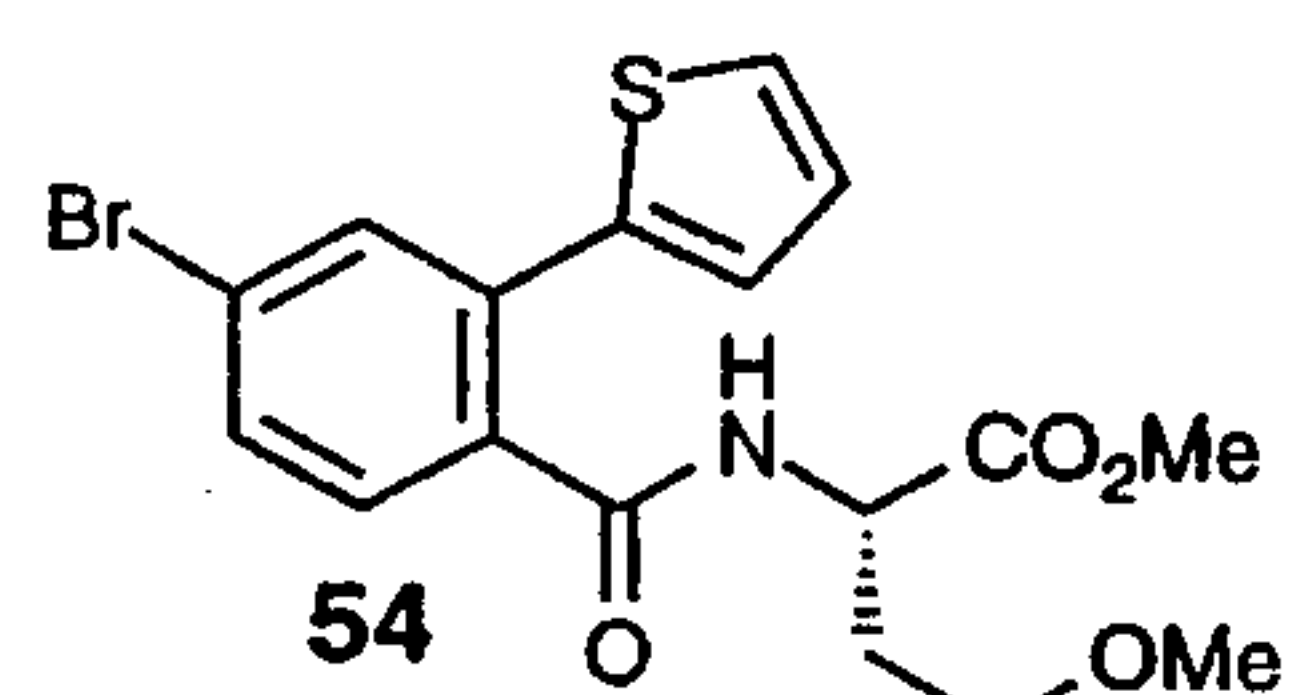
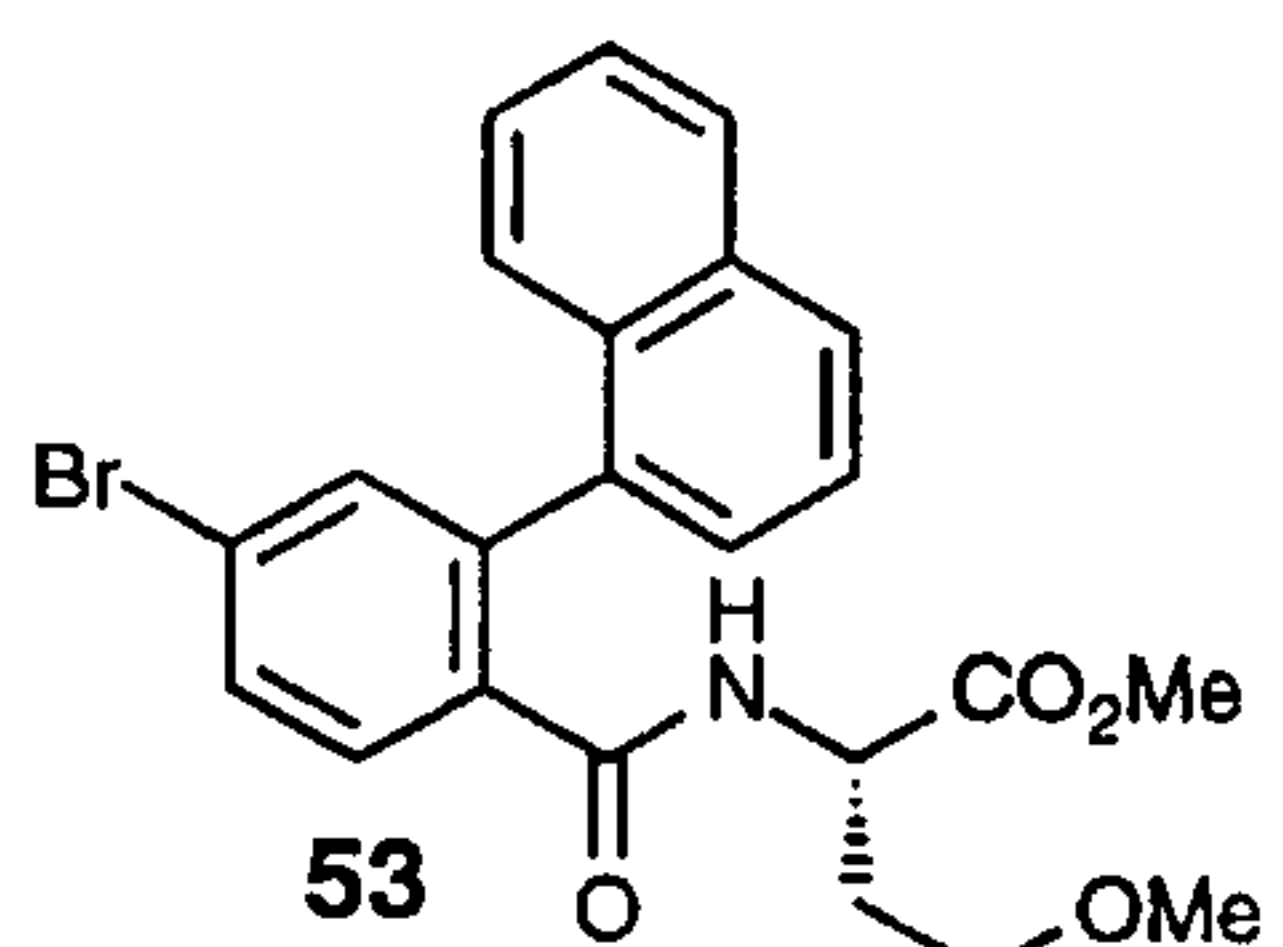
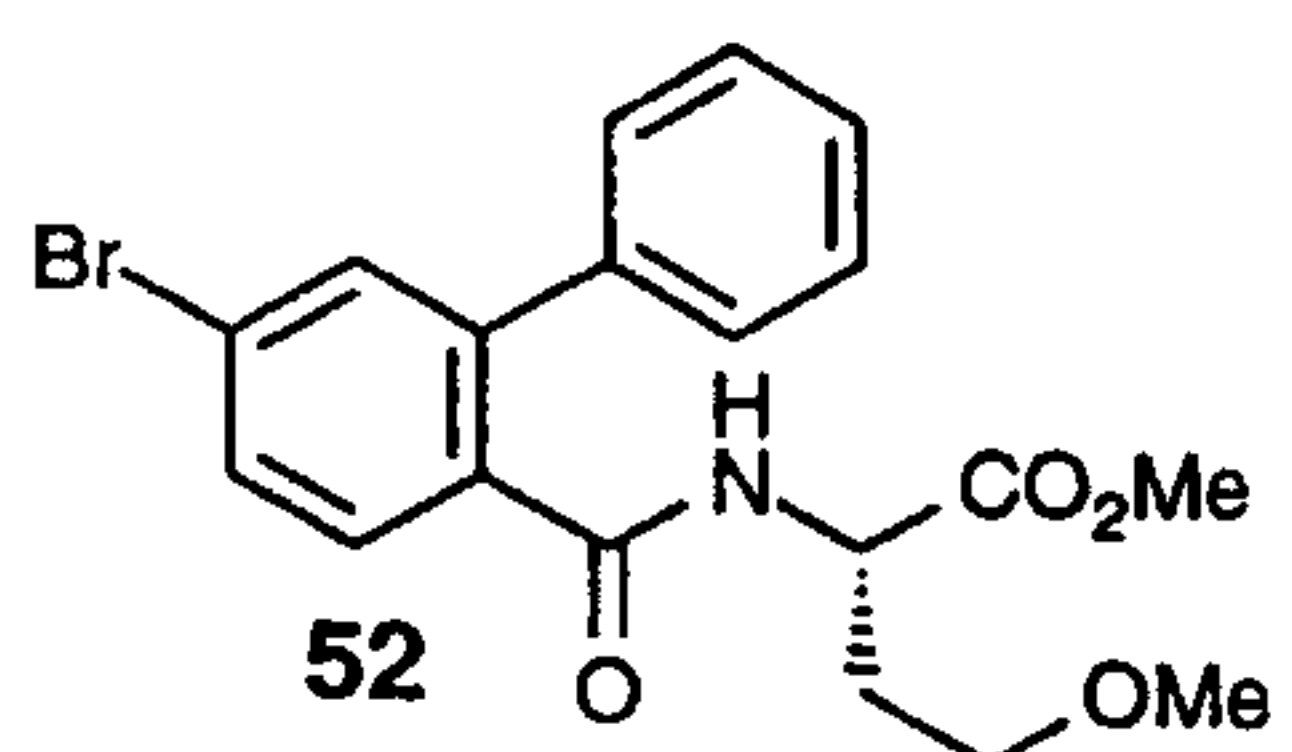
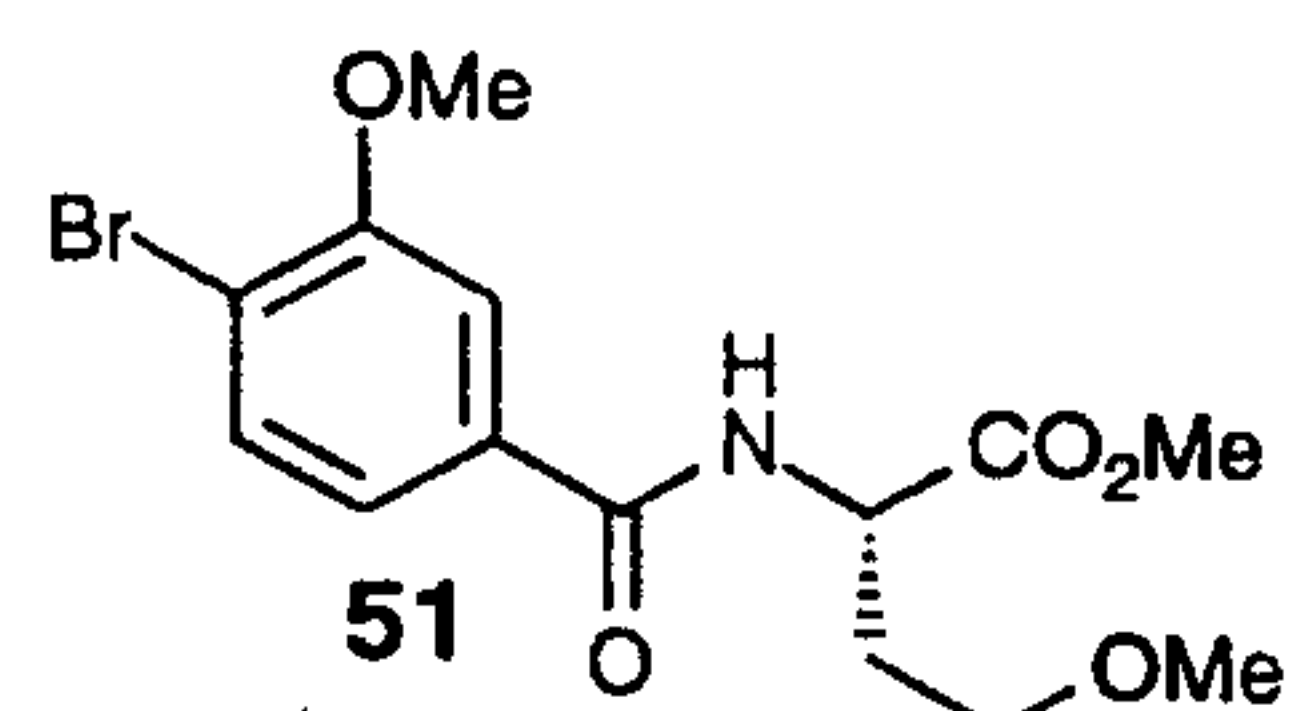
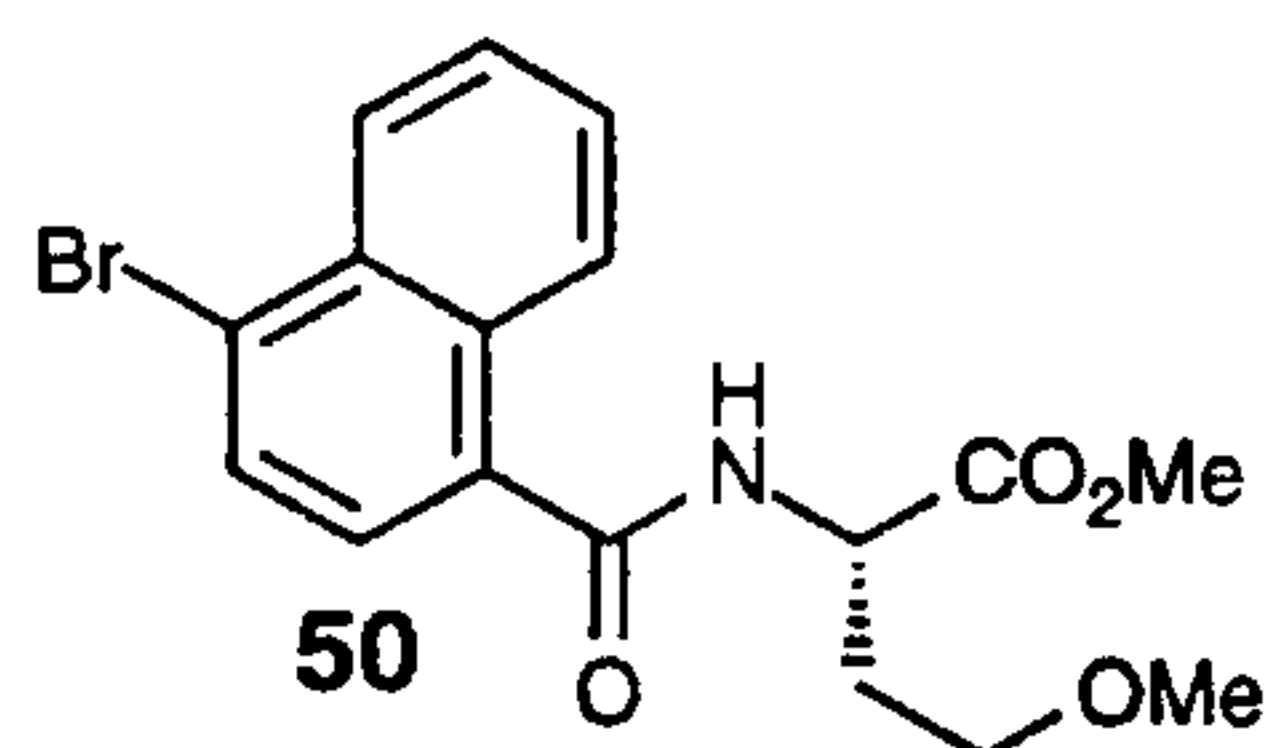
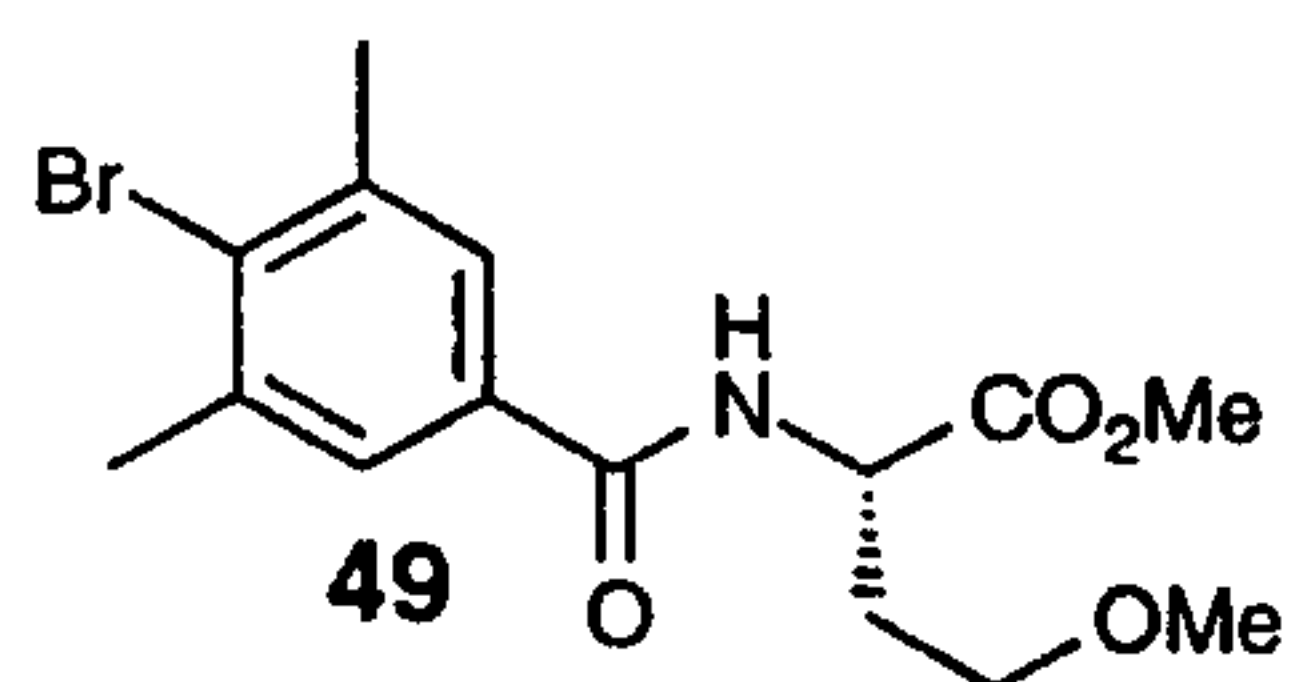
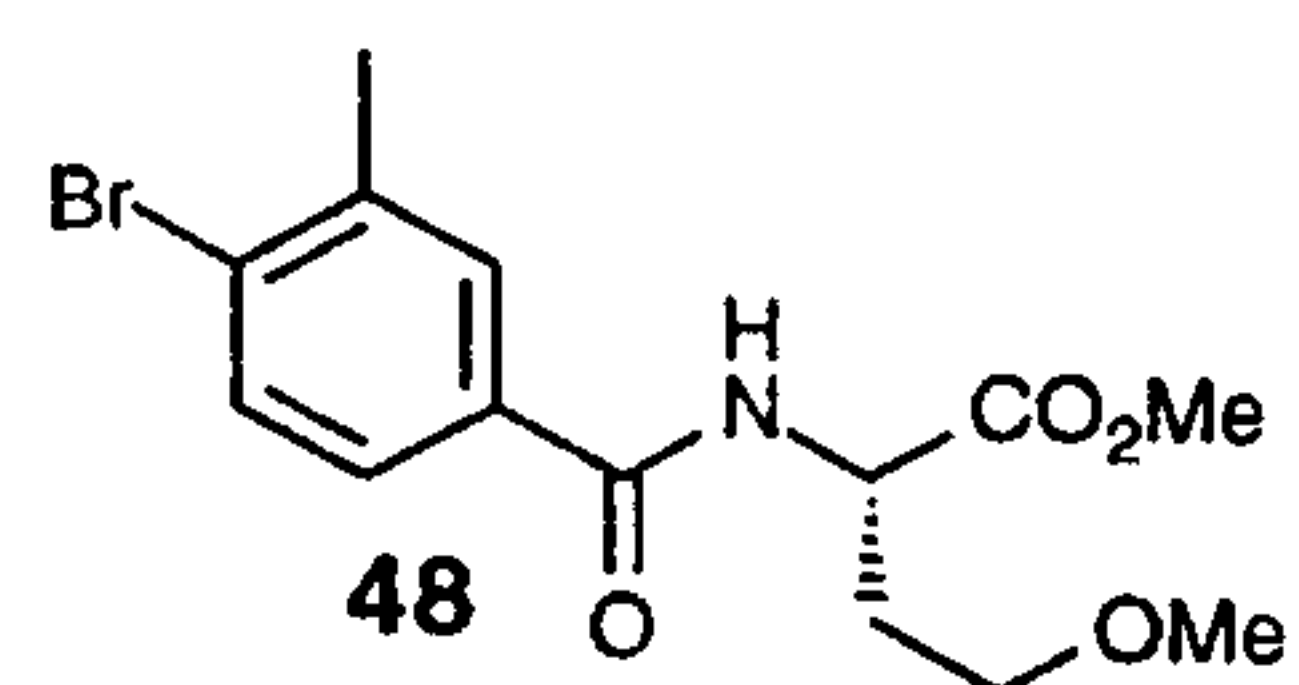
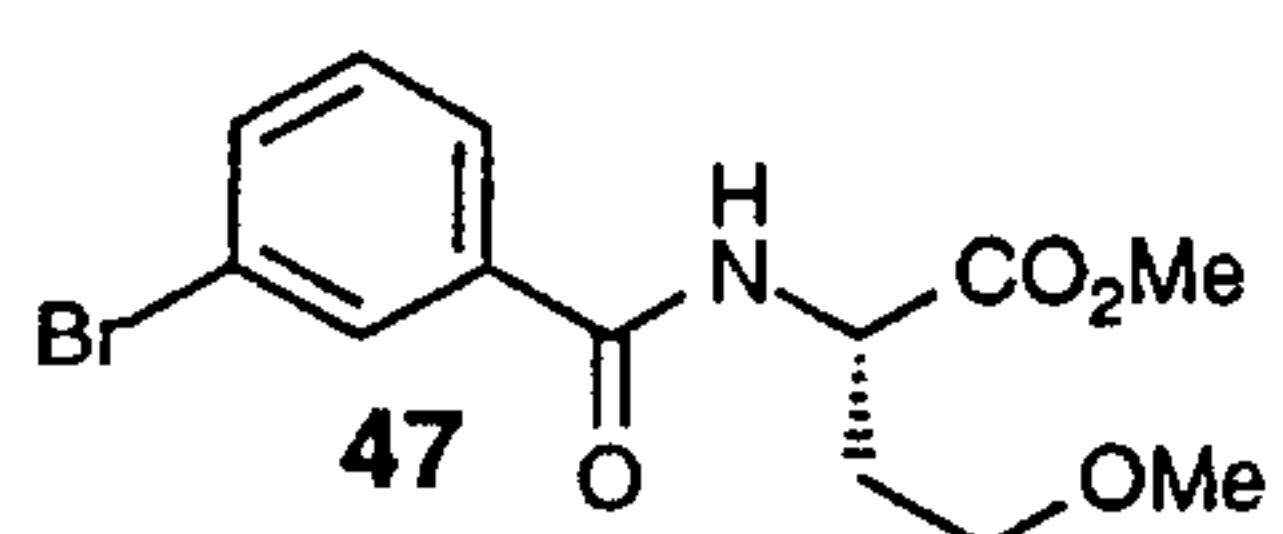
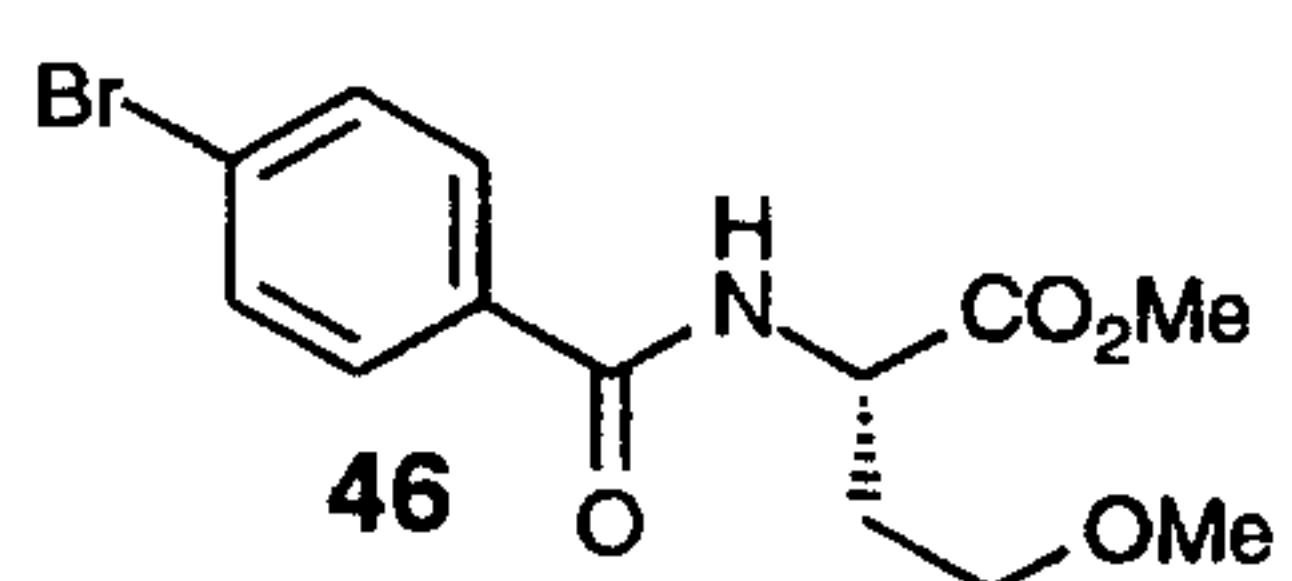


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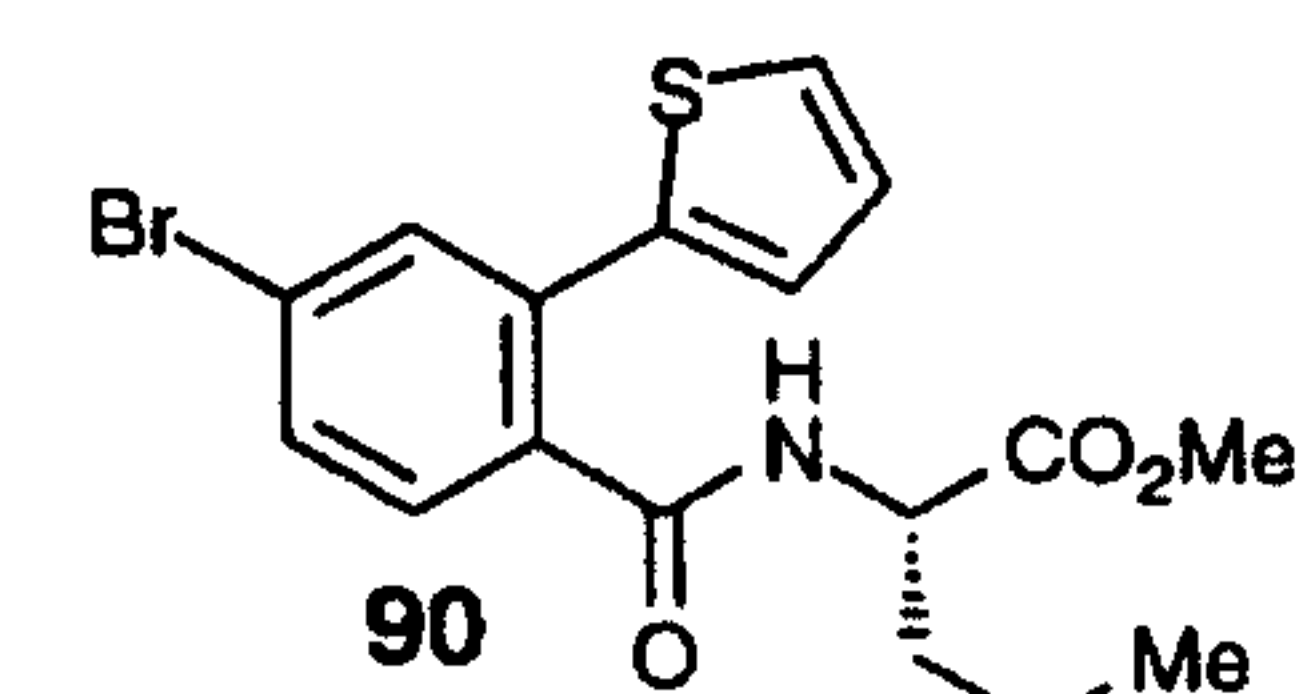
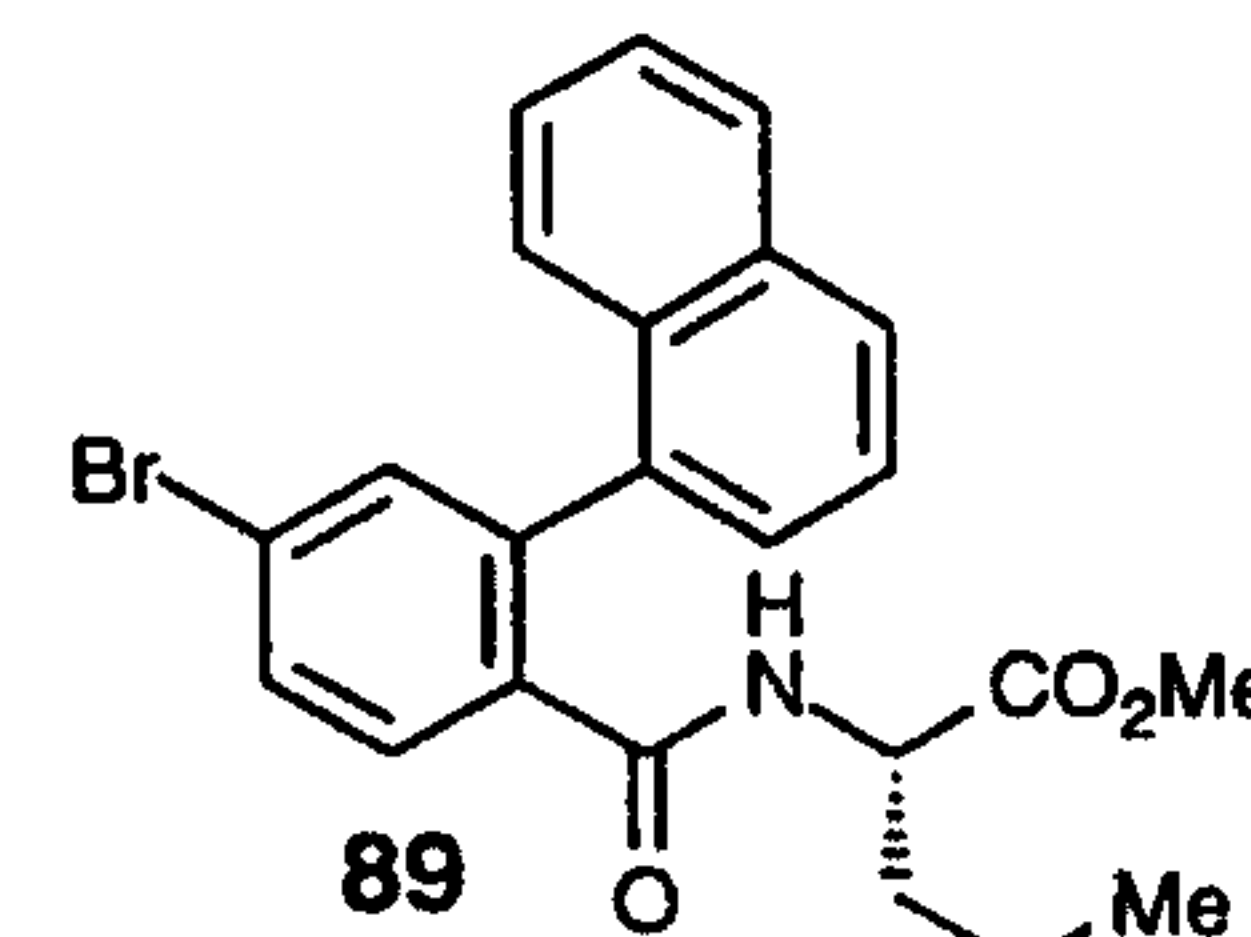
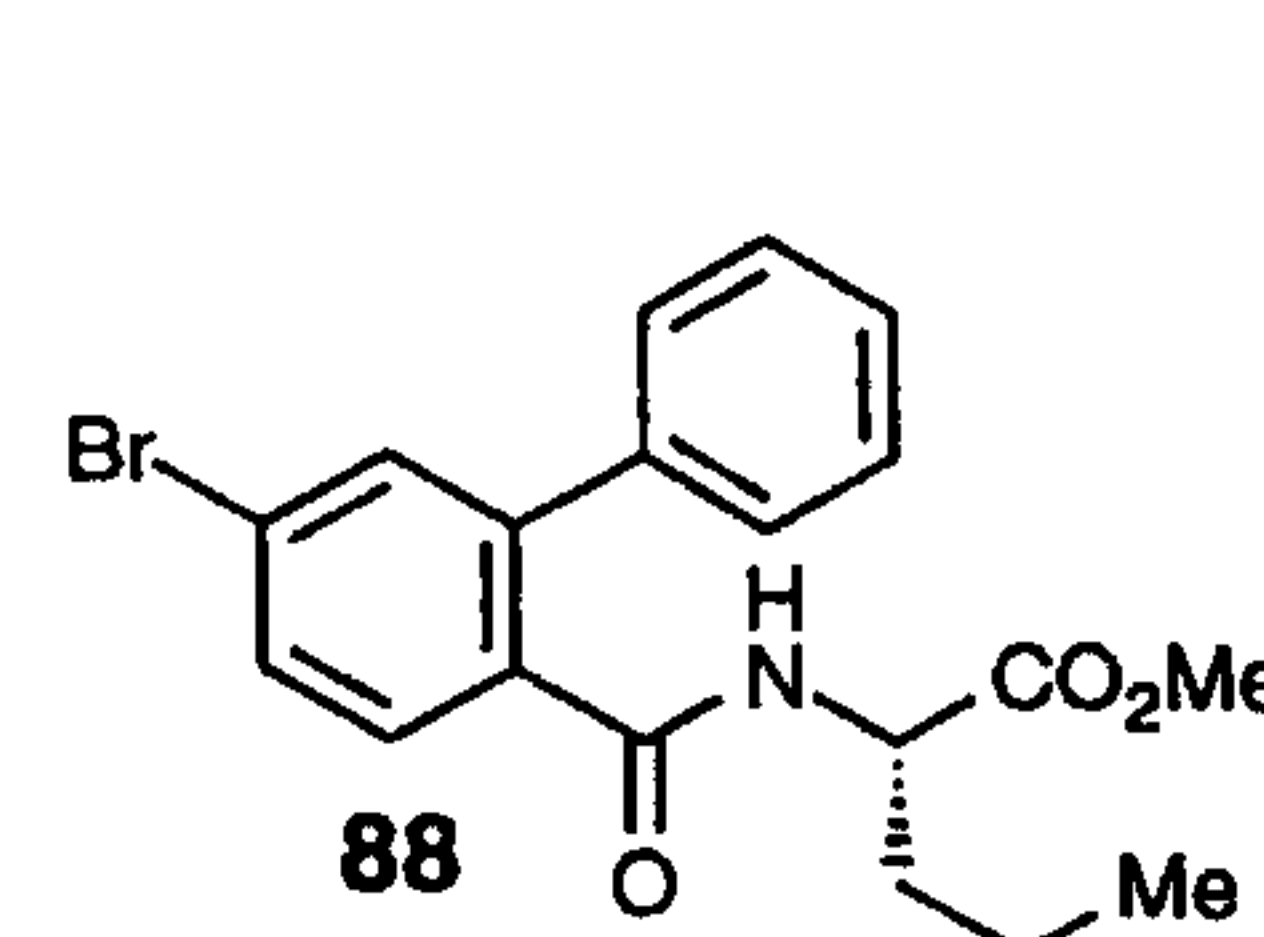
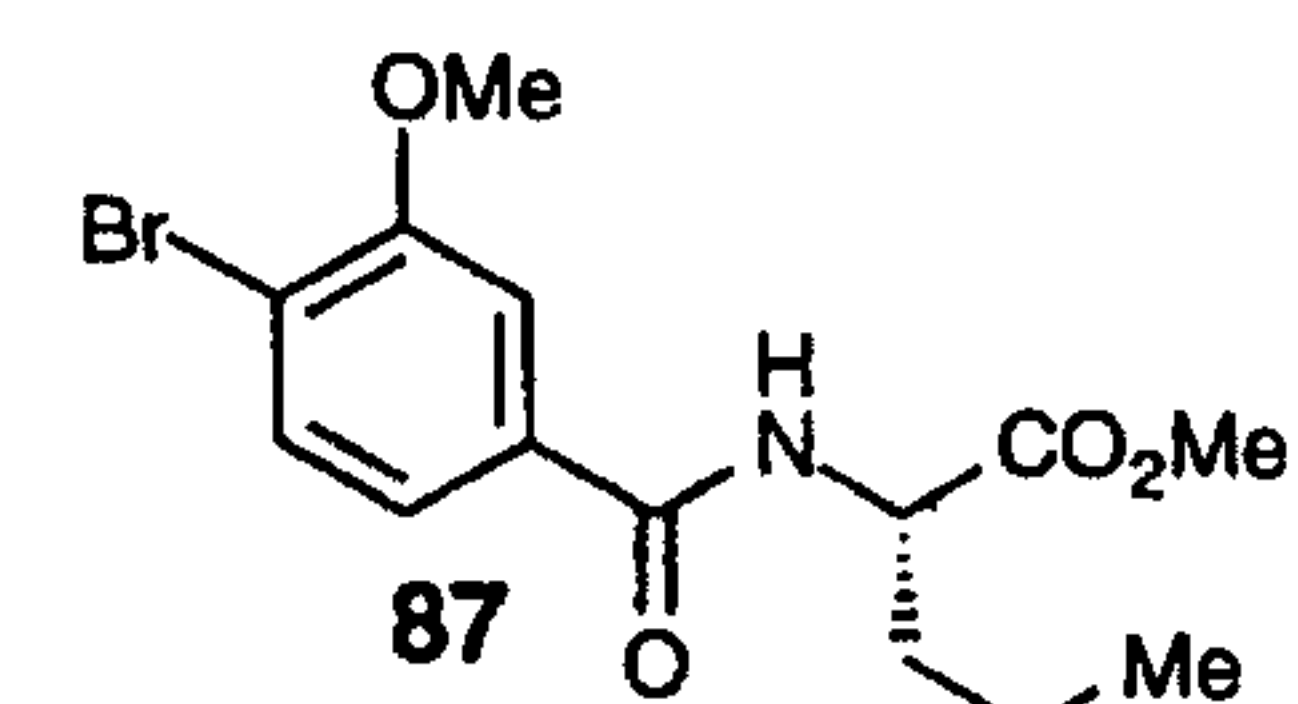
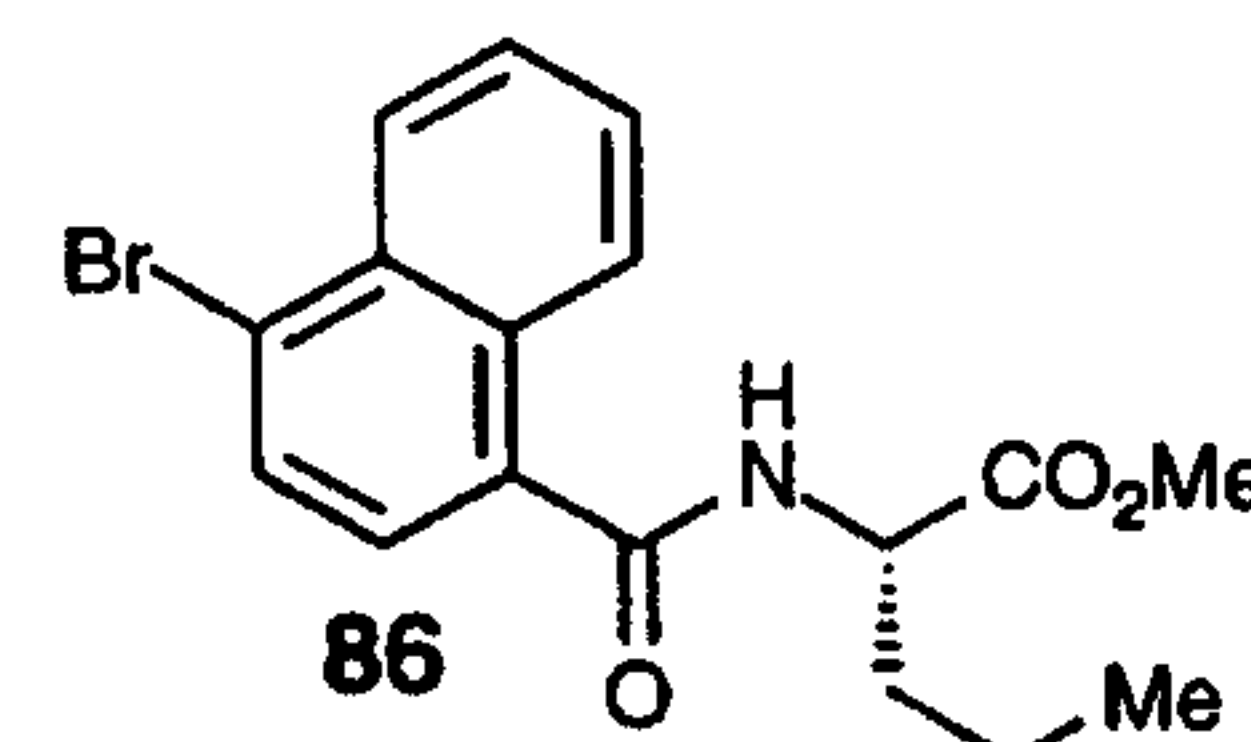
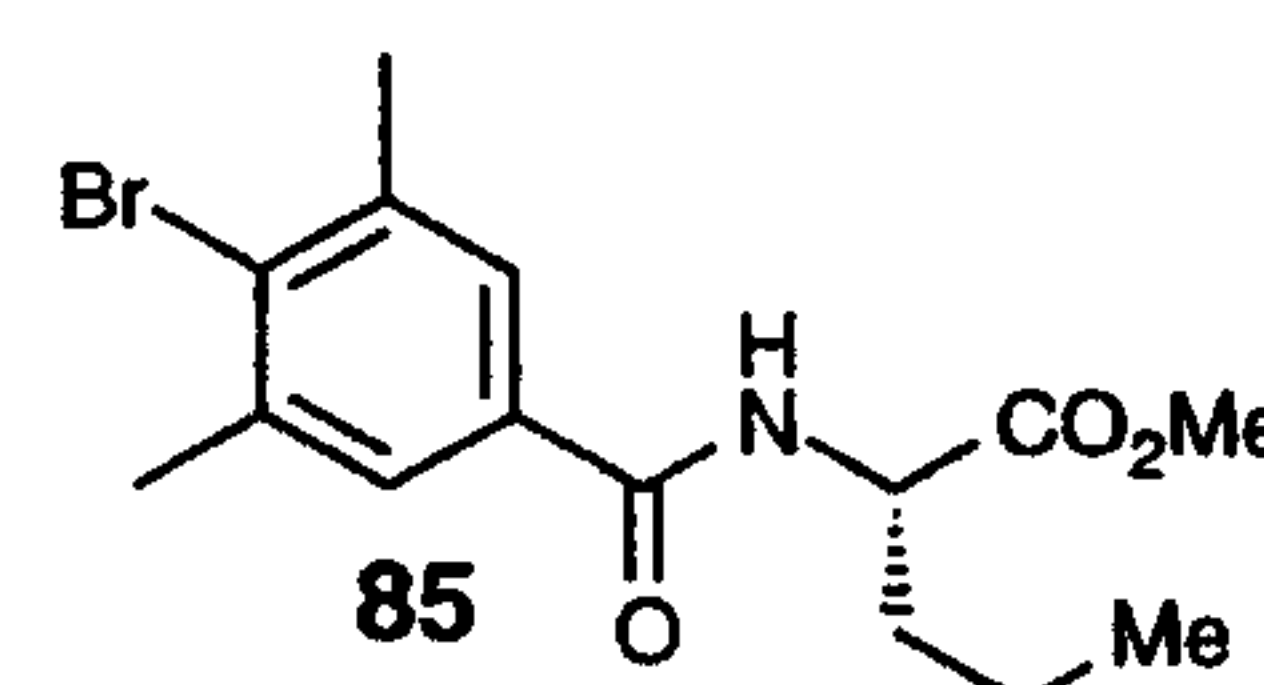
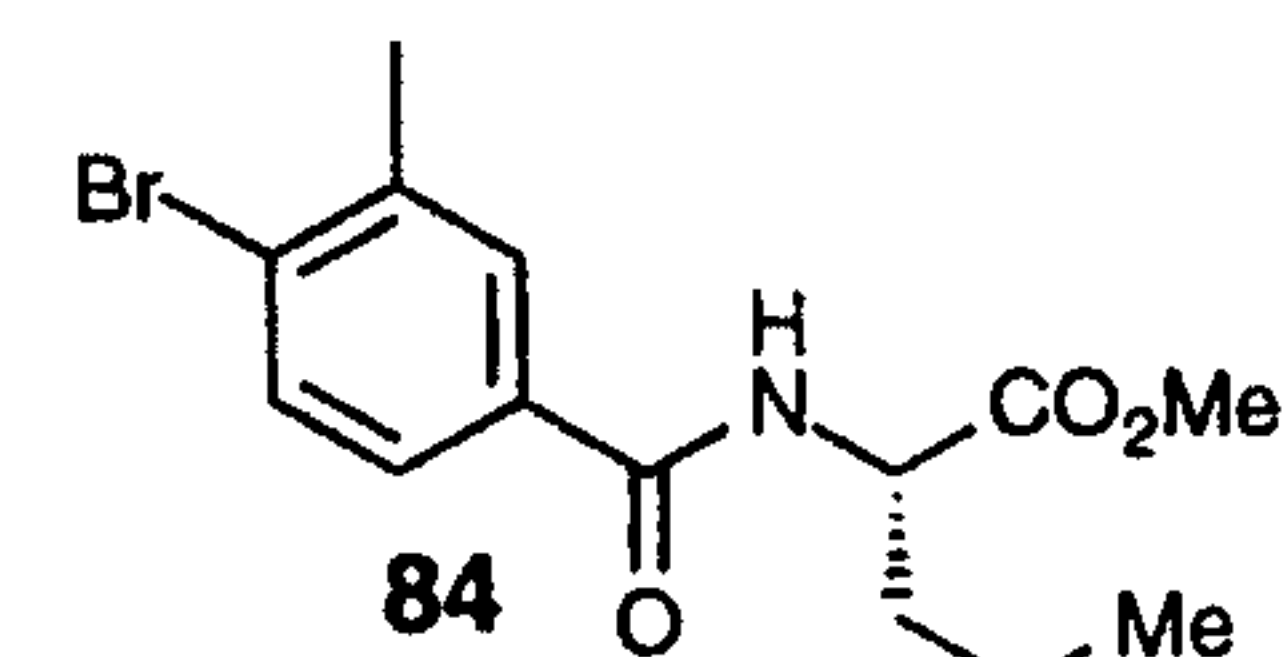
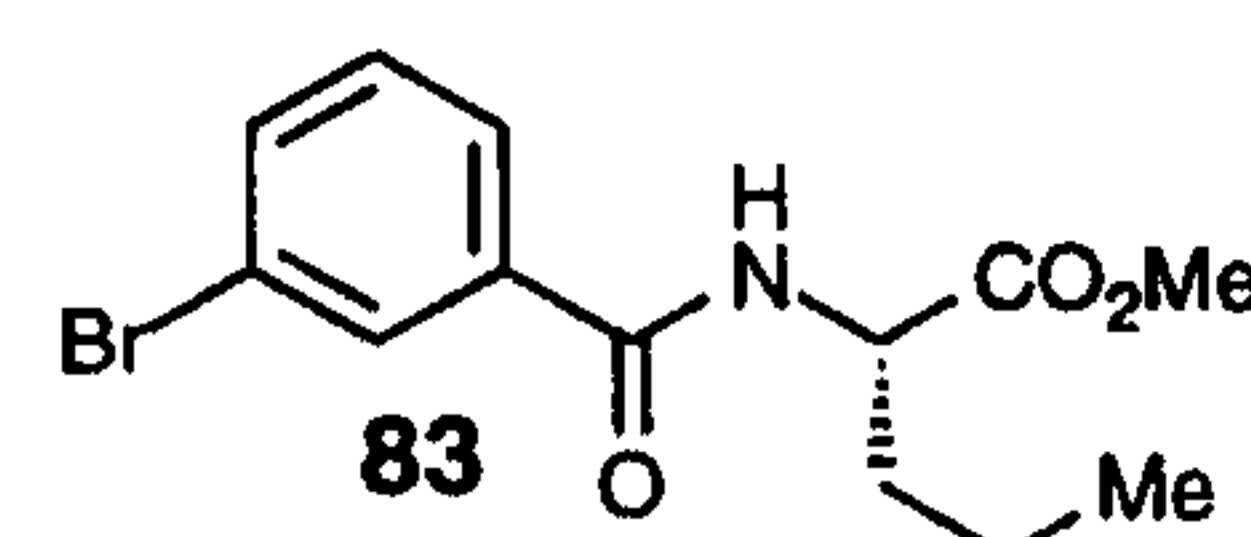
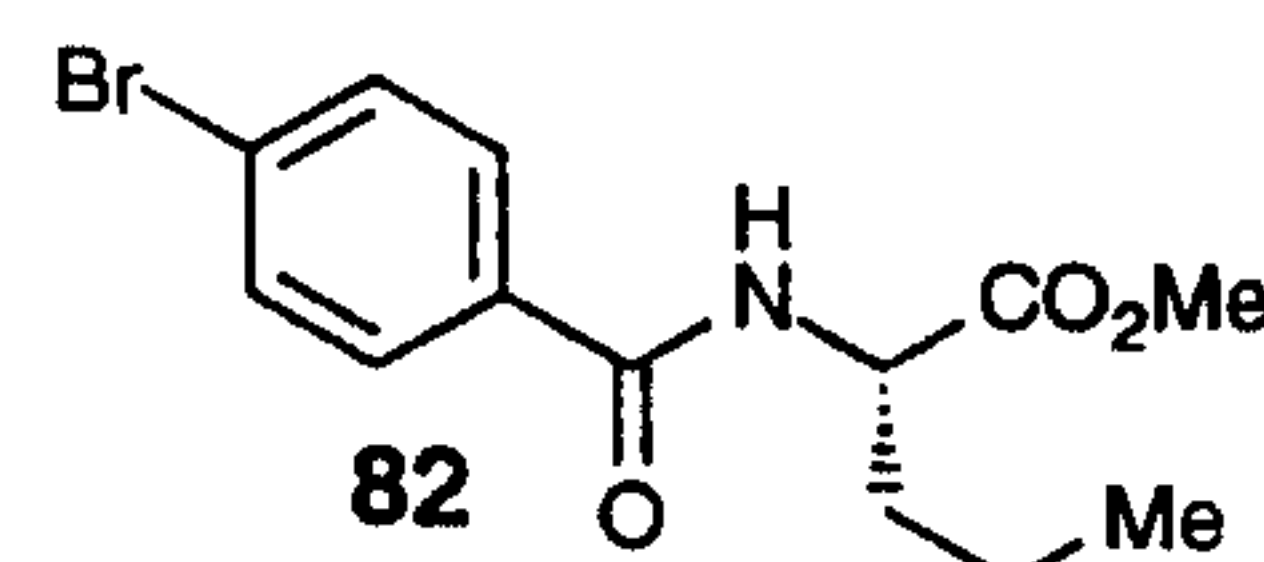
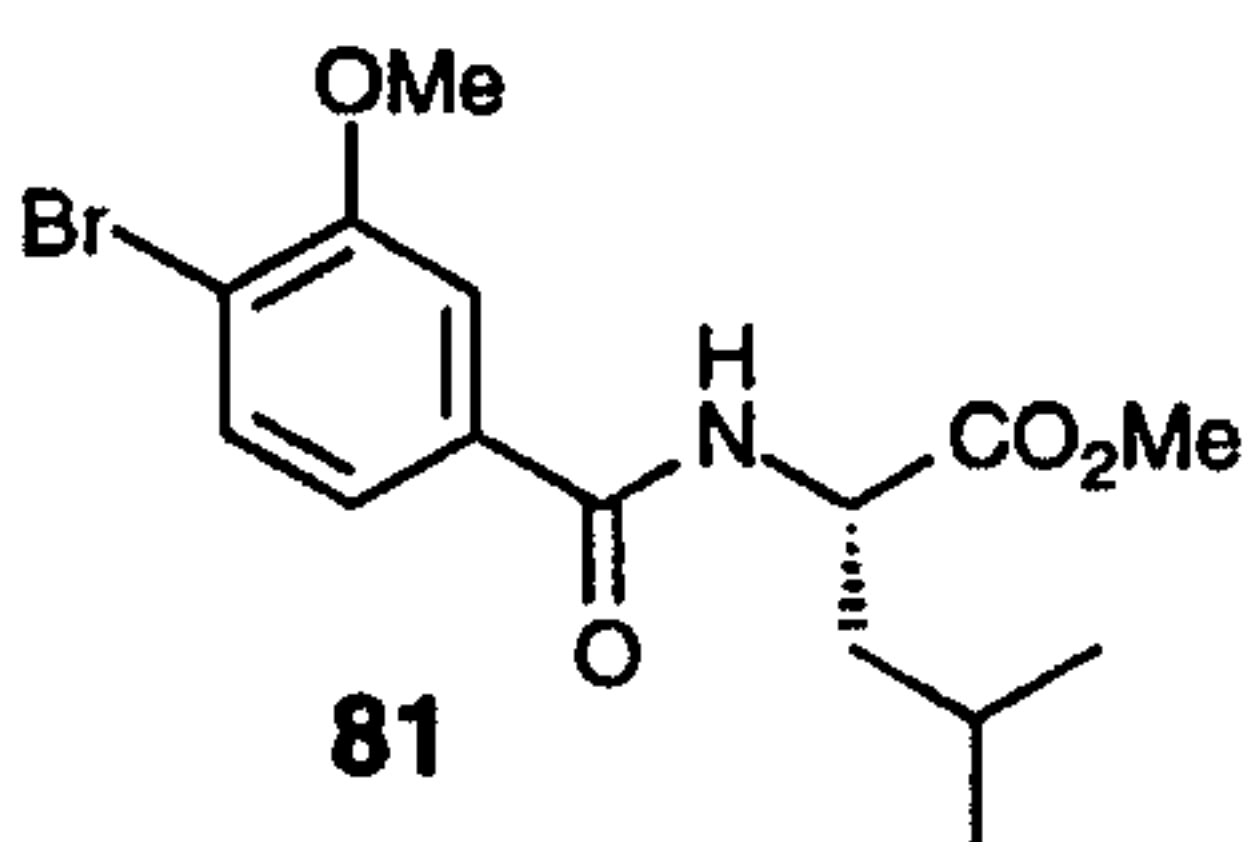
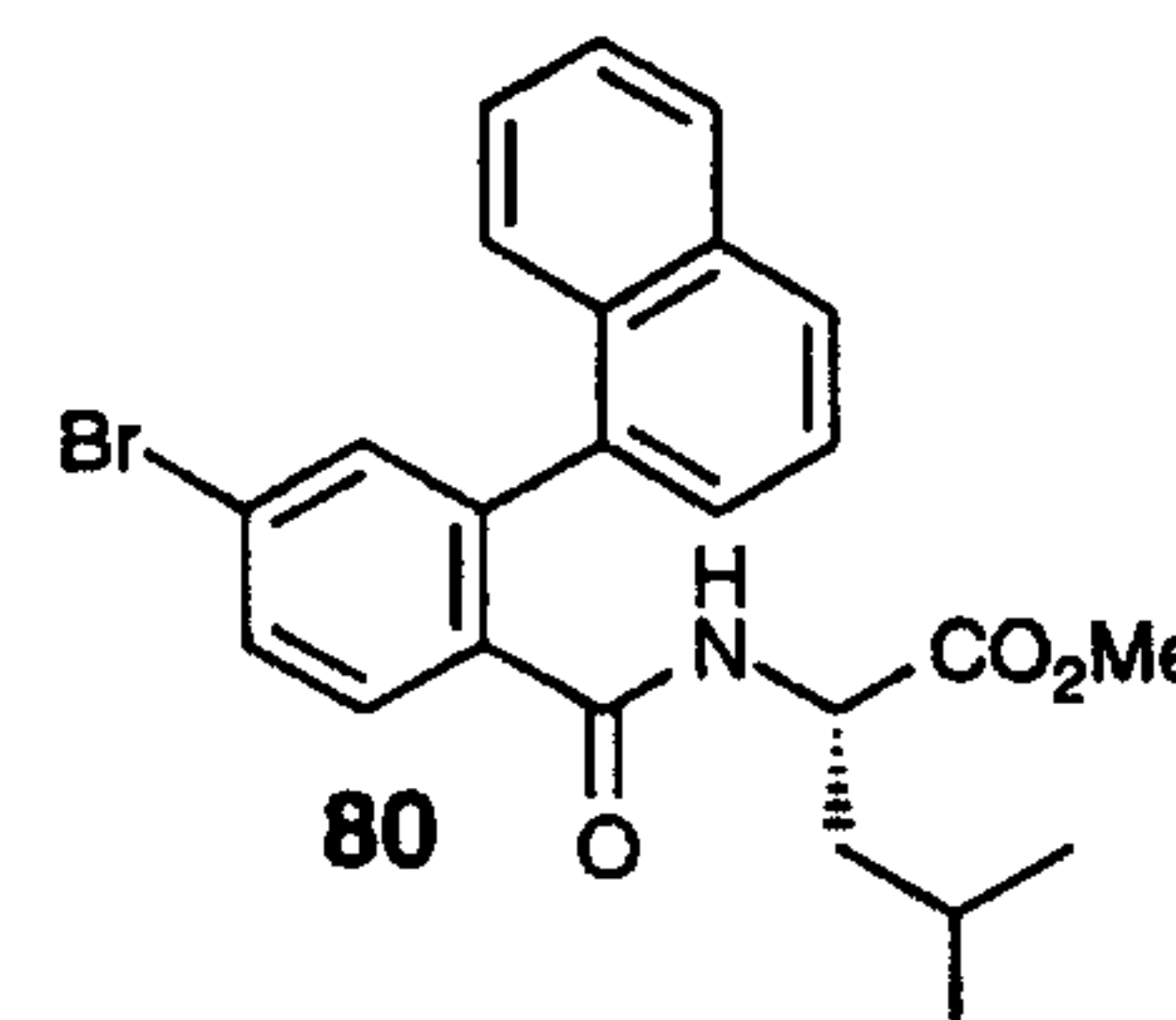
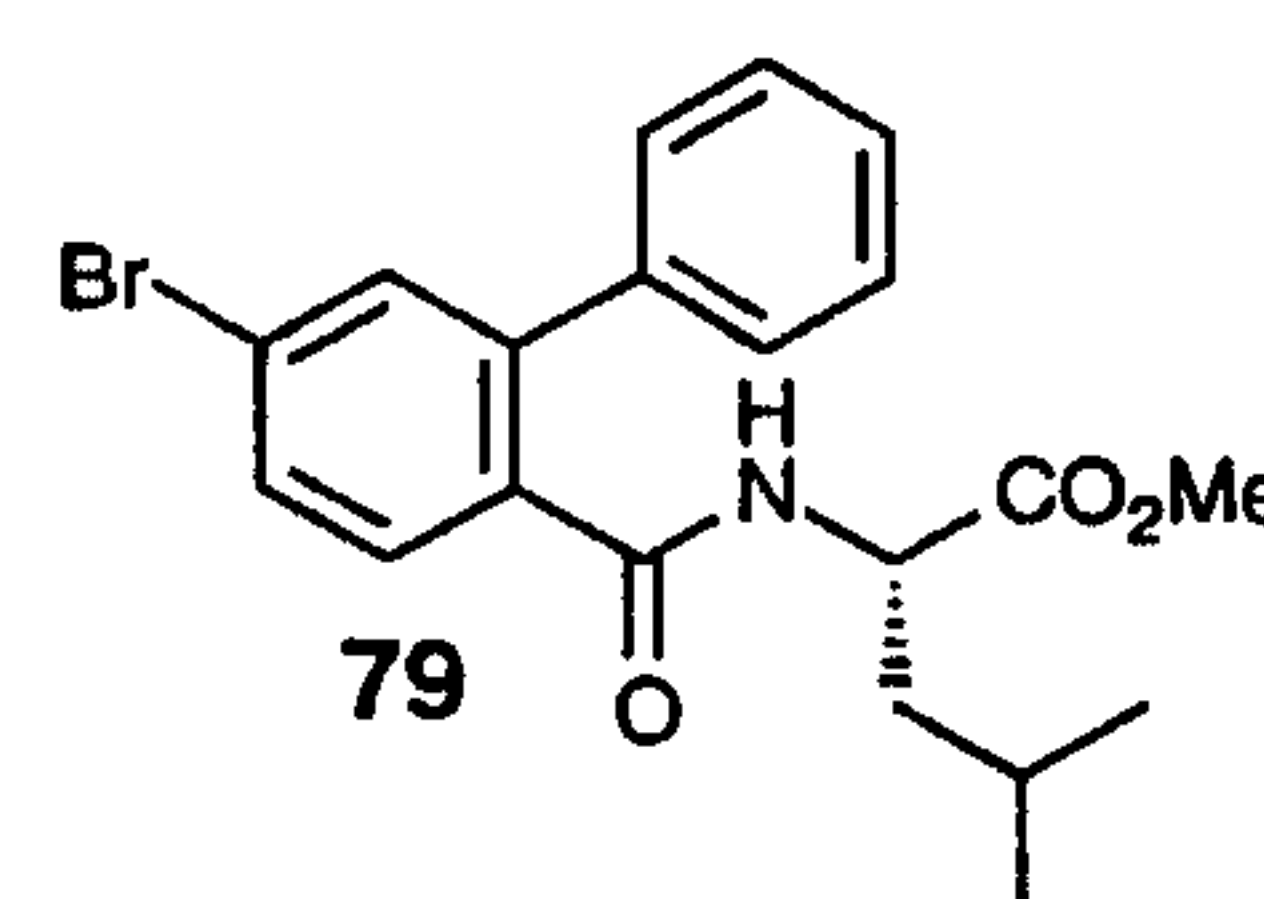
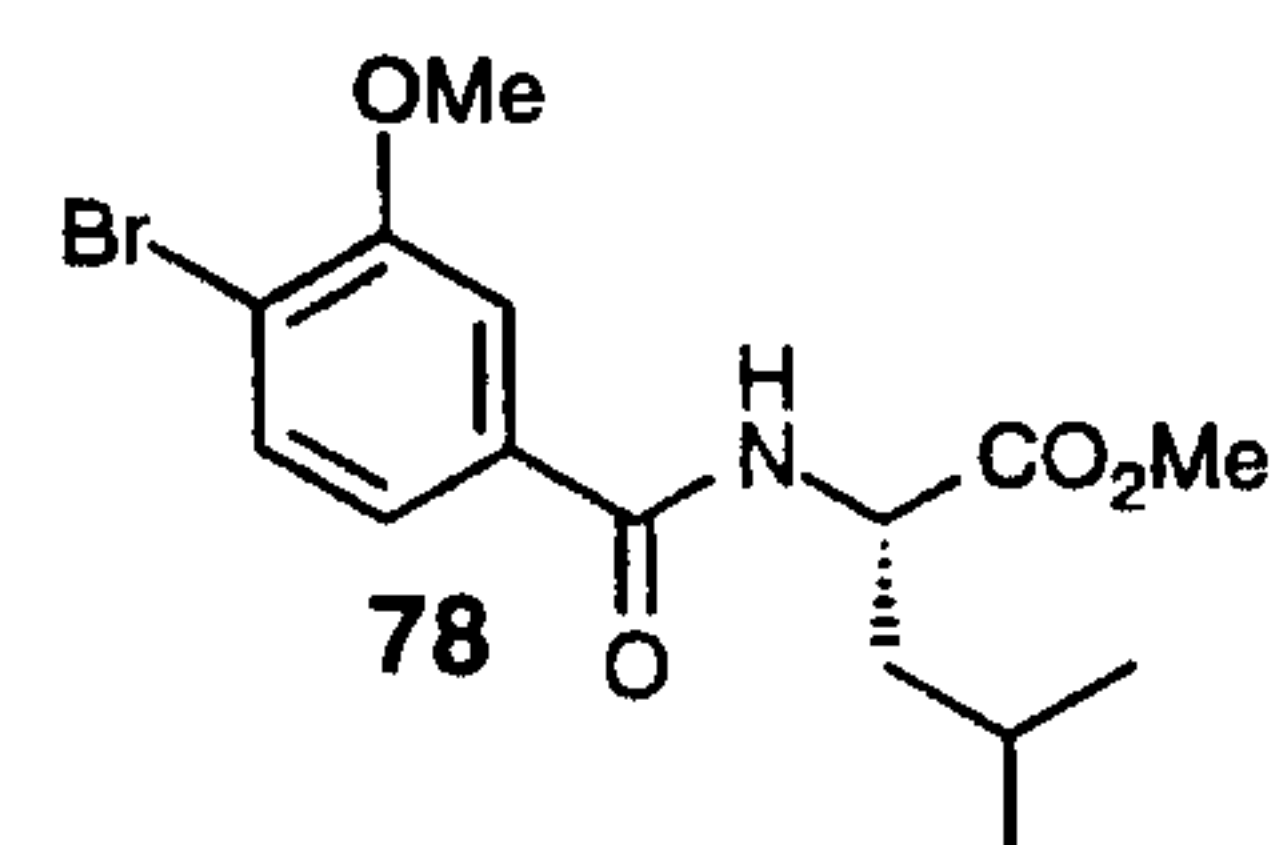
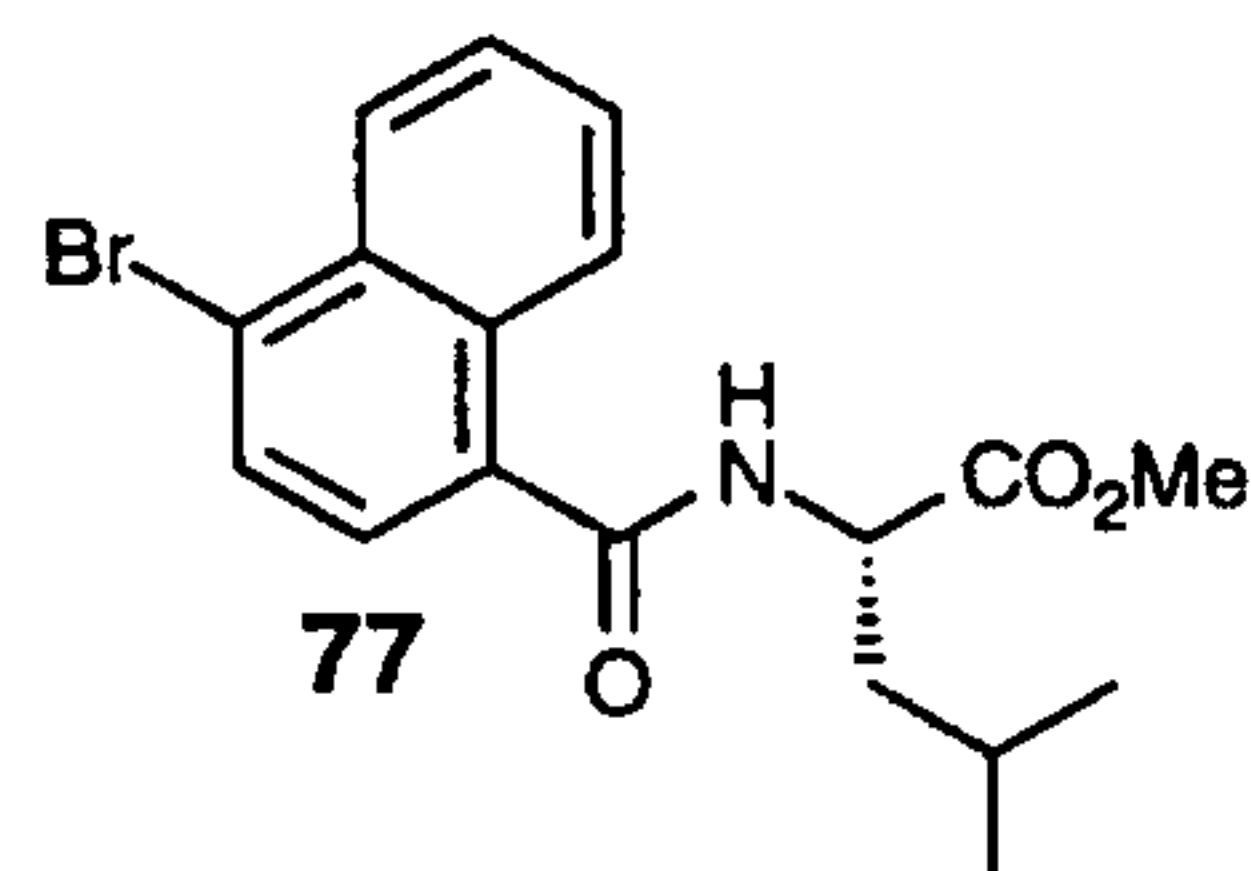
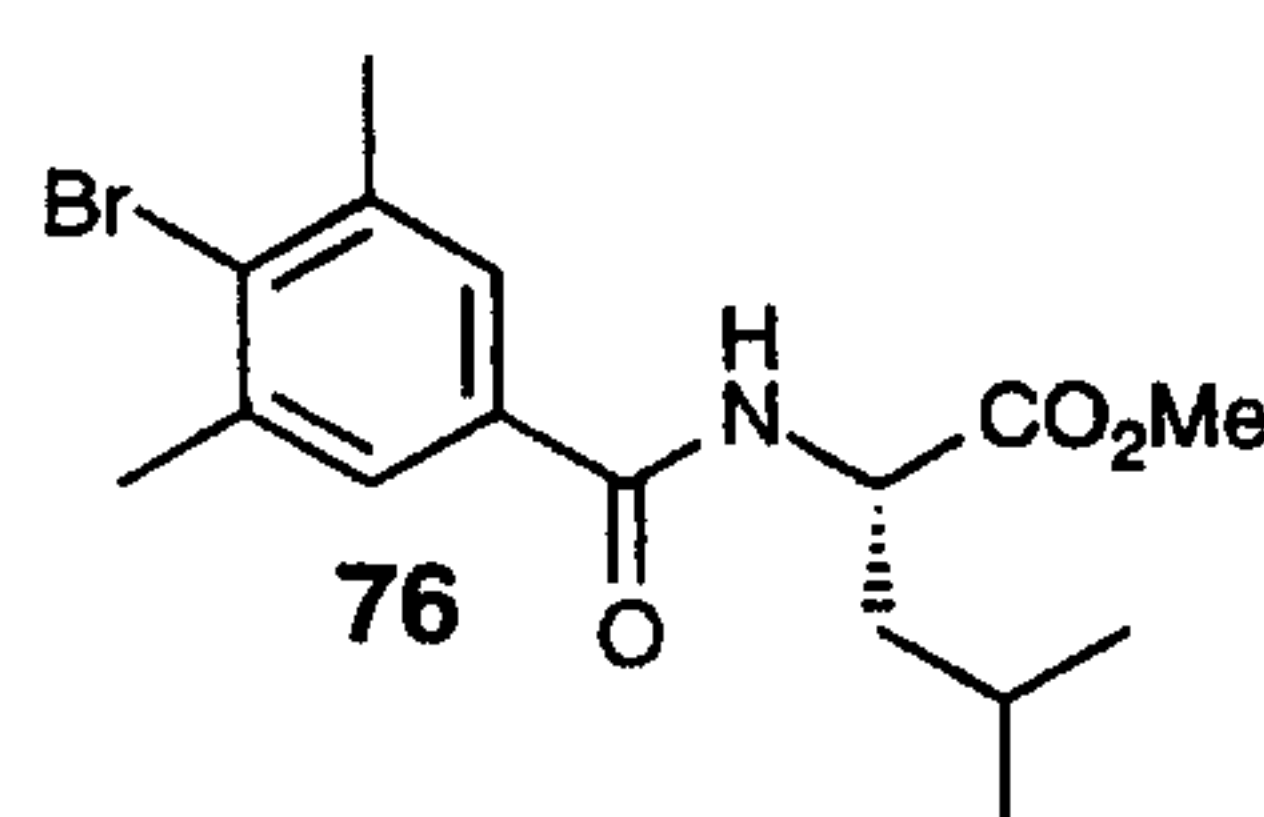
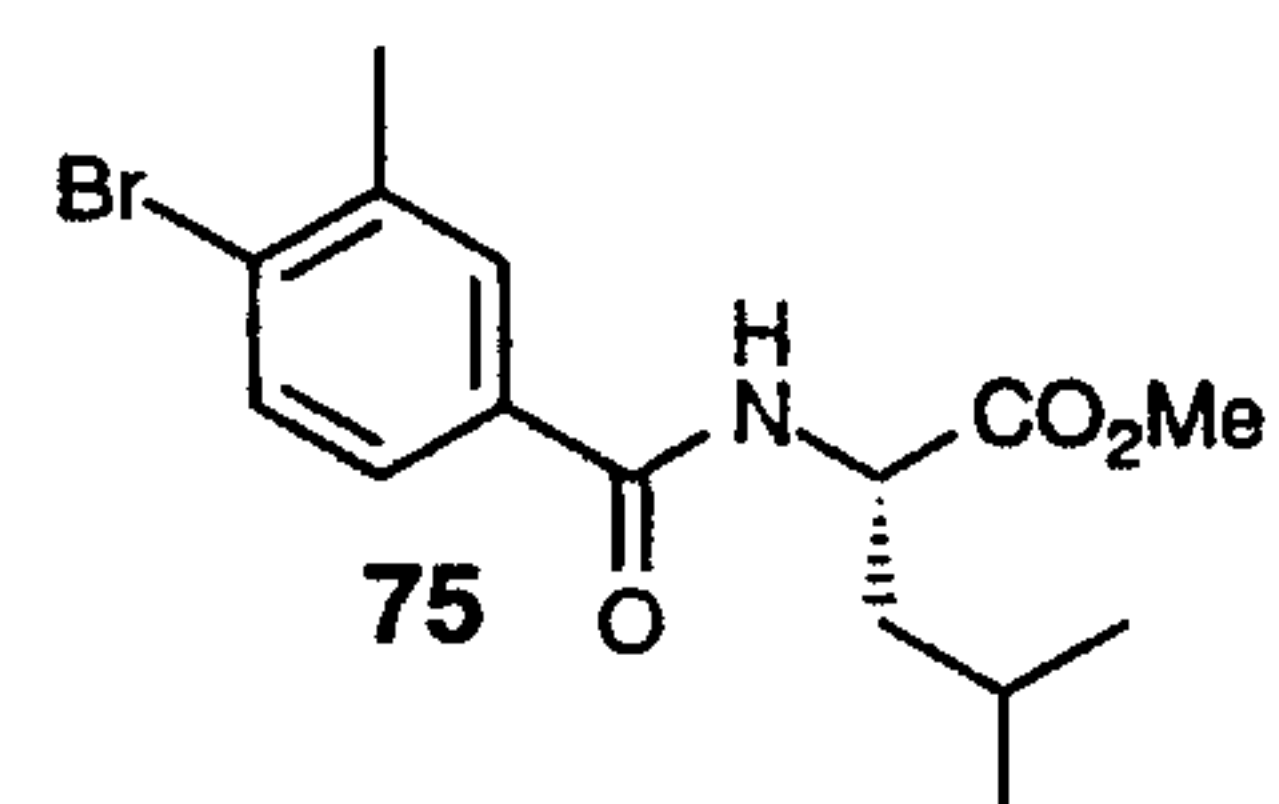
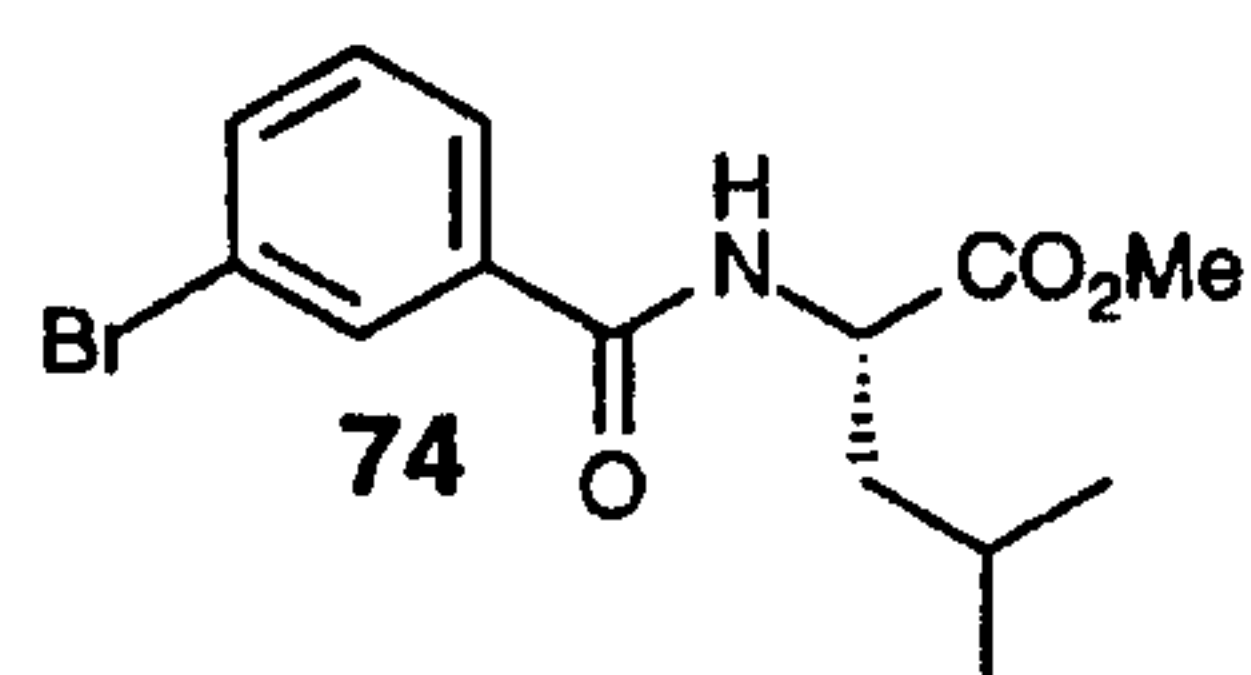
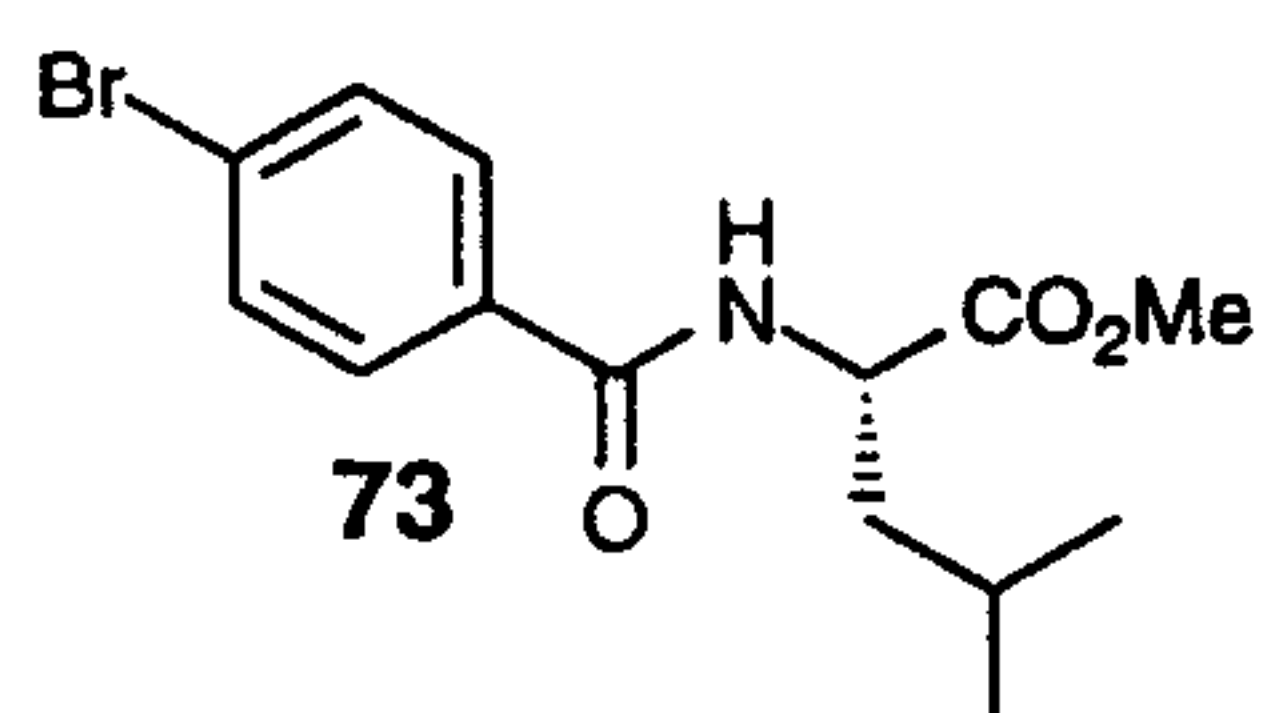
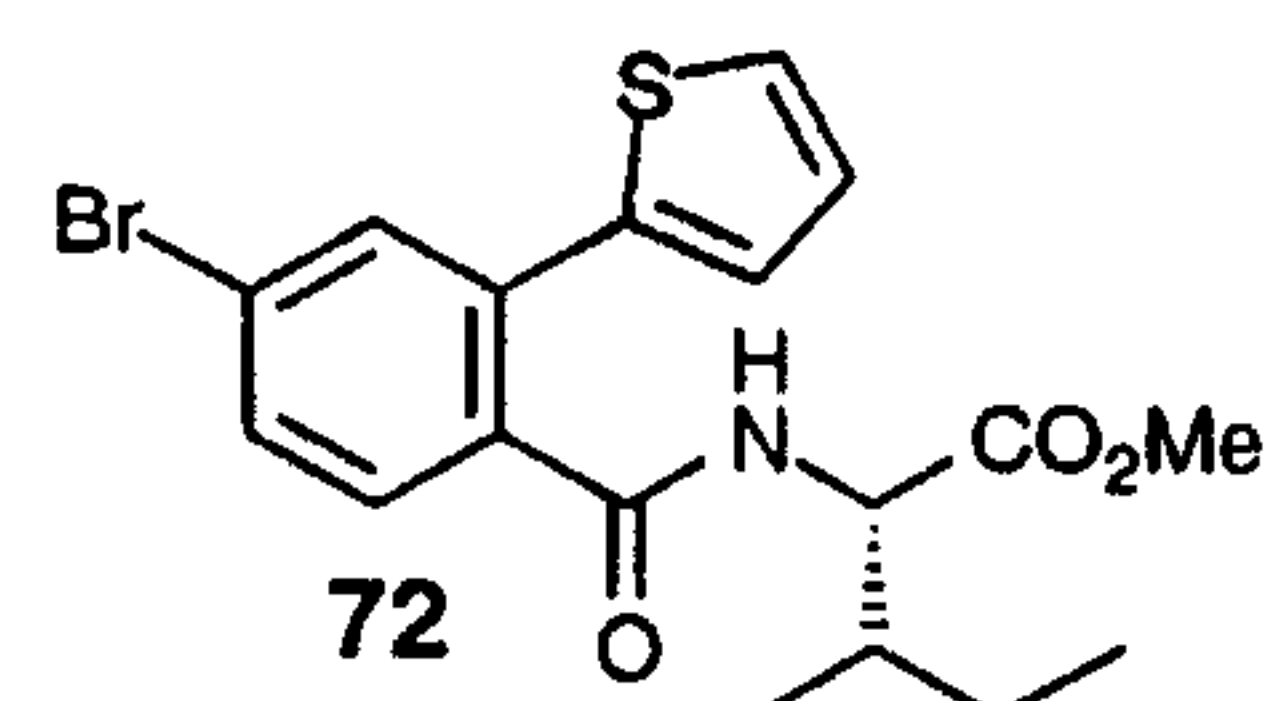
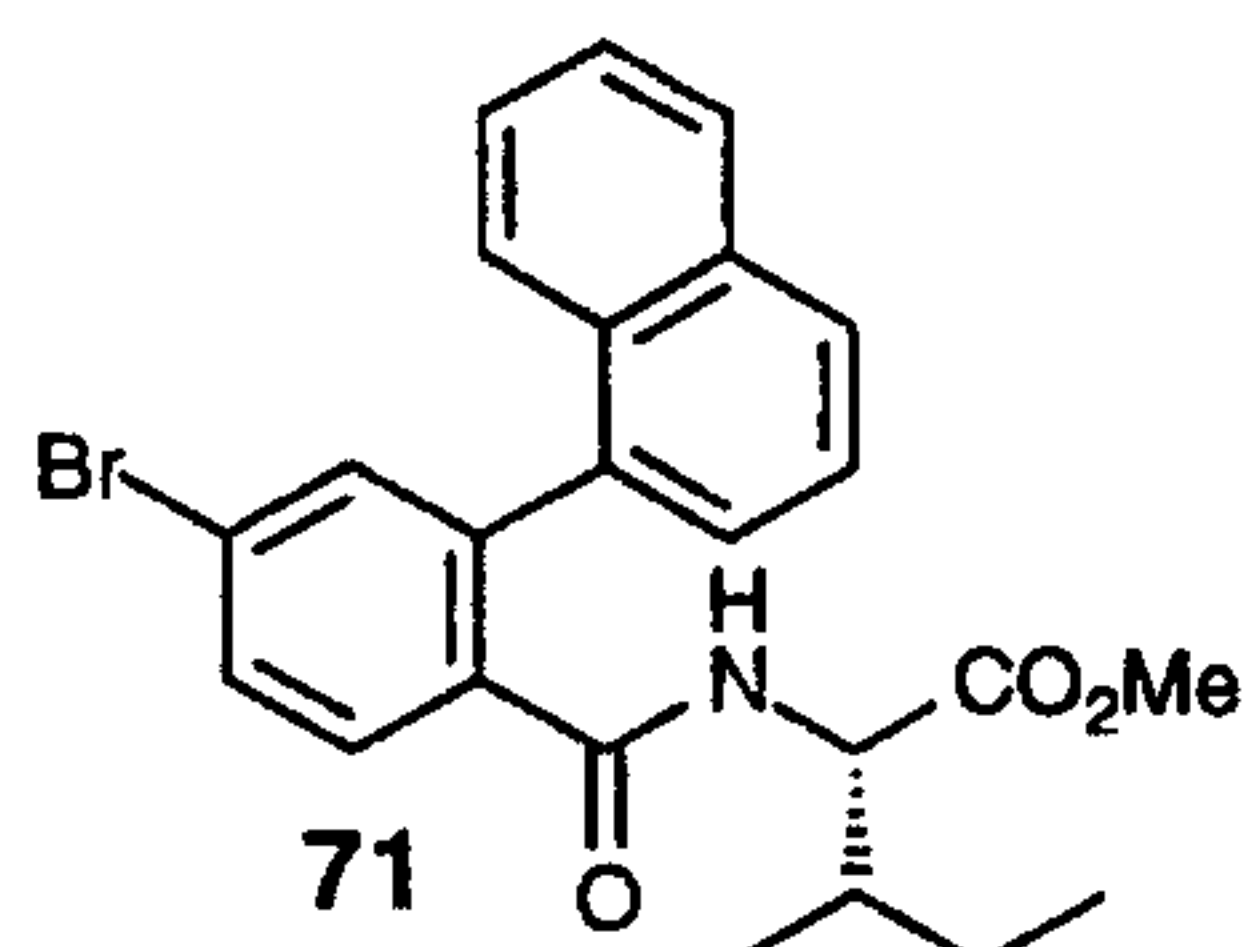
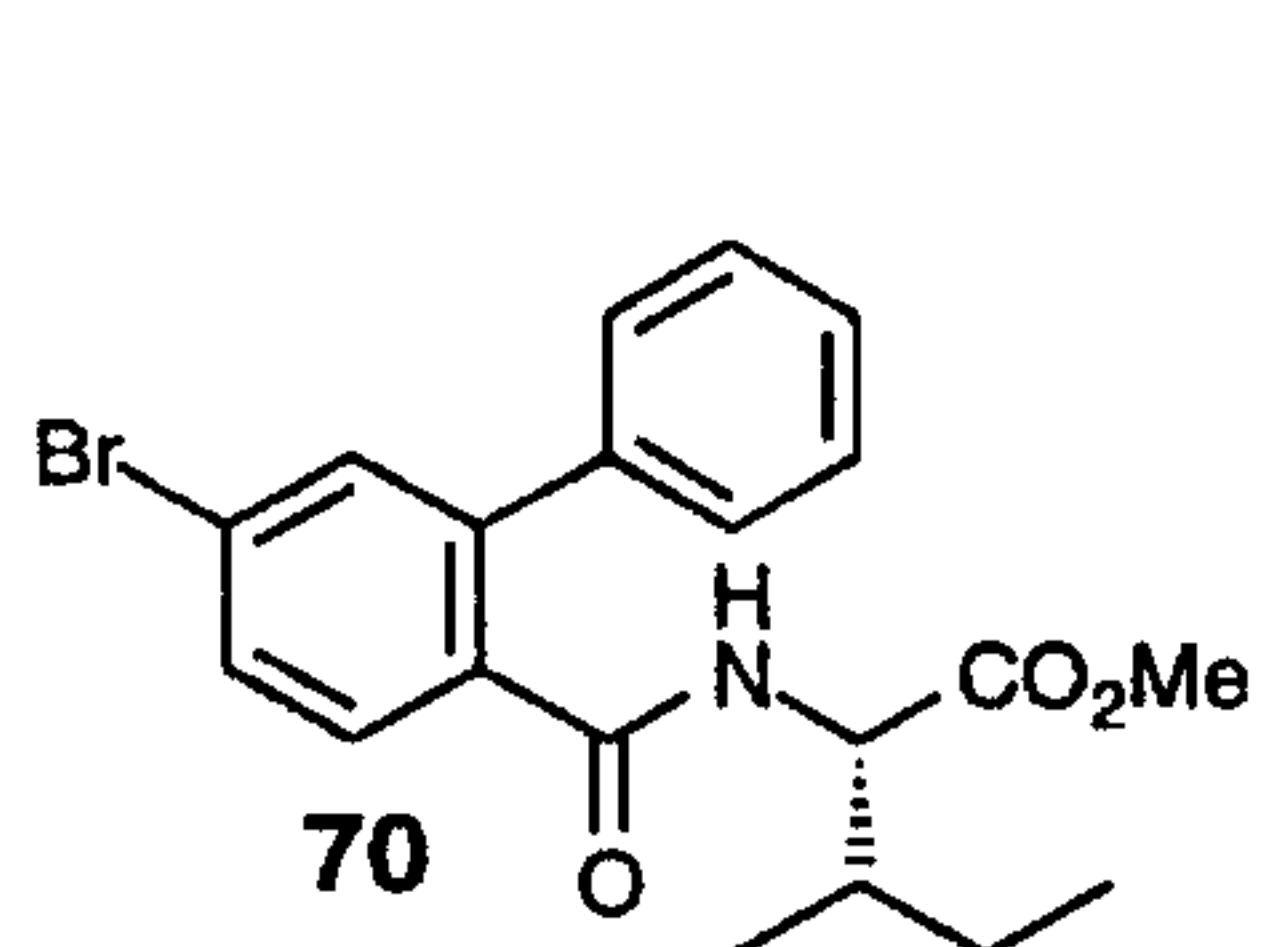


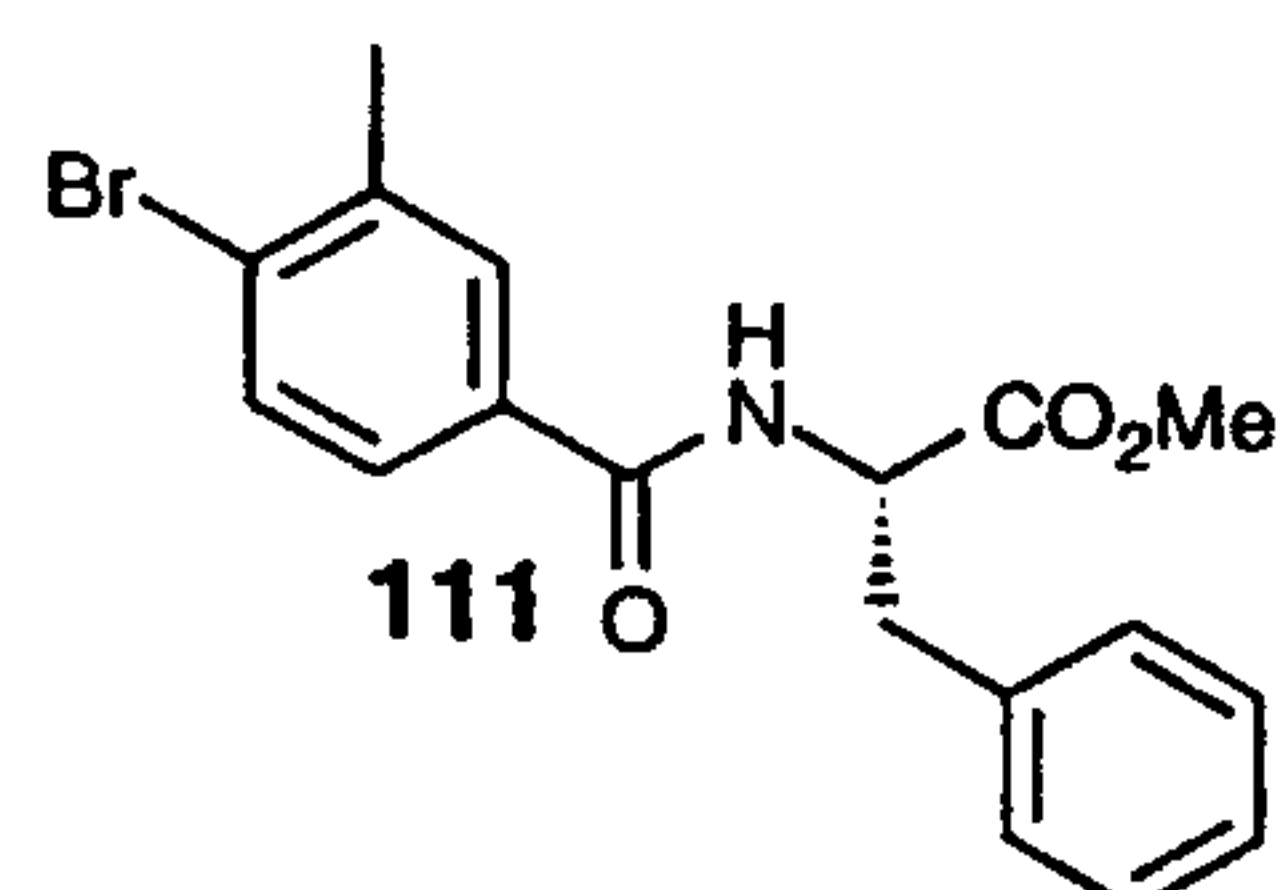
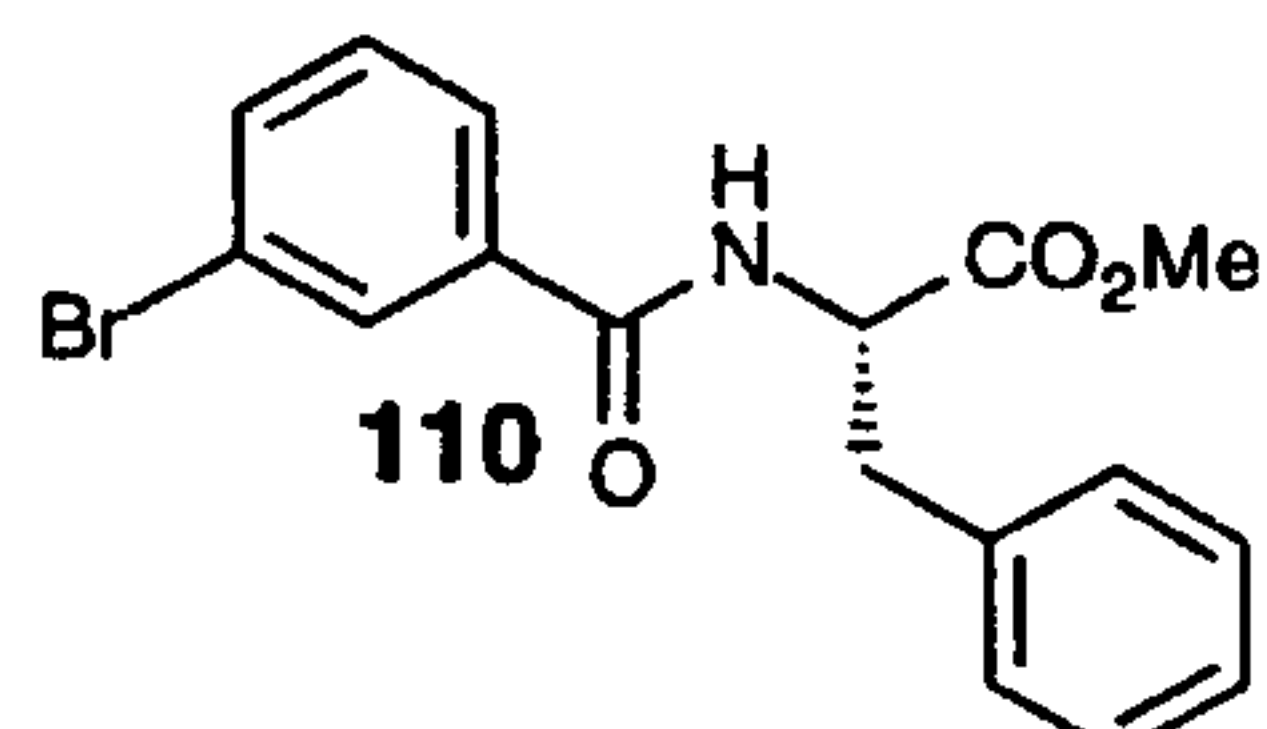
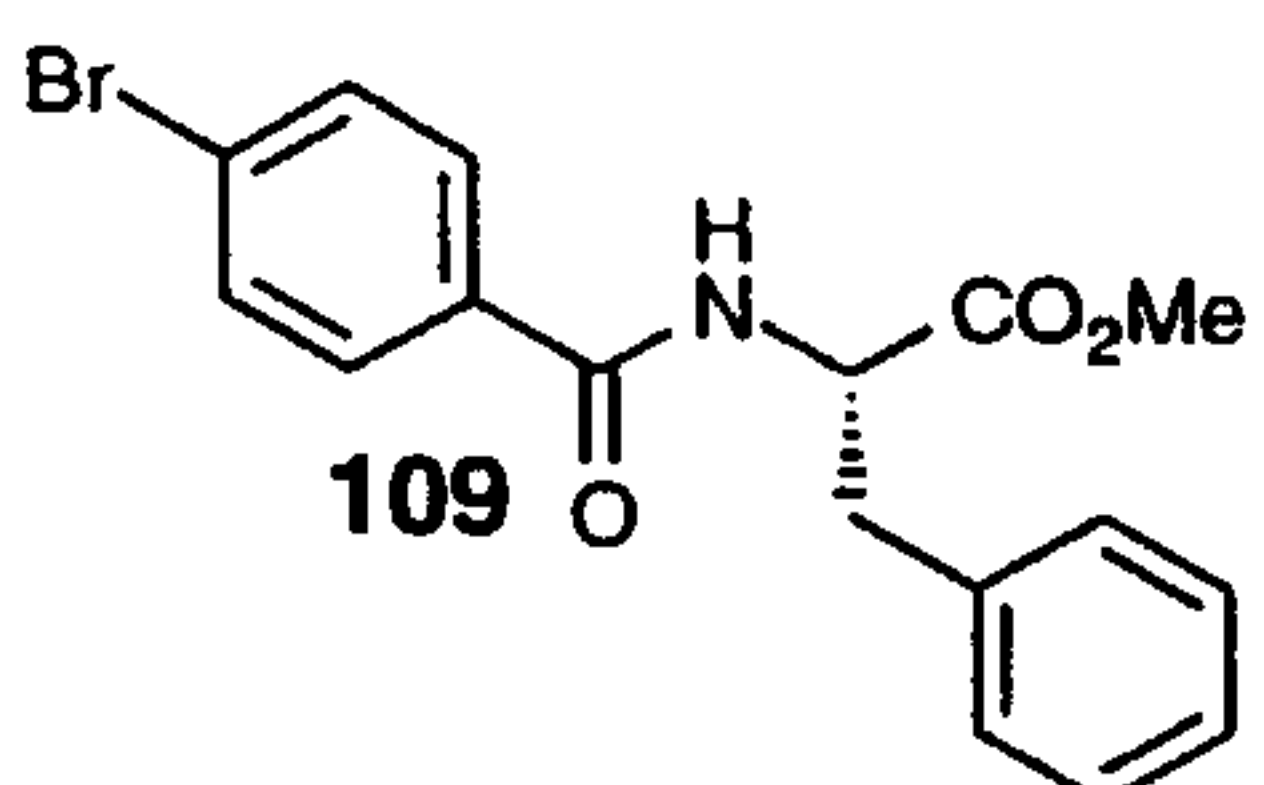
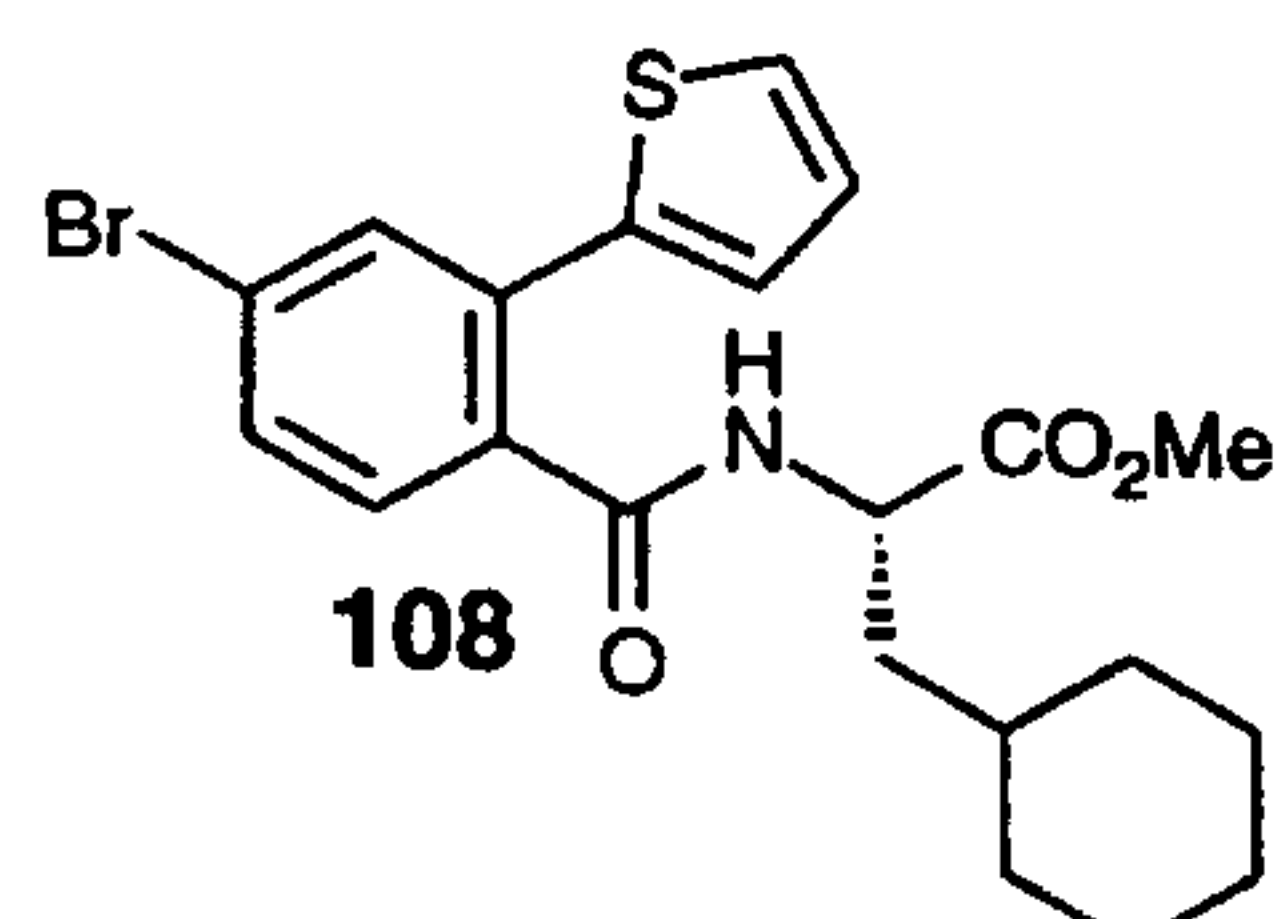
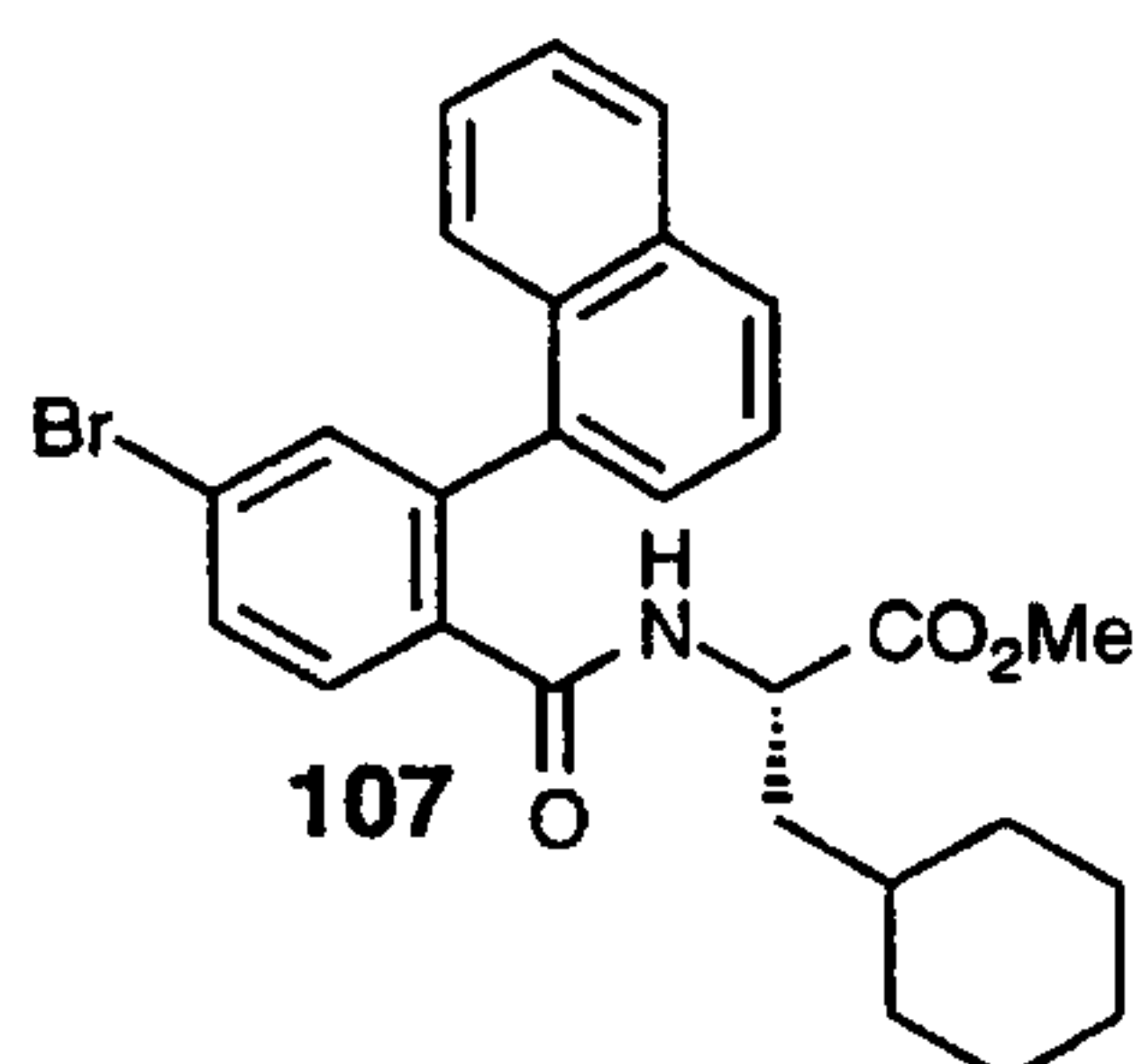
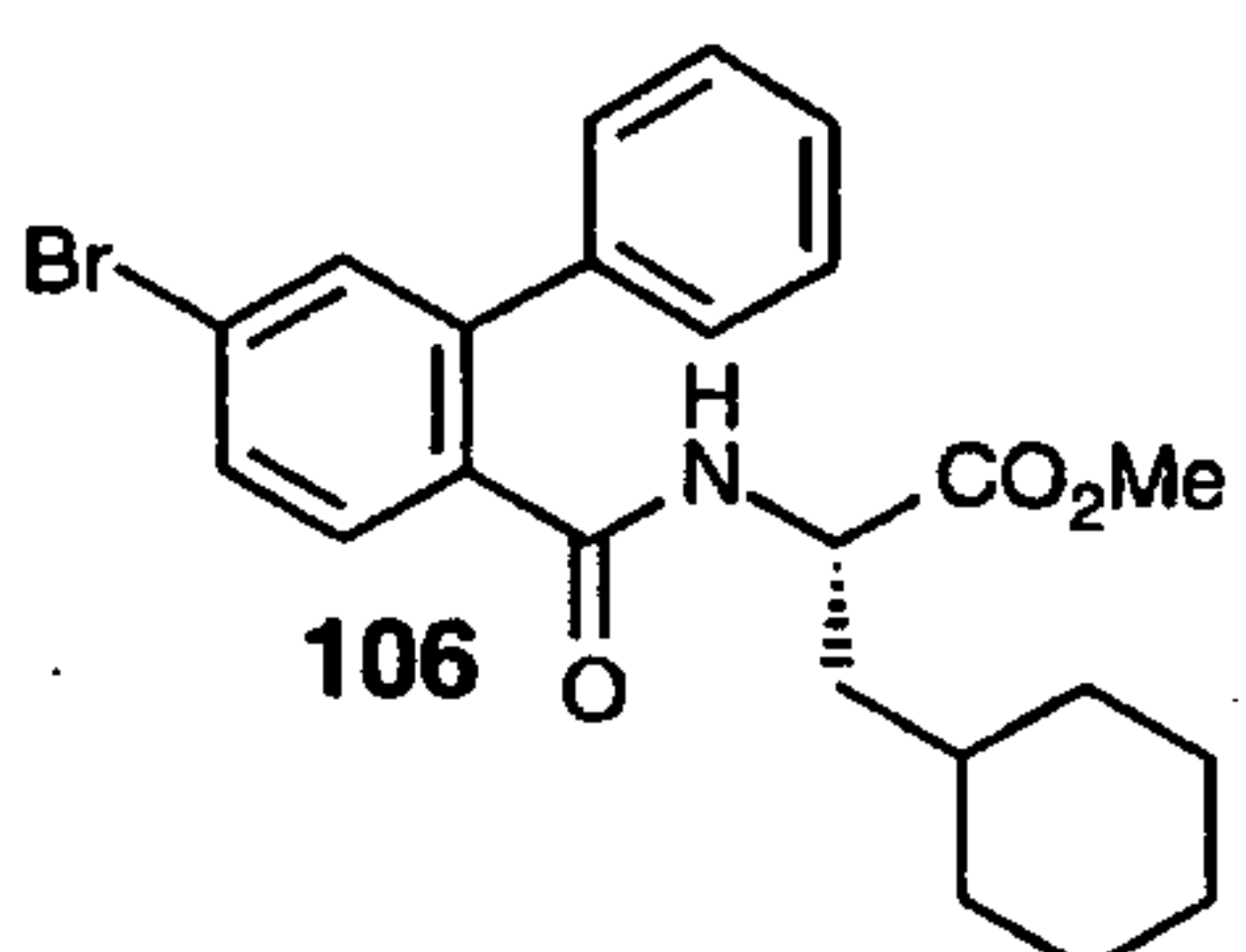
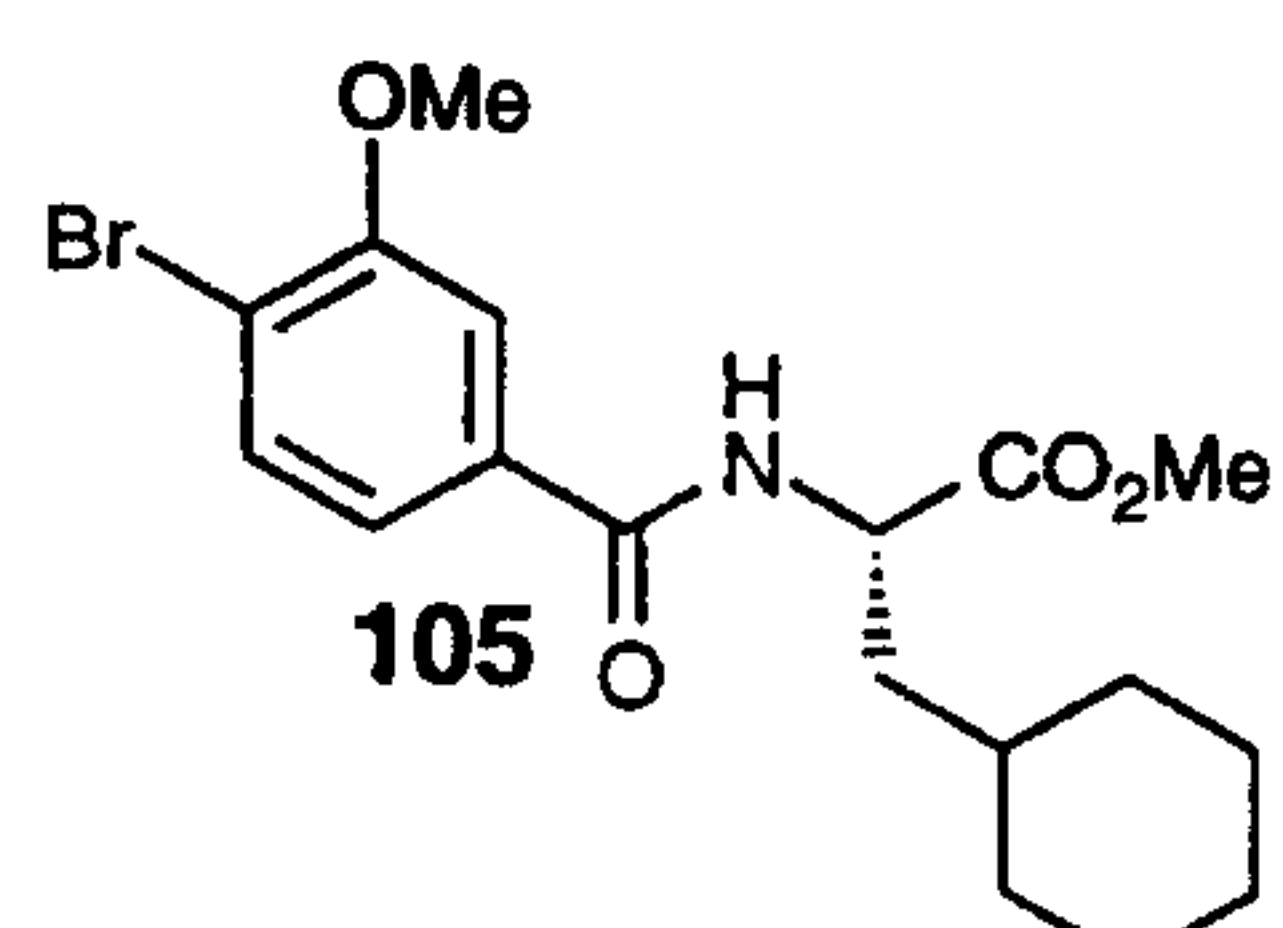
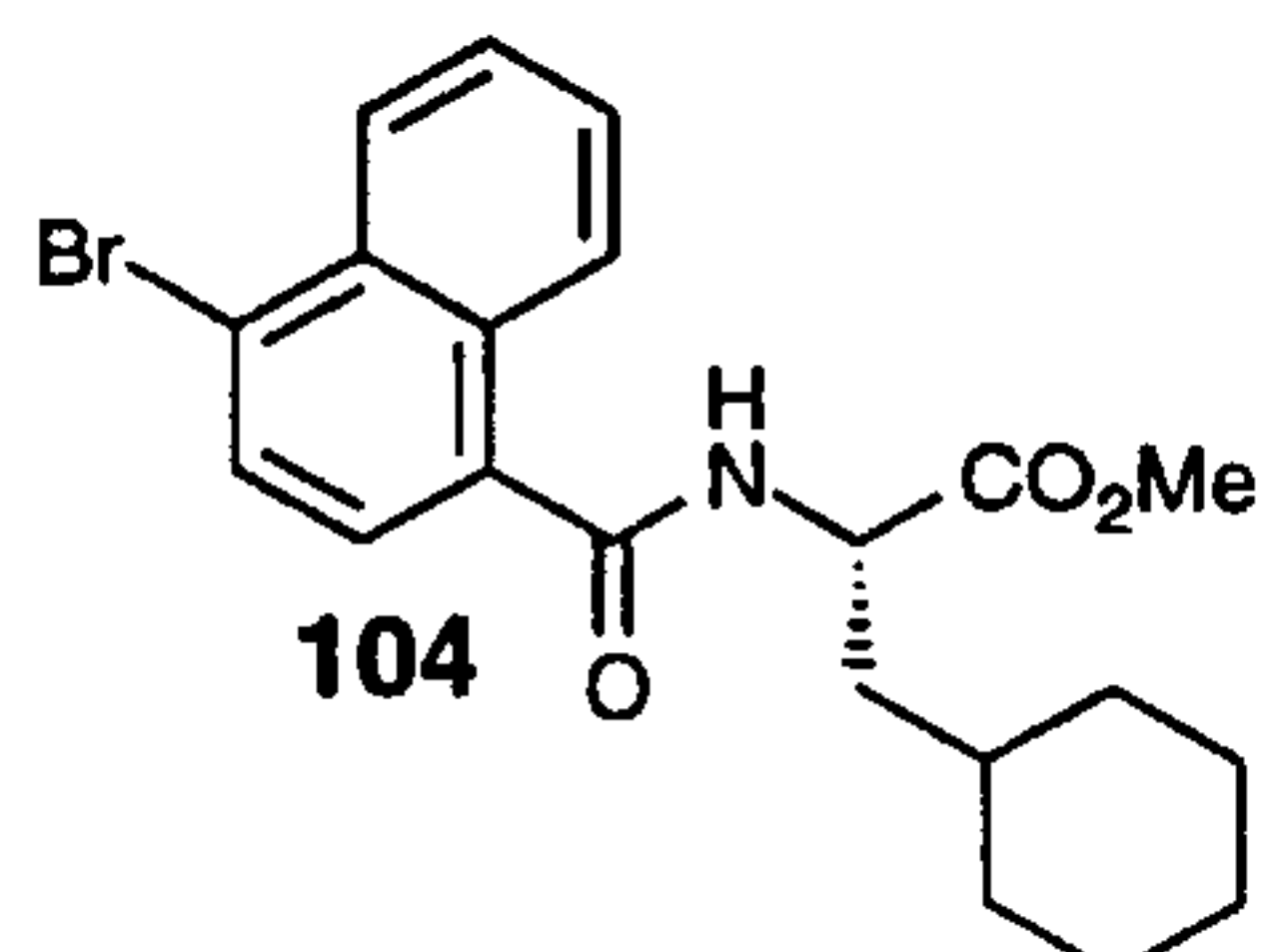
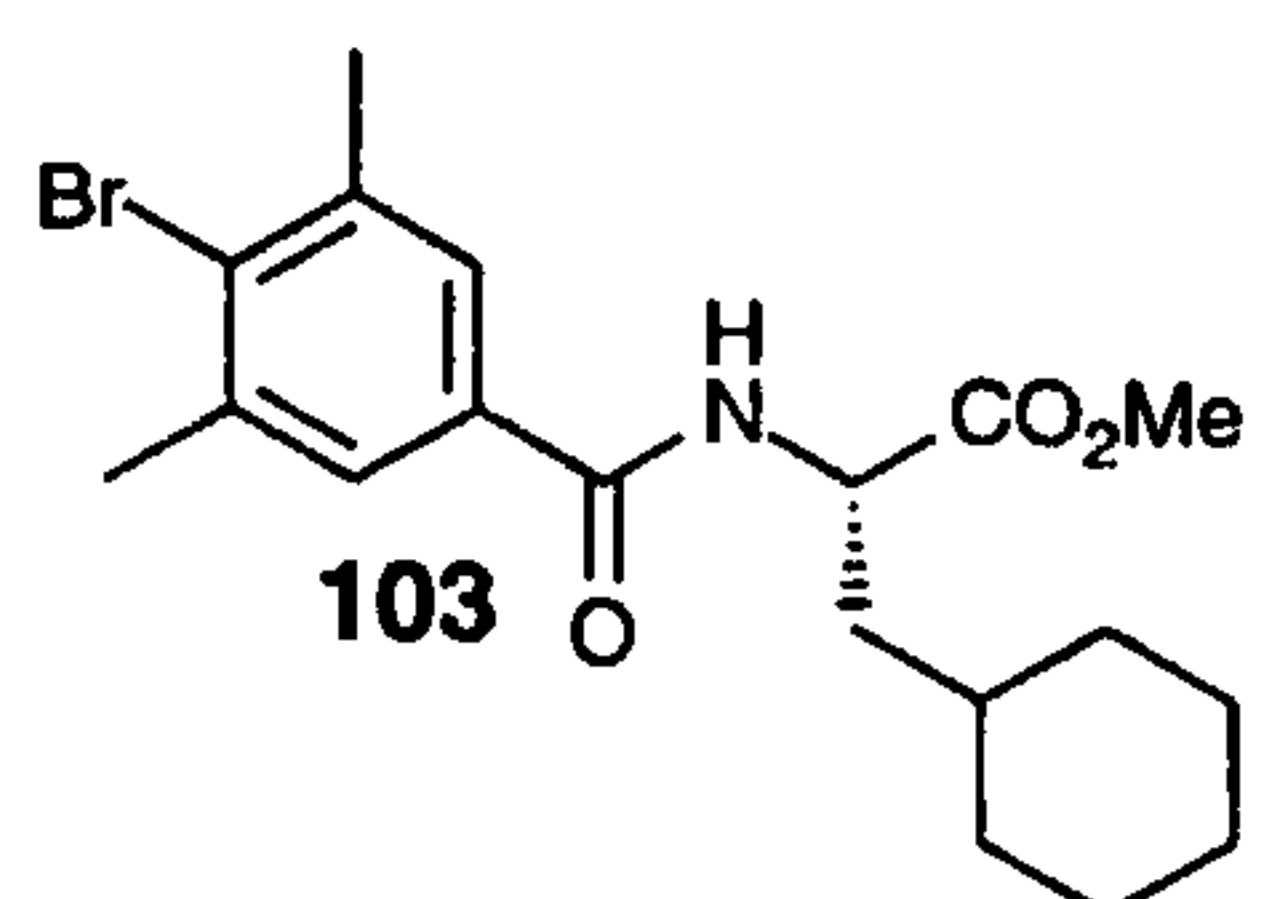
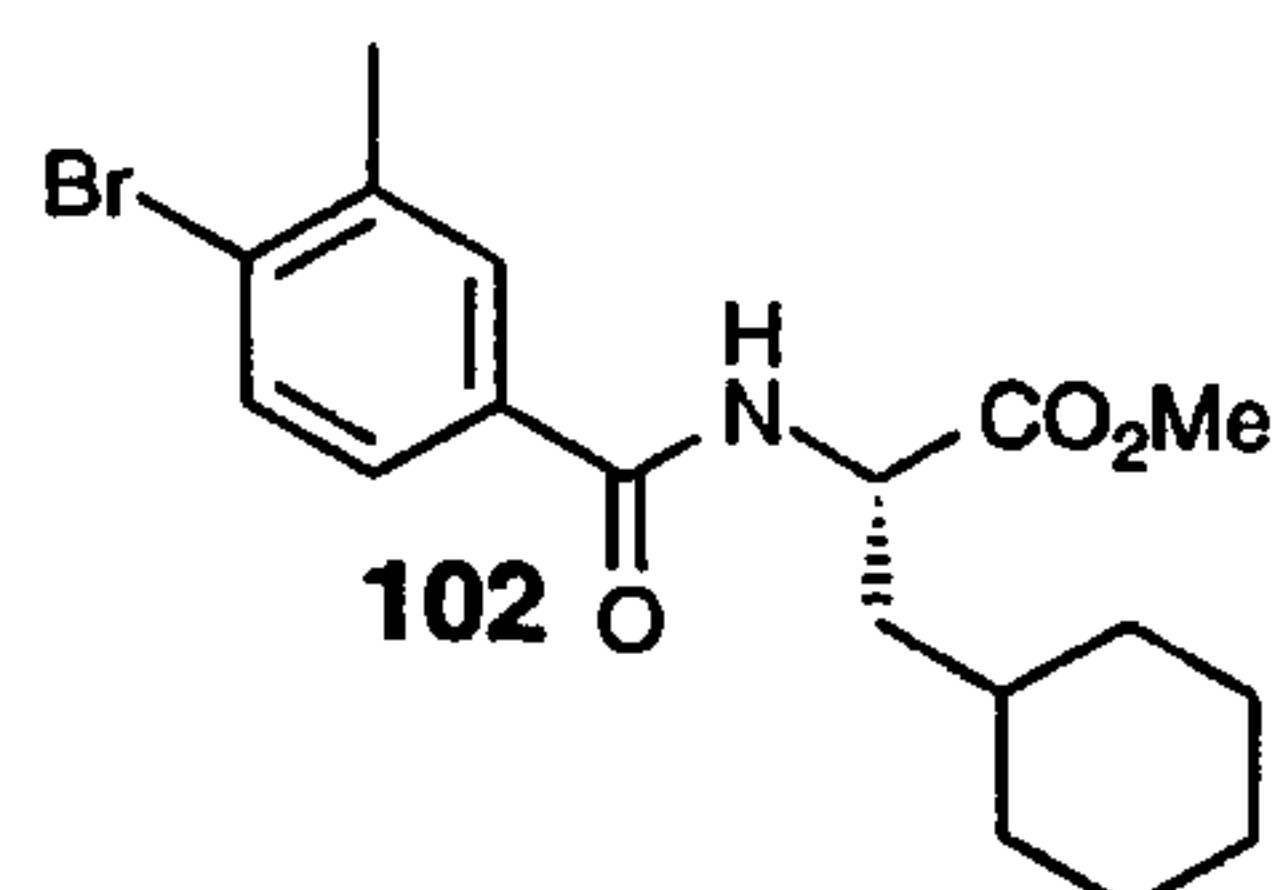
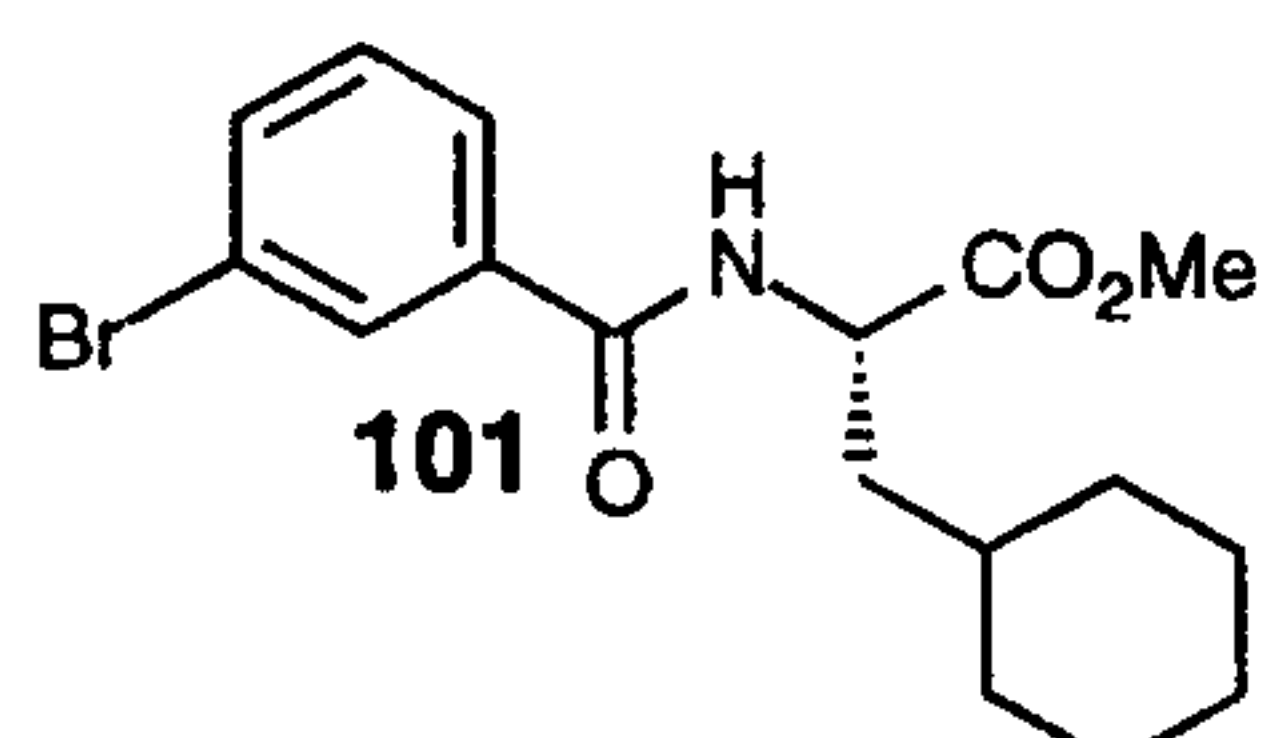
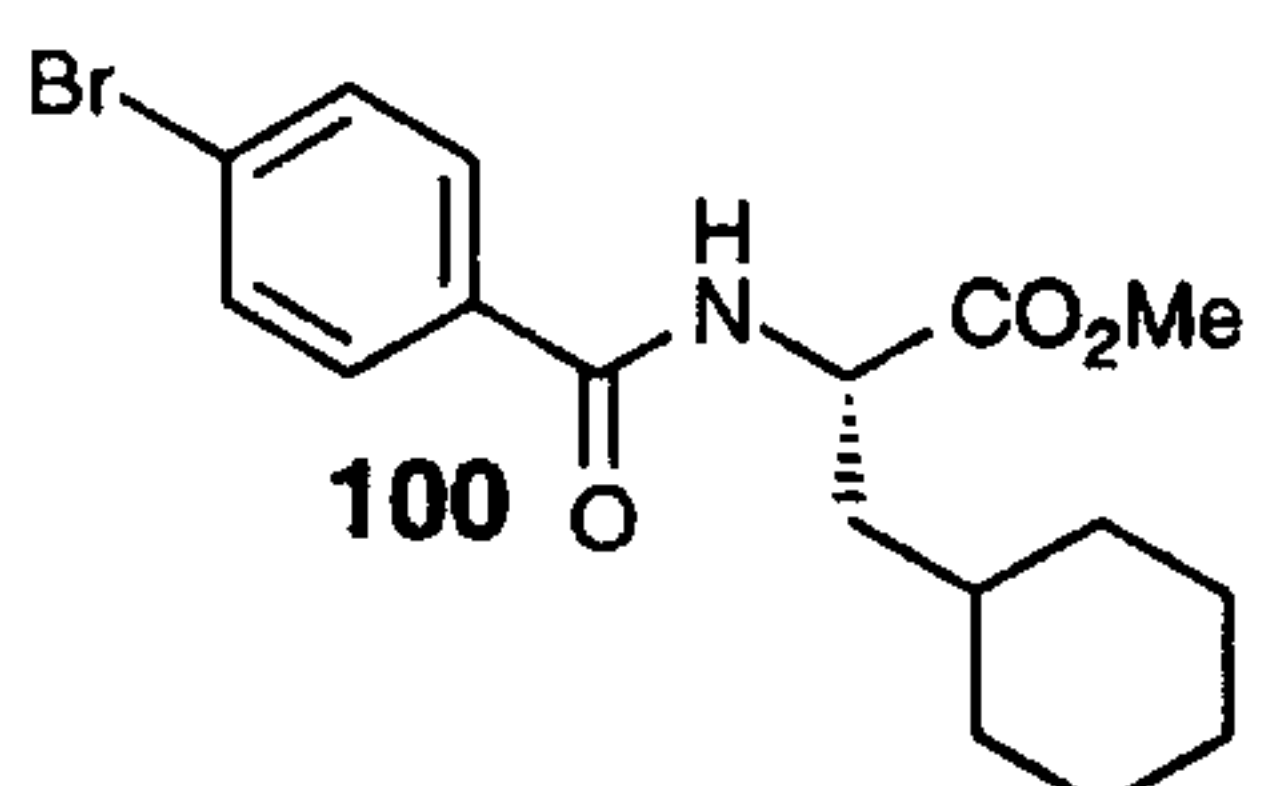
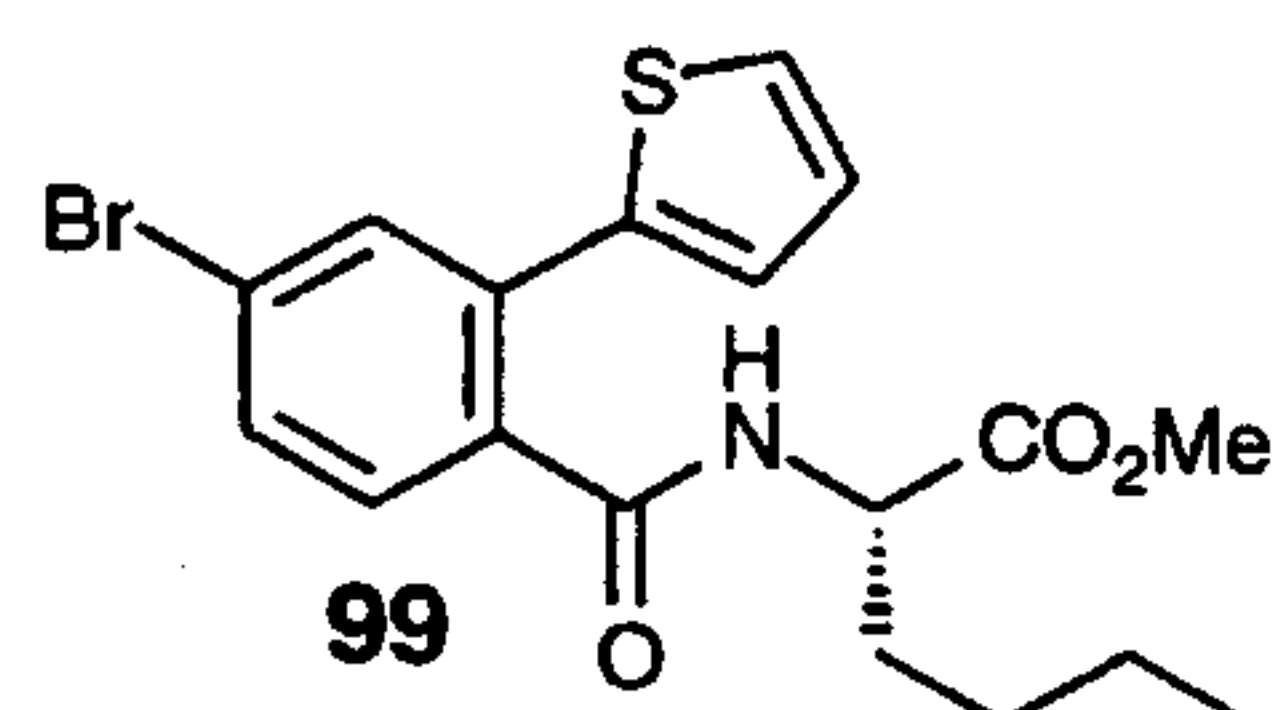
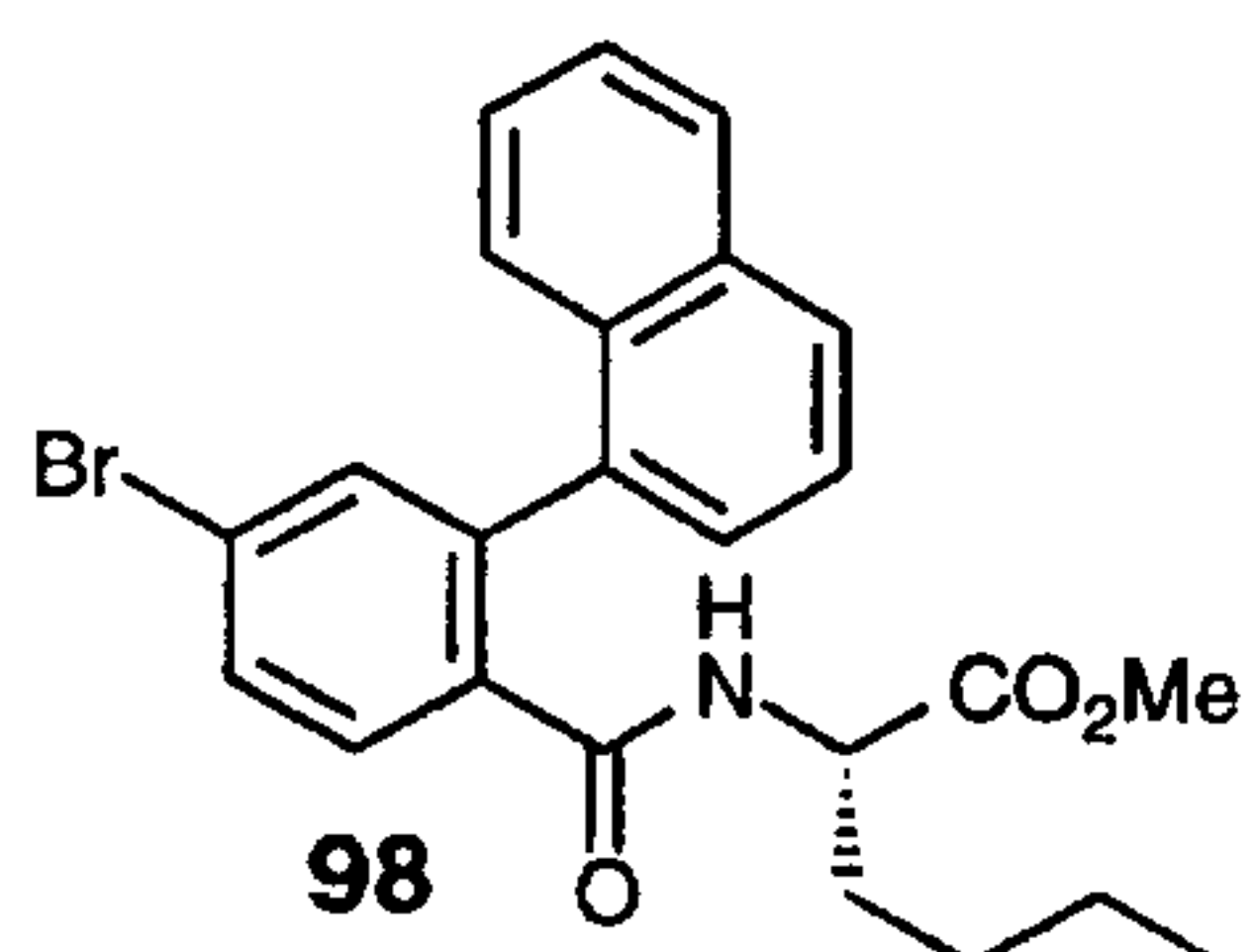
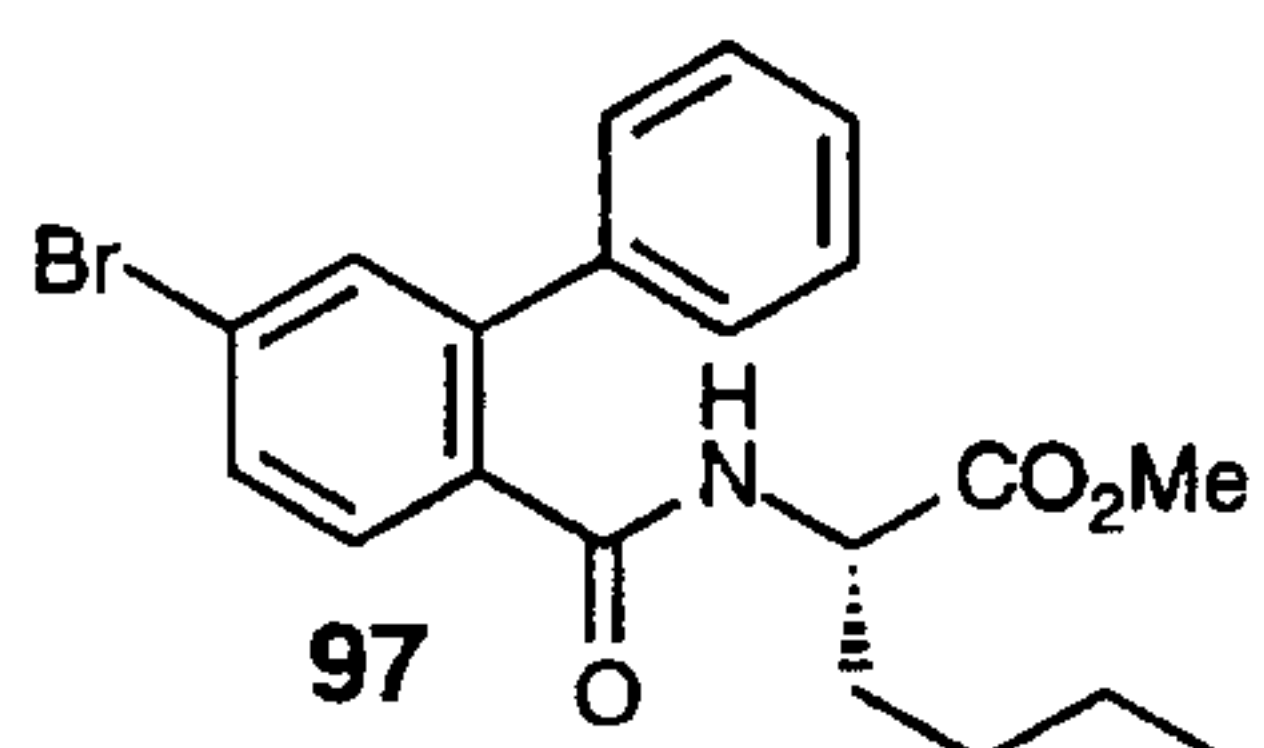
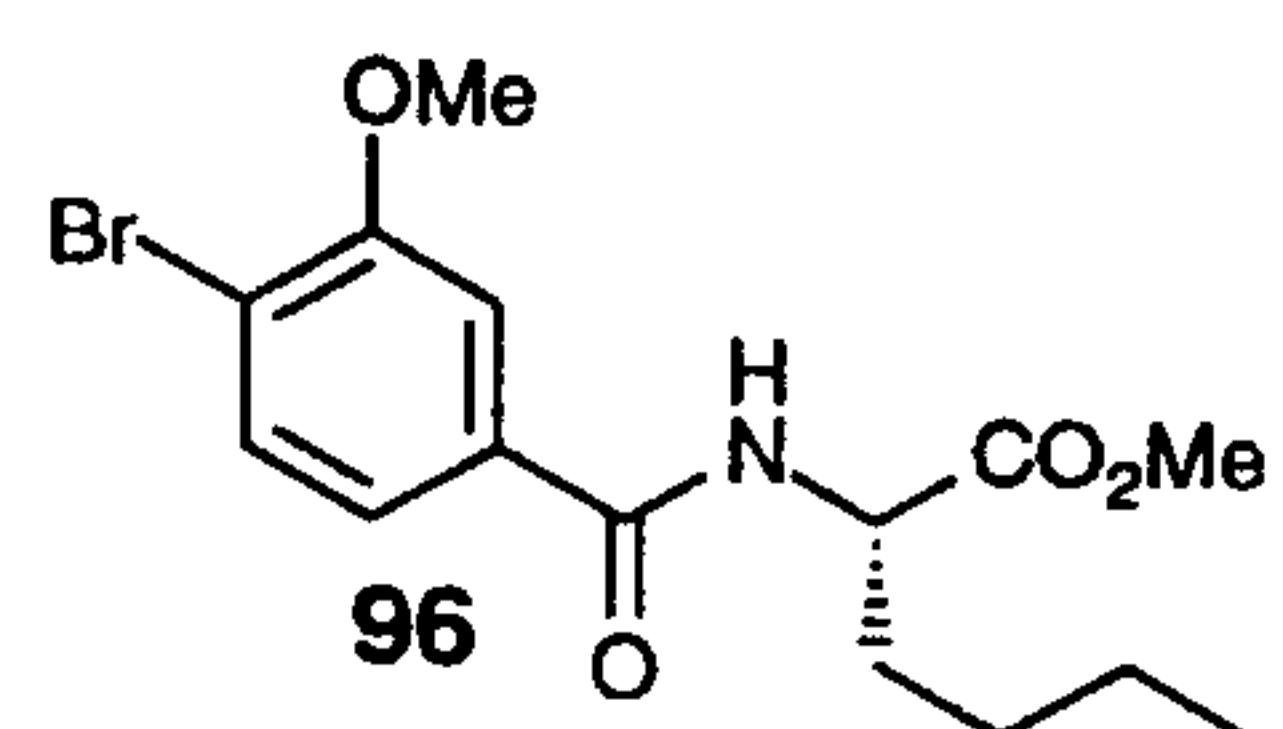
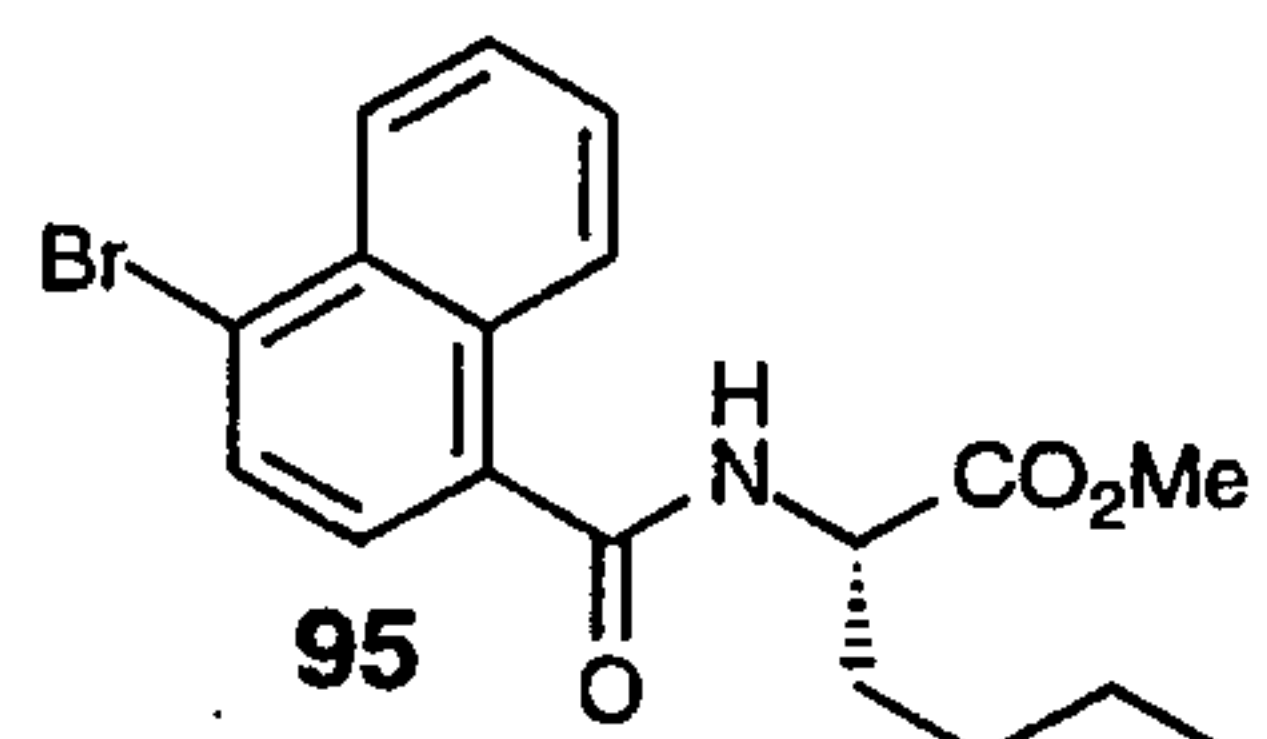
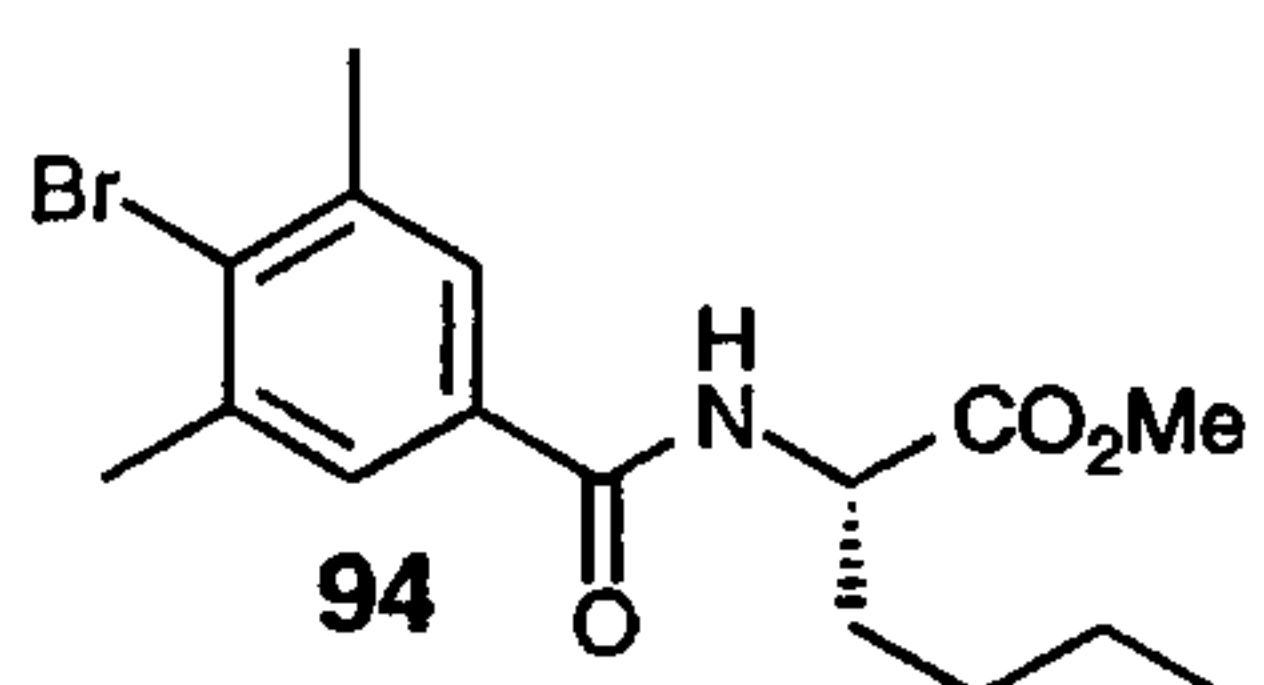
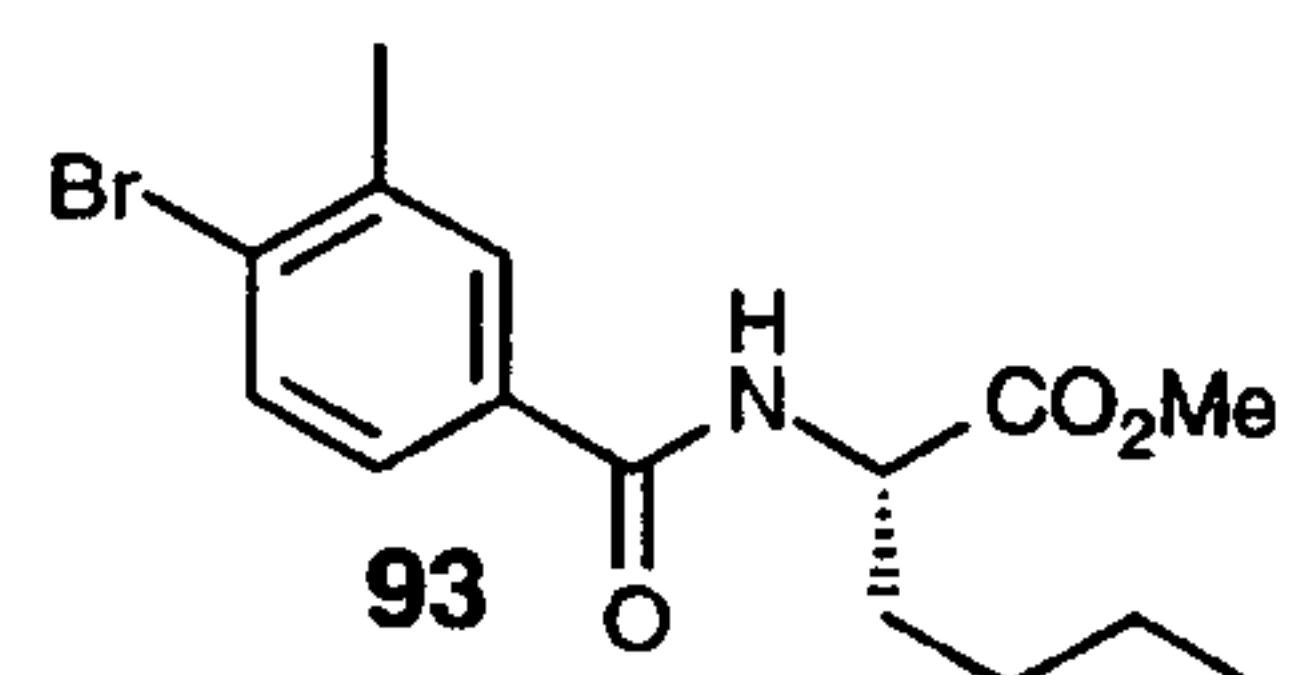
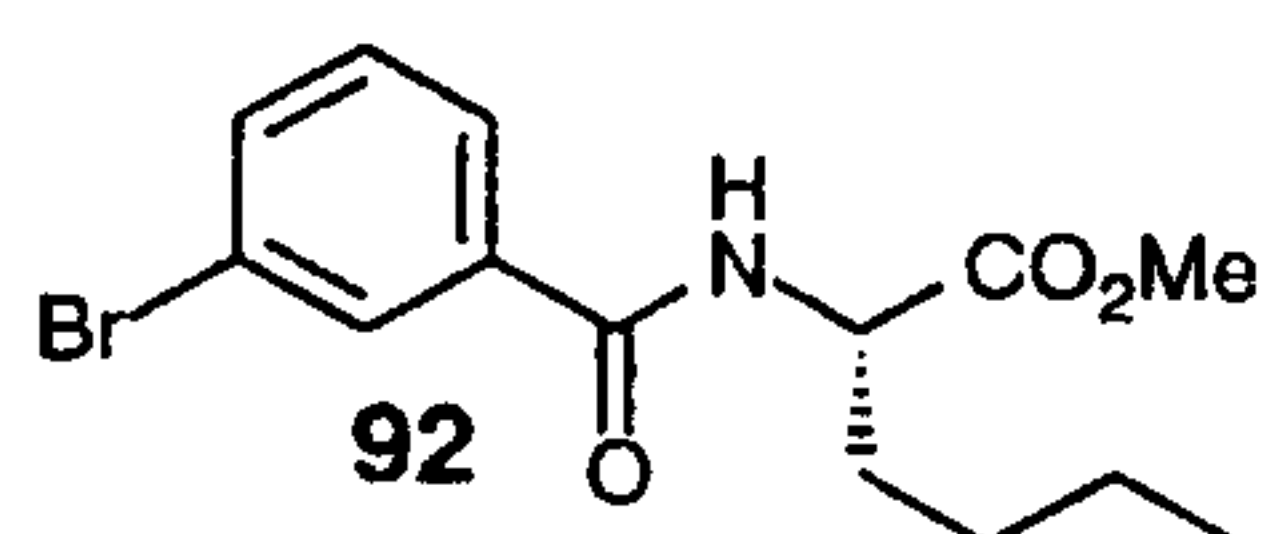
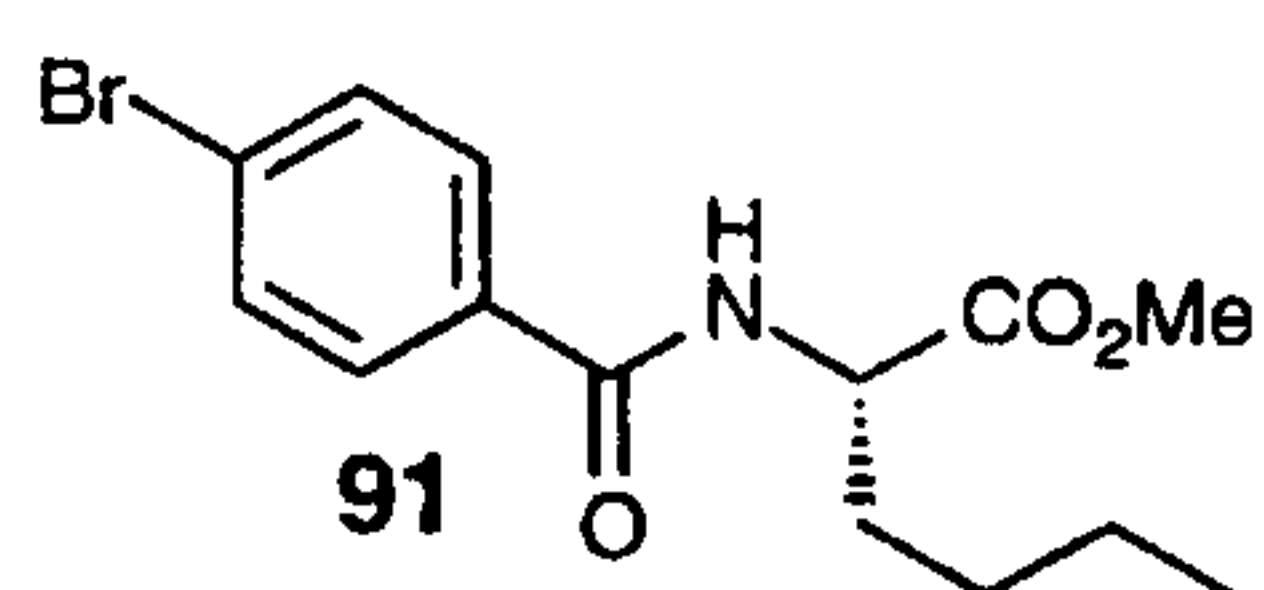


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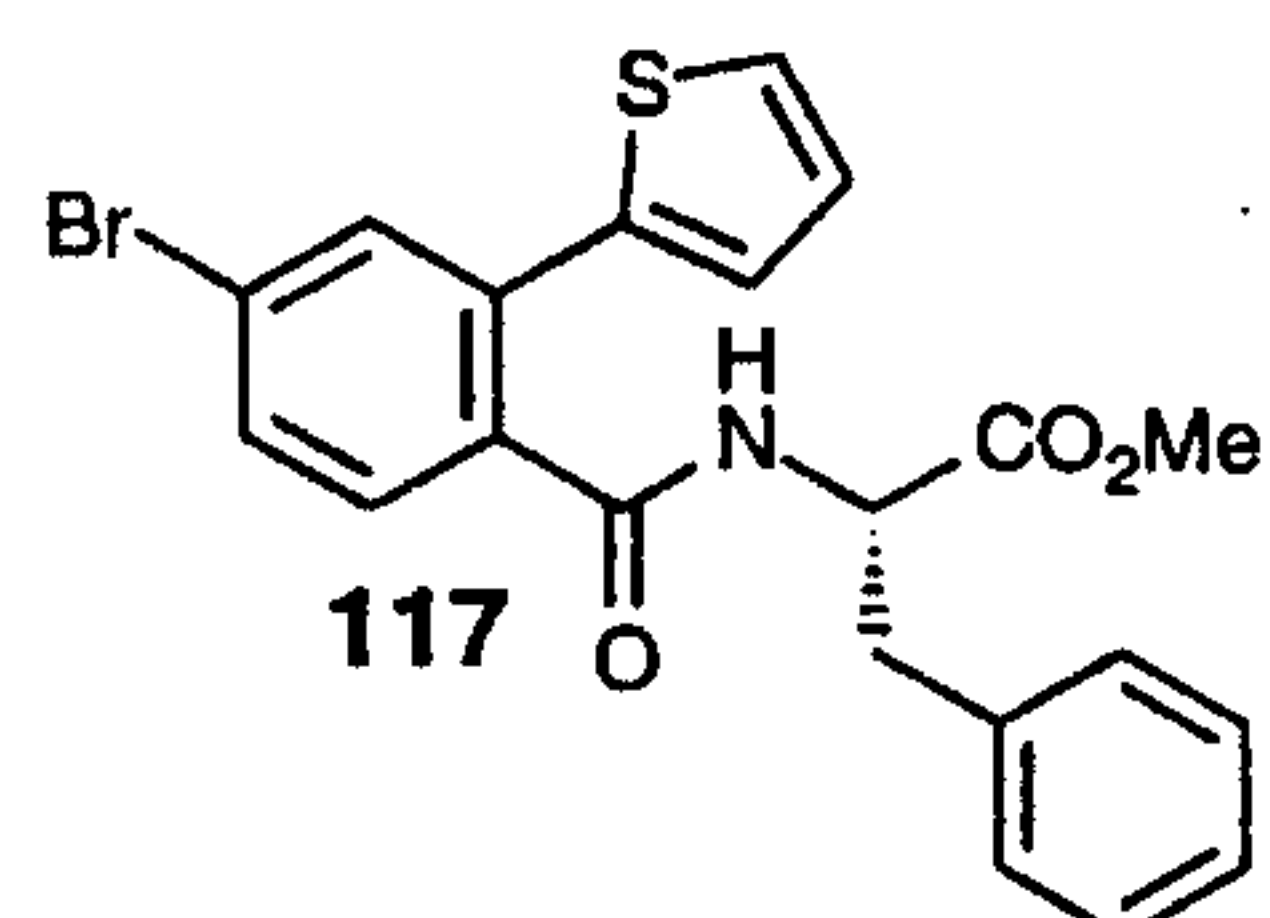
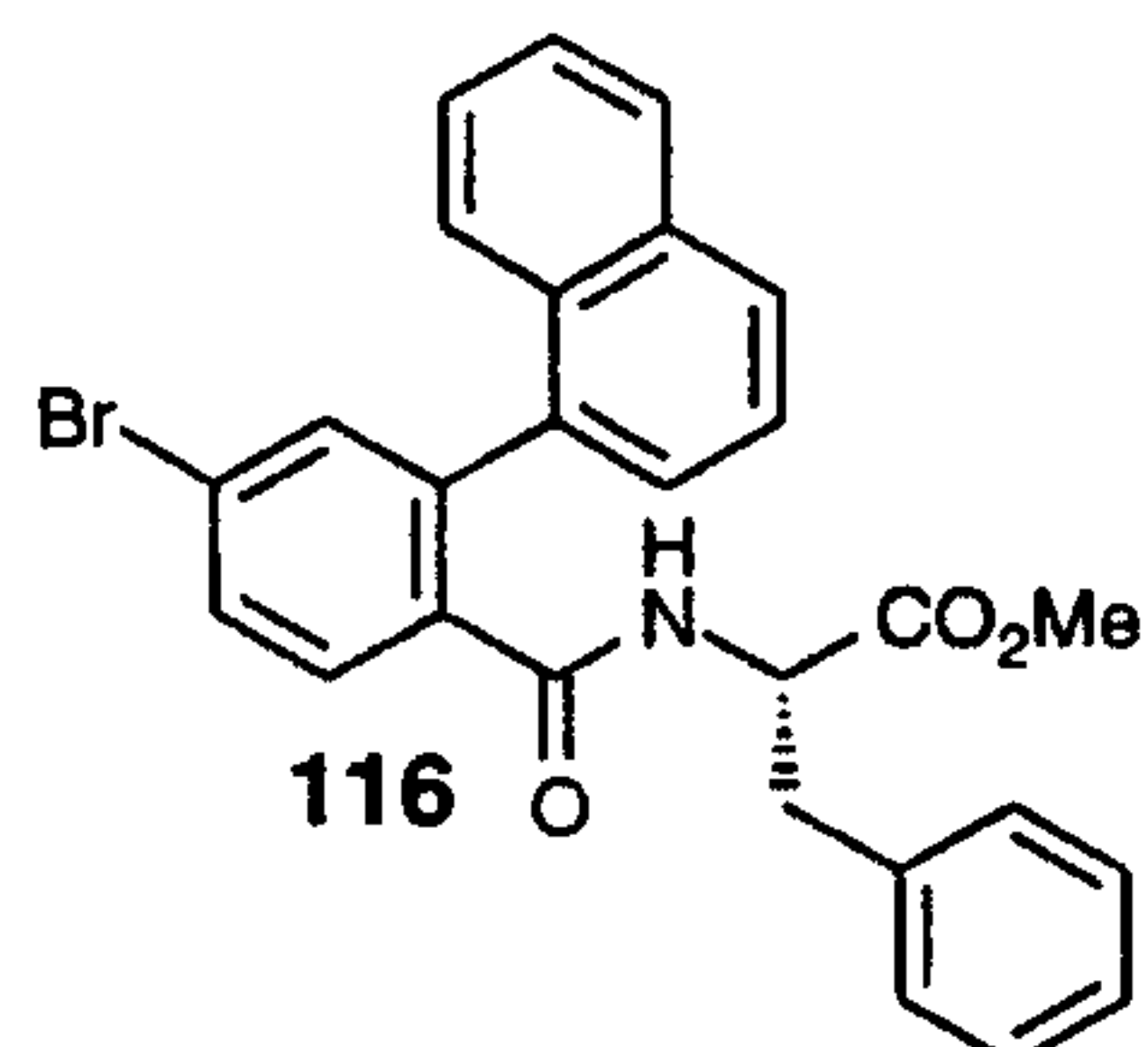
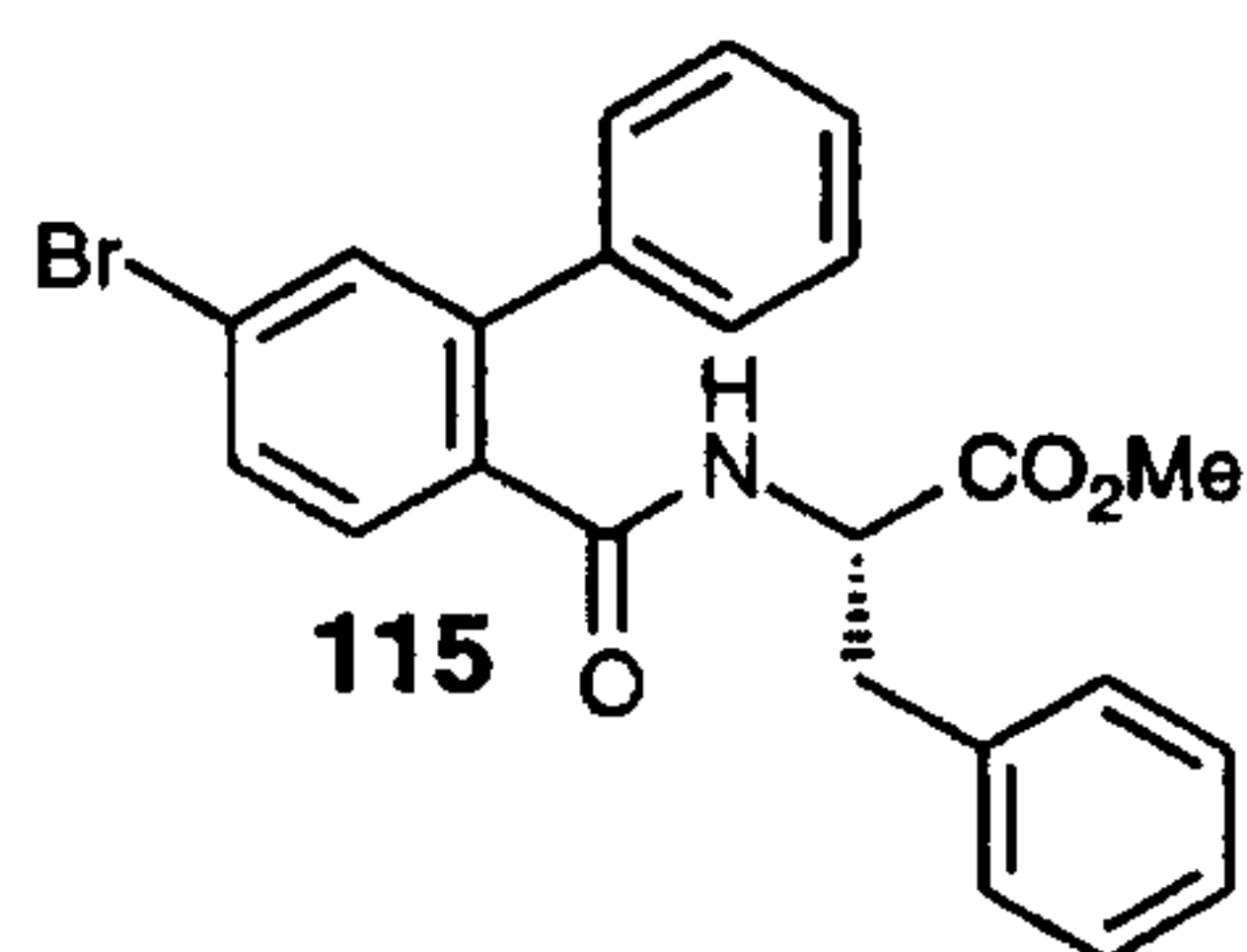
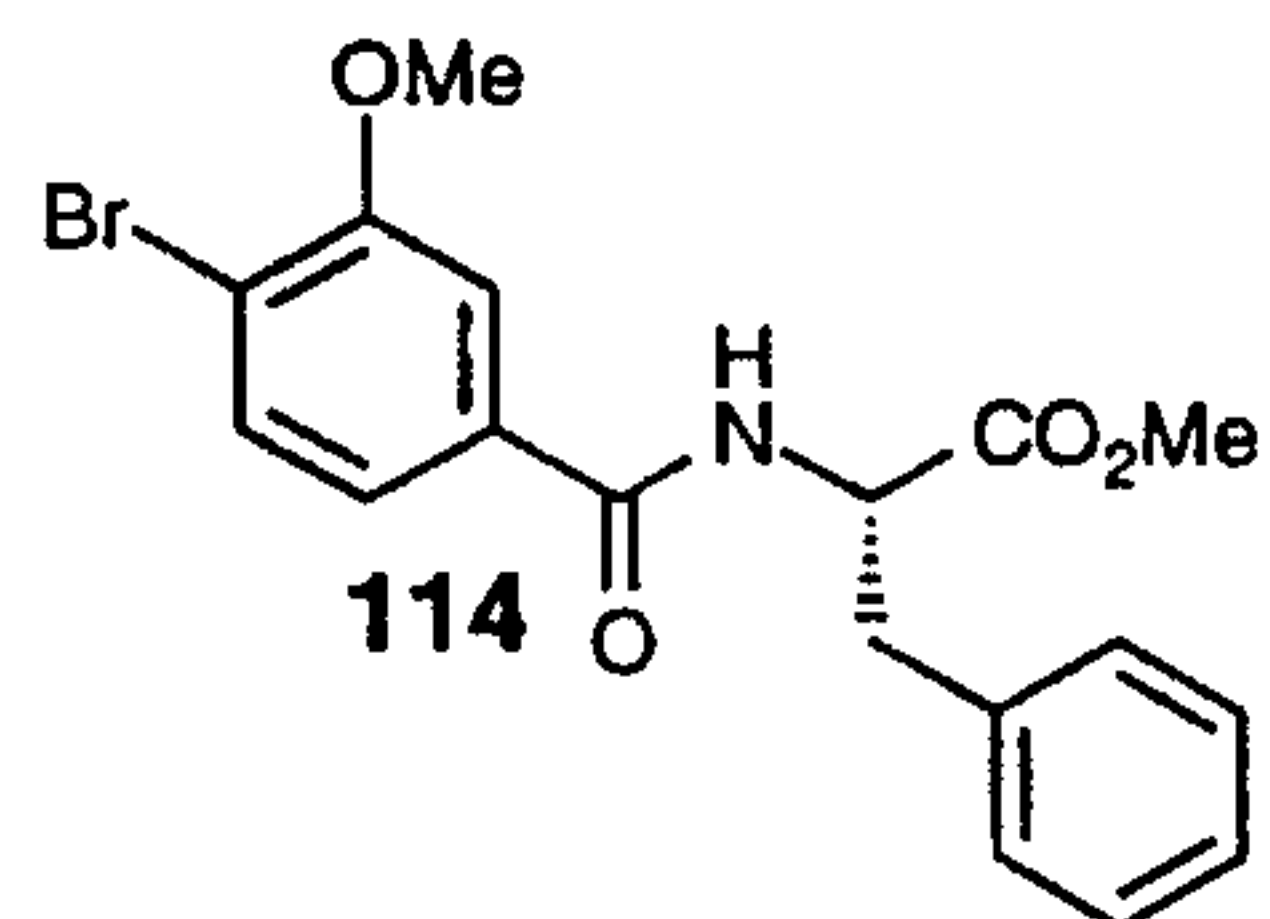
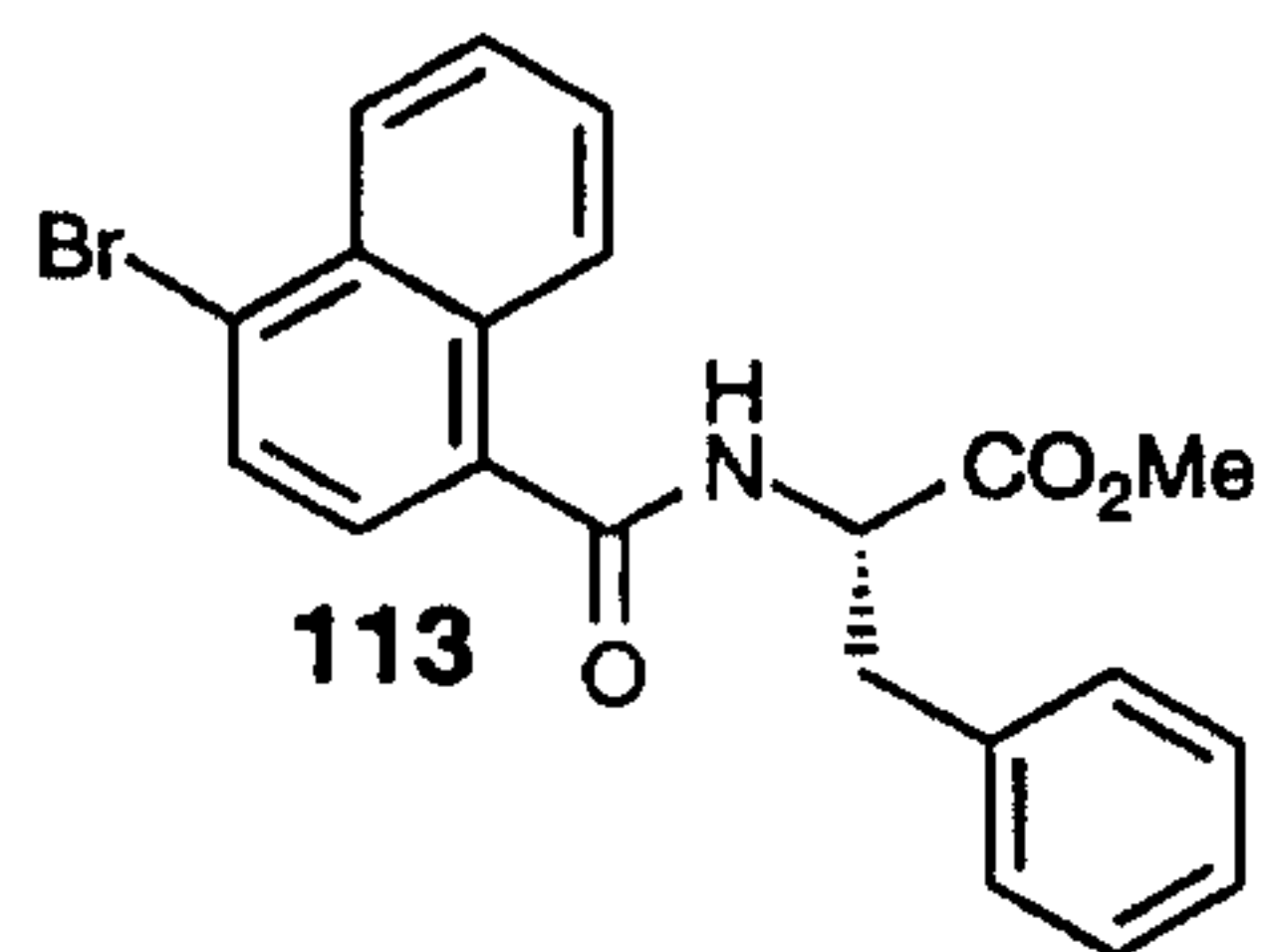
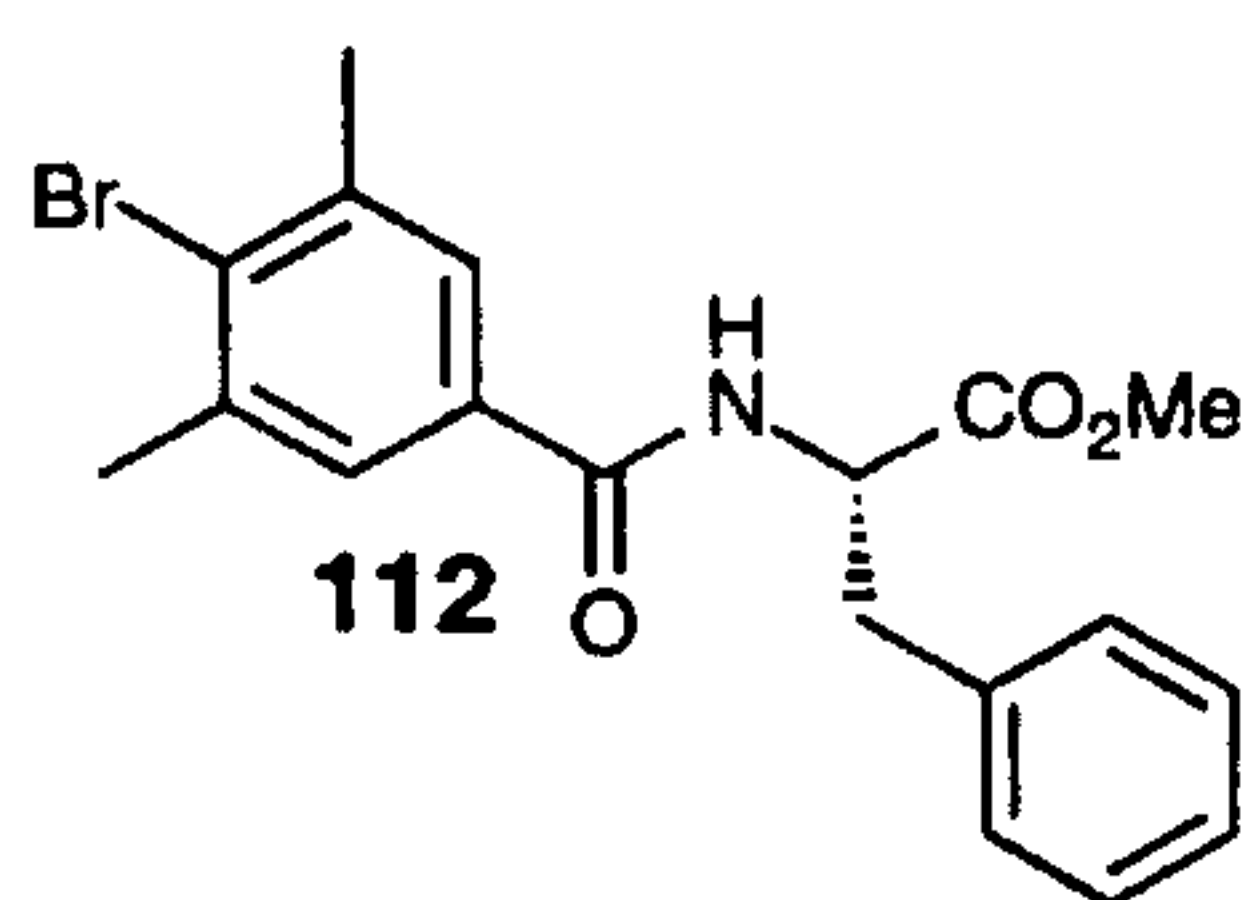
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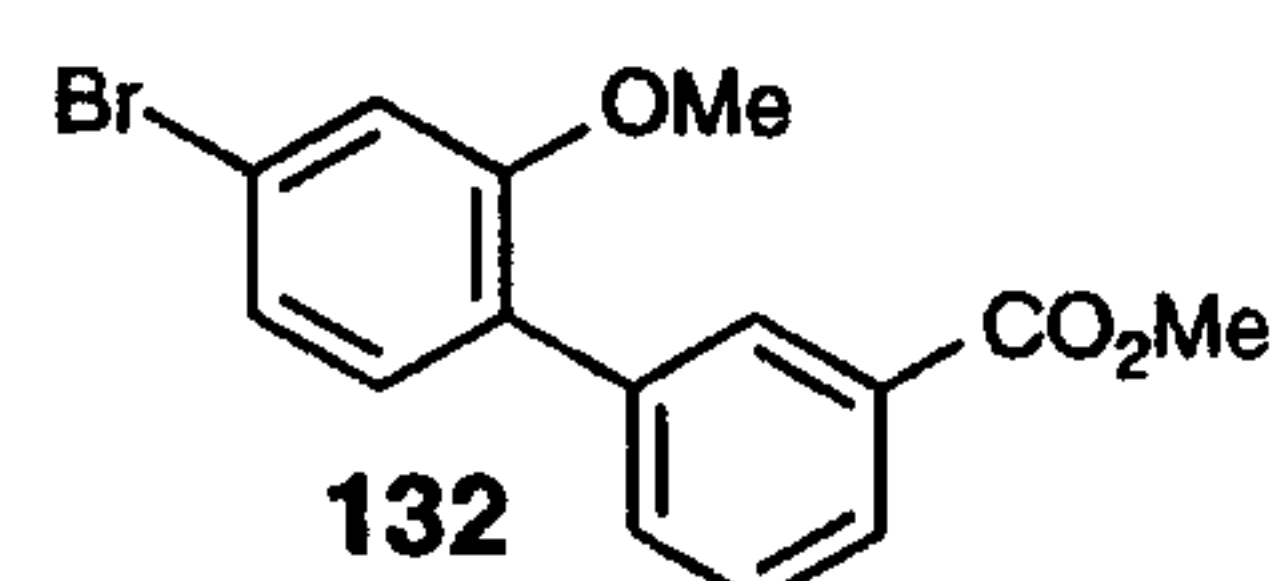
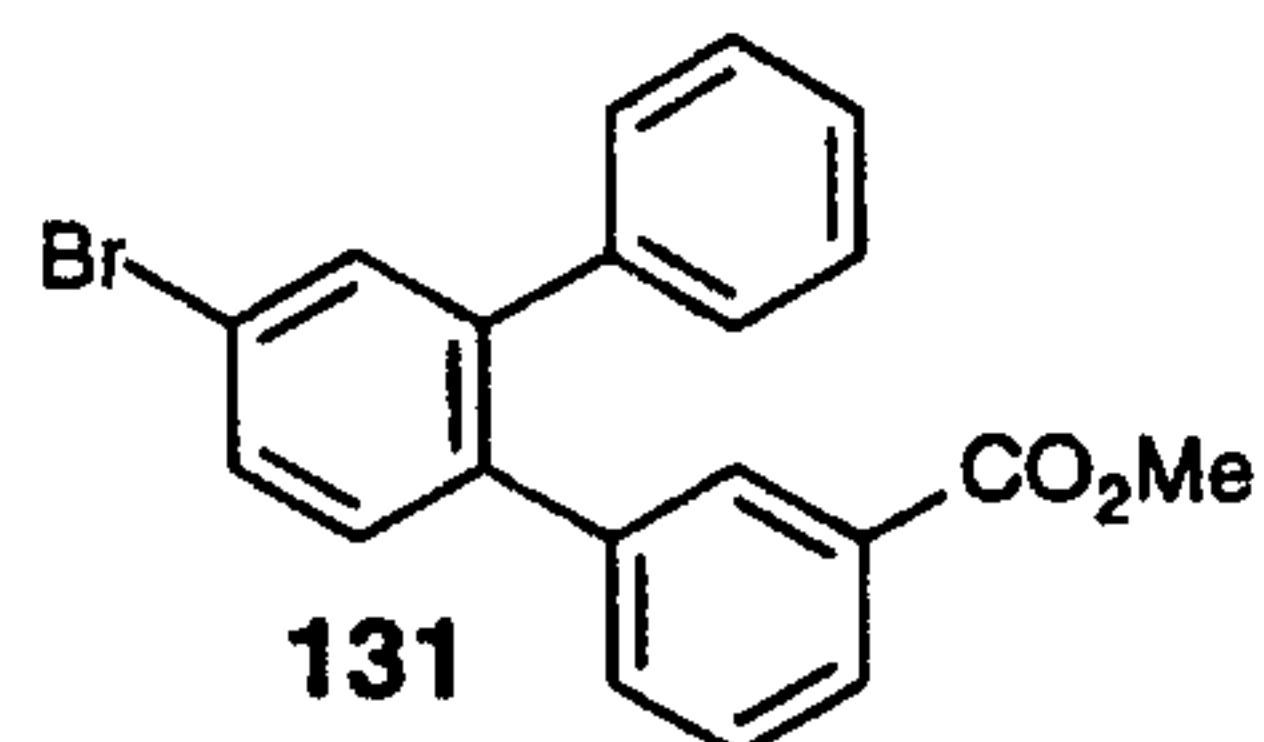
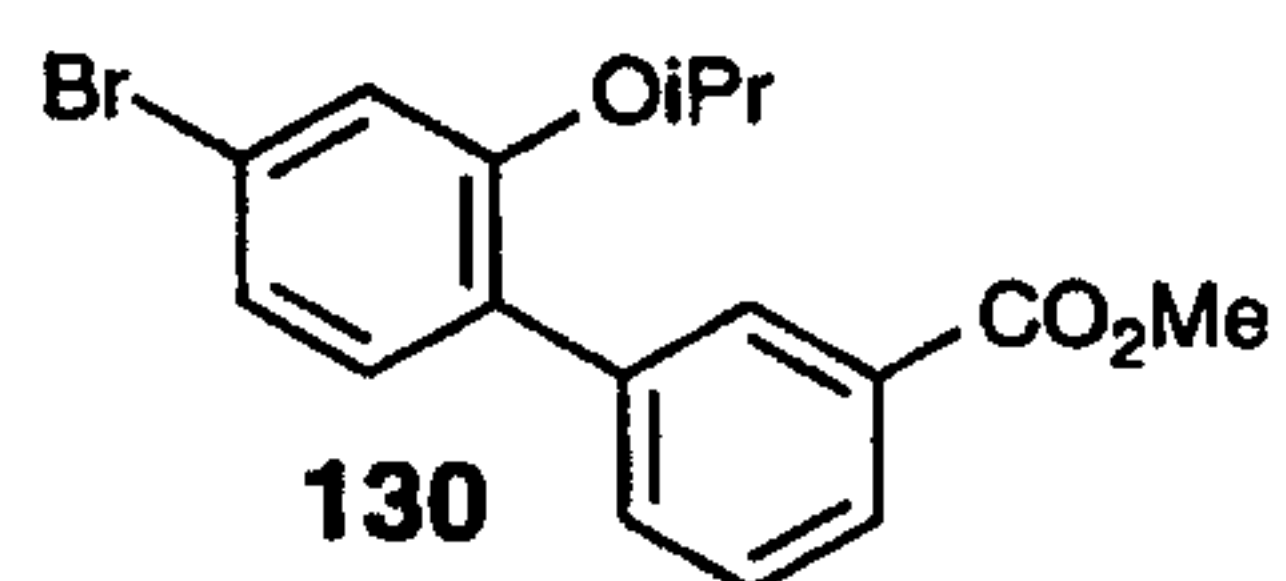
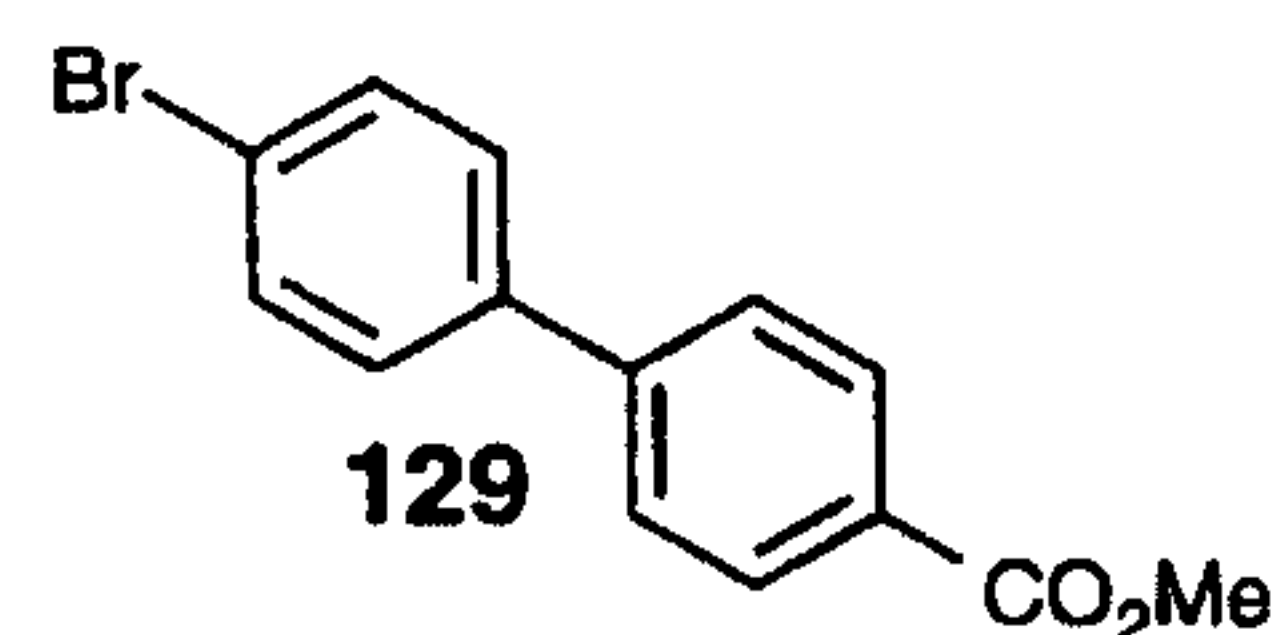
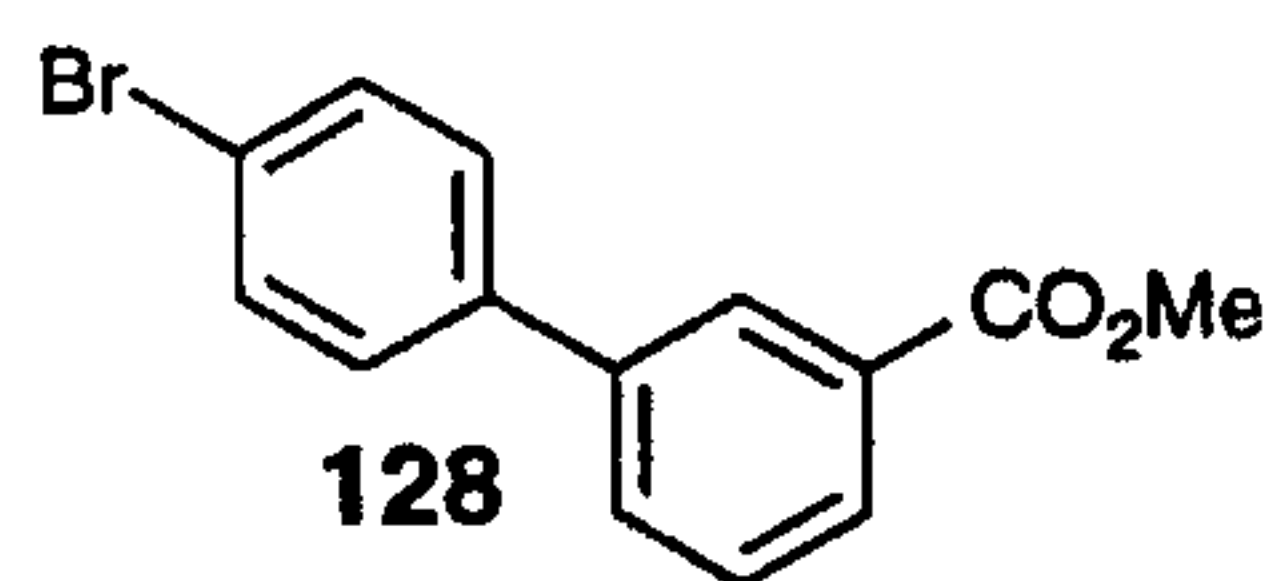
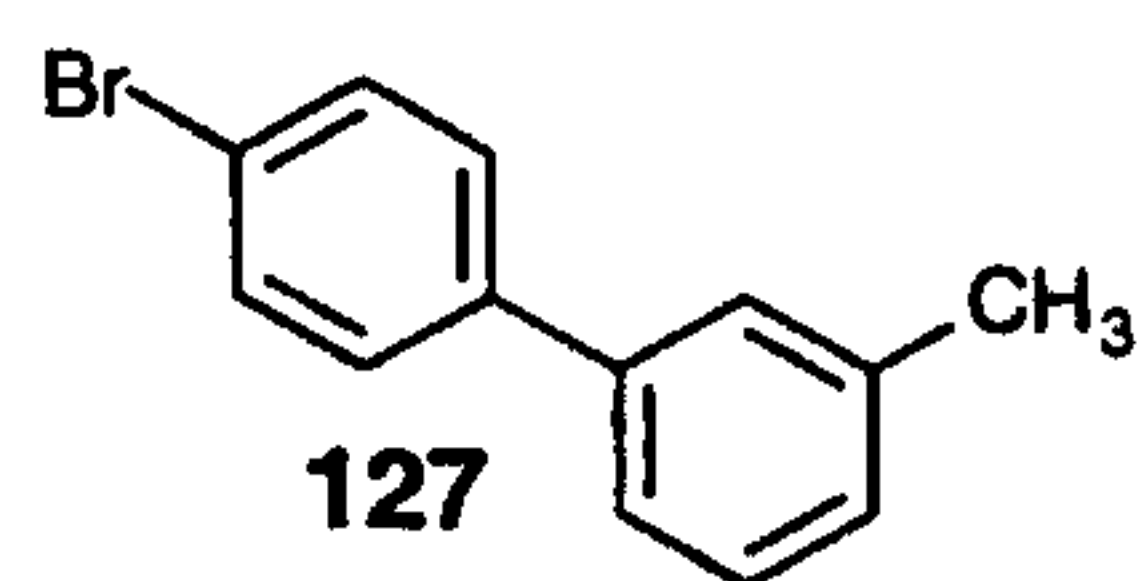
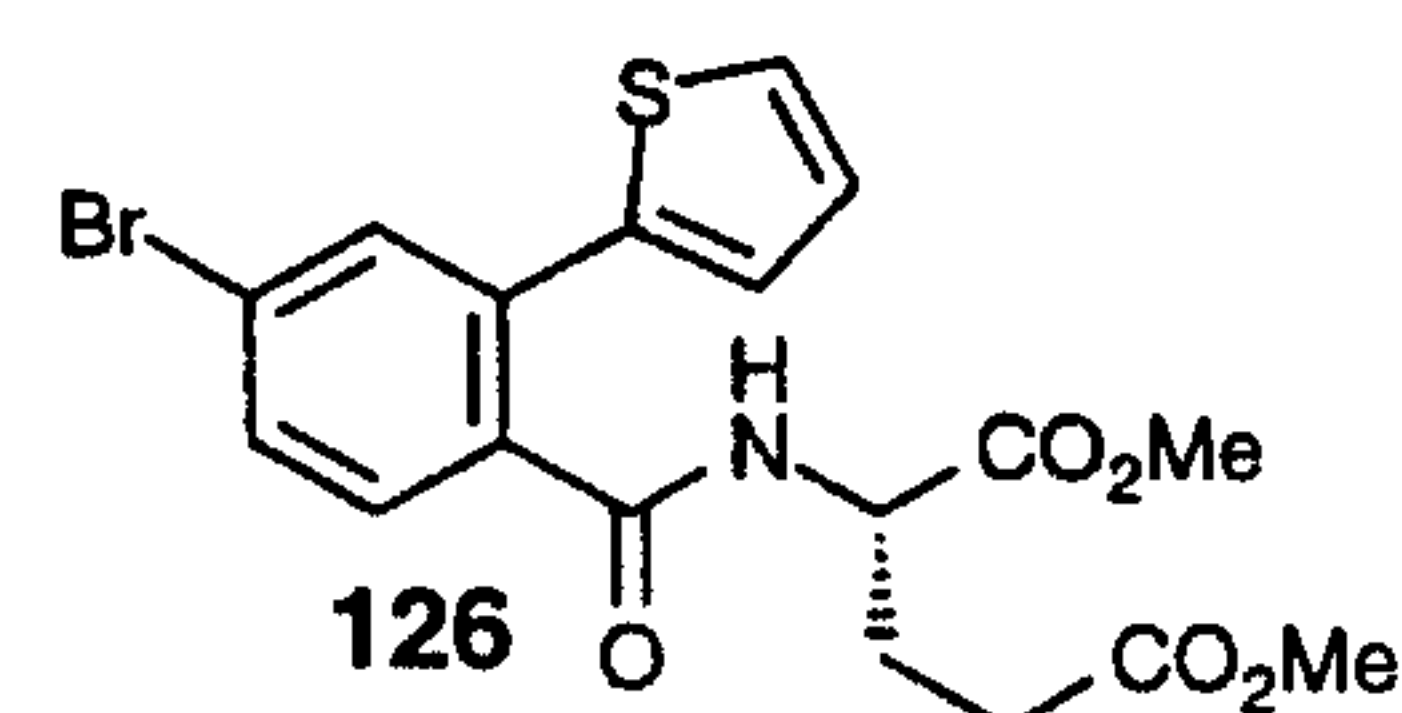
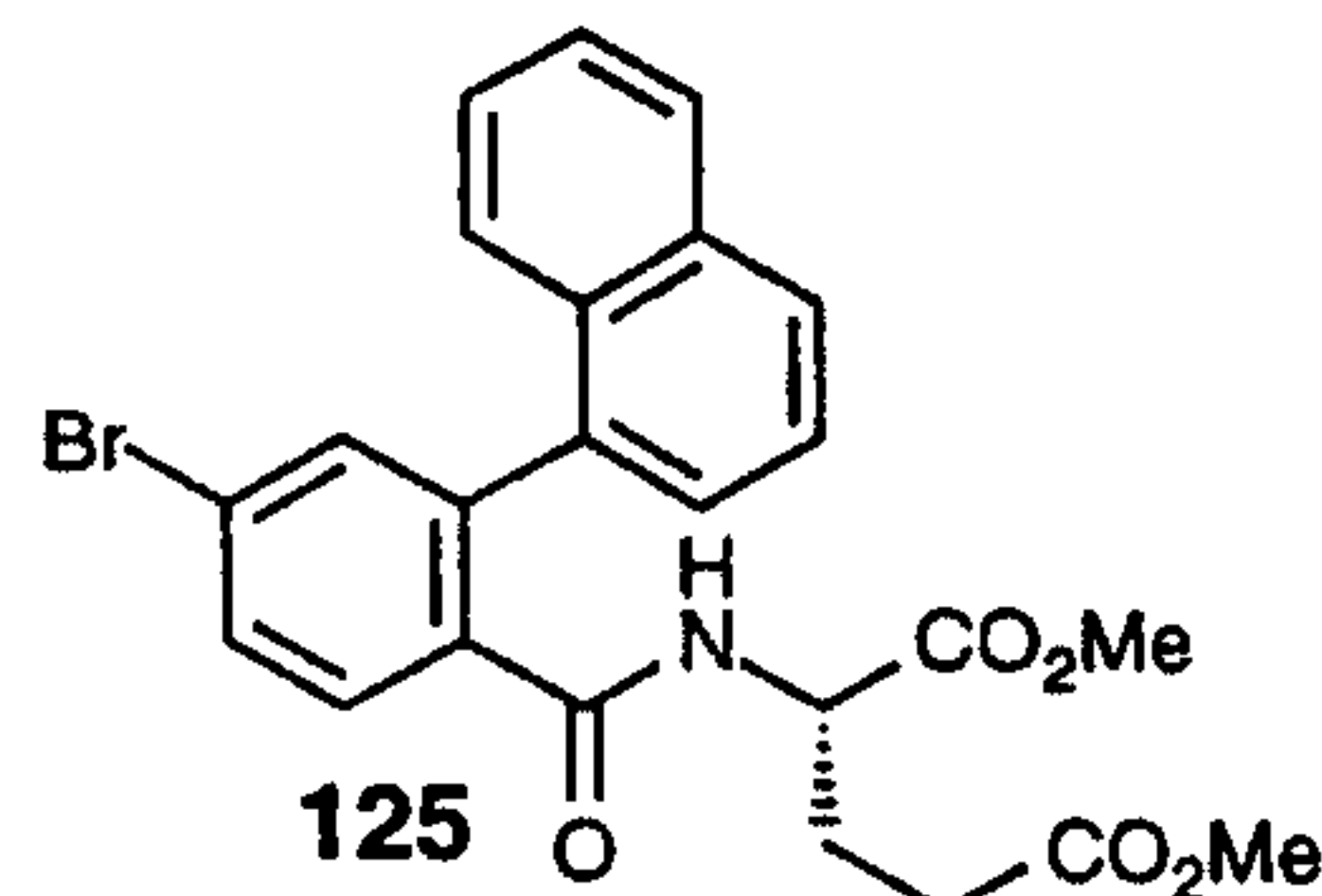
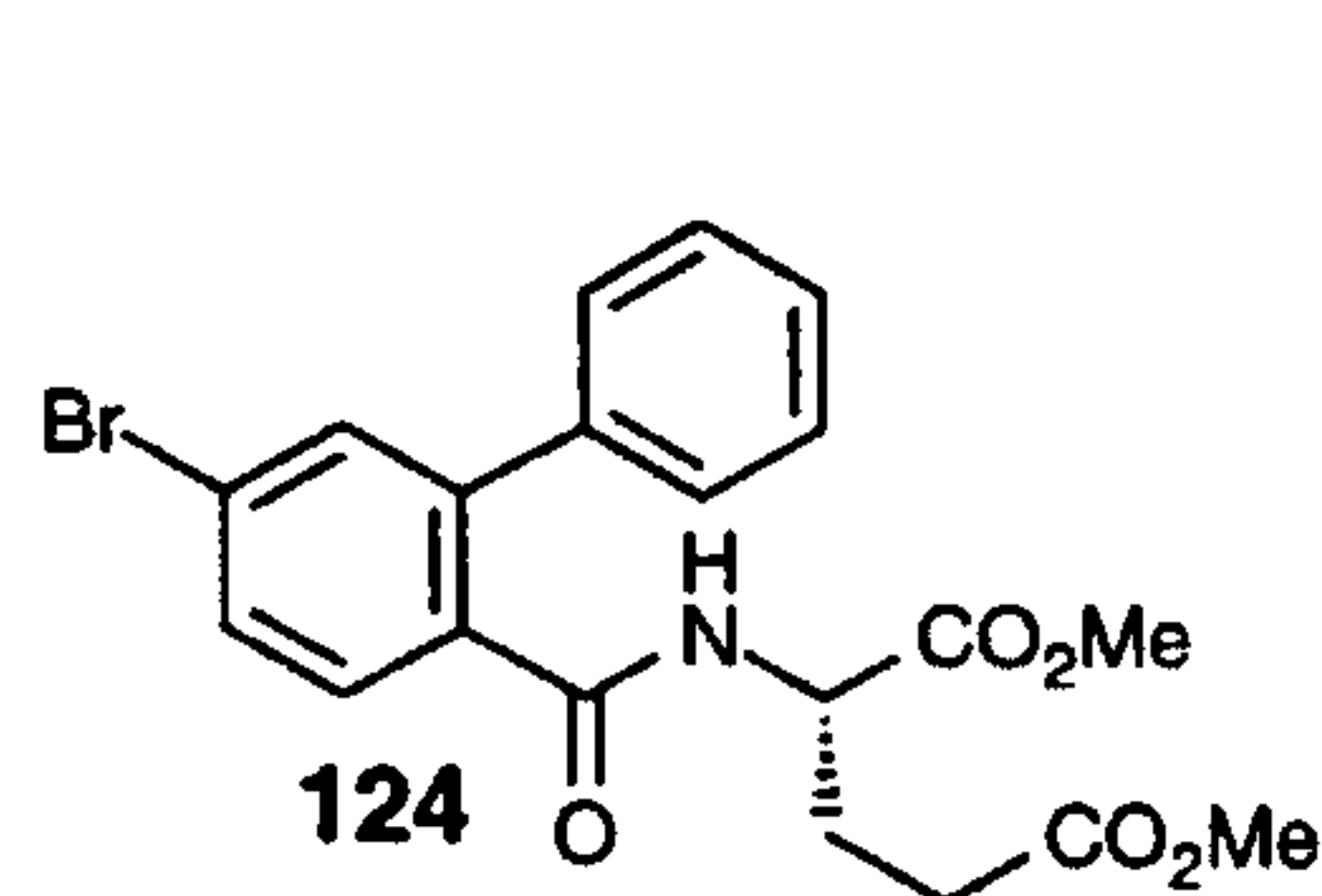
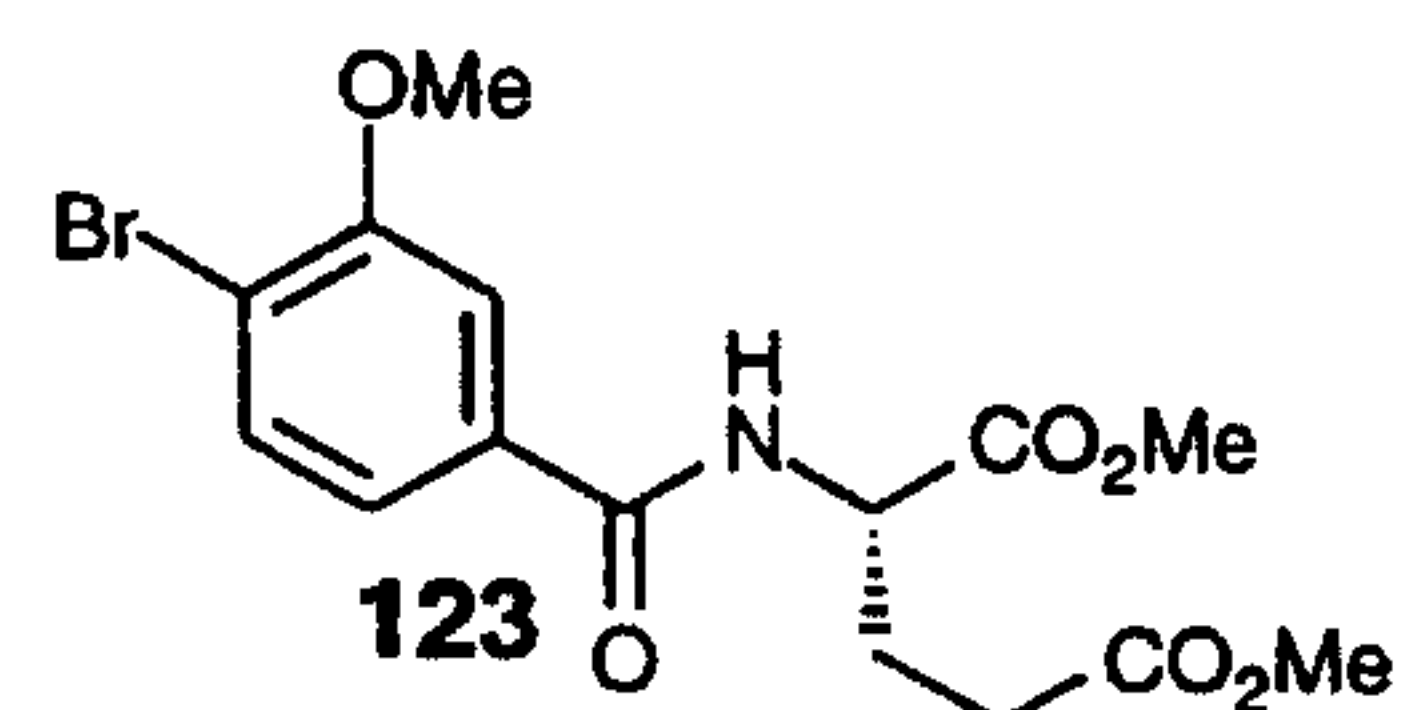
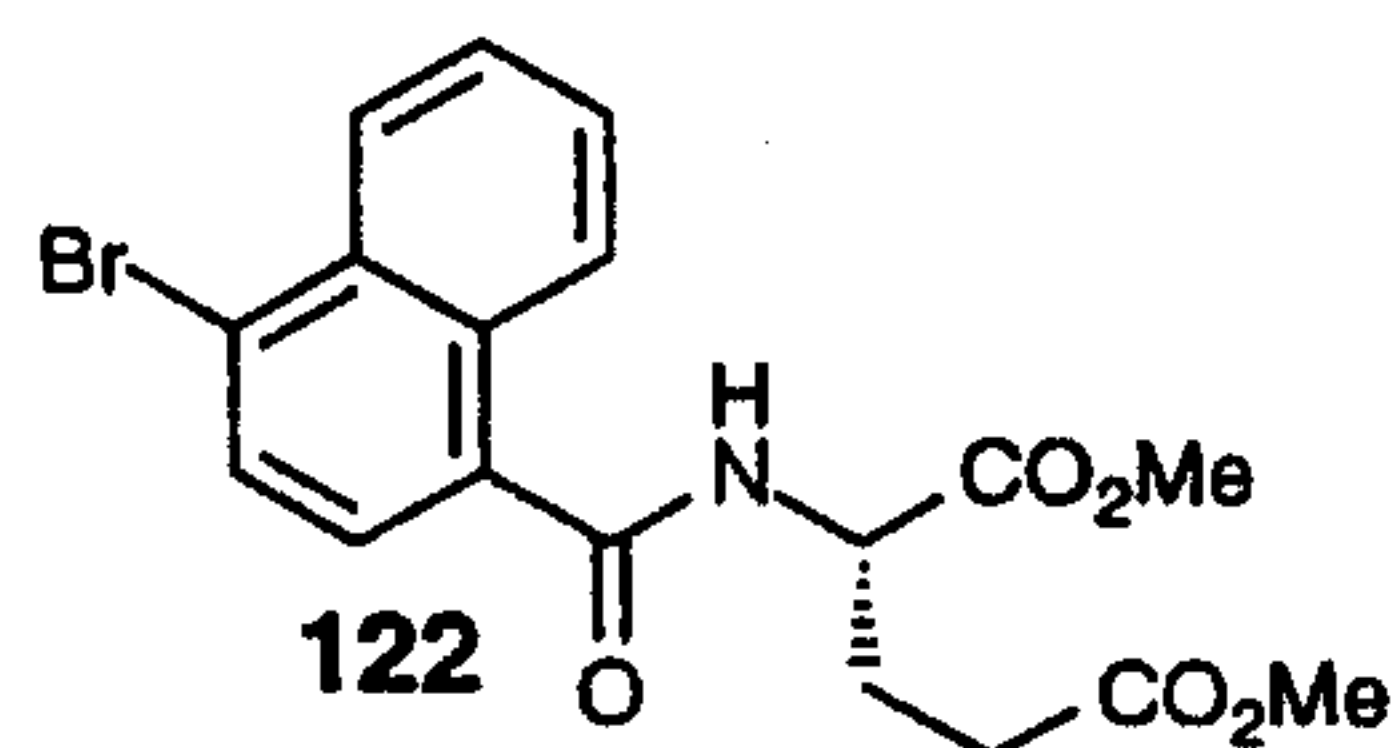
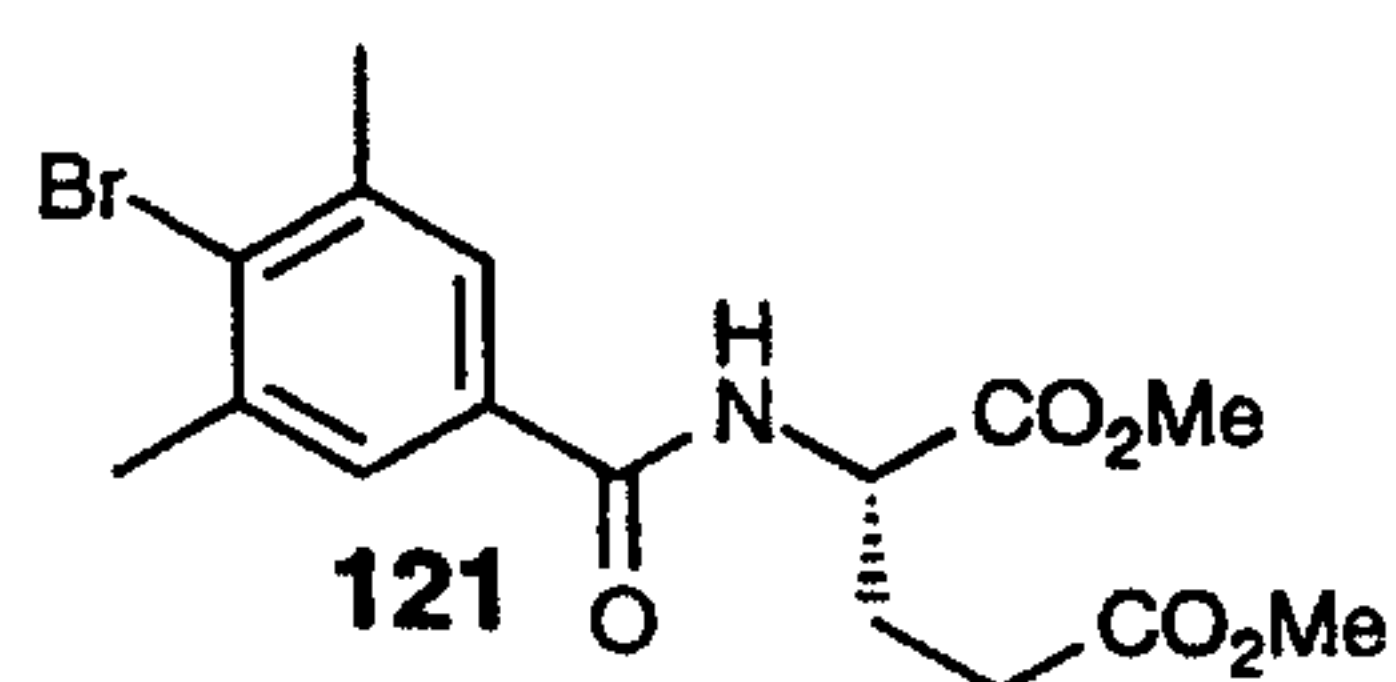
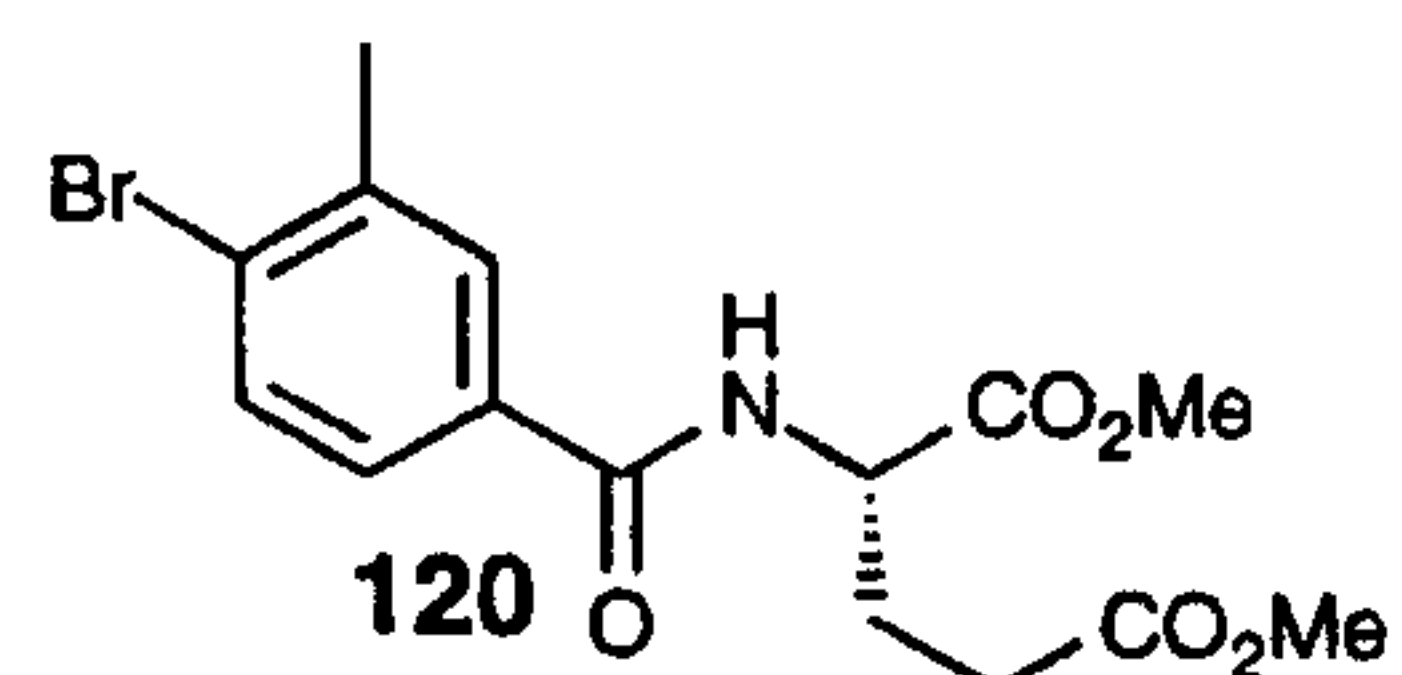
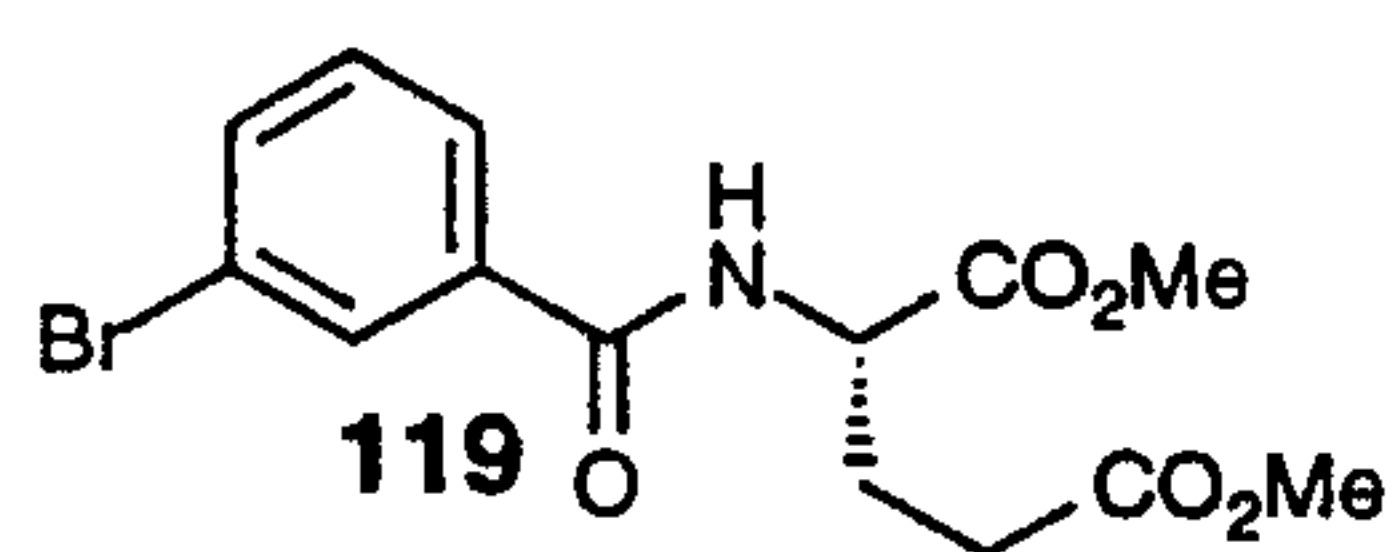
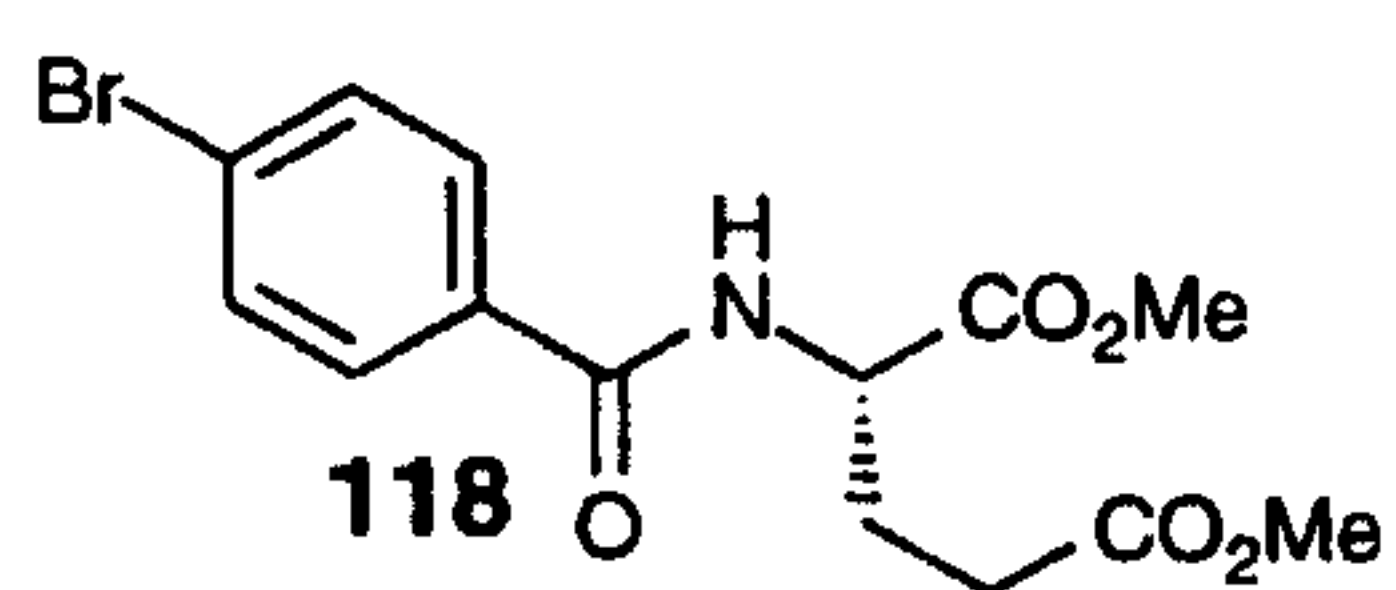




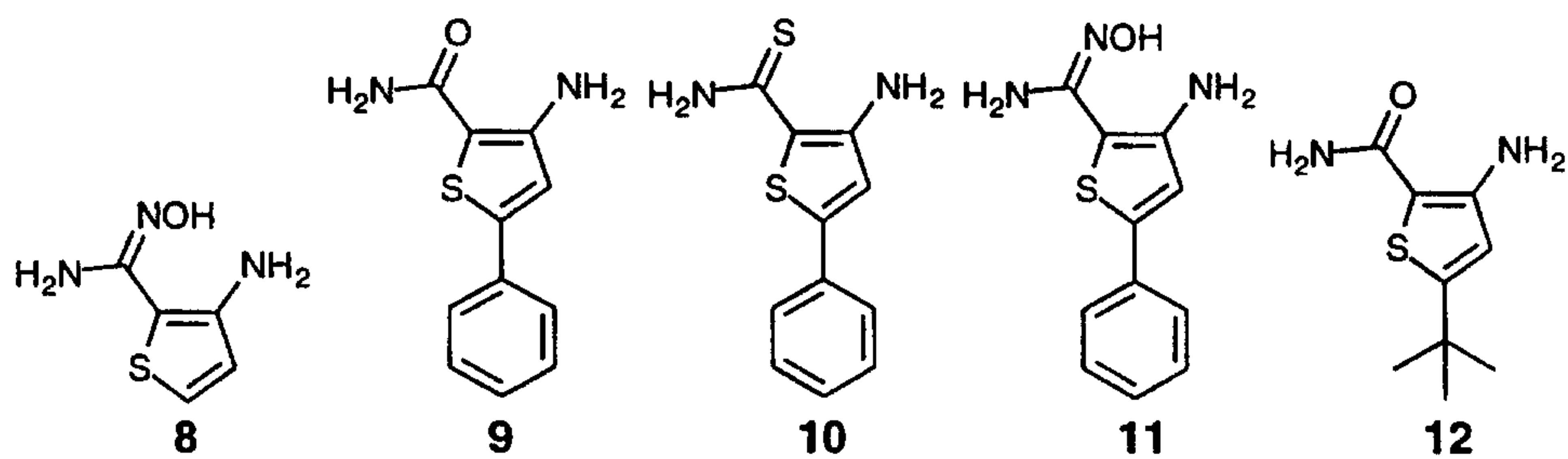
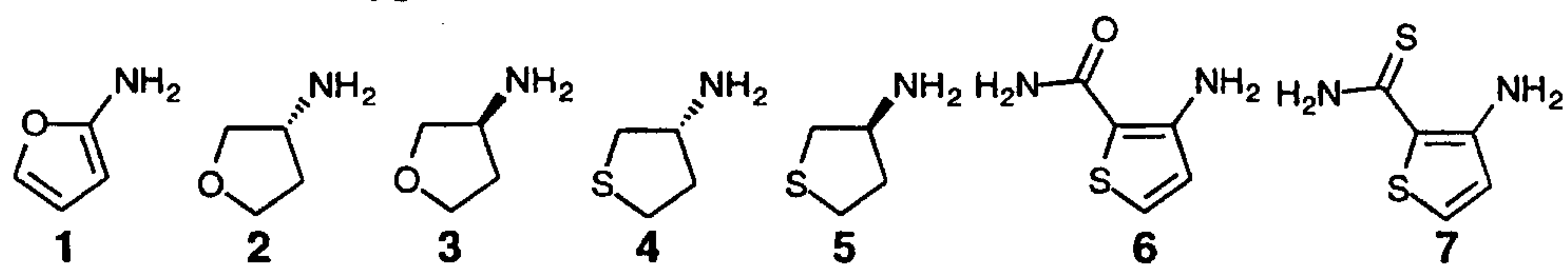
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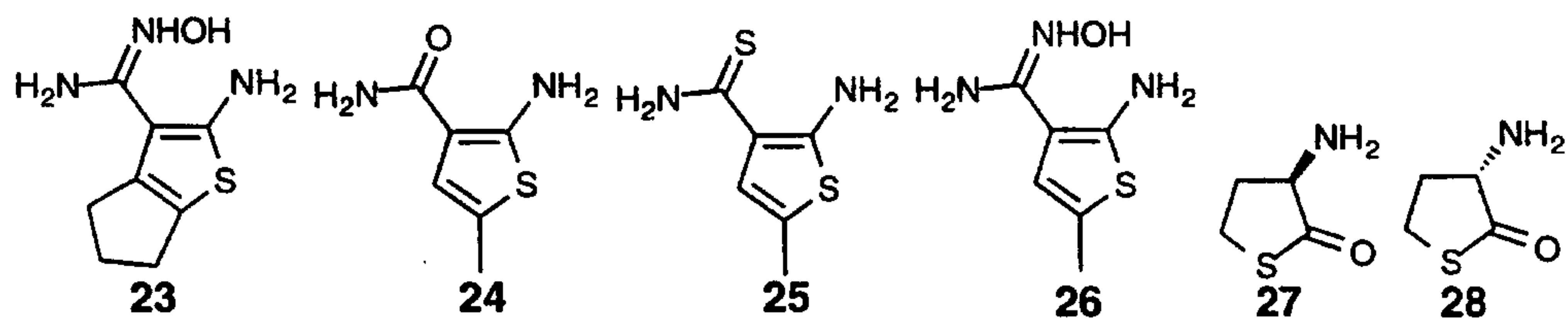
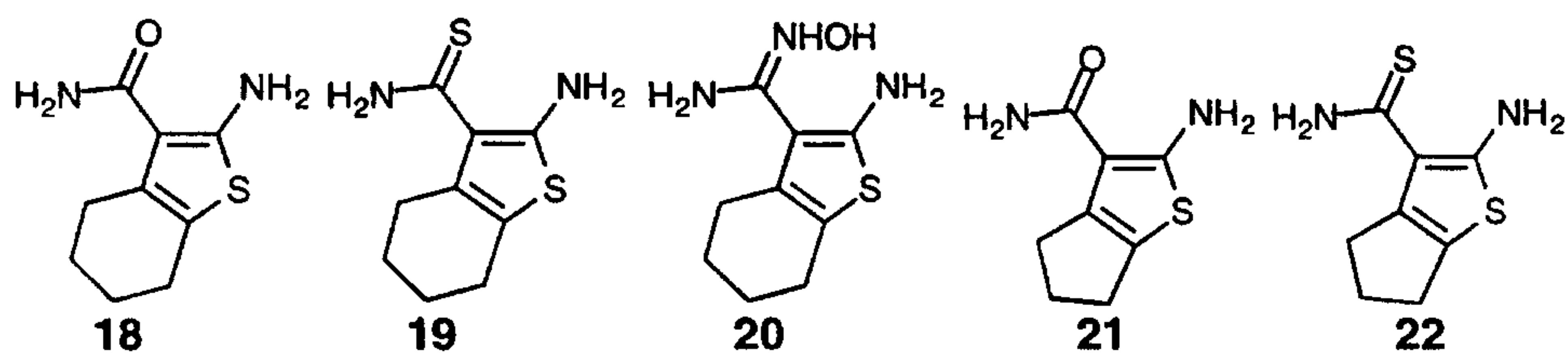
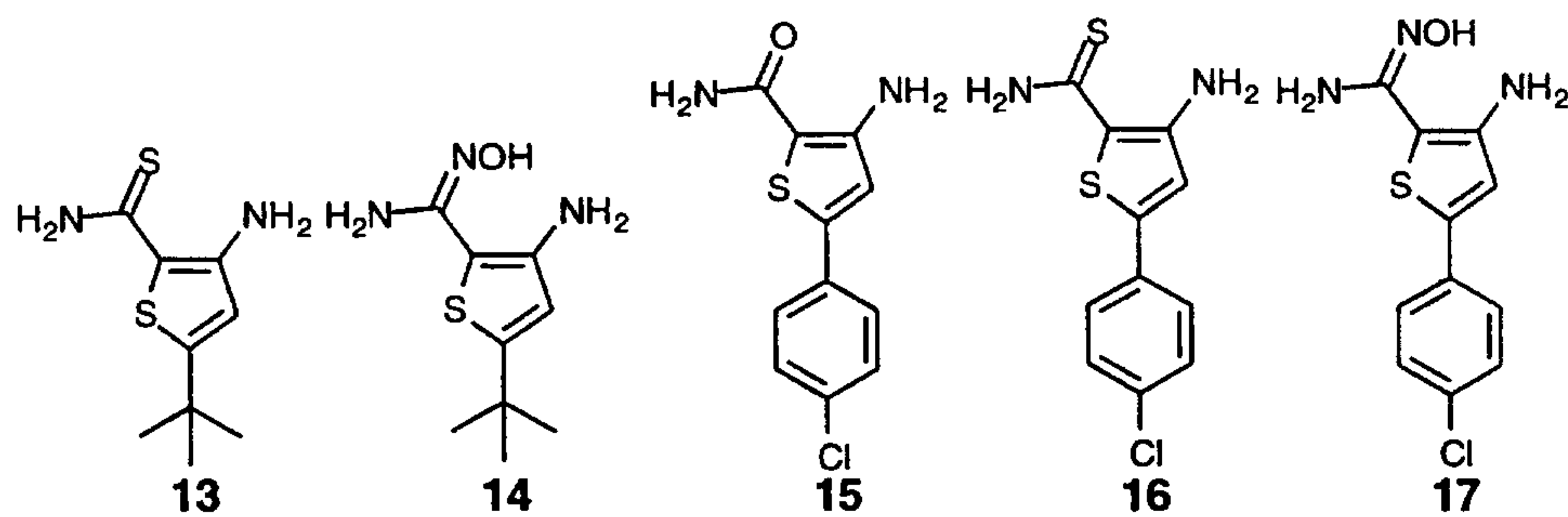
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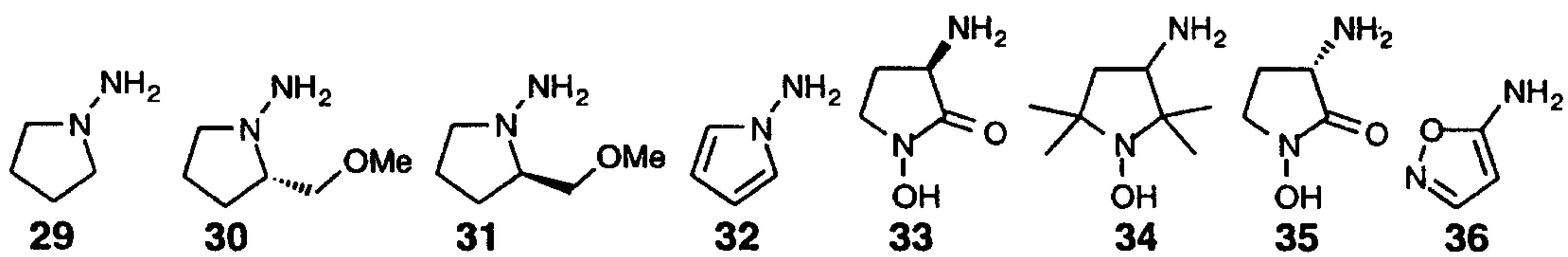
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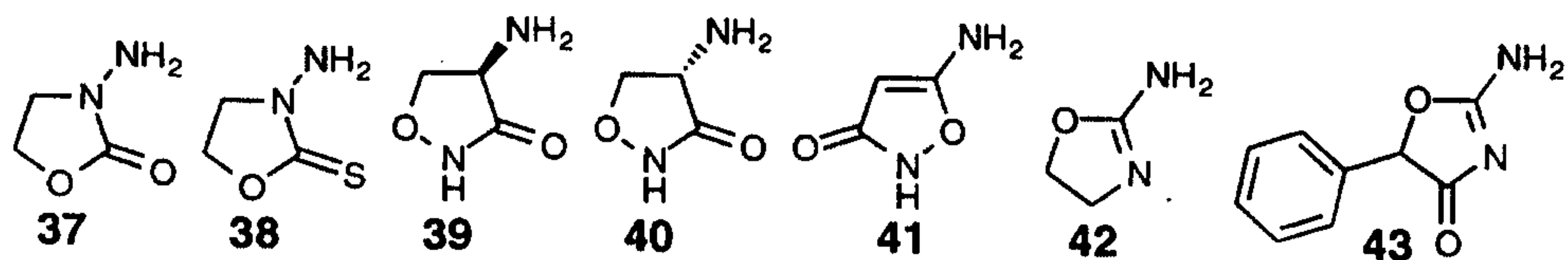
Table 12. Amines of the type A-NH₂

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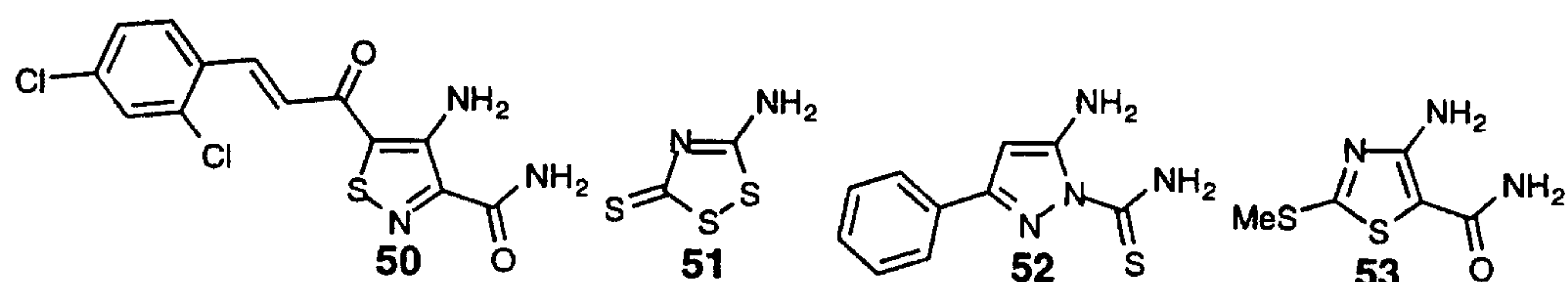
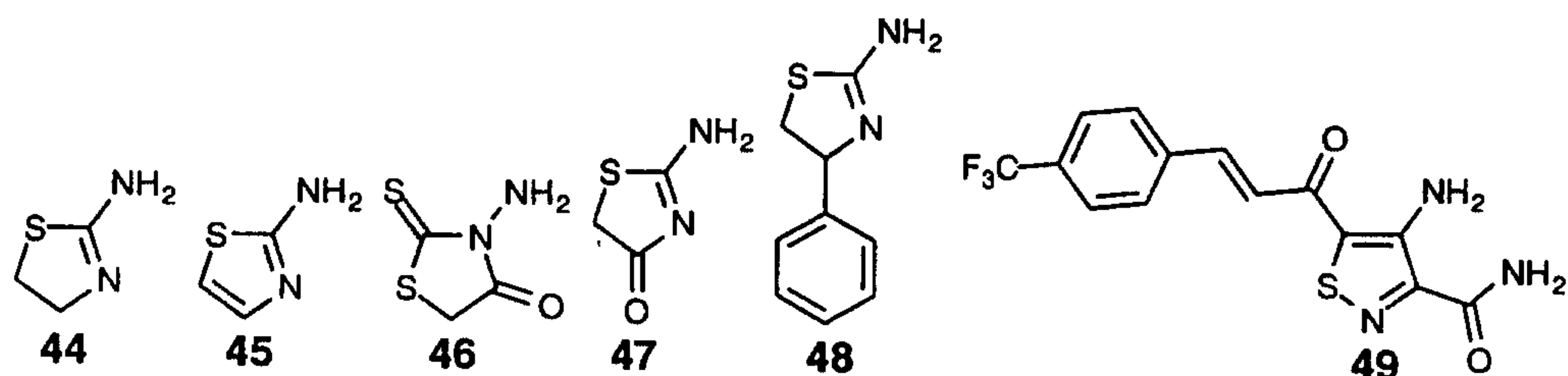


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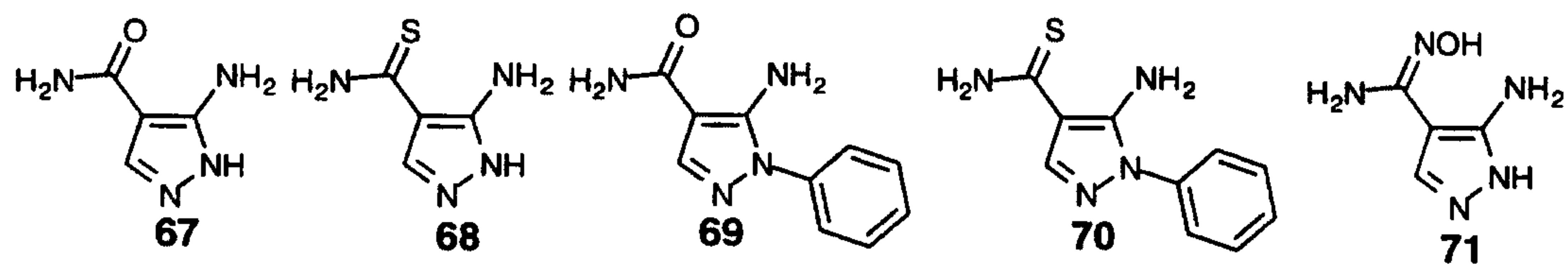
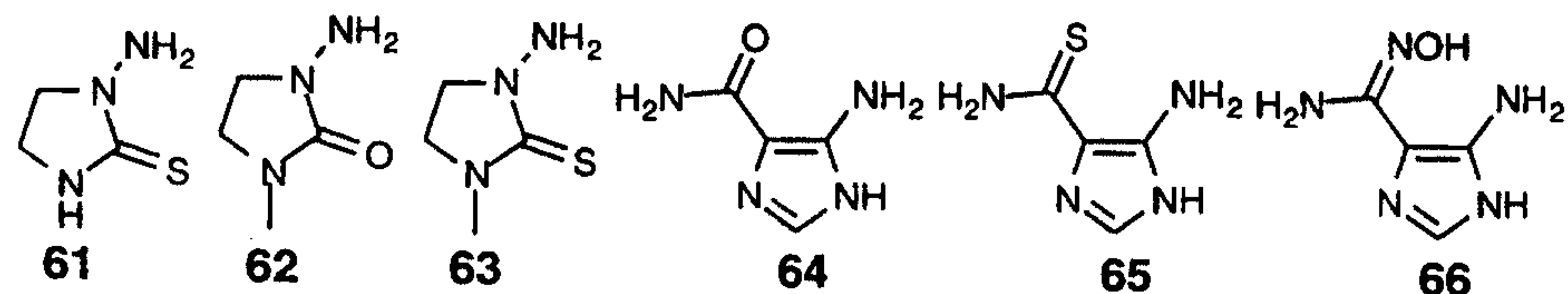
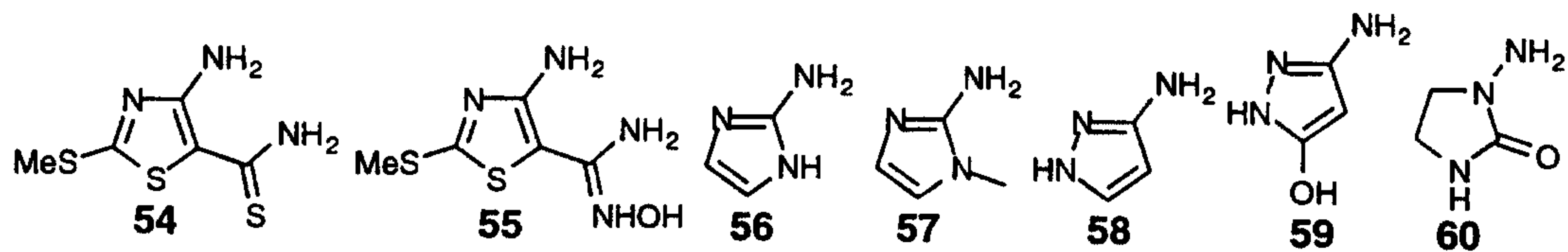




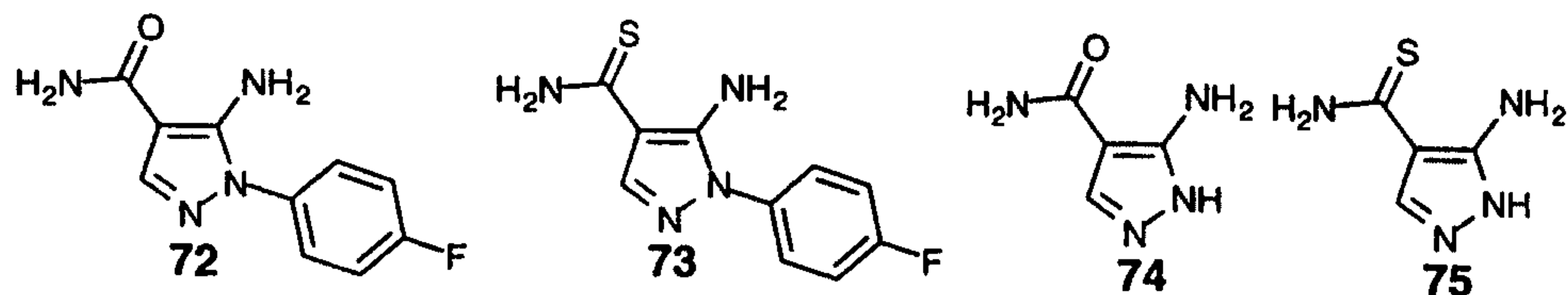
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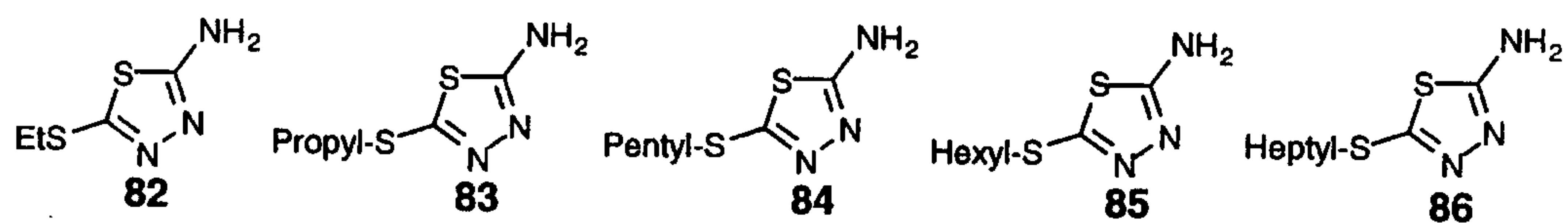
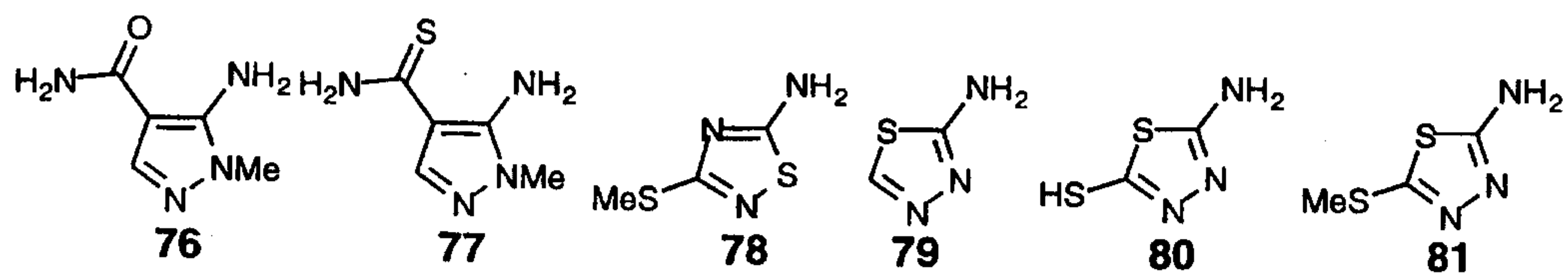


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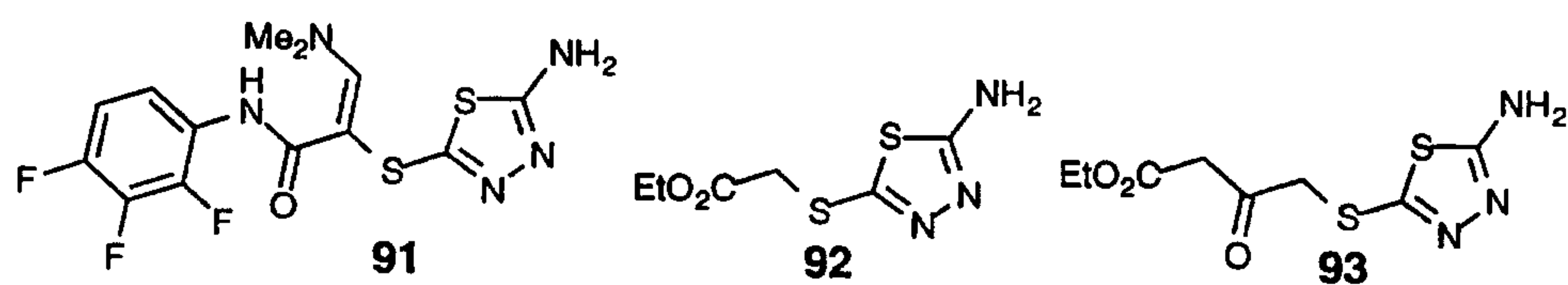
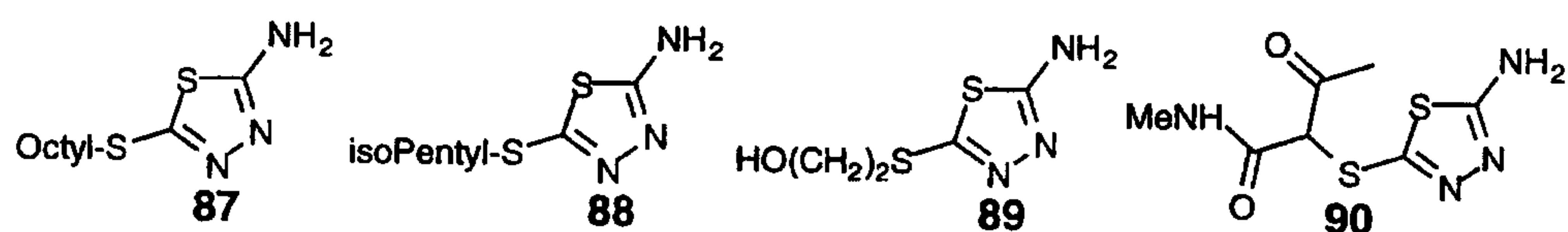


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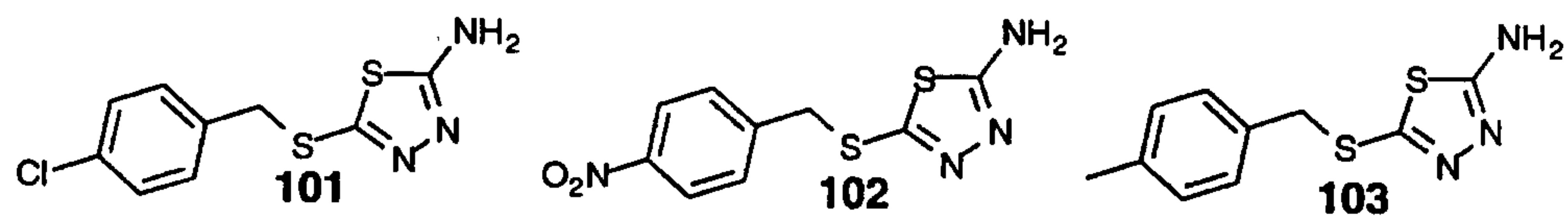
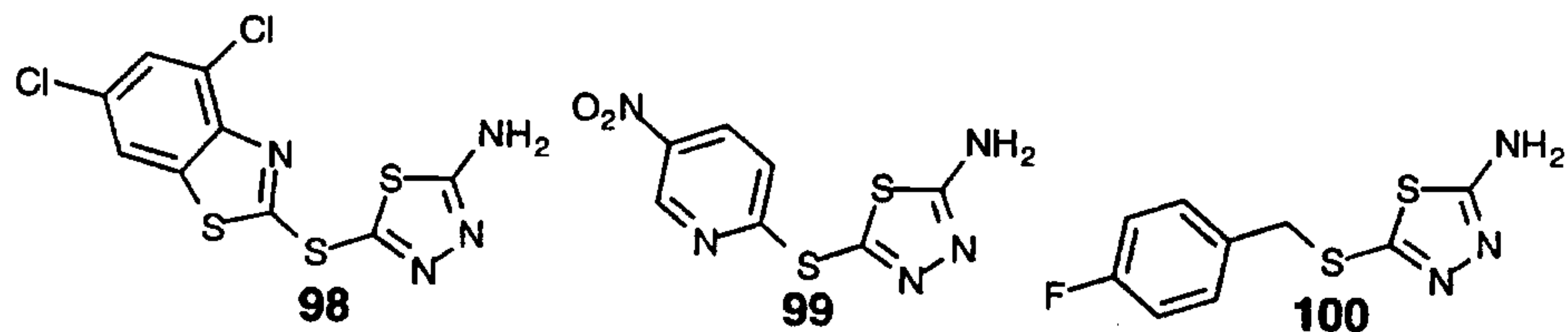
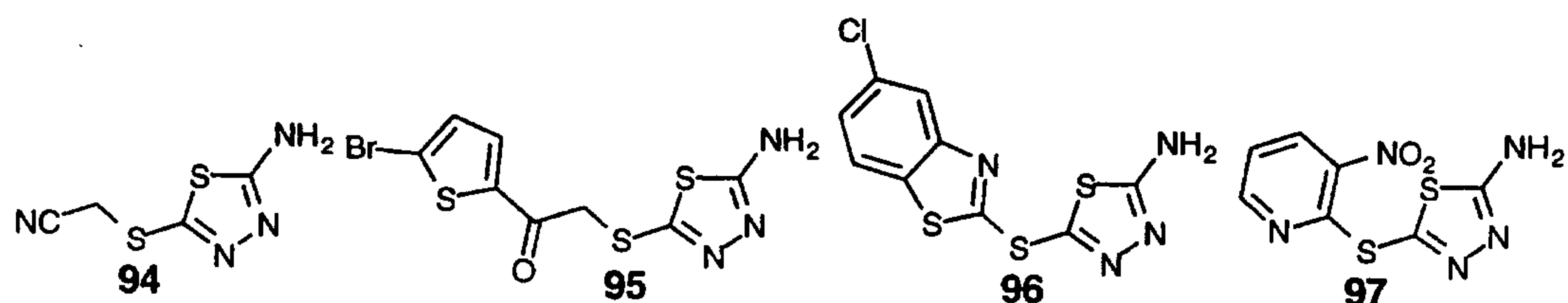
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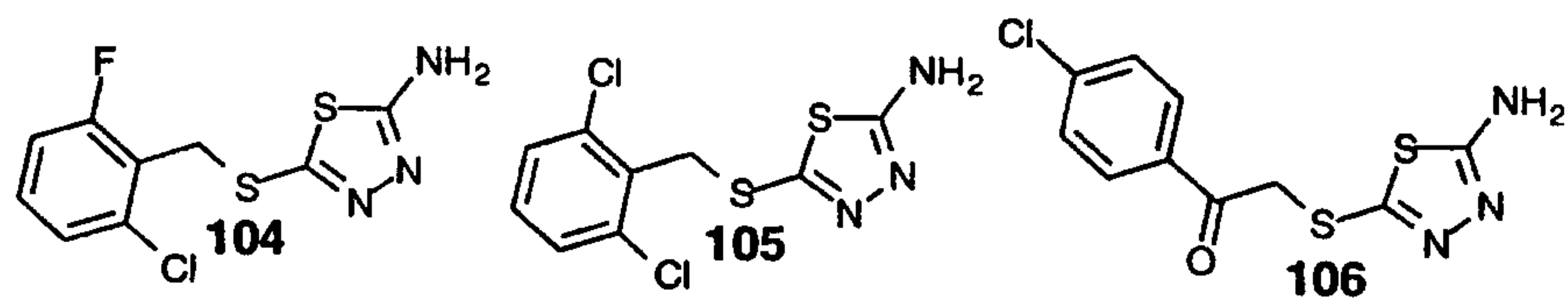
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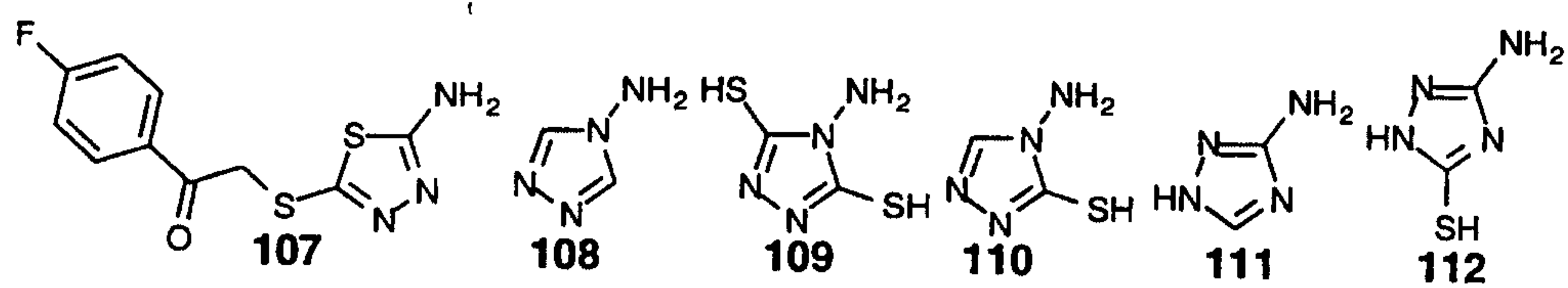


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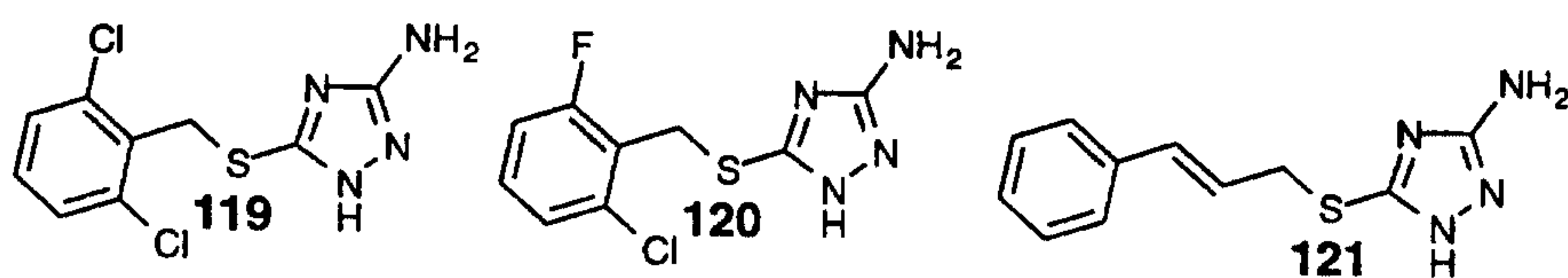
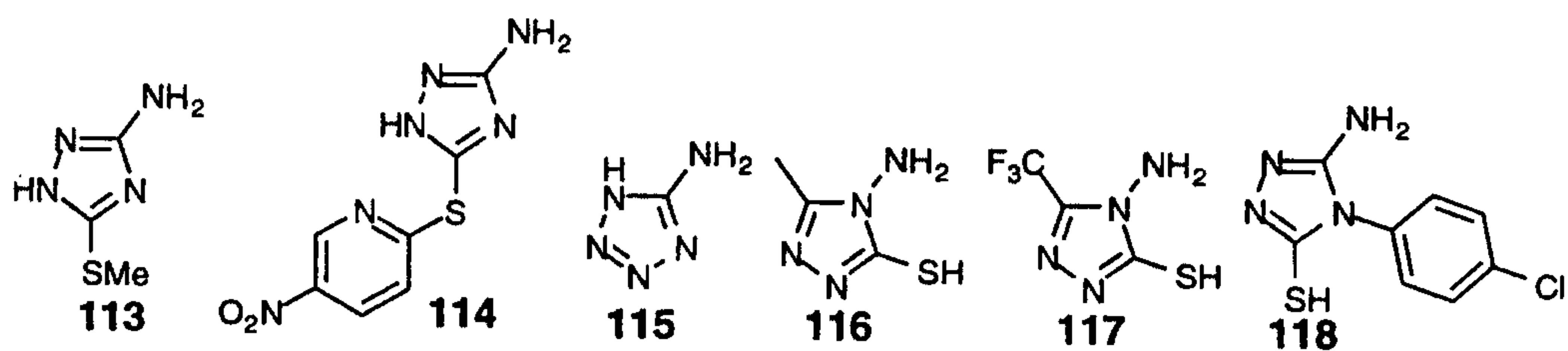


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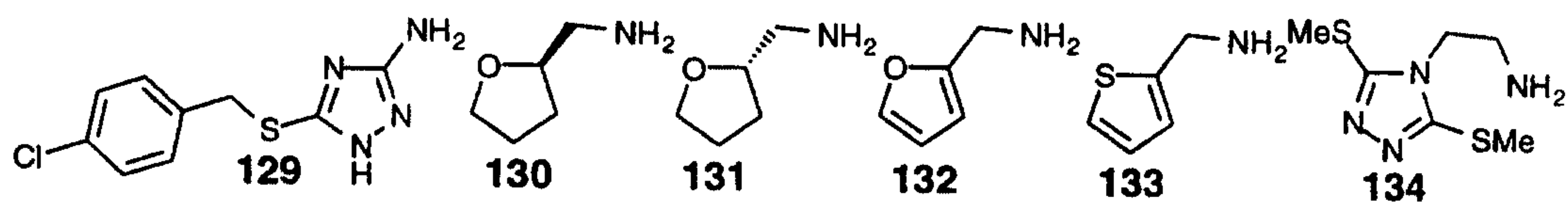
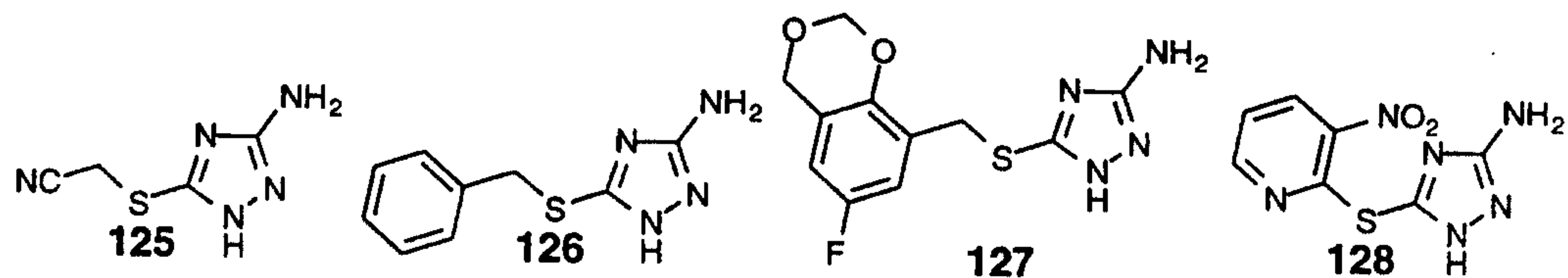
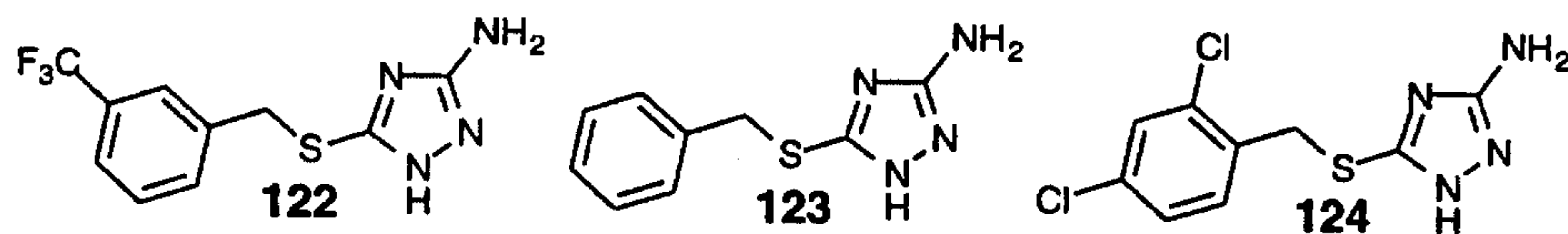




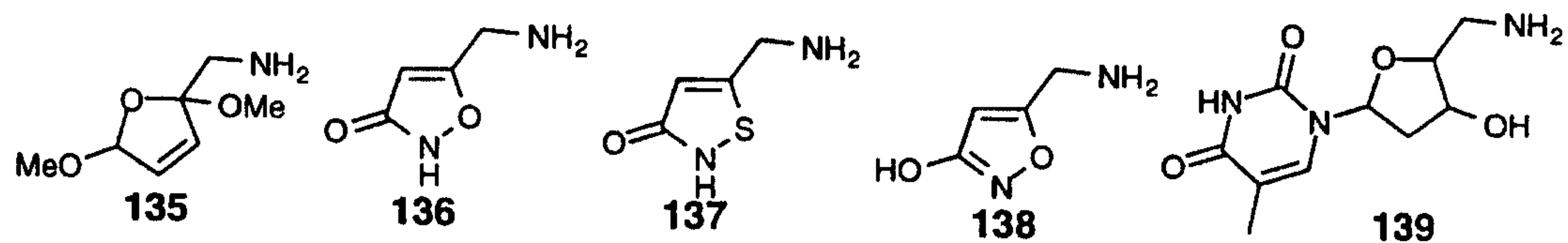
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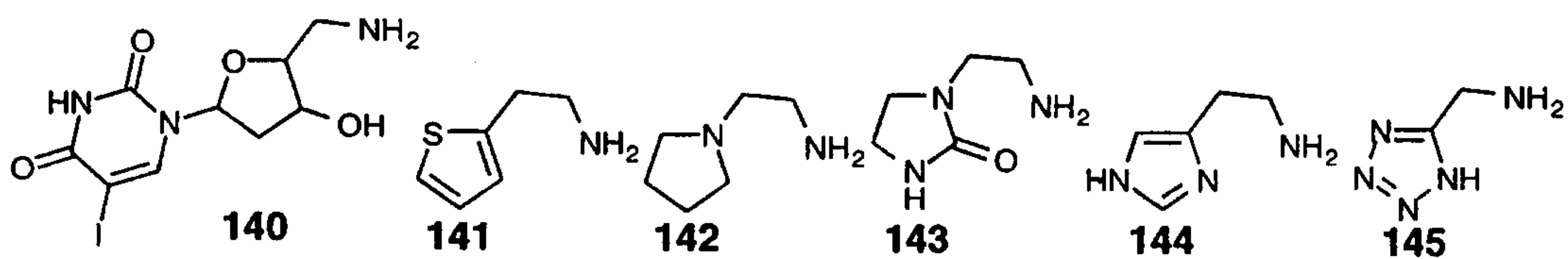


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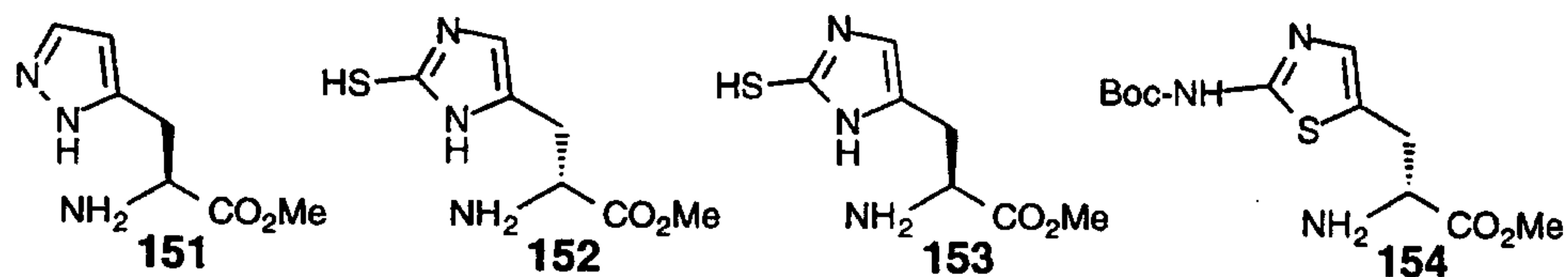
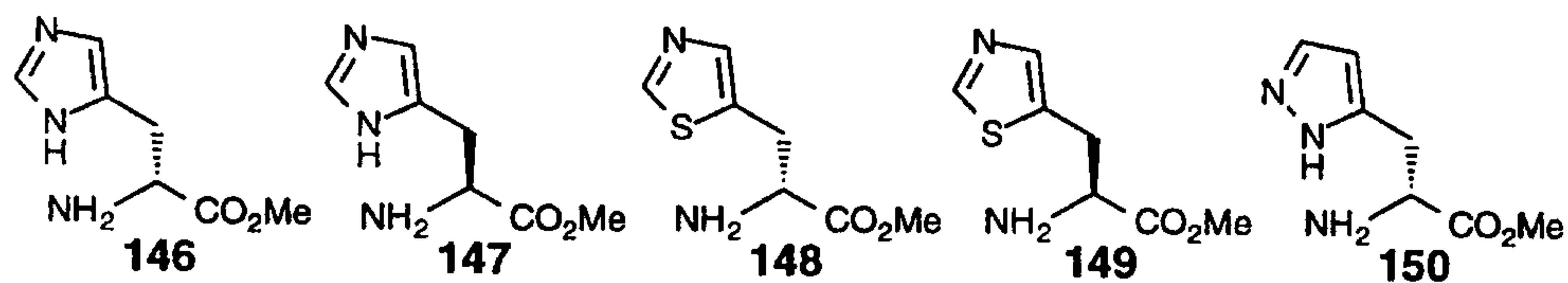


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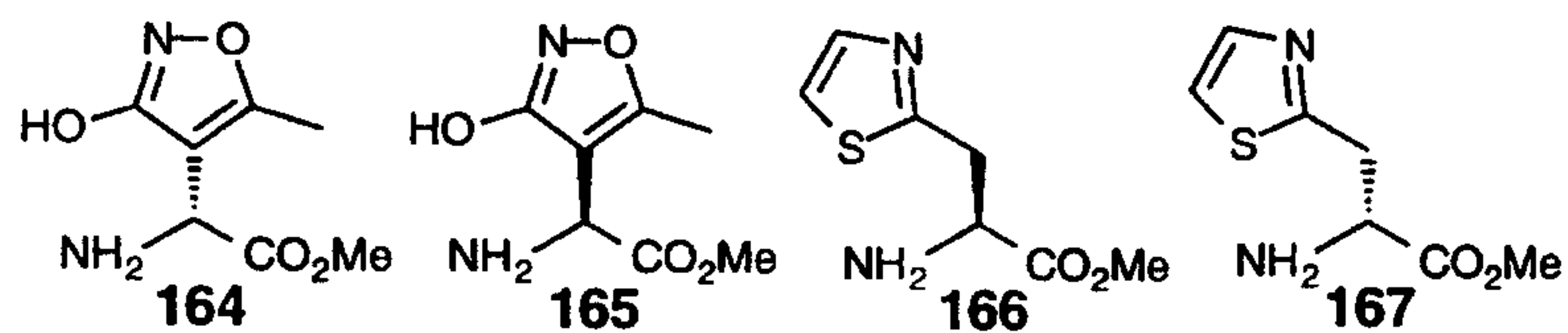
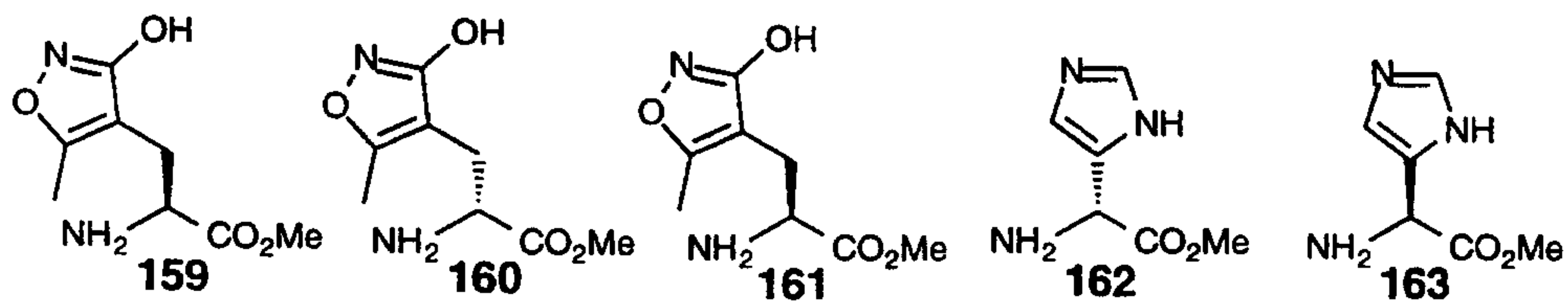
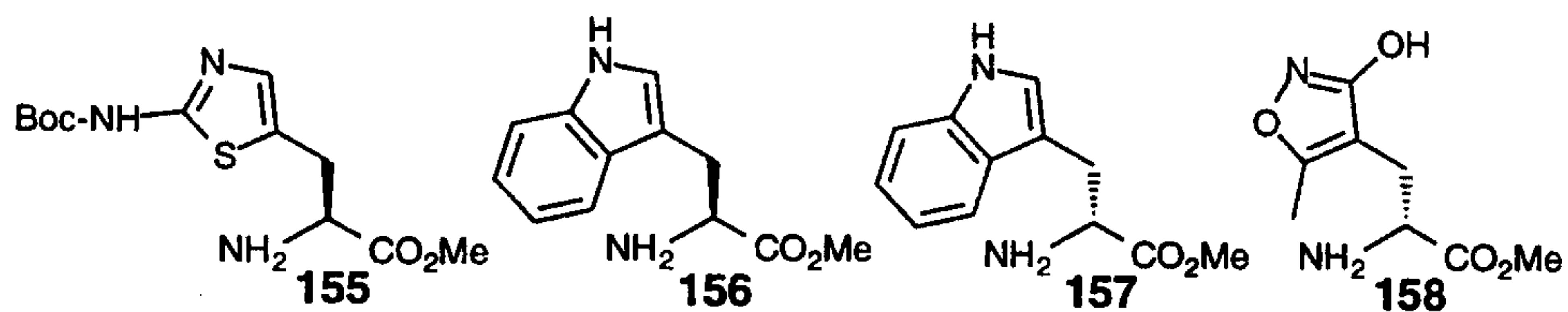




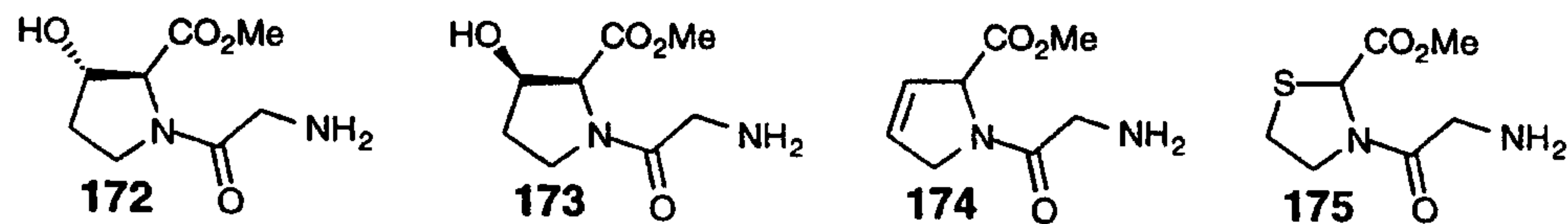
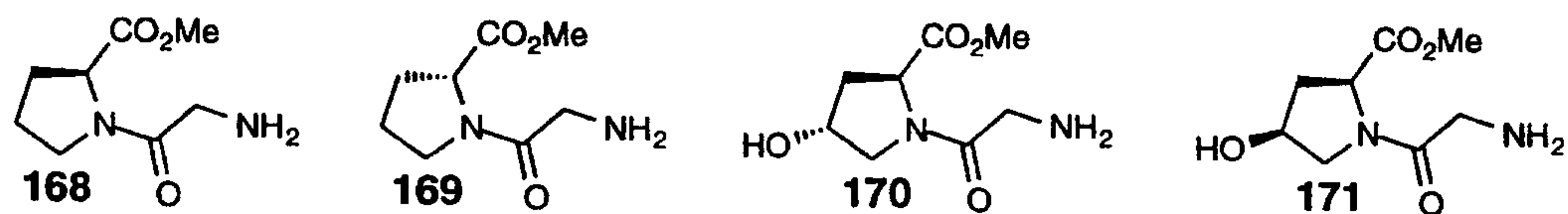
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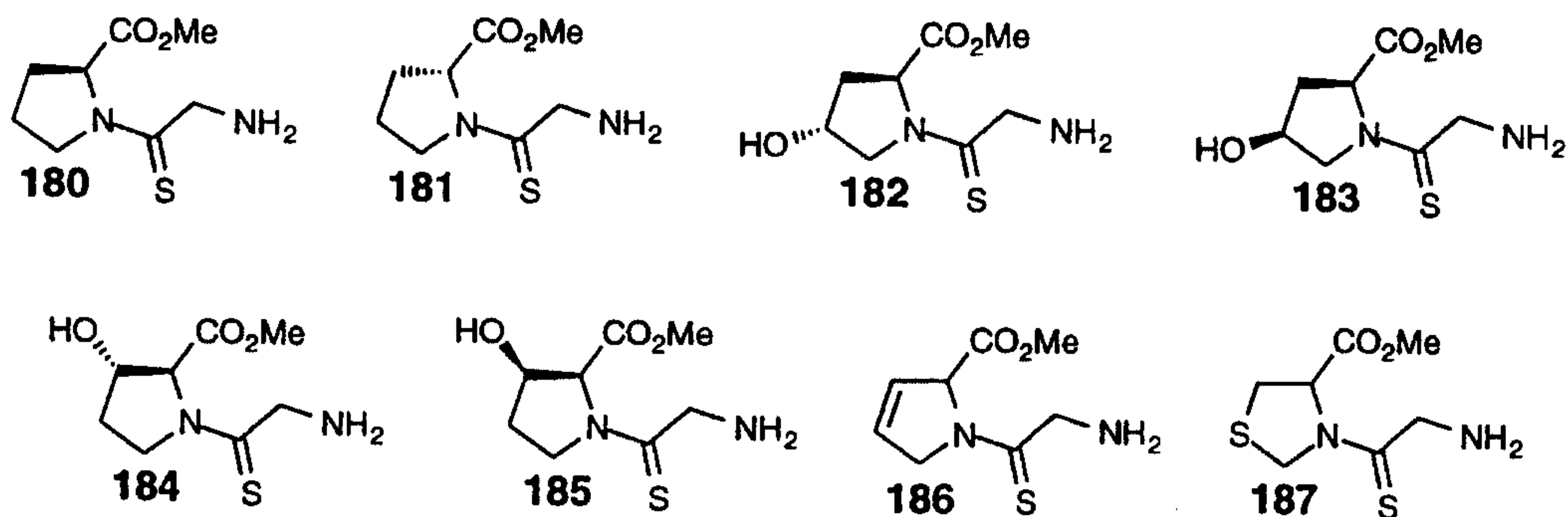
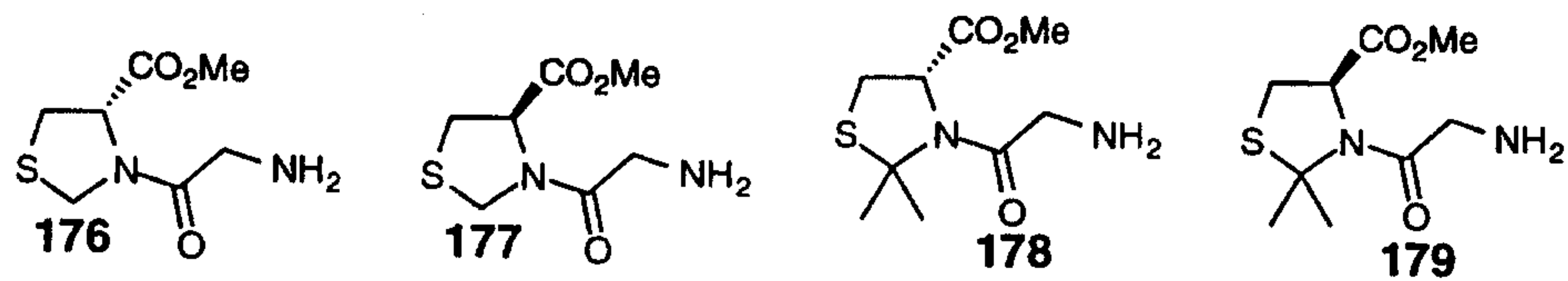
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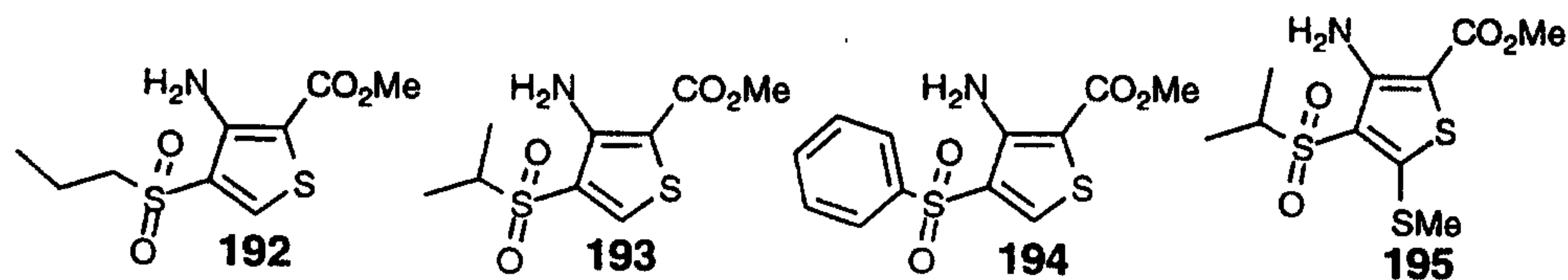
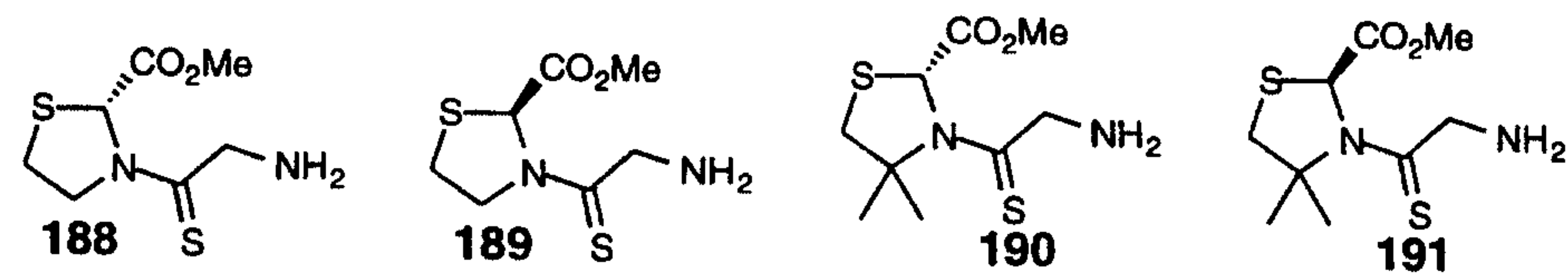
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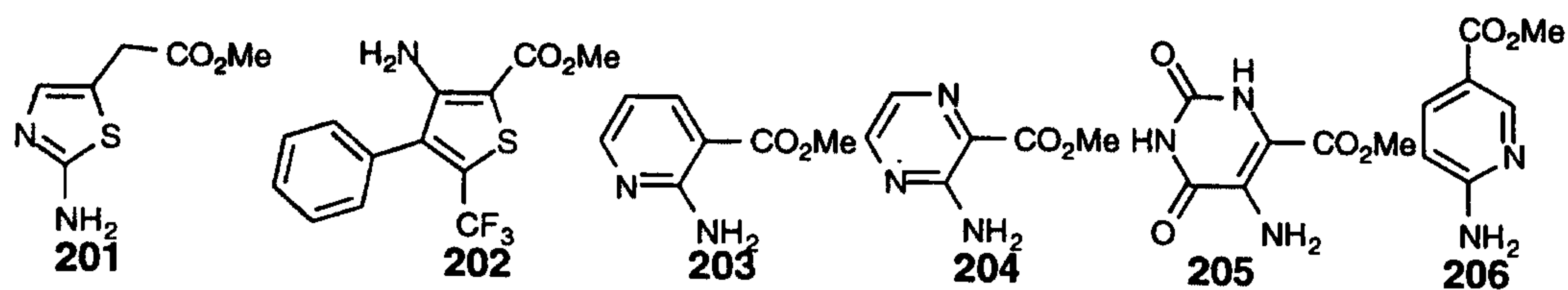
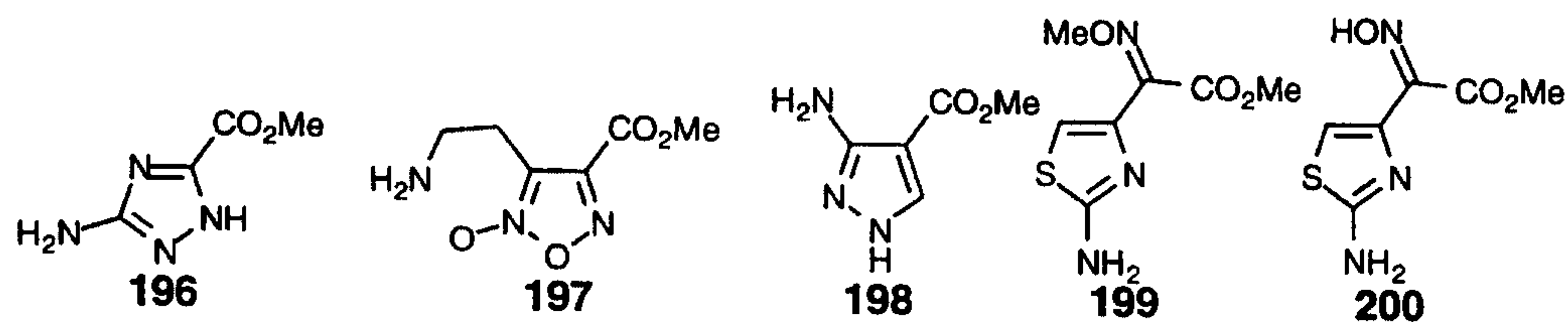
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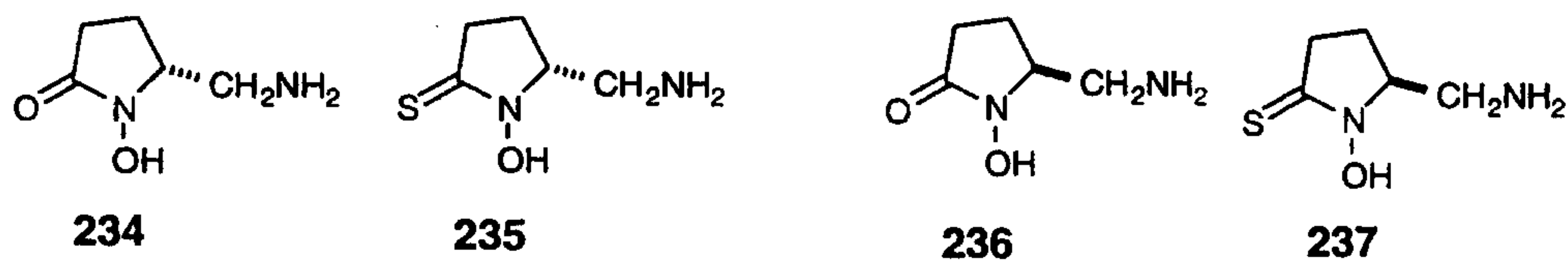
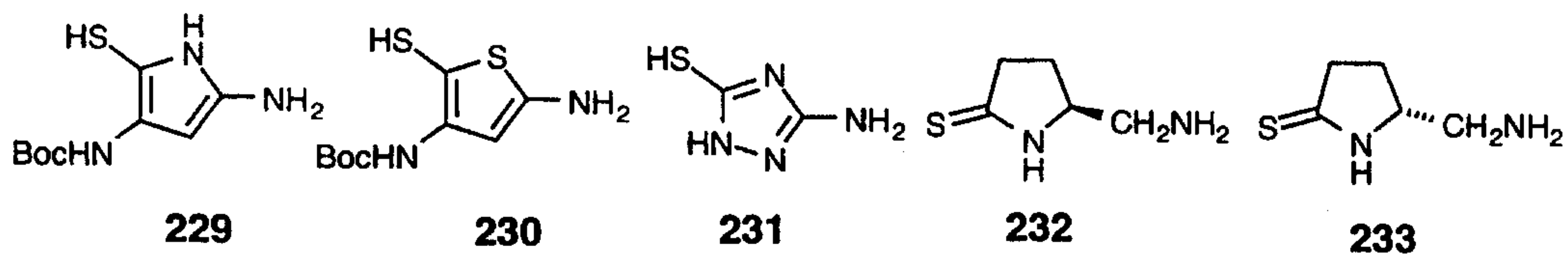
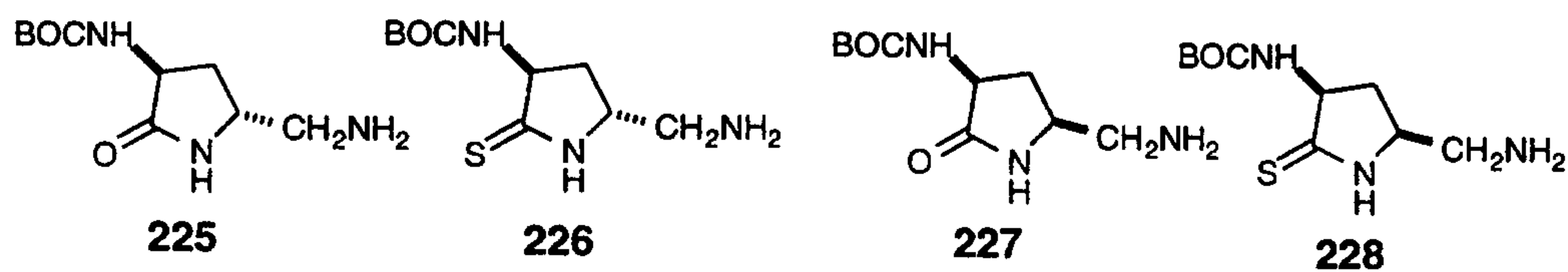
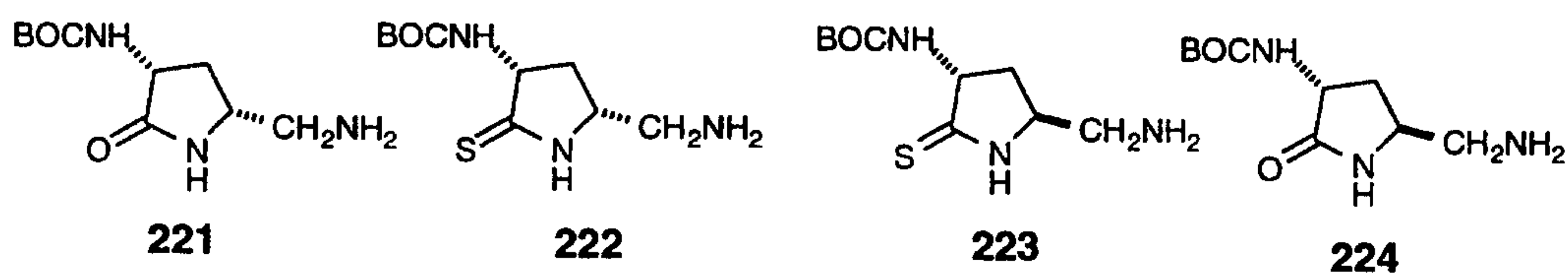
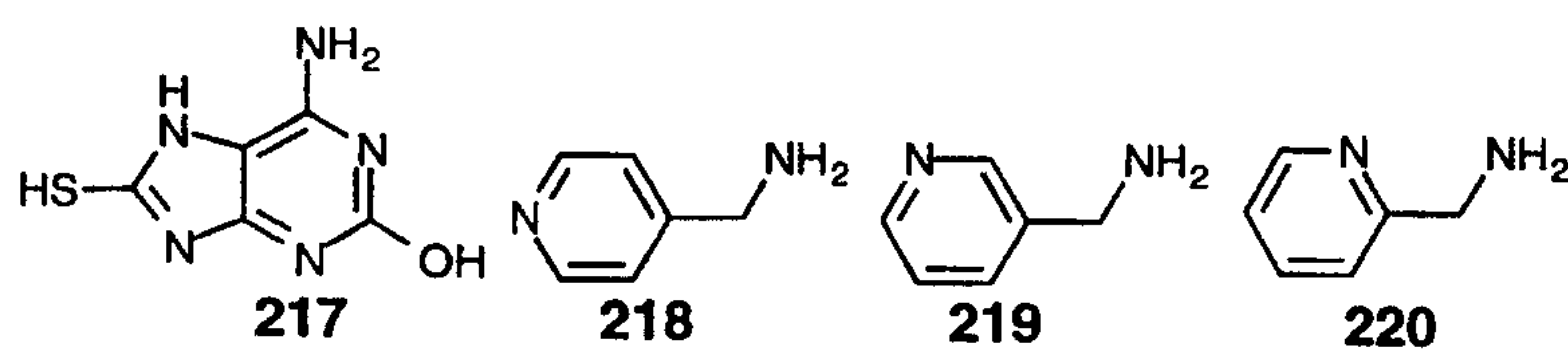
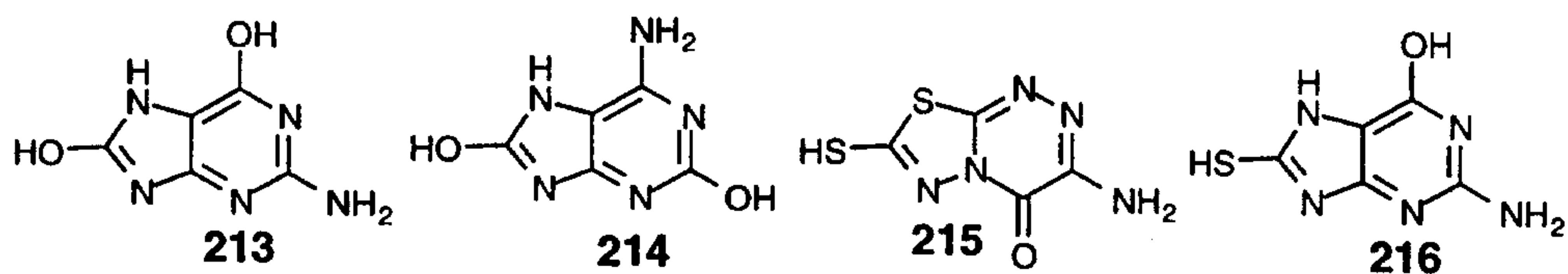
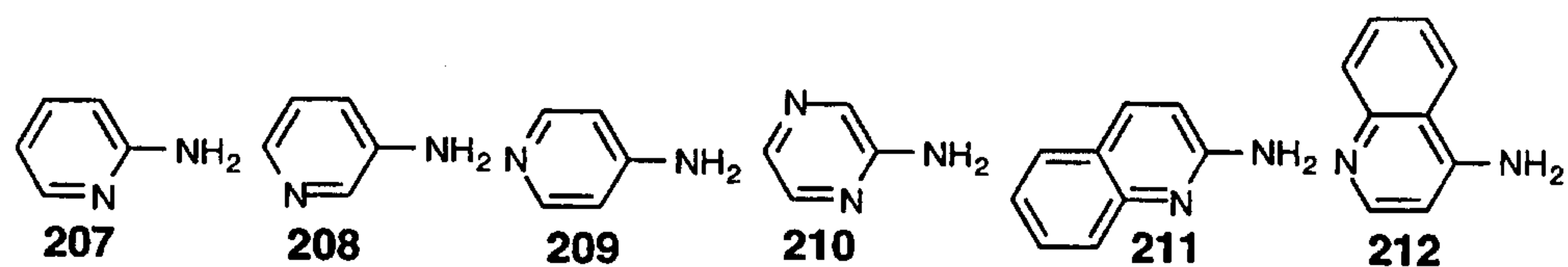
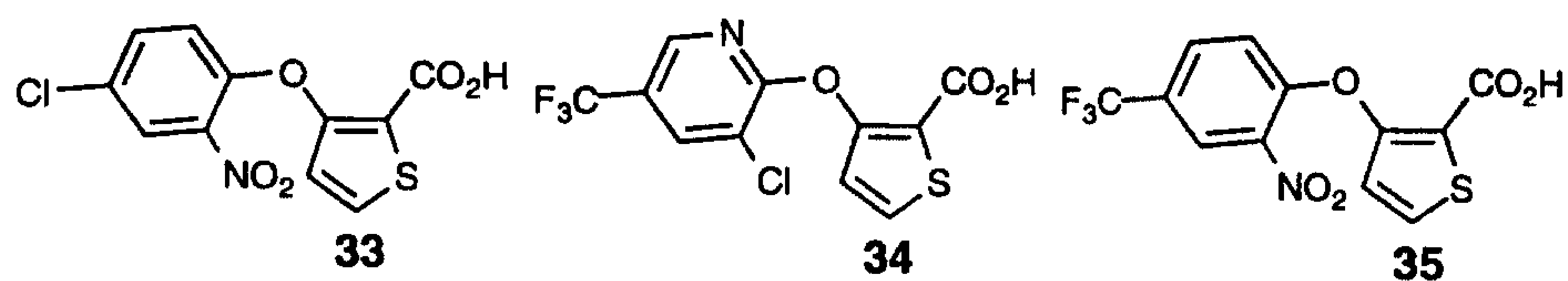
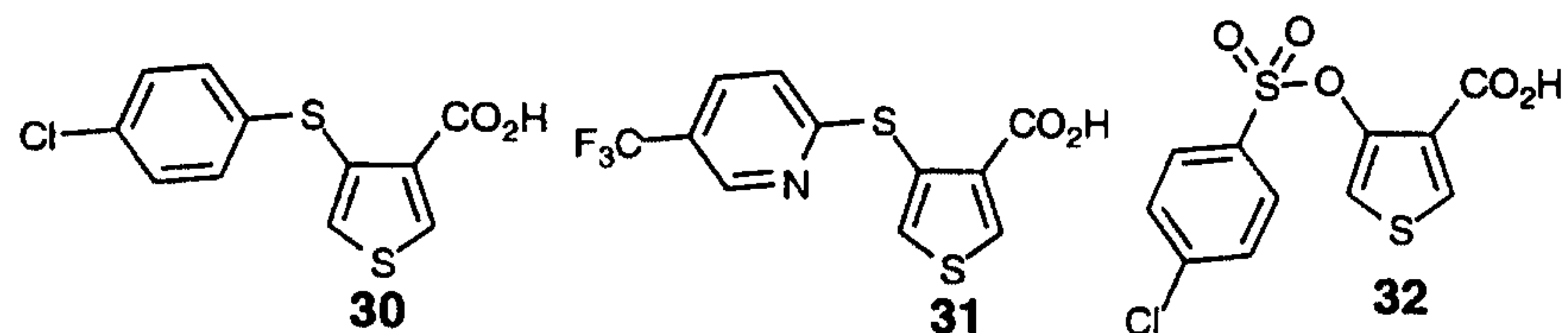
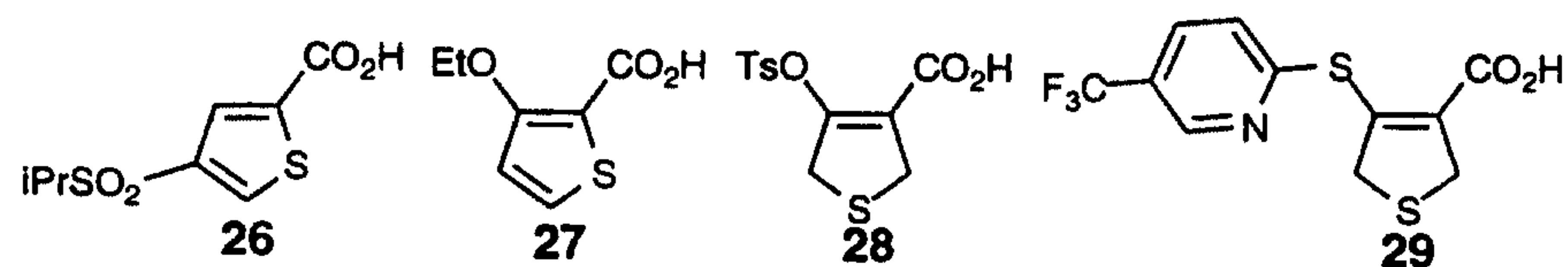
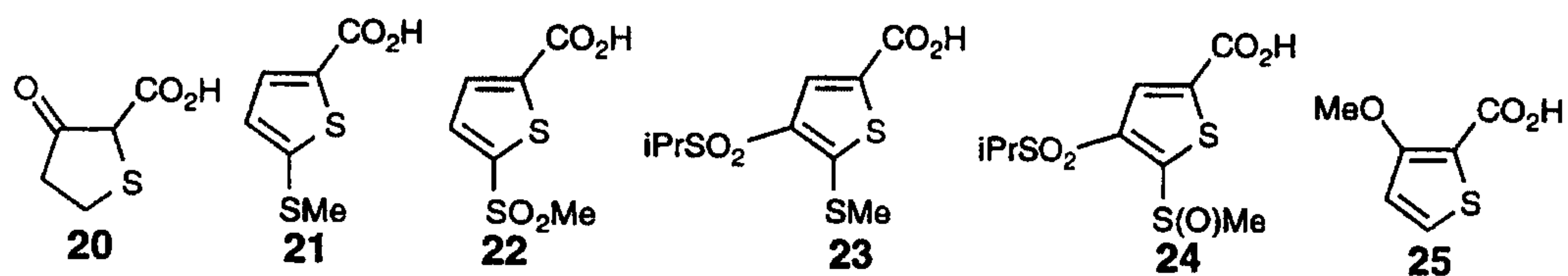
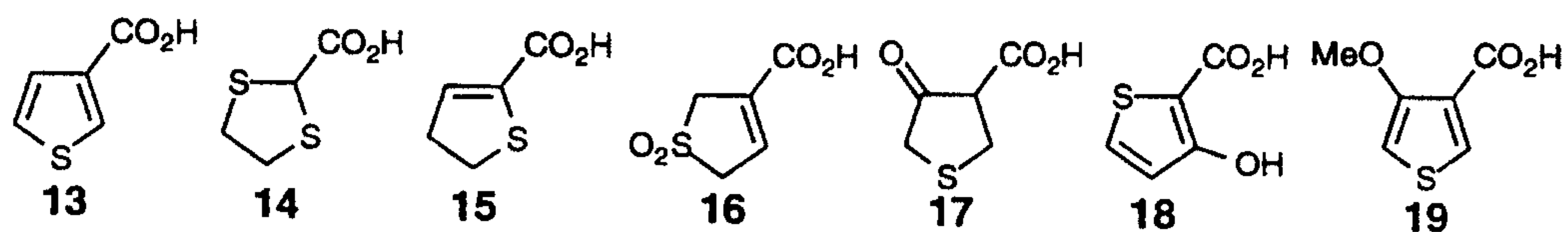
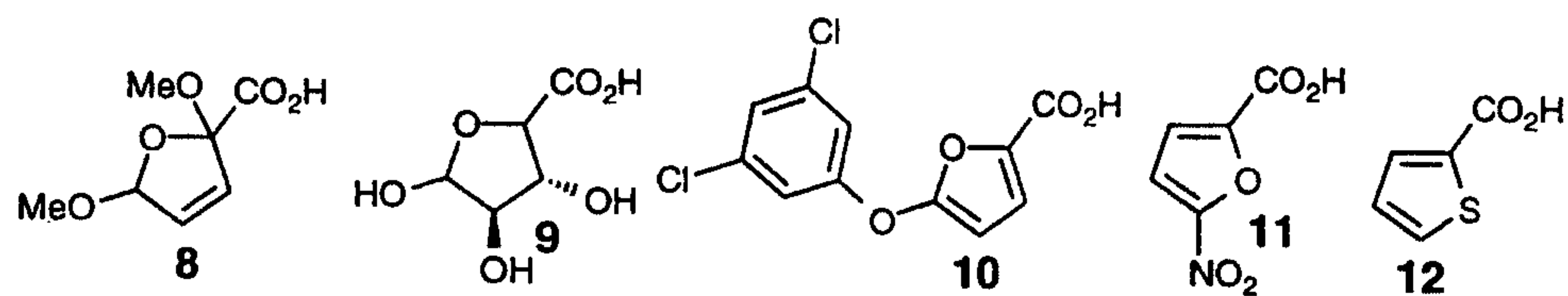
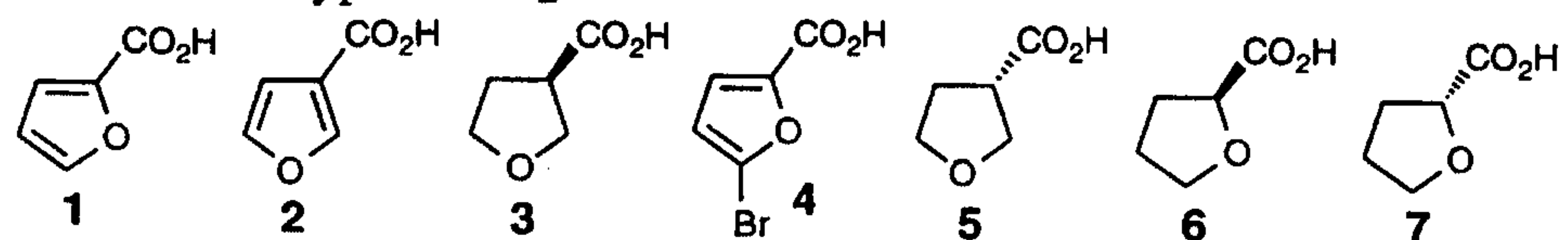
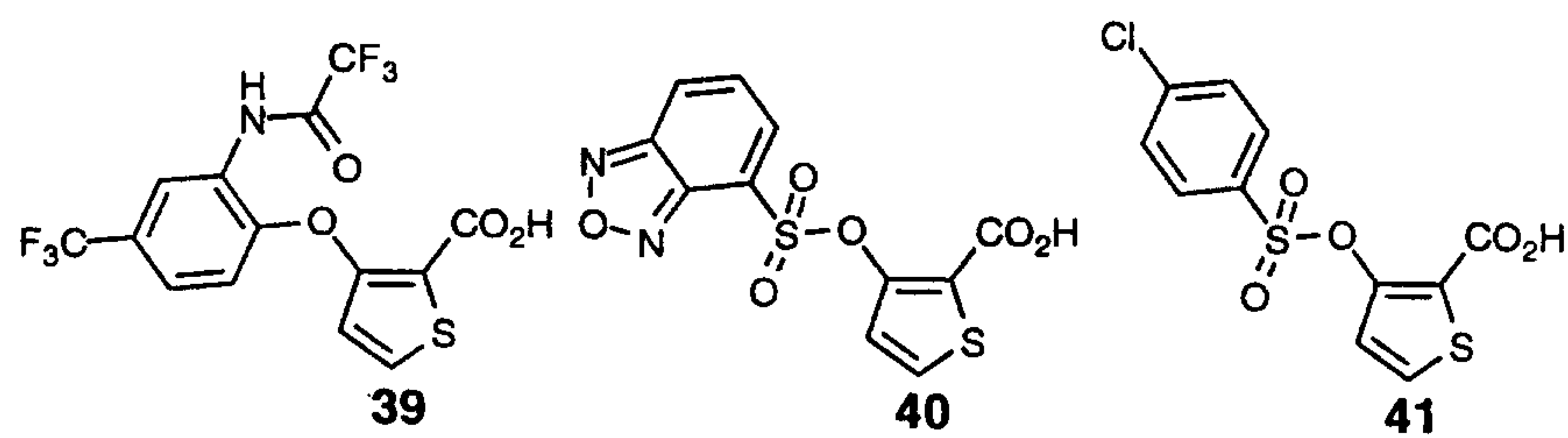
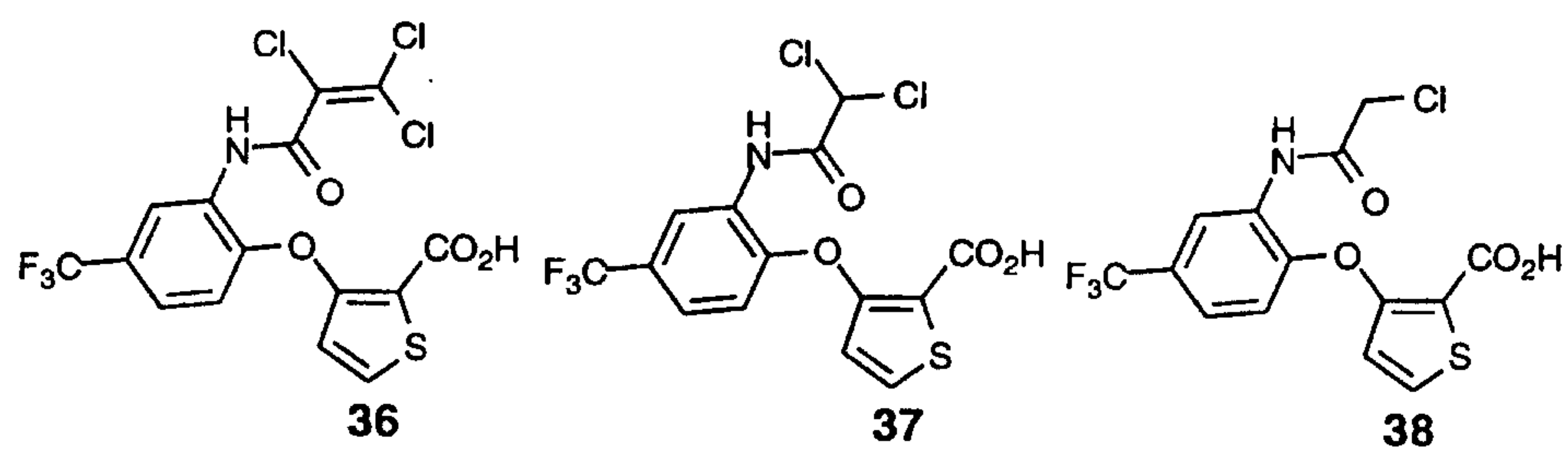
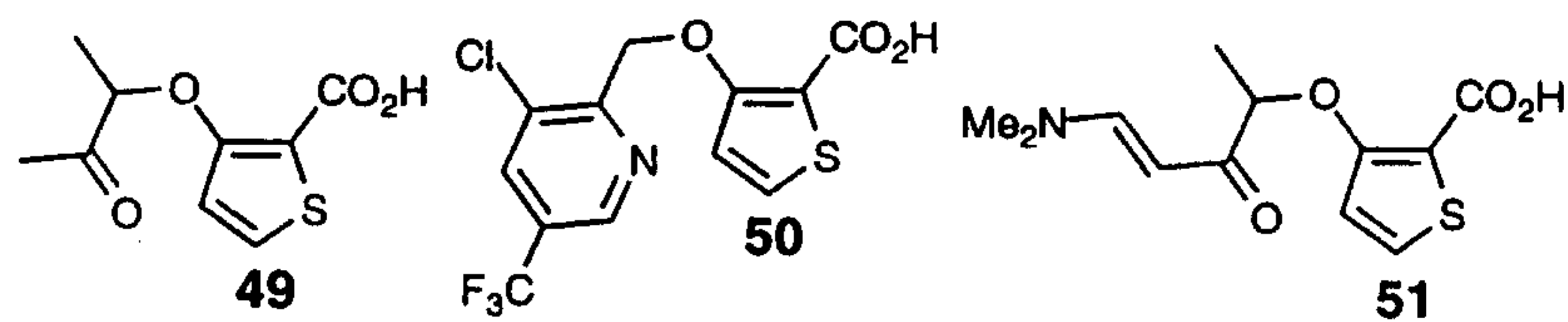
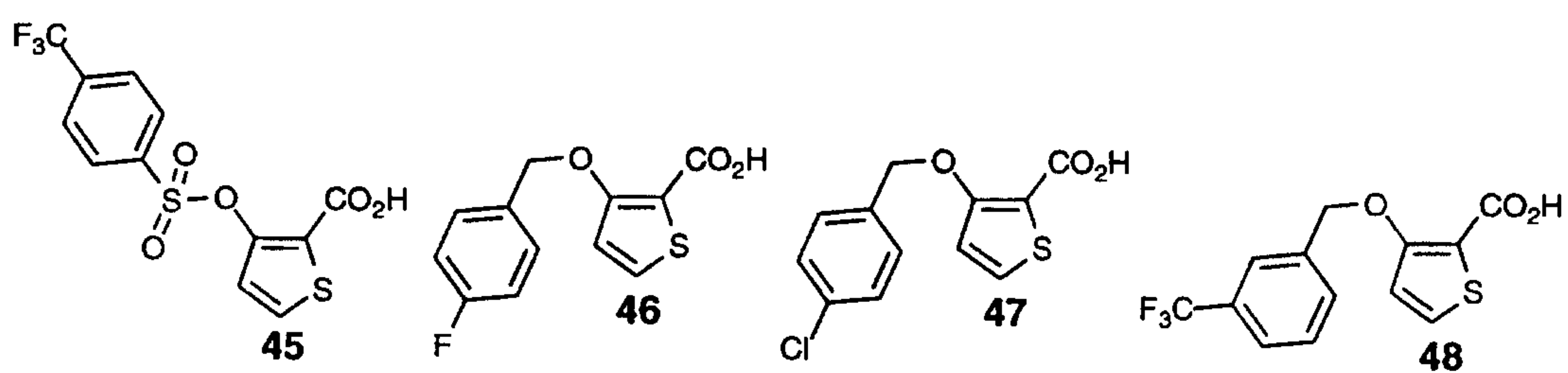
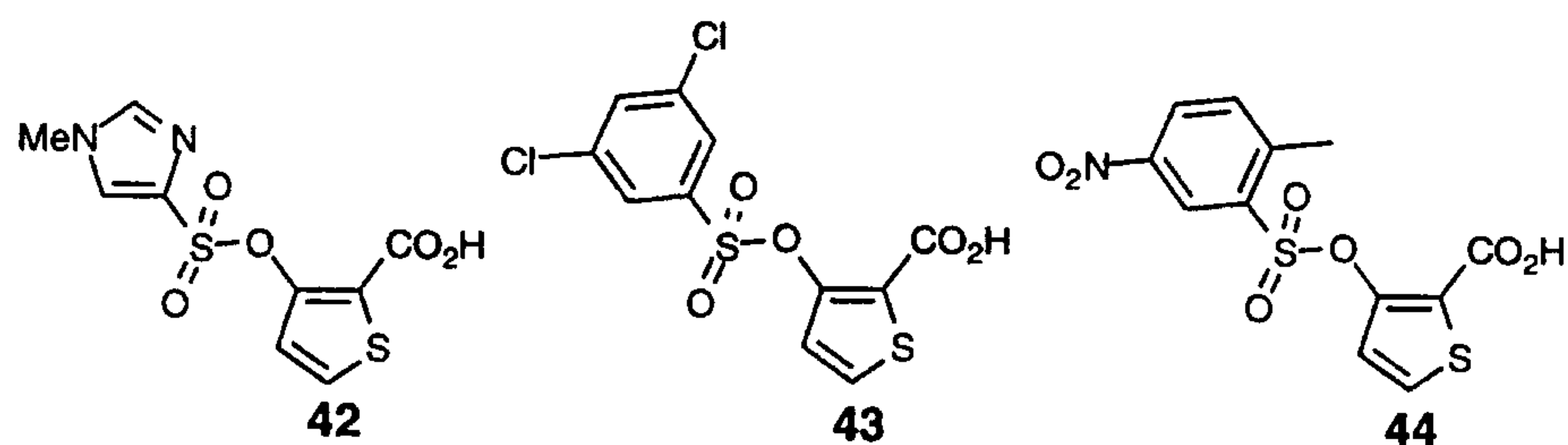


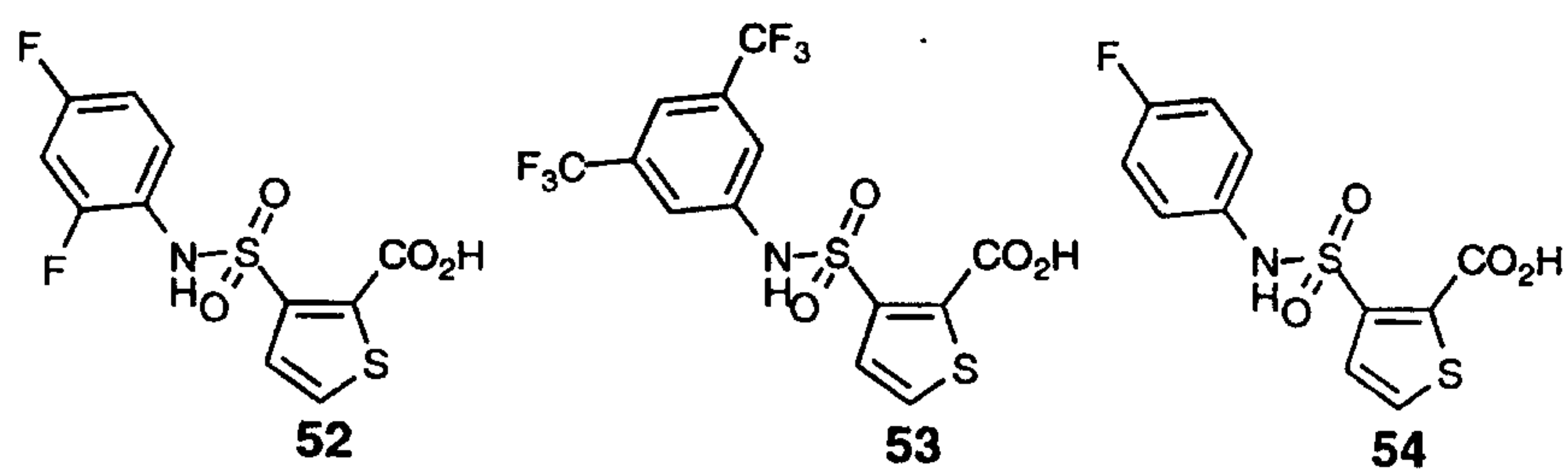
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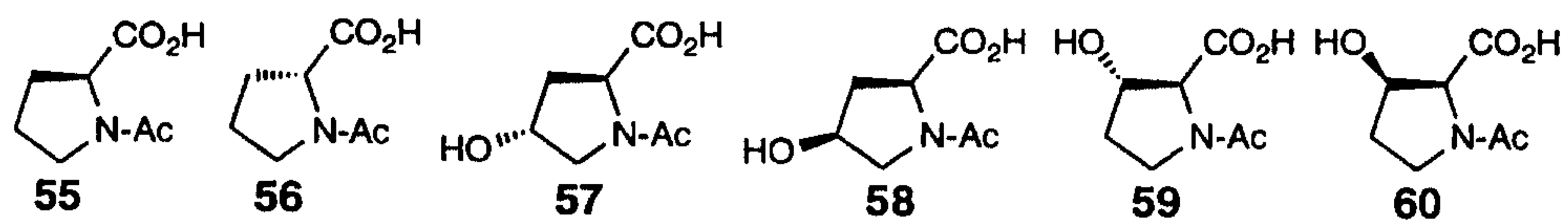


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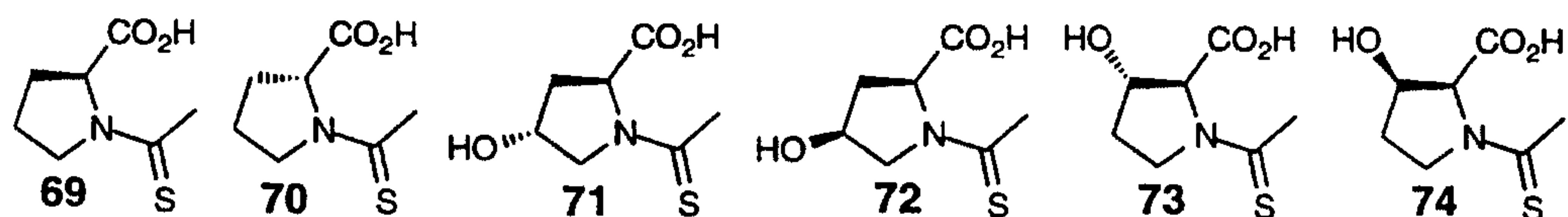
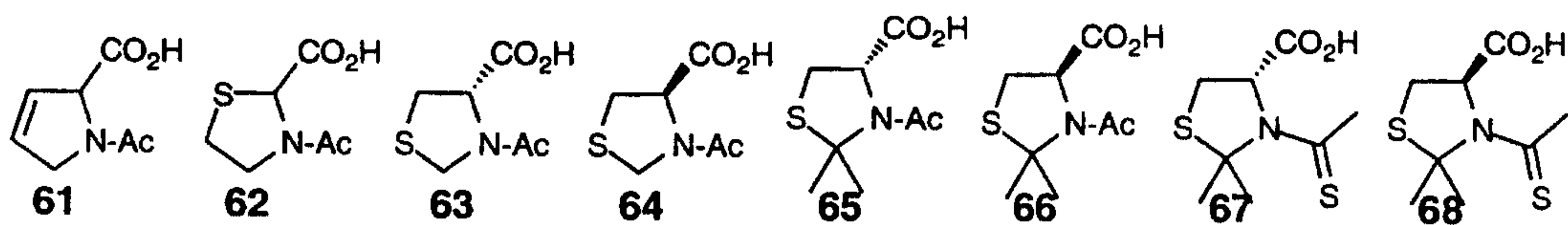


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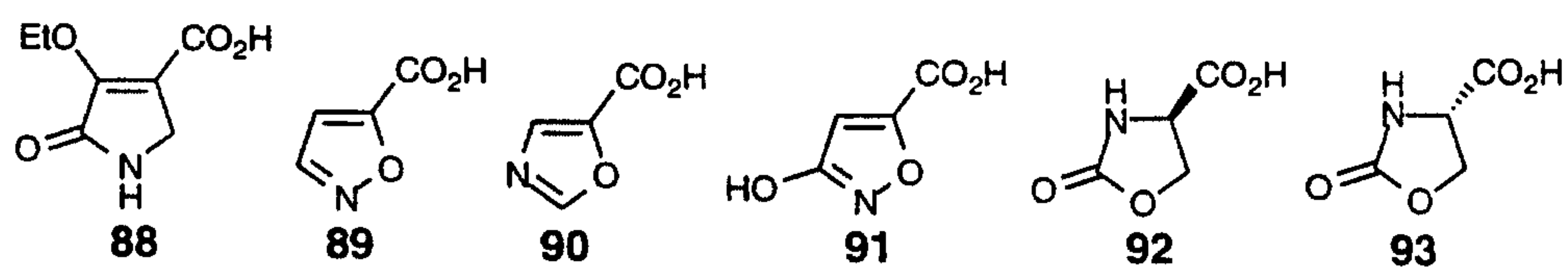
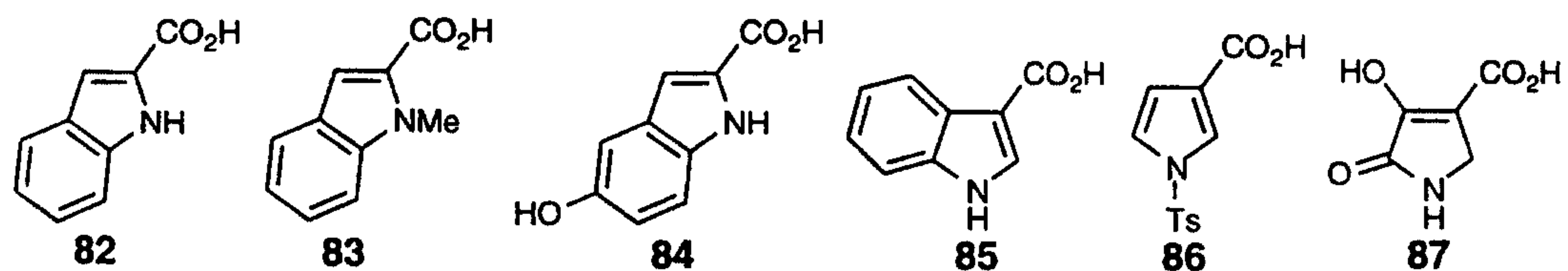
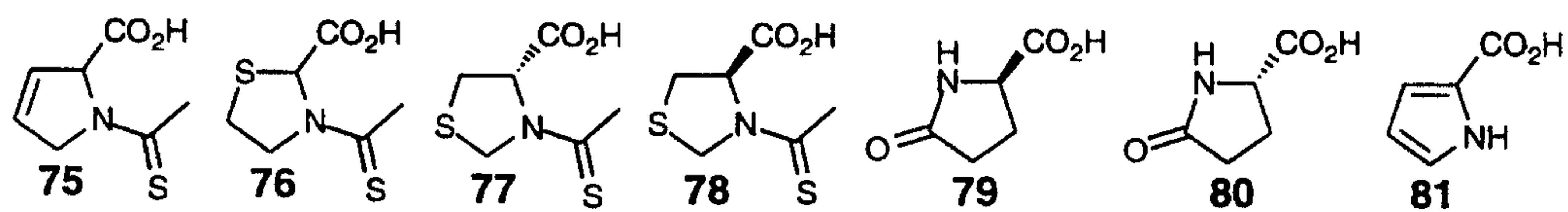




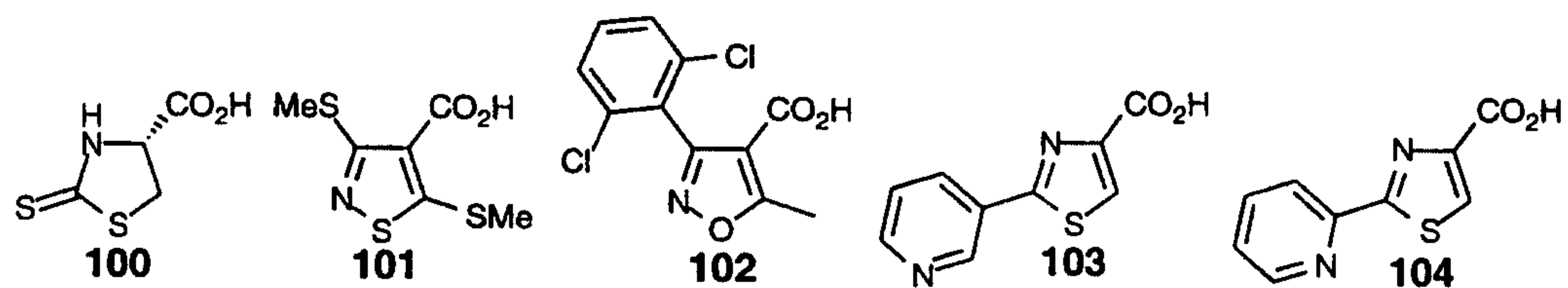
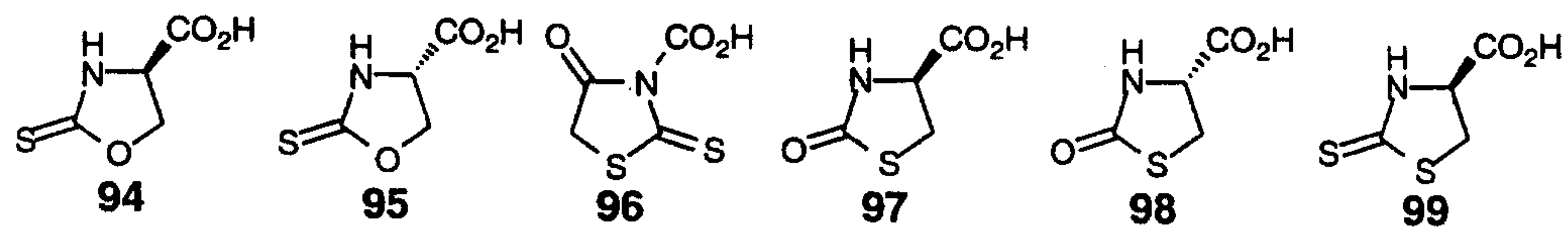
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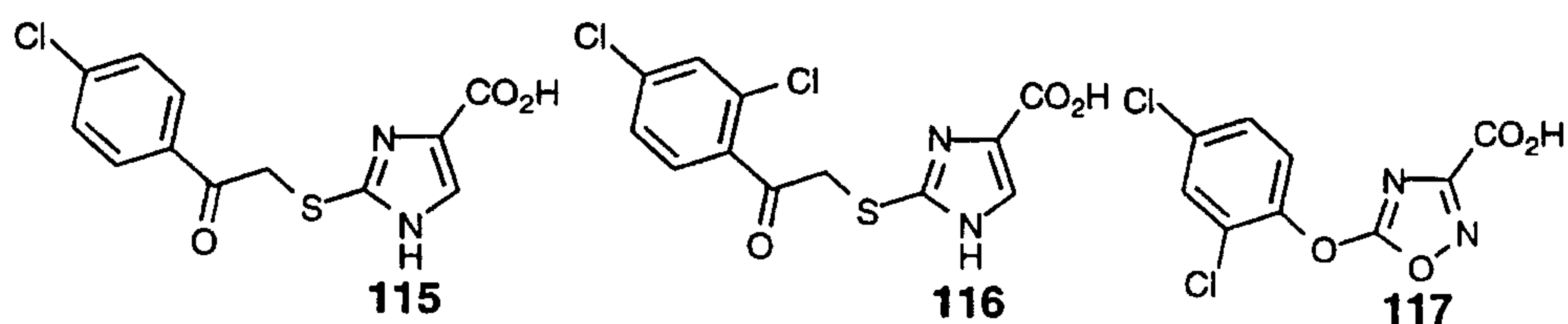
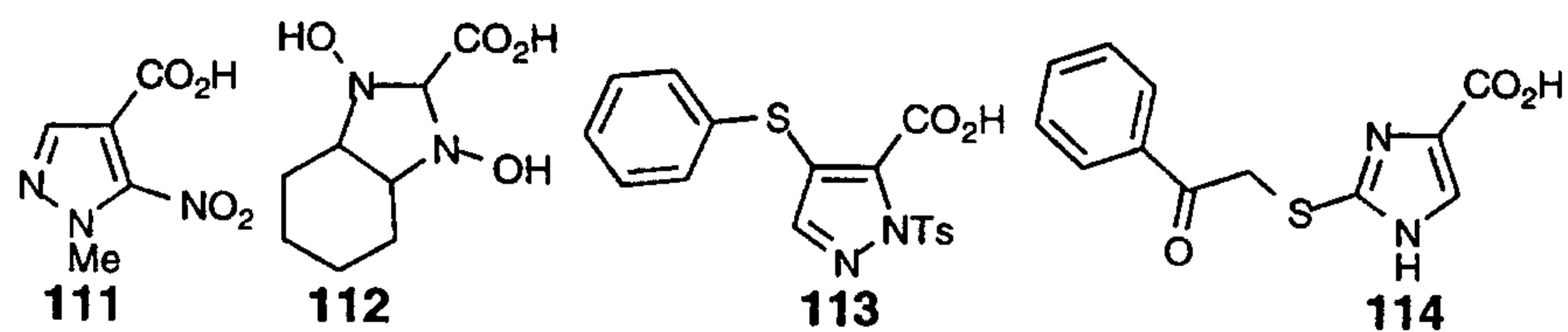
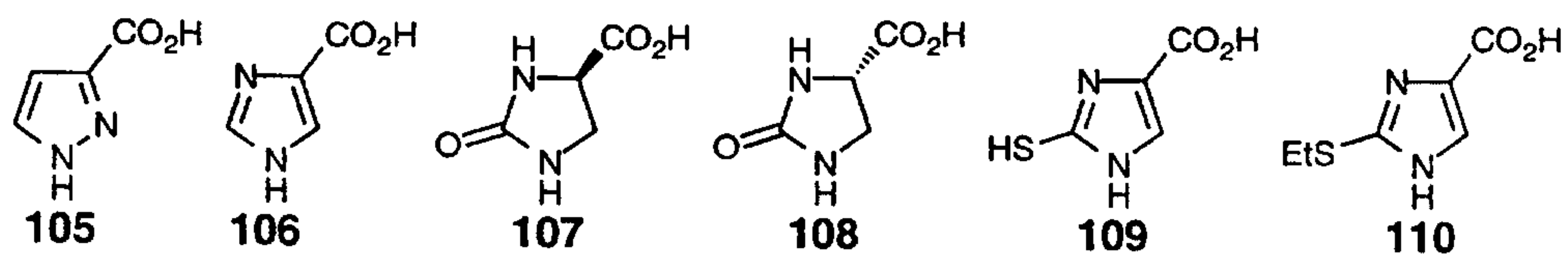
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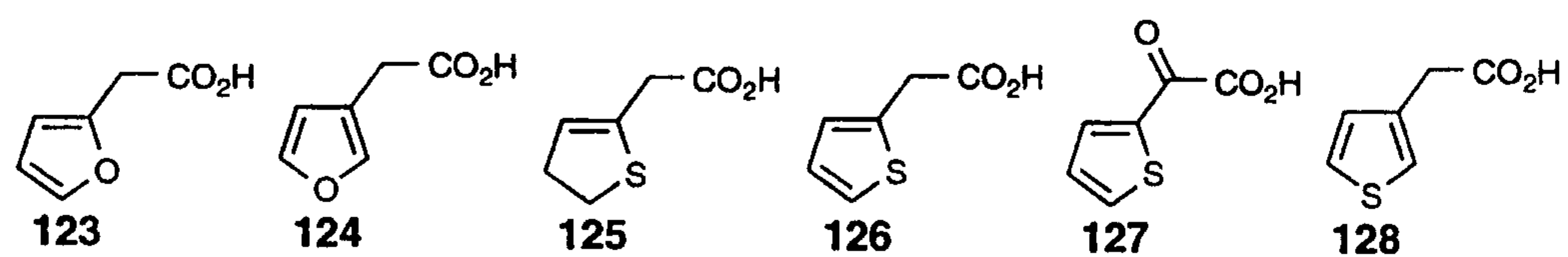
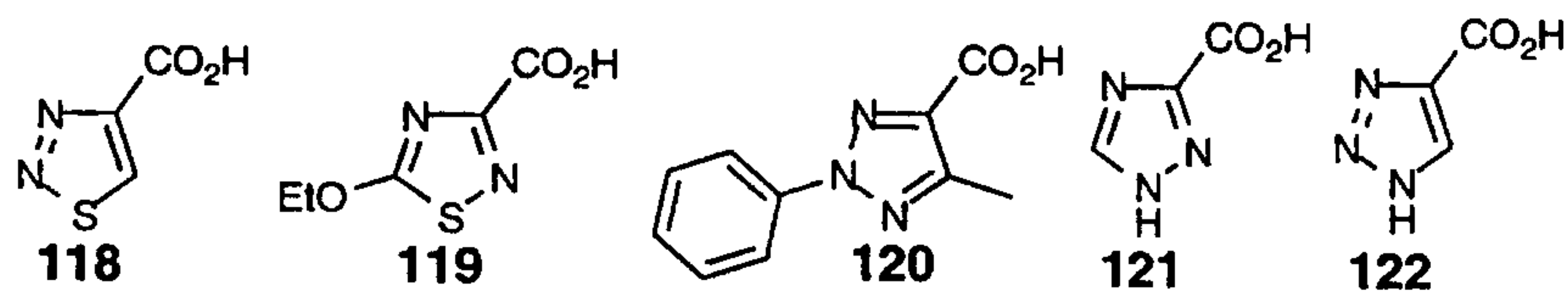
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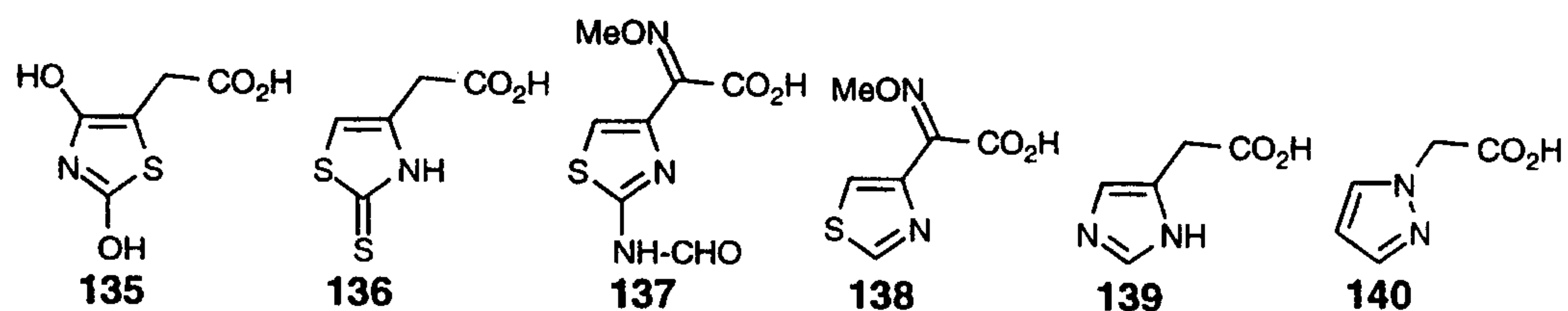
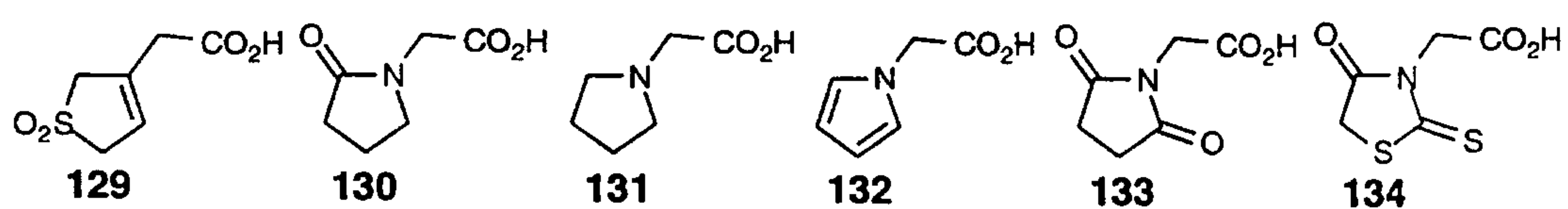
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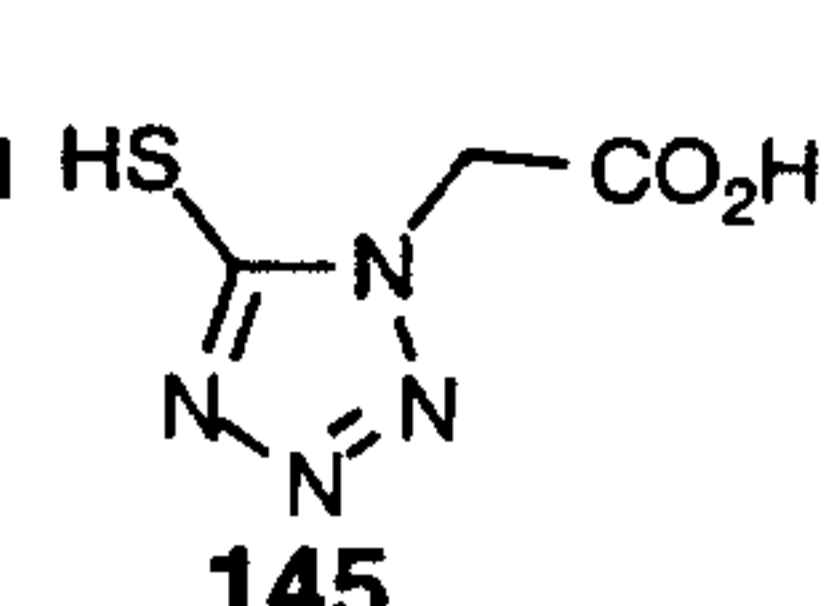
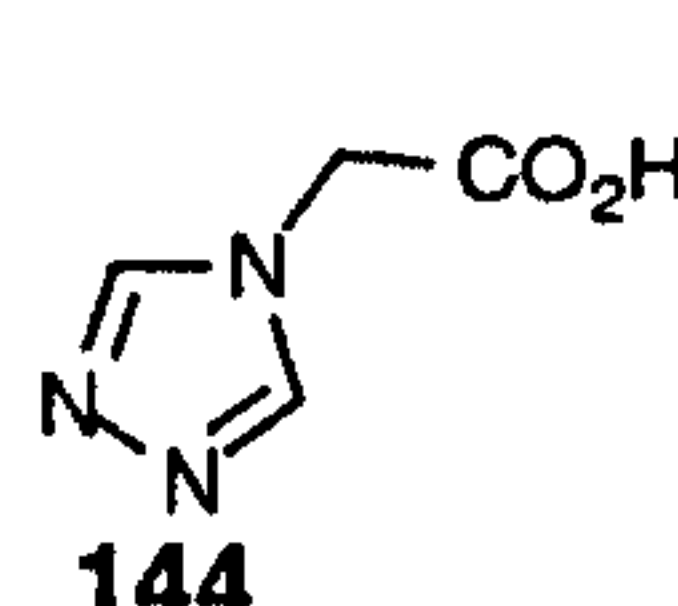
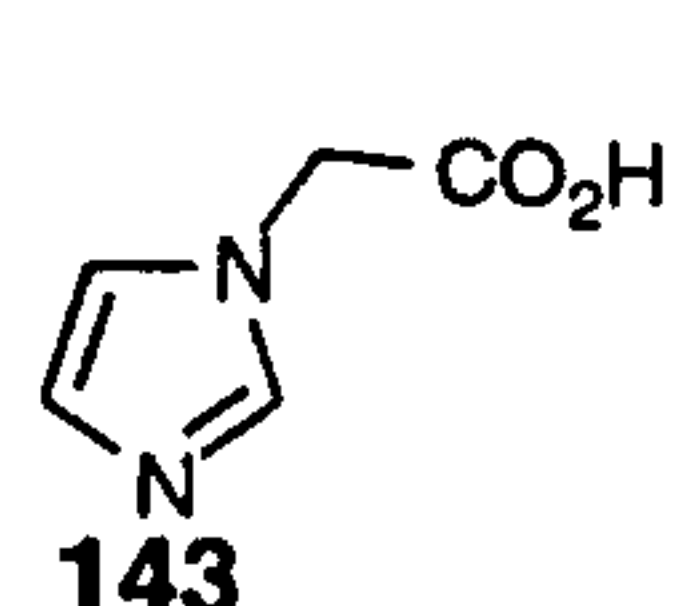
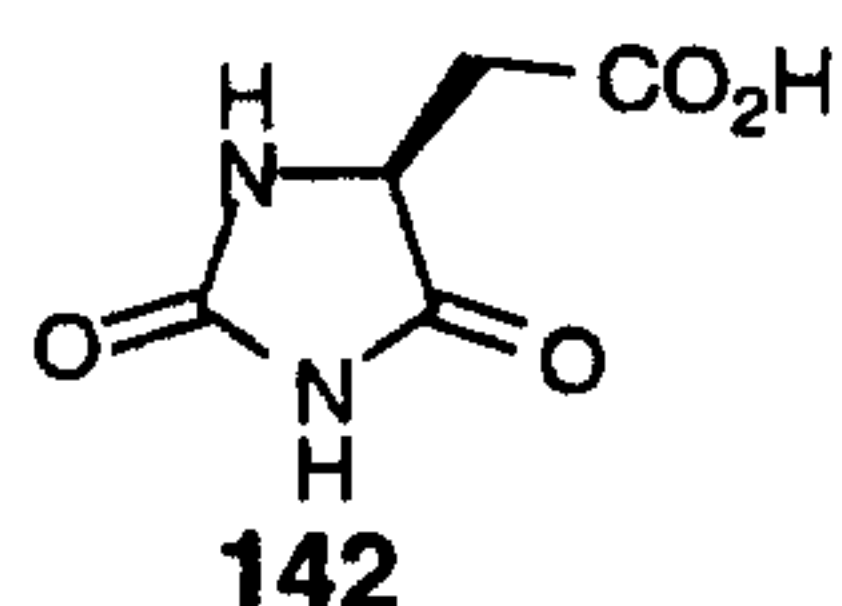
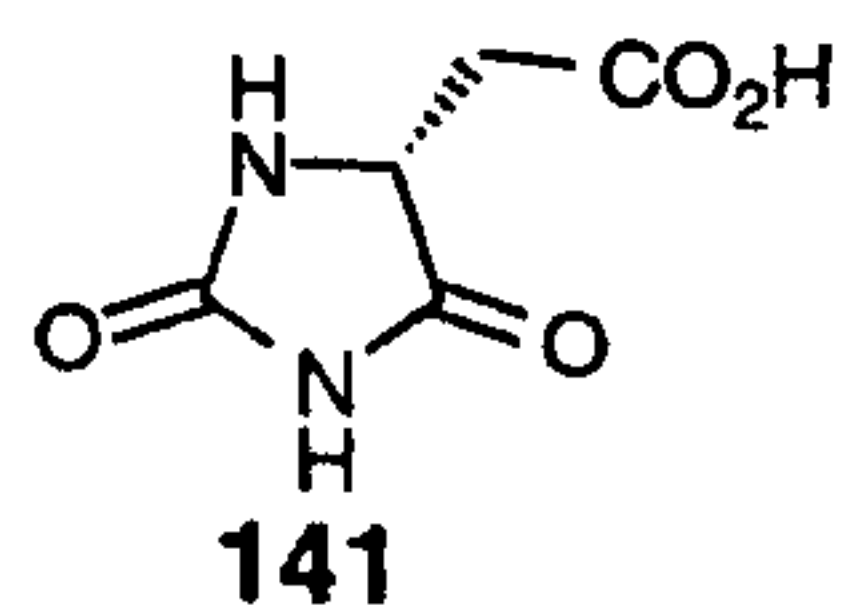


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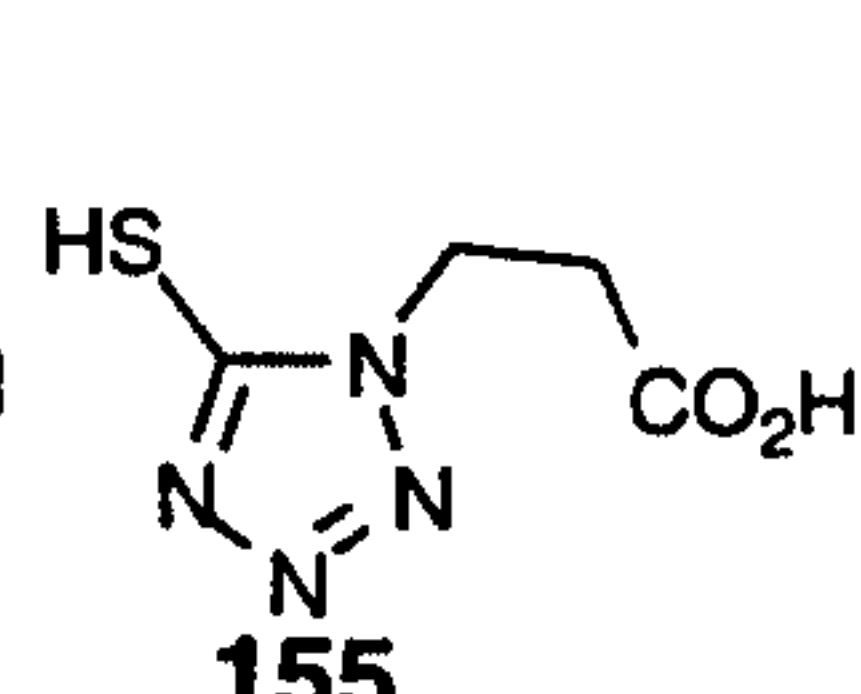
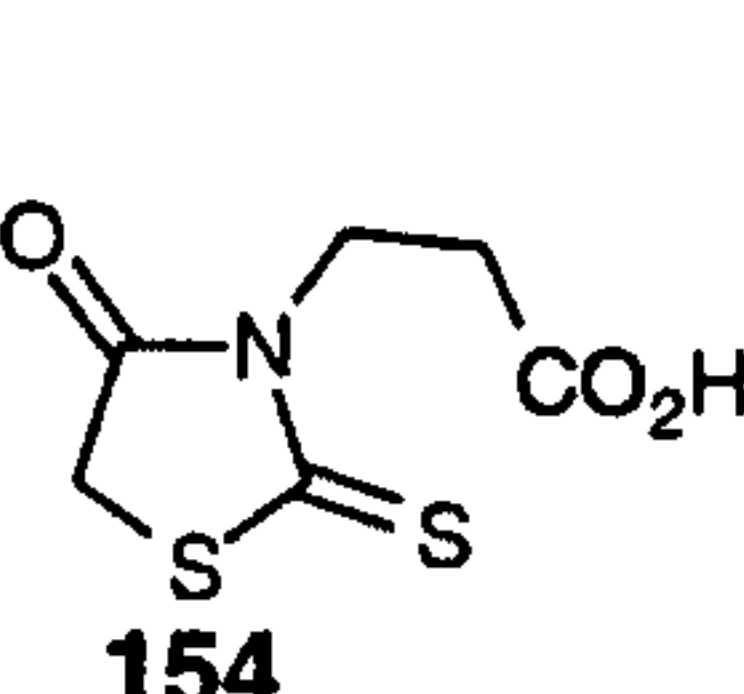
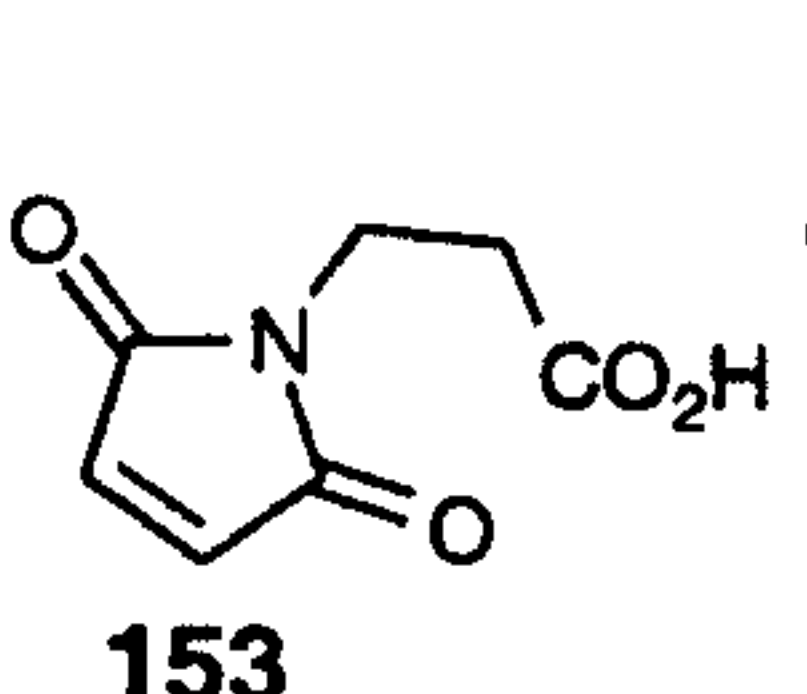
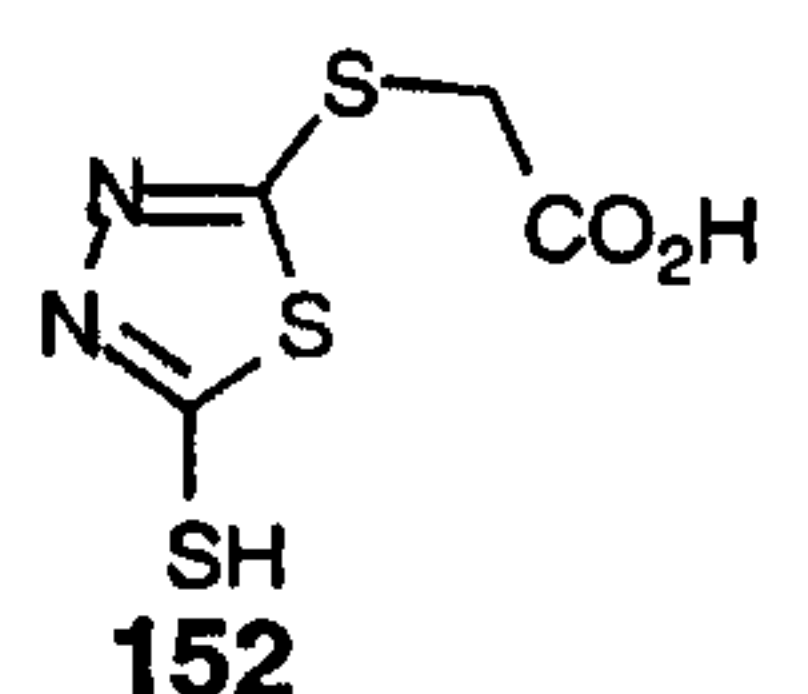
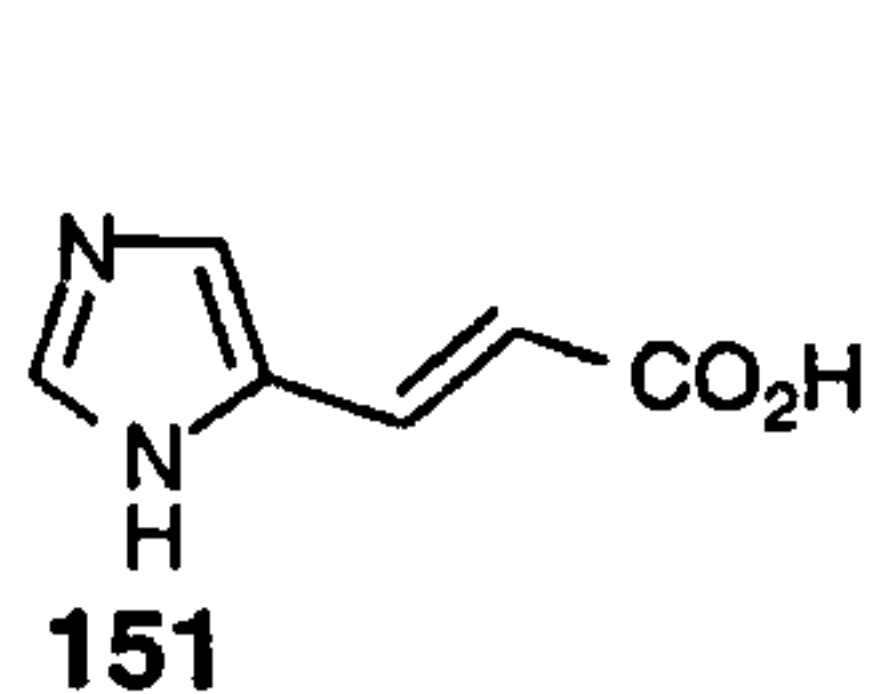
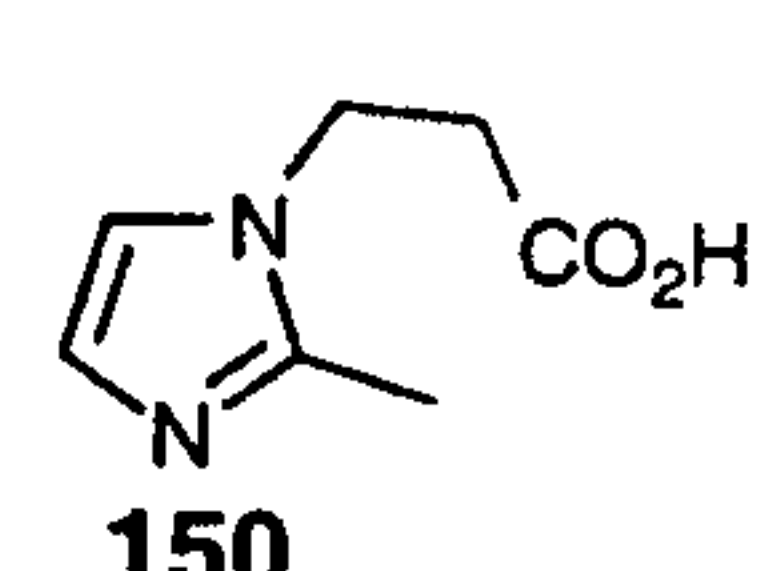
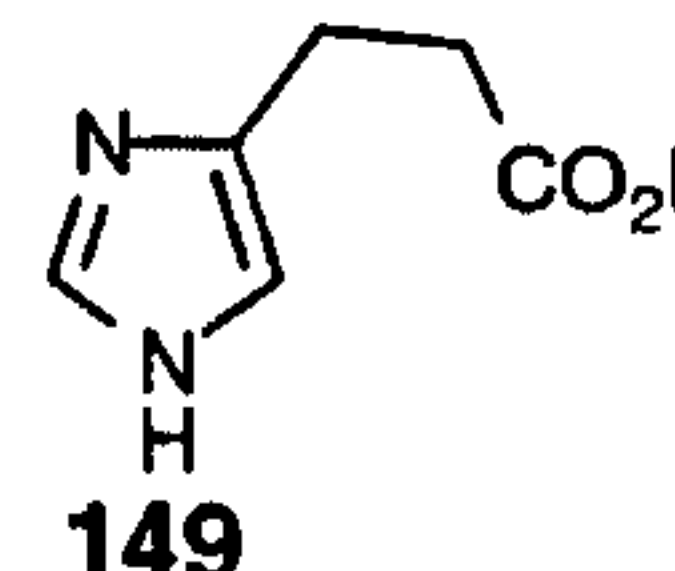
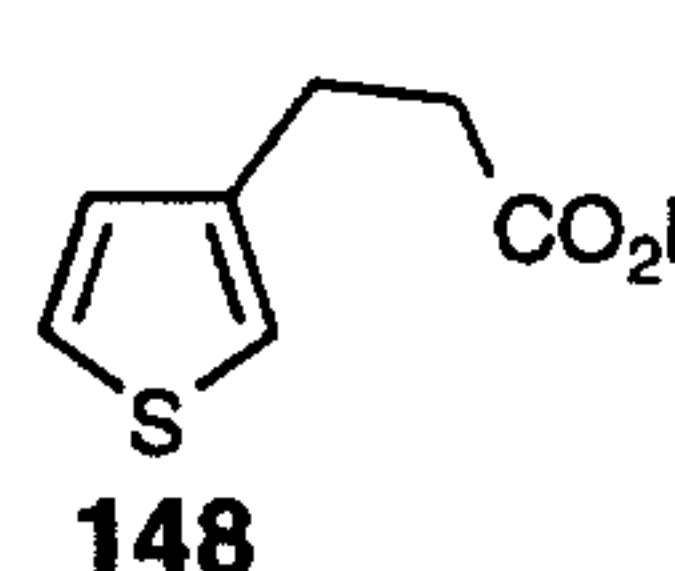
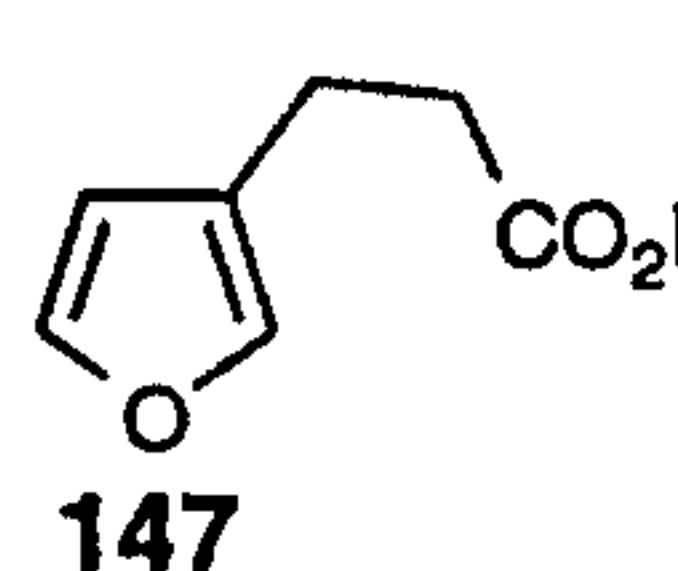
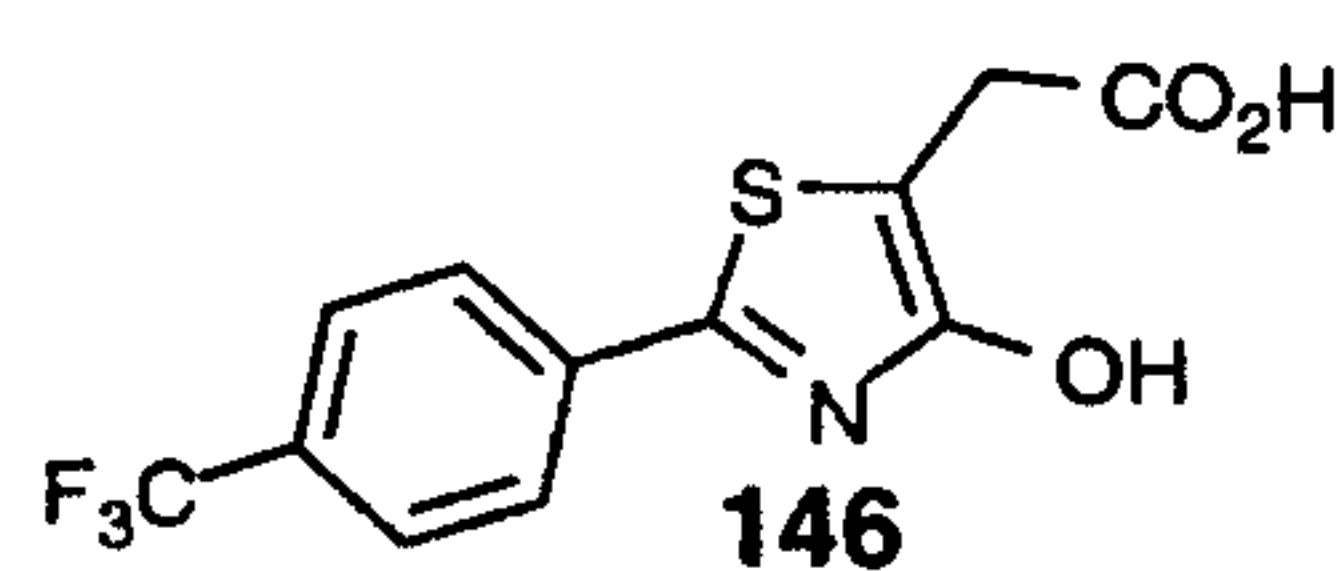


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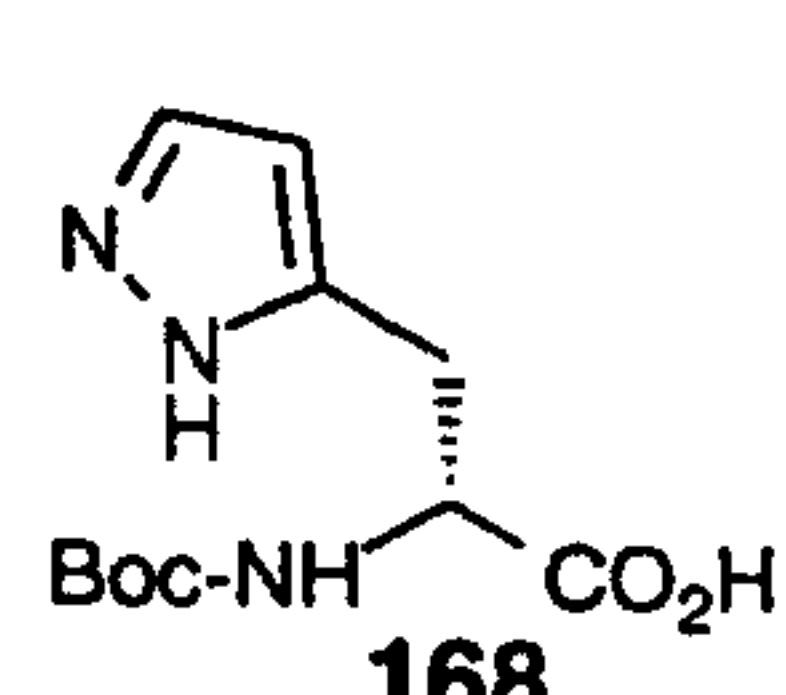
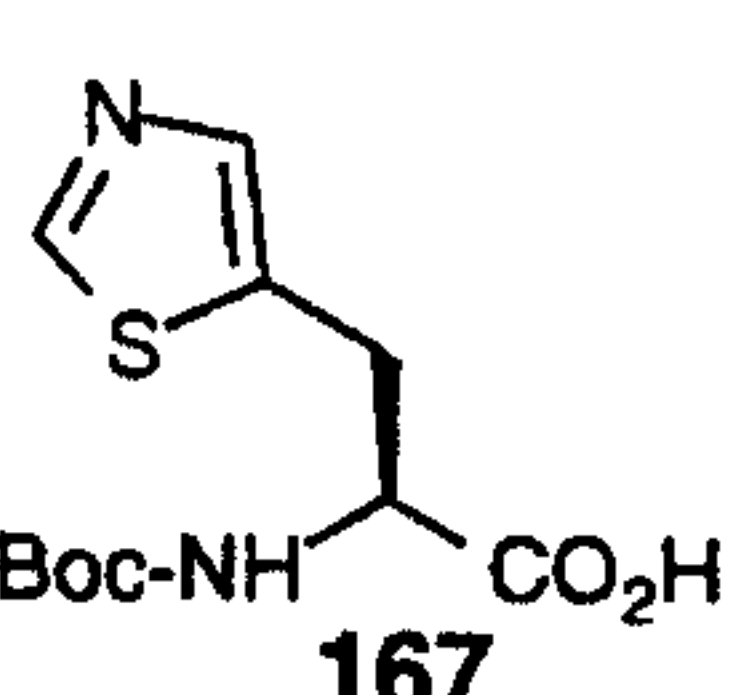
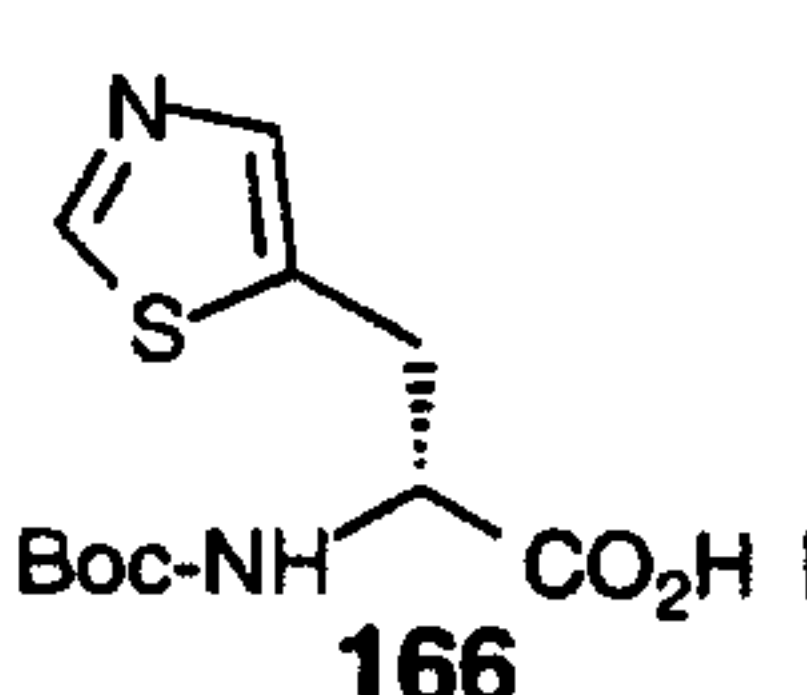
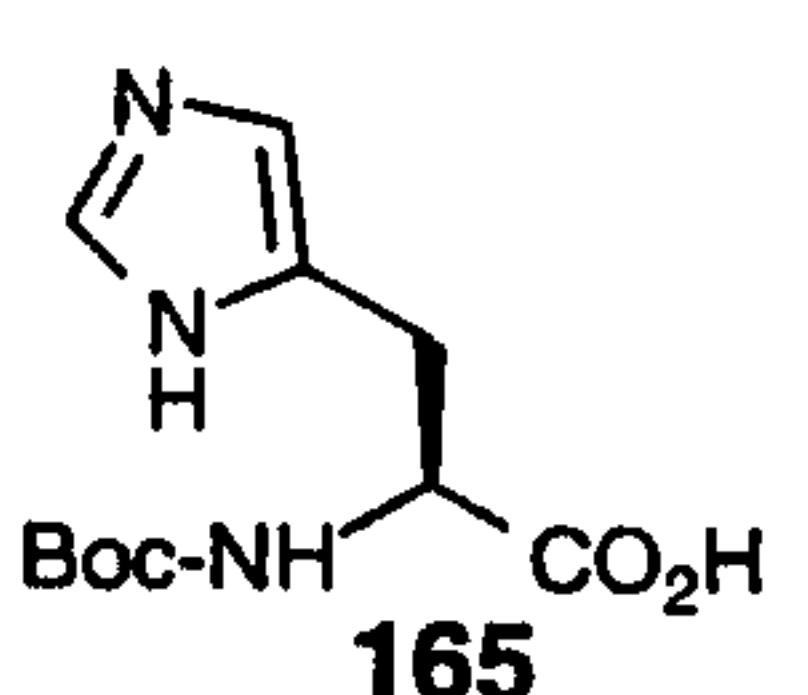
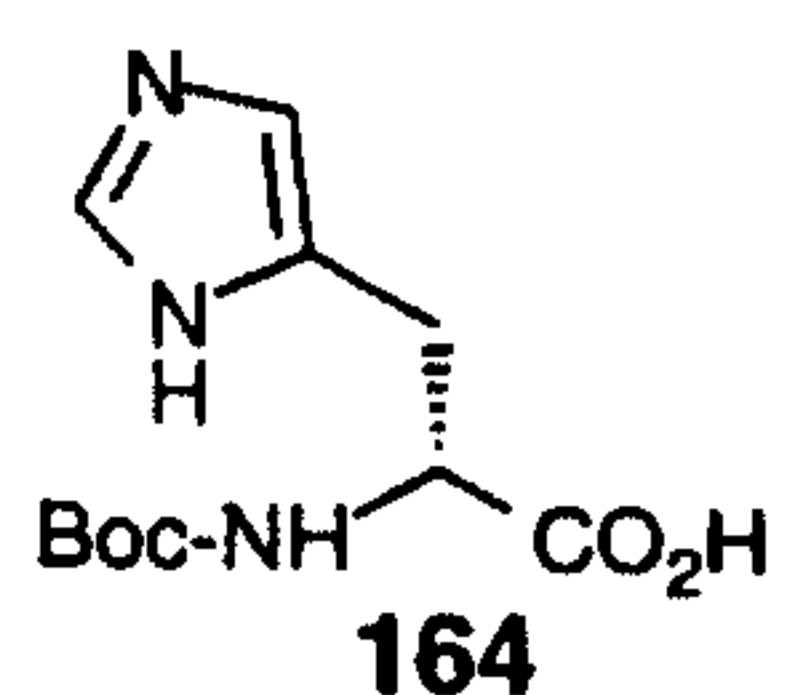
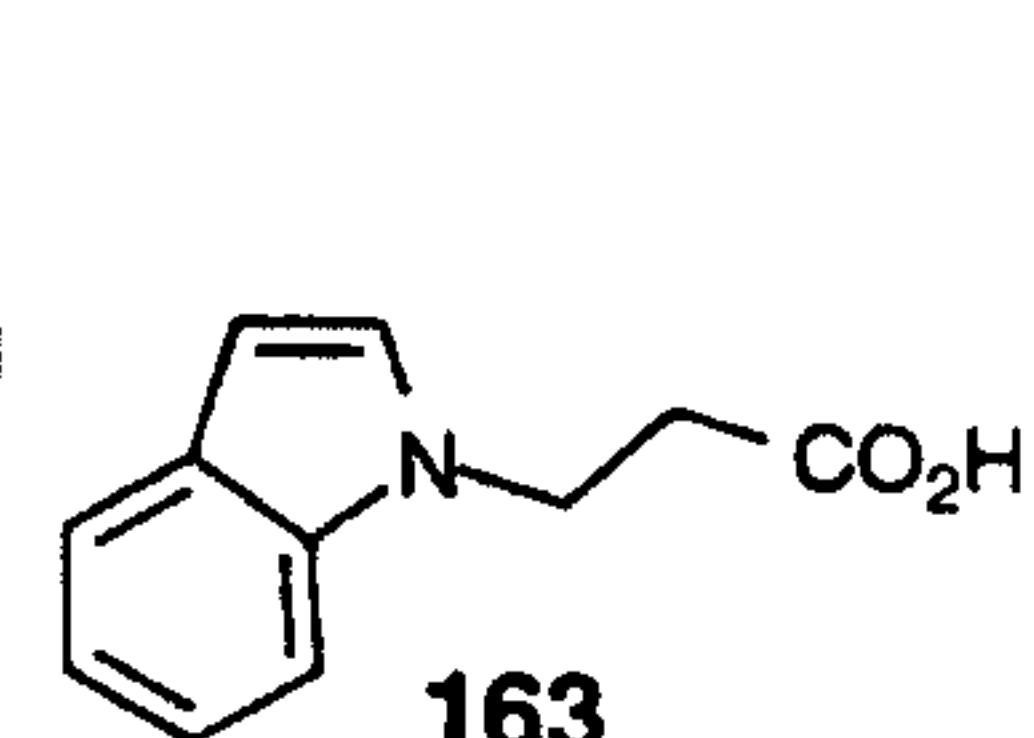
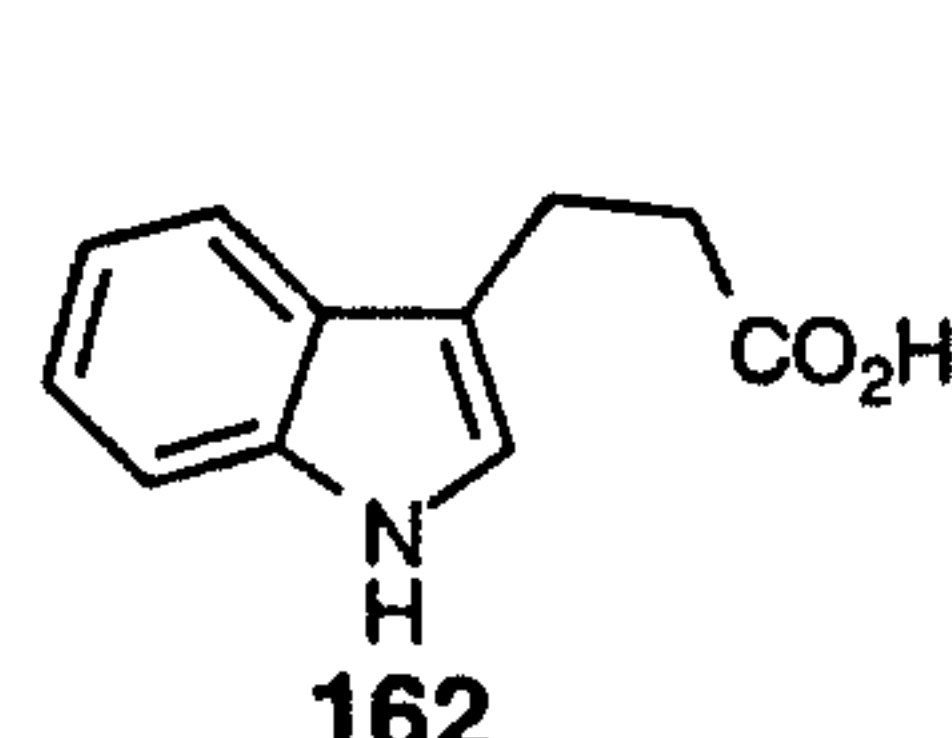
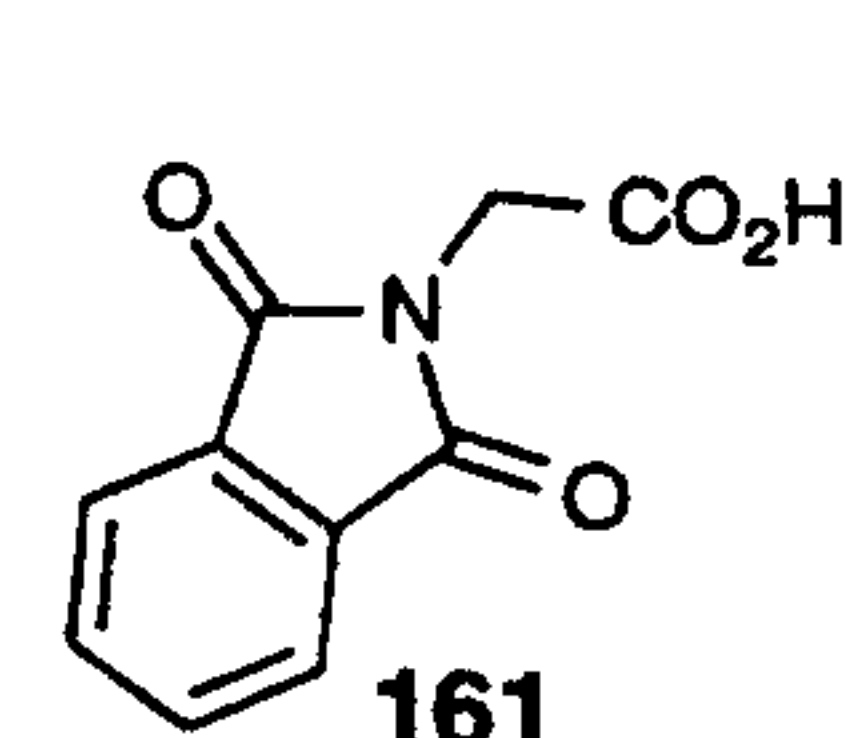
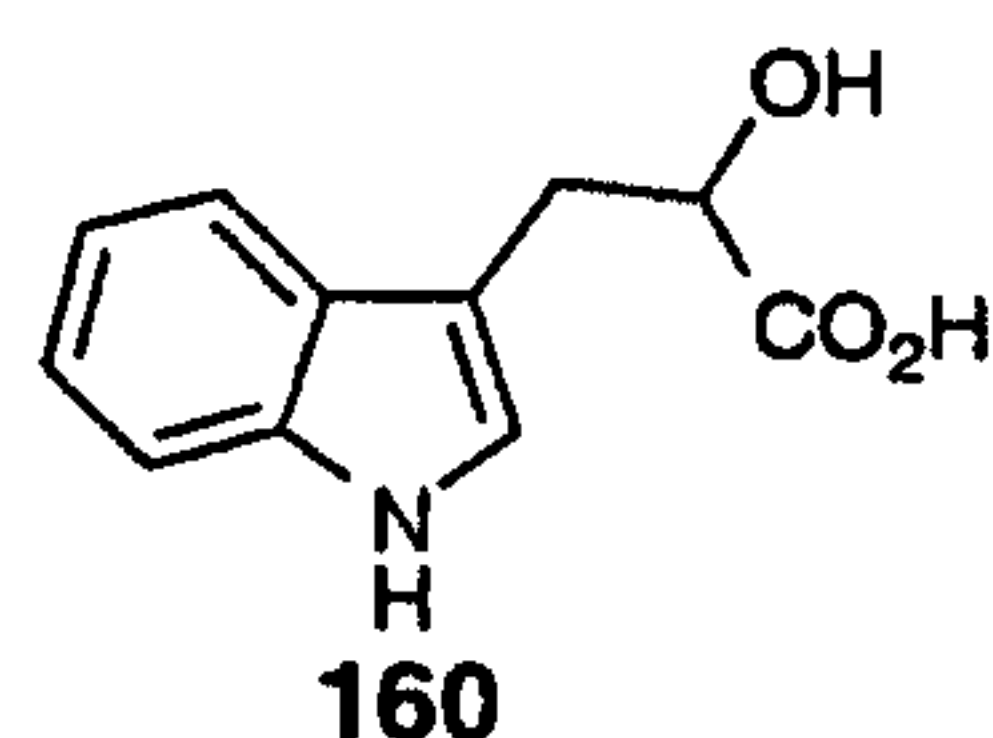
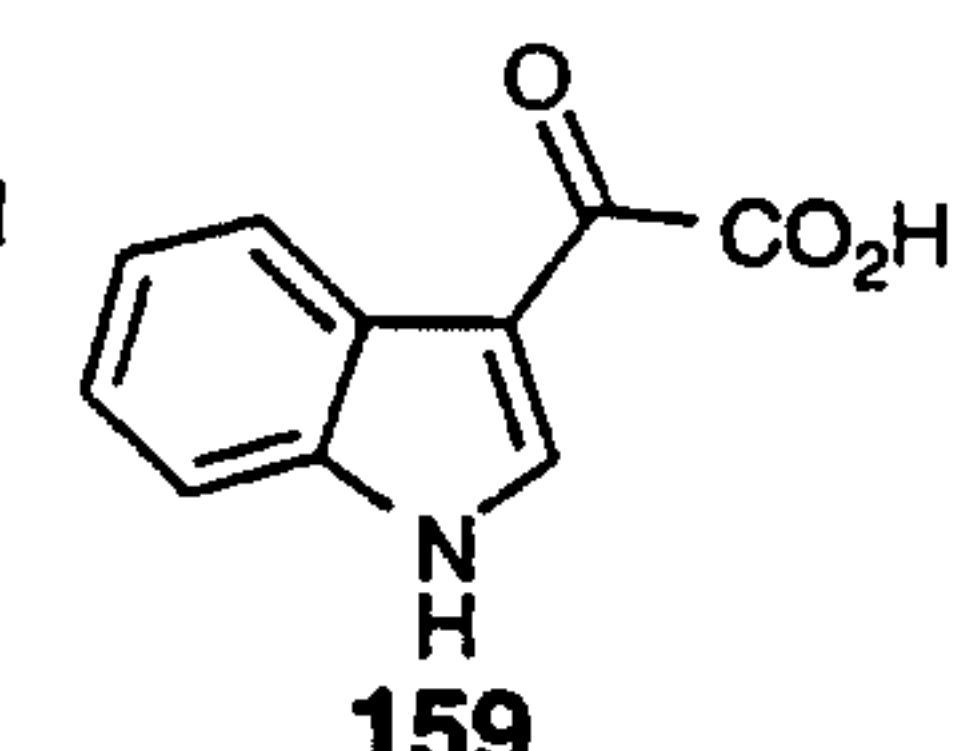
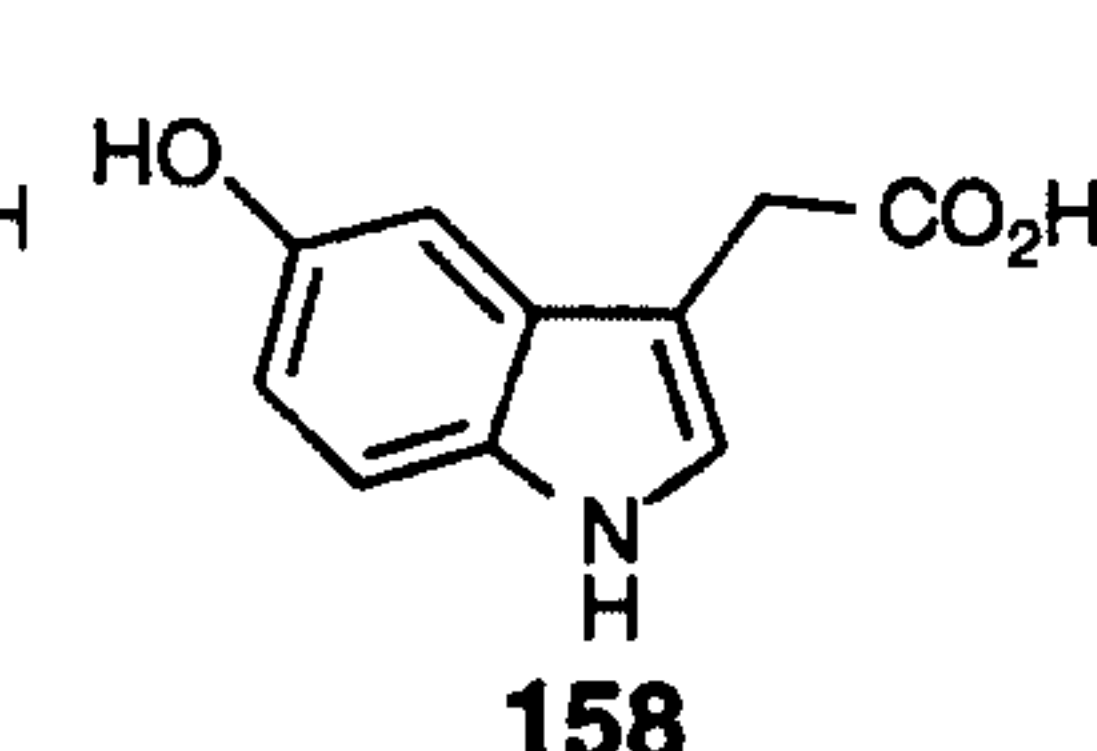
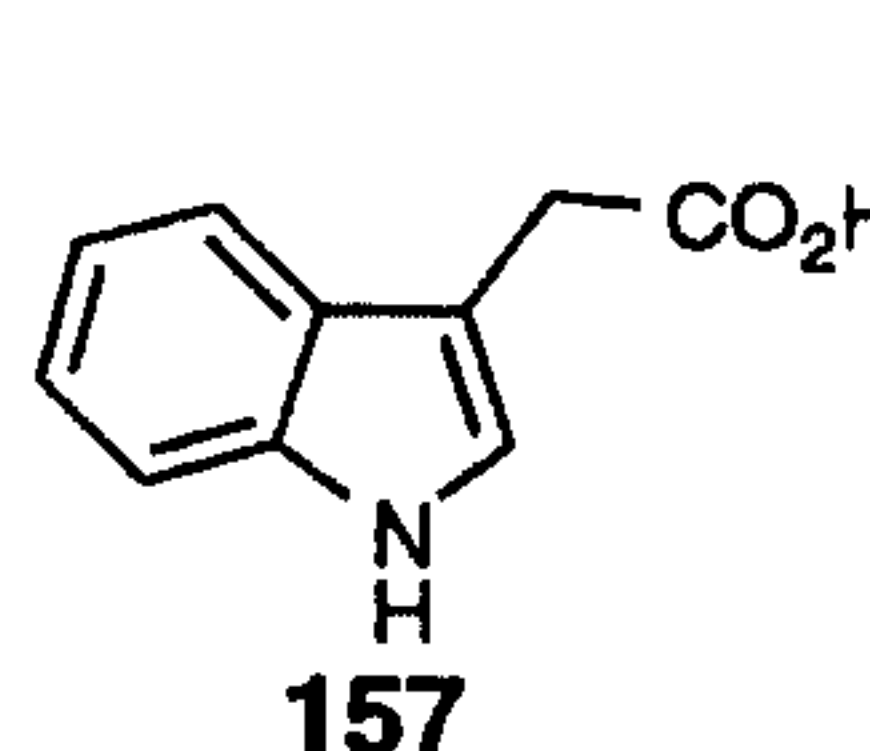
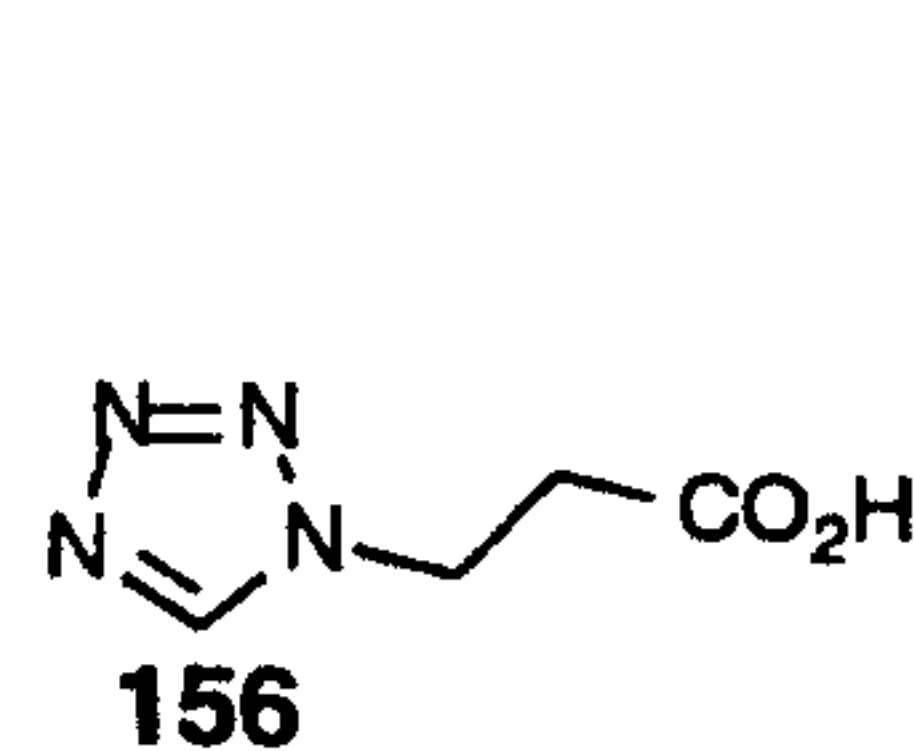




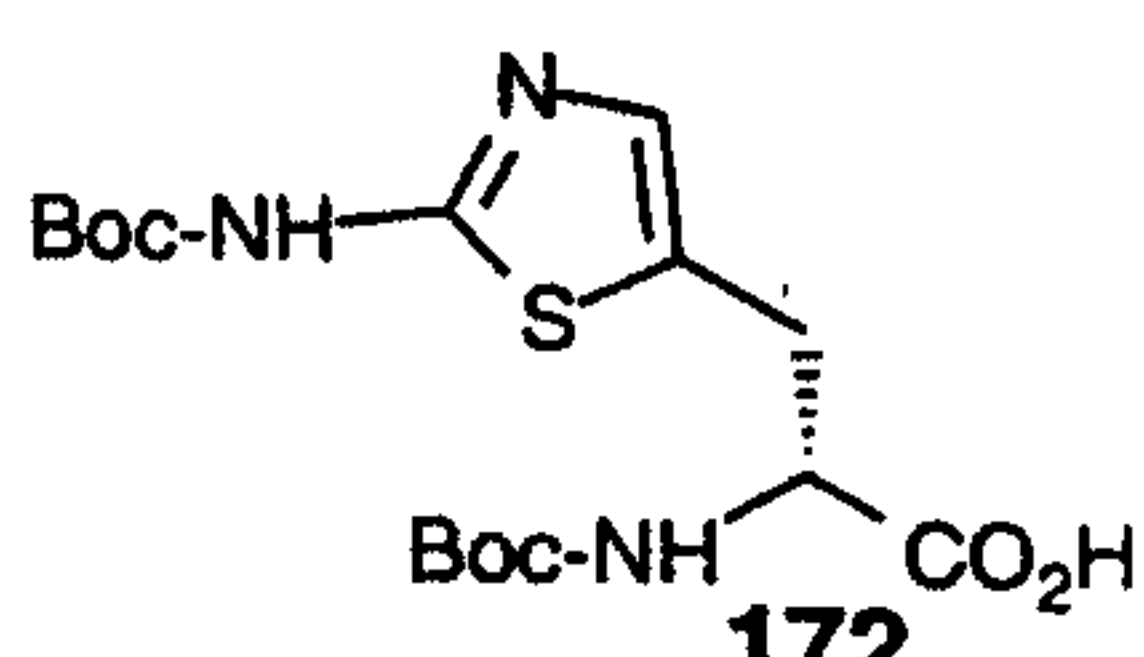
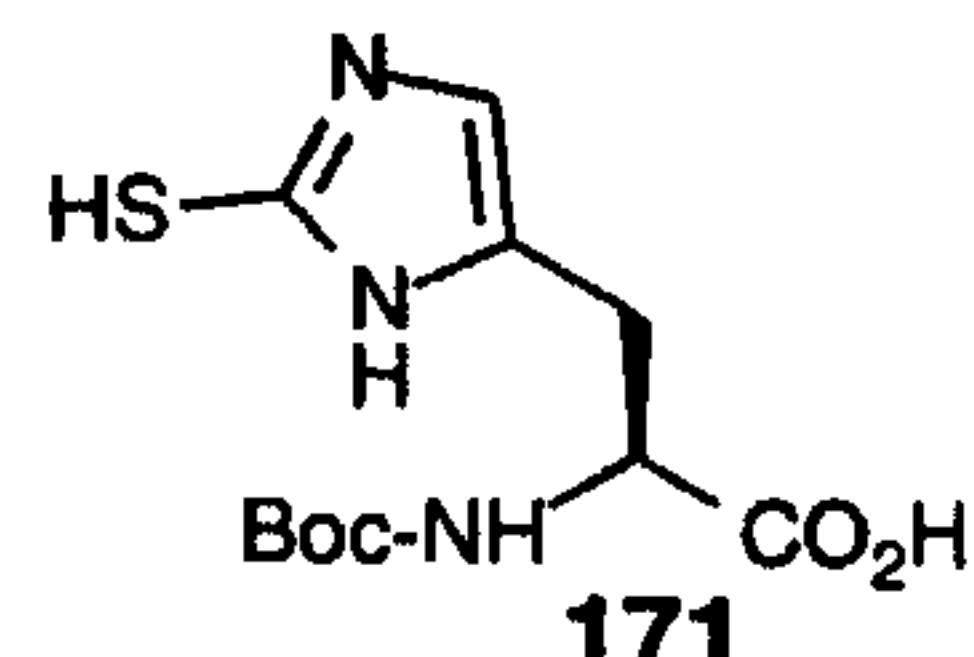
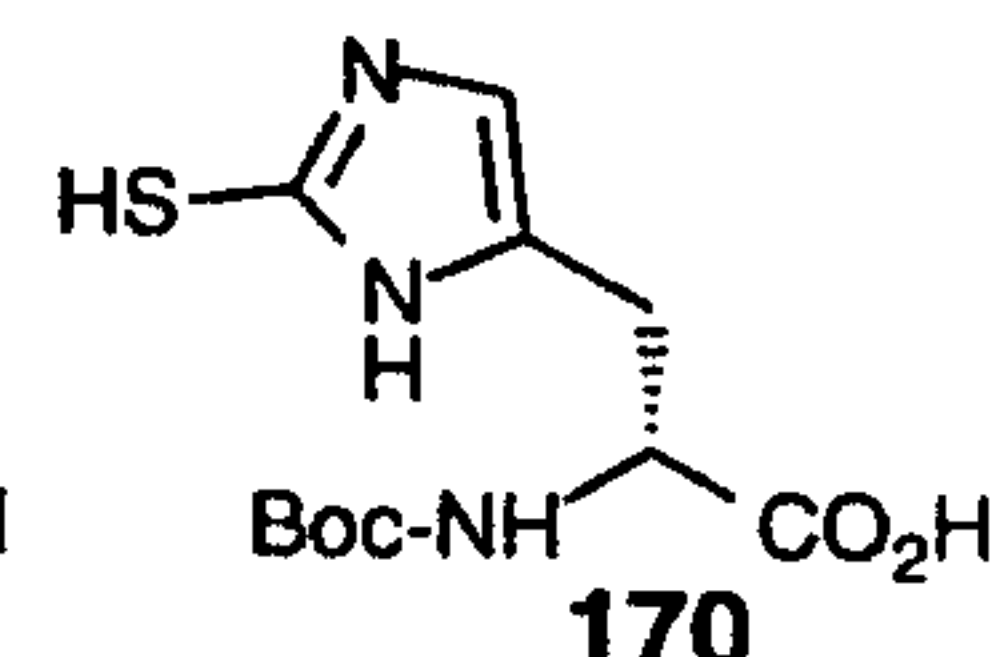
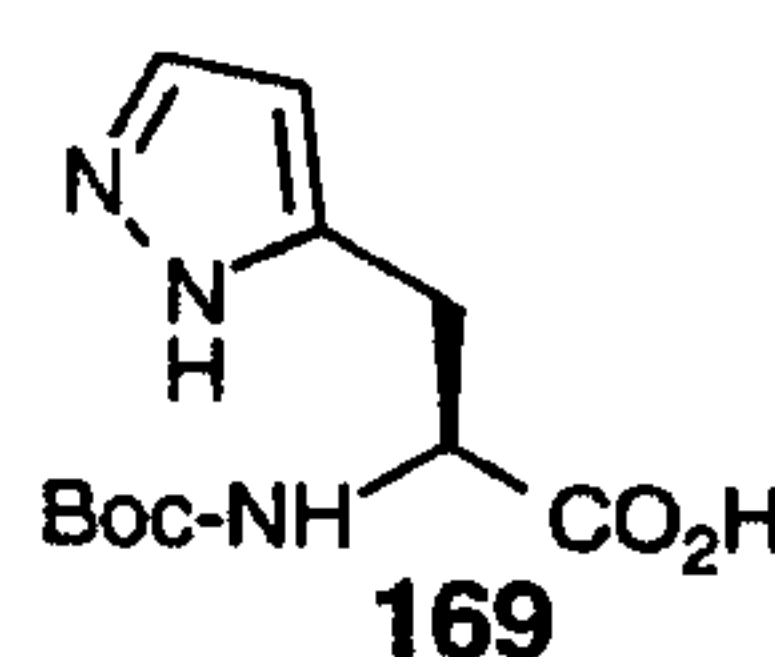
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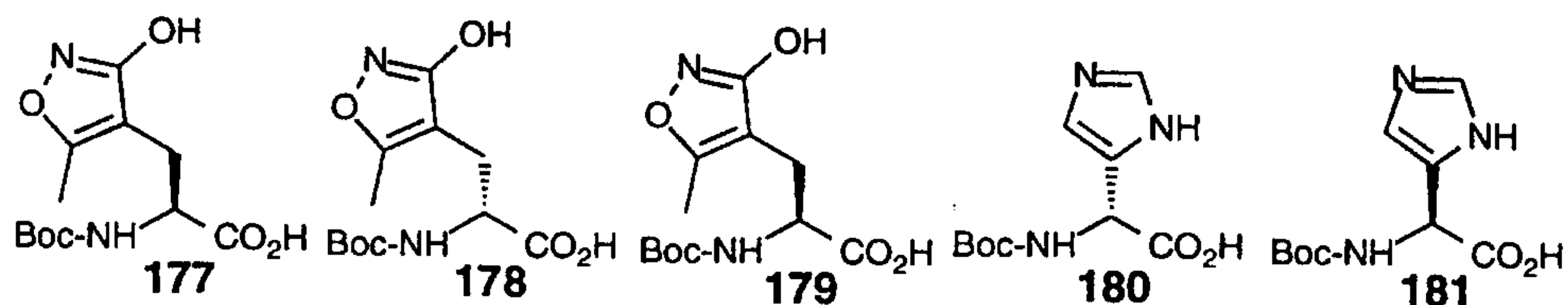
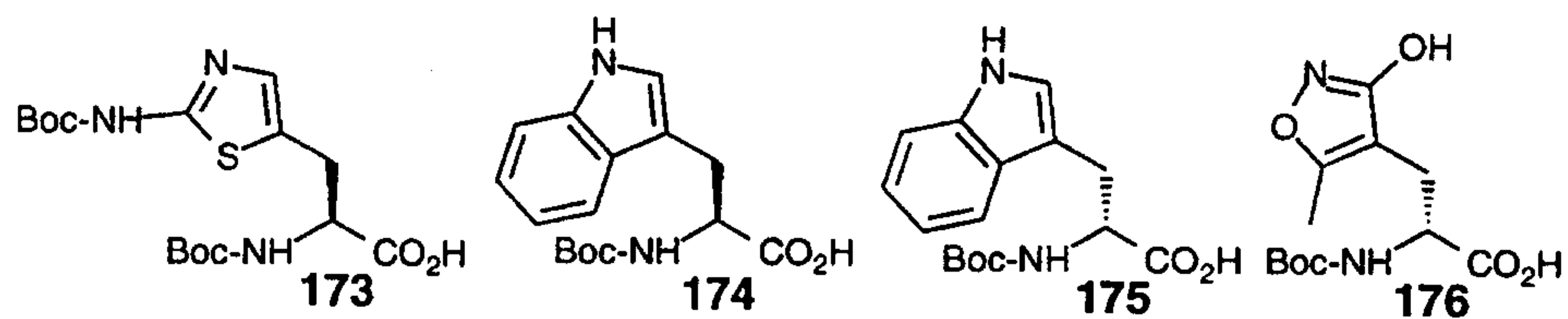


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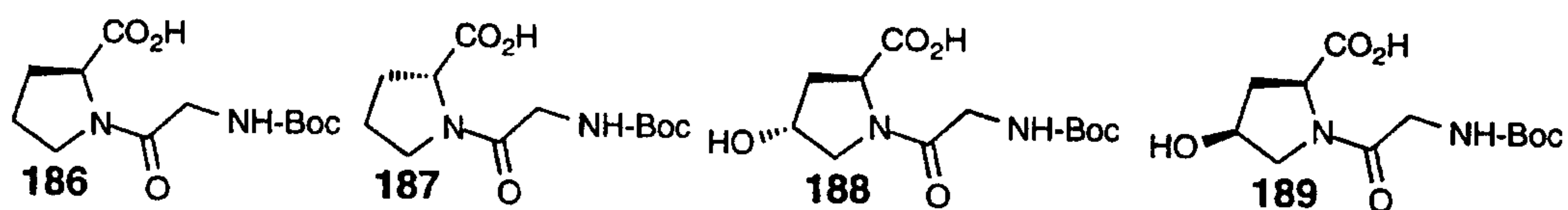
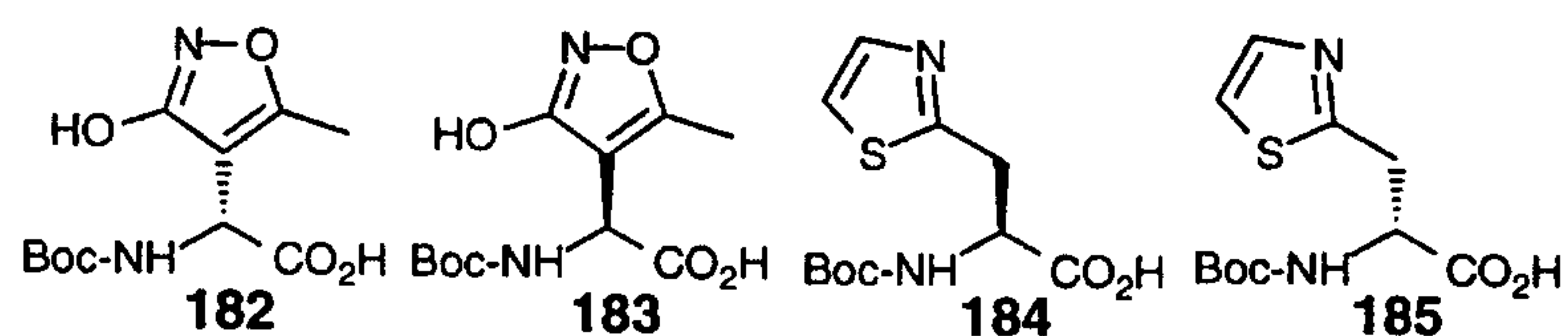


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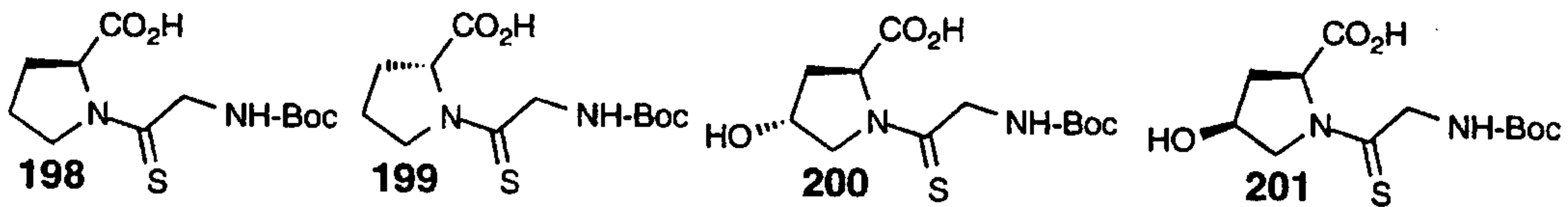
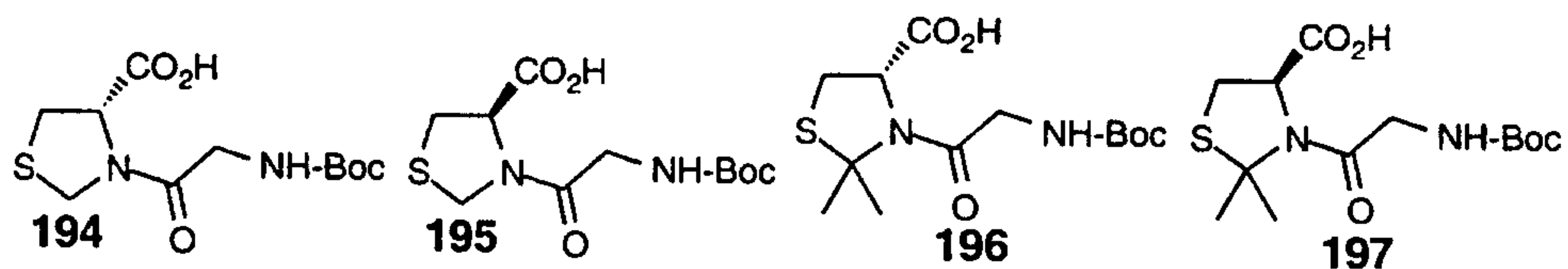
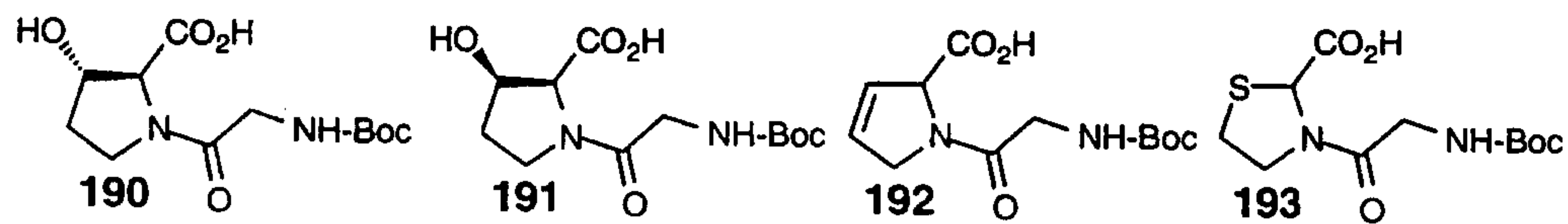




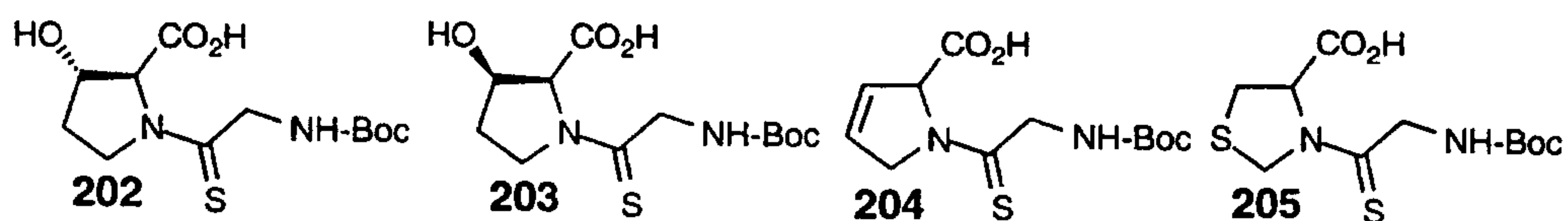
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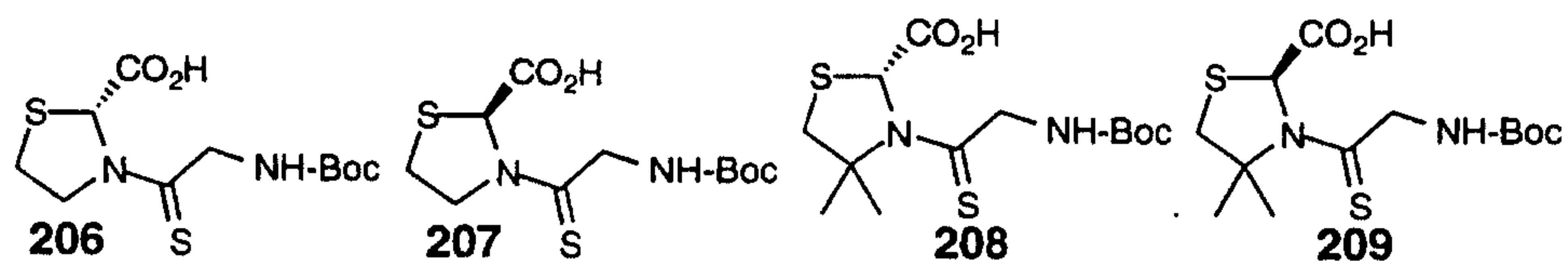


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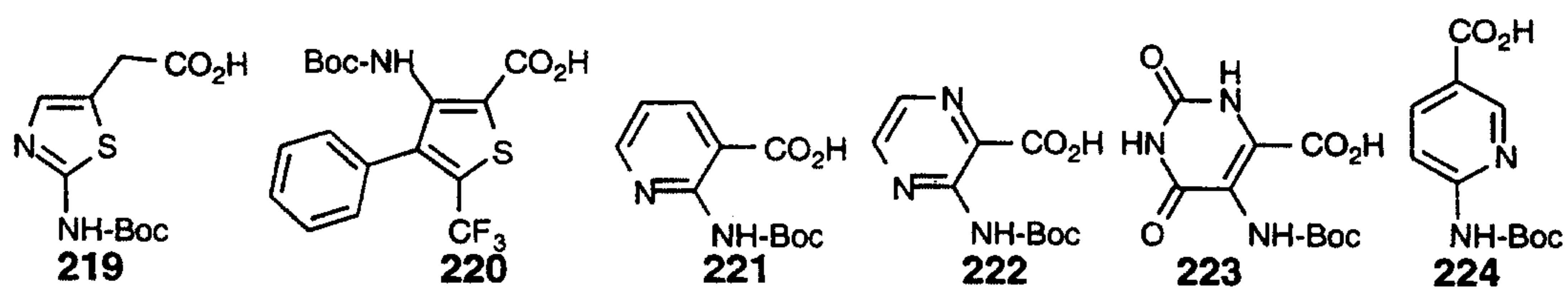
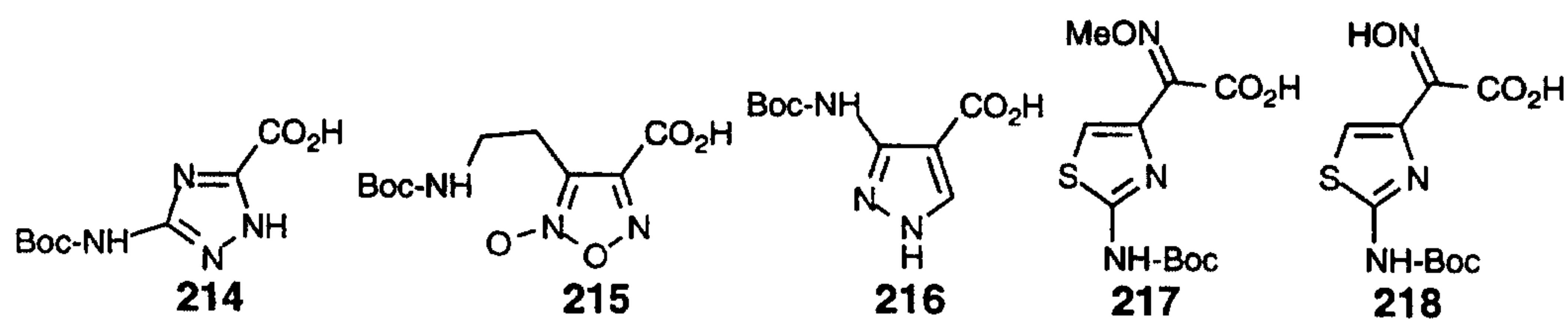
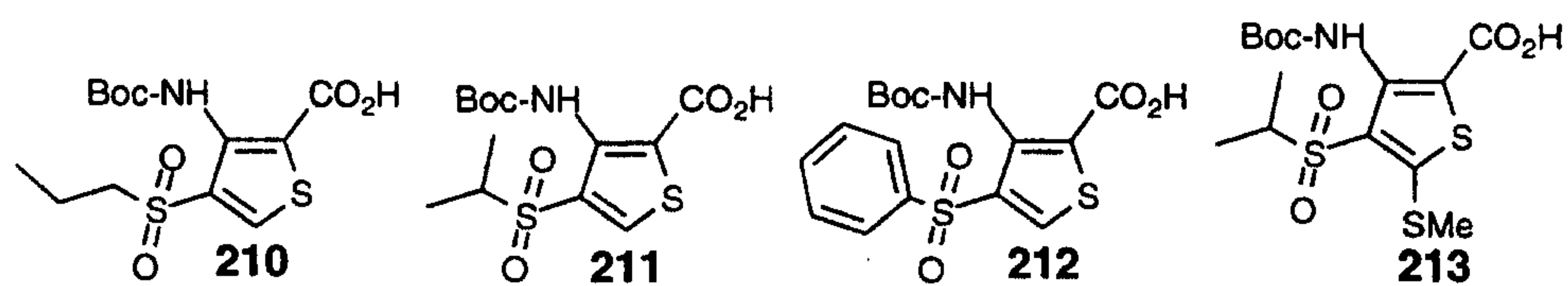


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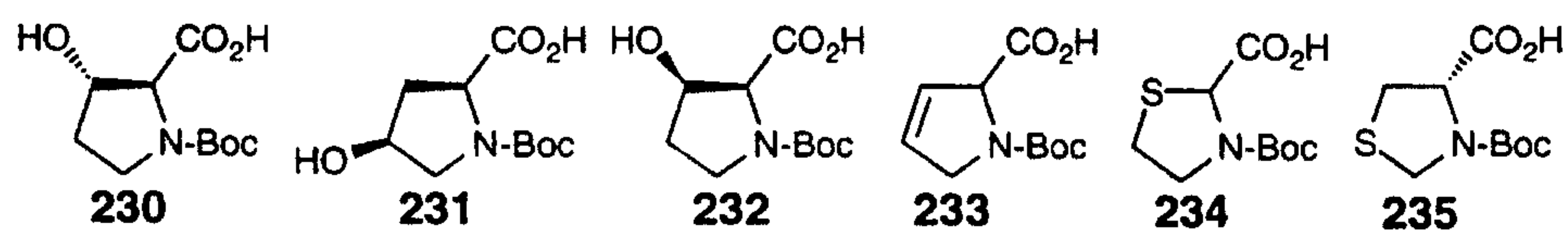
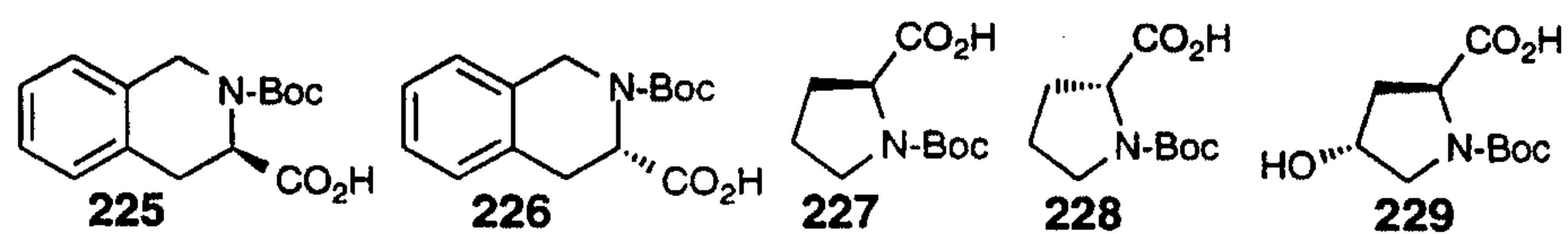




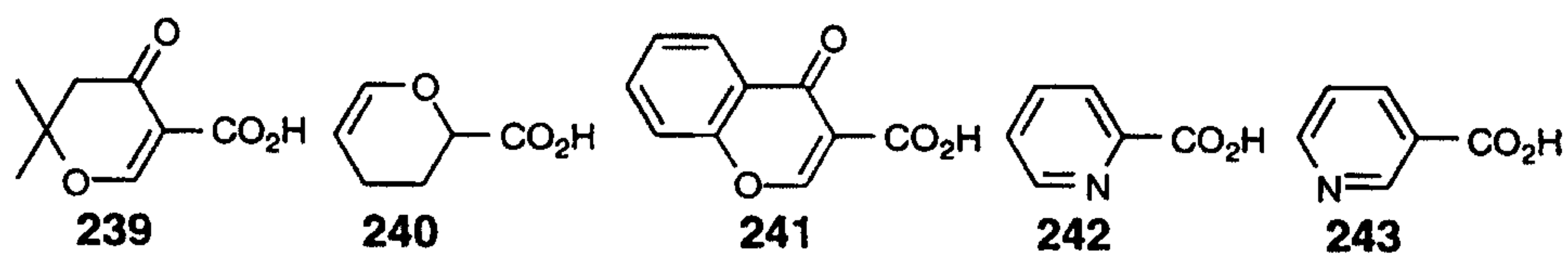
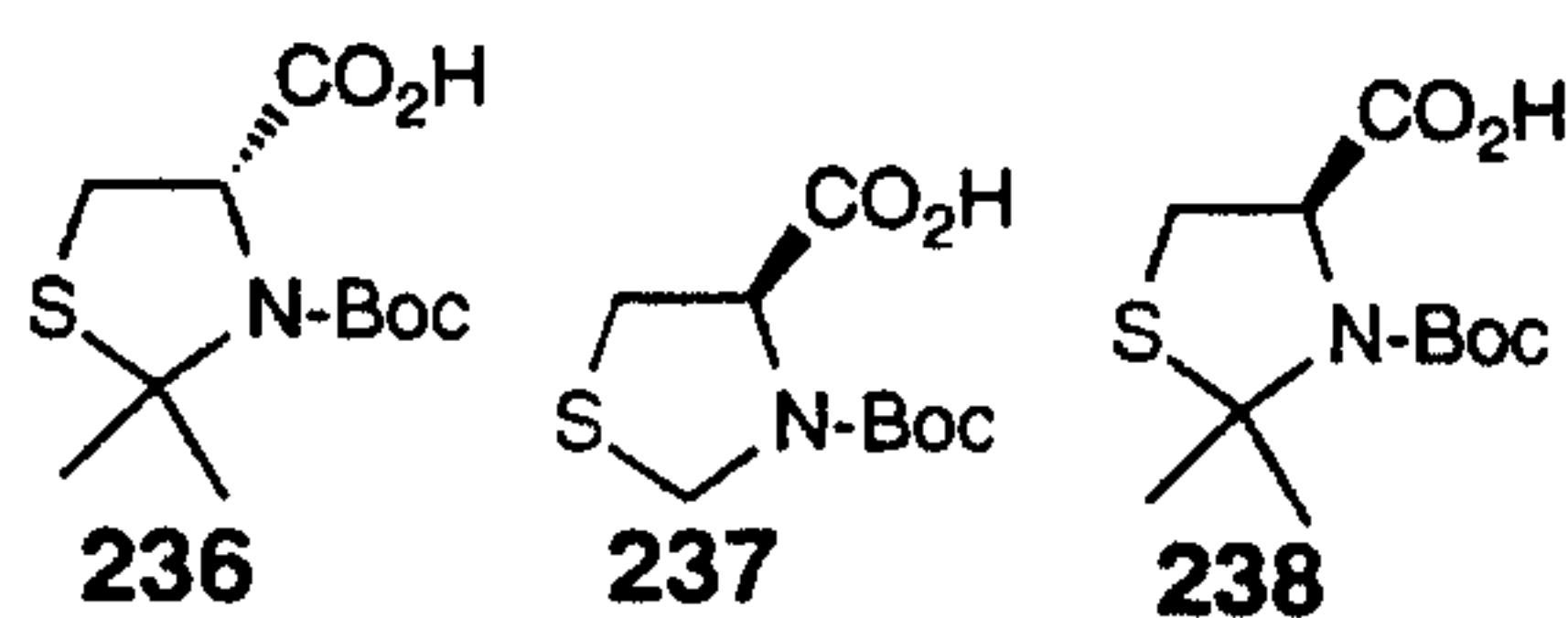
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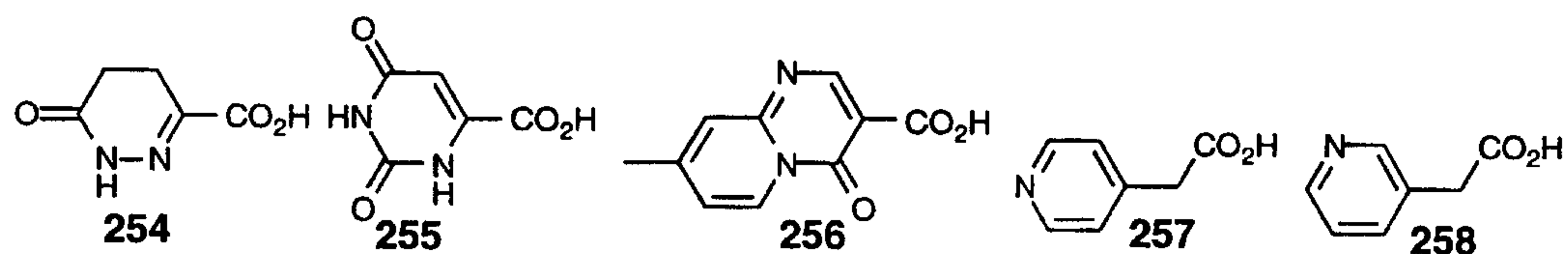
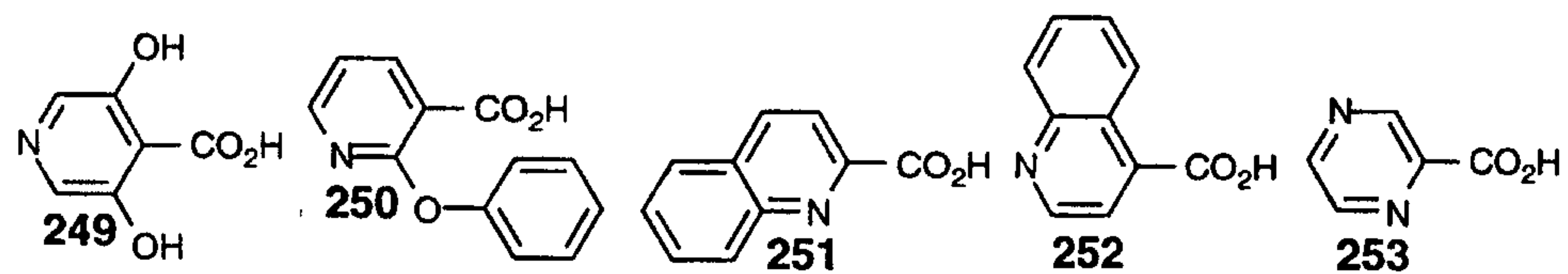
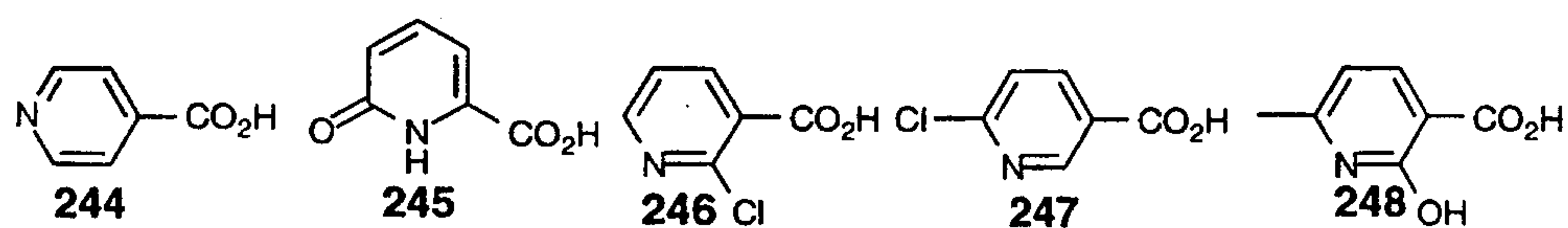
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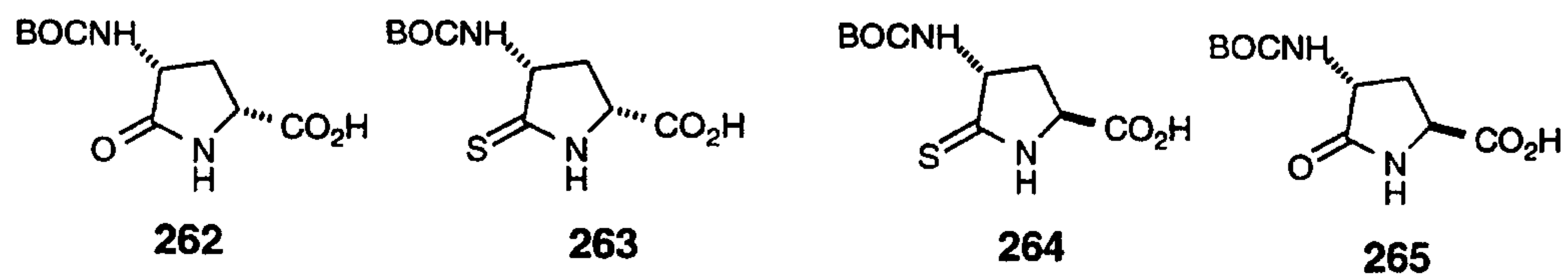
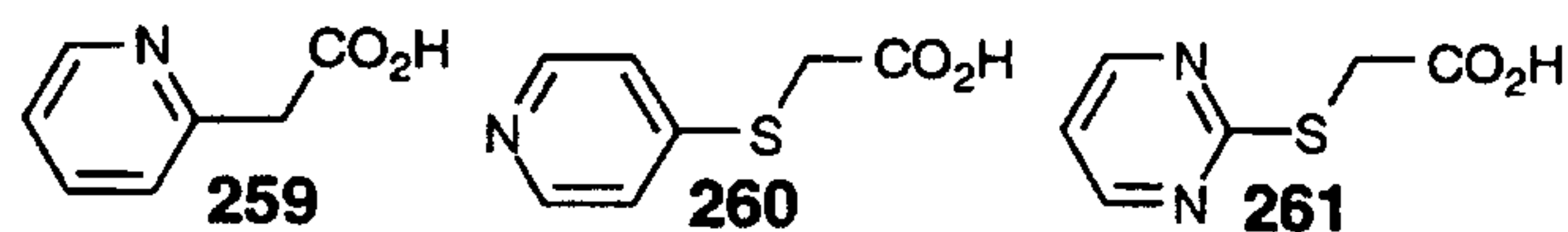
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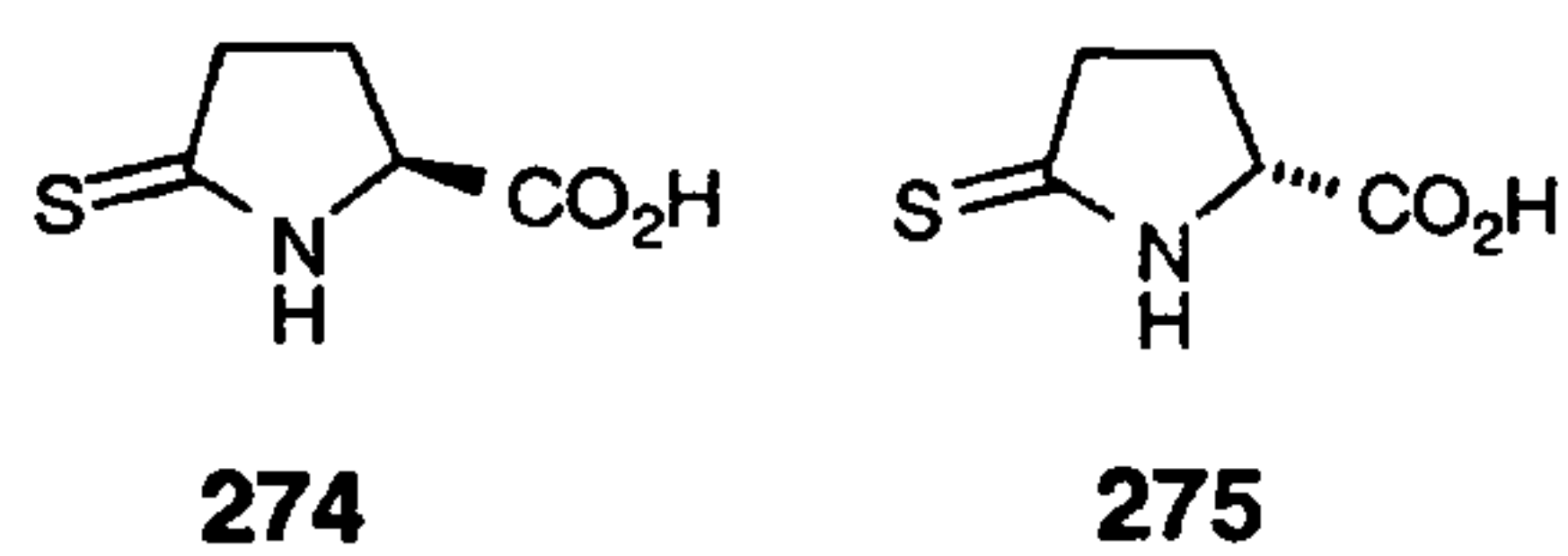
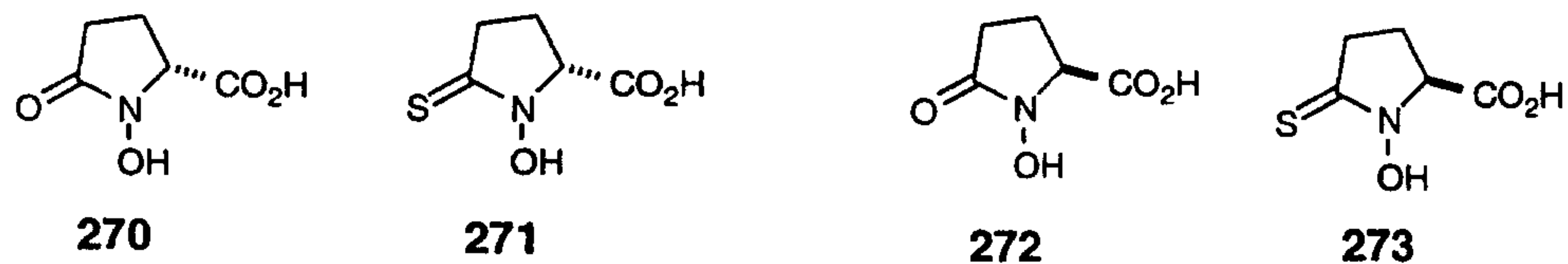
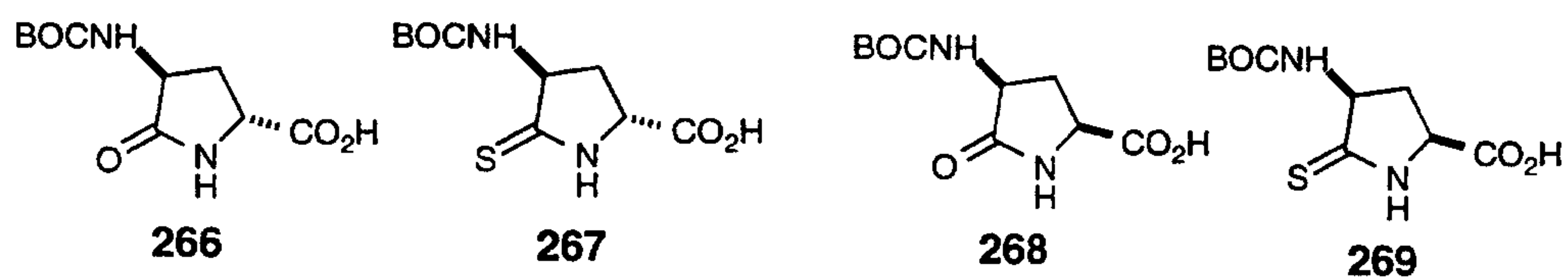
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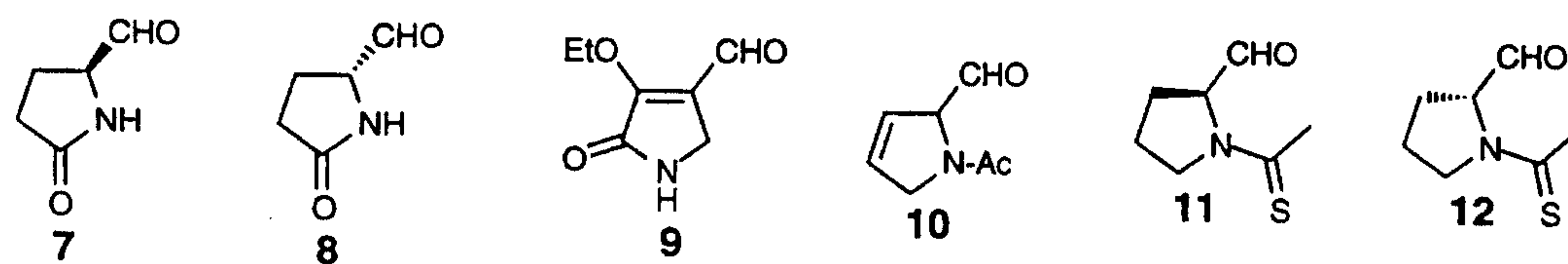
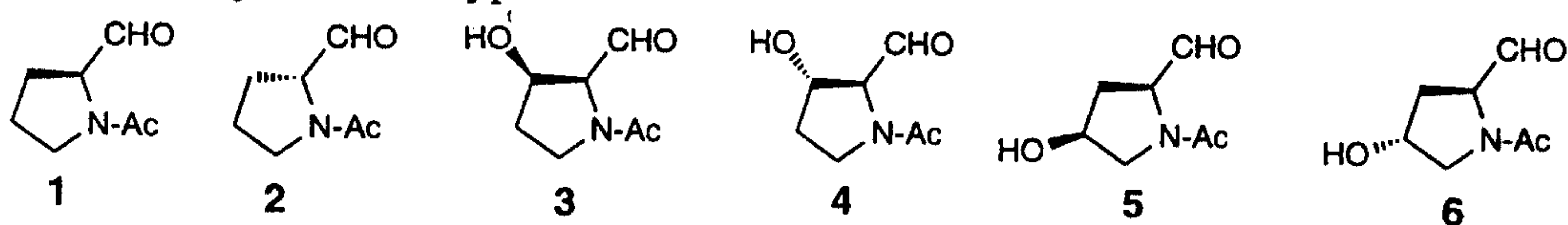


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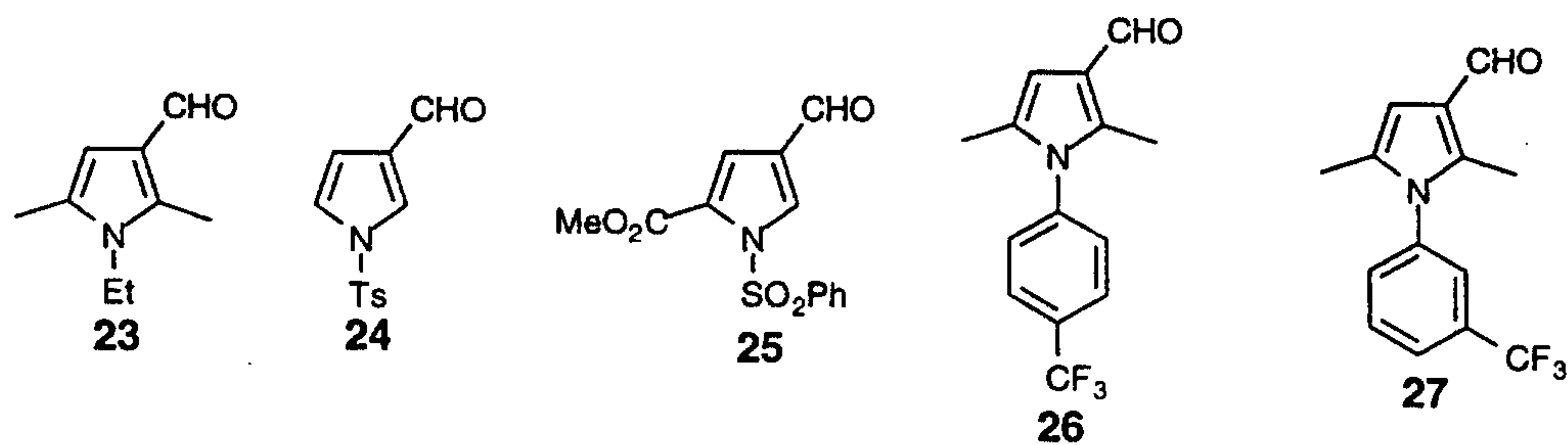
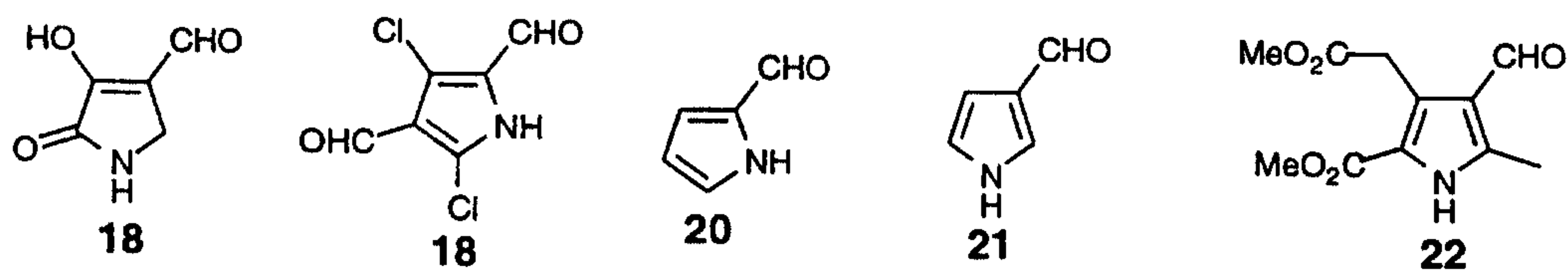
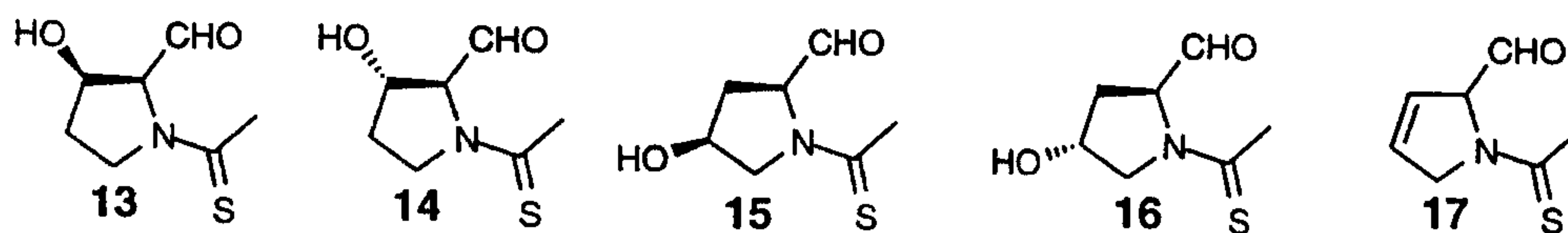
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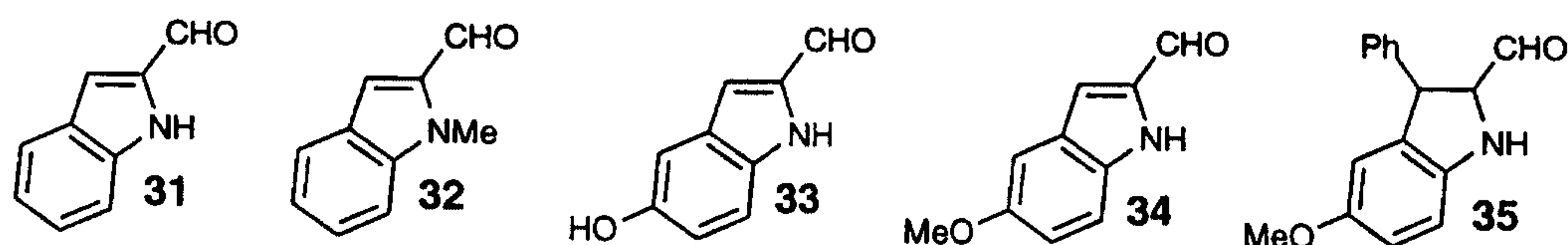
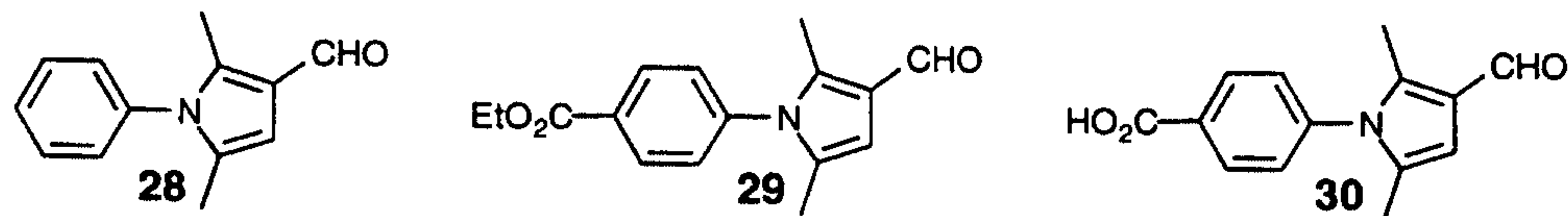
Table 14. Aldehydes of the type A-CHO



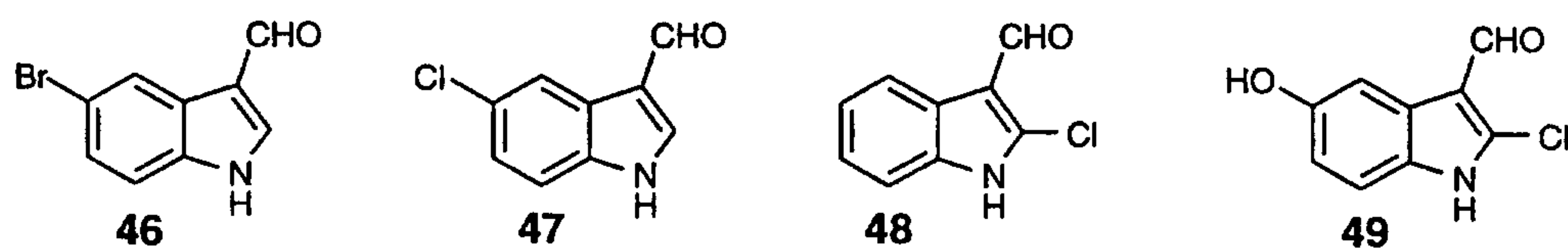
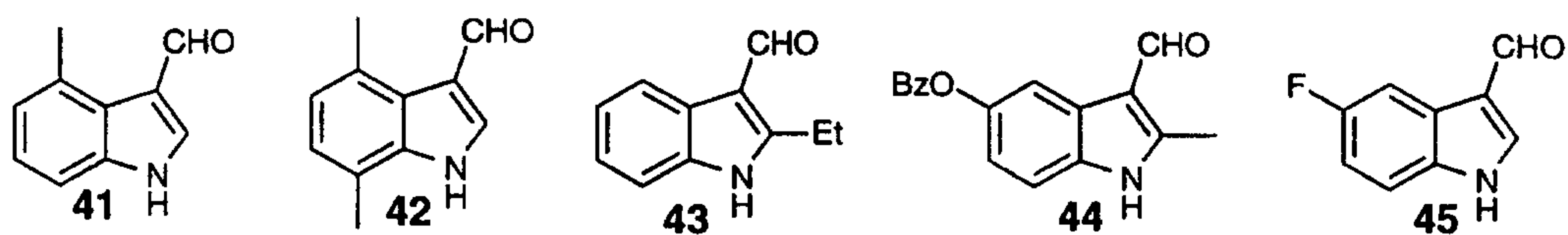
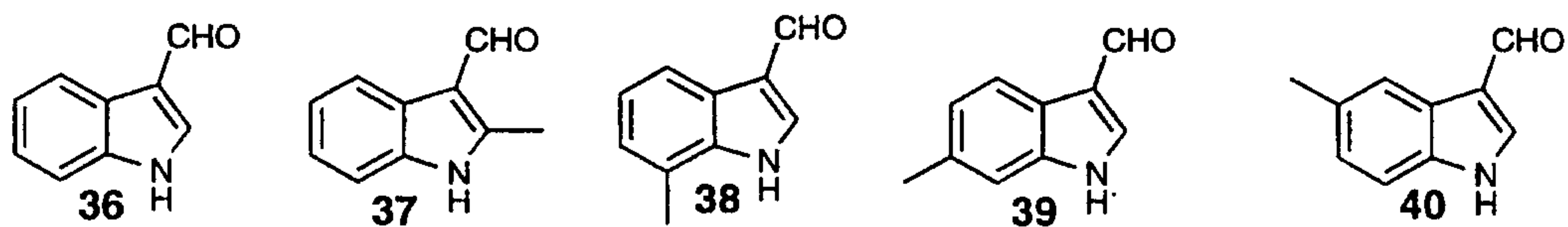
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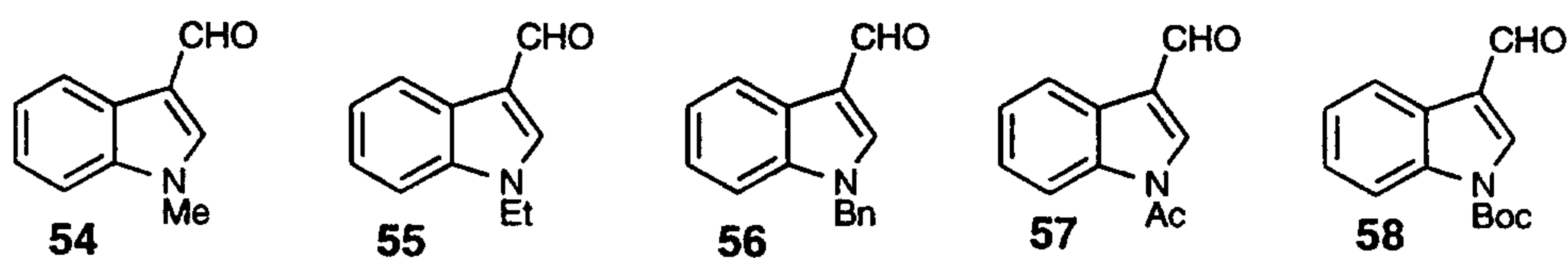
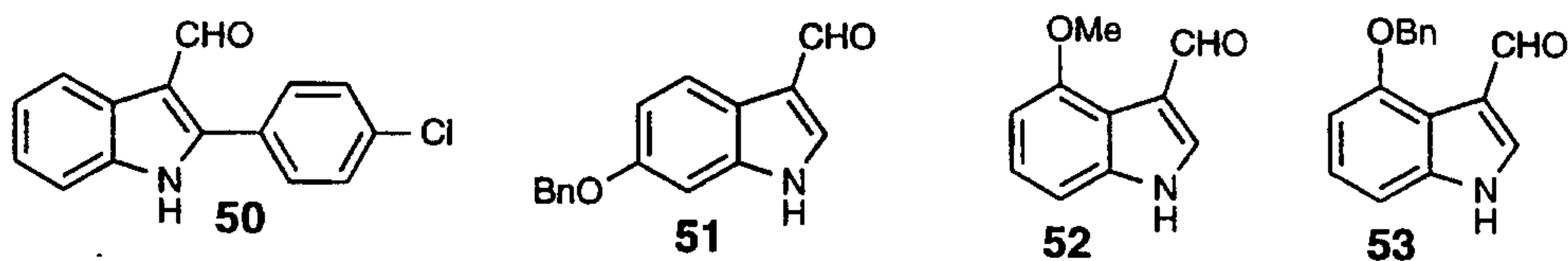
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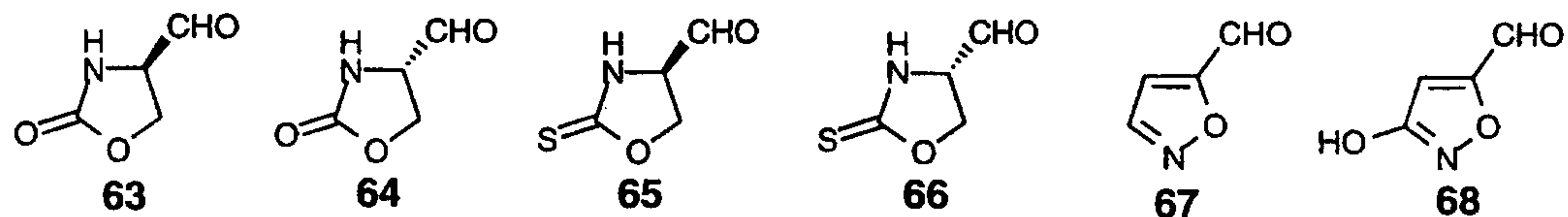
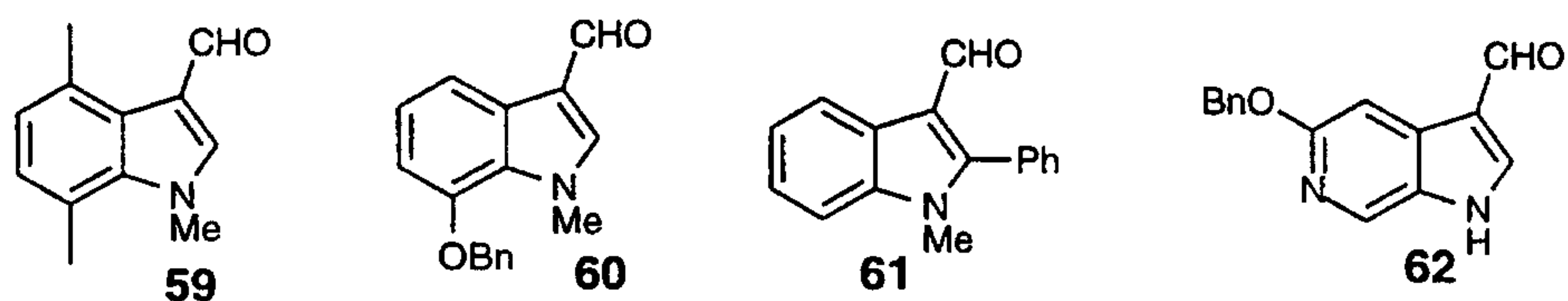
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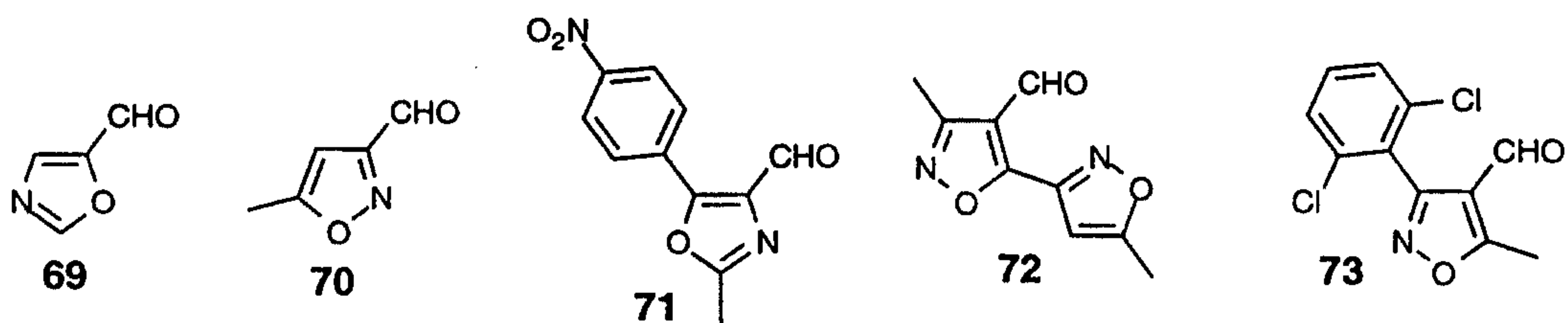


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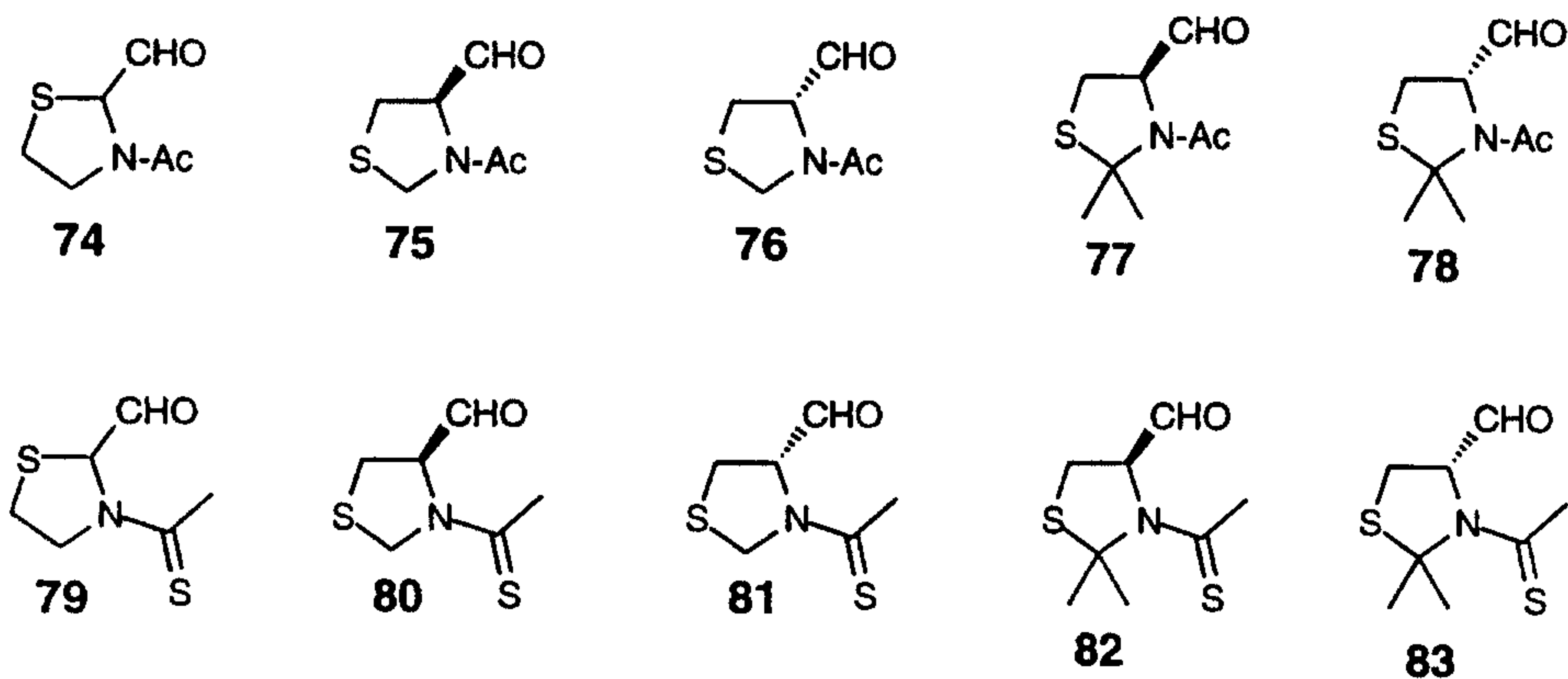


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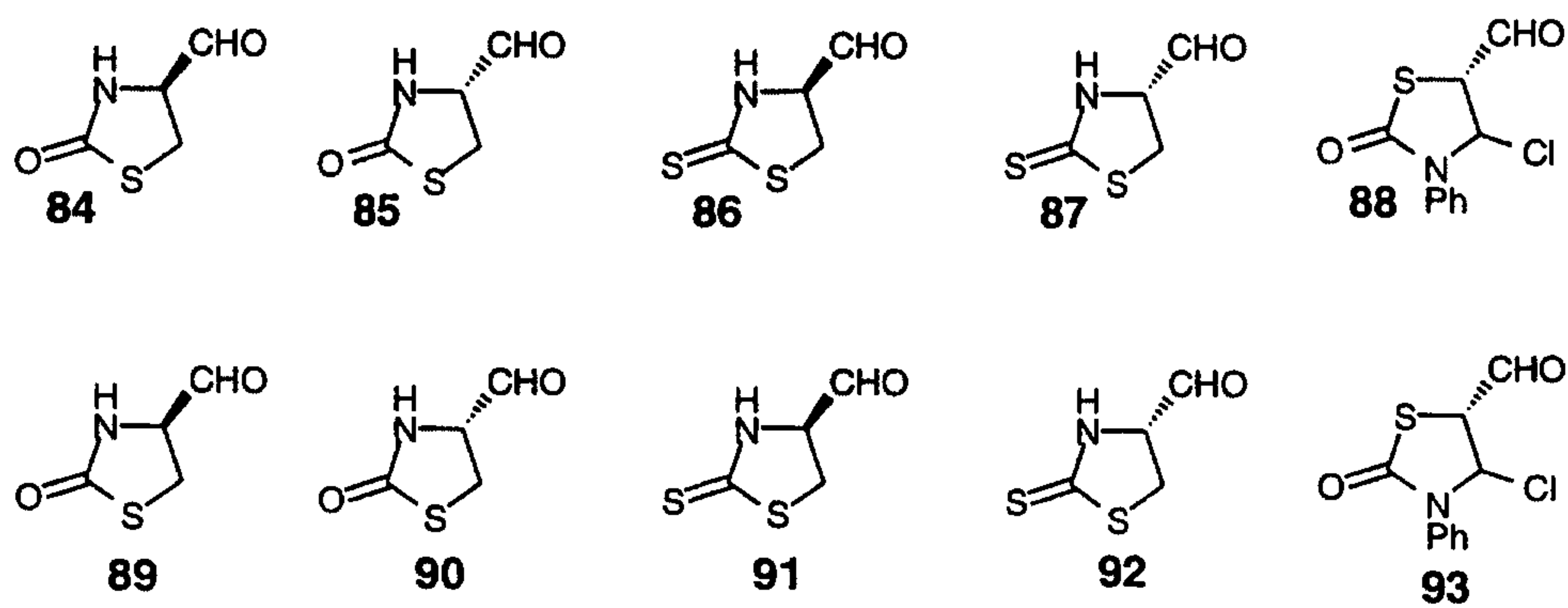
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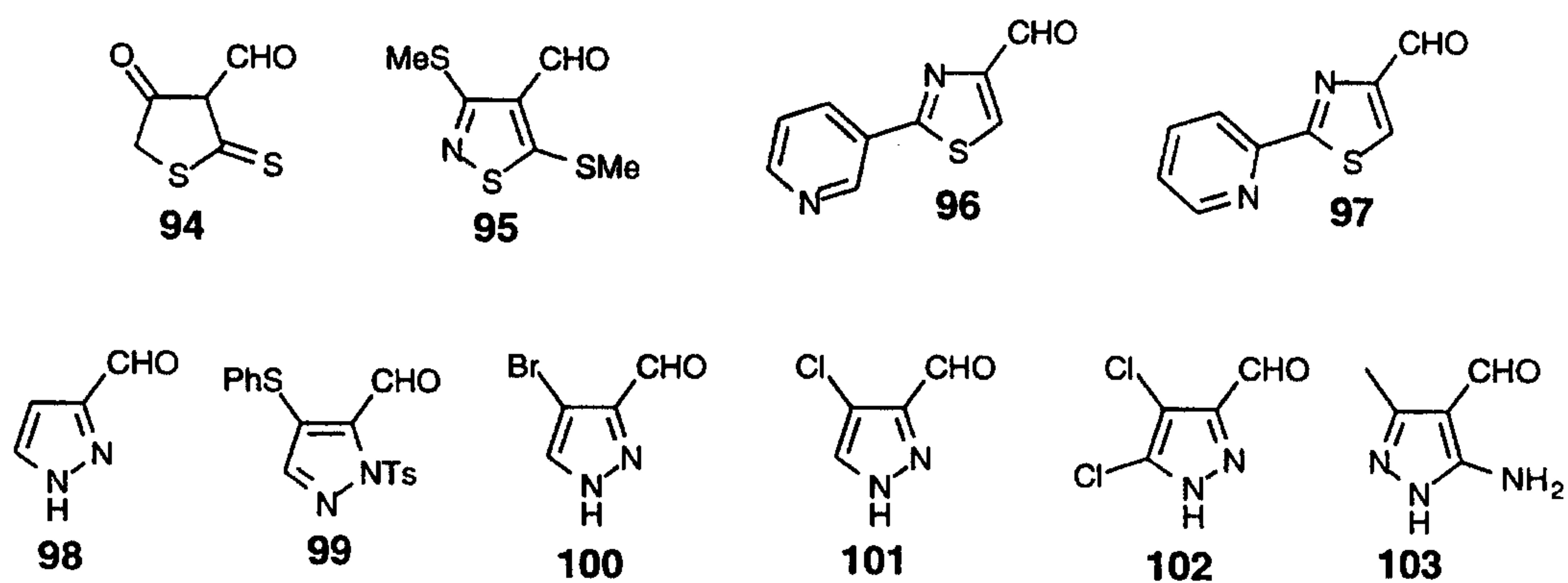
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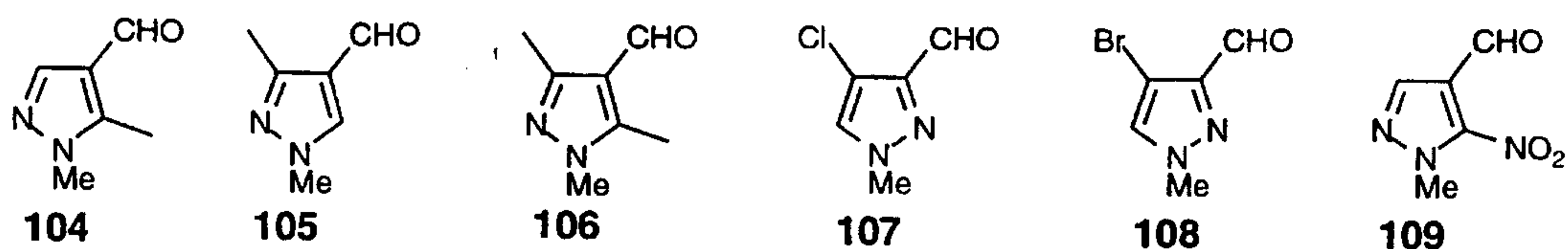


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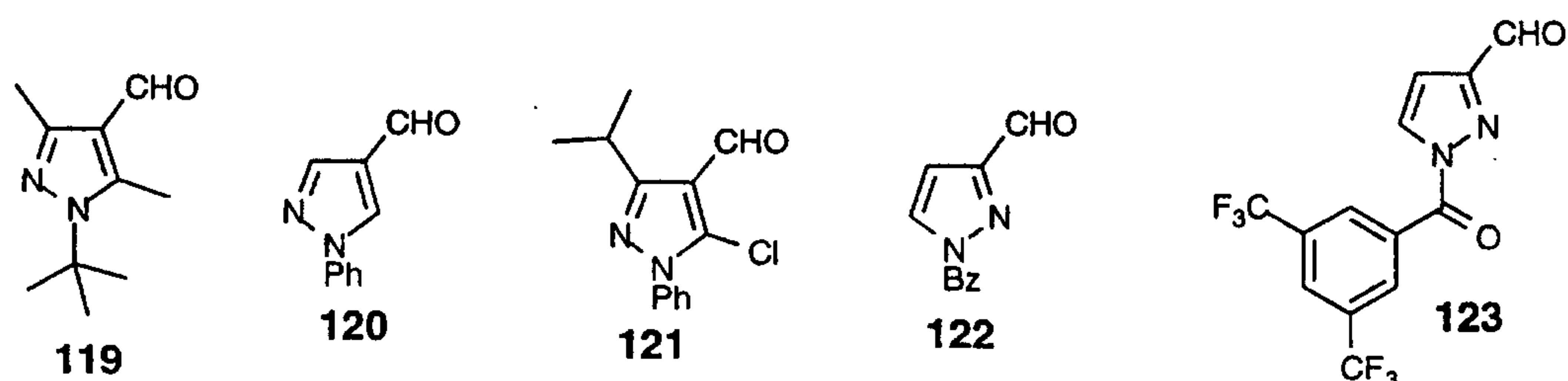
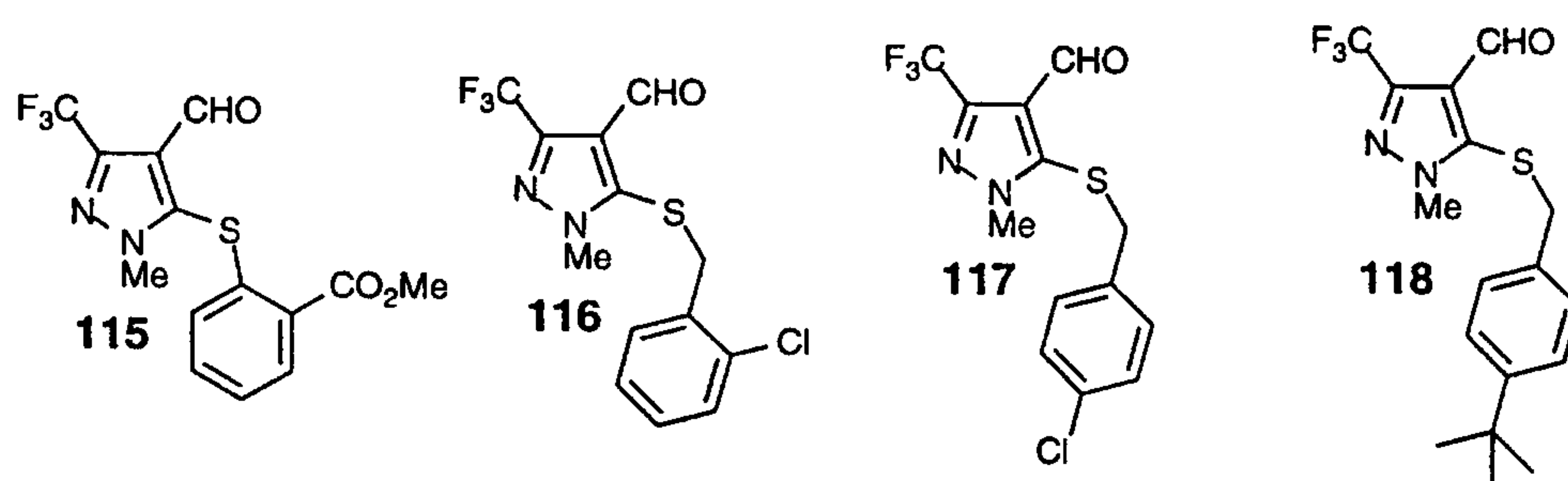
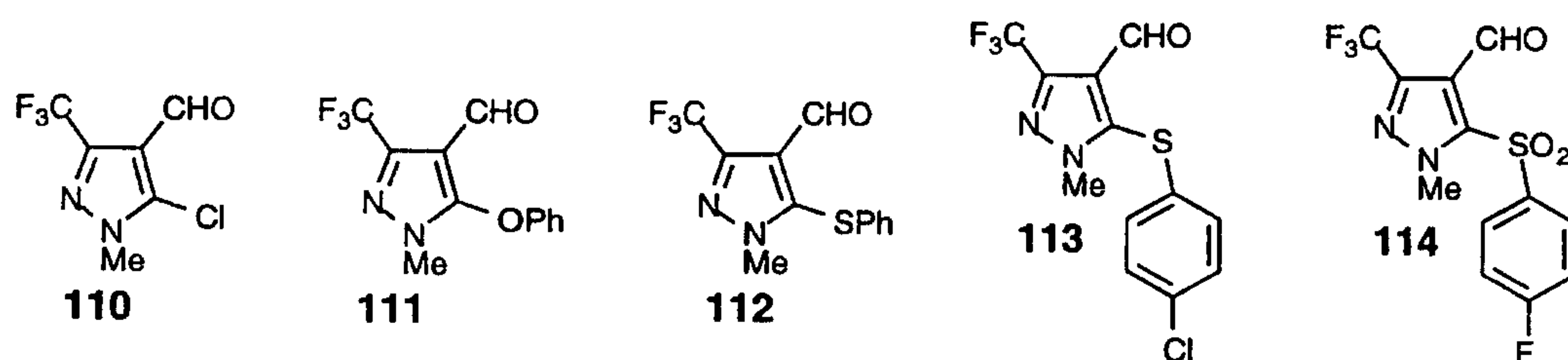


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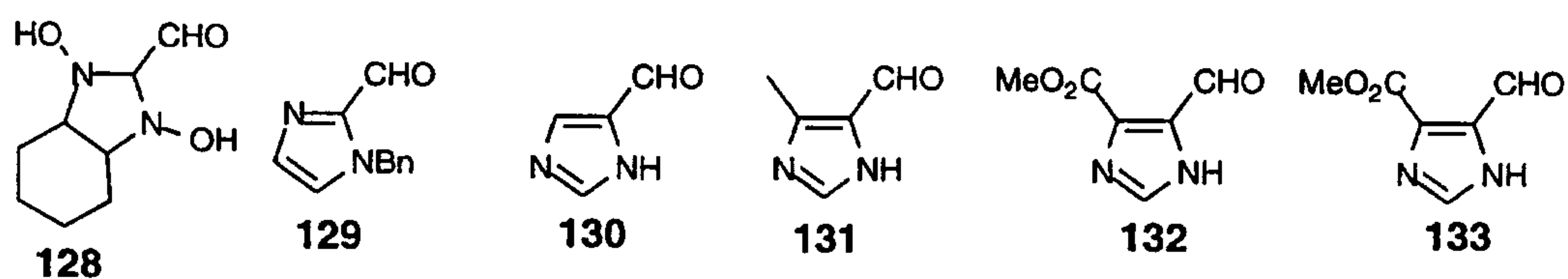
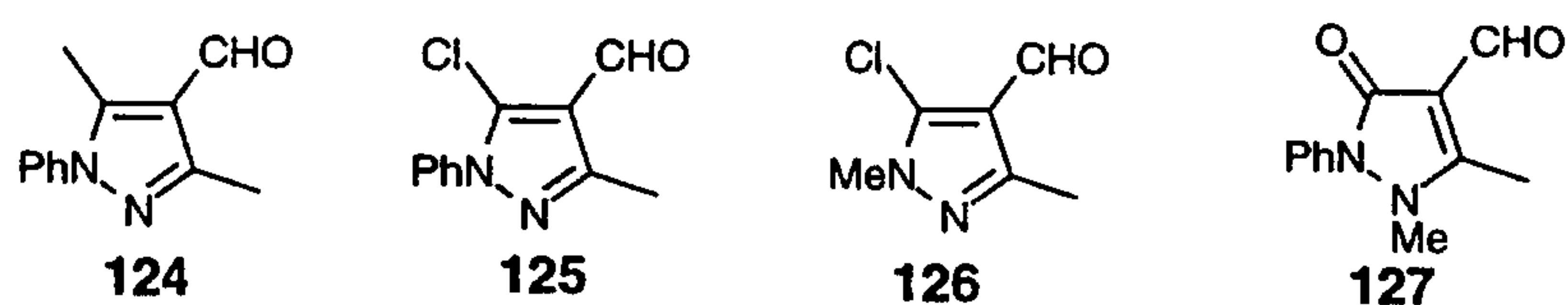
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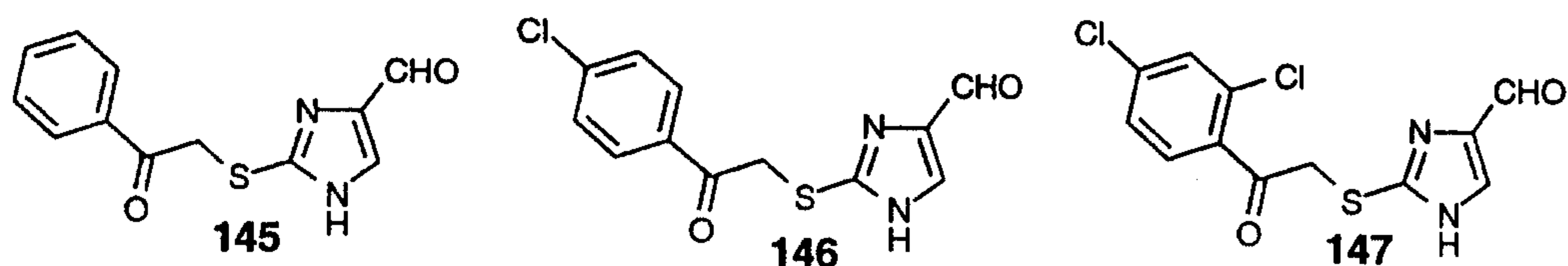
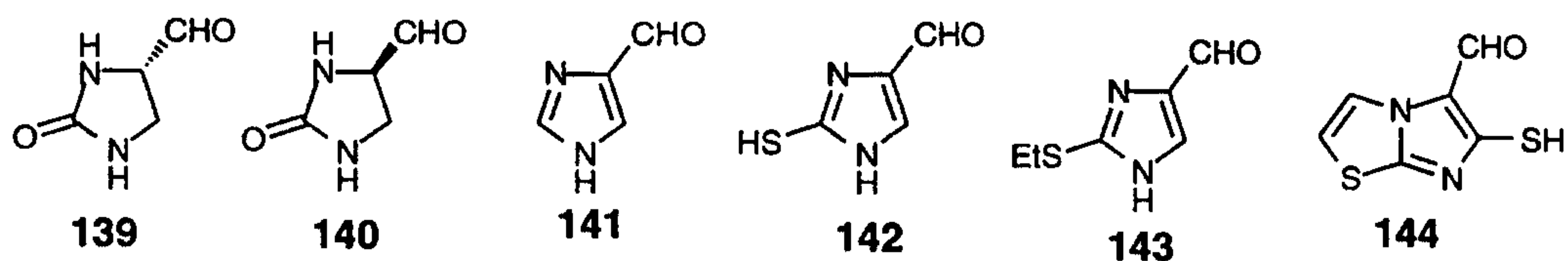
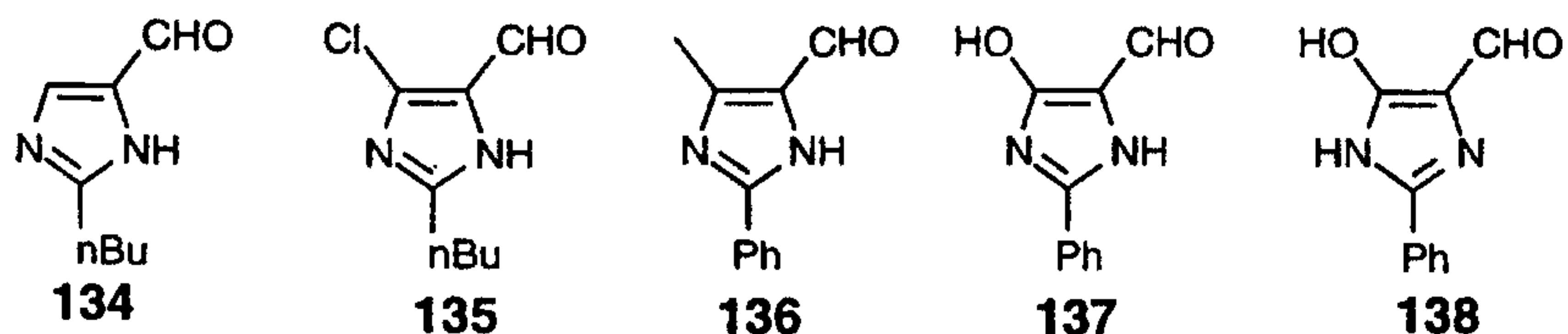
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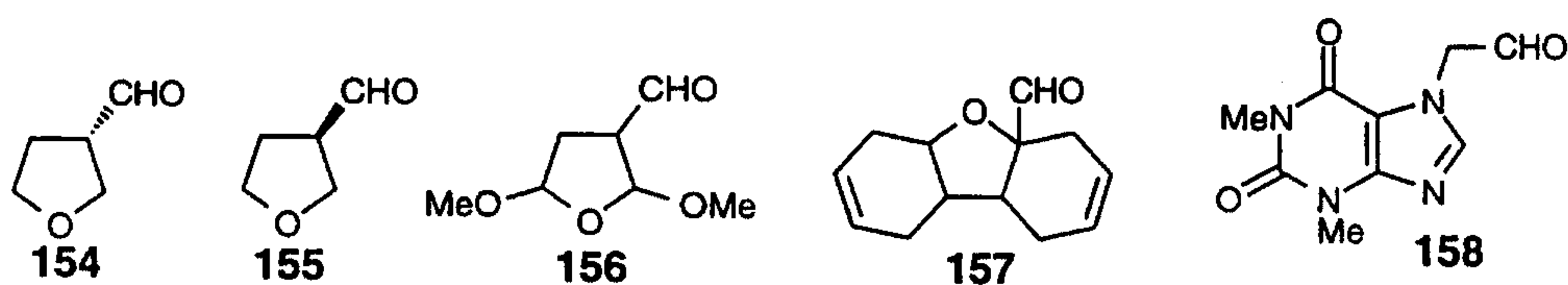
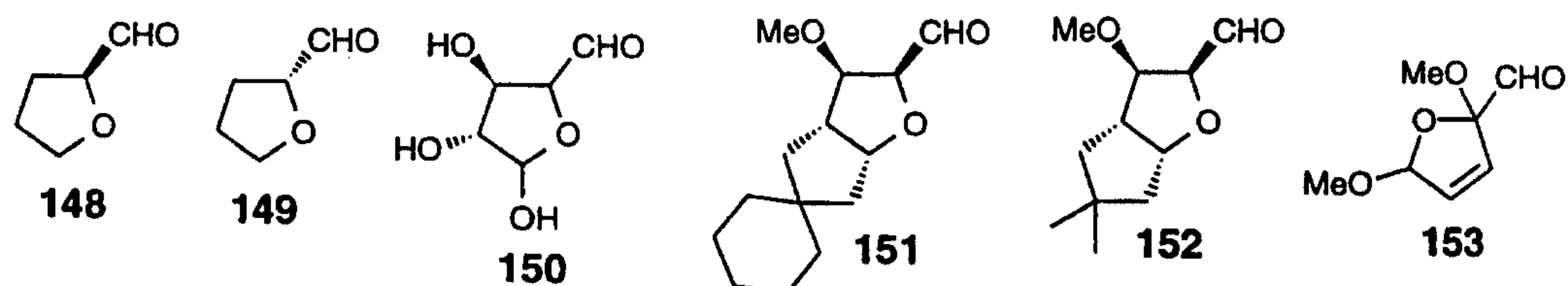
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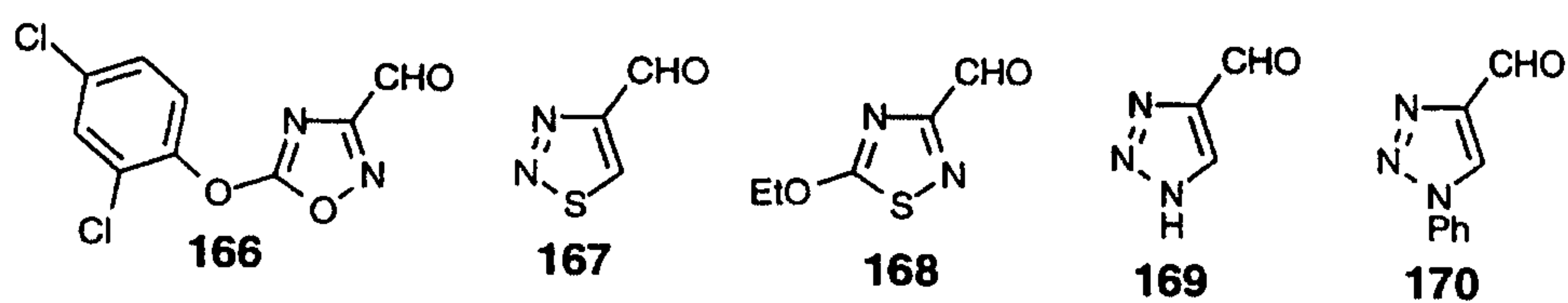
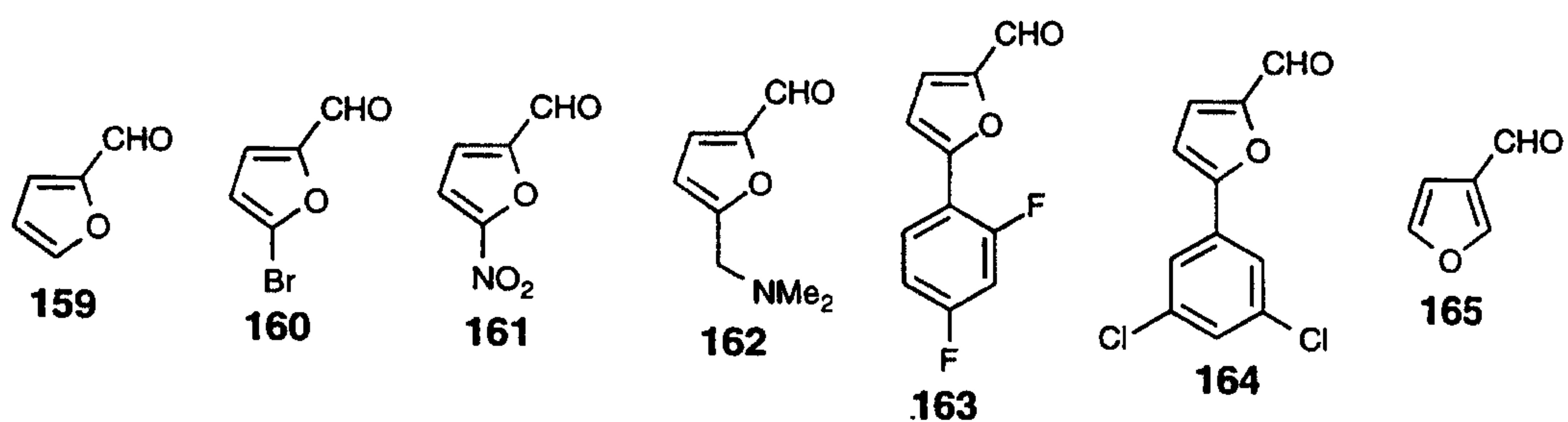
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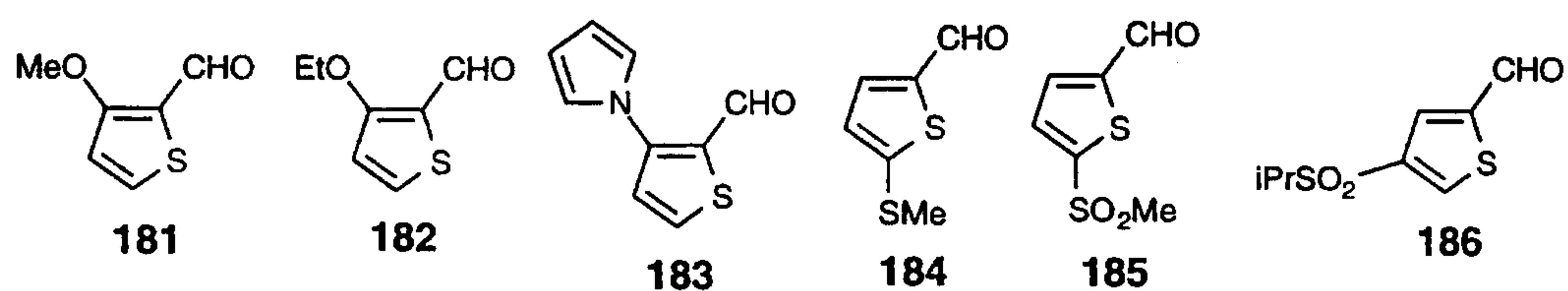
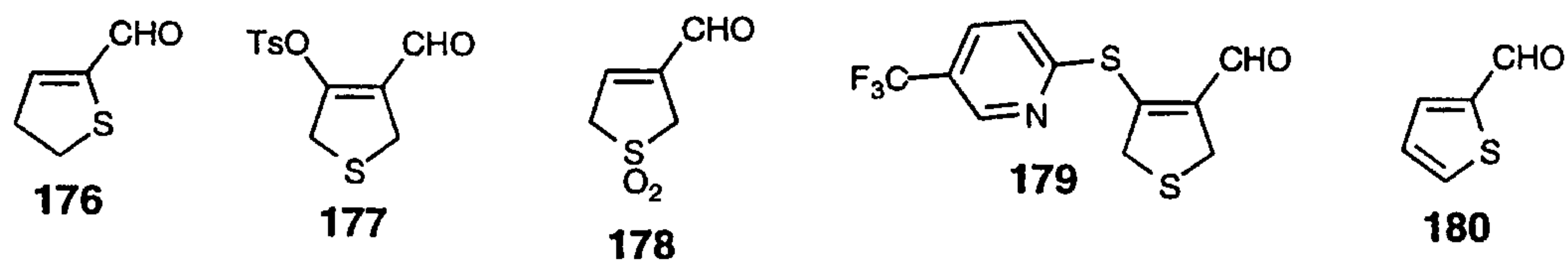
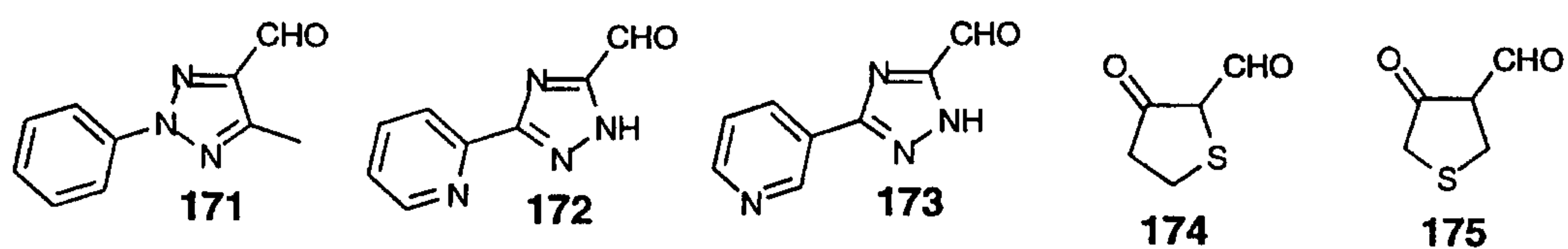
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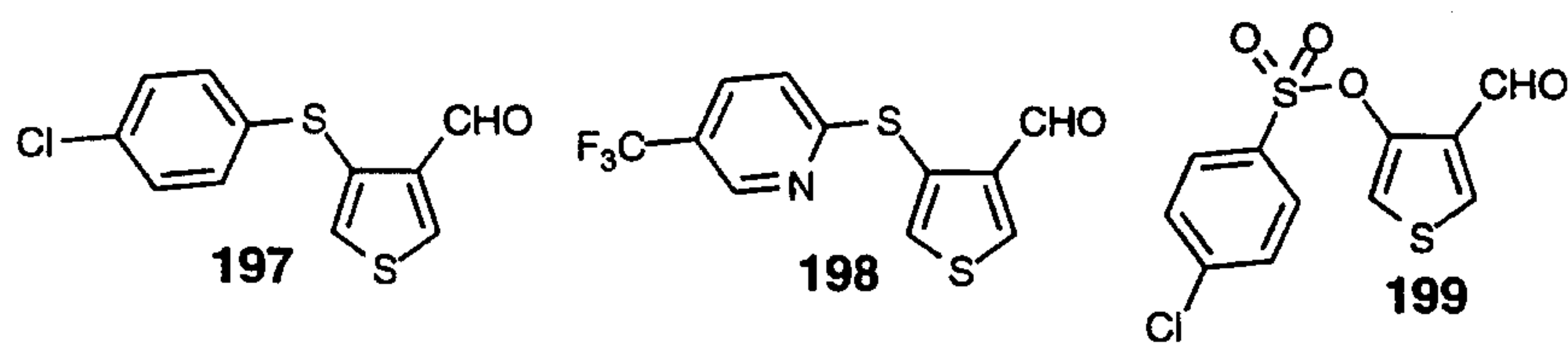
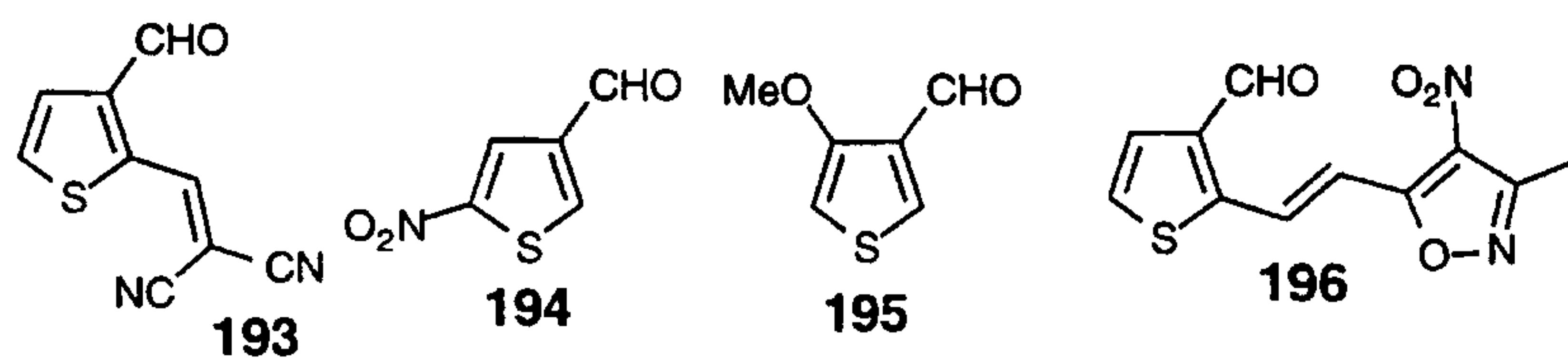
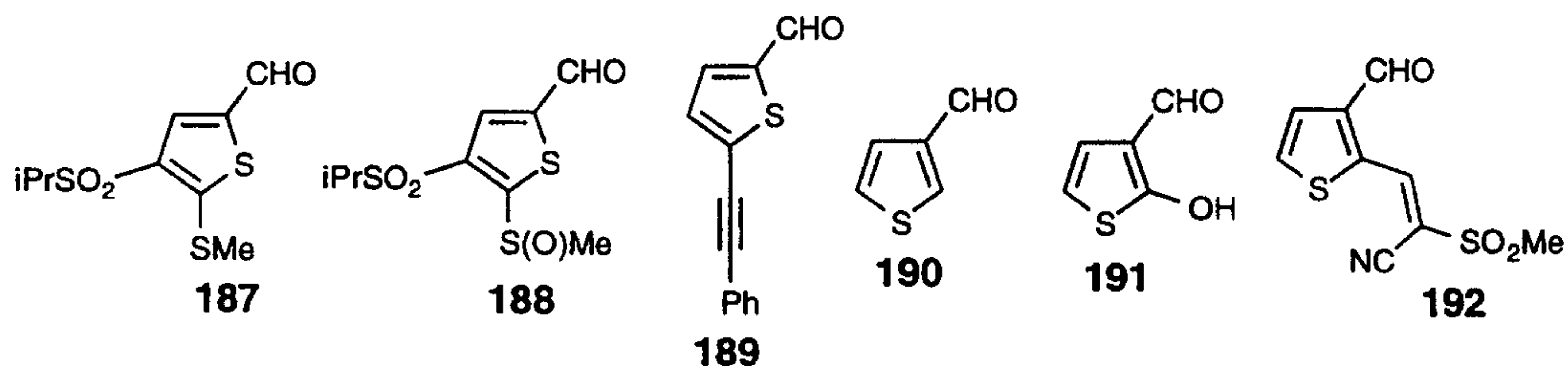
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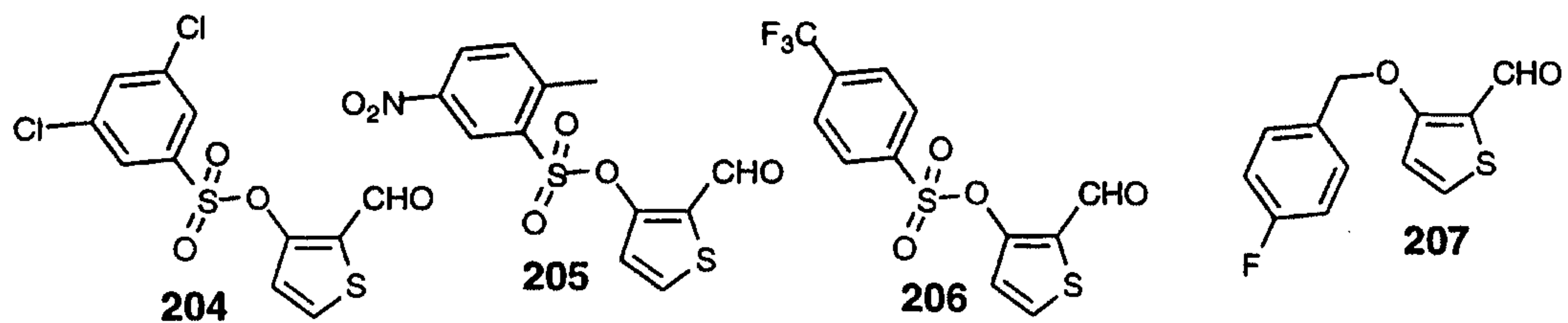
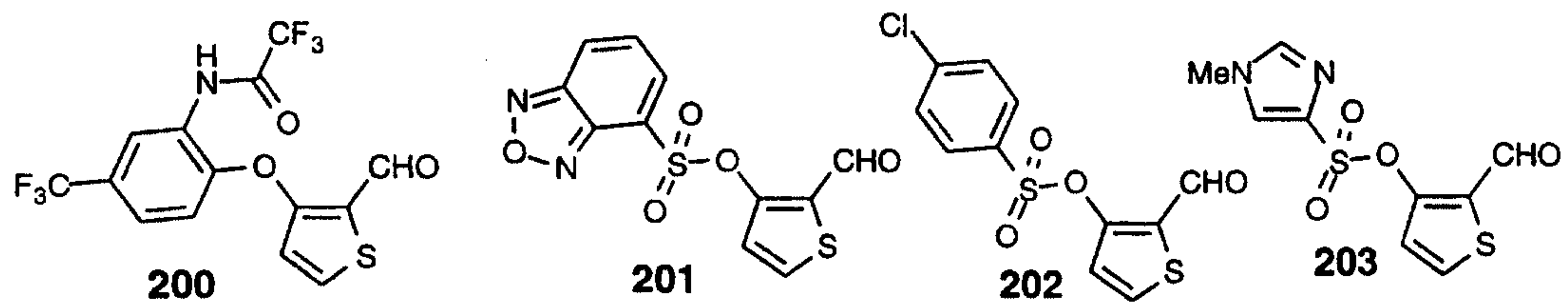
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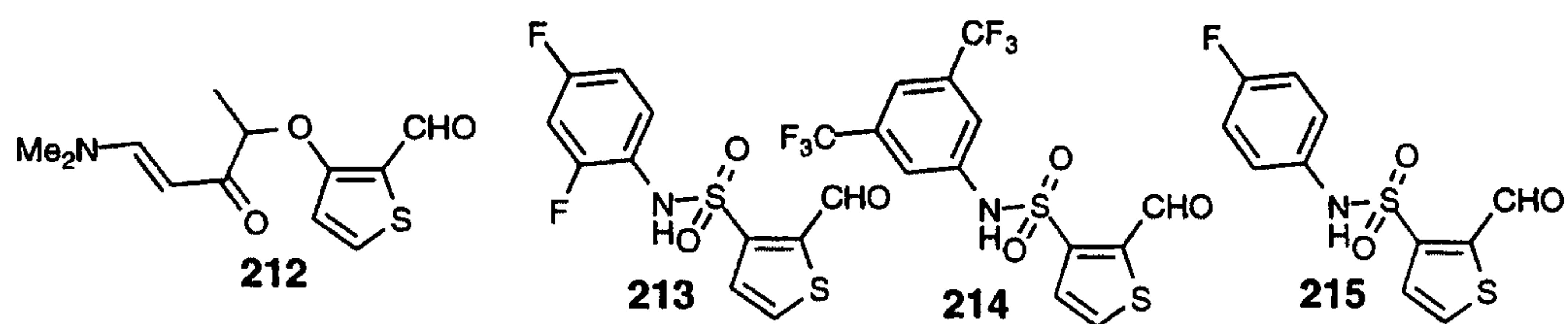
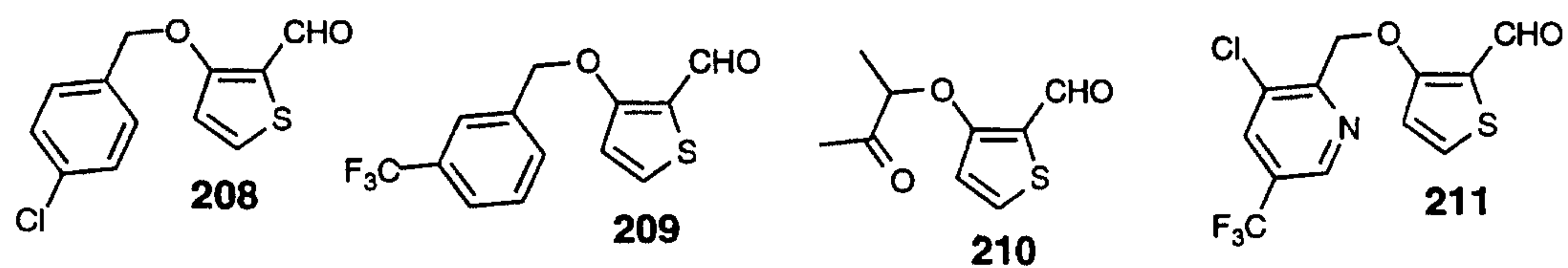
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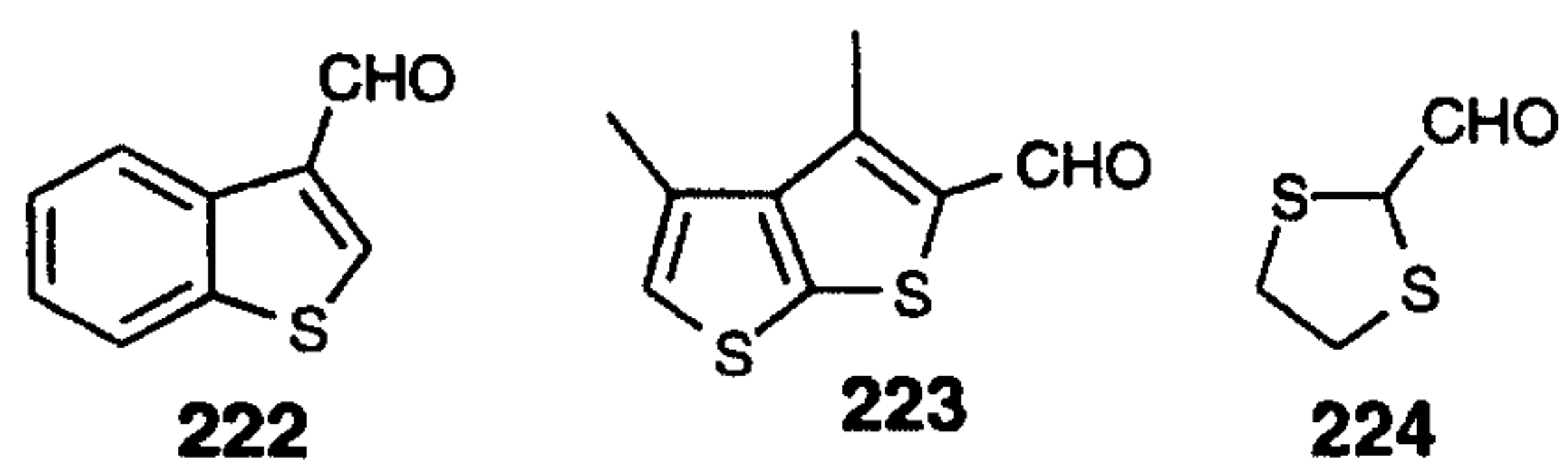
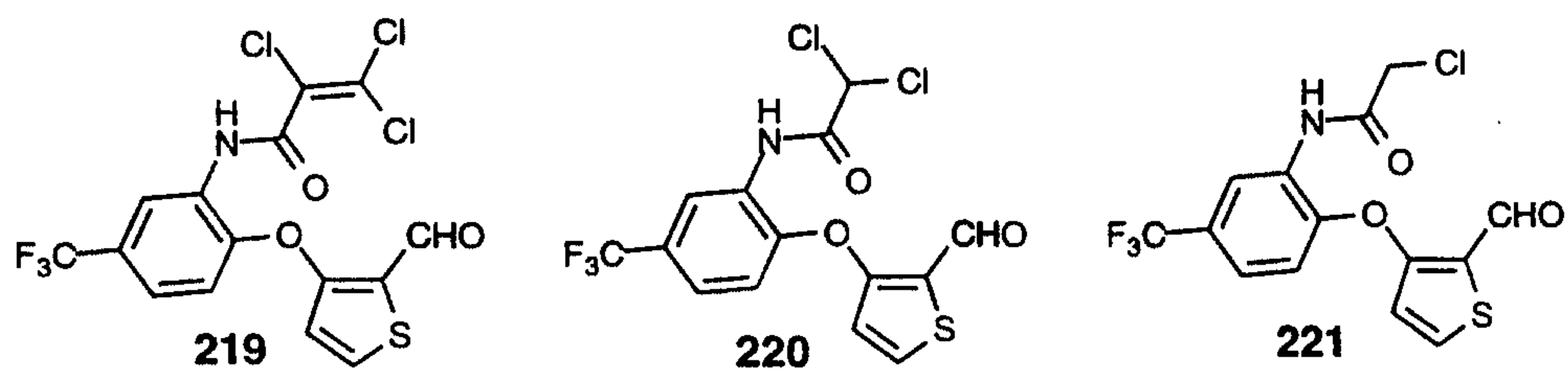
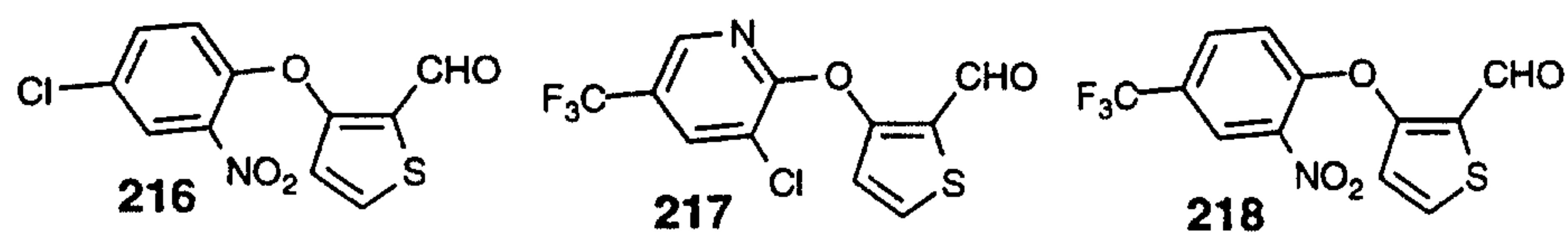
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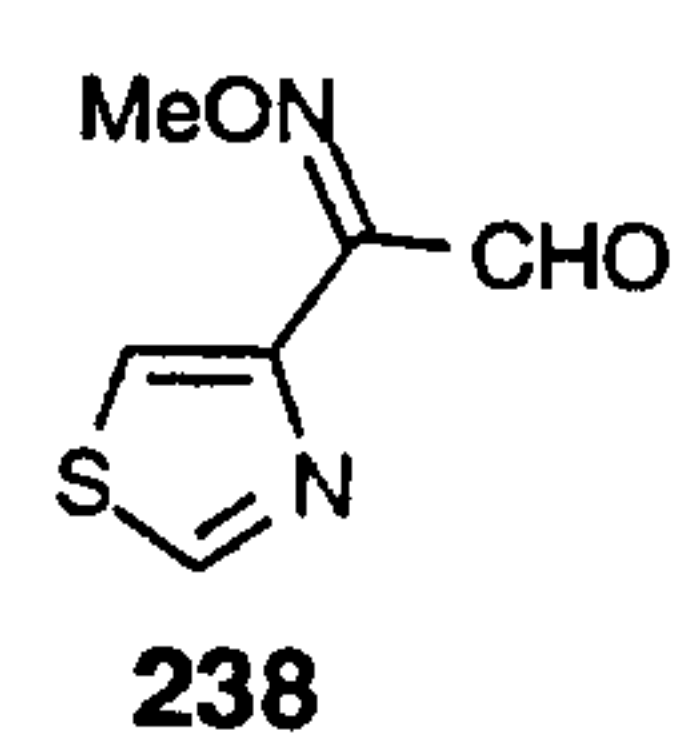
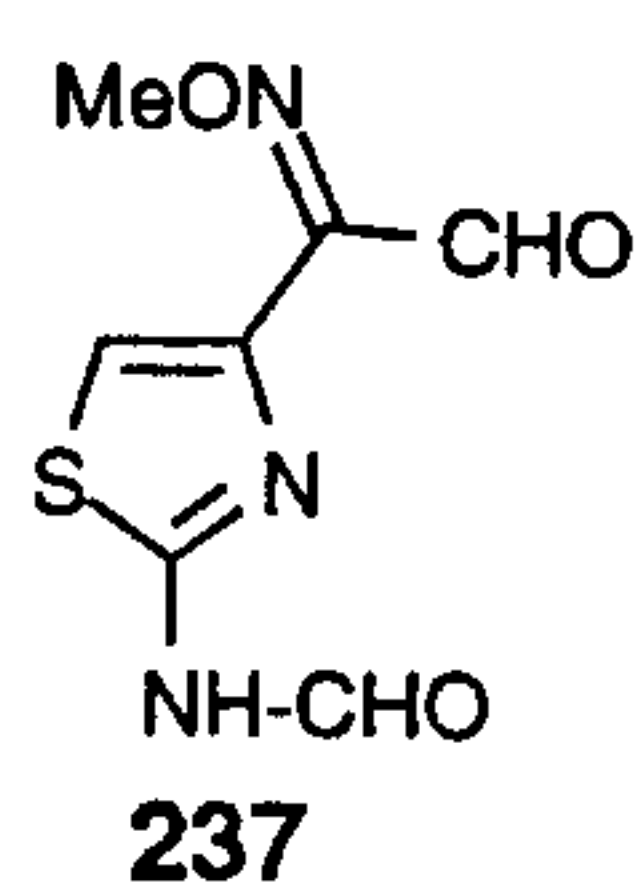
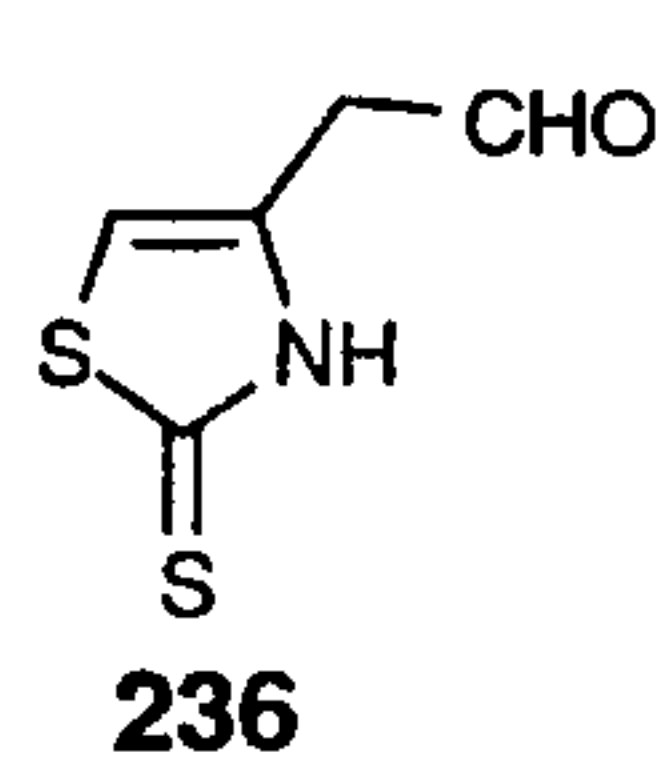
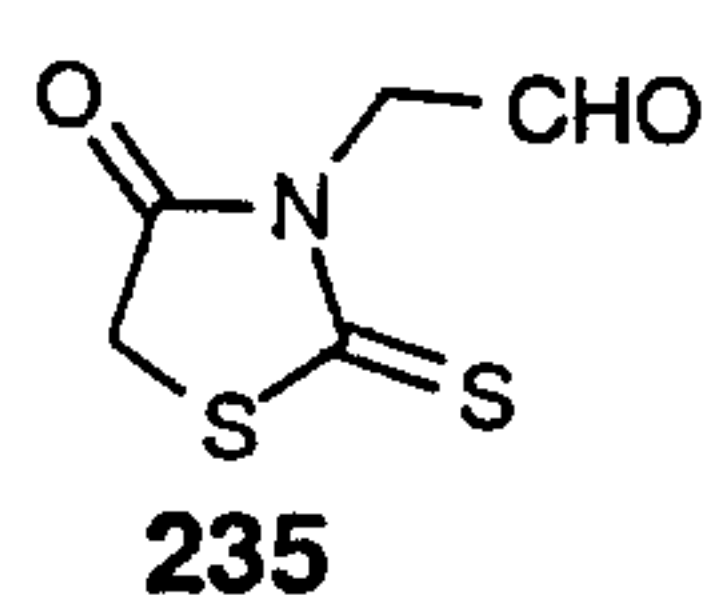
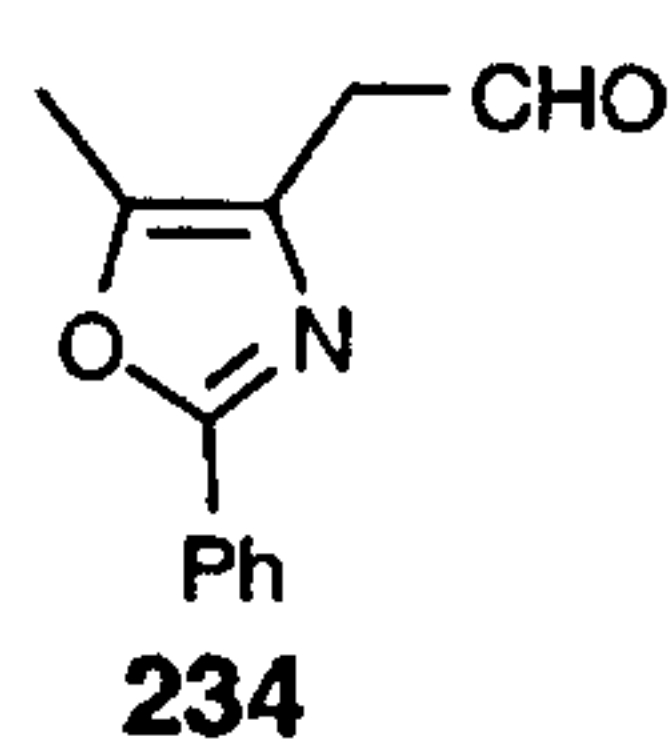
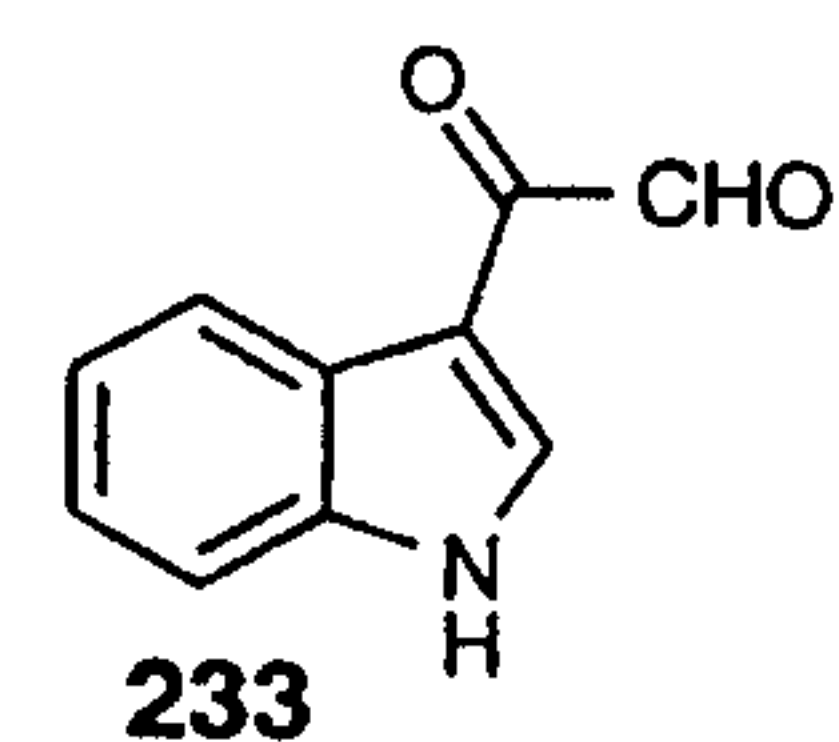
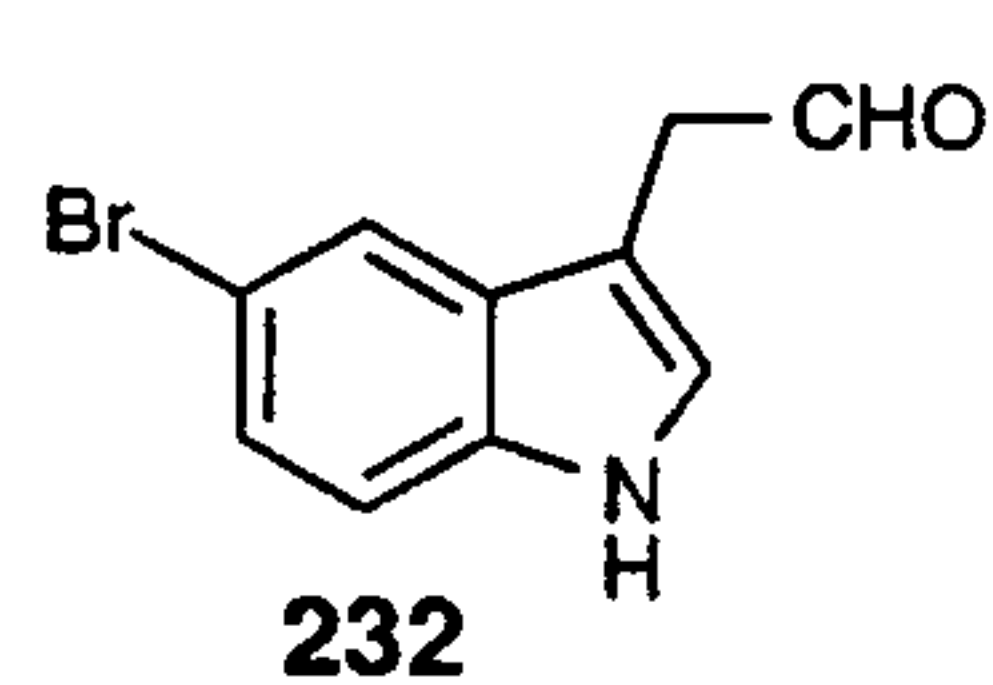
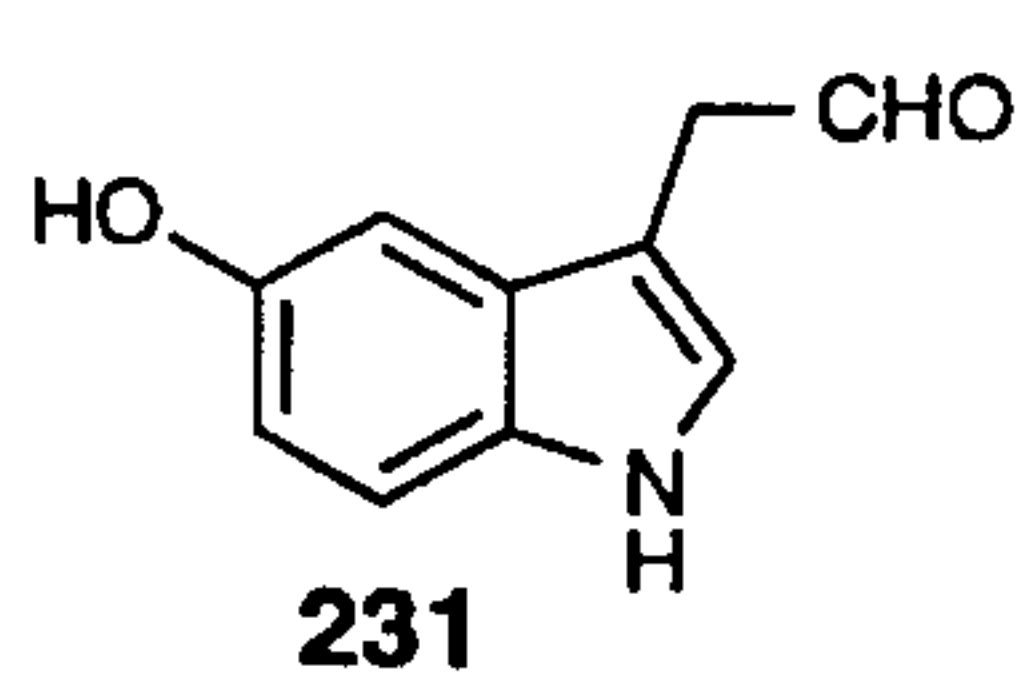
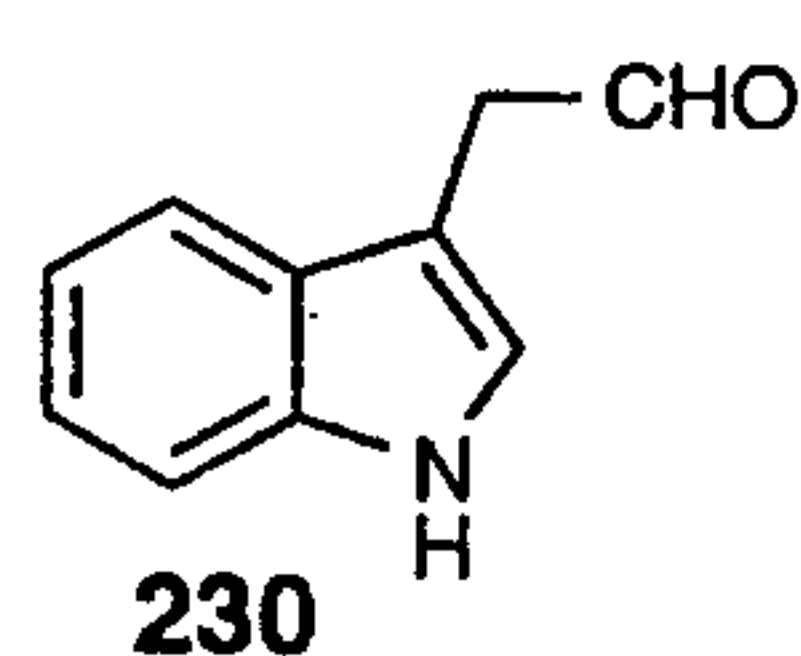
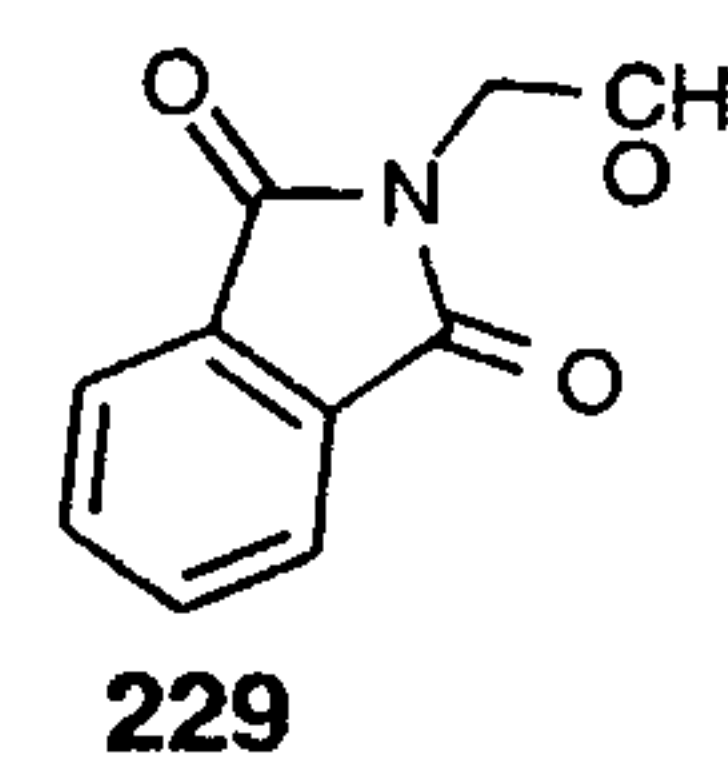
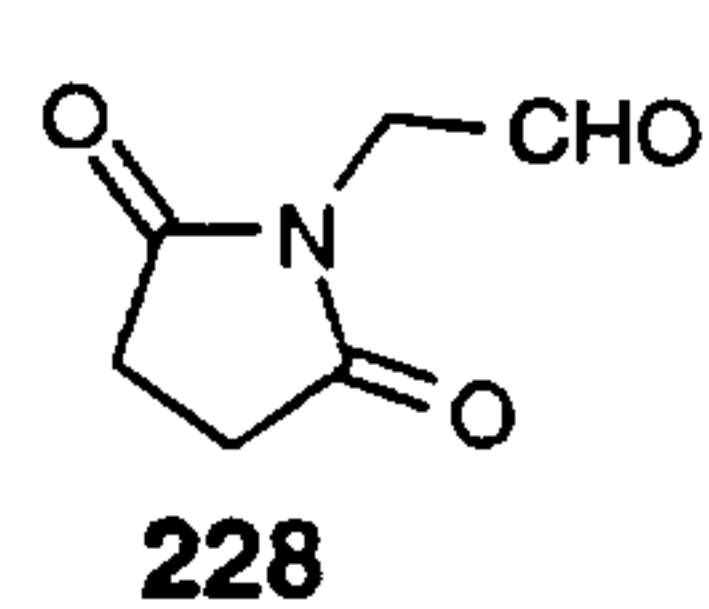
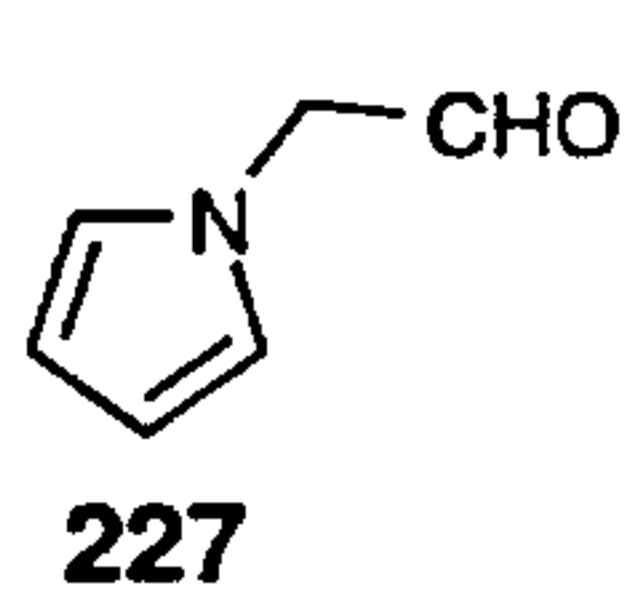
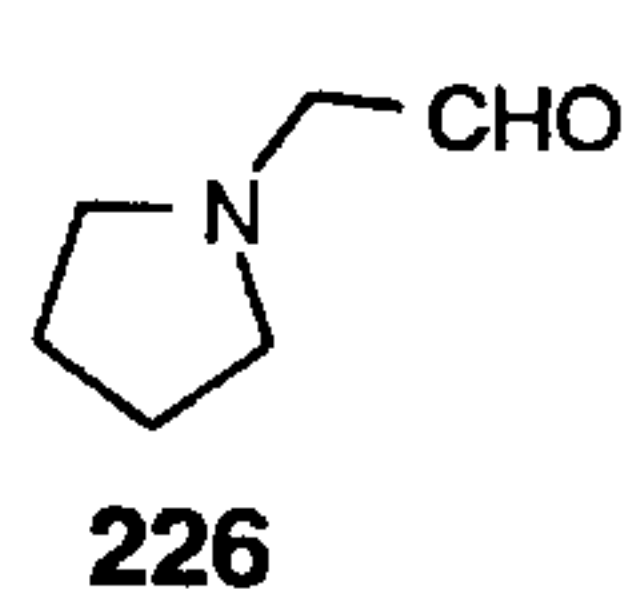
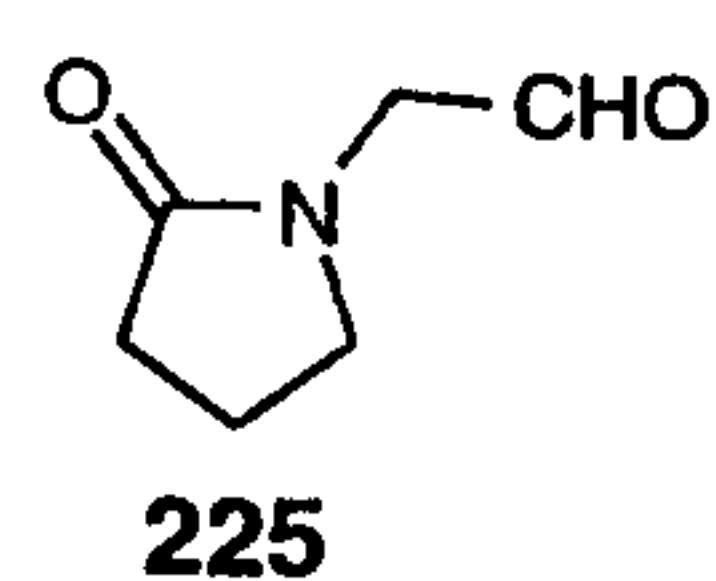
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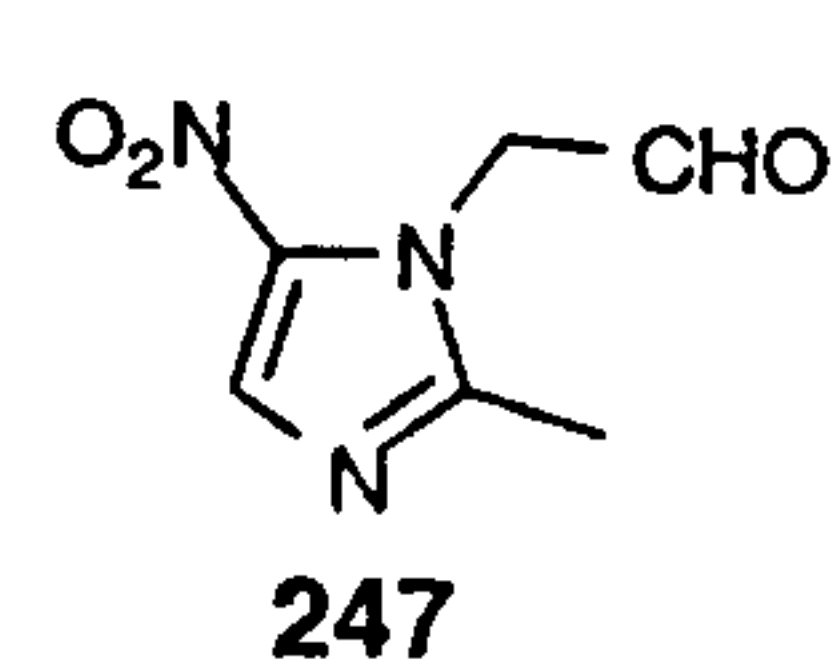
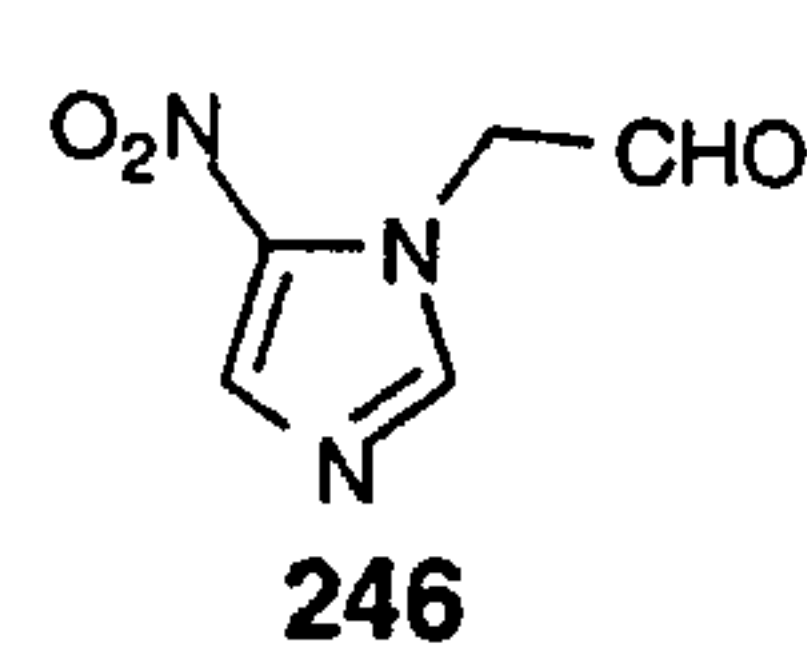
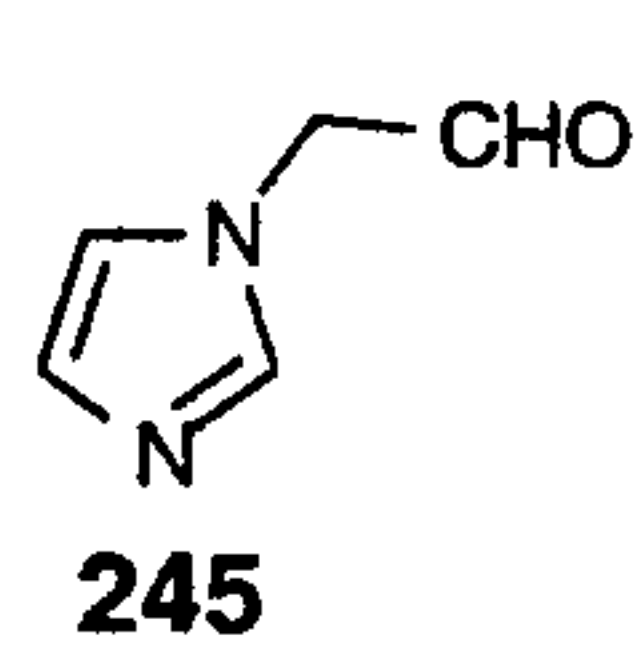
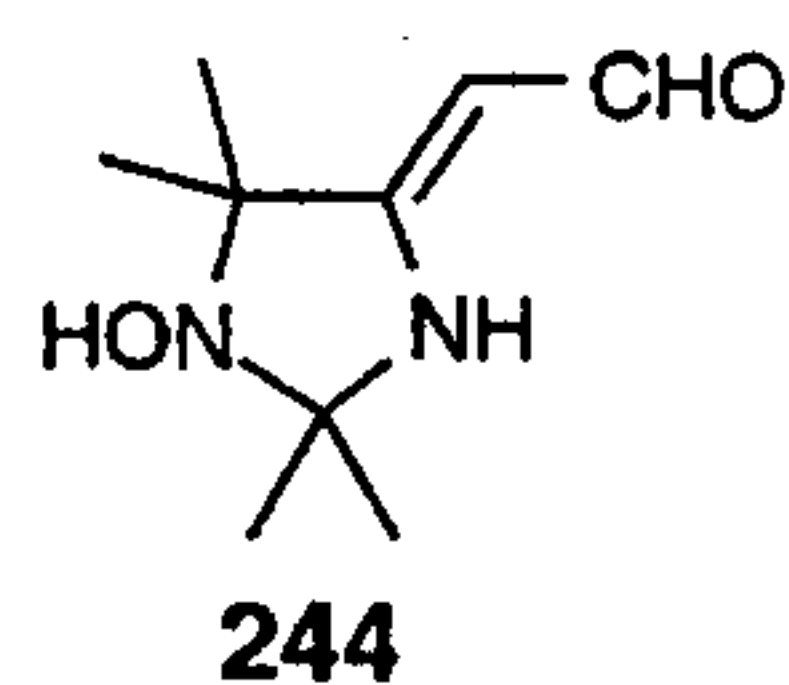
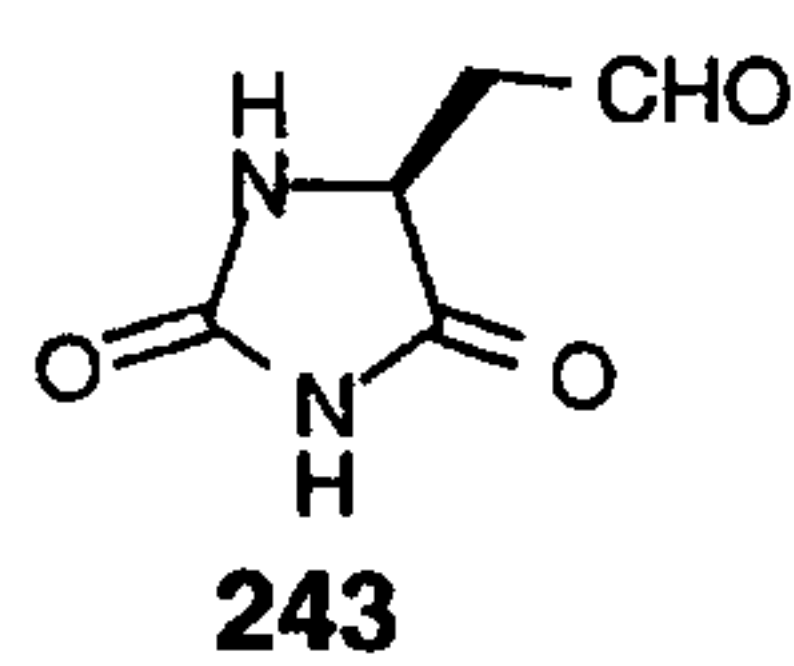
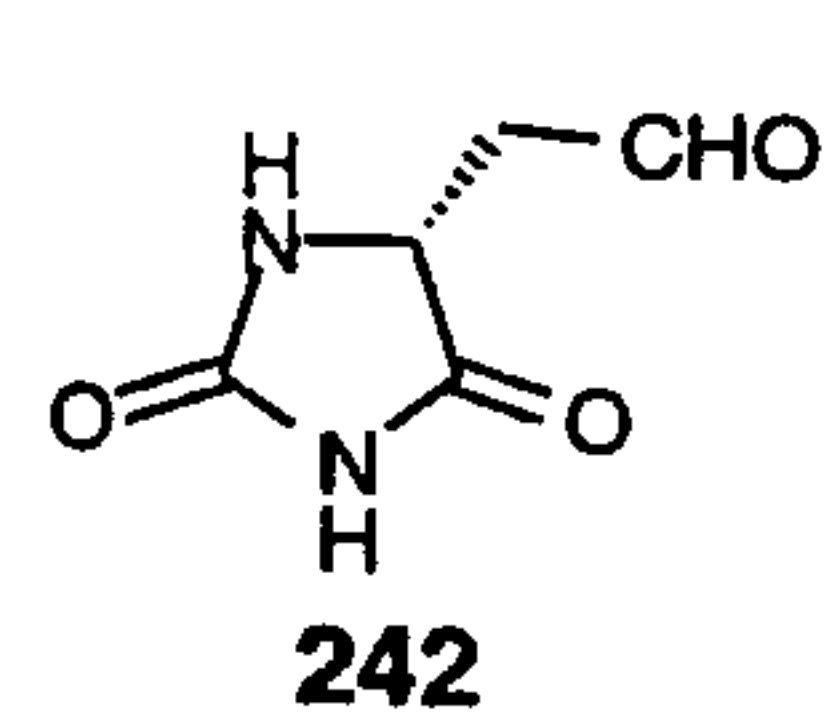
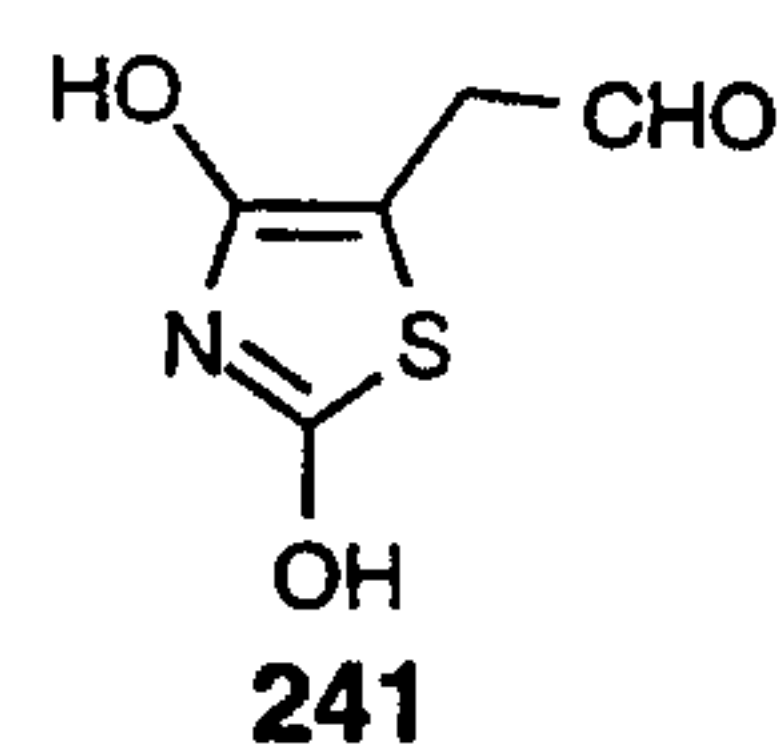
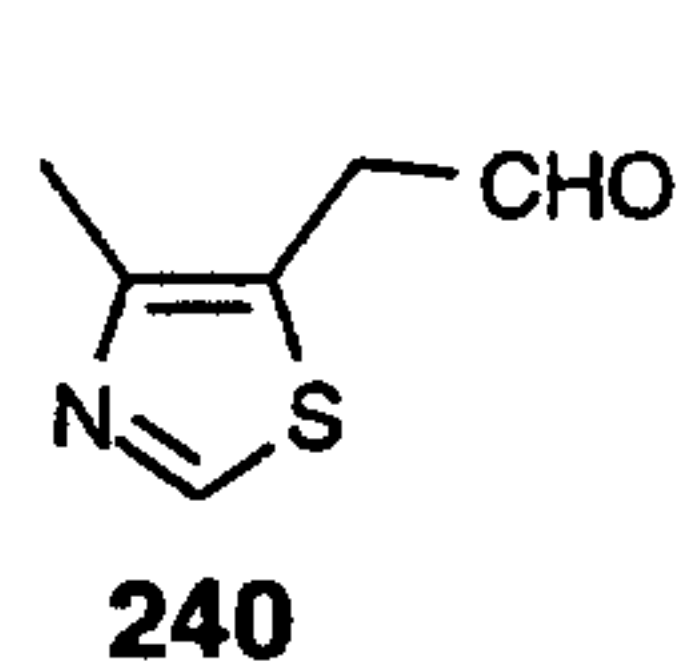
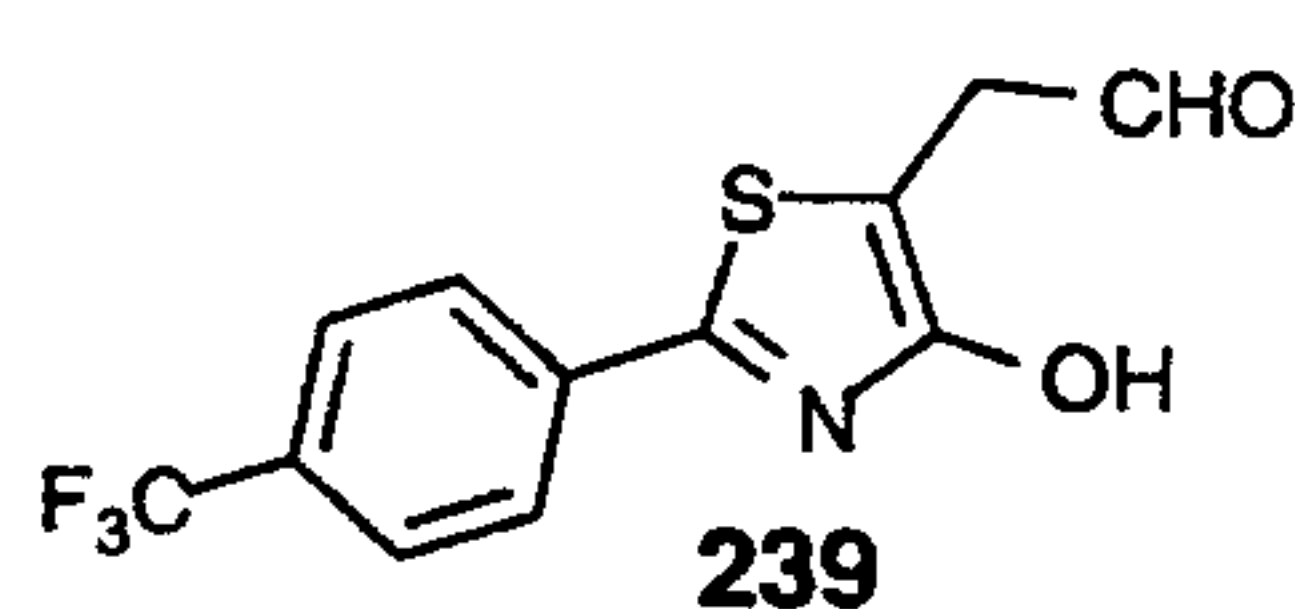
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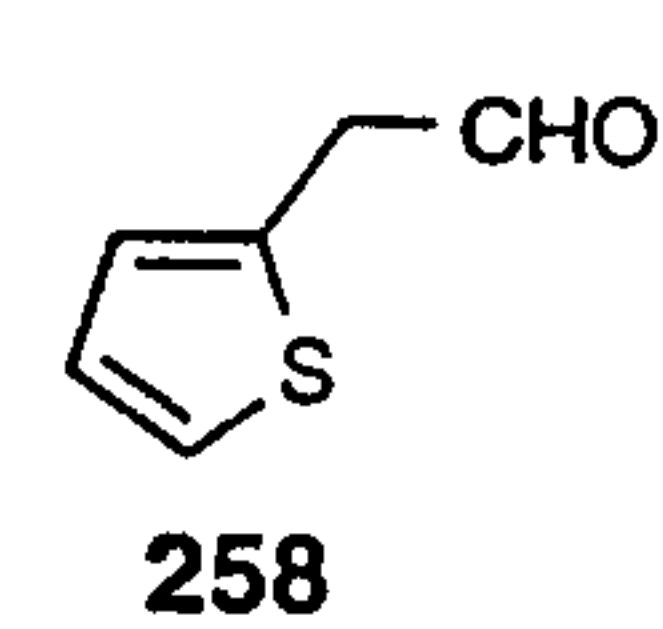
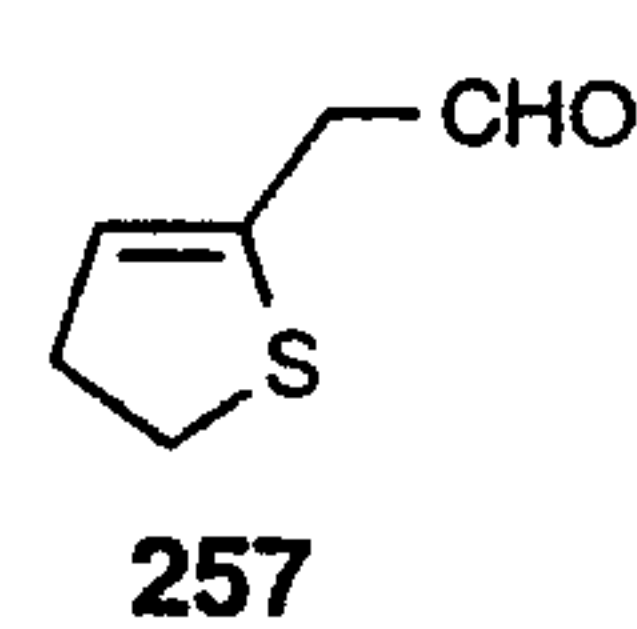
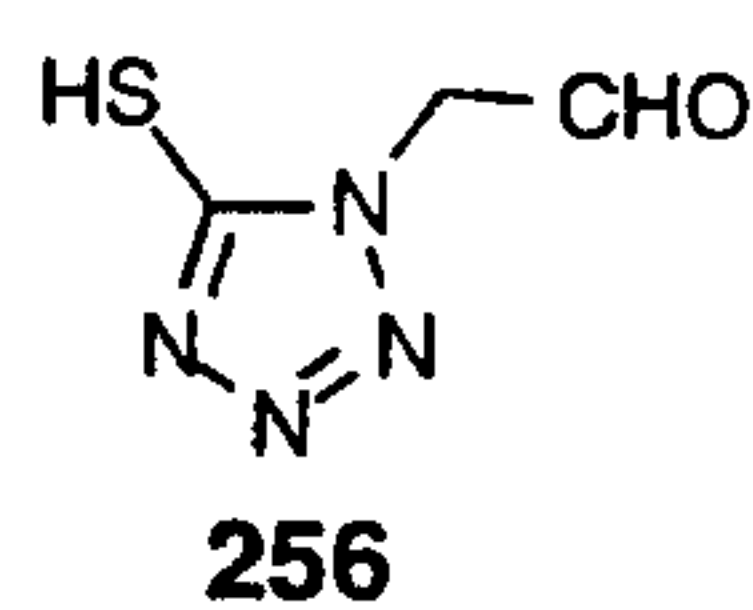
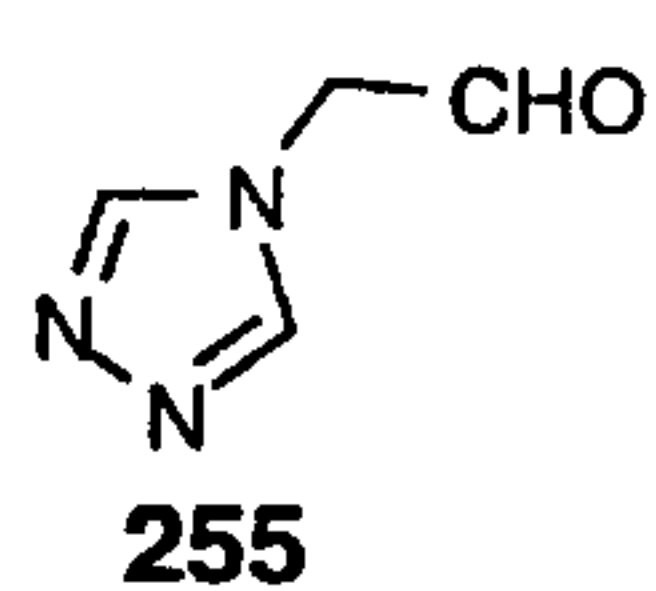
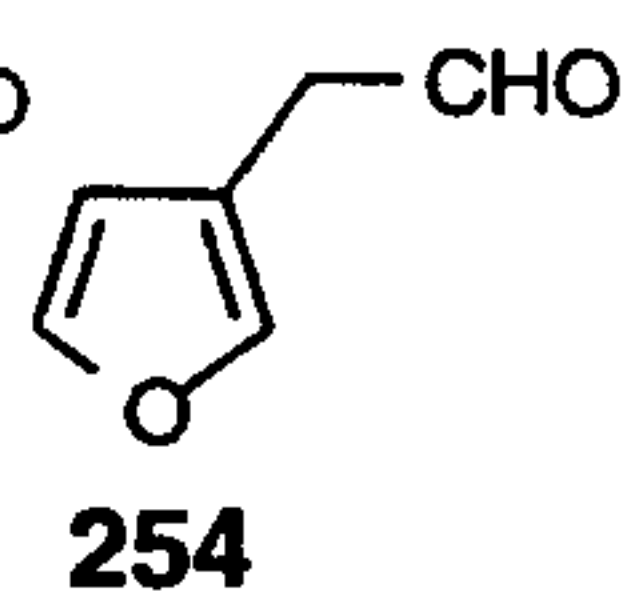
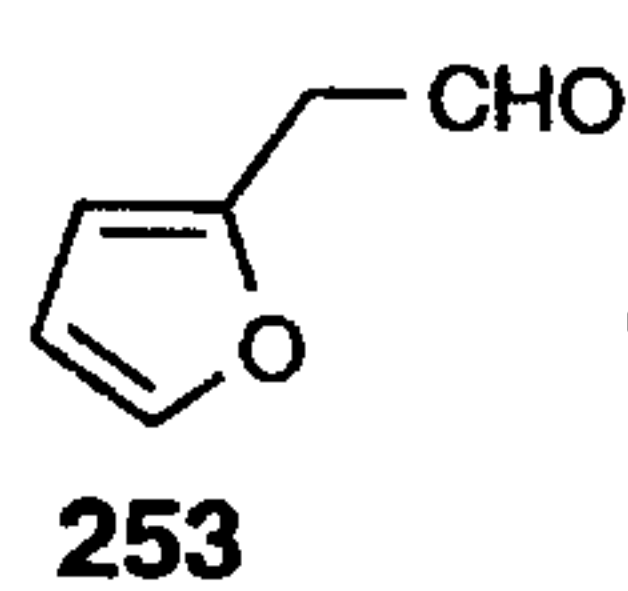
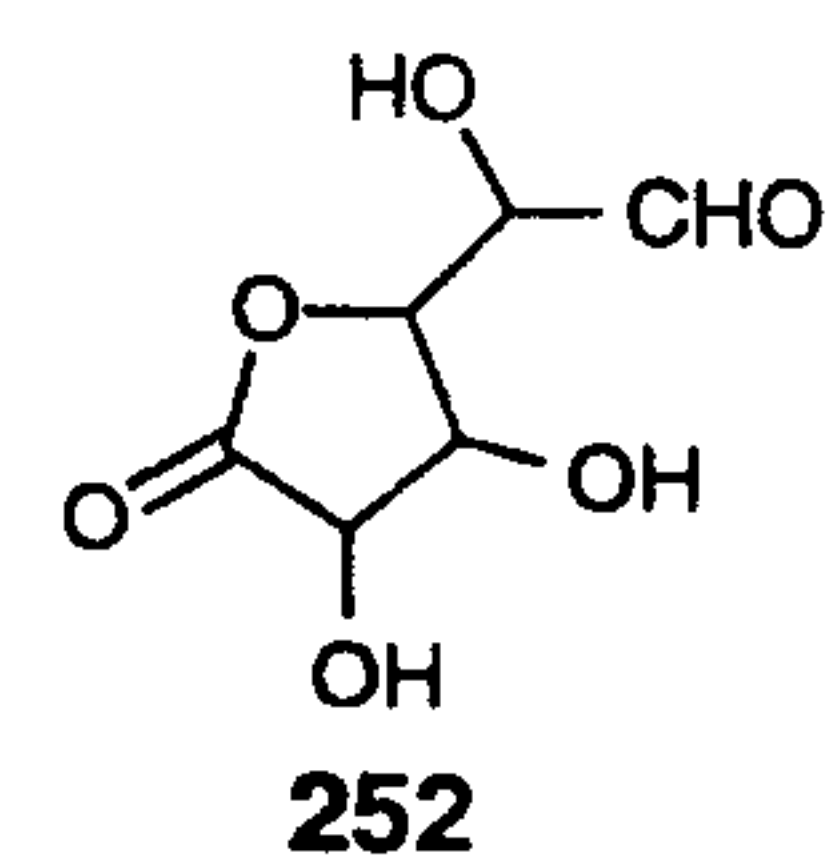
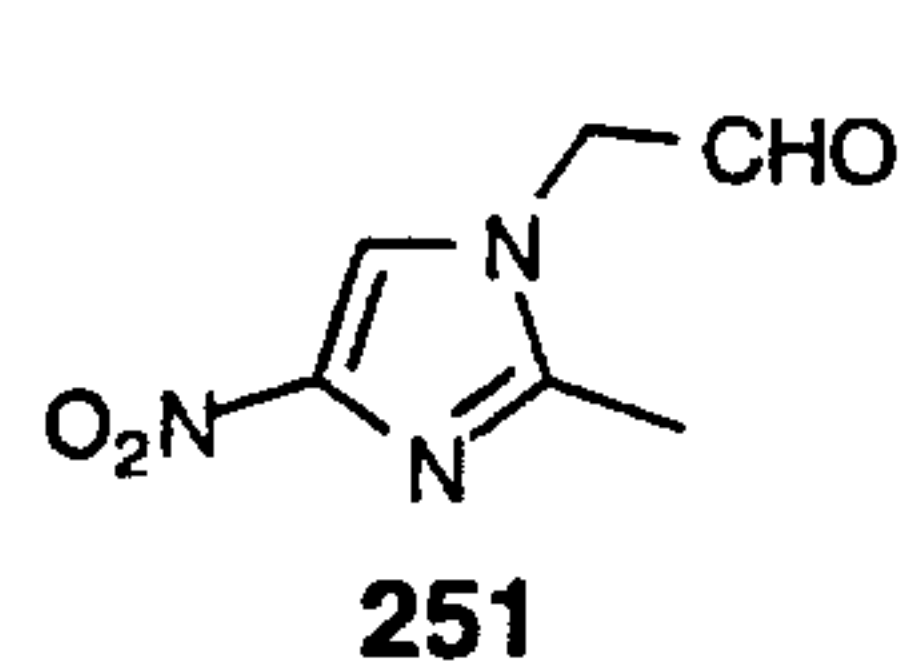
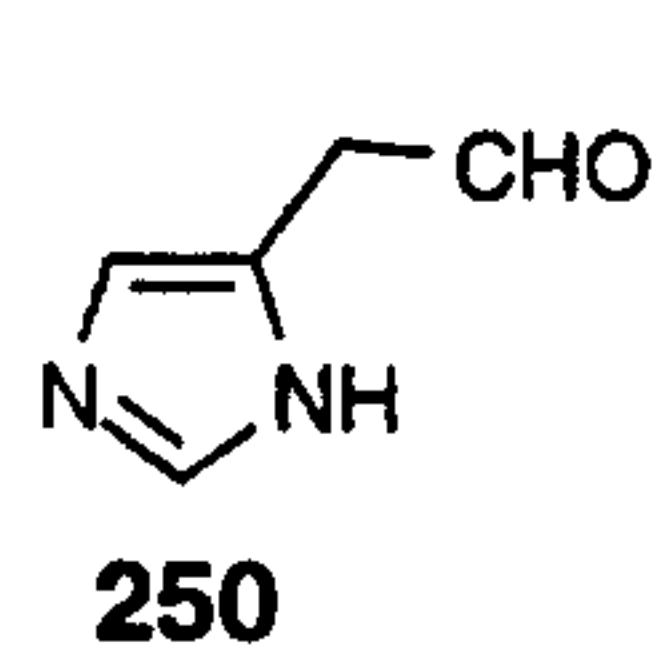
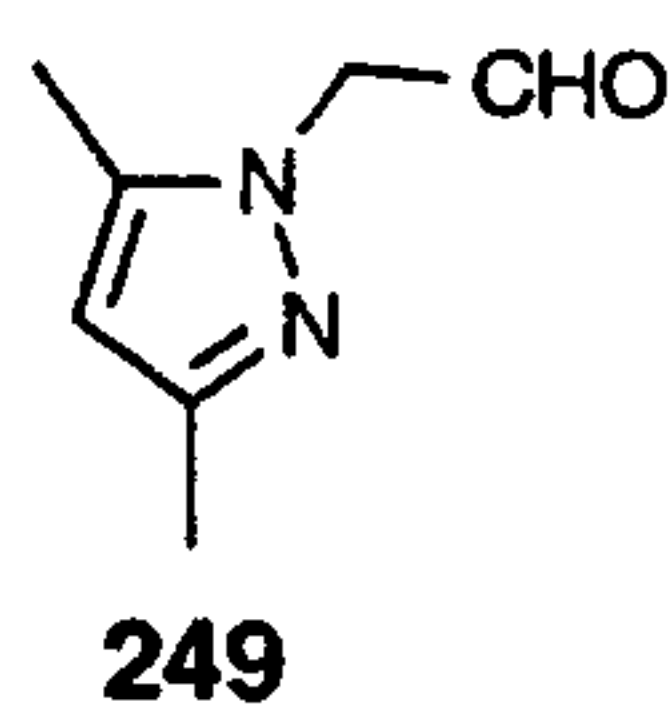
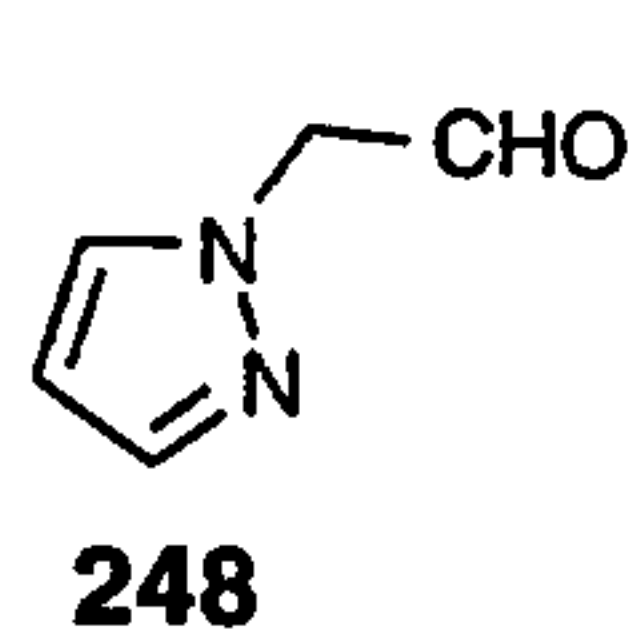
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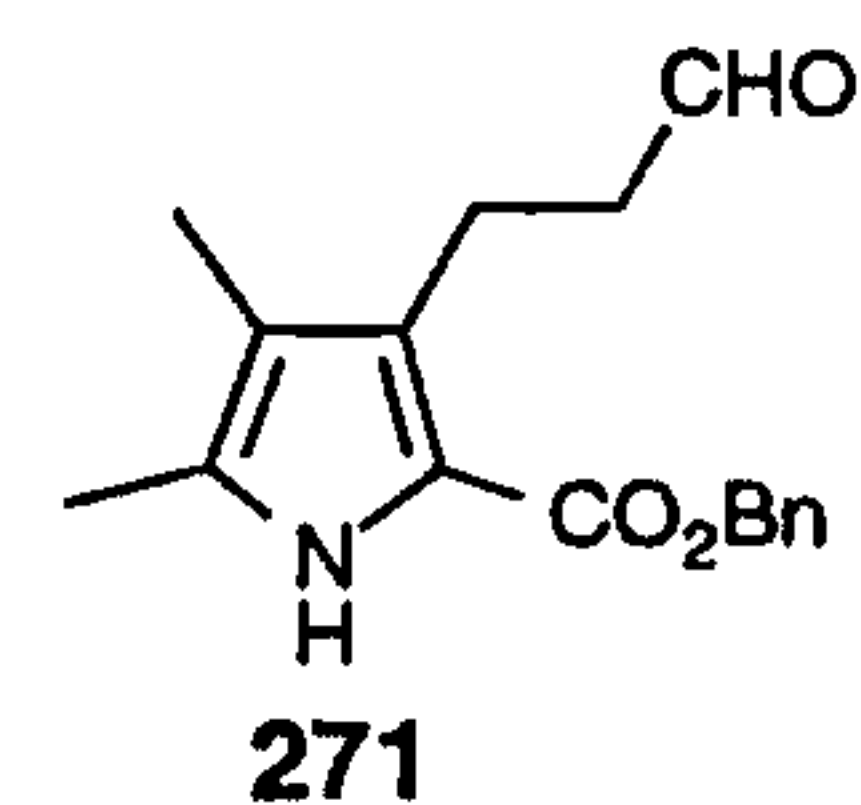
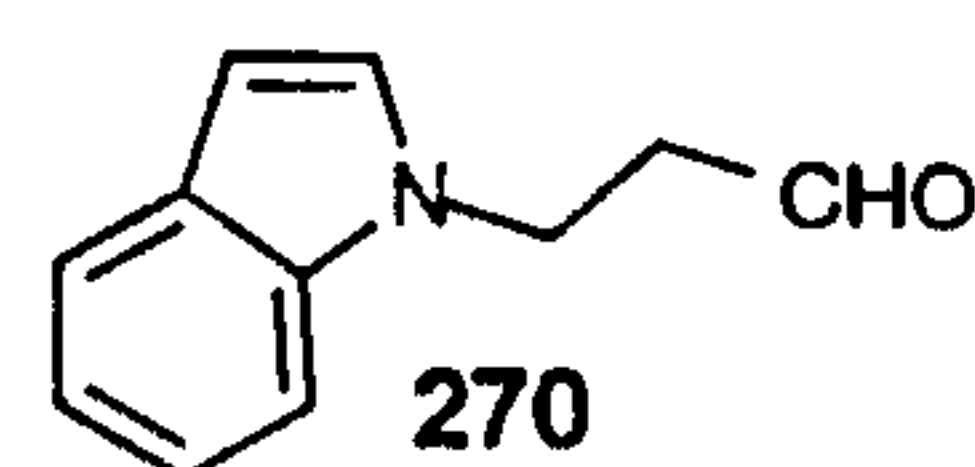
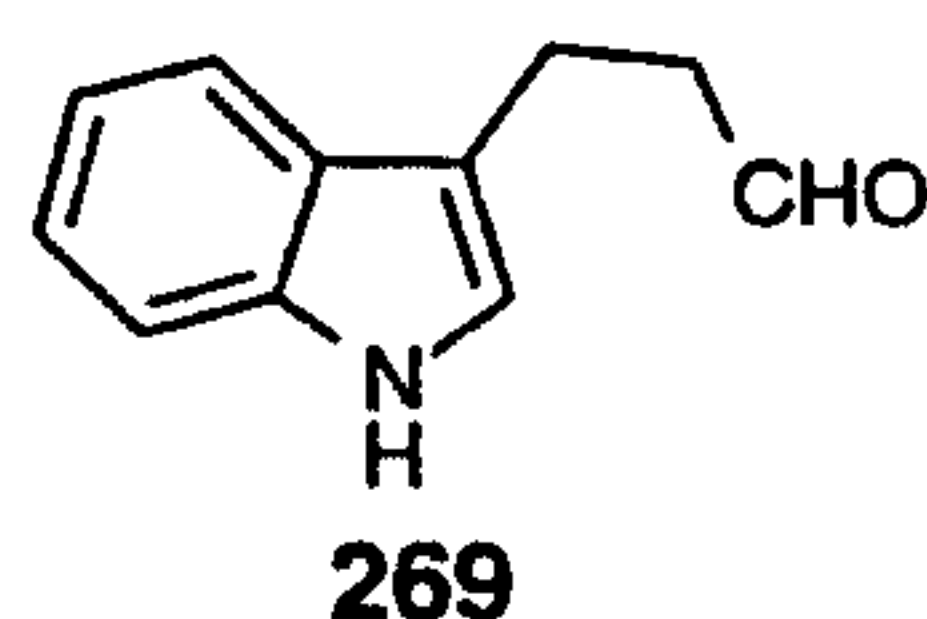
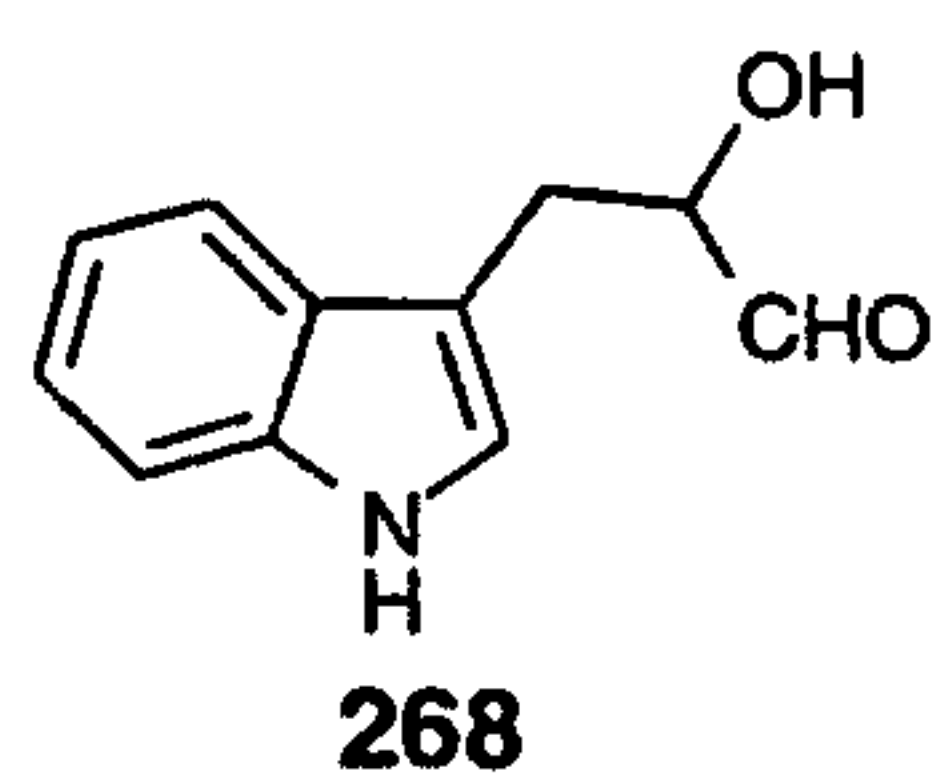
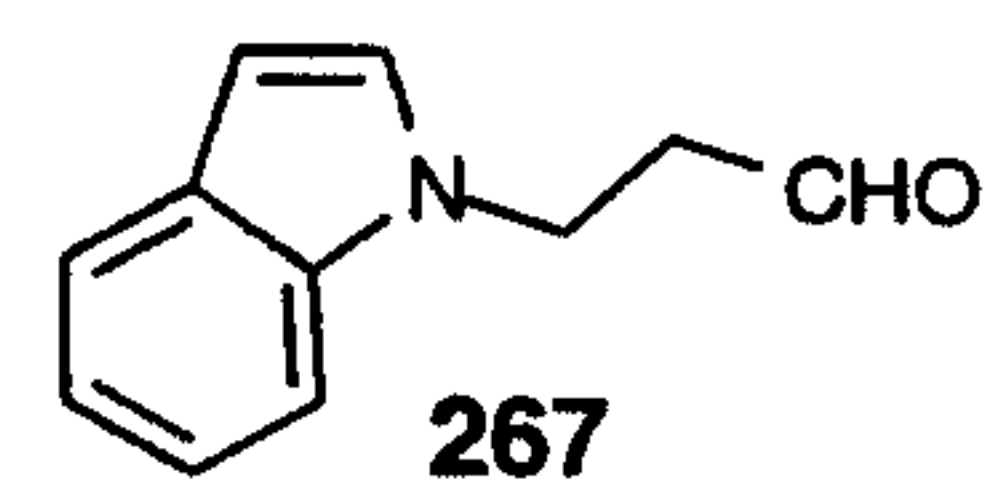
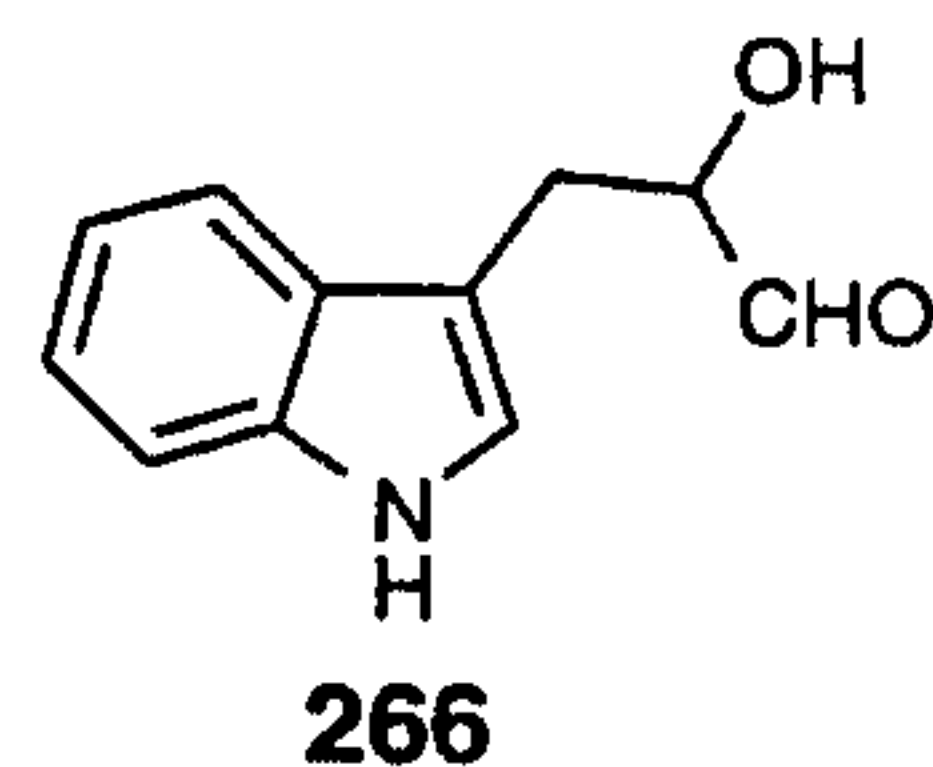
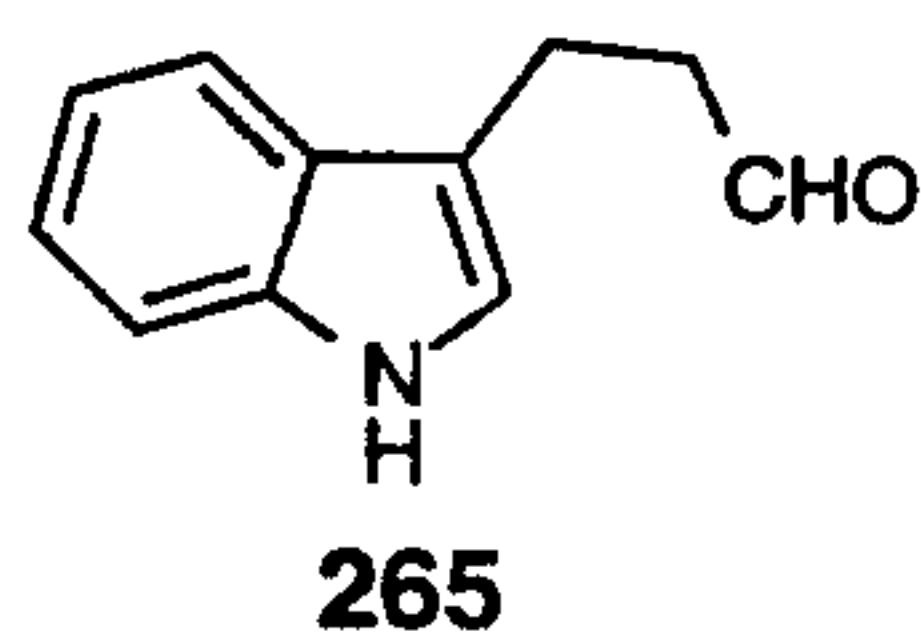
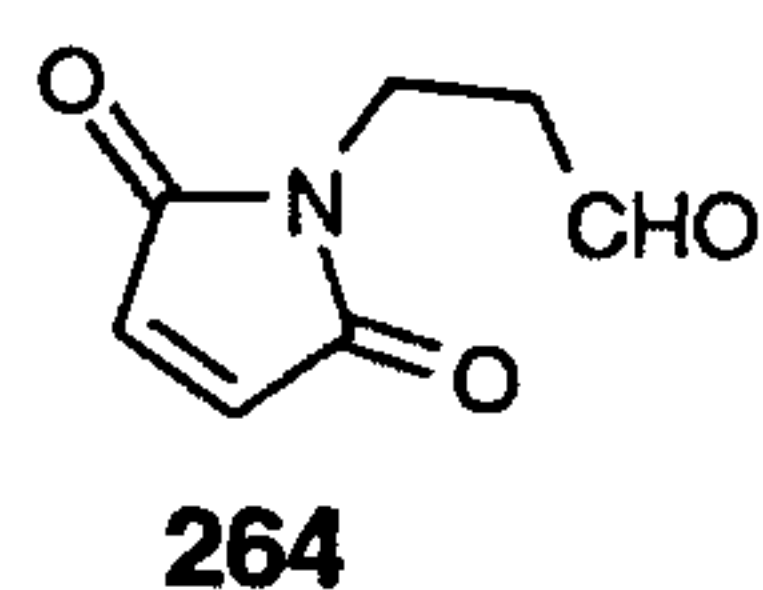
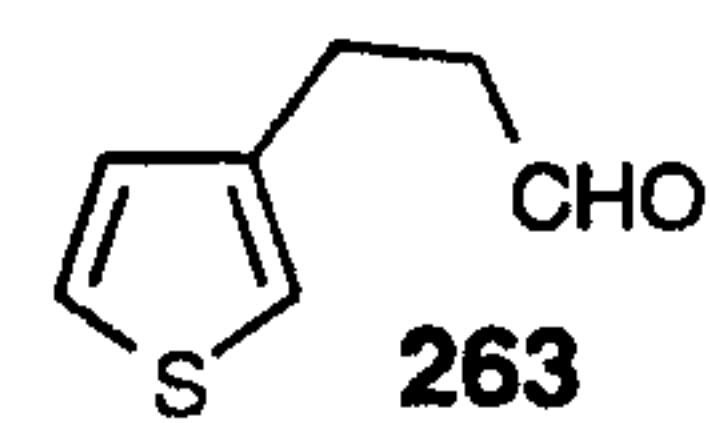
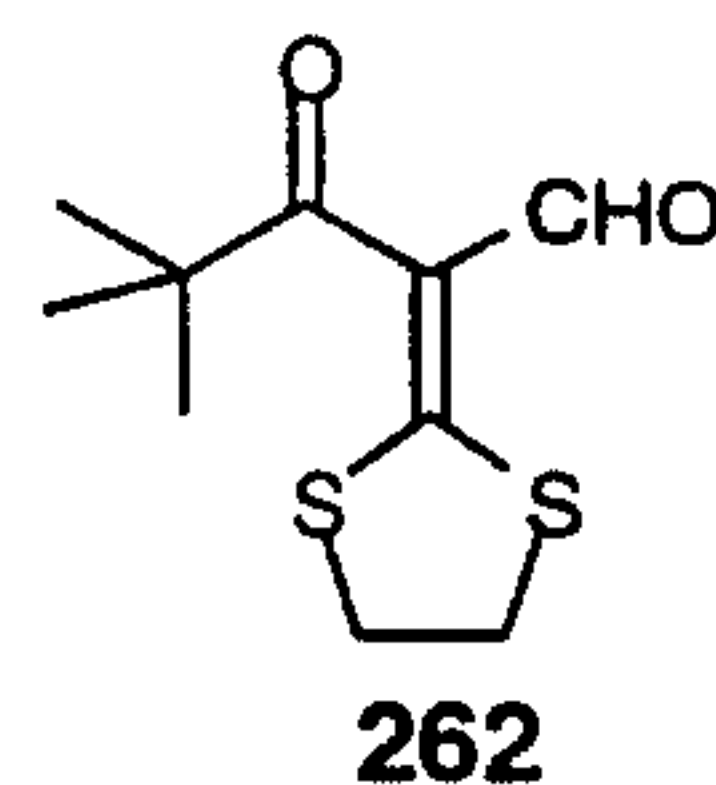
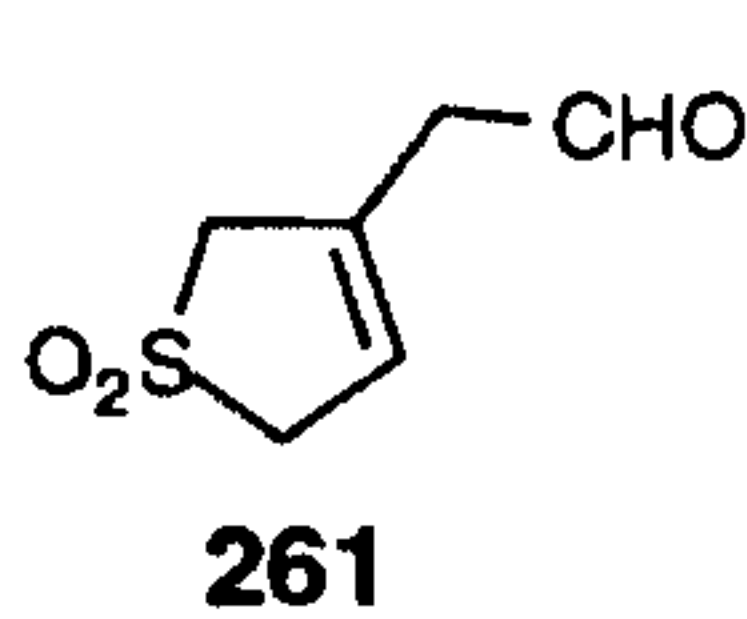
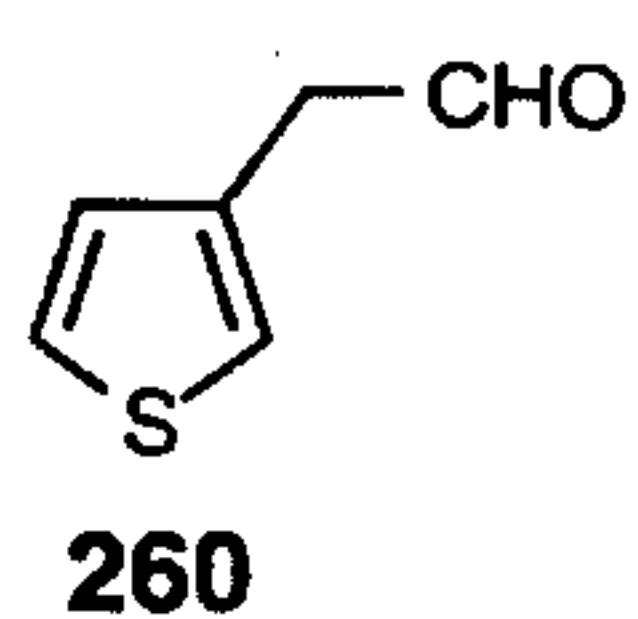
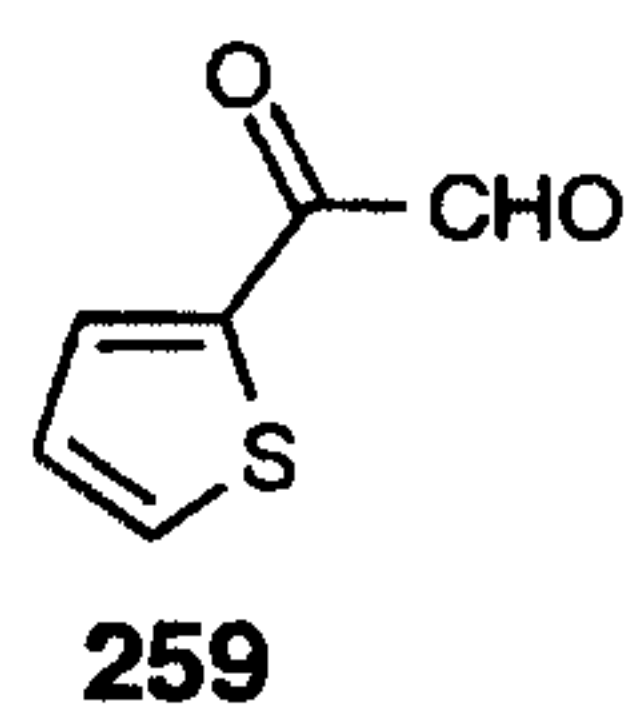
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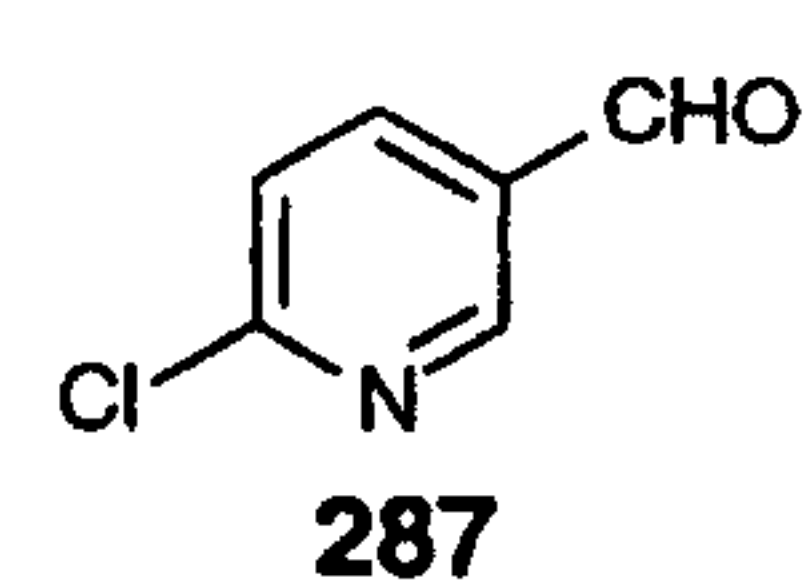
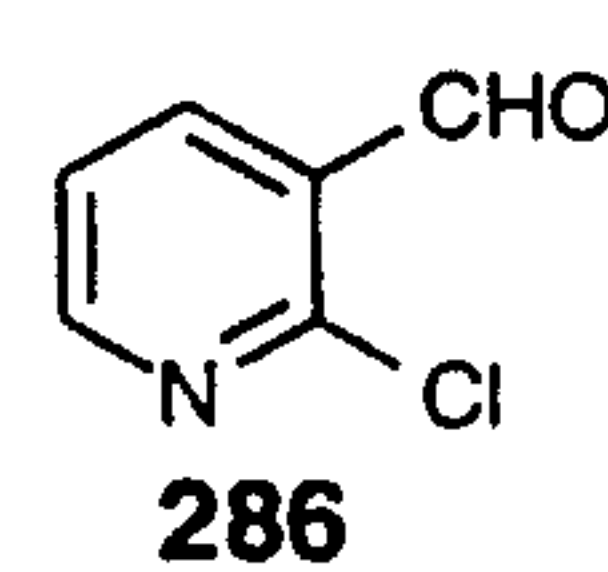
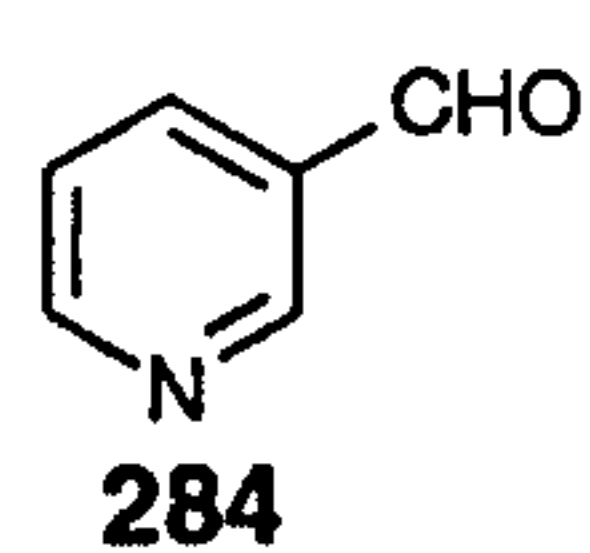
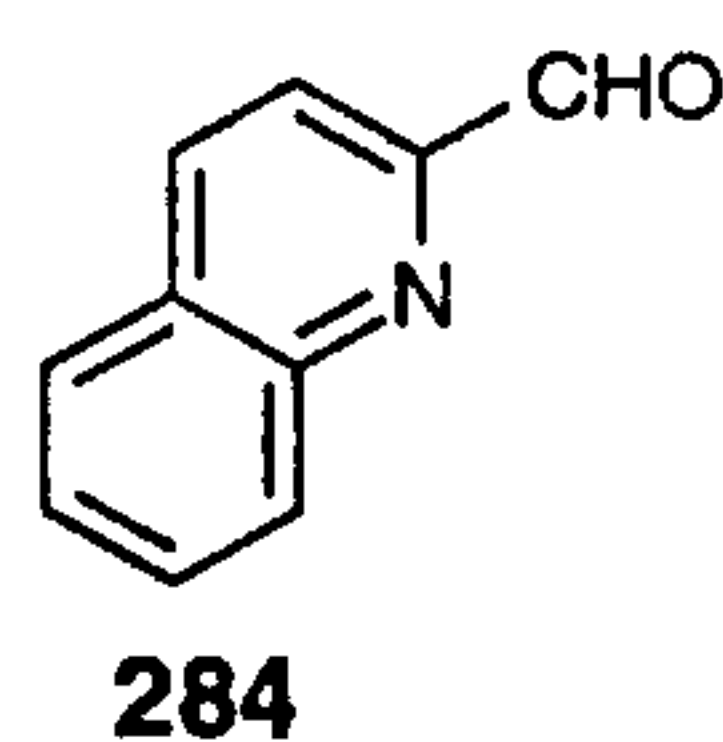
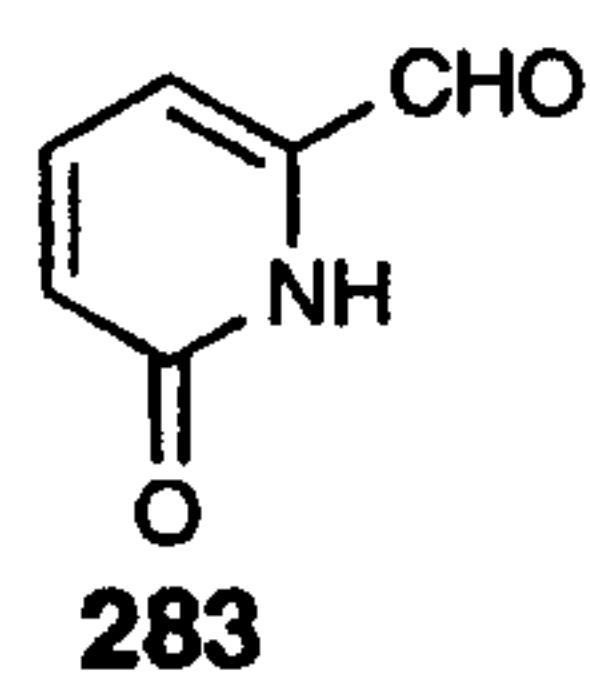
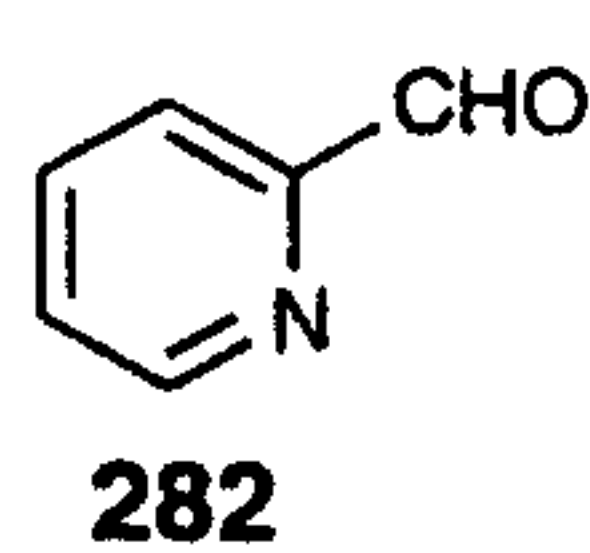
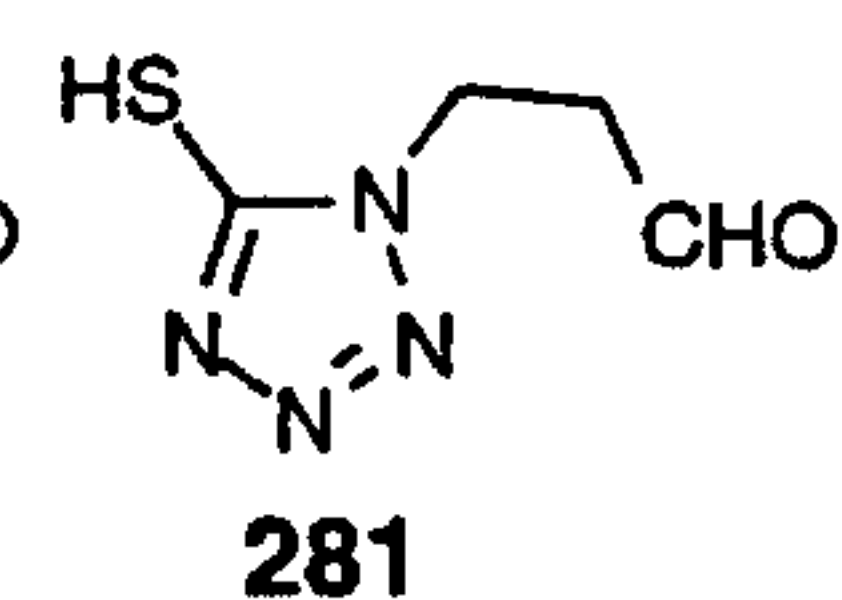
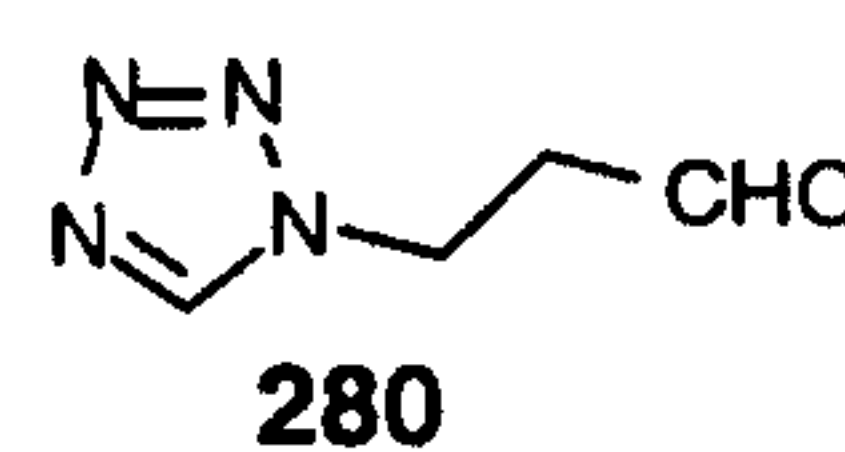
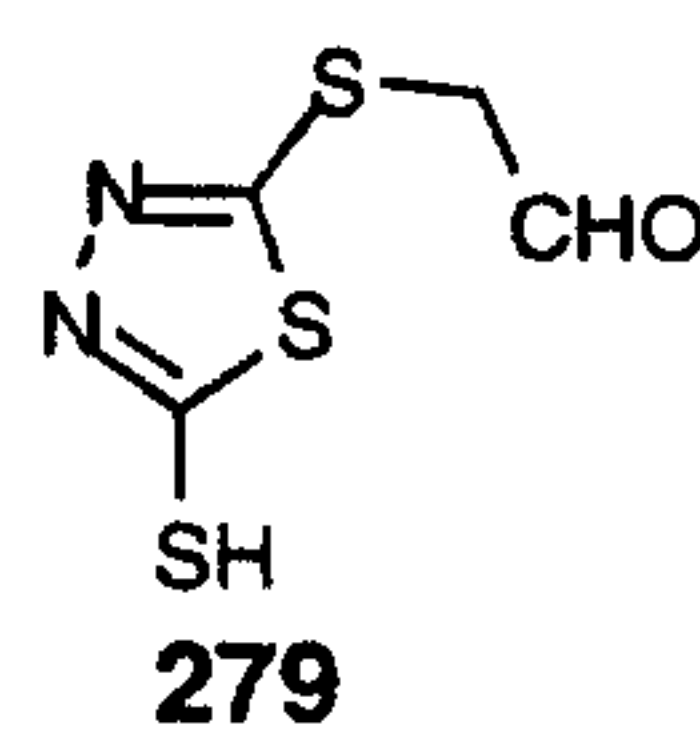
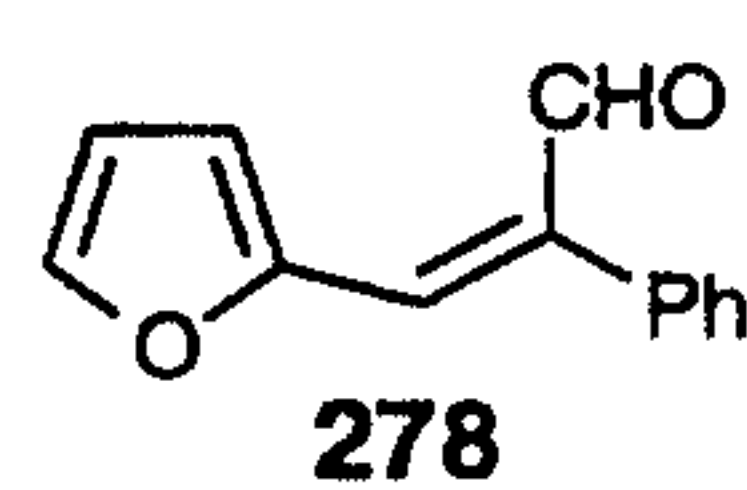
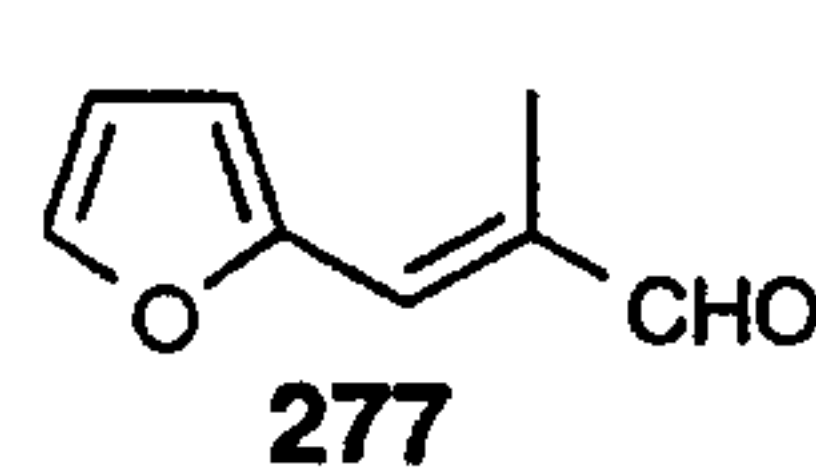
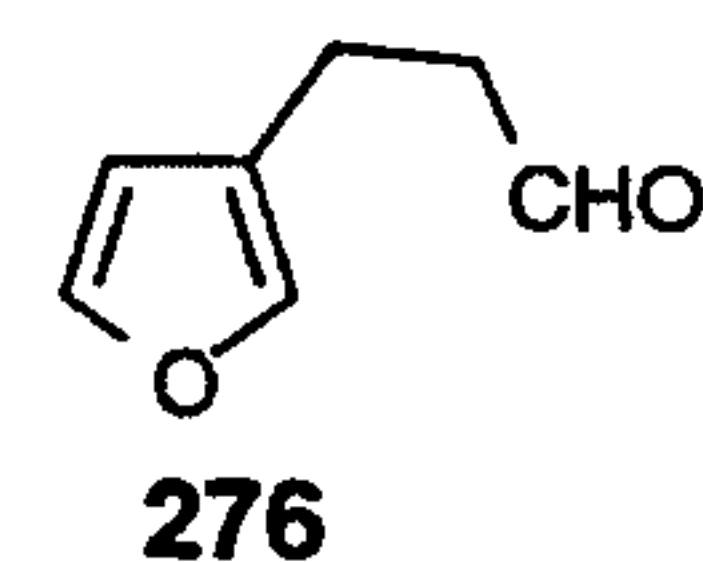
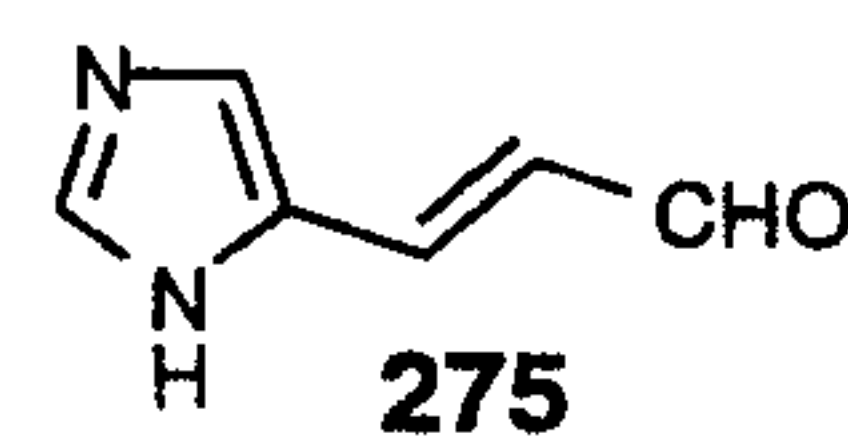
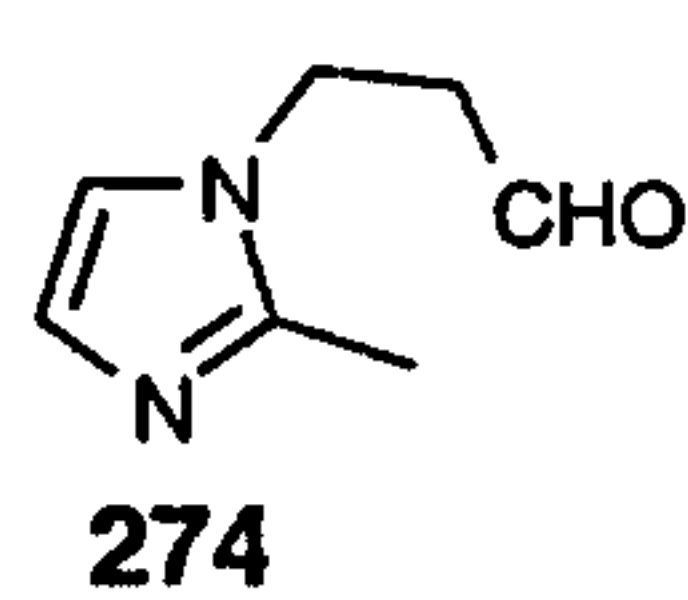
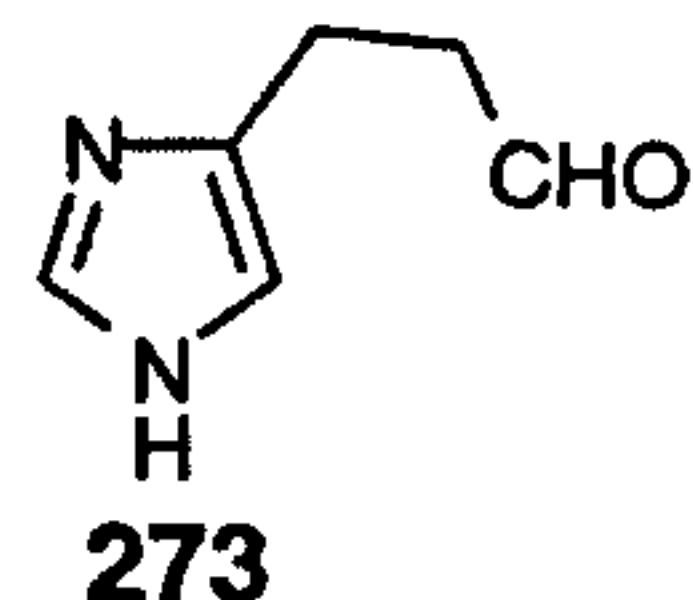
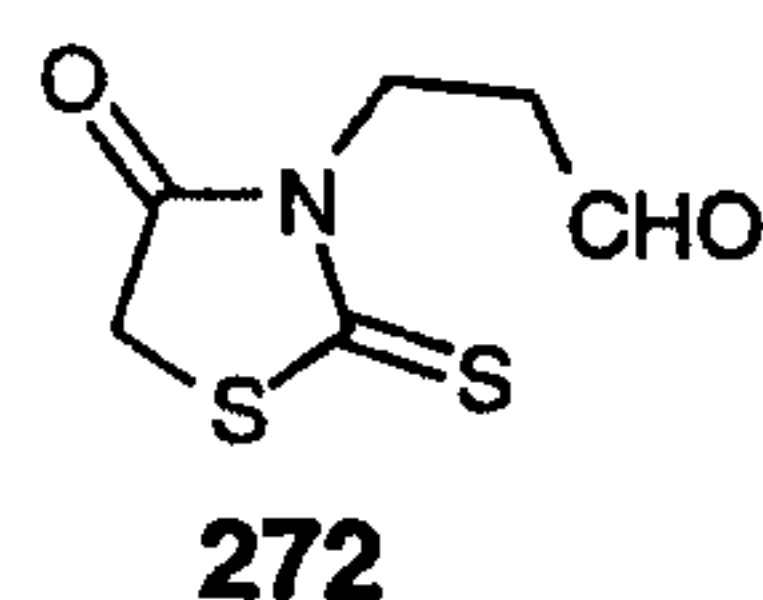
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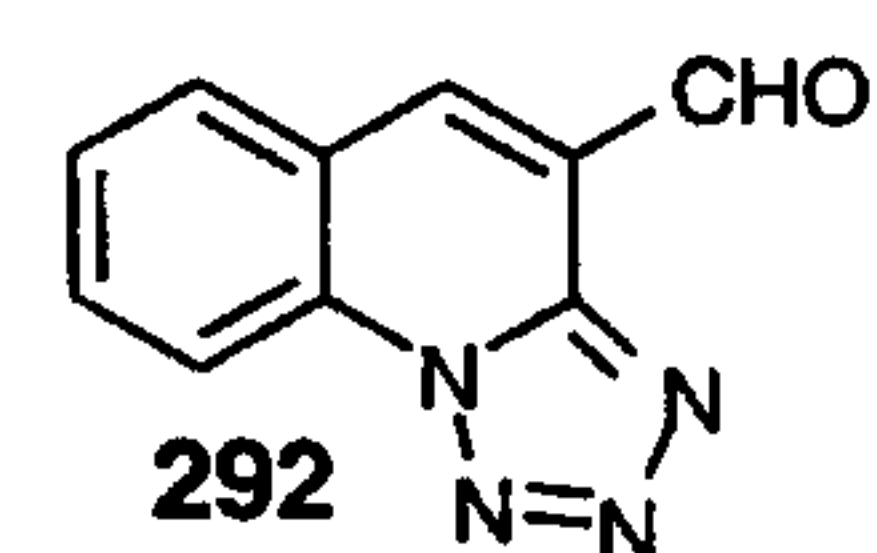
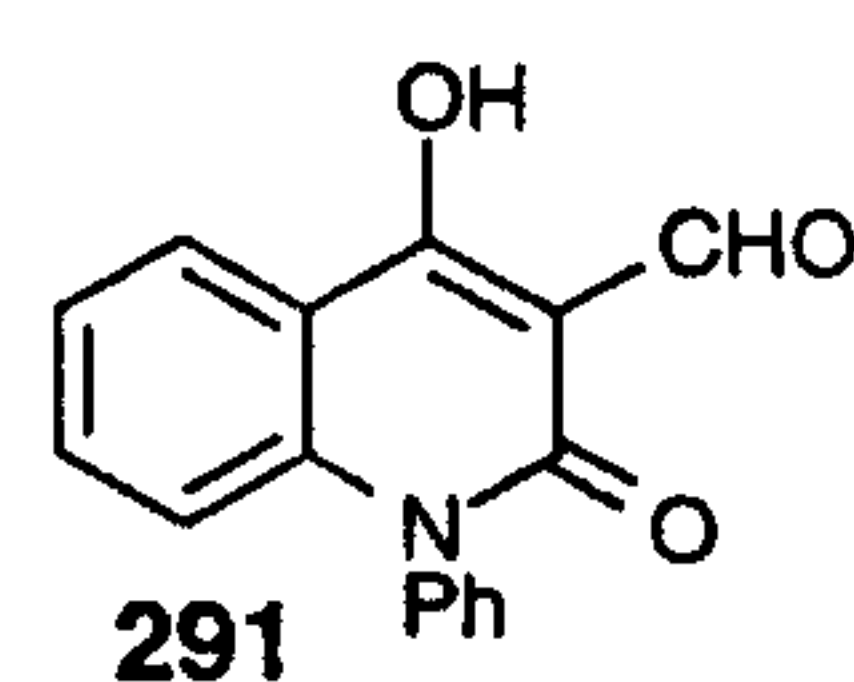
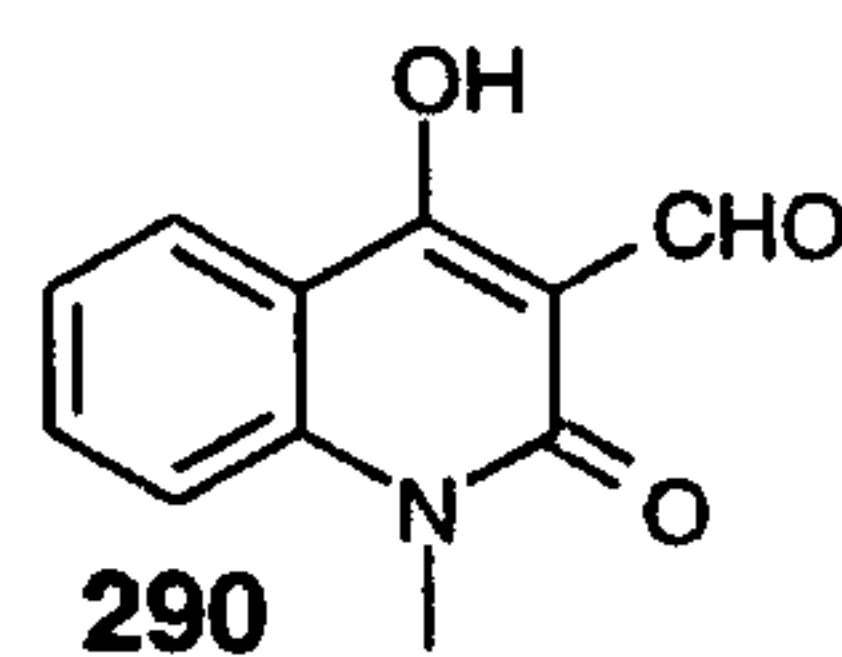
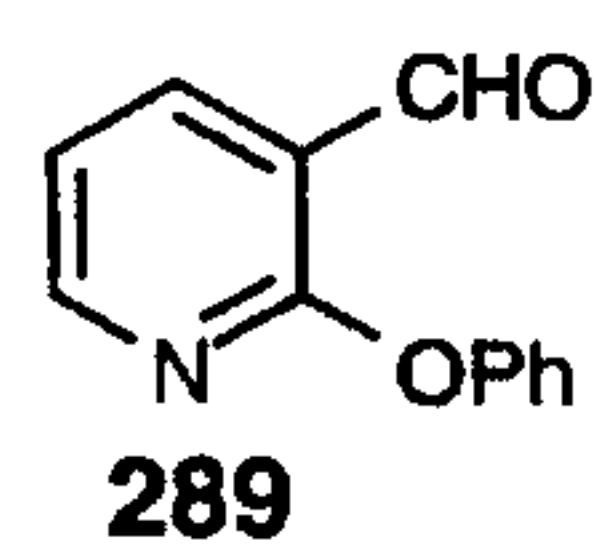
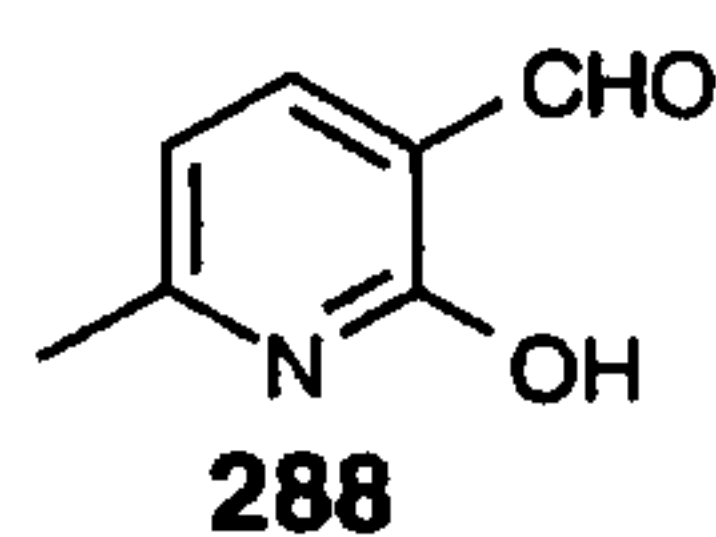
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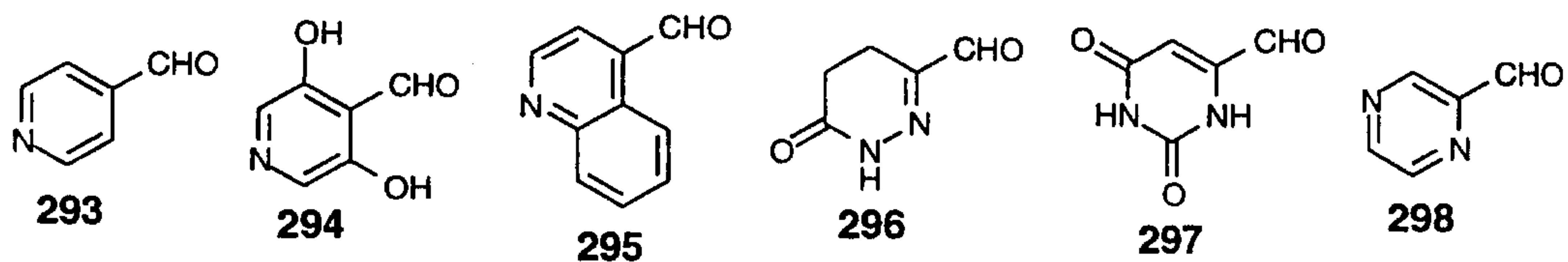


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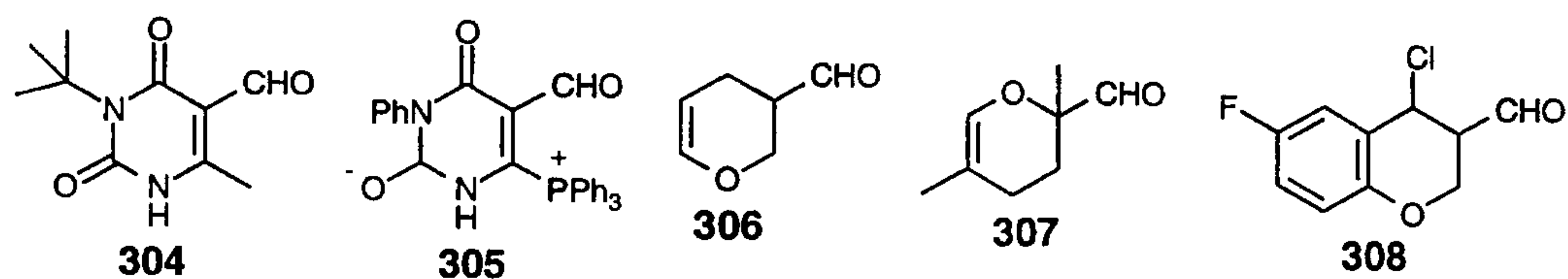
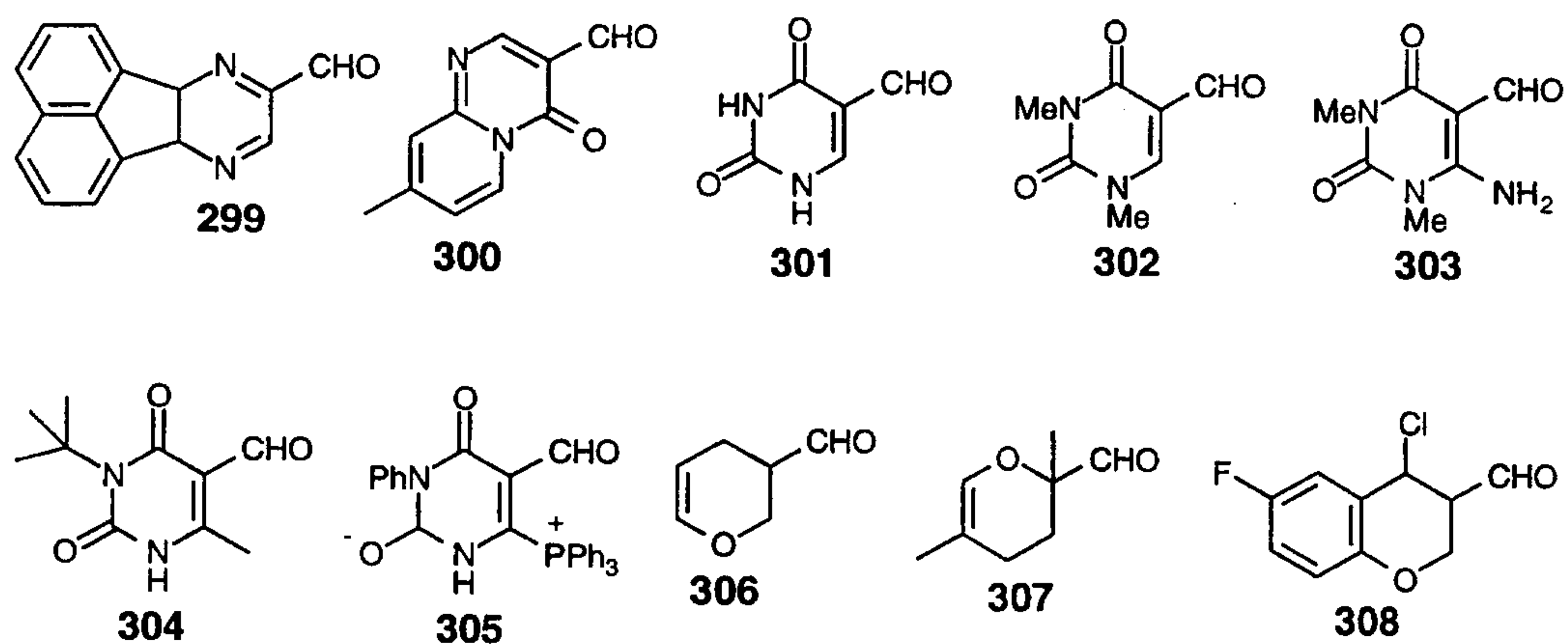


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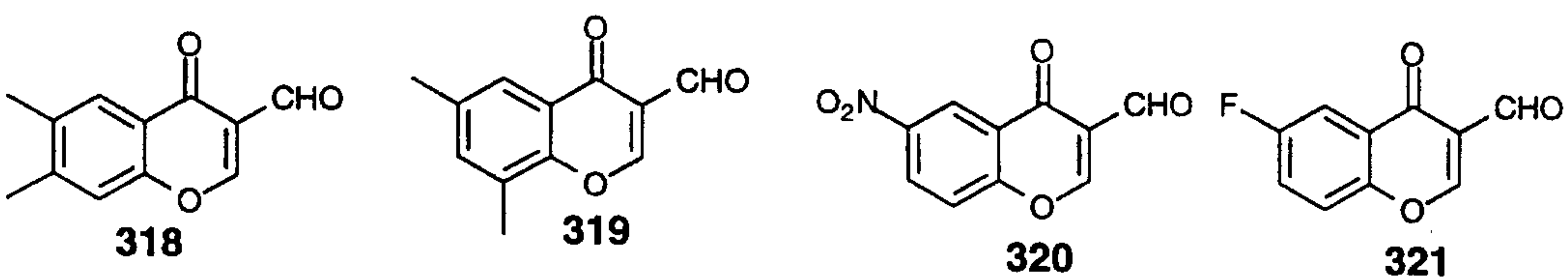
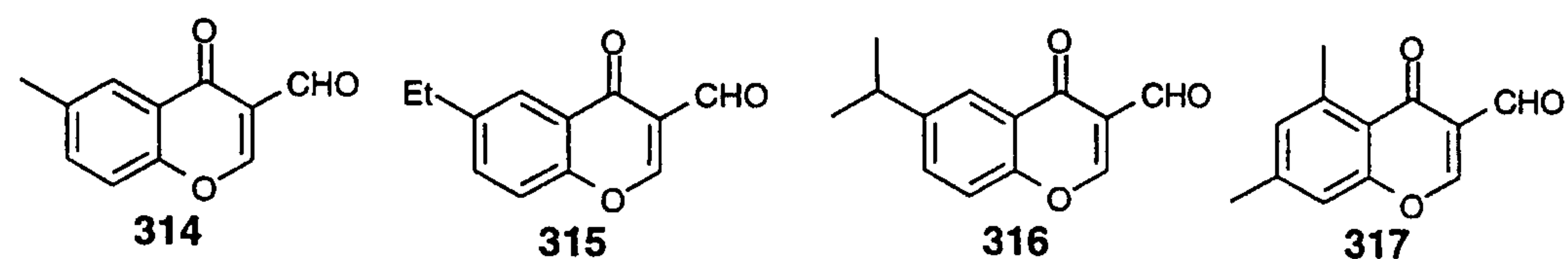
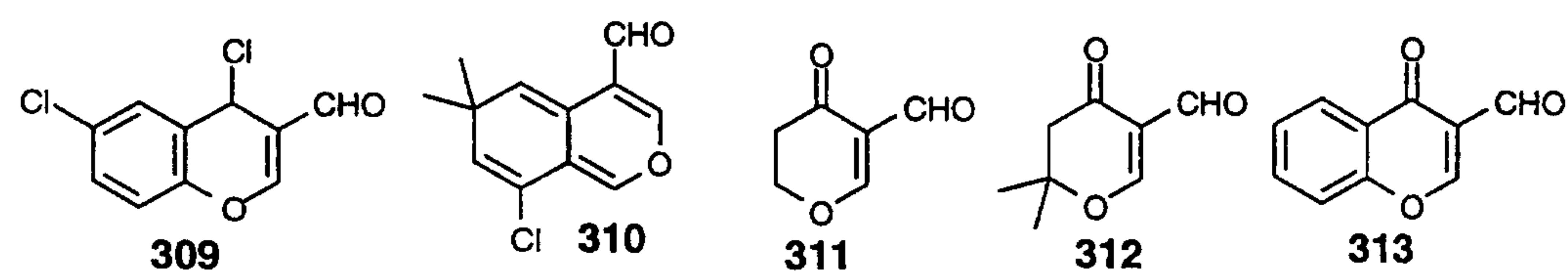
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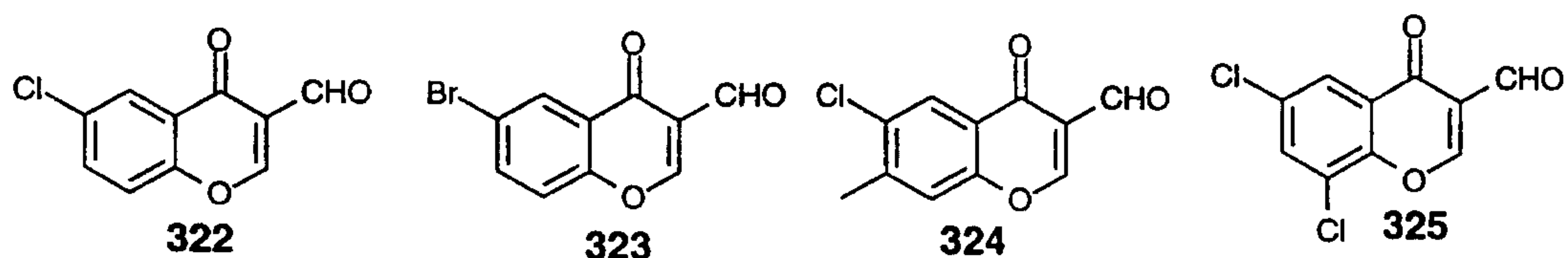
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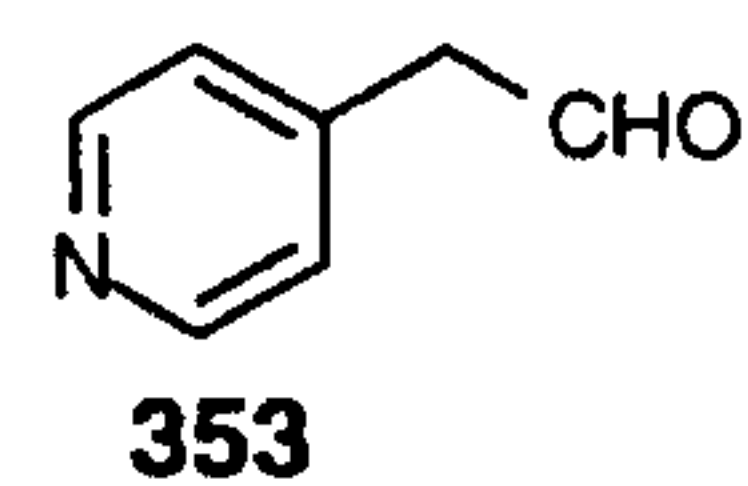
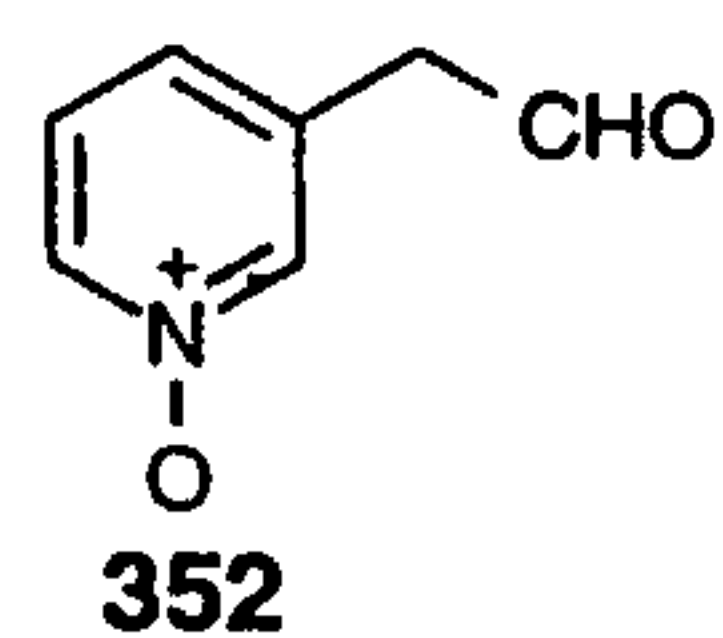
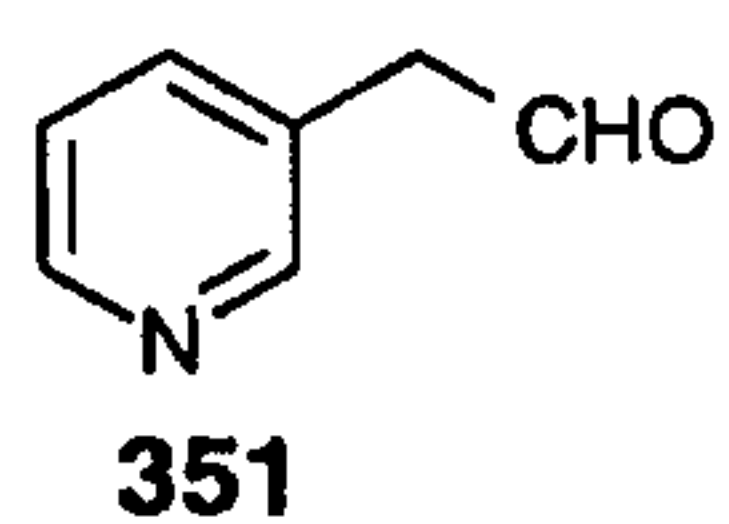
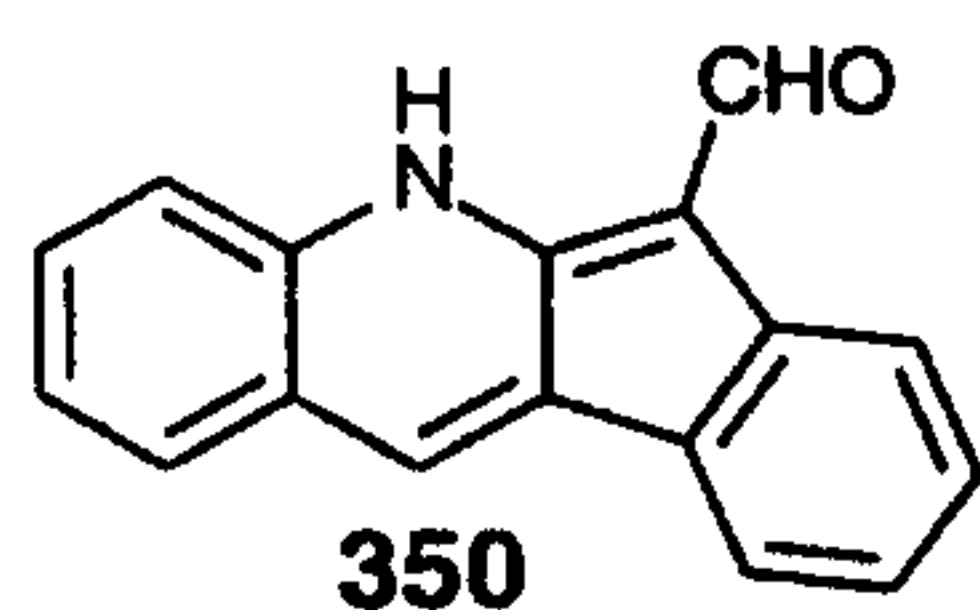
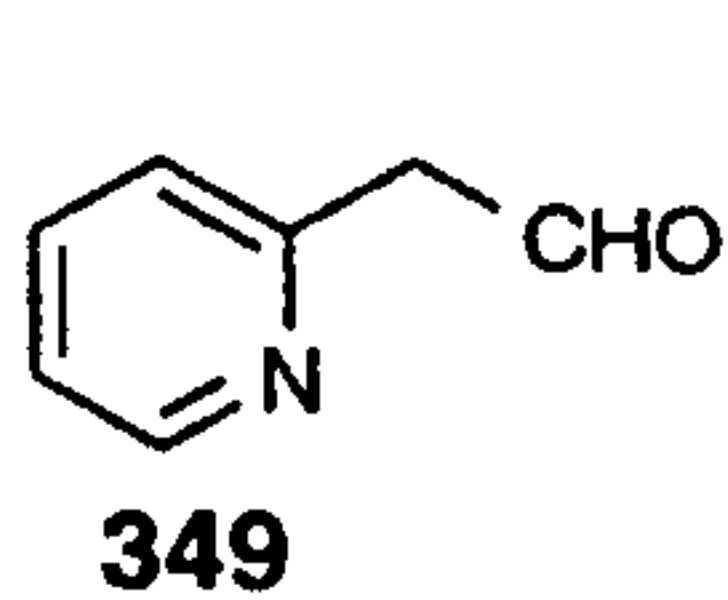
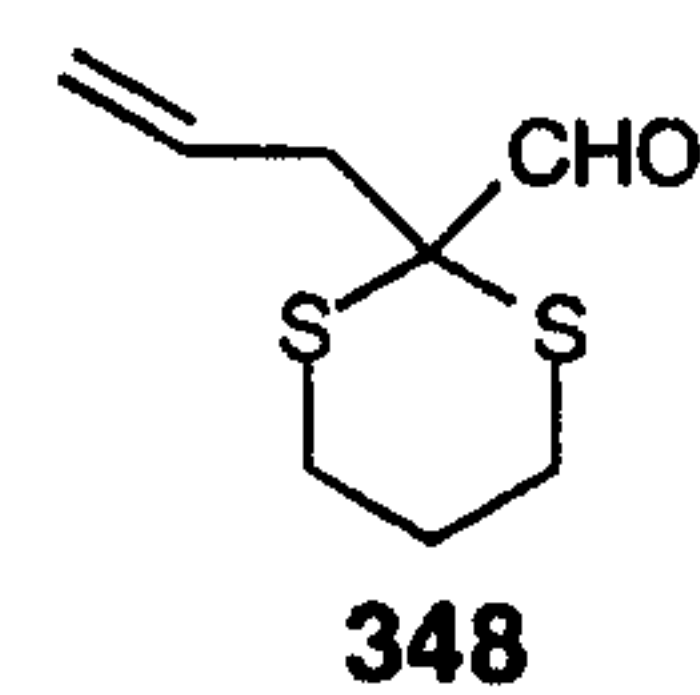
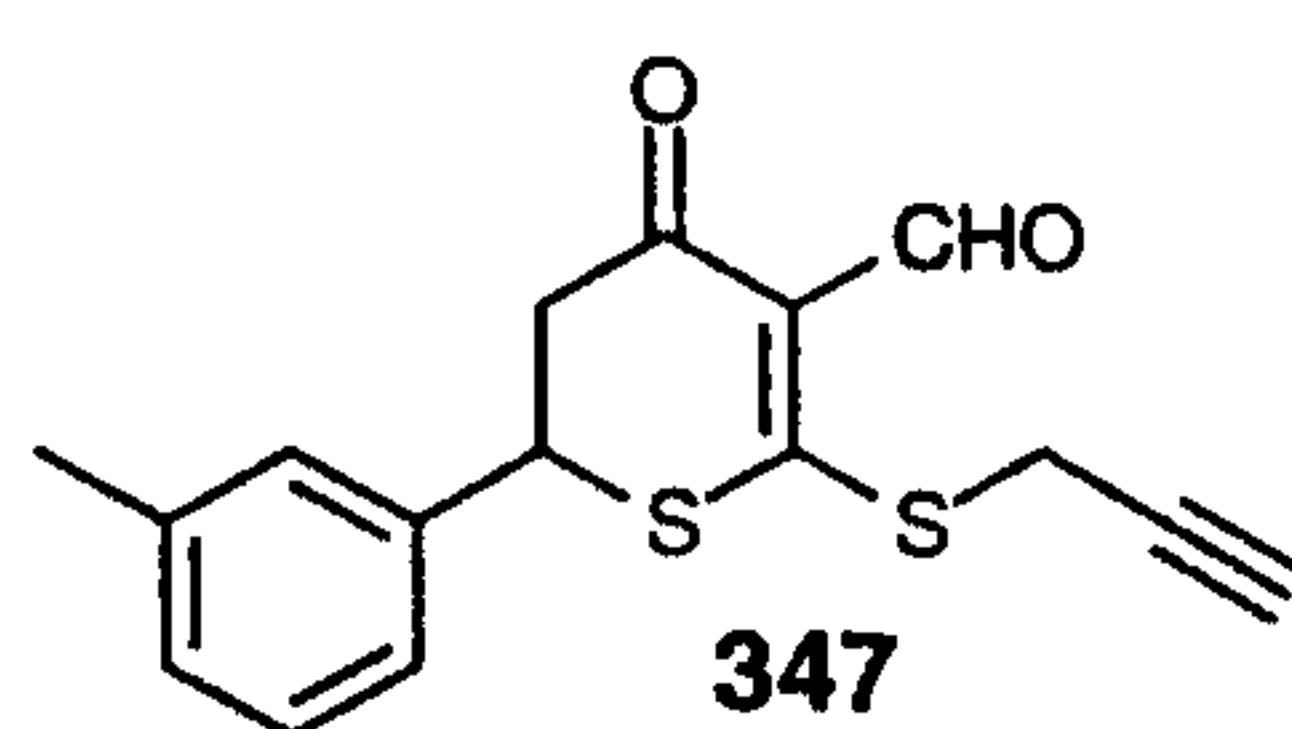
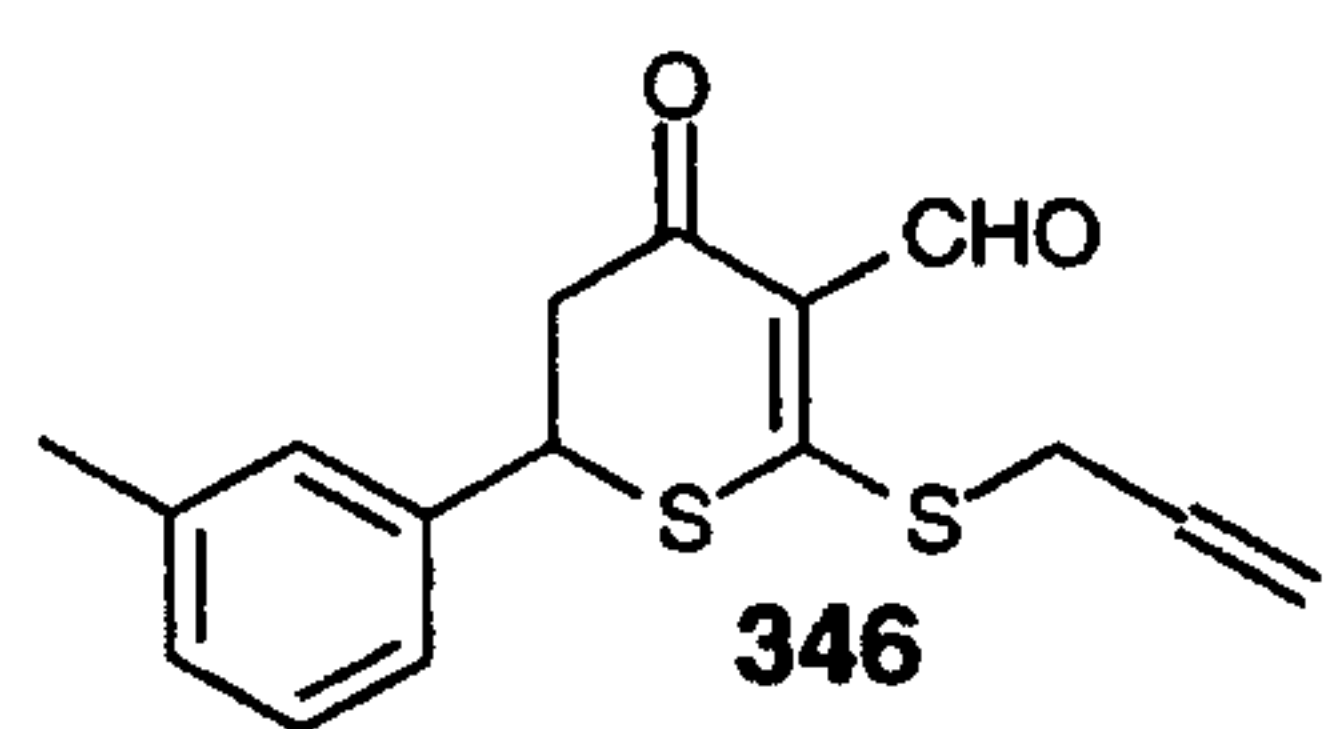
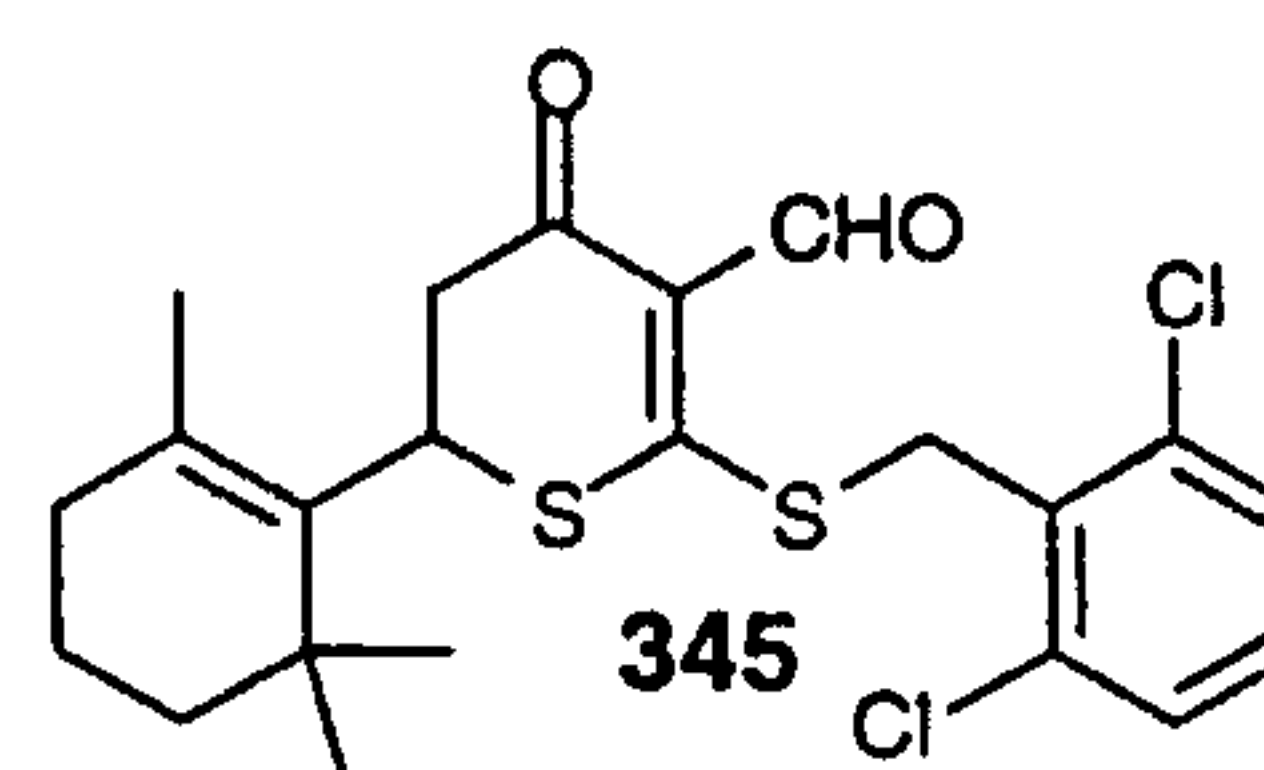
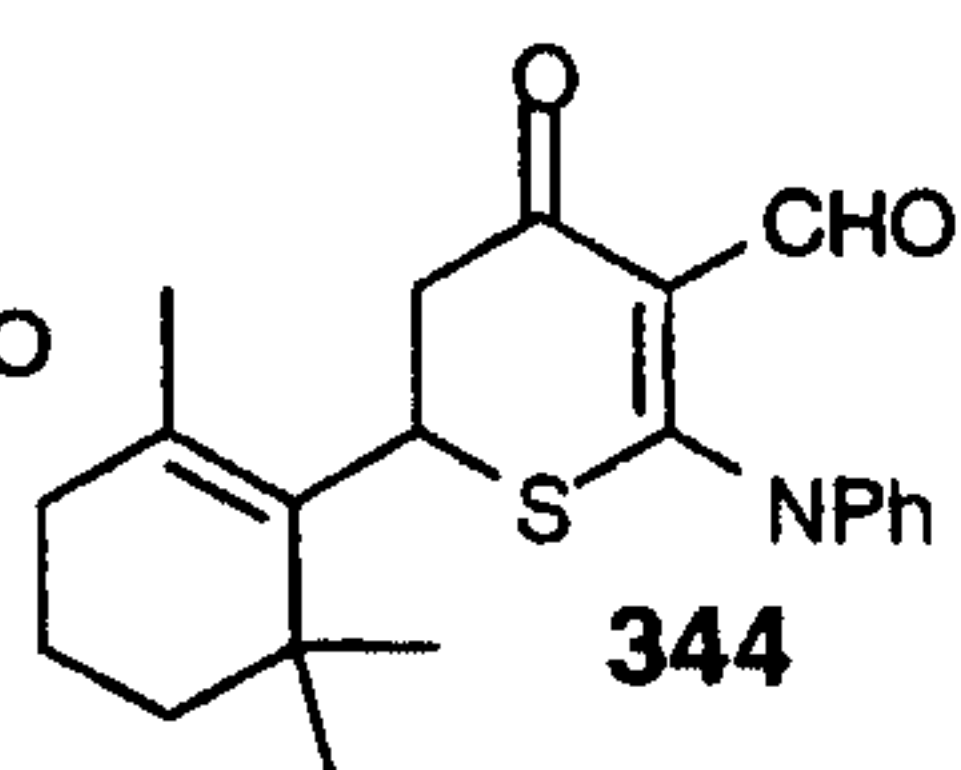
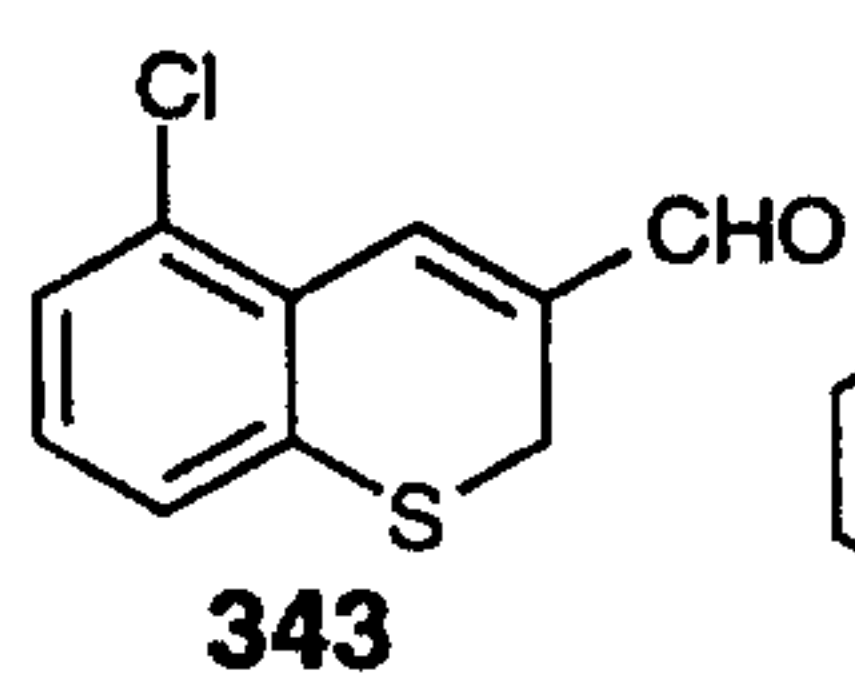
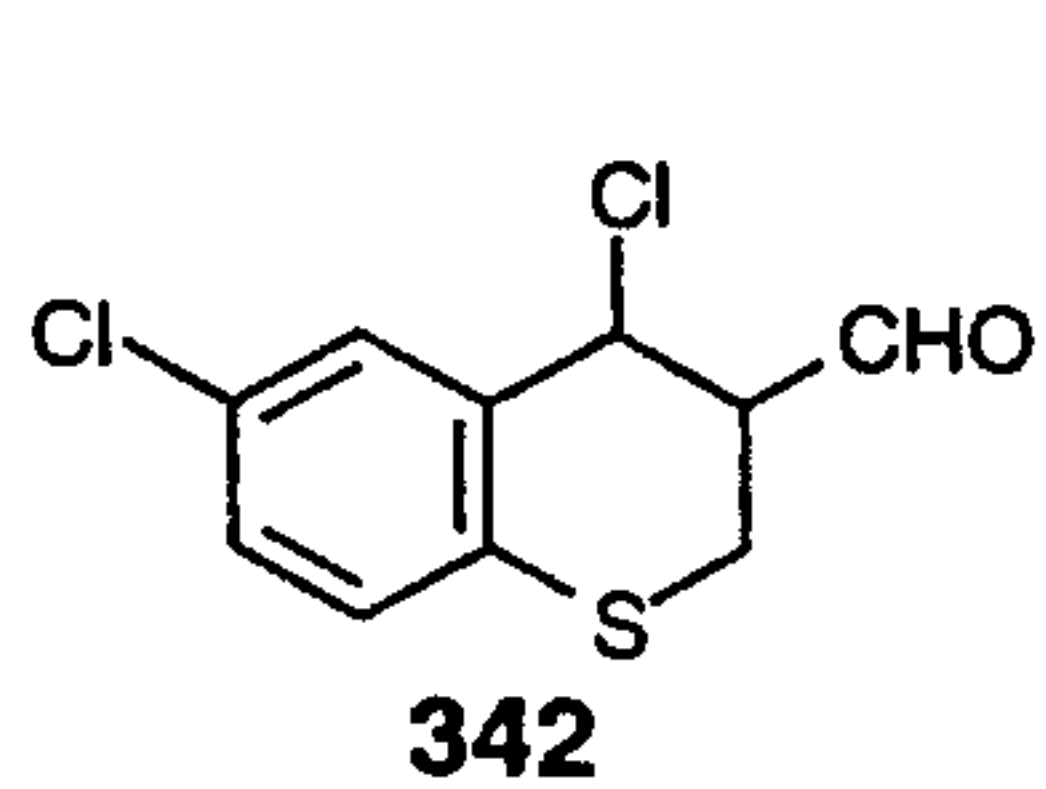
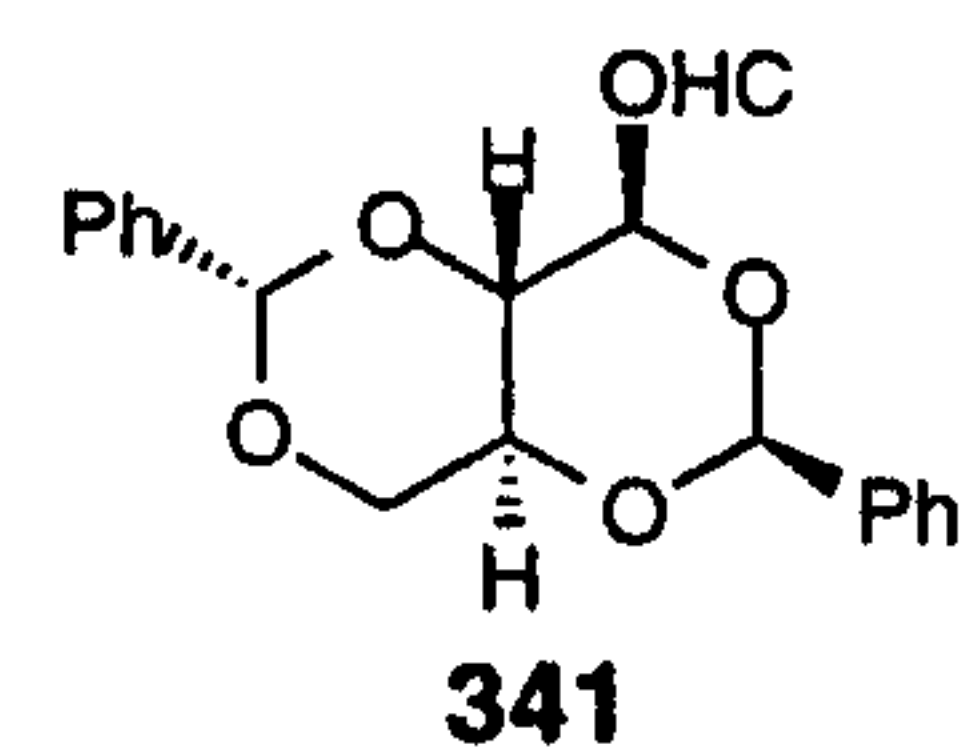
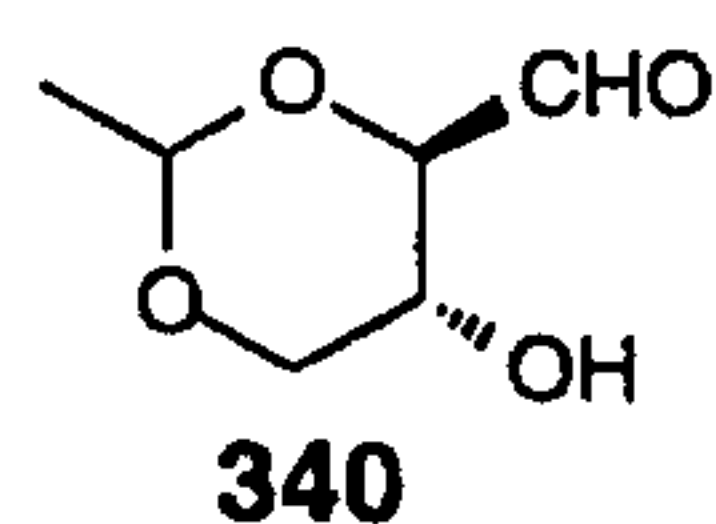
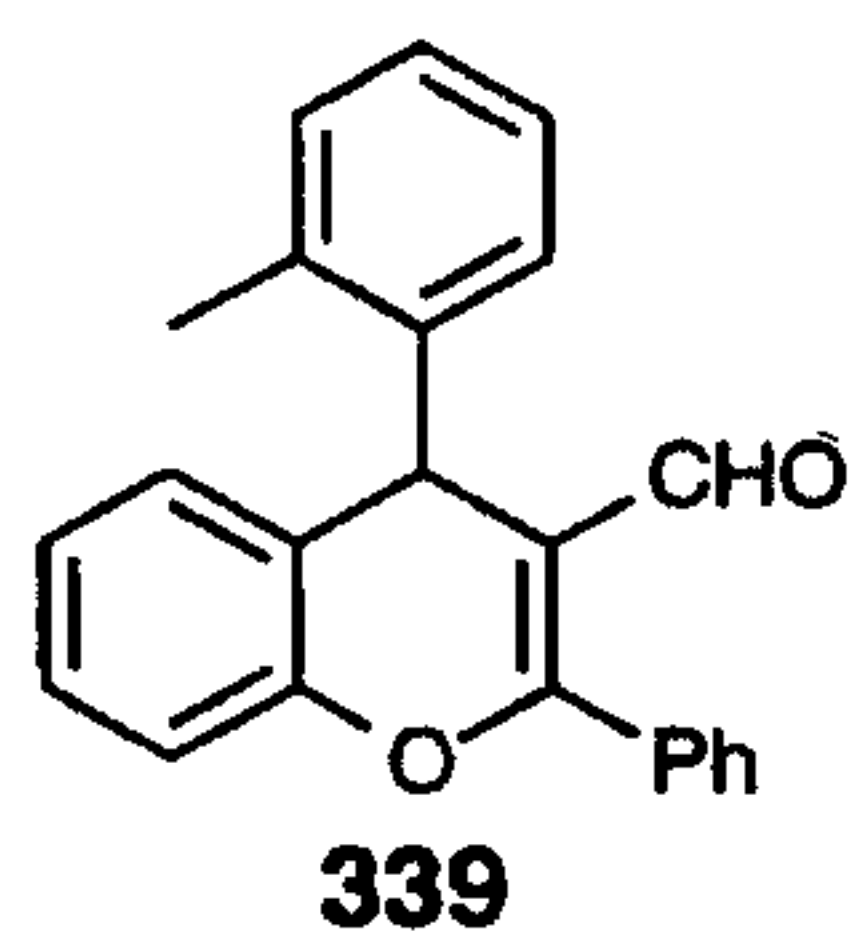
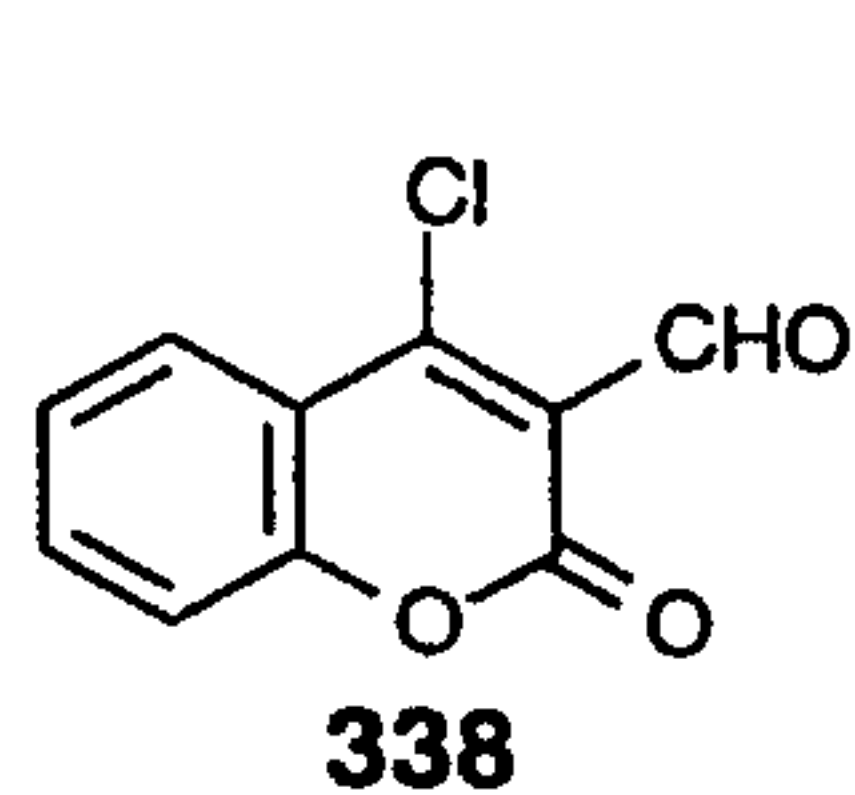
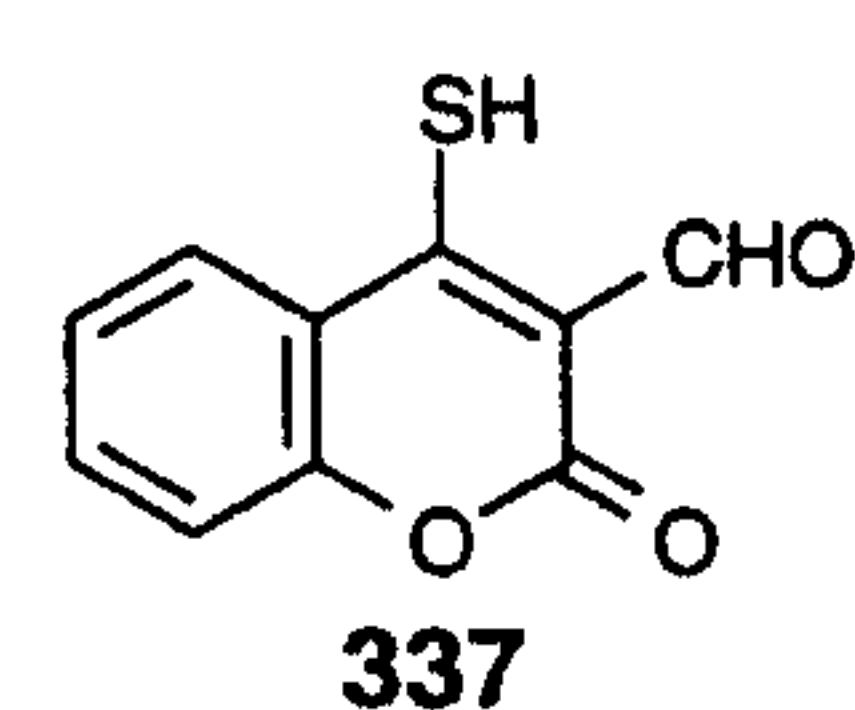
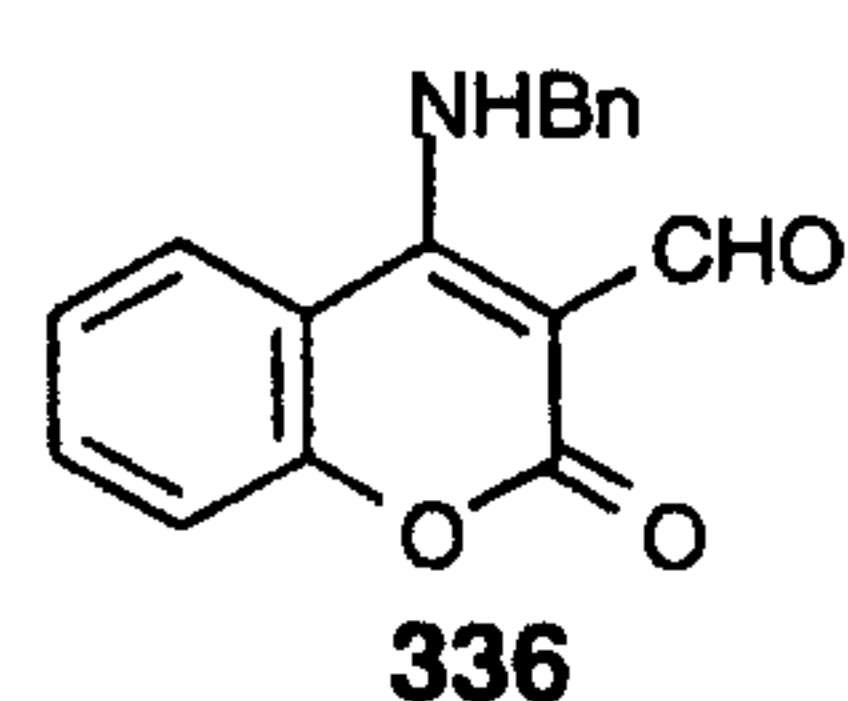
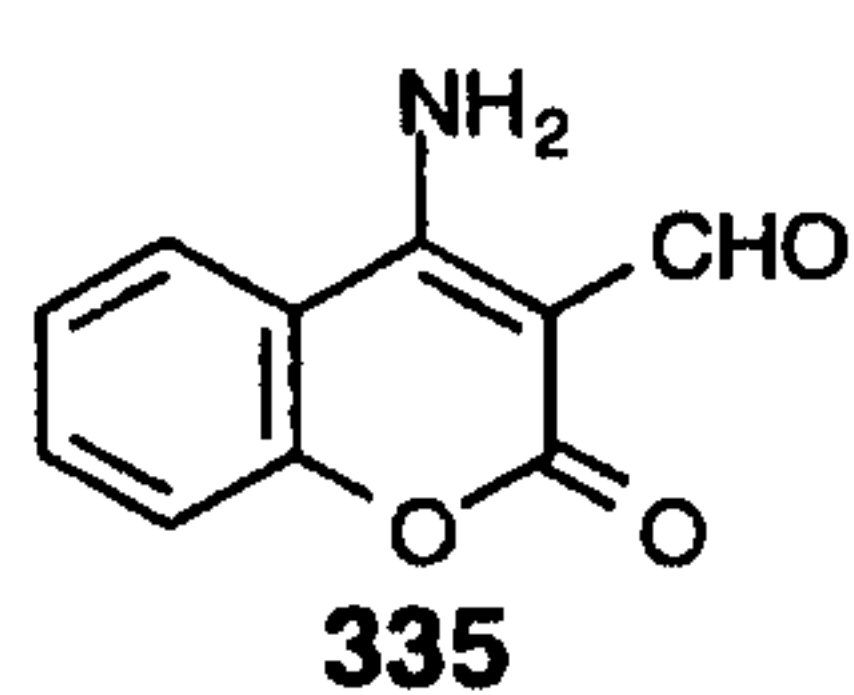
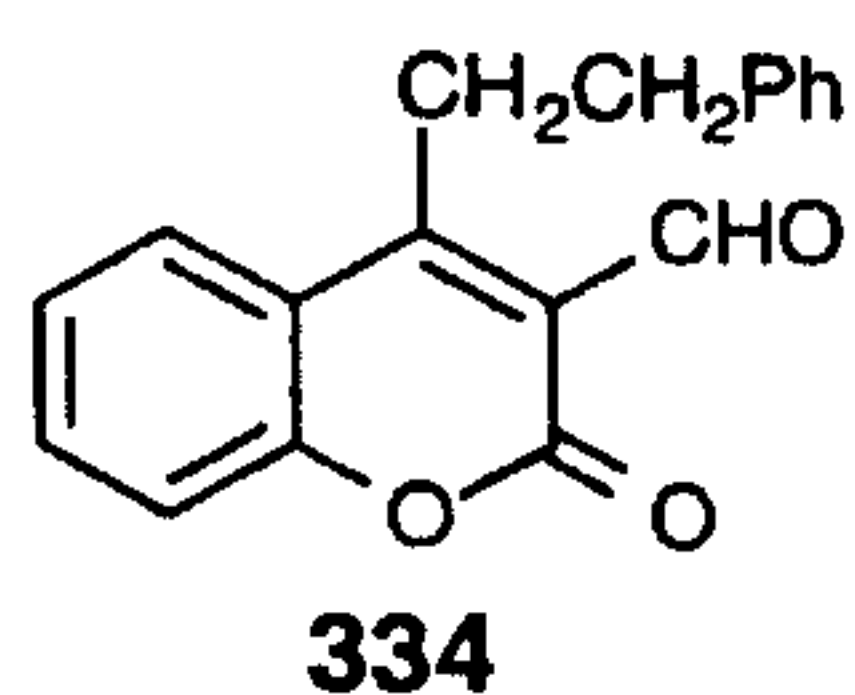
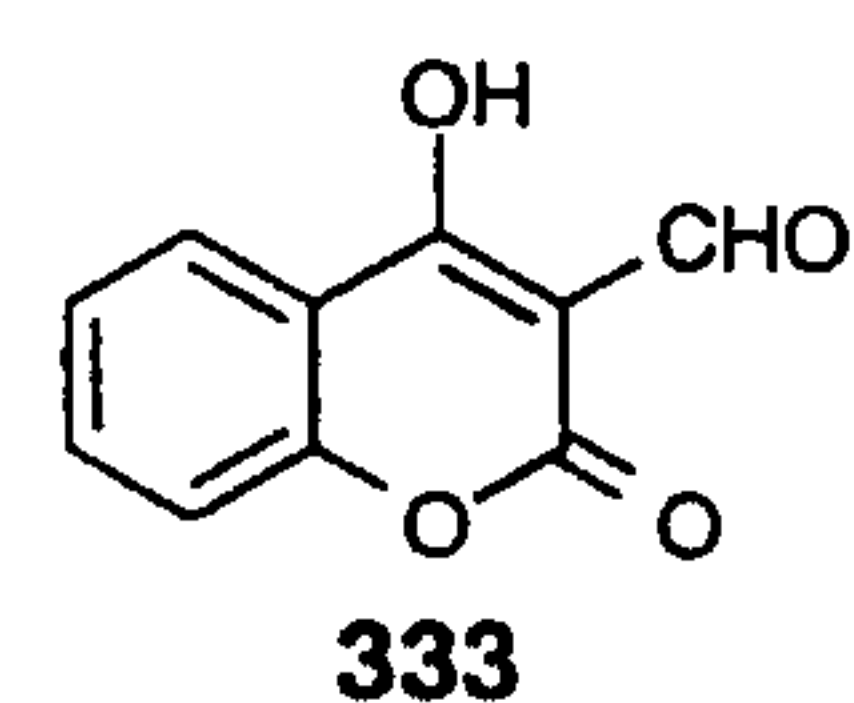
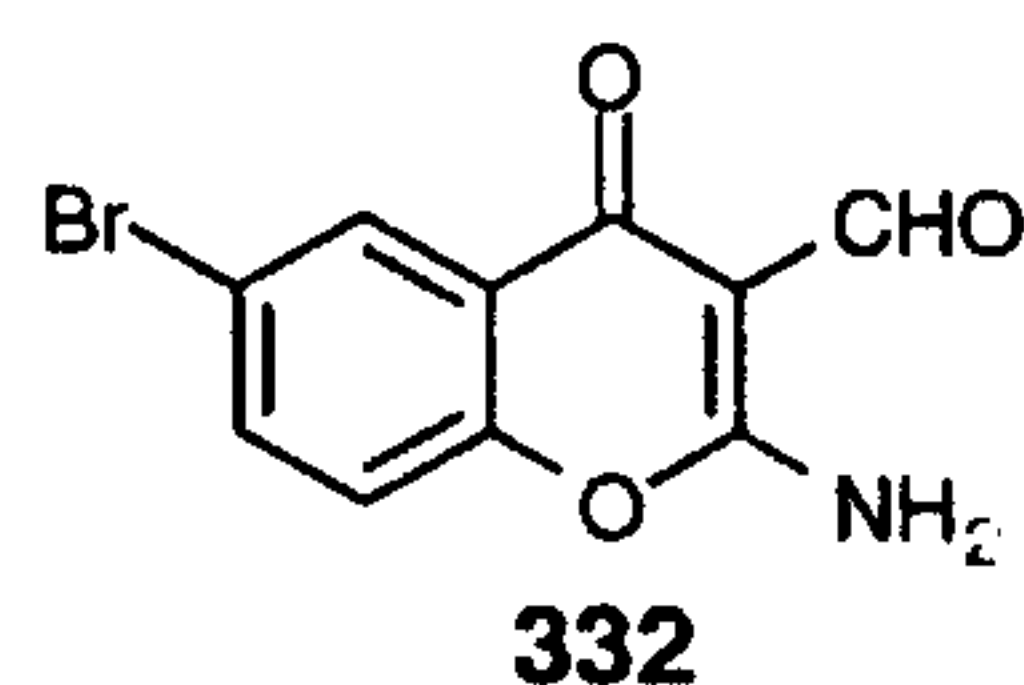
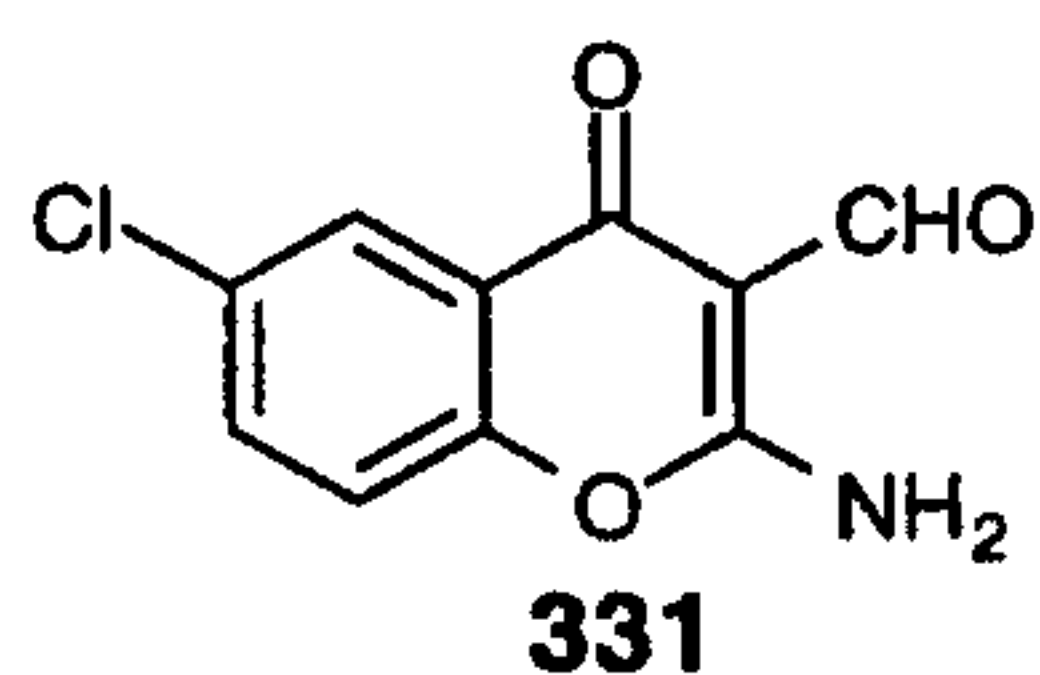
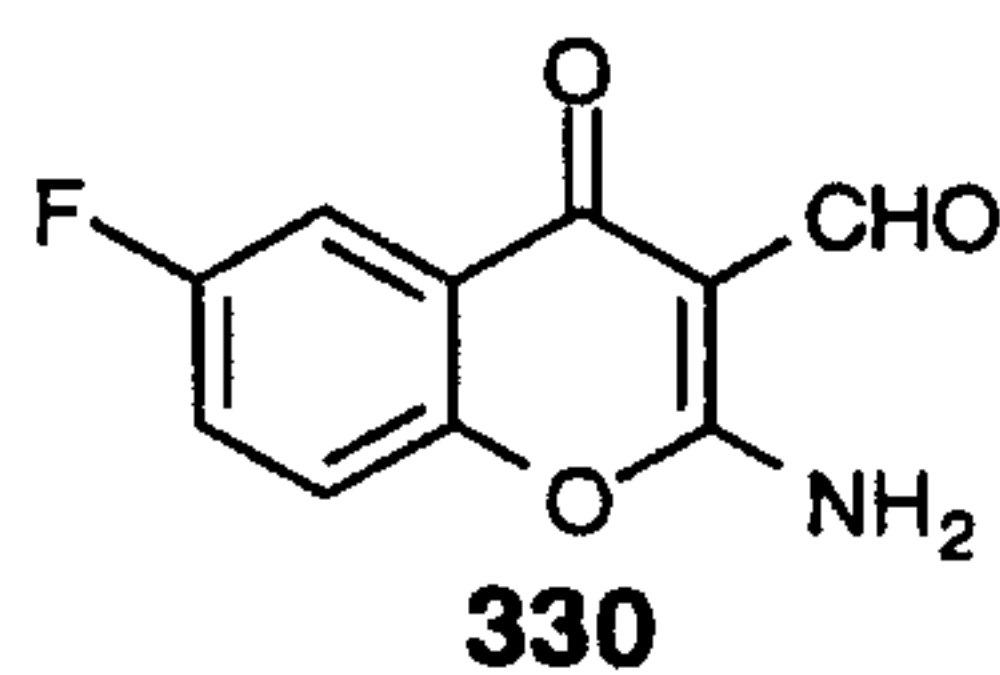
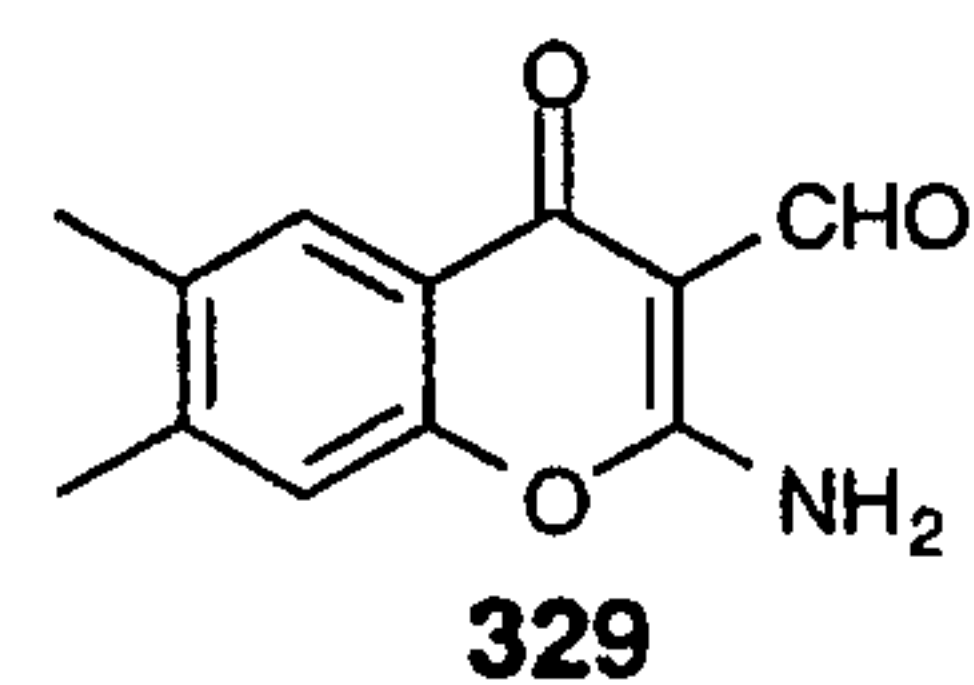
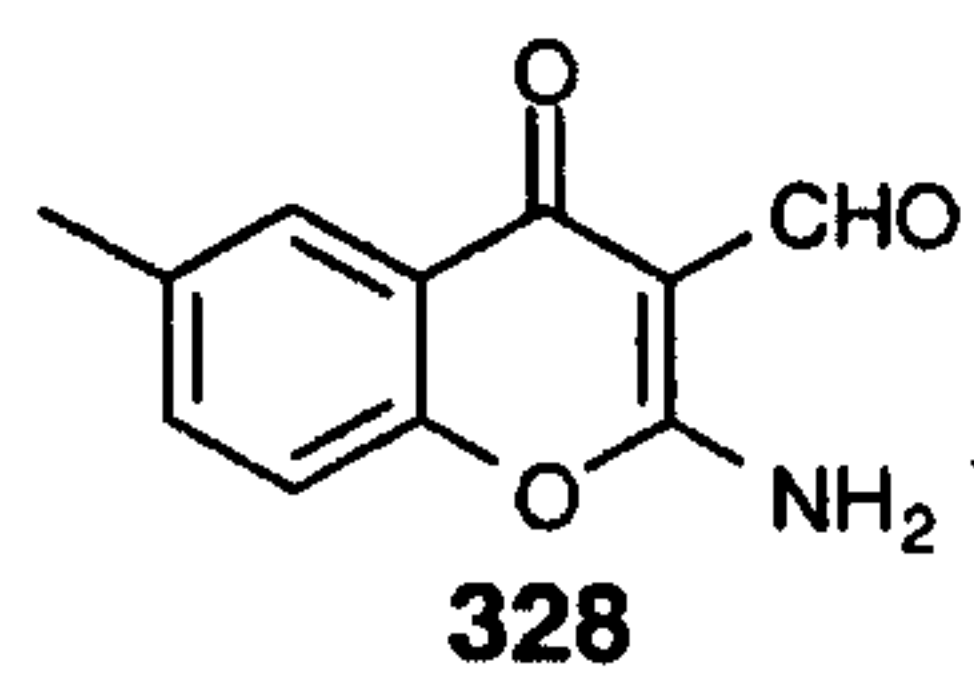
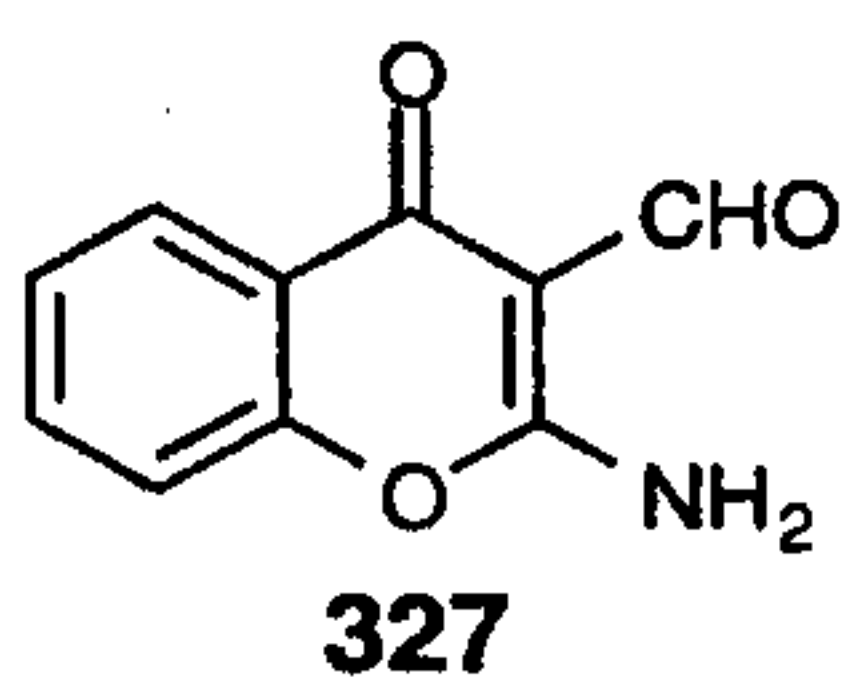
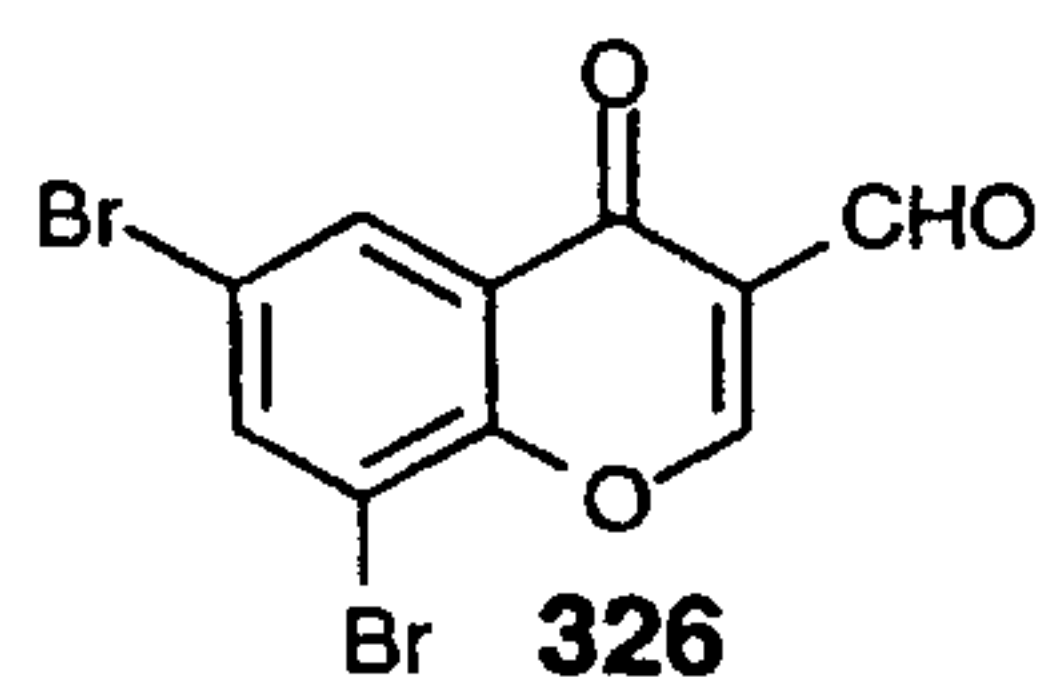


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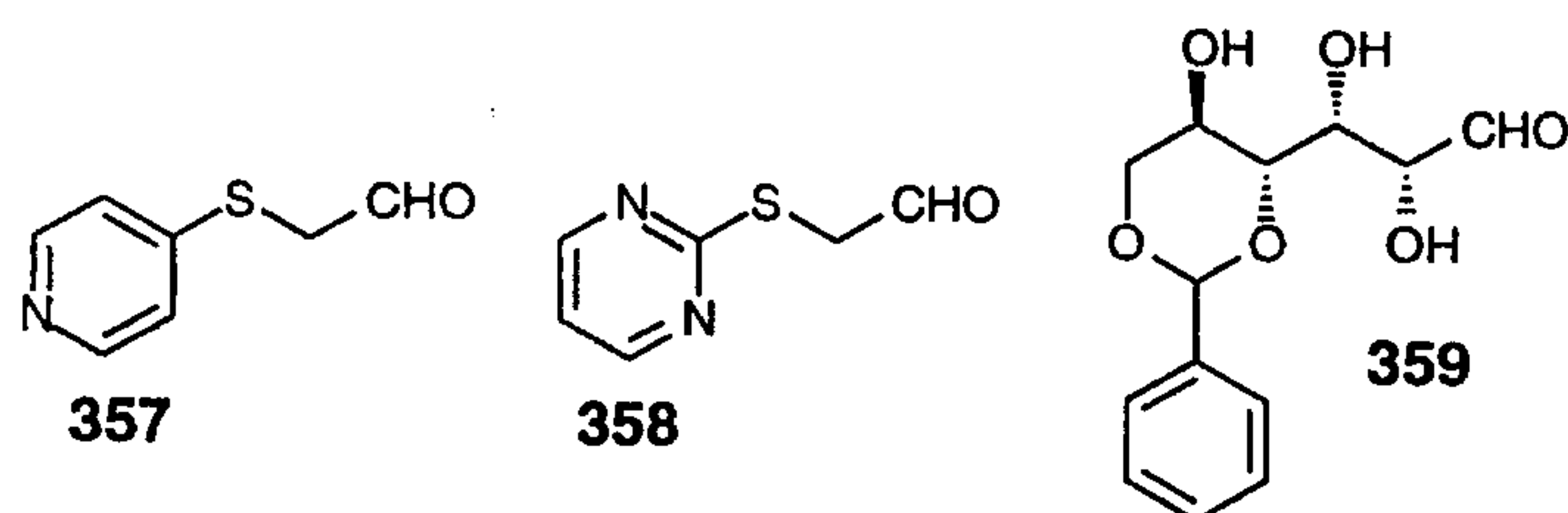
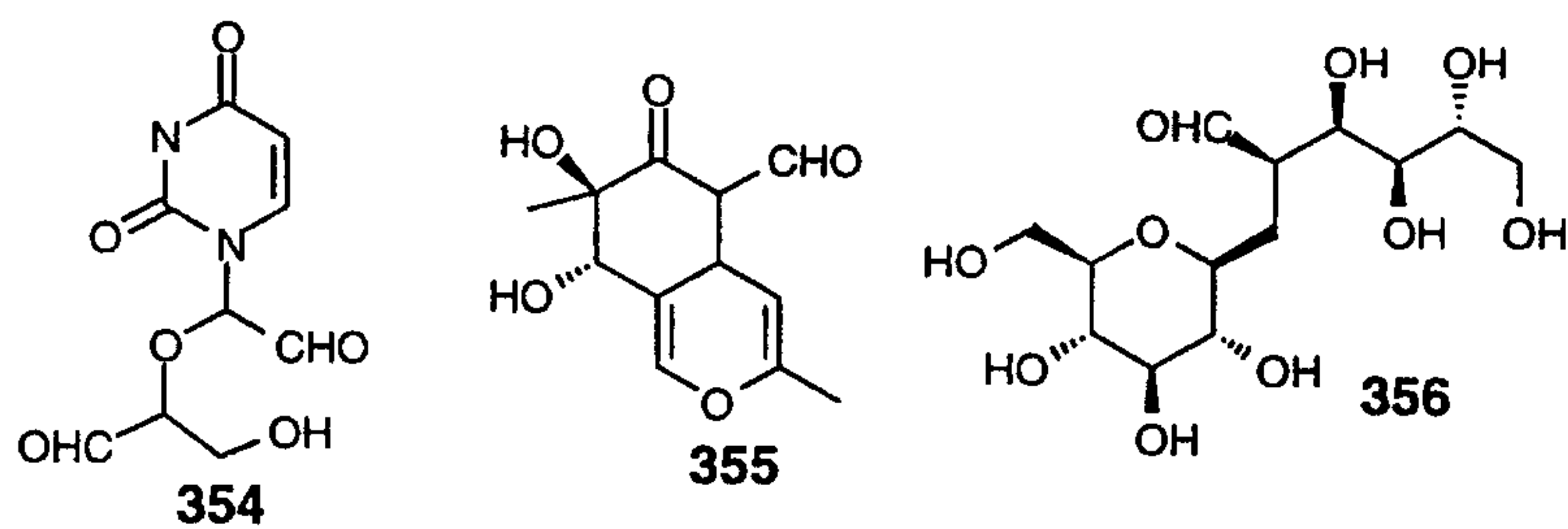
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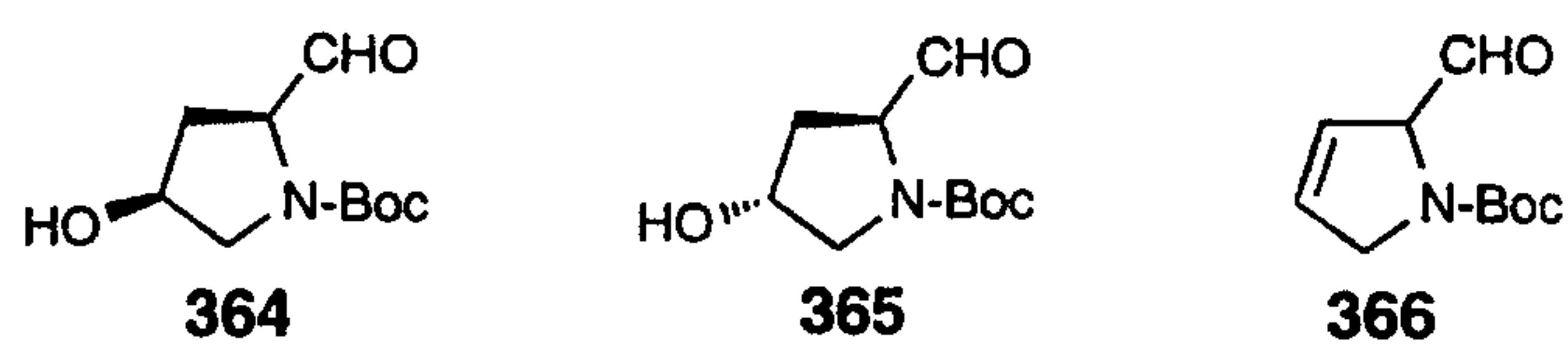
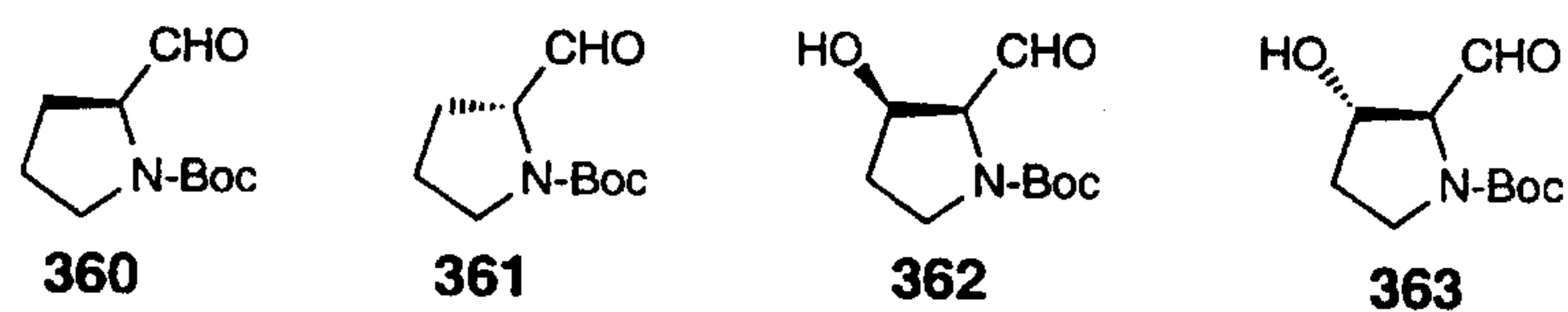


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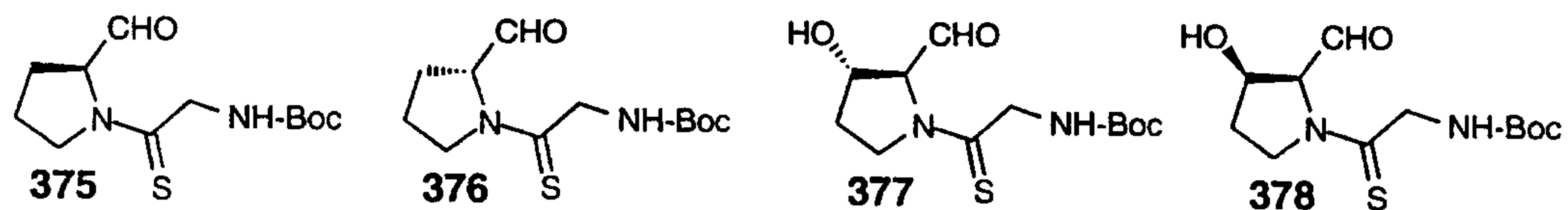
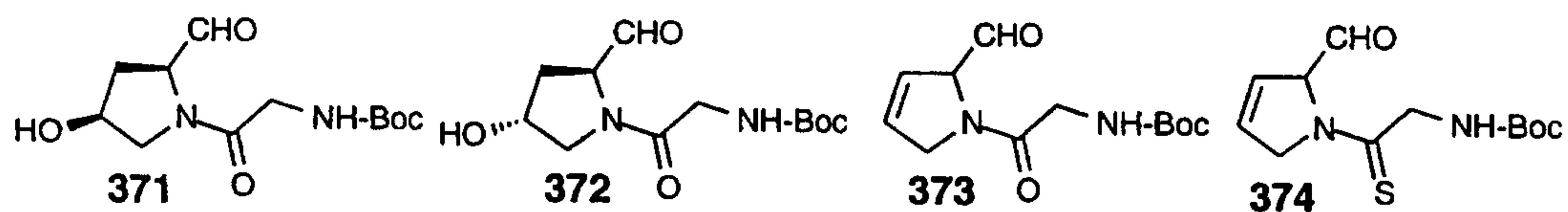
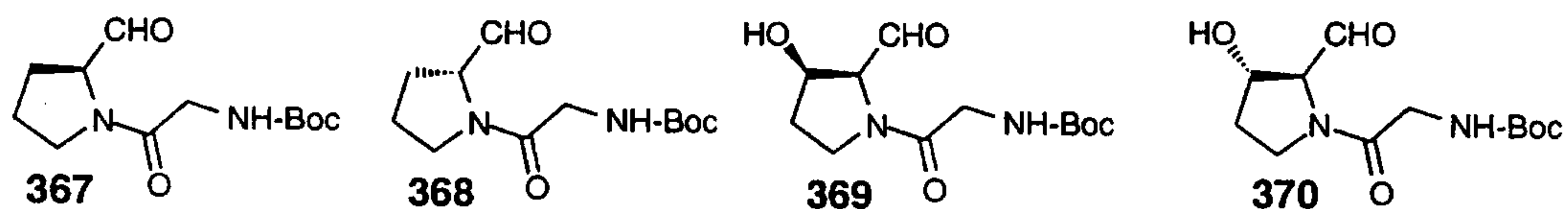
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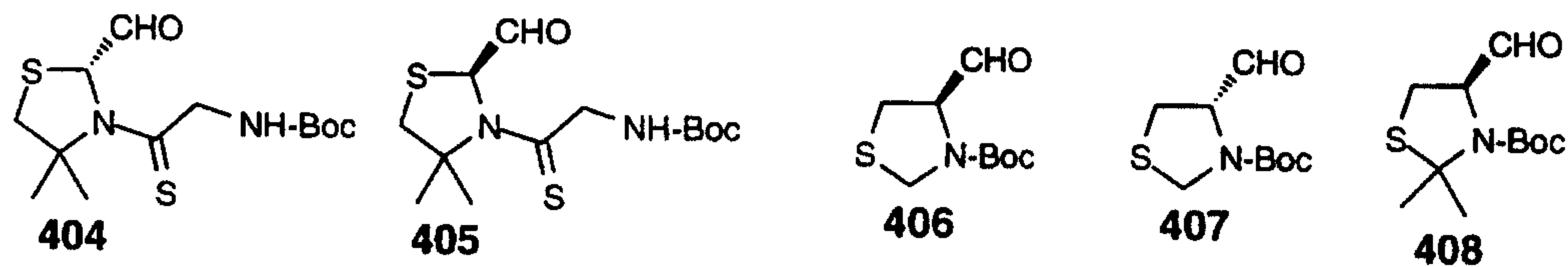
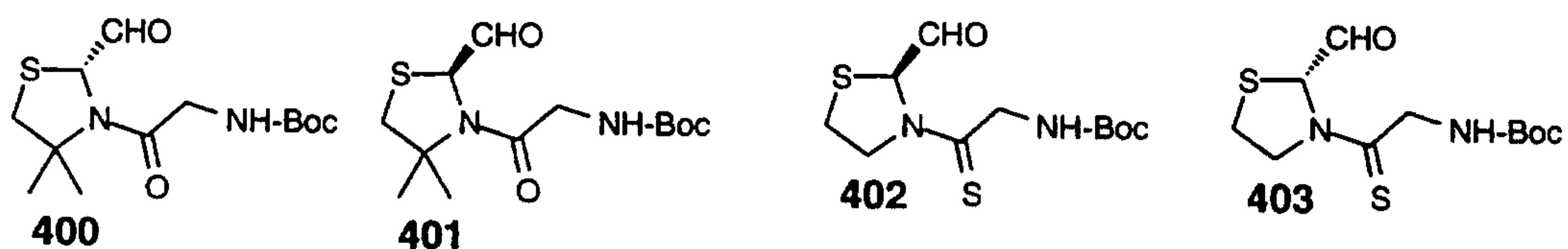
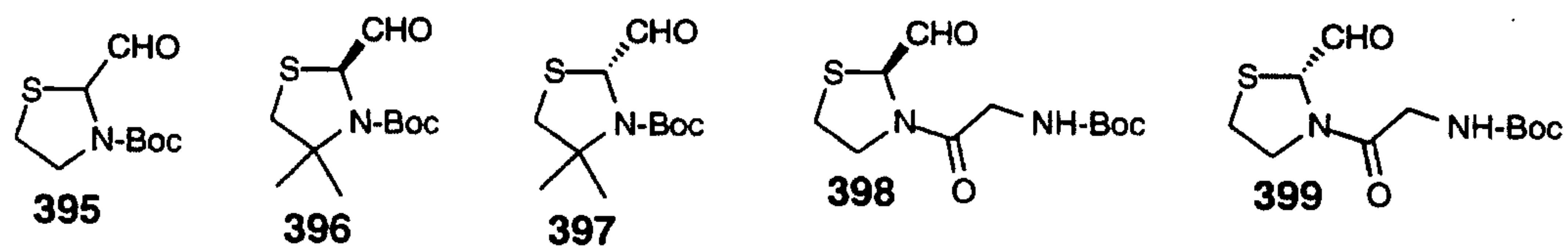
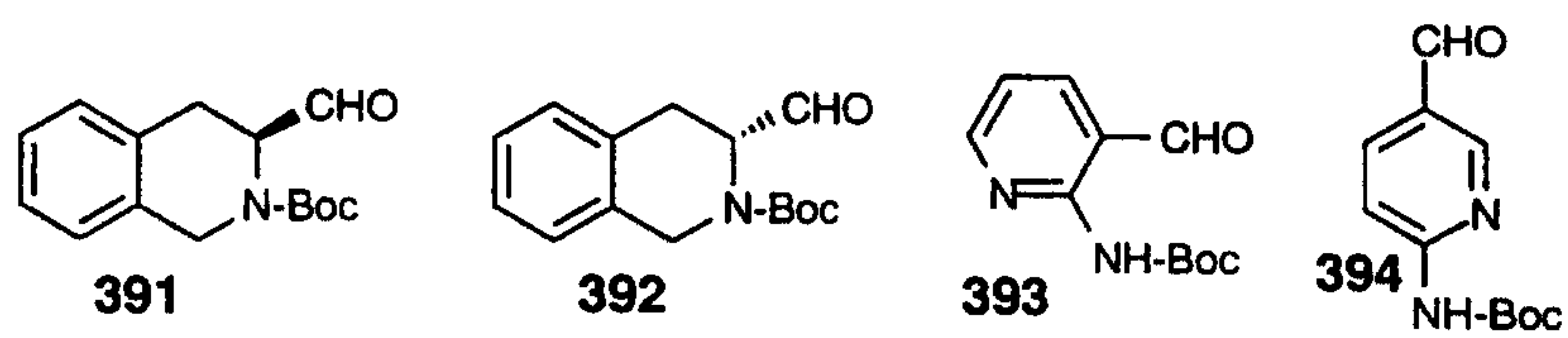
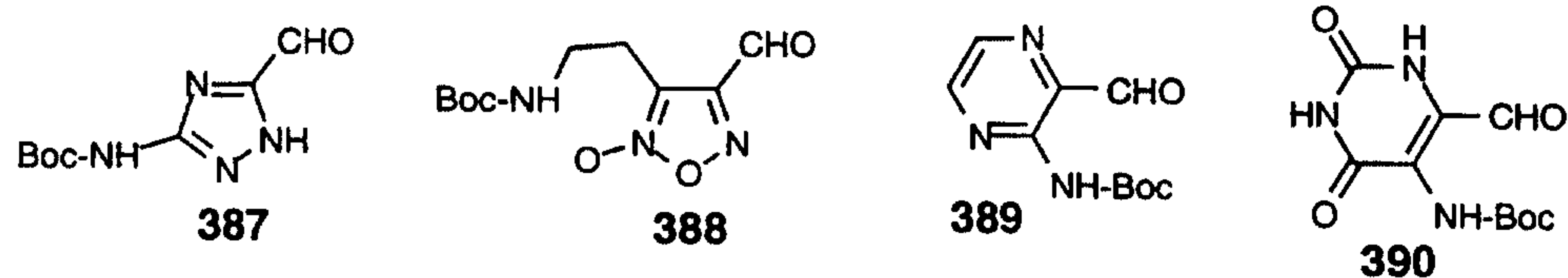
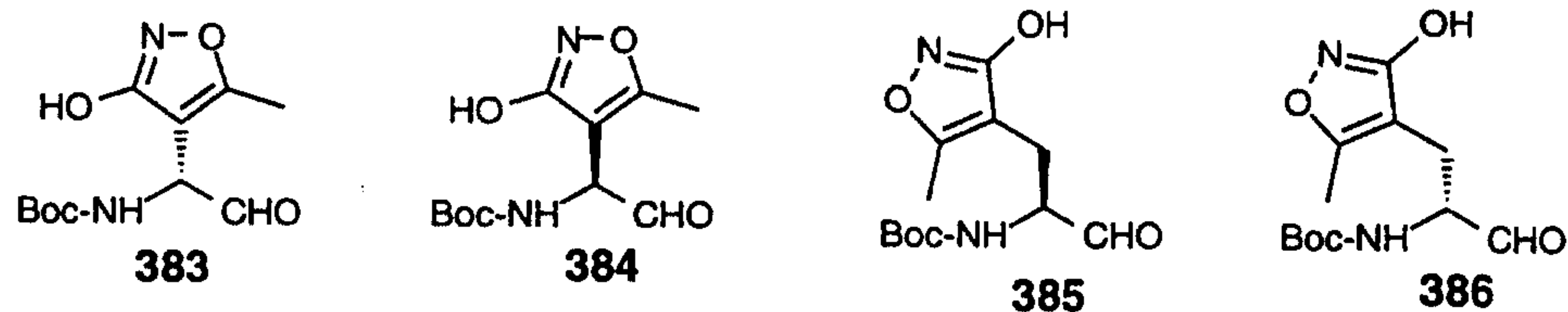
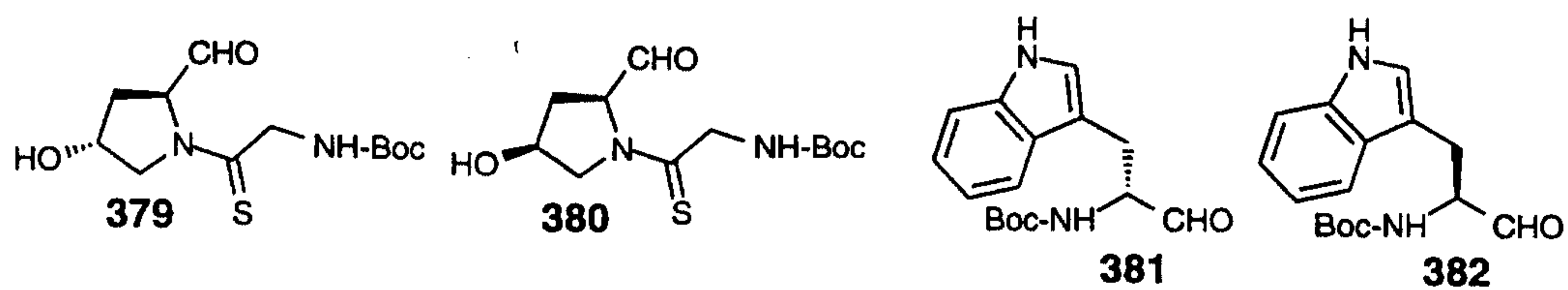
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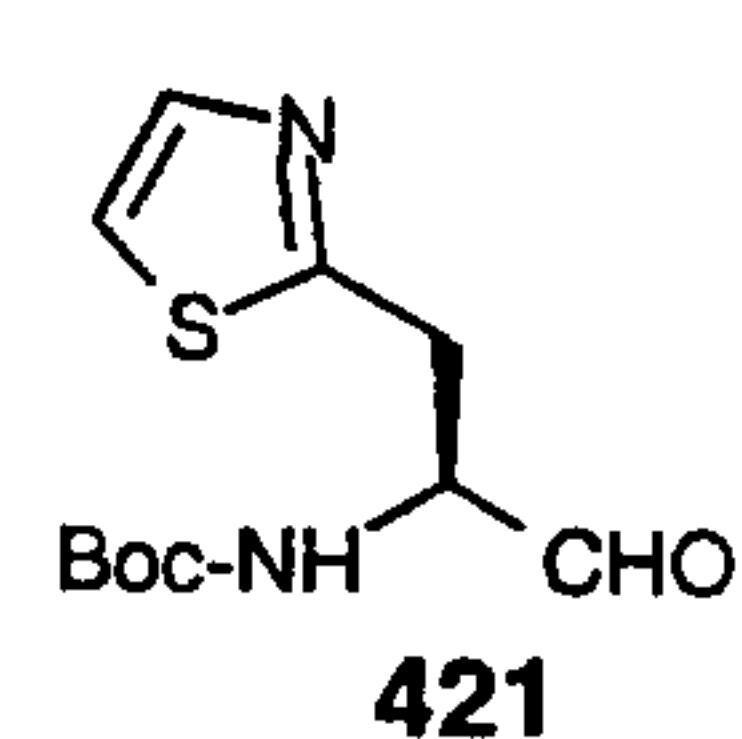
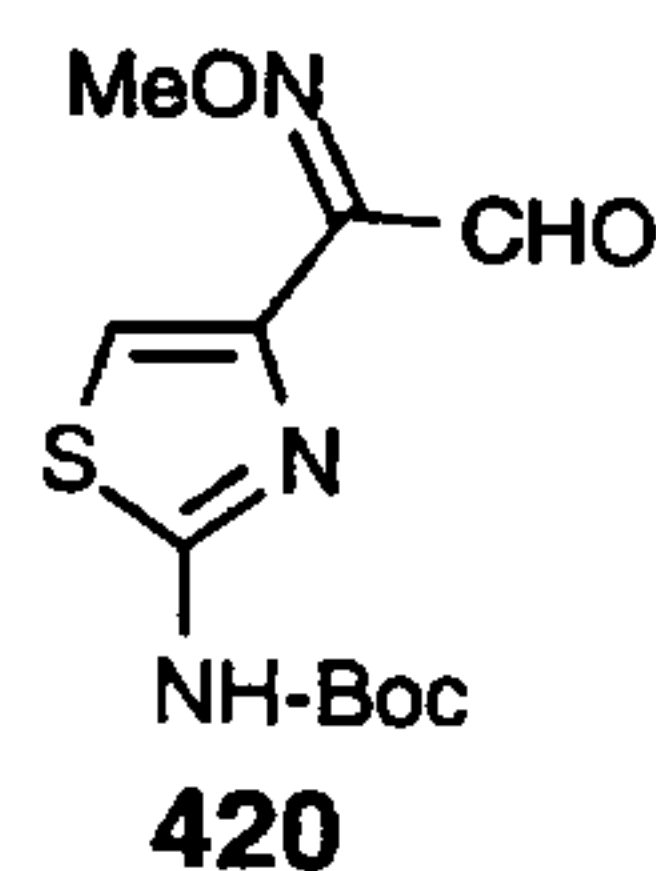
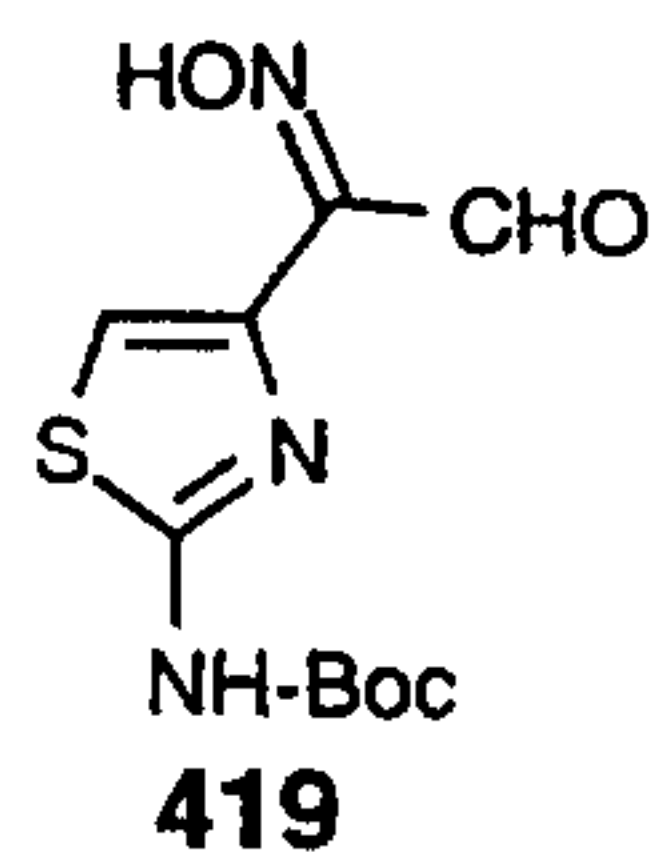
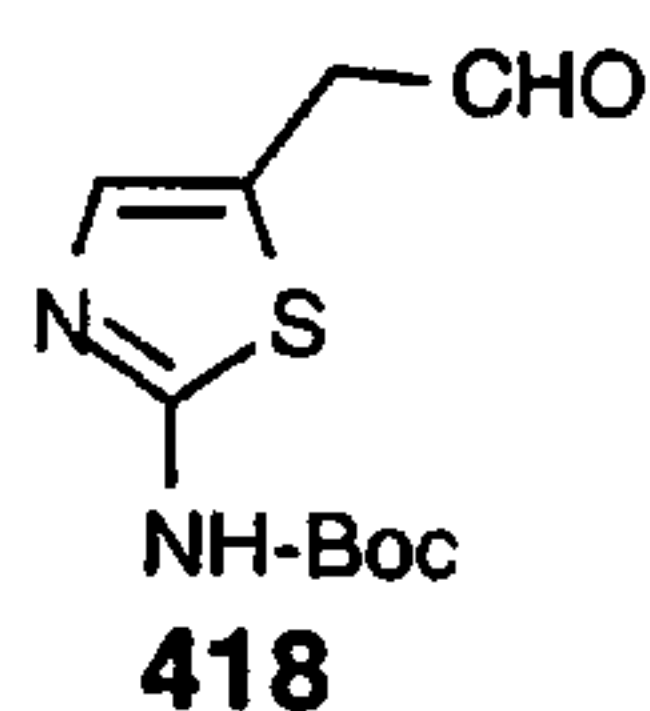
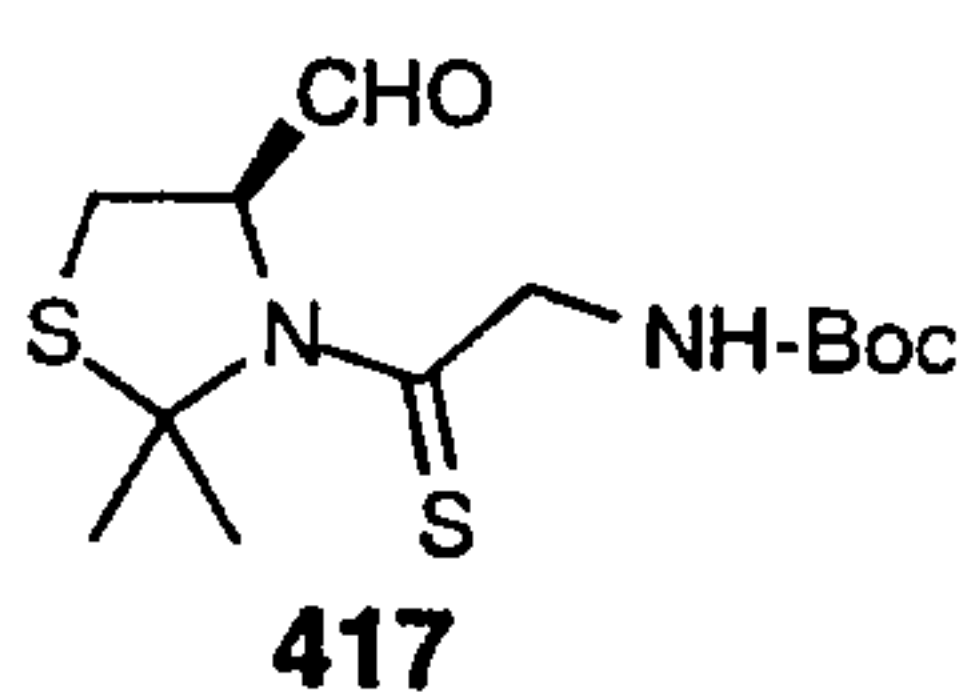
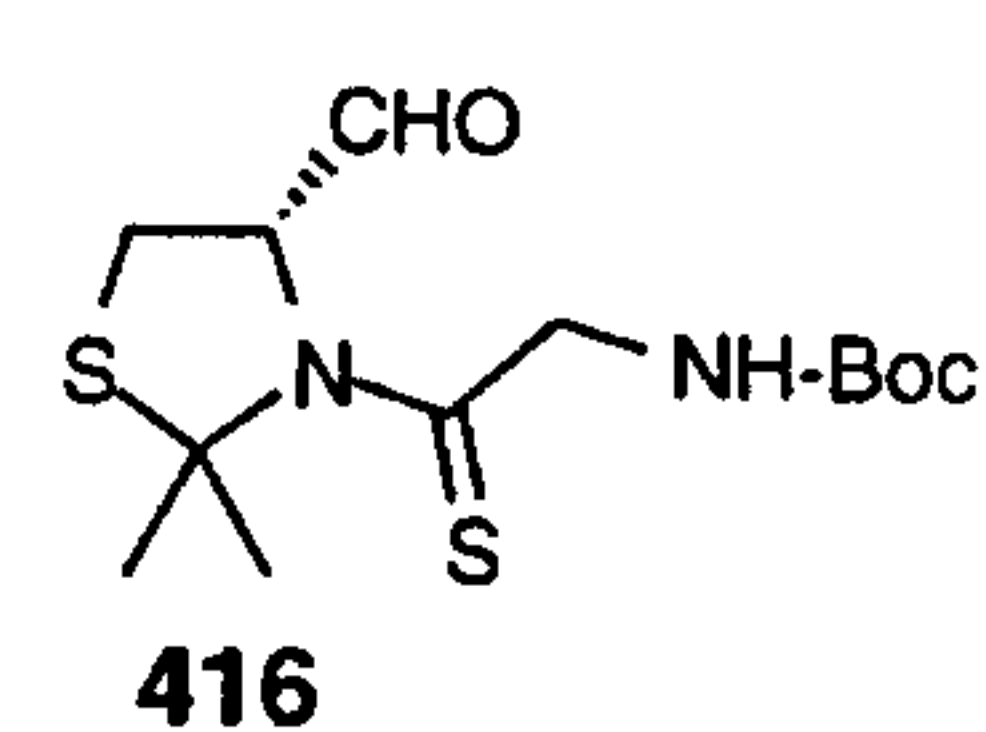
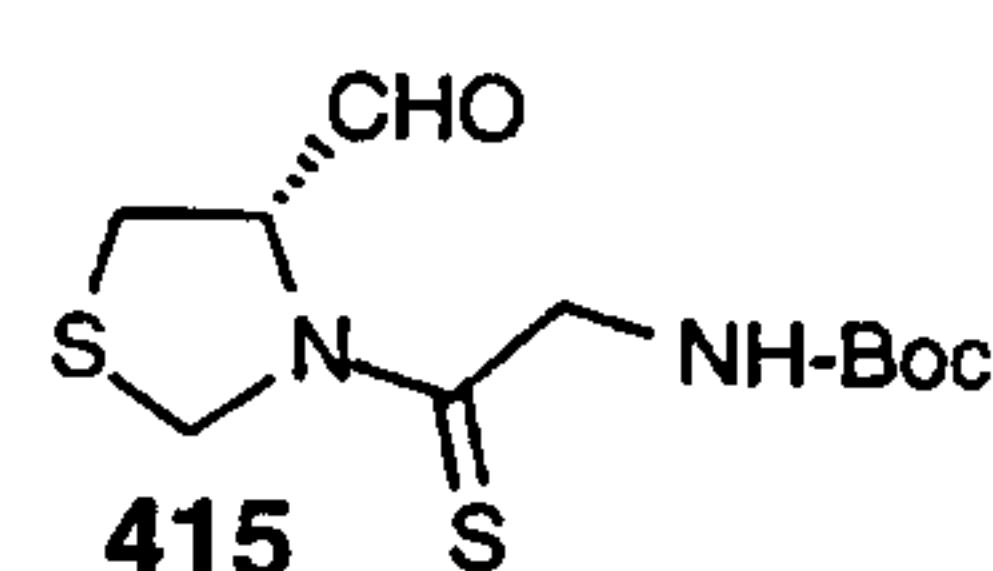
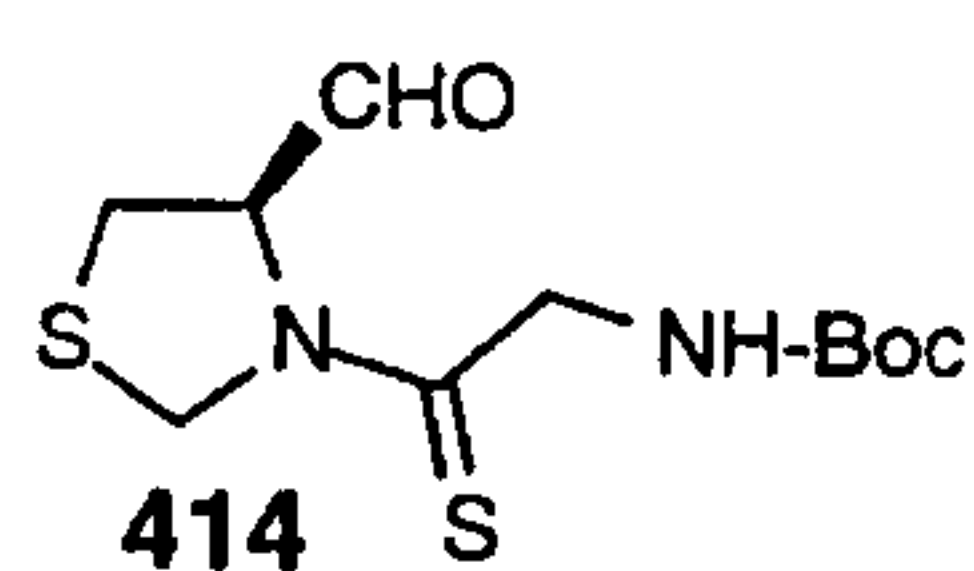
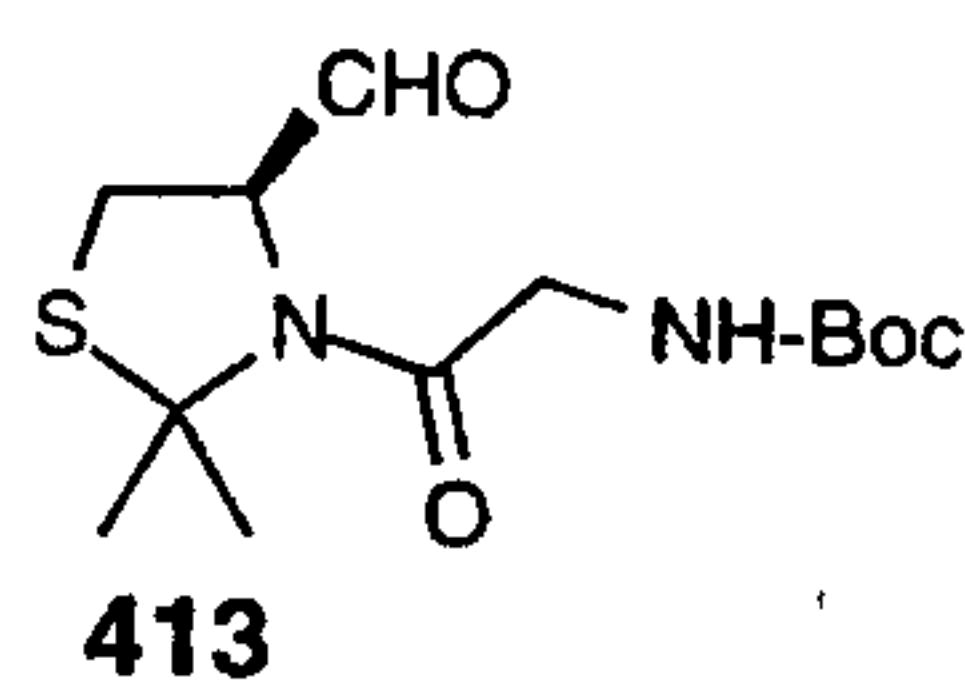
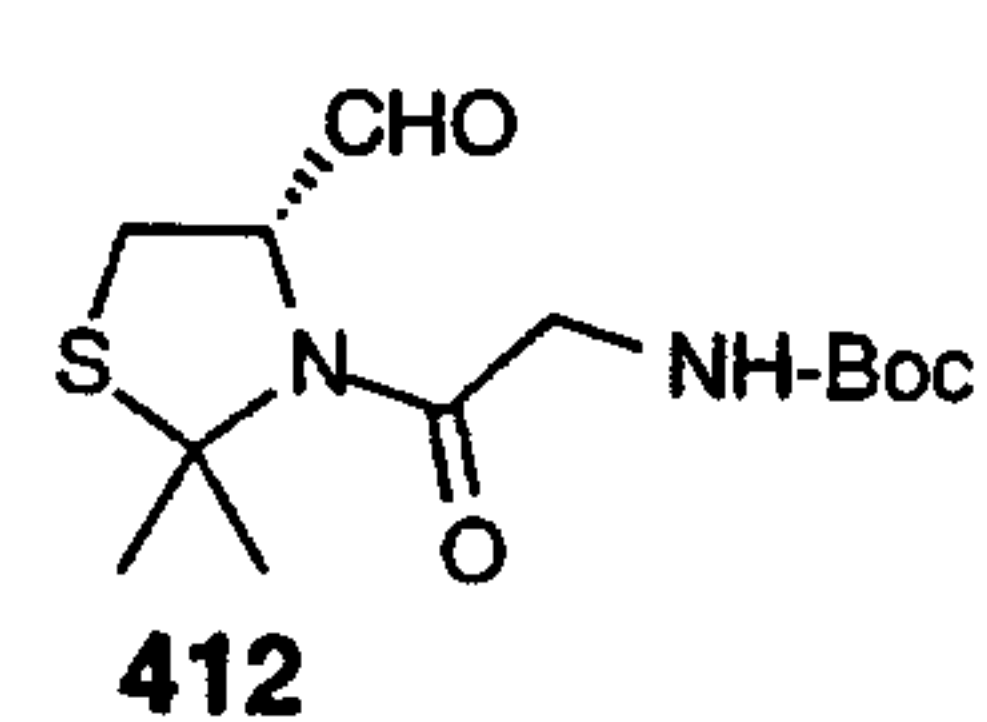
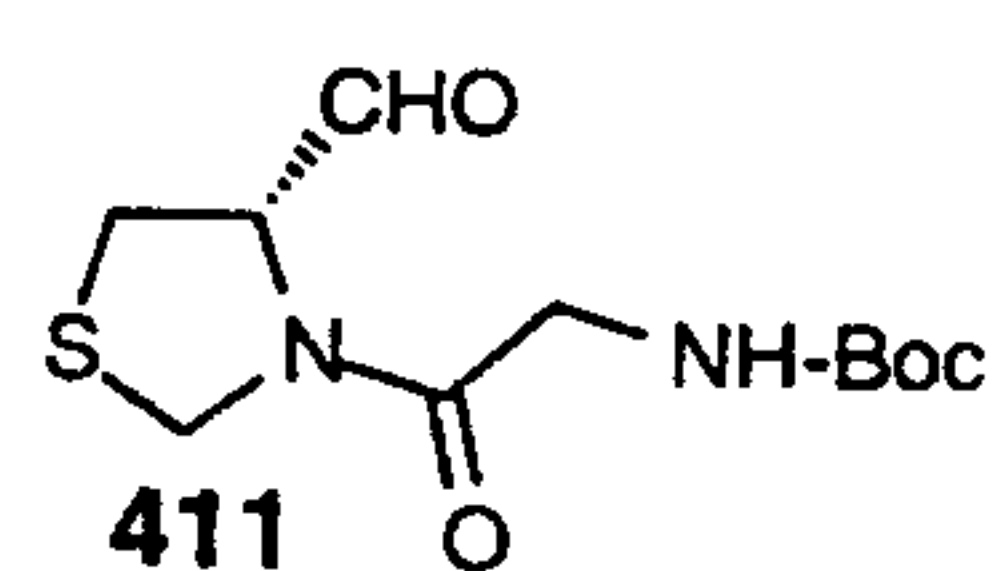
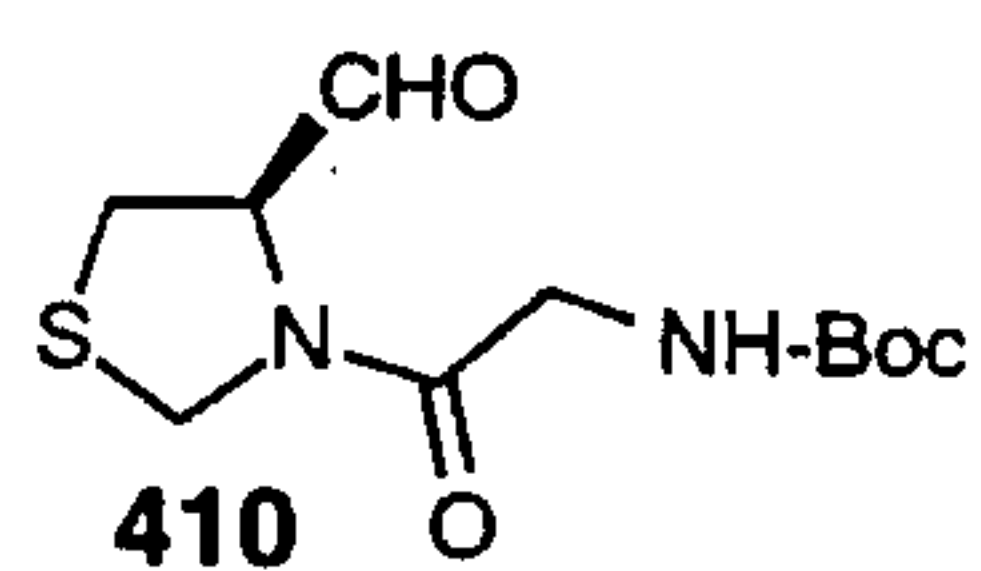
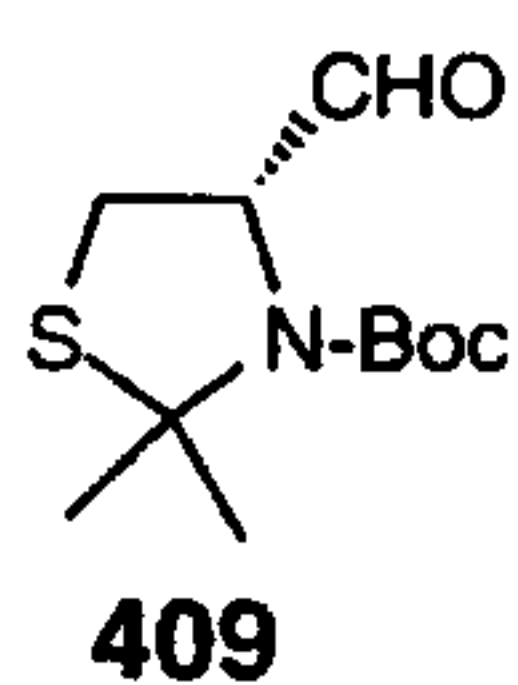
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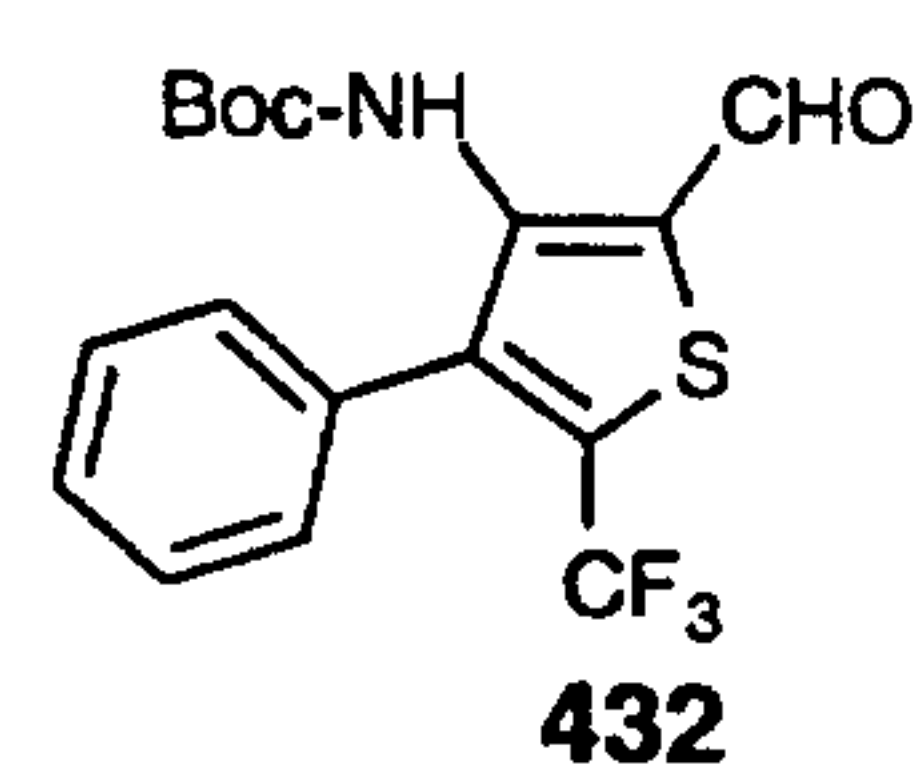
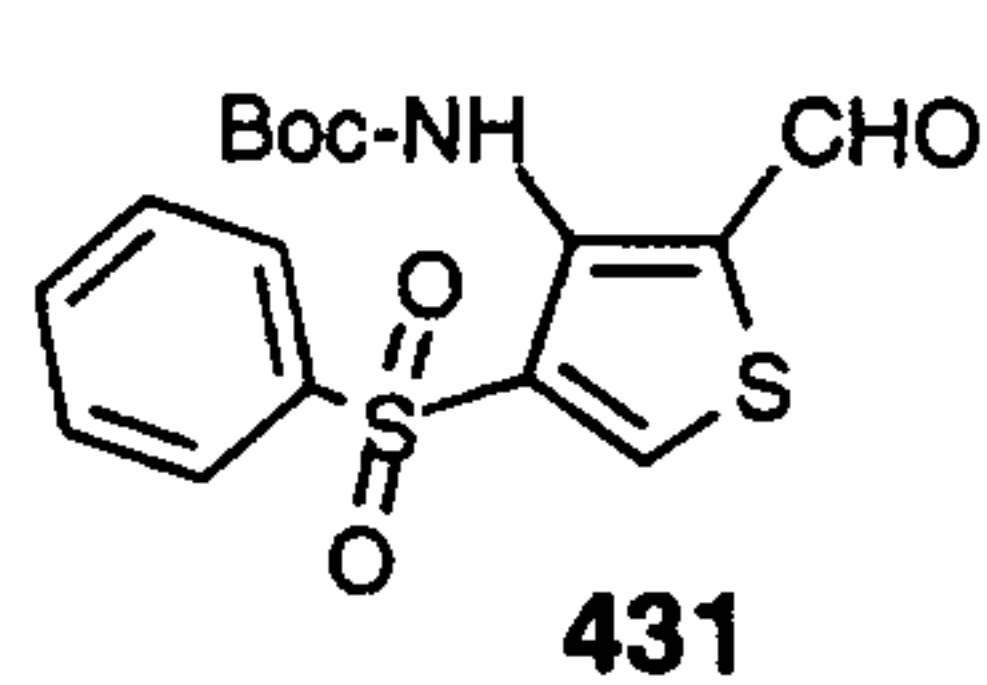
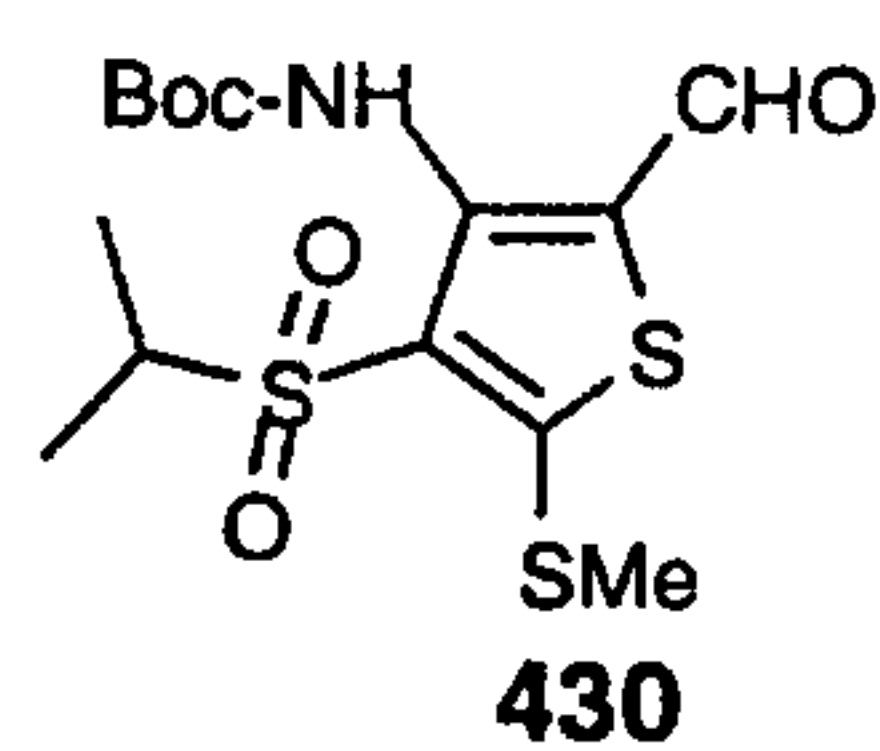
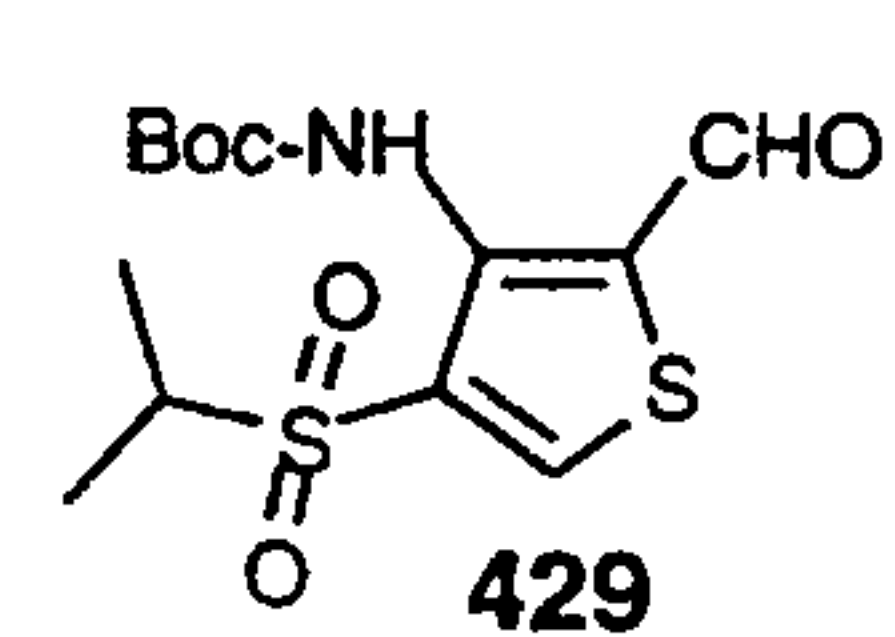
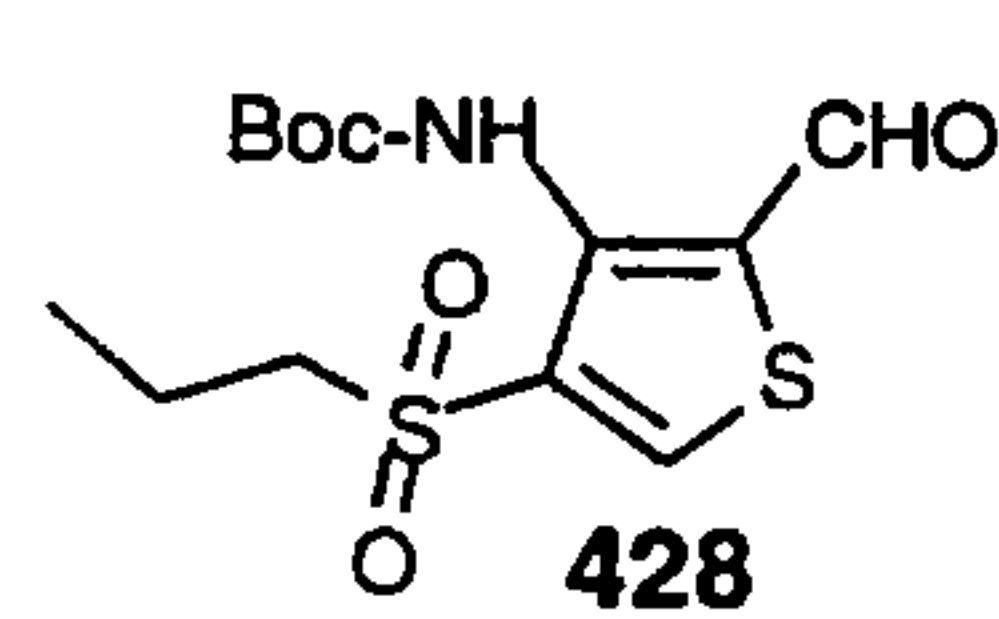
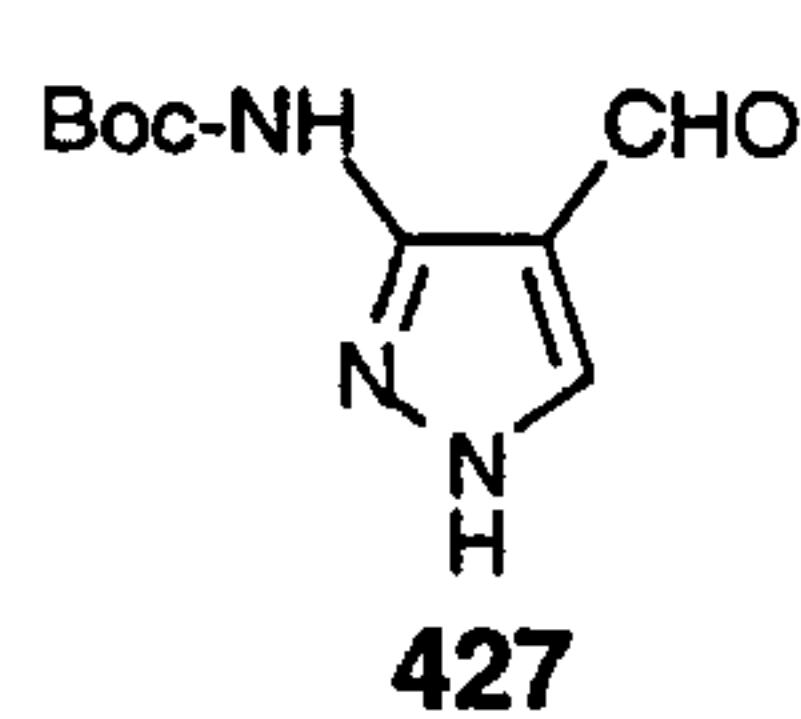
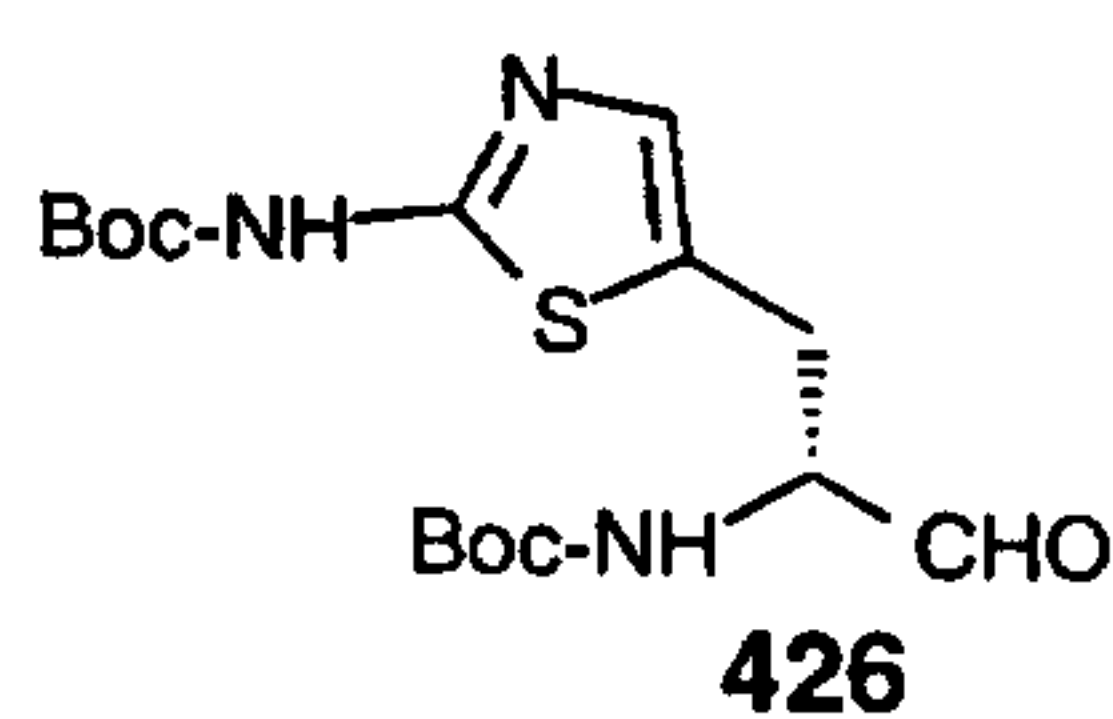
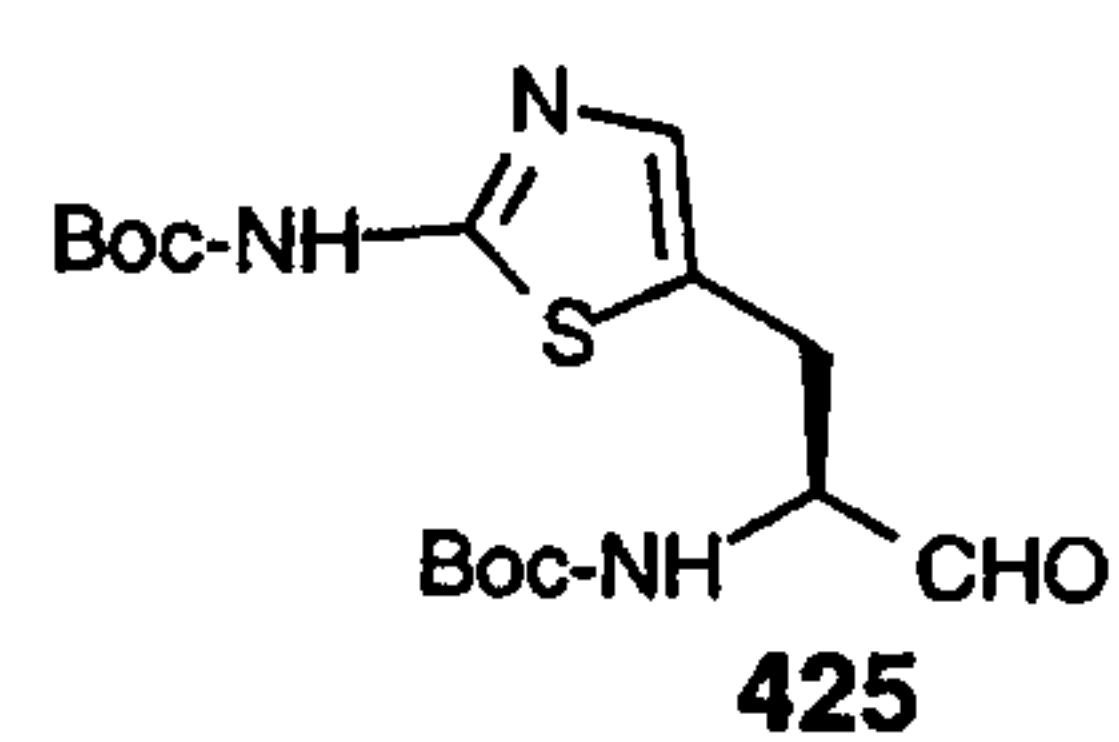
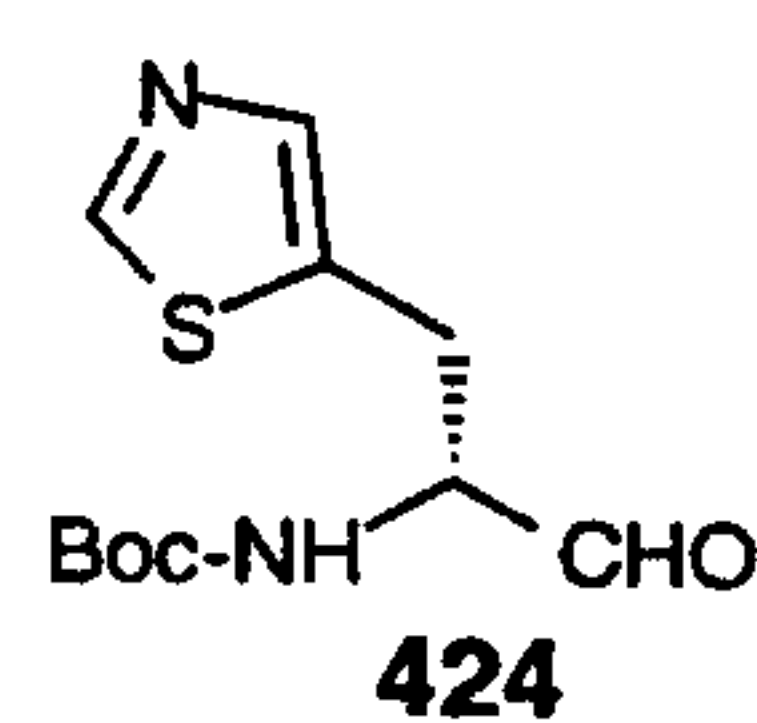
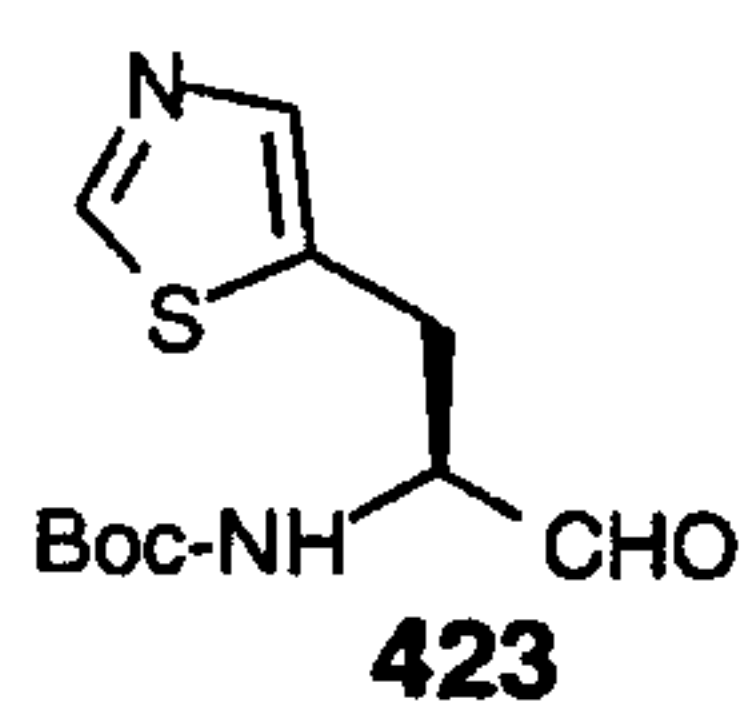
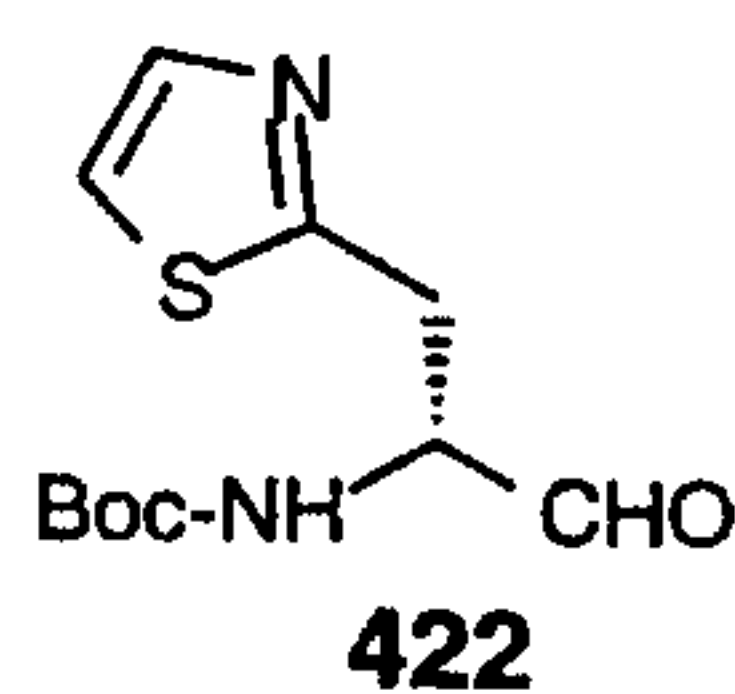
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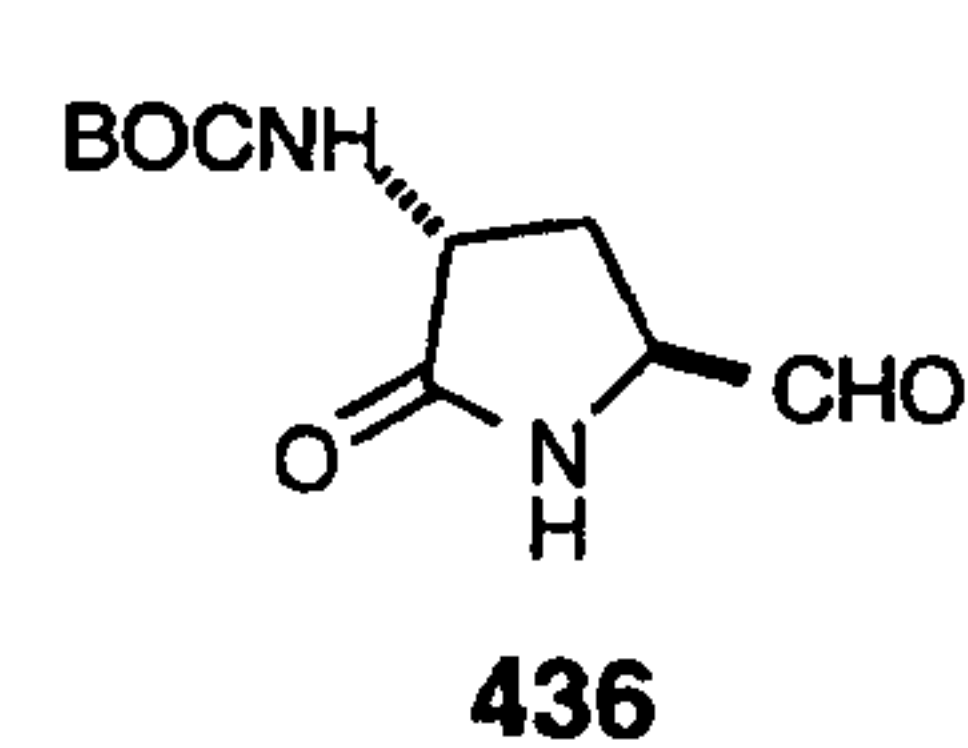
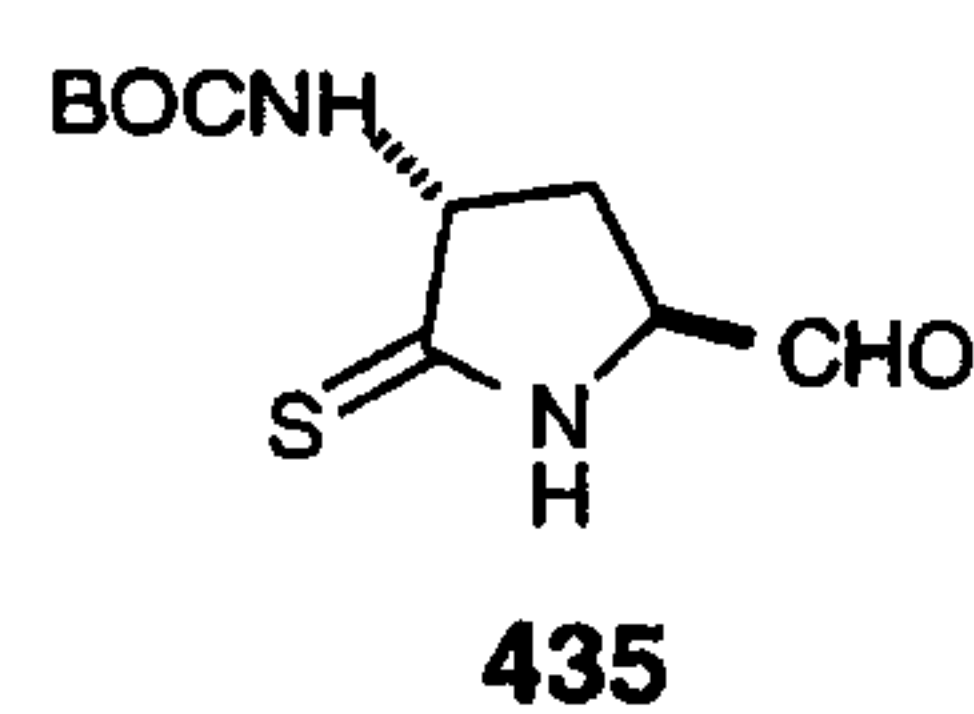
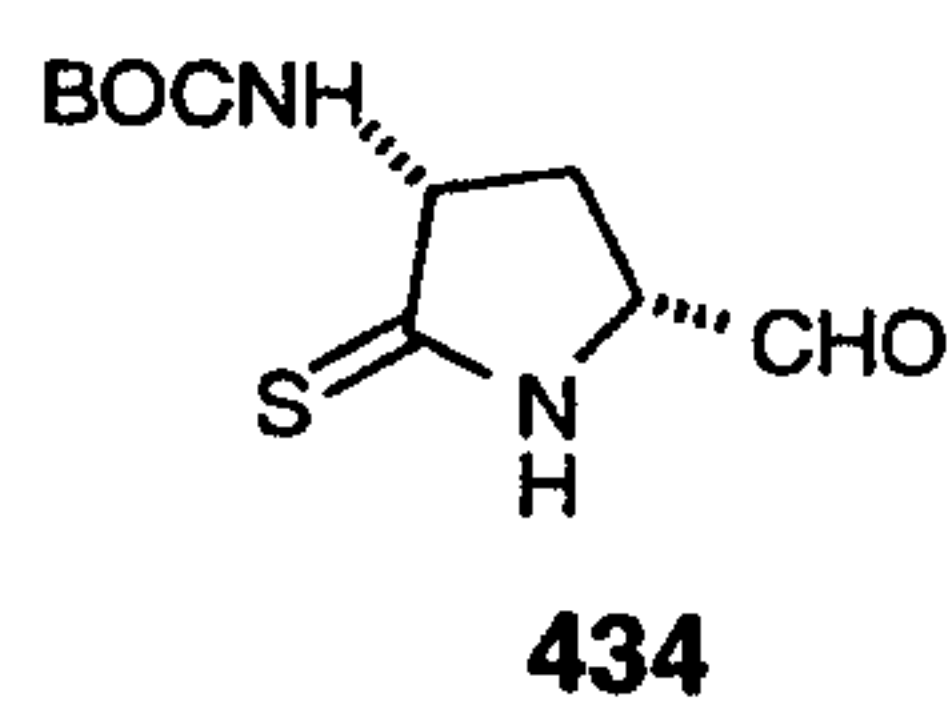
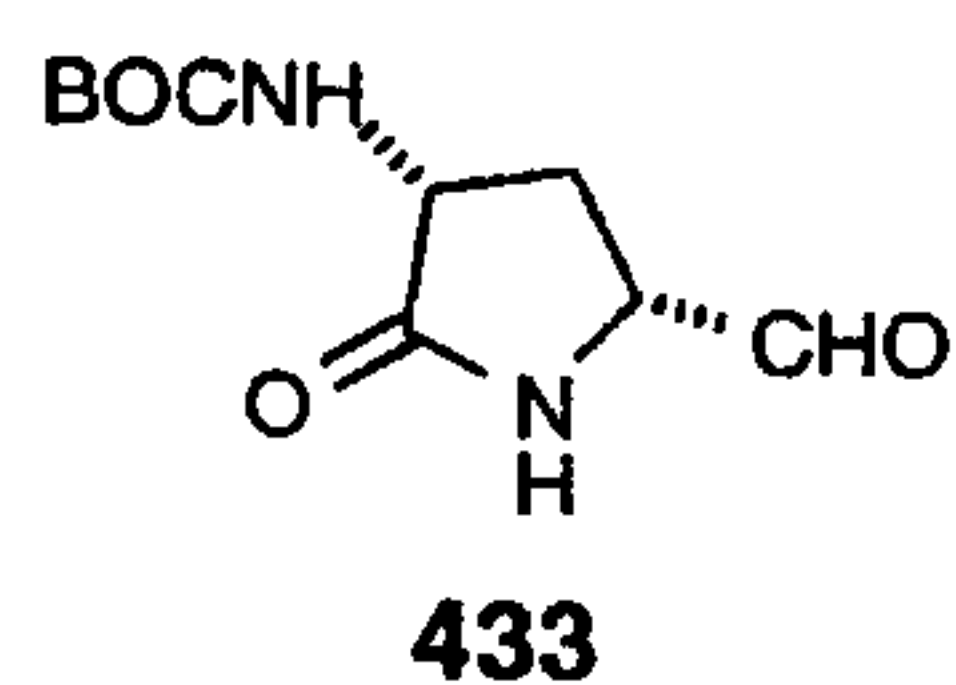
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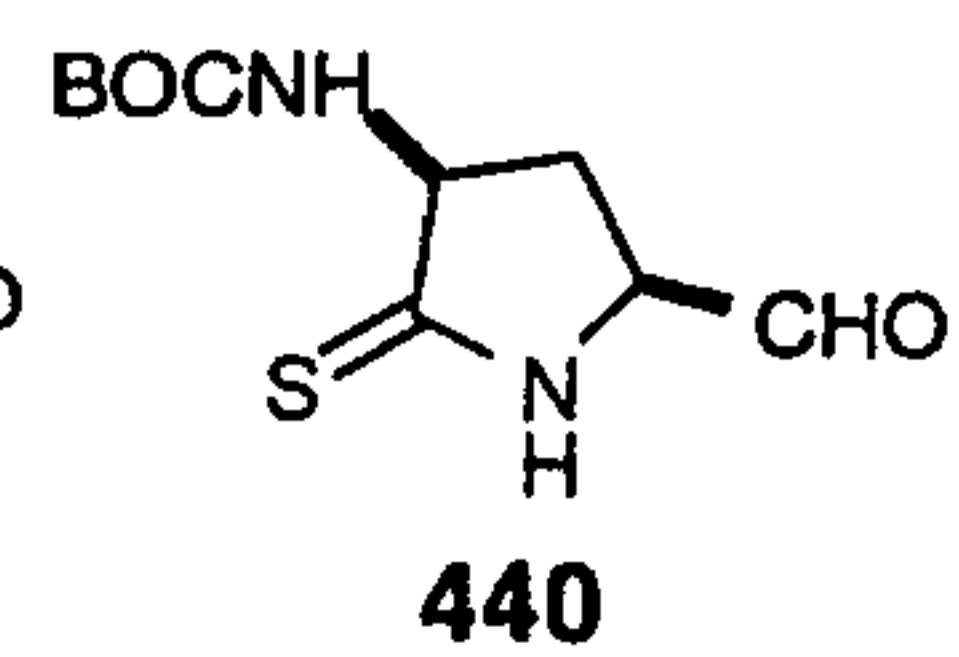
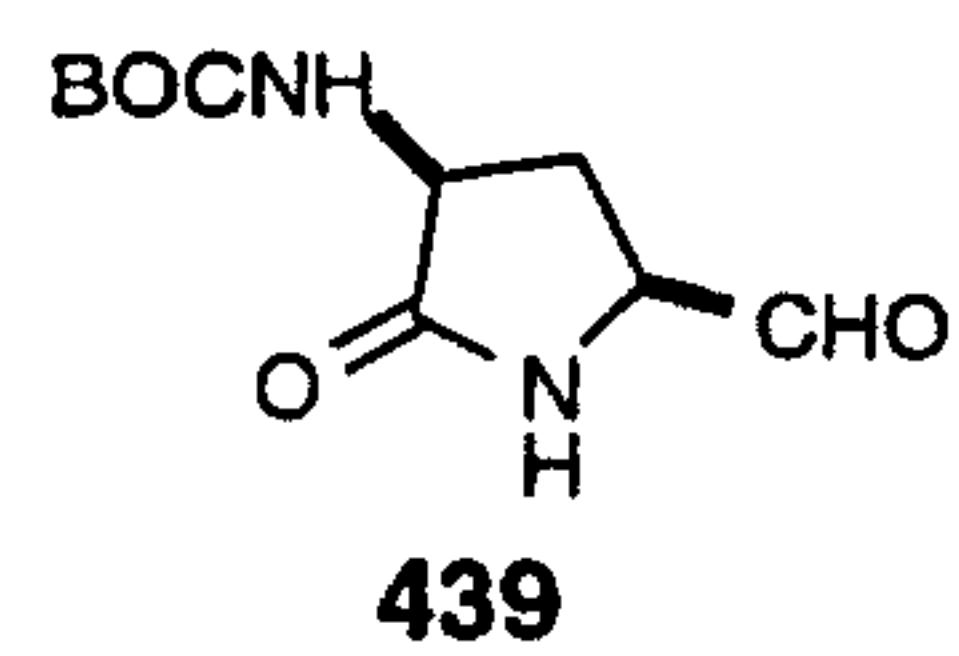
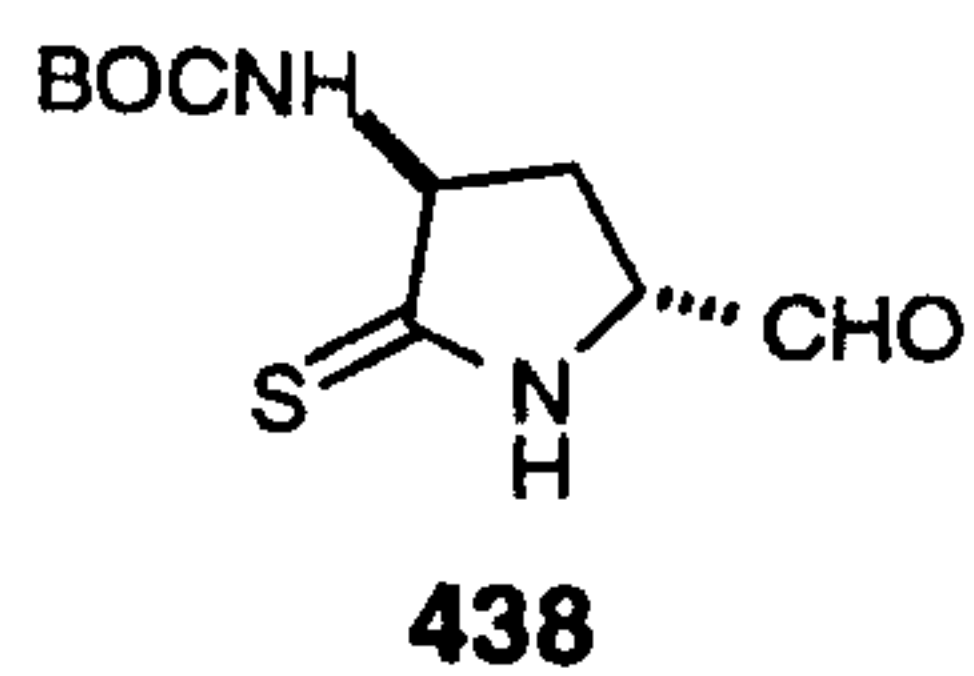
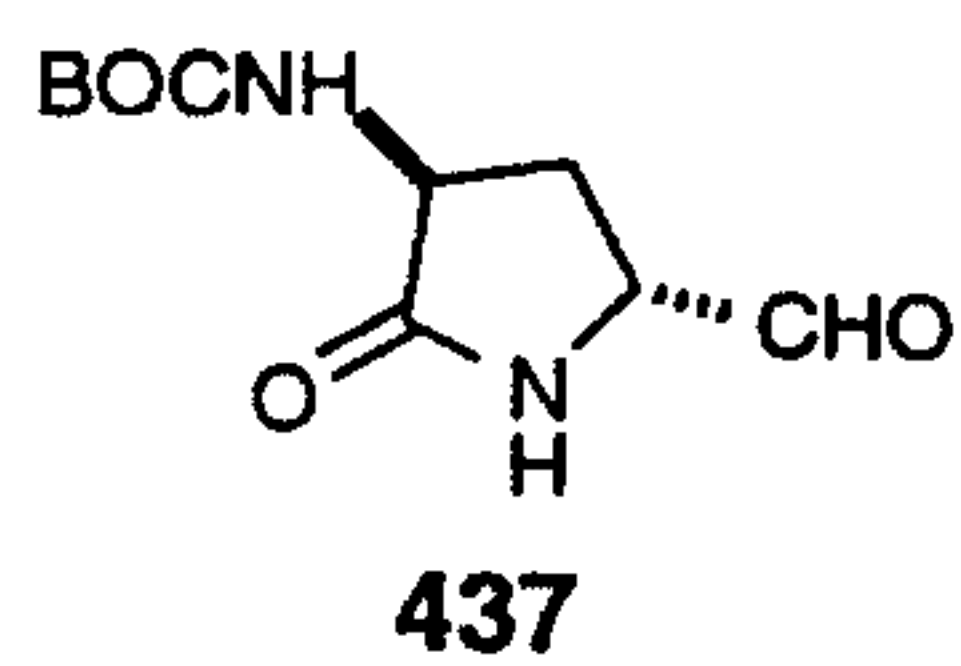


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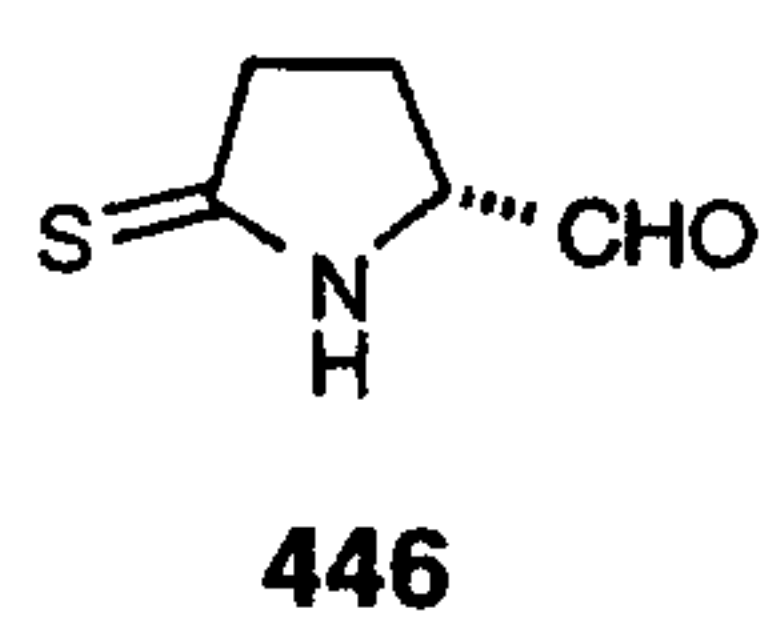
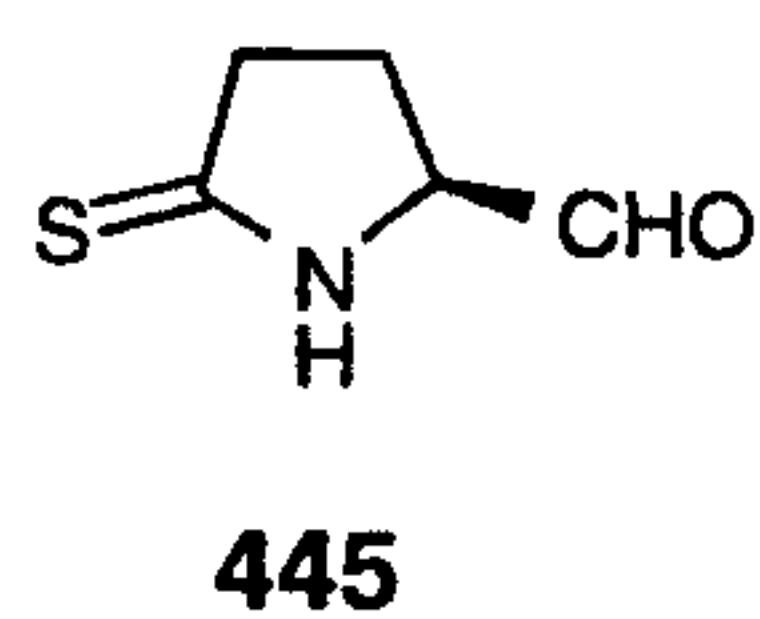
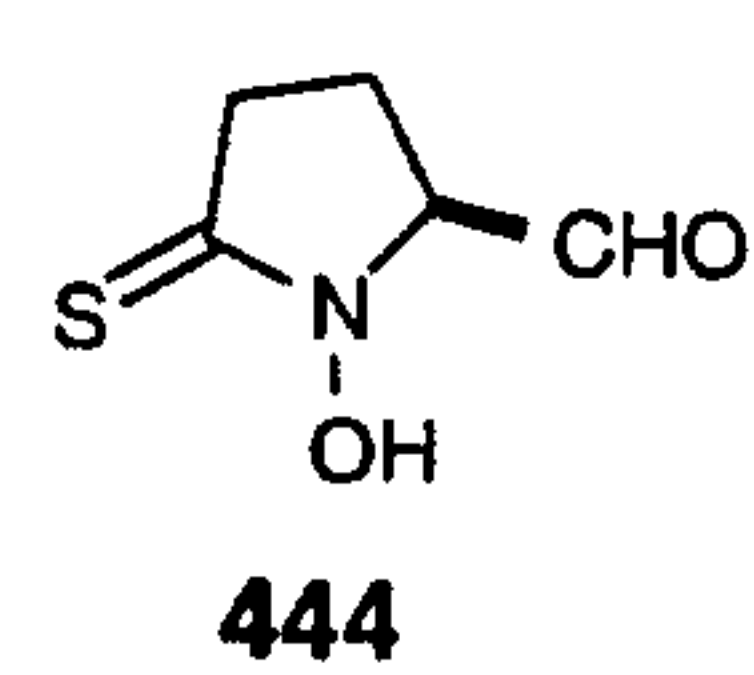
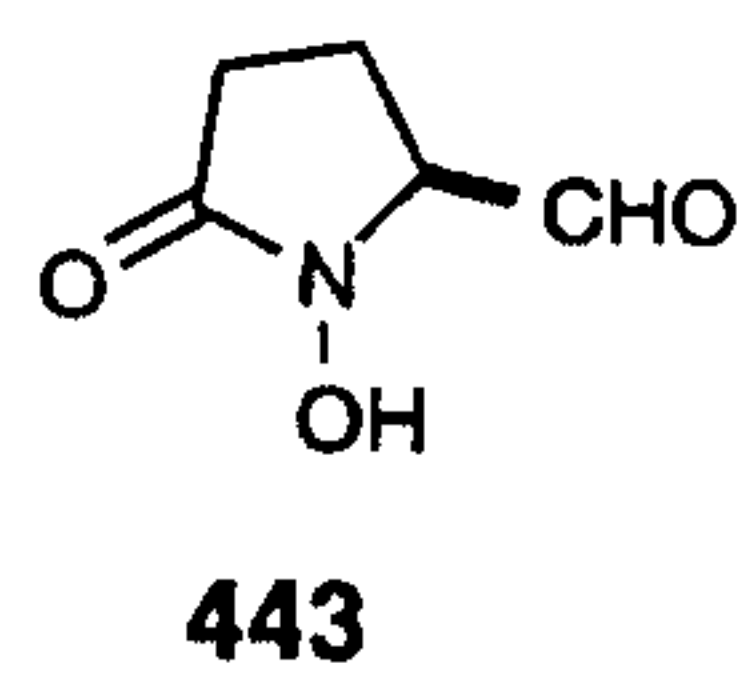
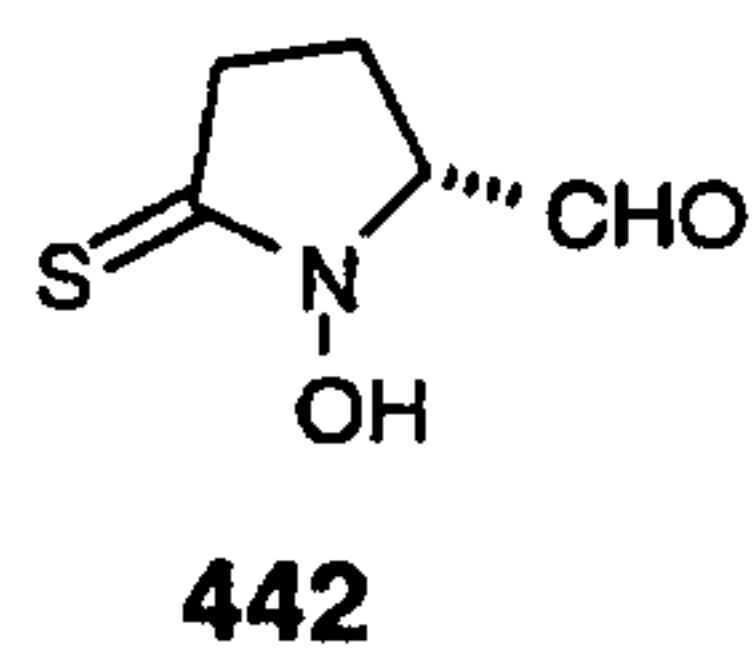
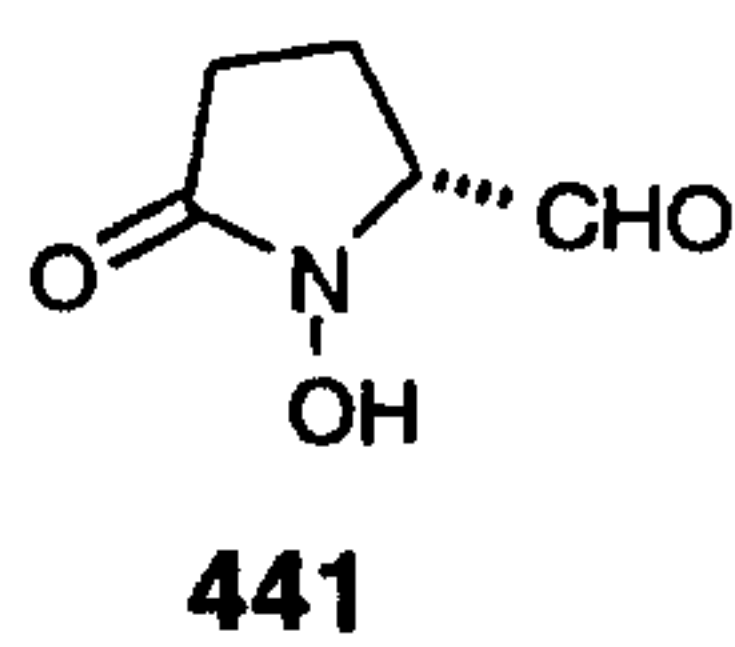


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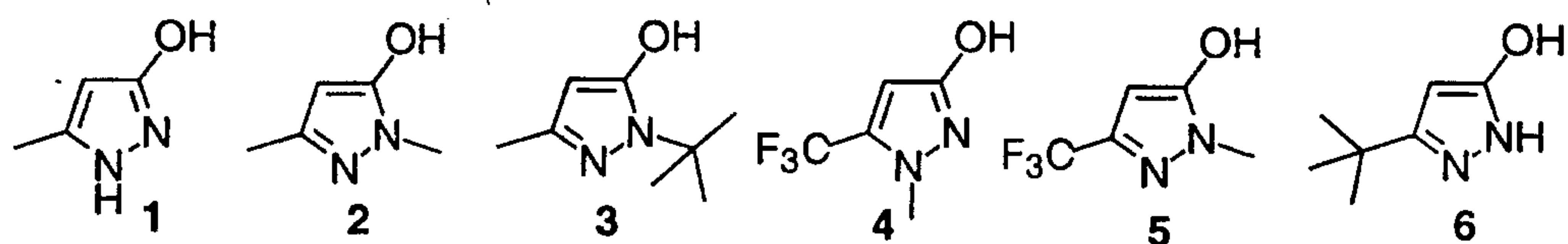
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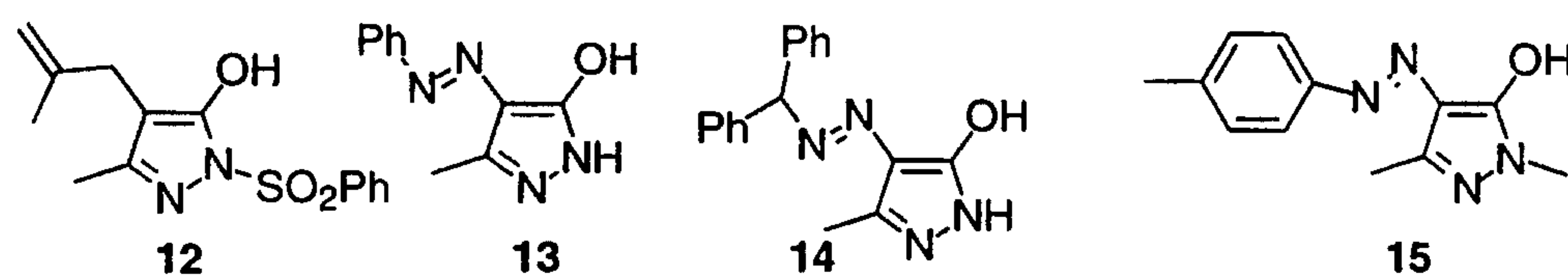
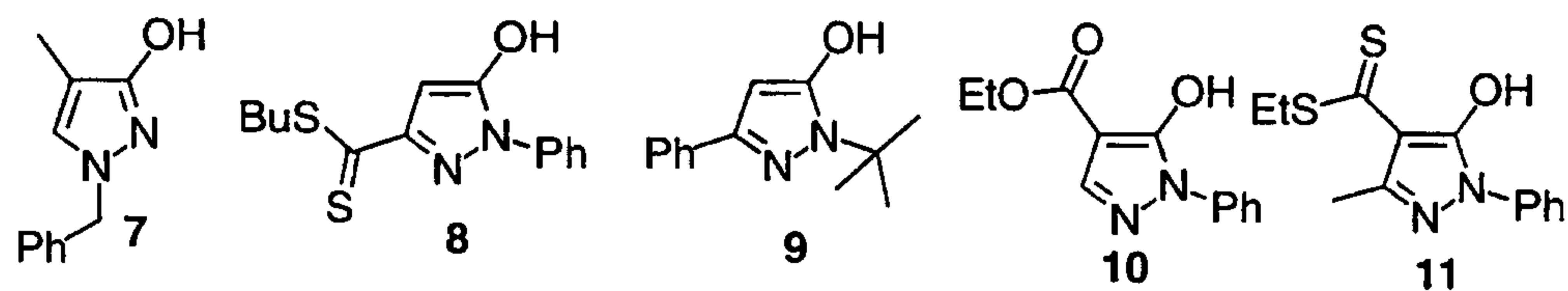
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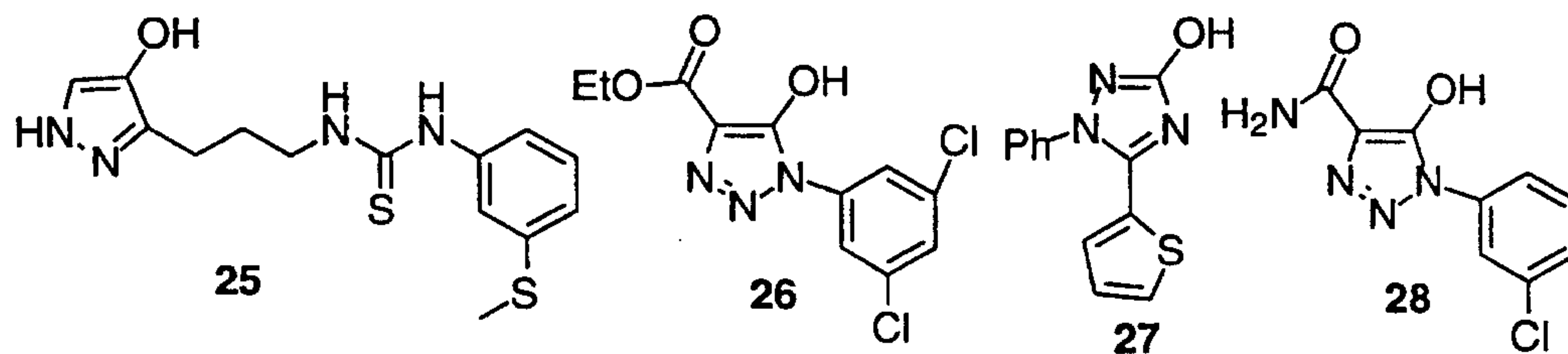
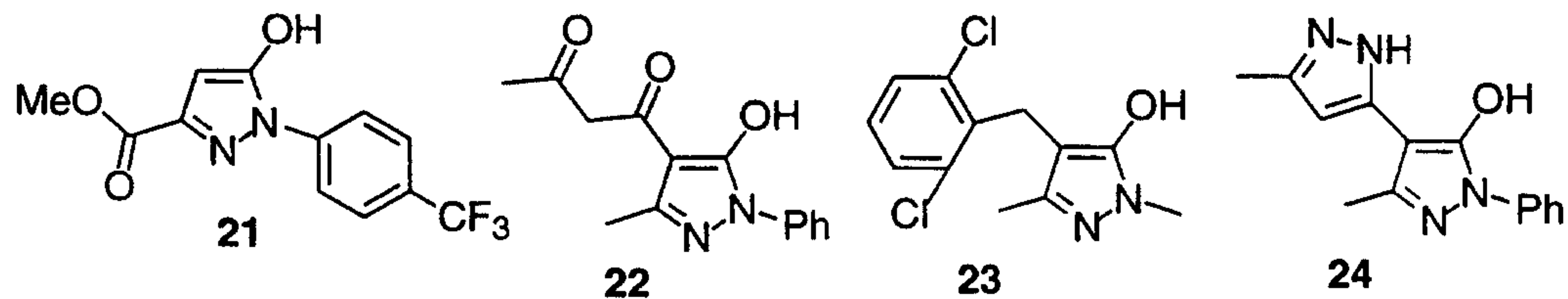
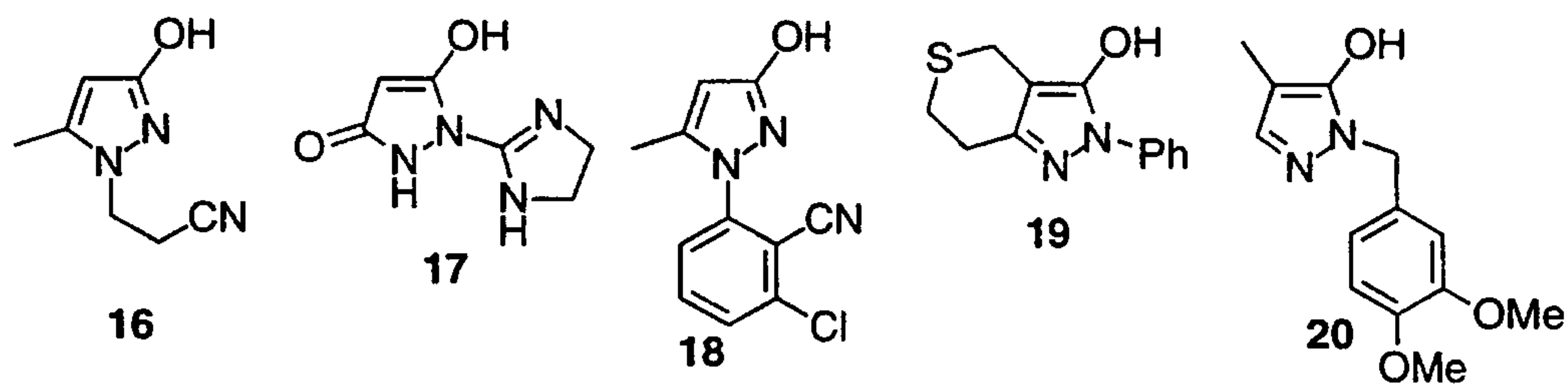
Table 15. Alcohols of the type A-OH



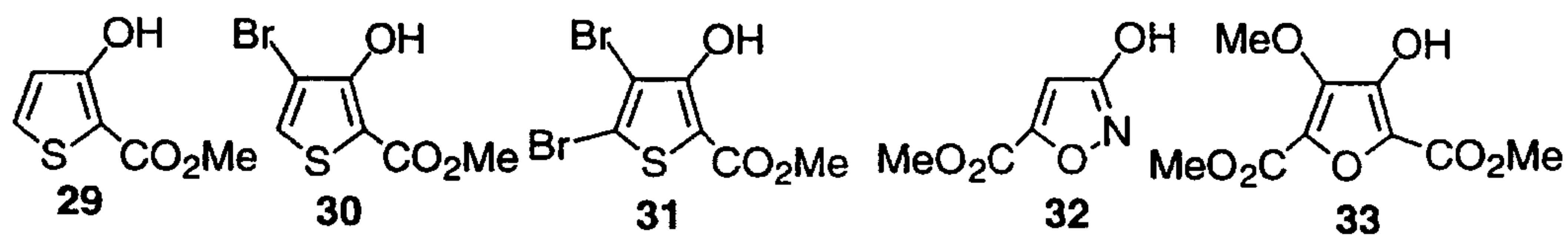
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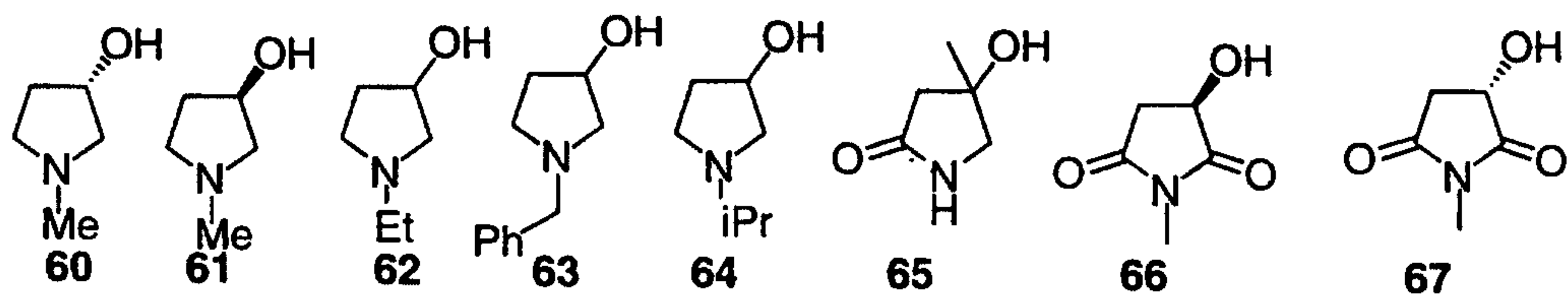
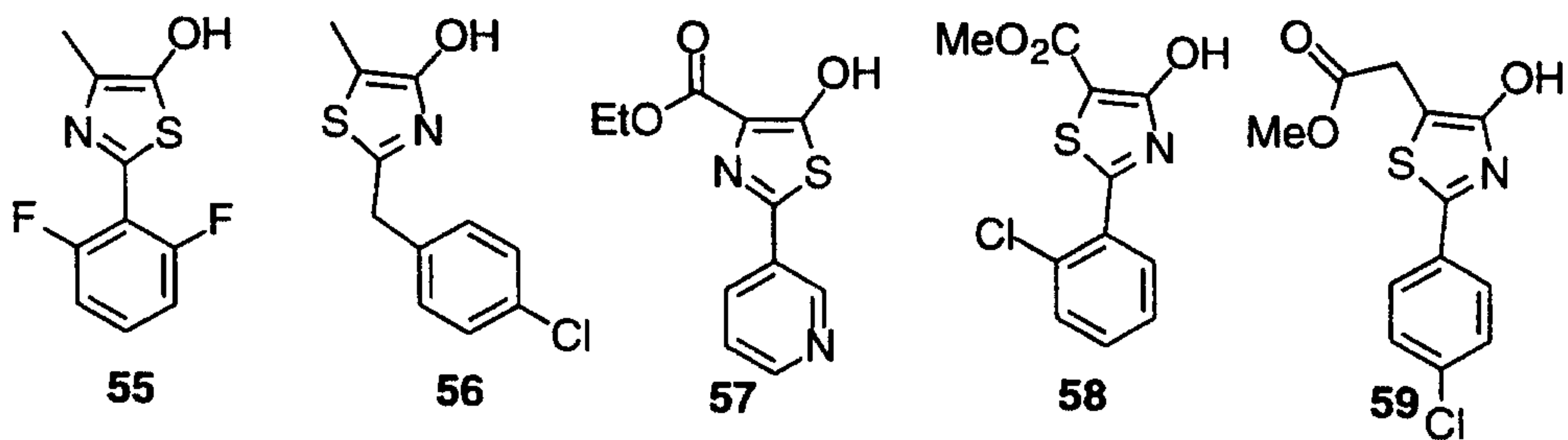
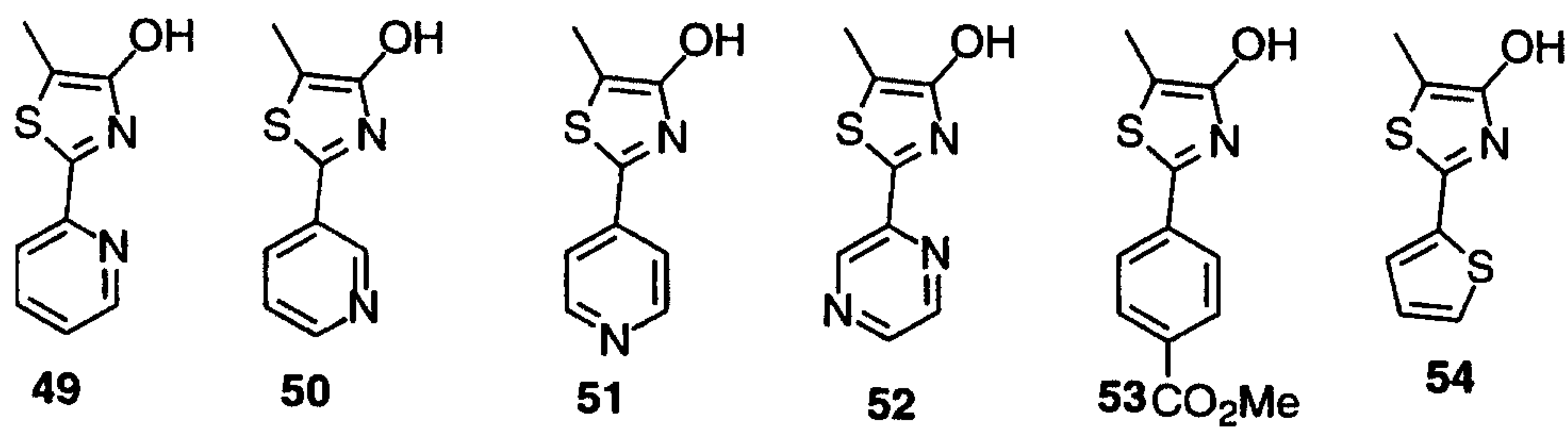
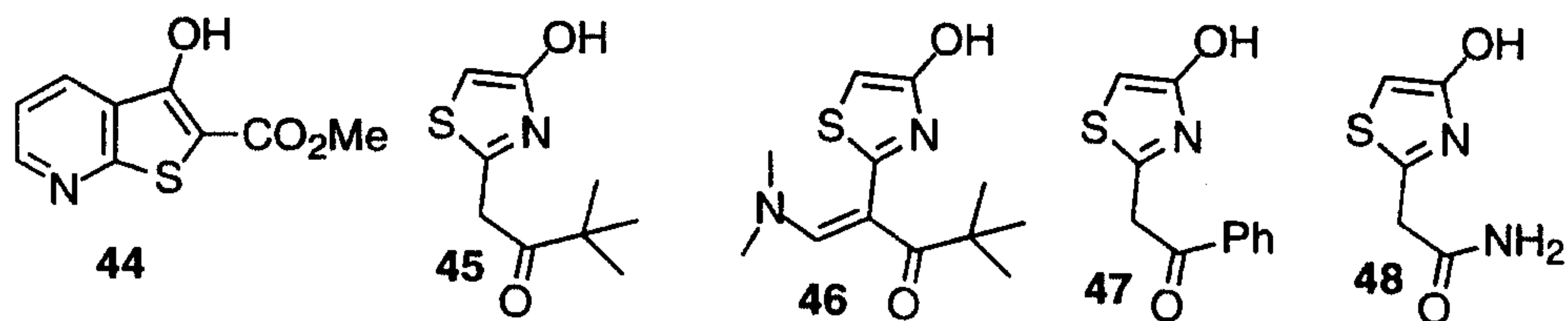
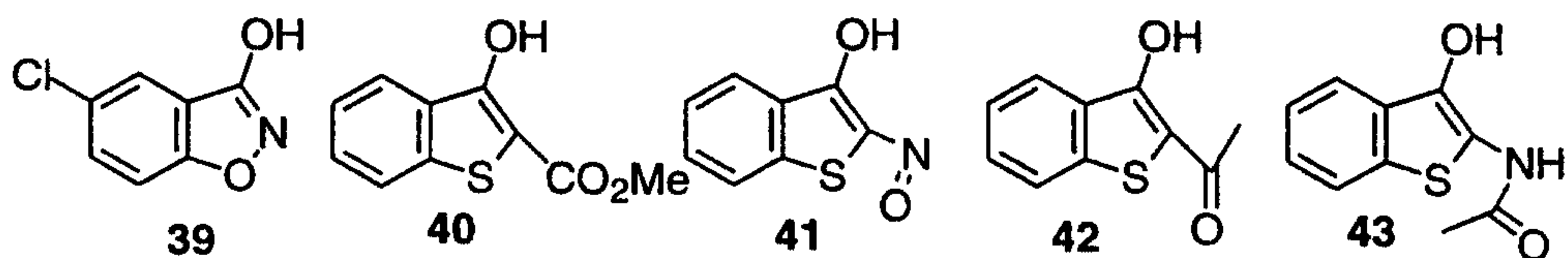
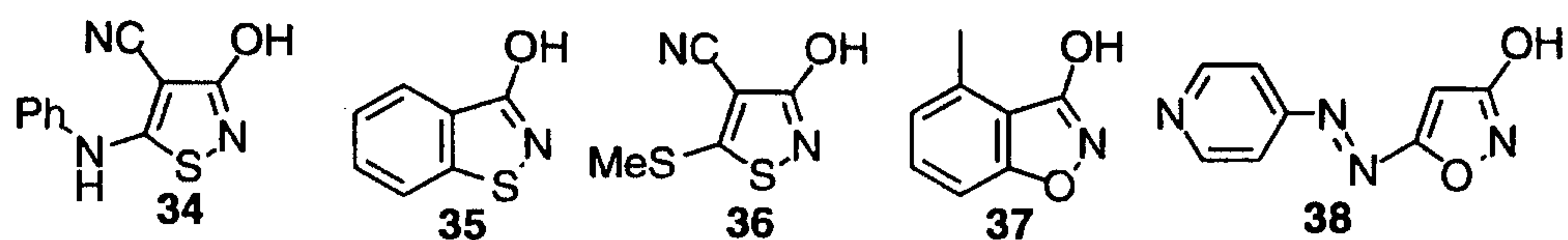


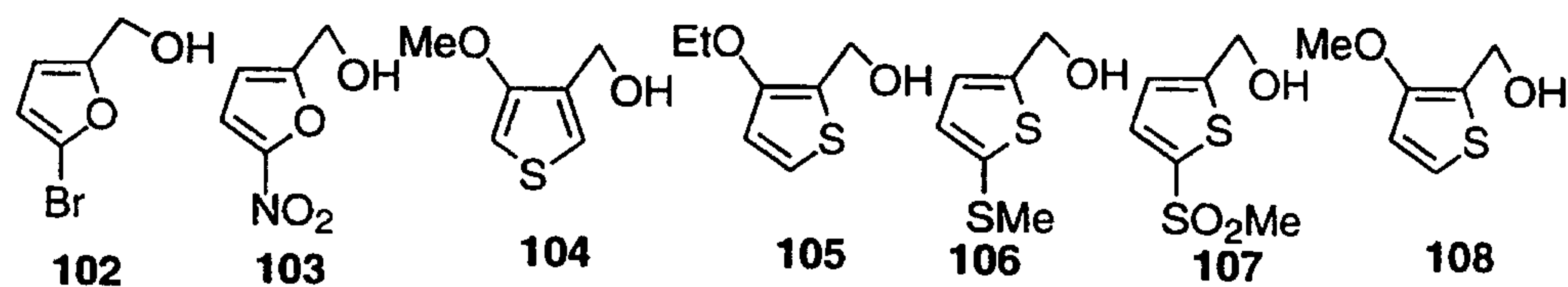
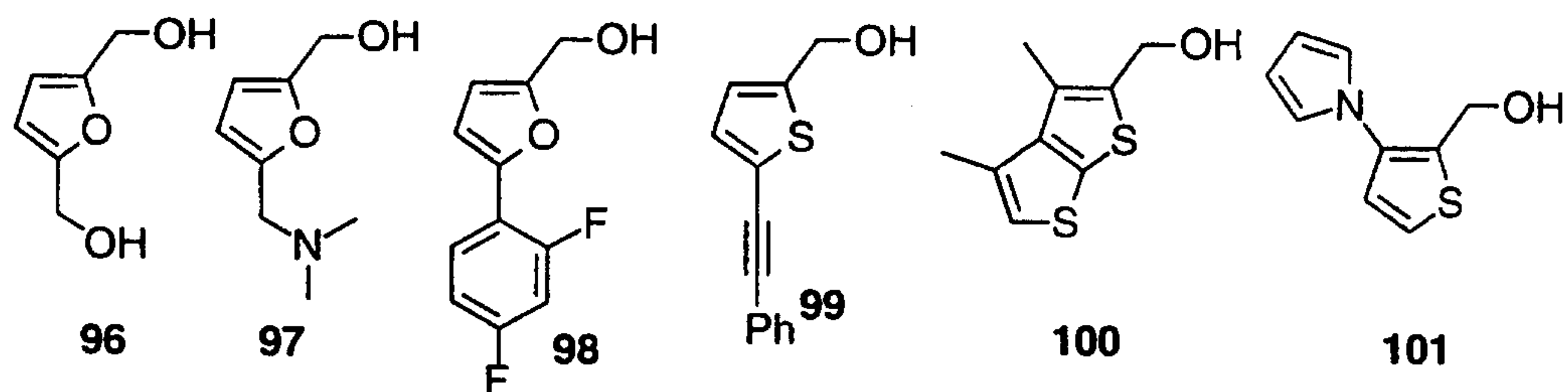
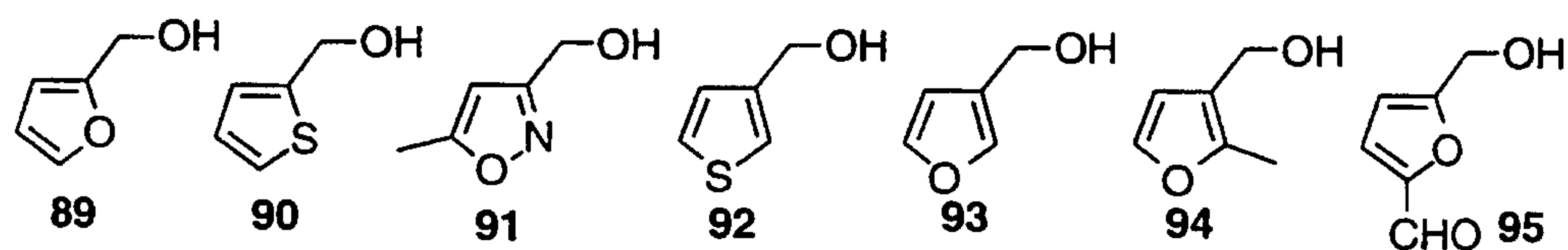
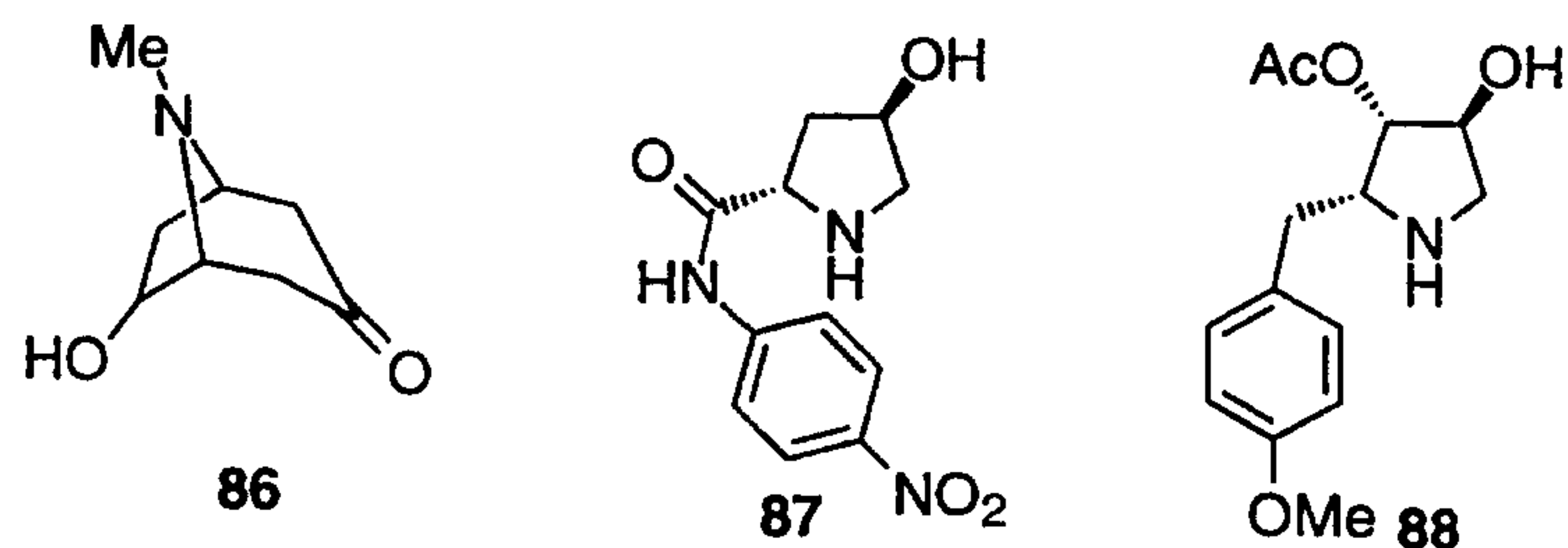
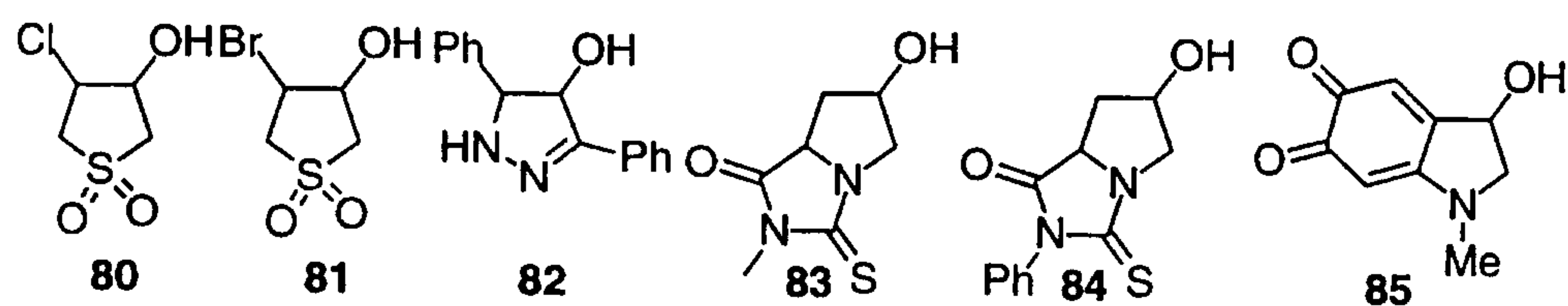
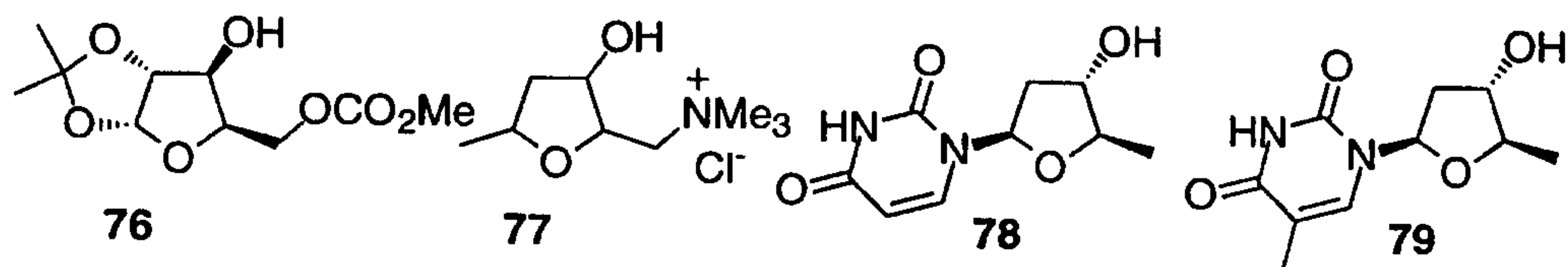
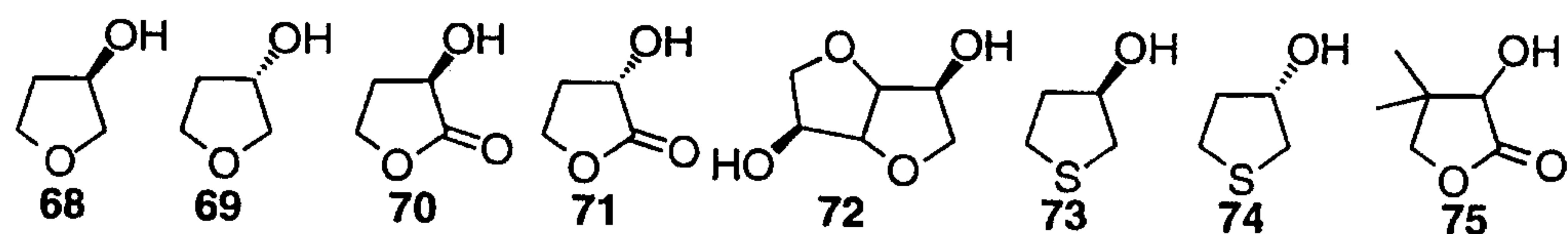
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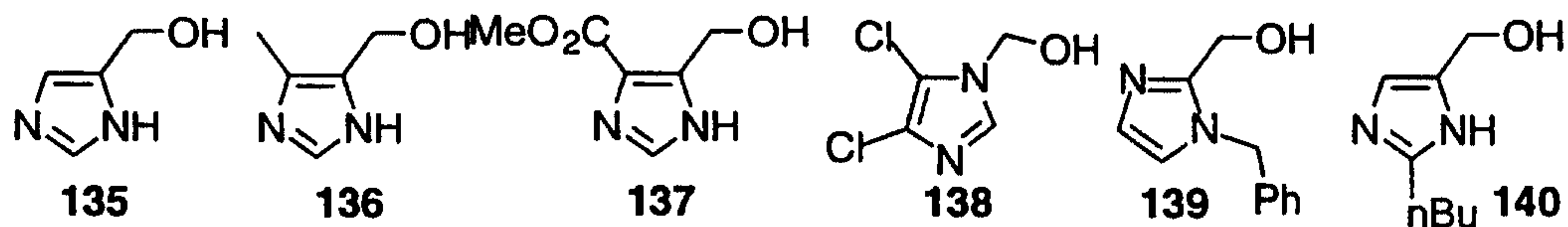
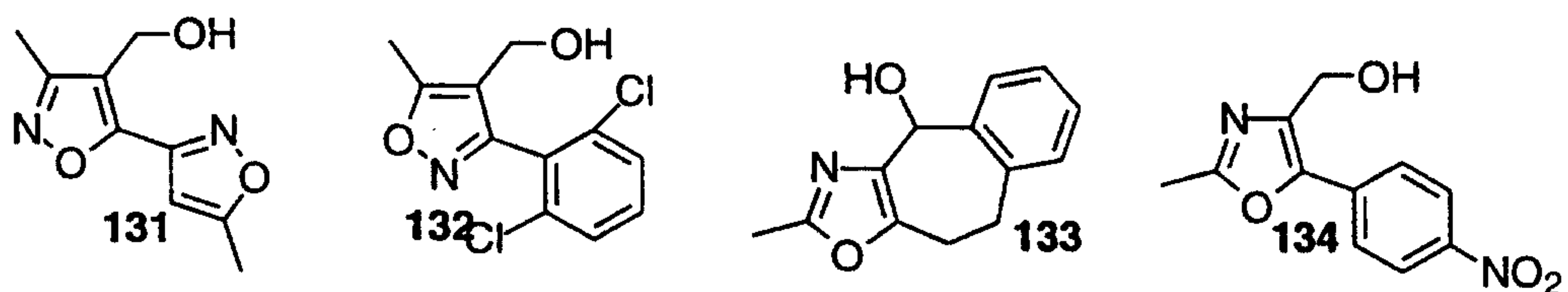
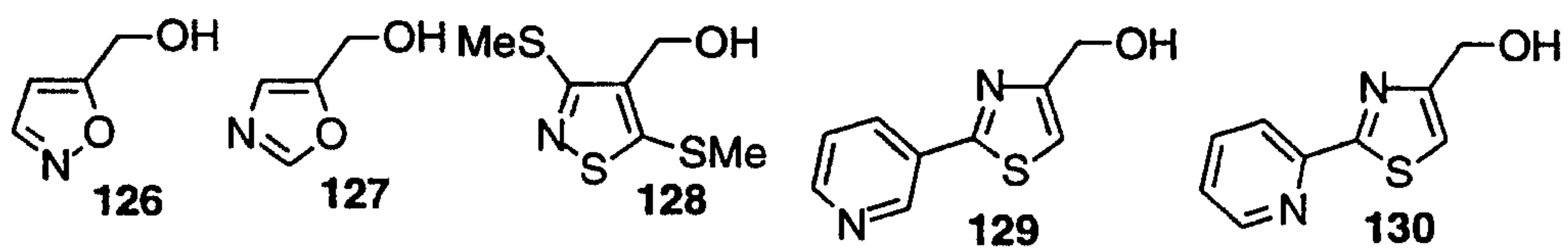
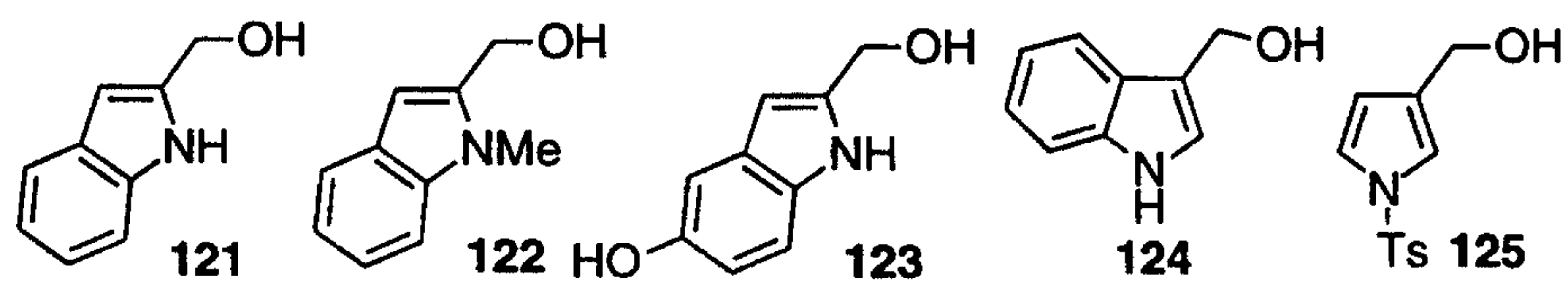
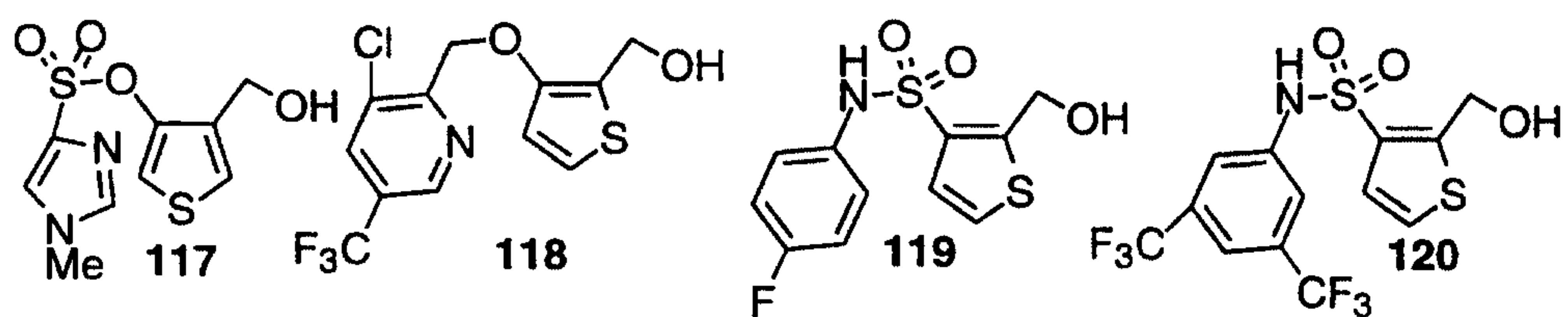
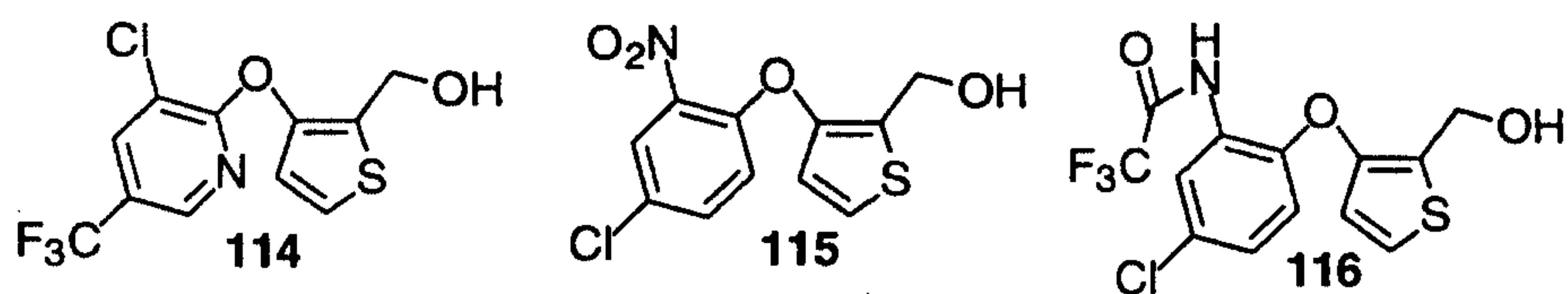
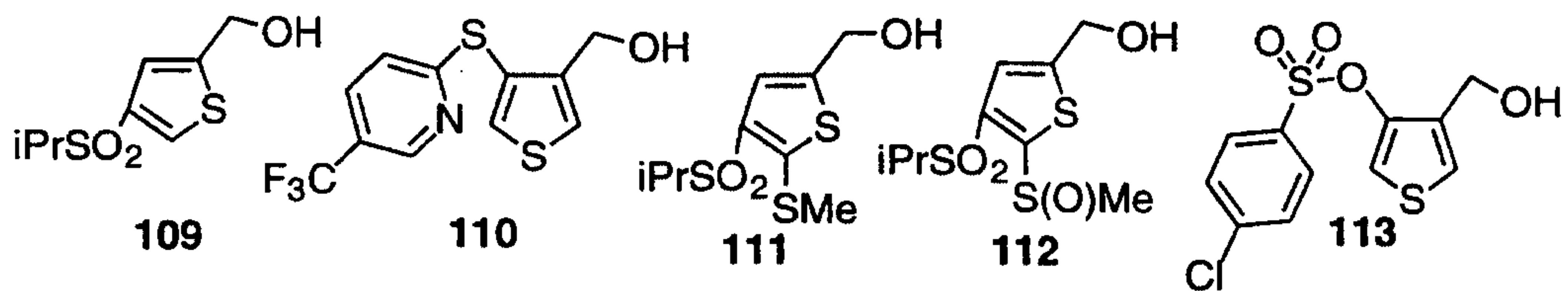


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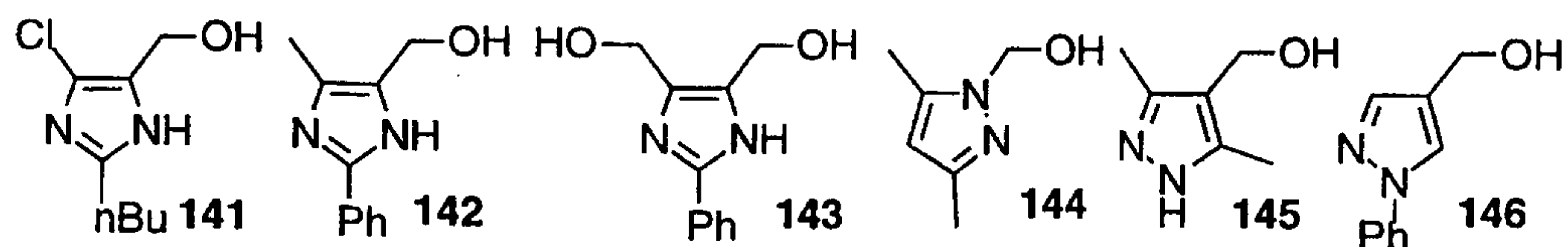




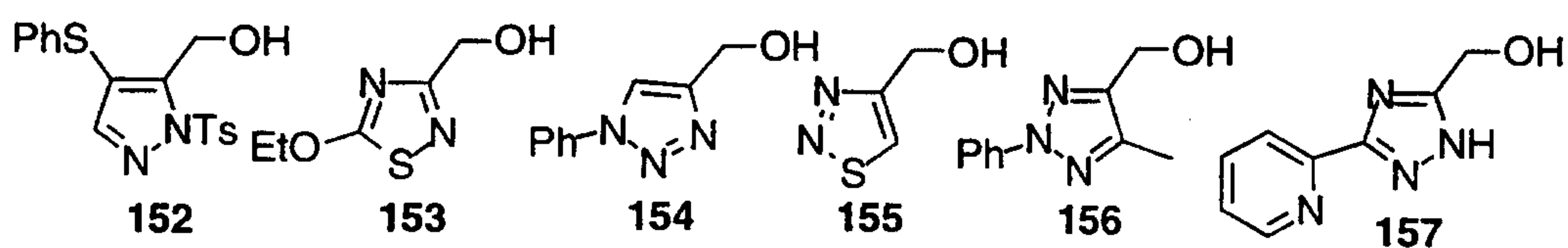
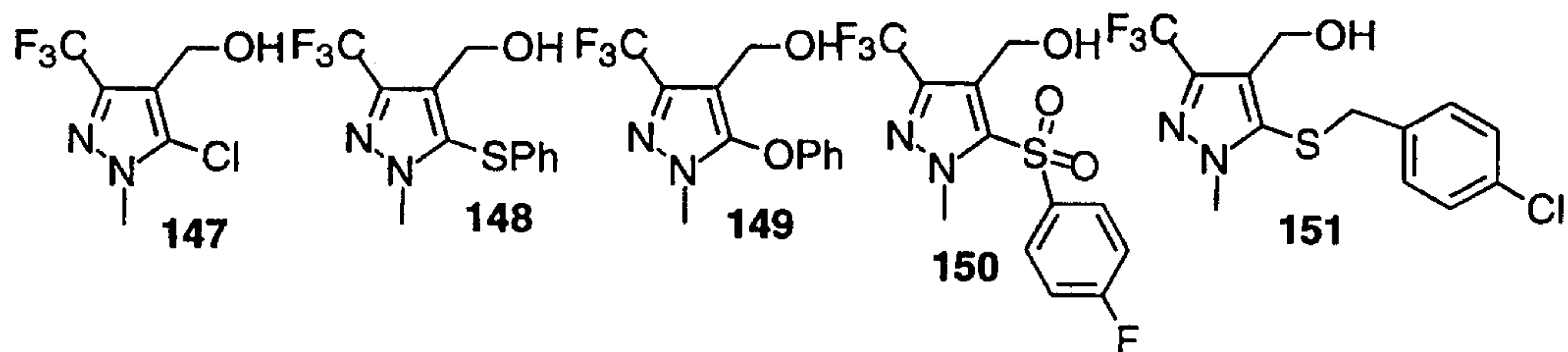


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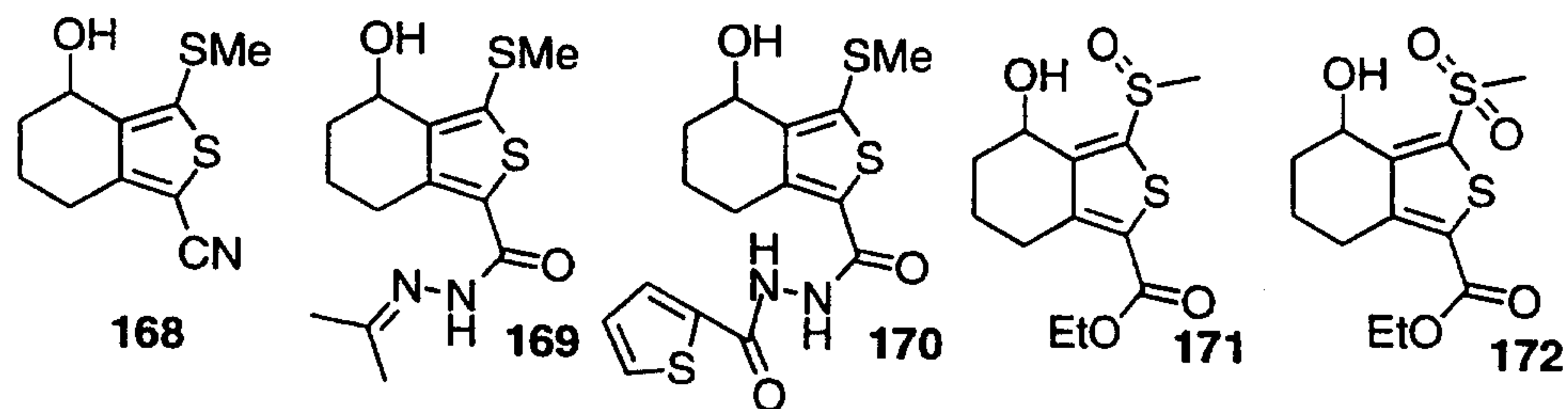
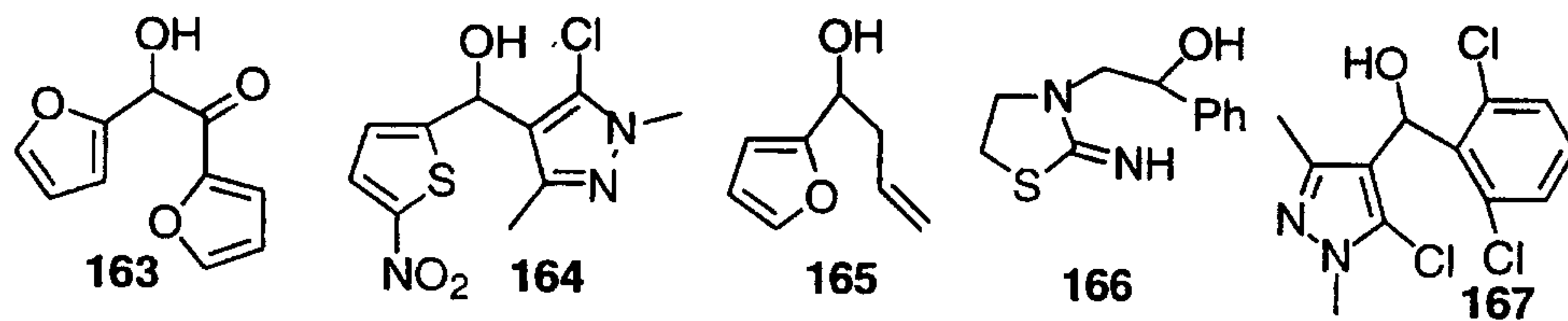
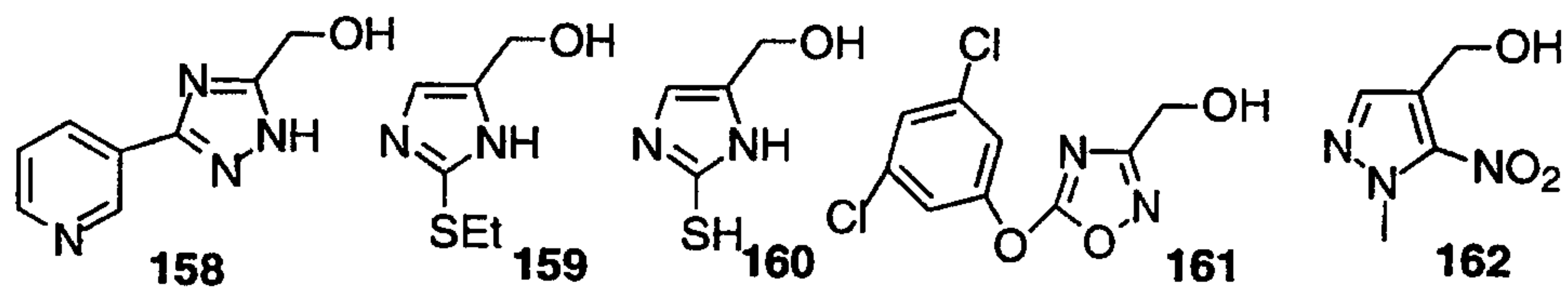
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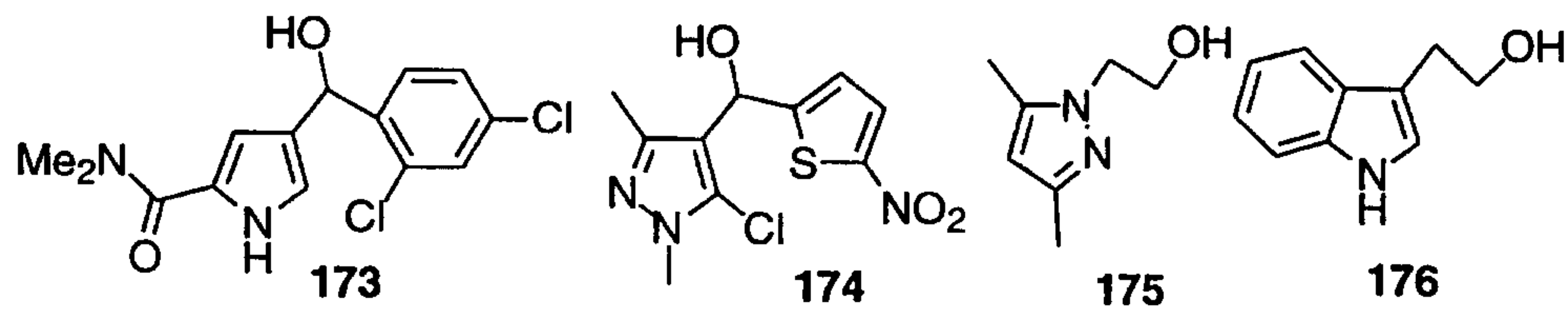
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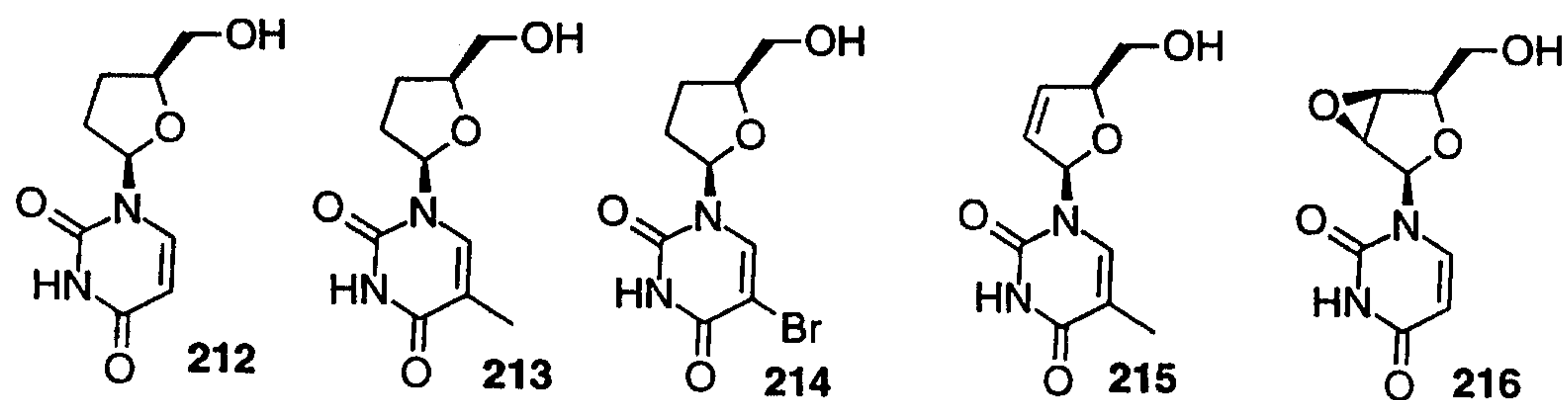
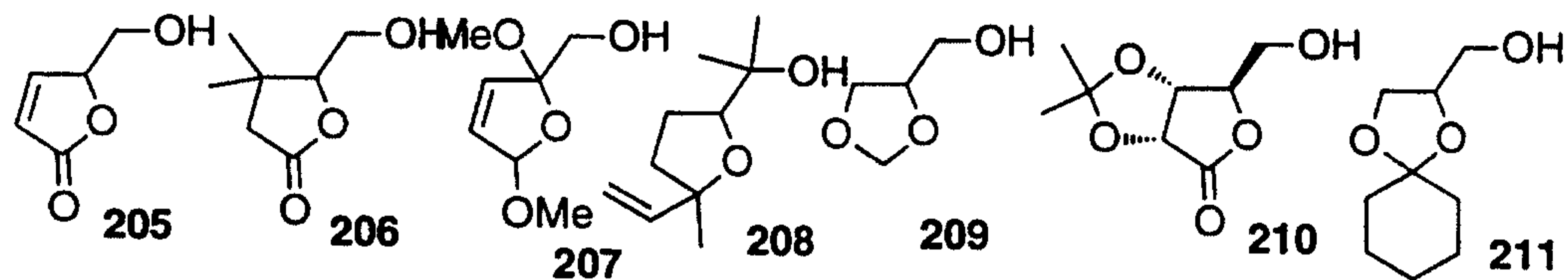
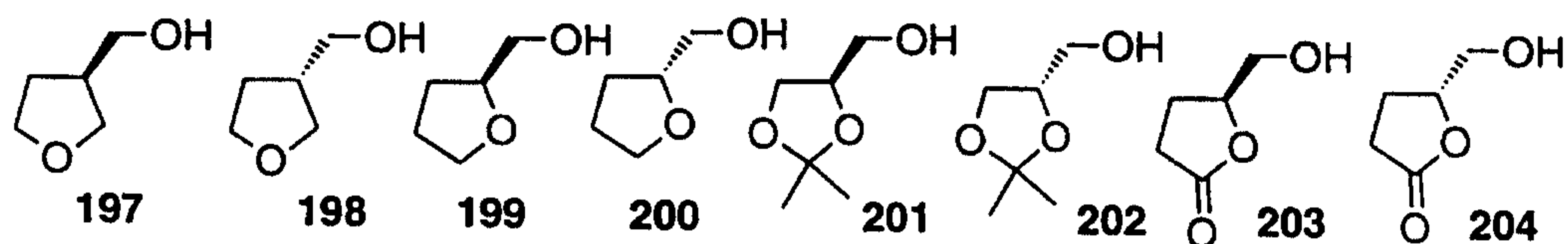
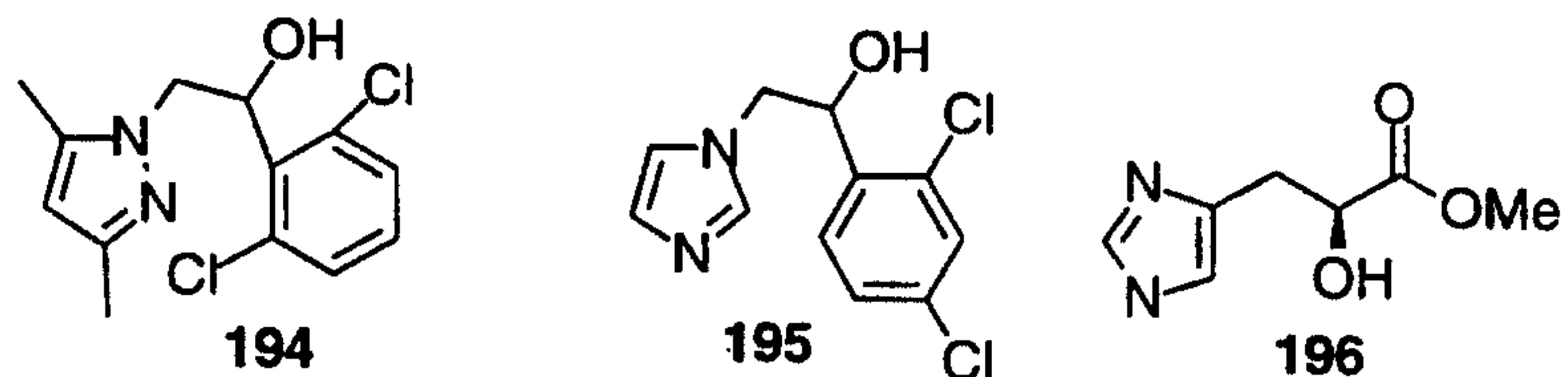
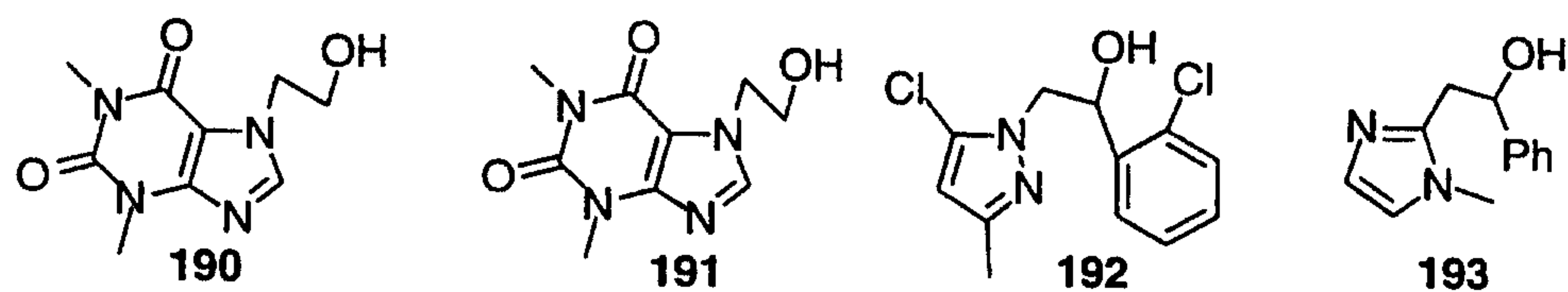
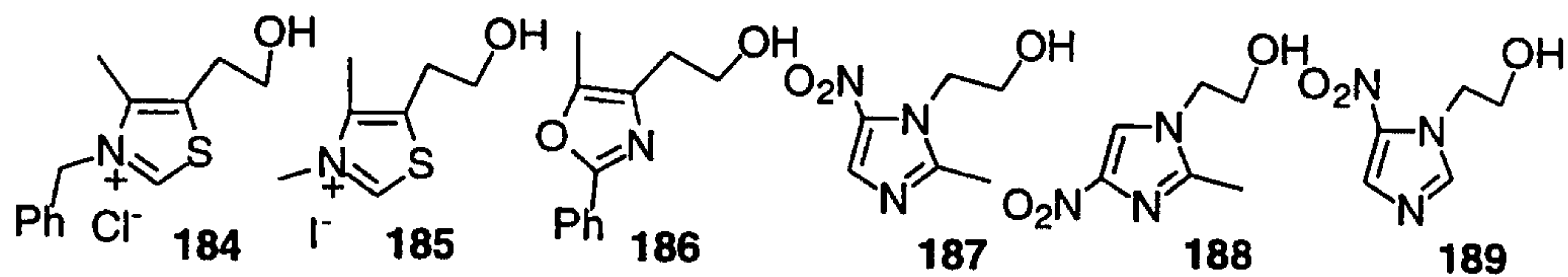
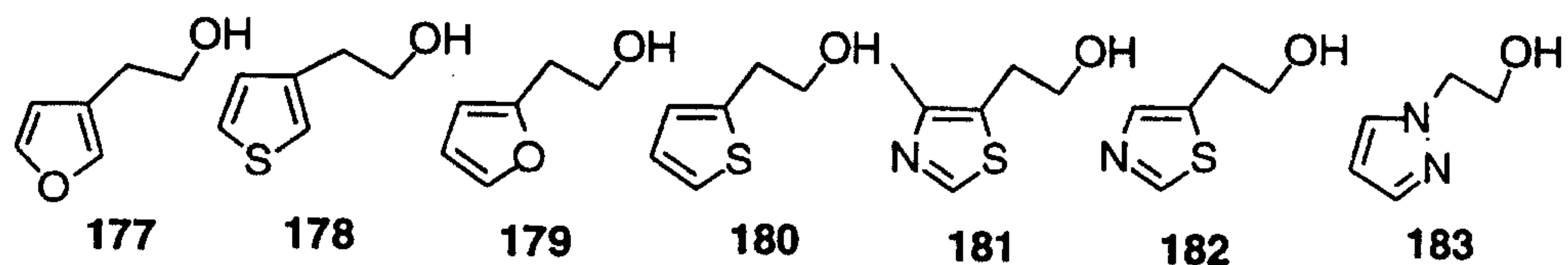


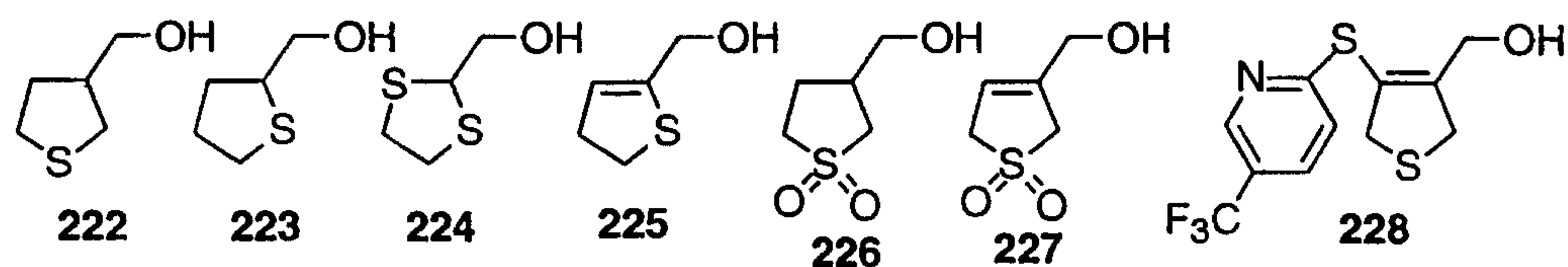
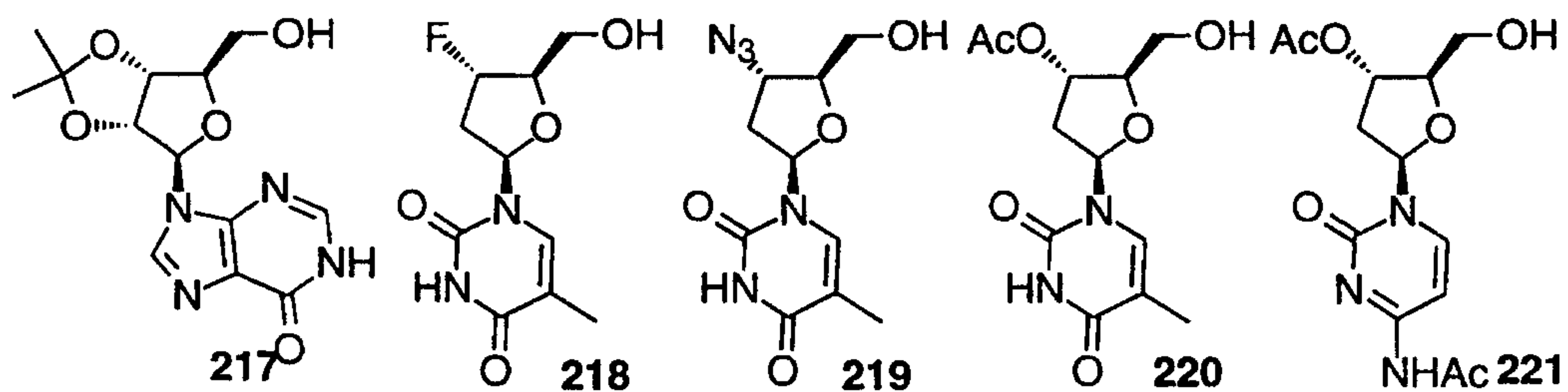
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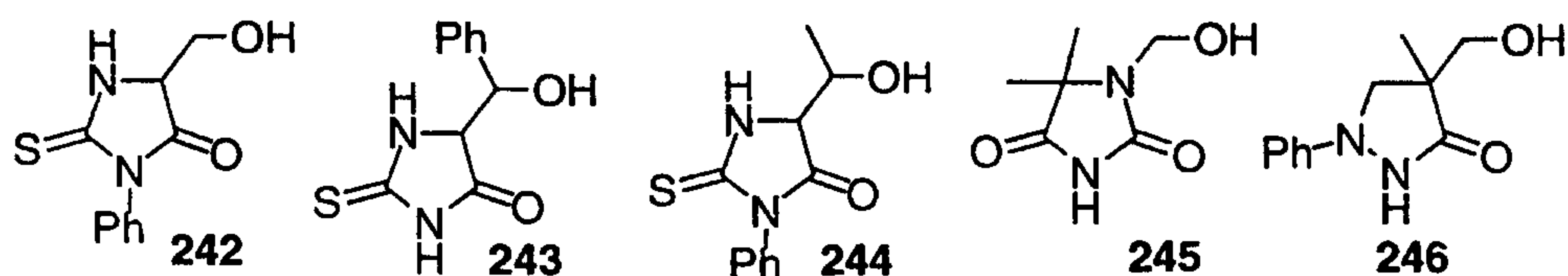
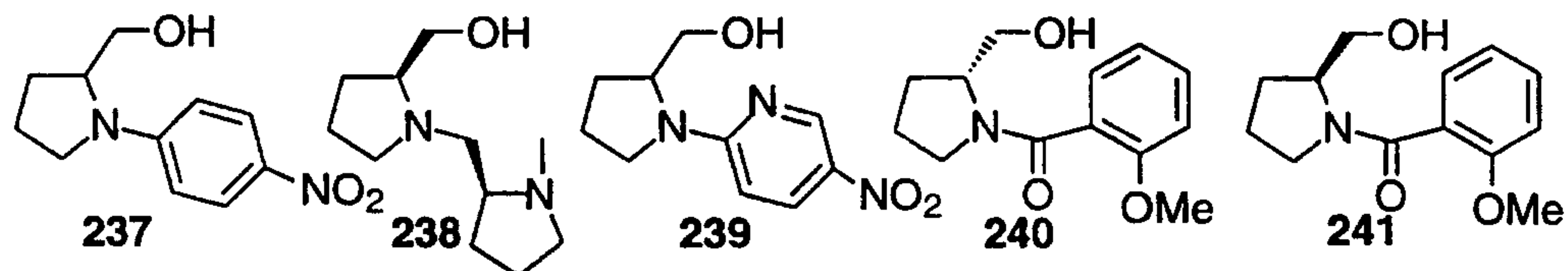
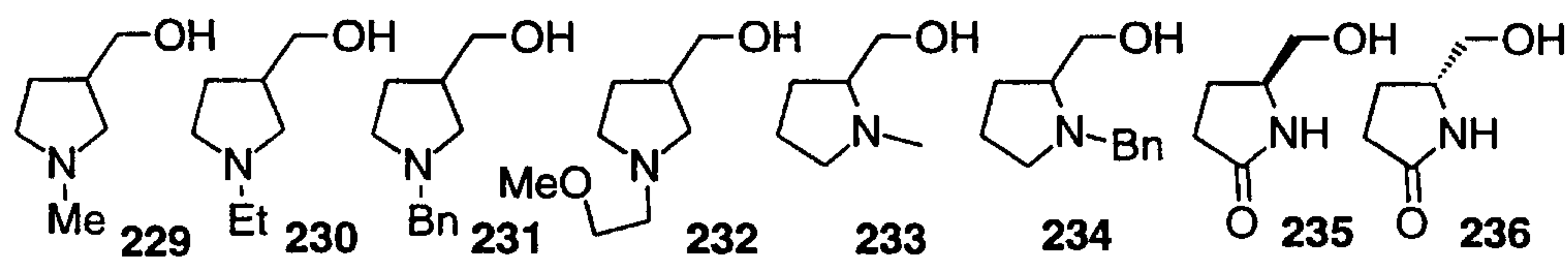
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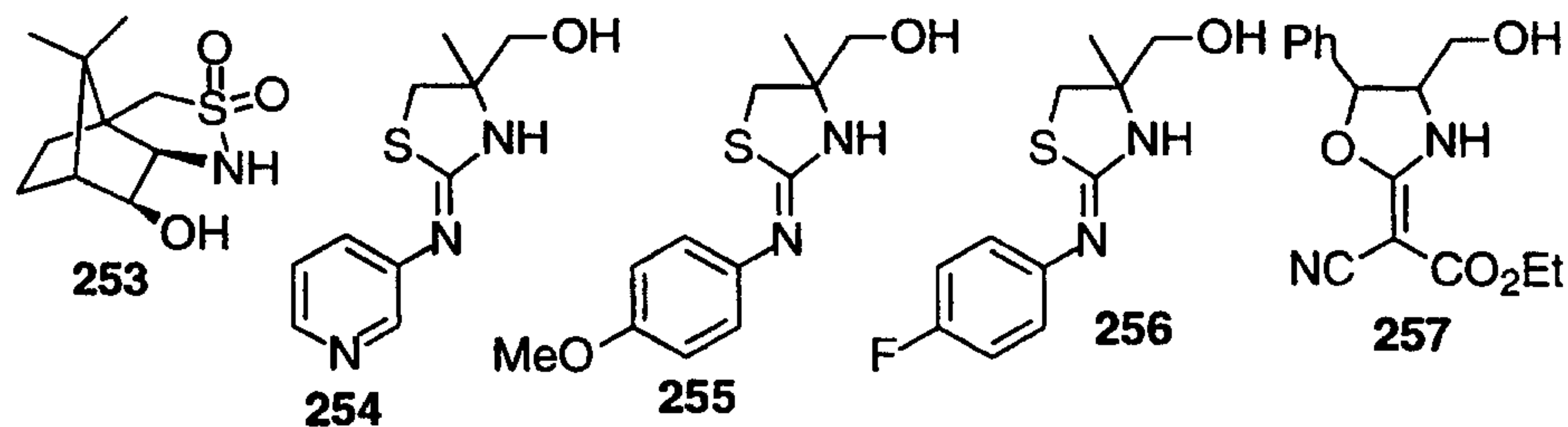
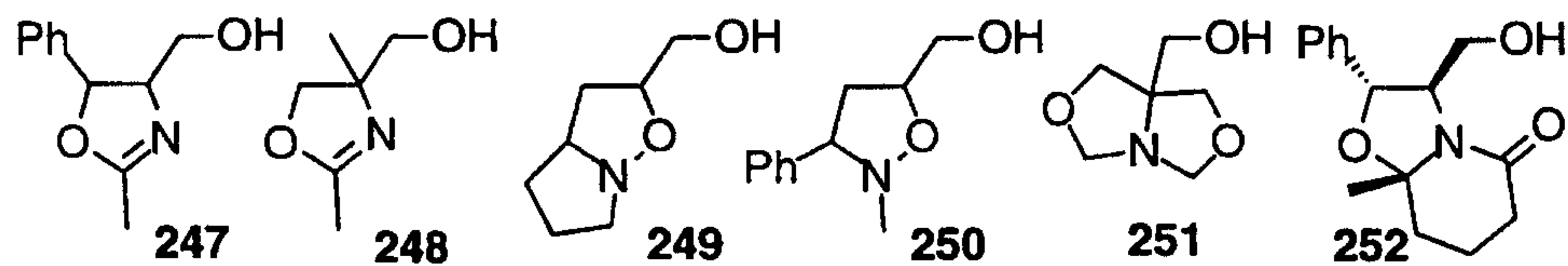




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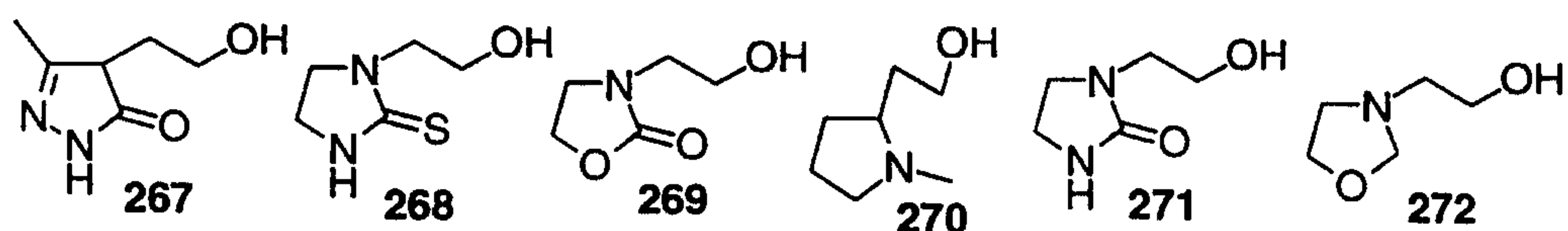
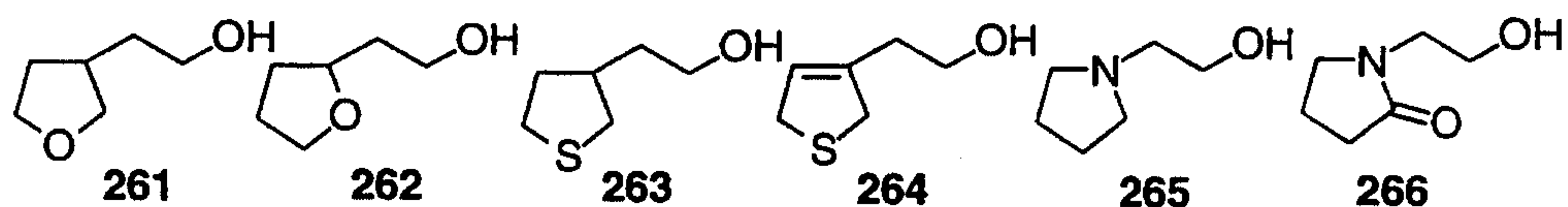
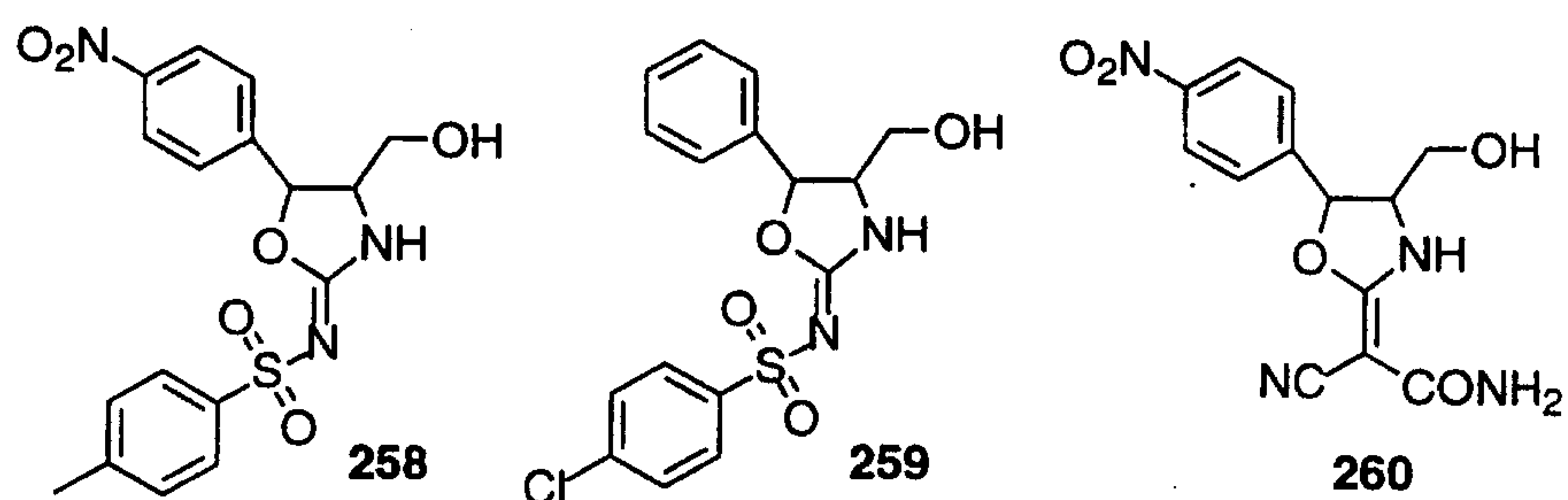
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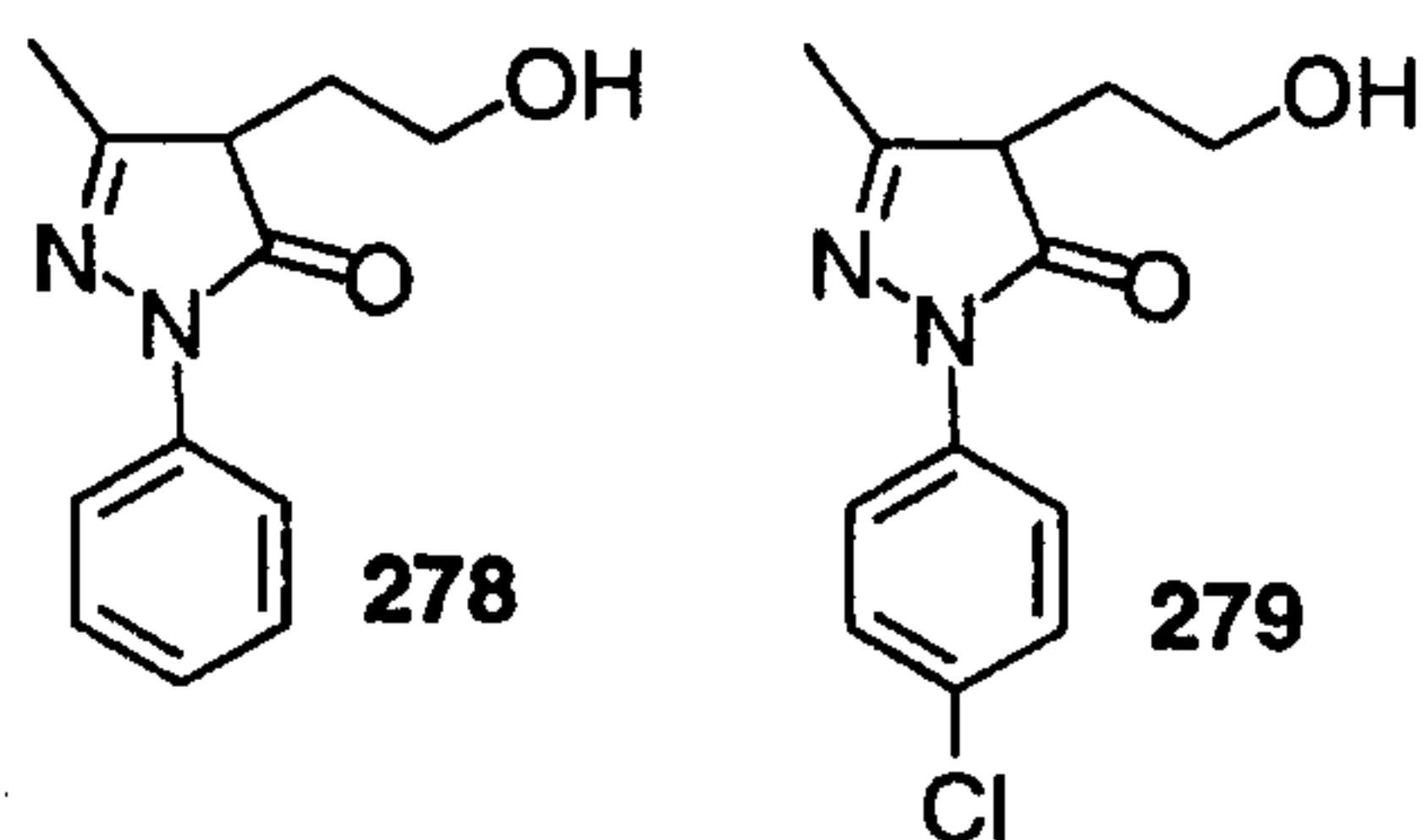
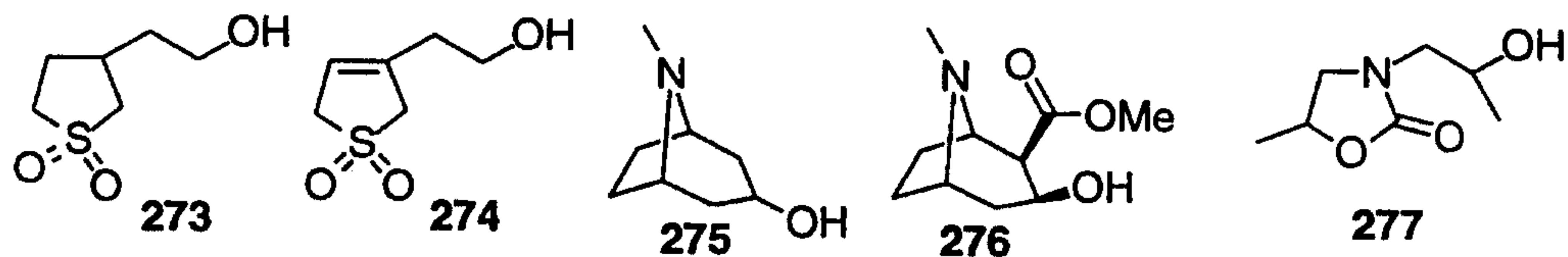
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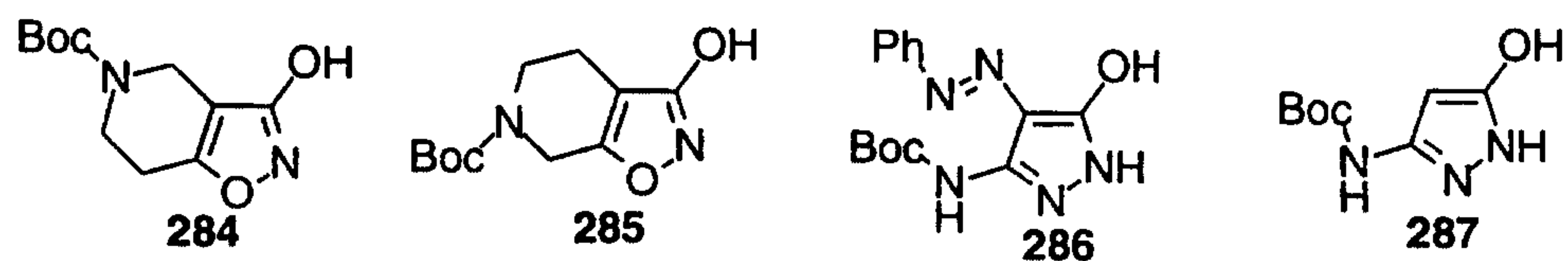
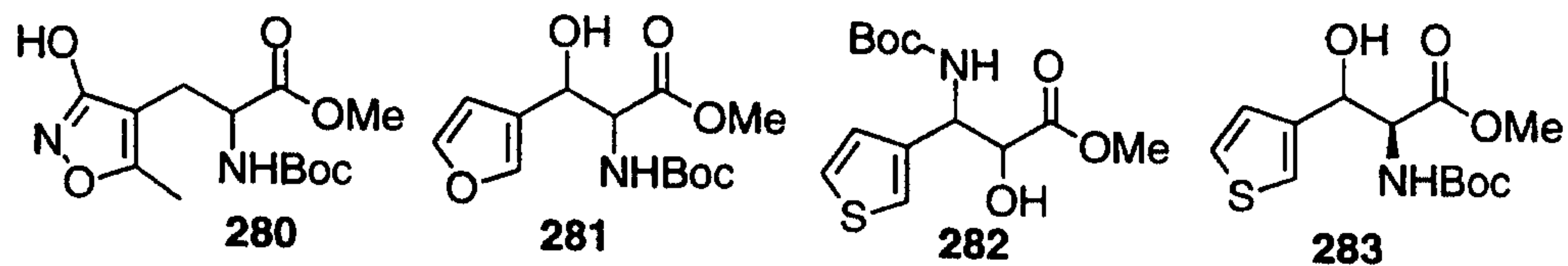
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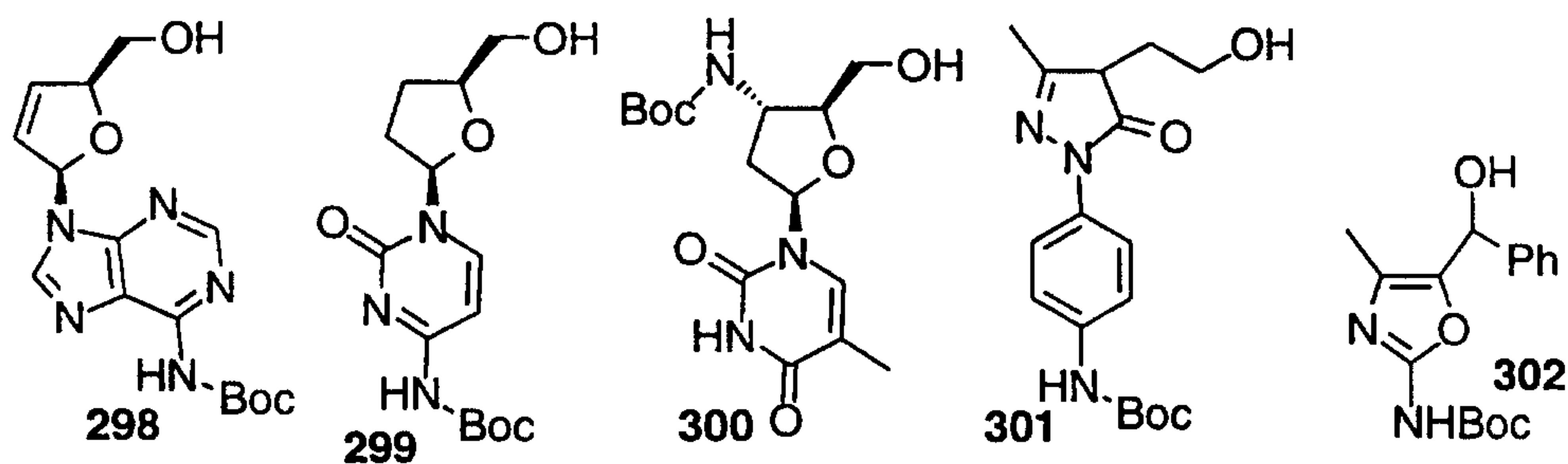
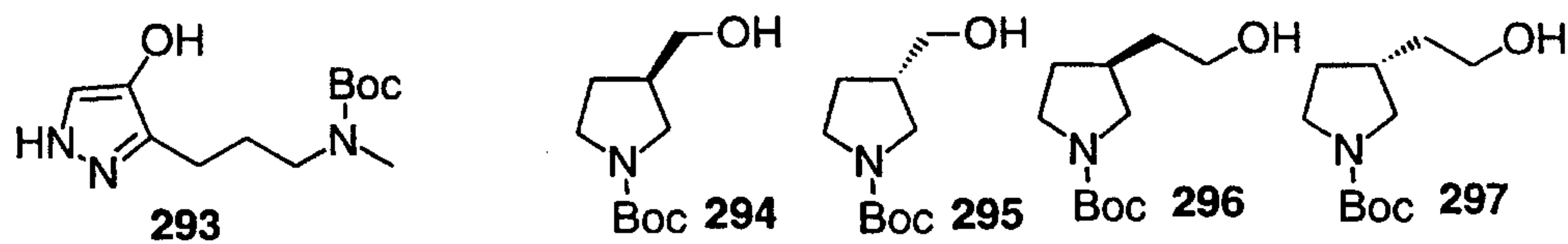
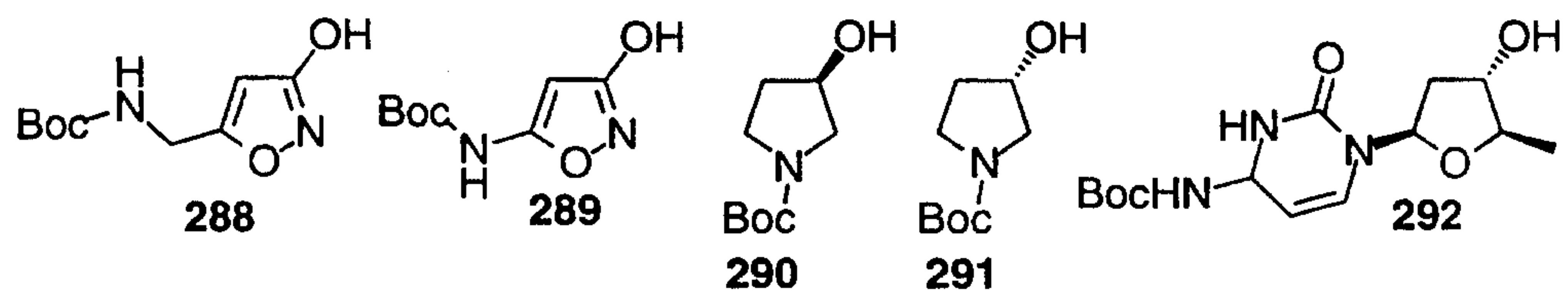
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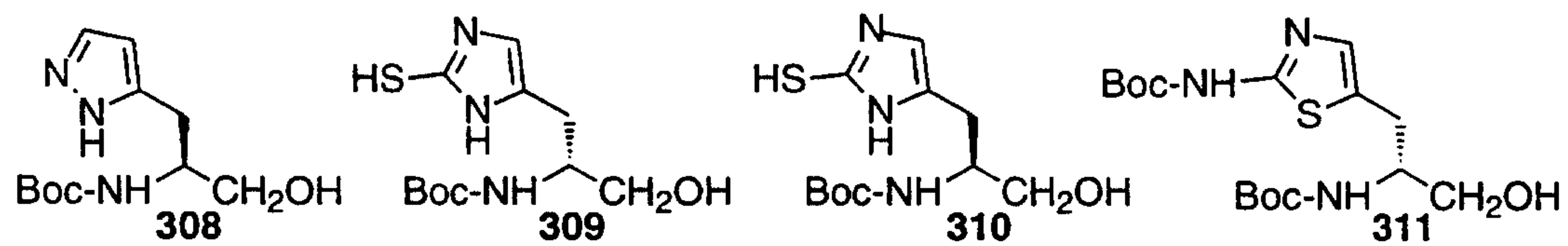
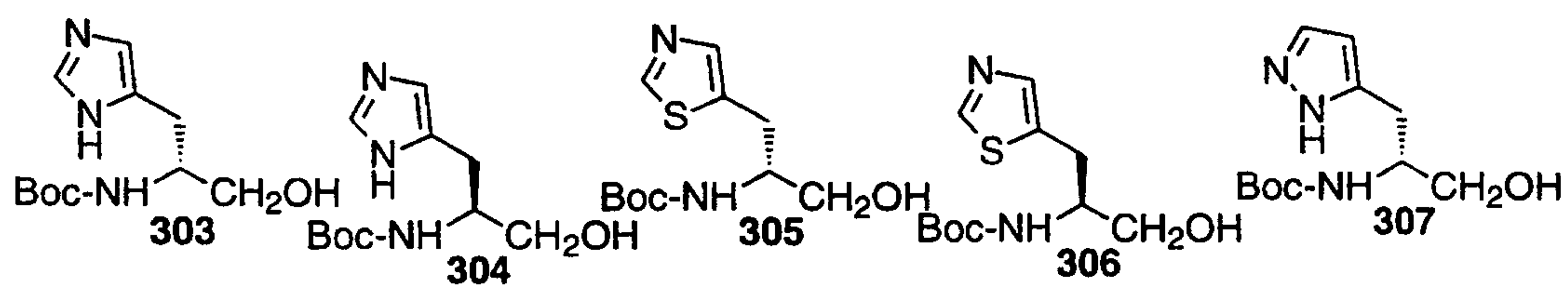
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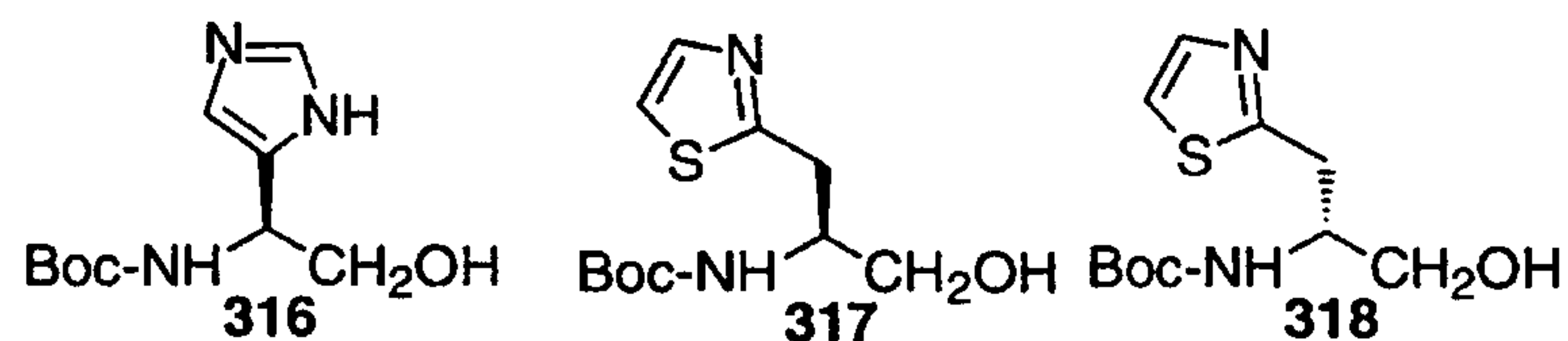
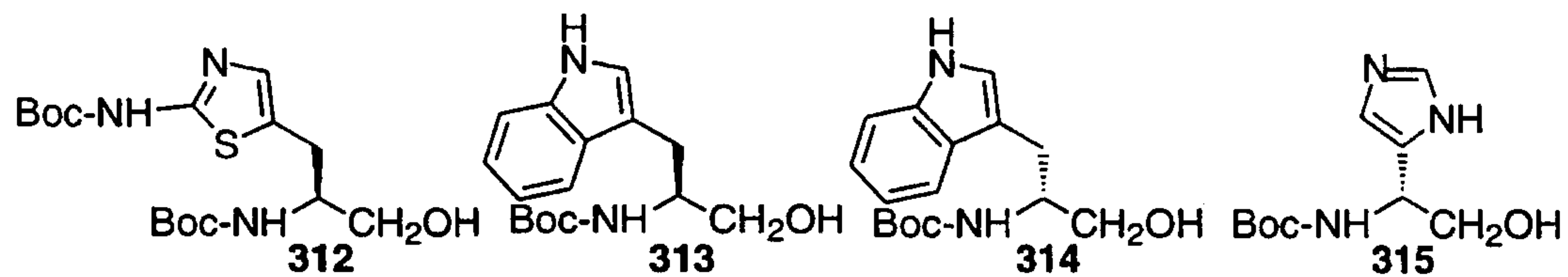
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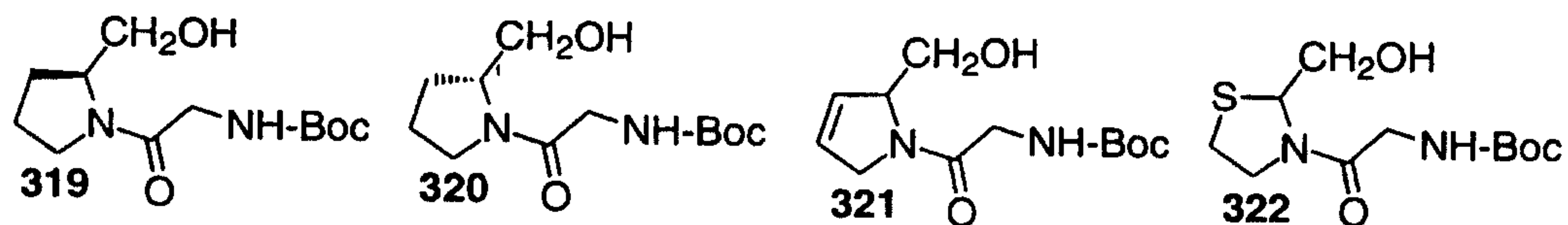


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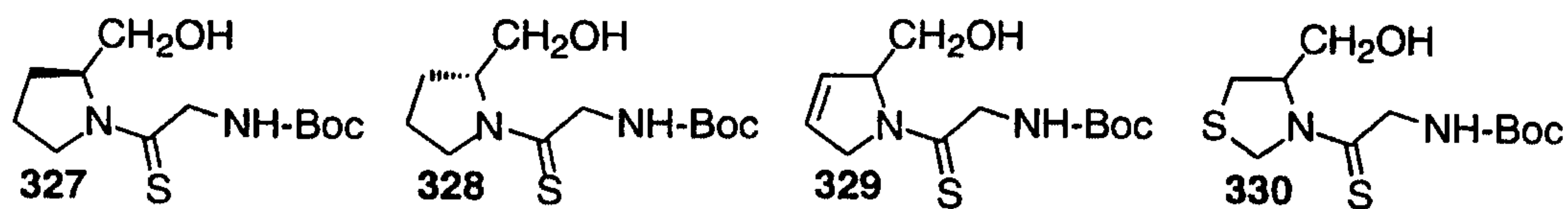
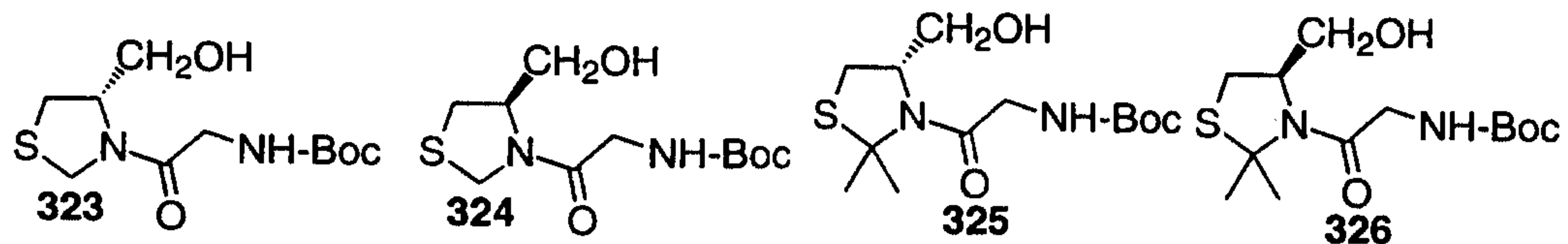


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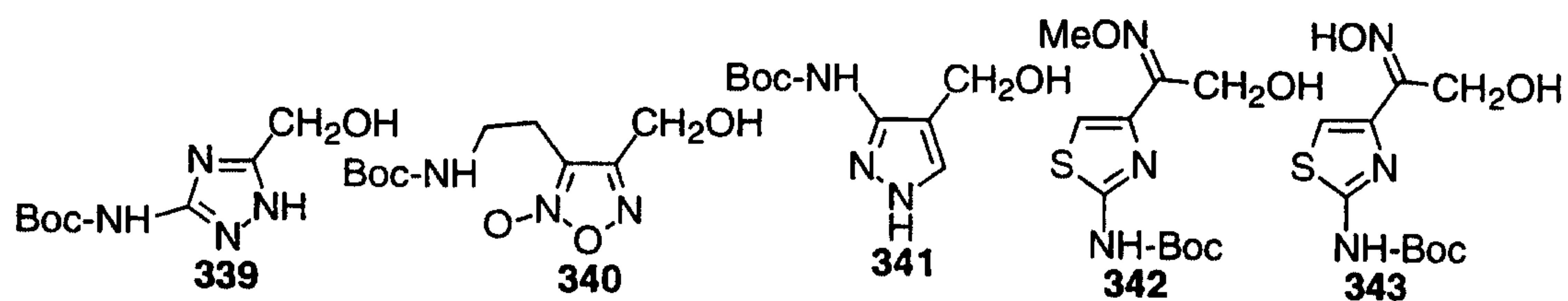
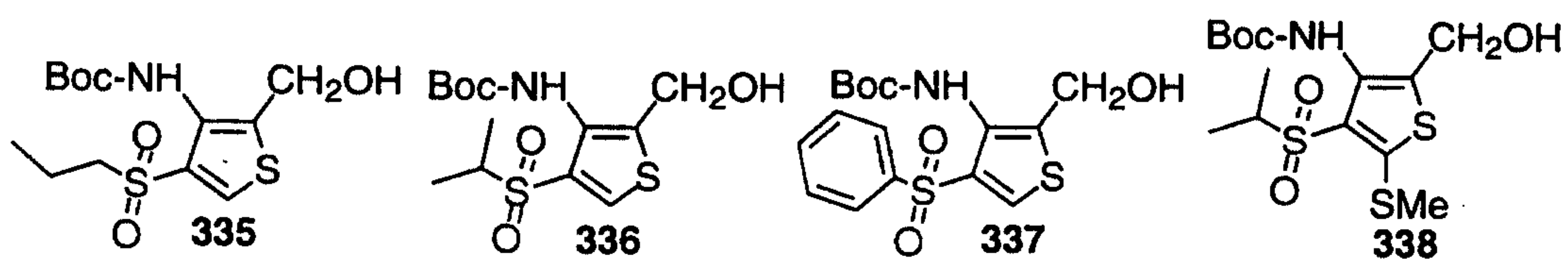
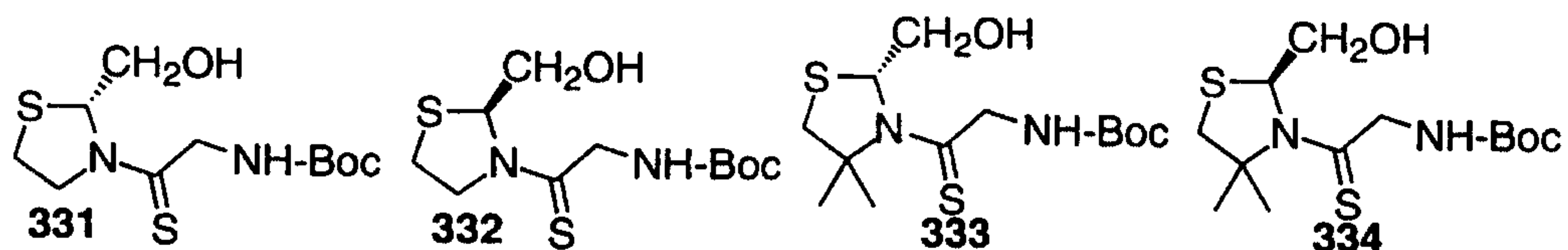
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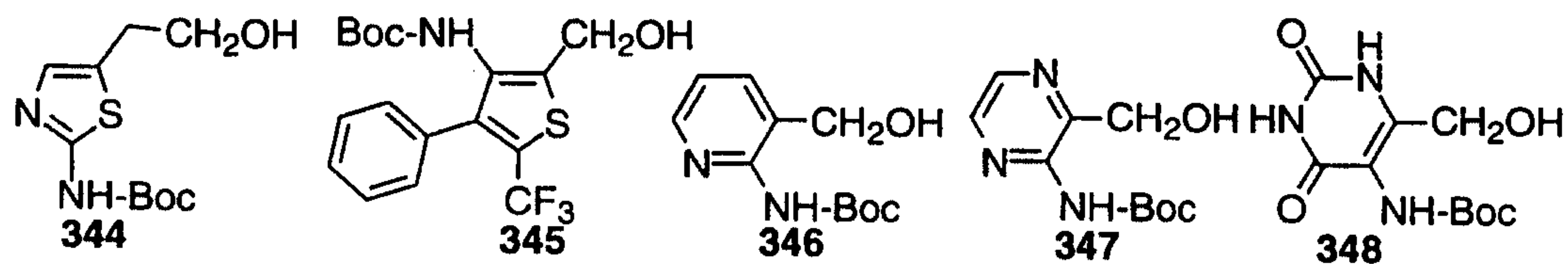
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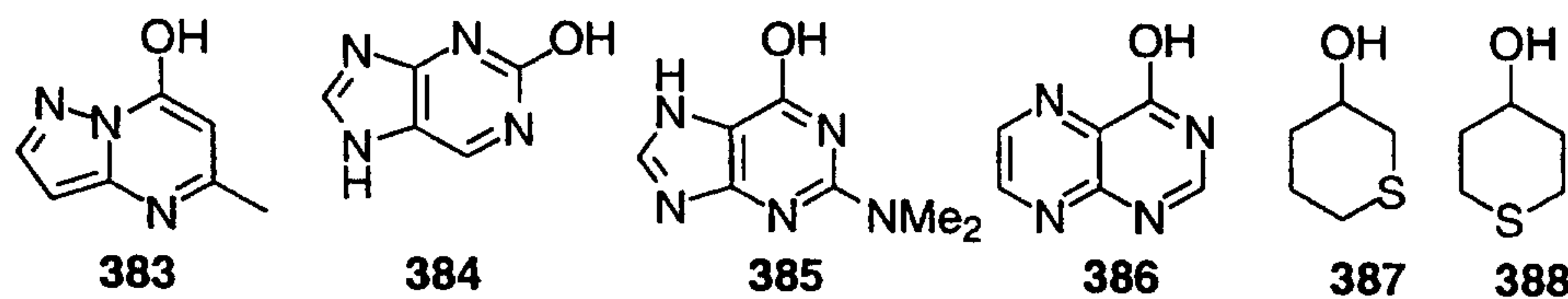
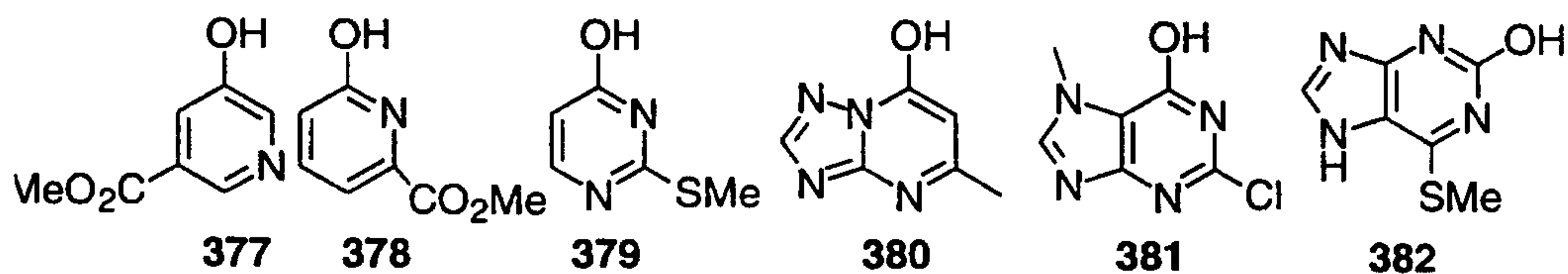
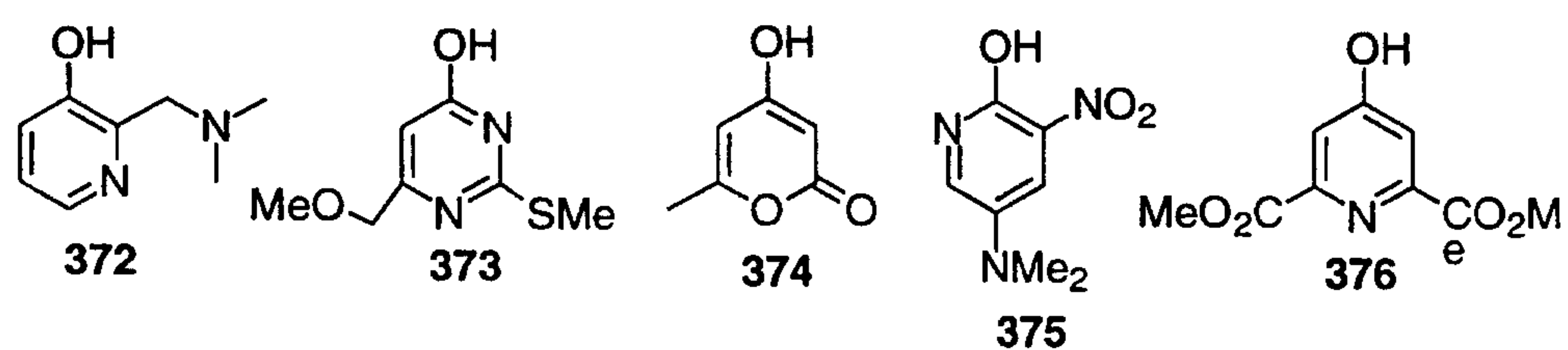
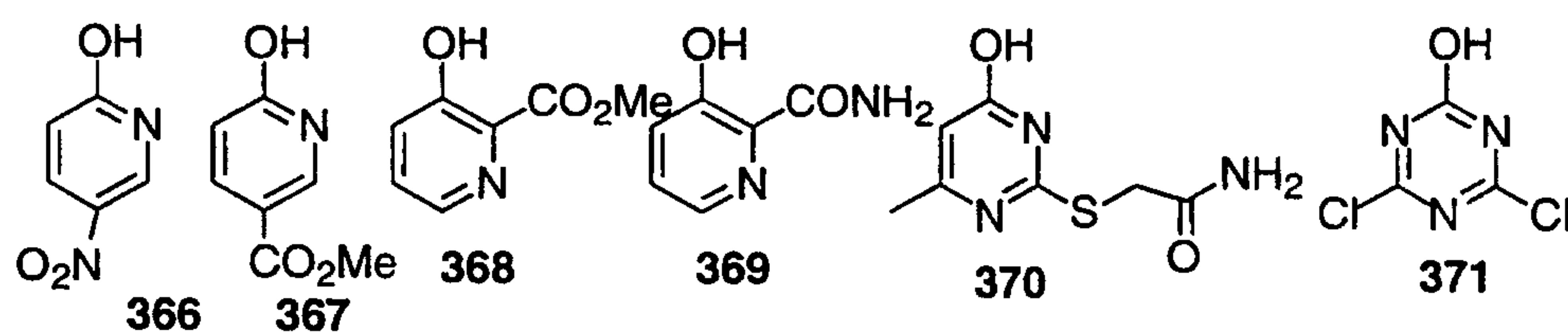
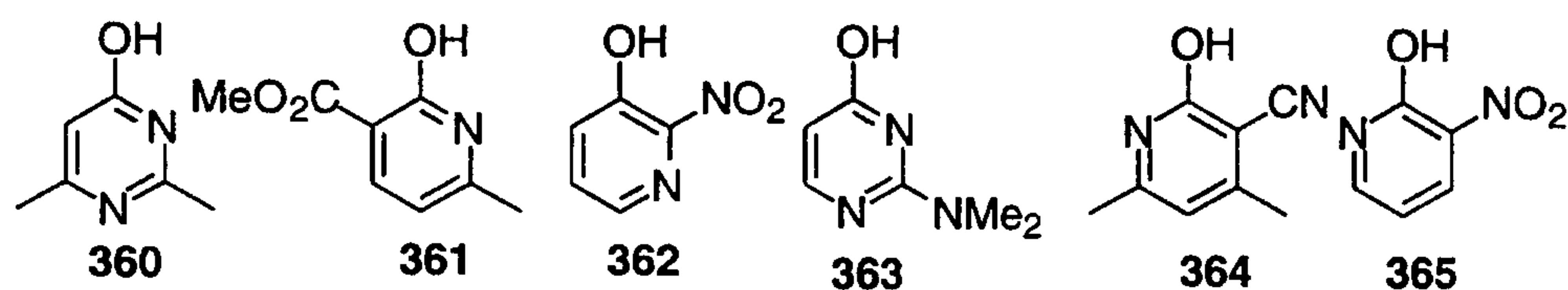
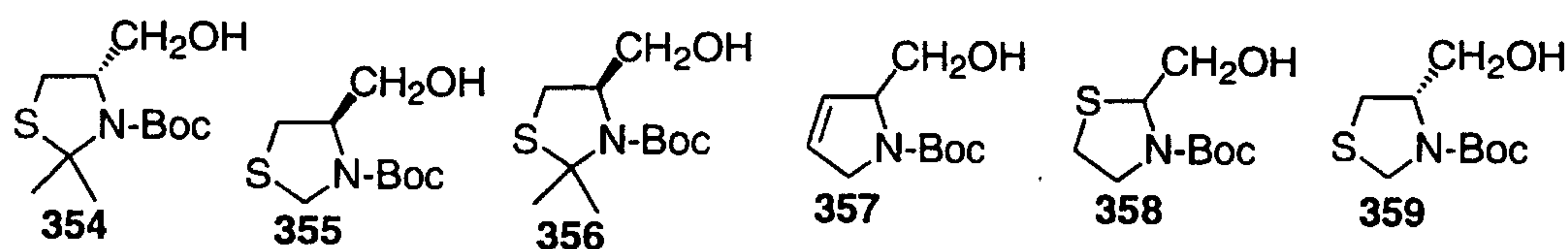
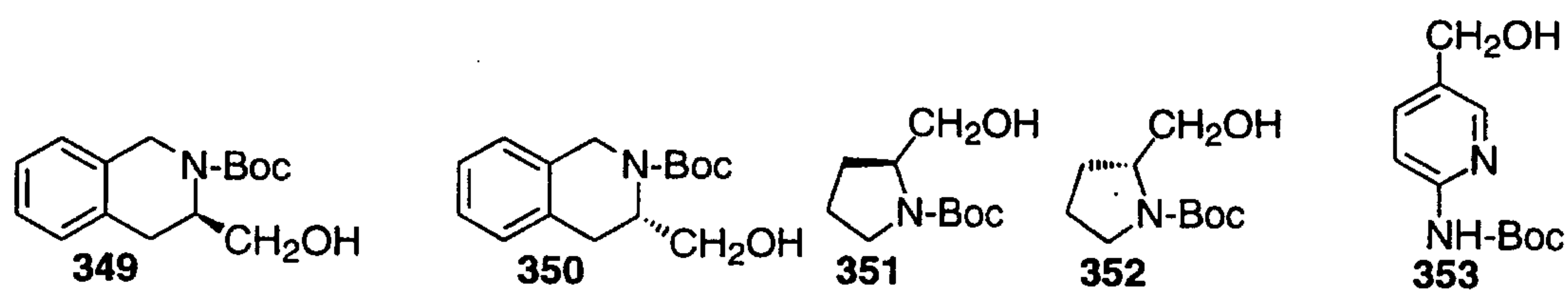


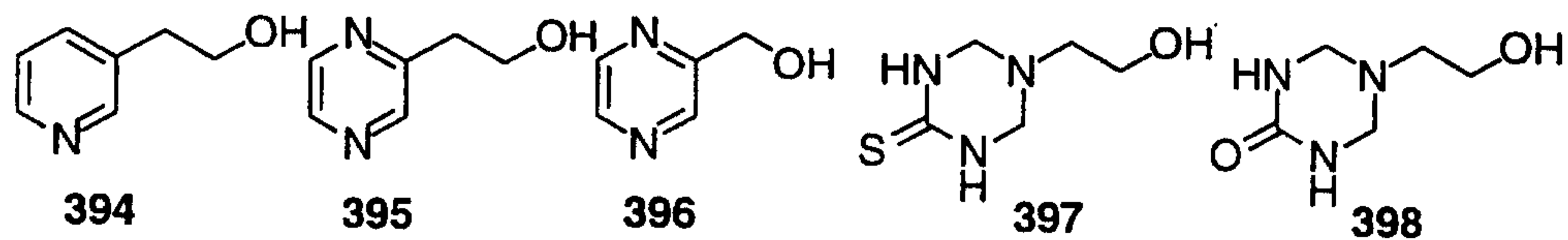
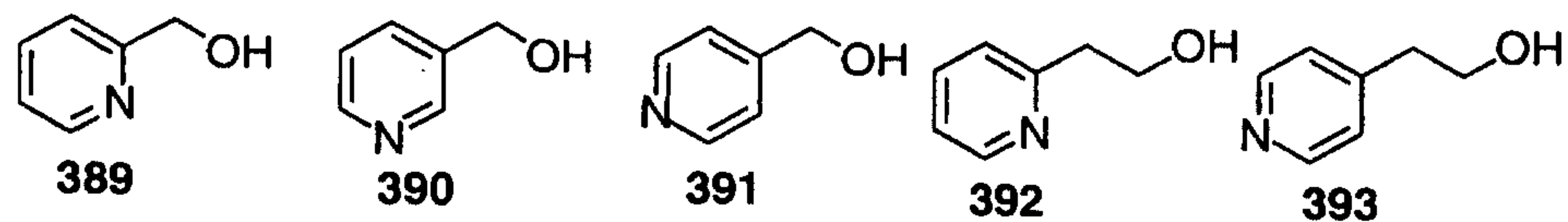
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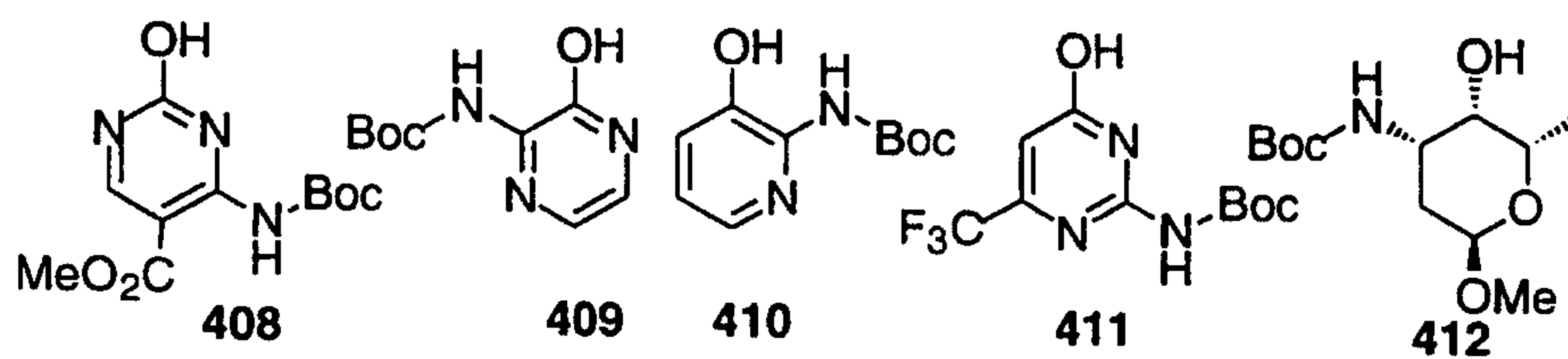
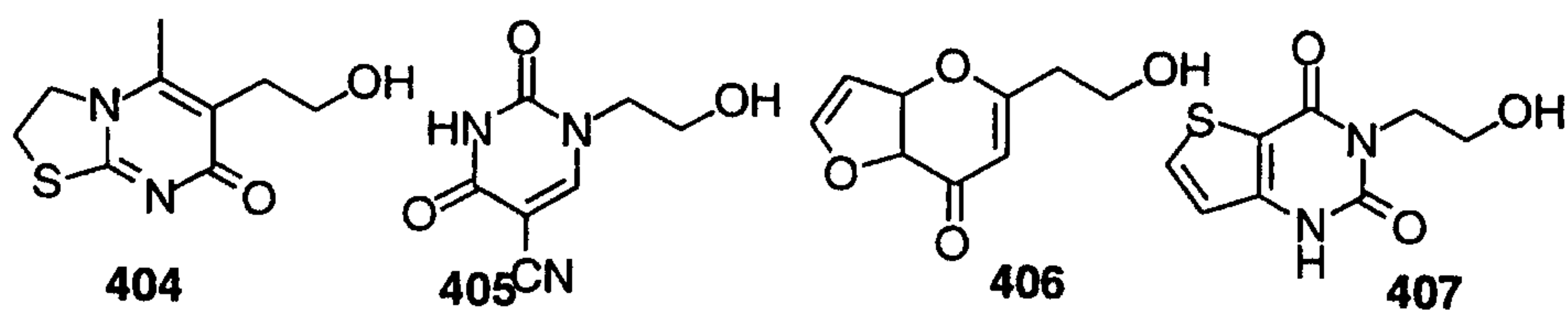
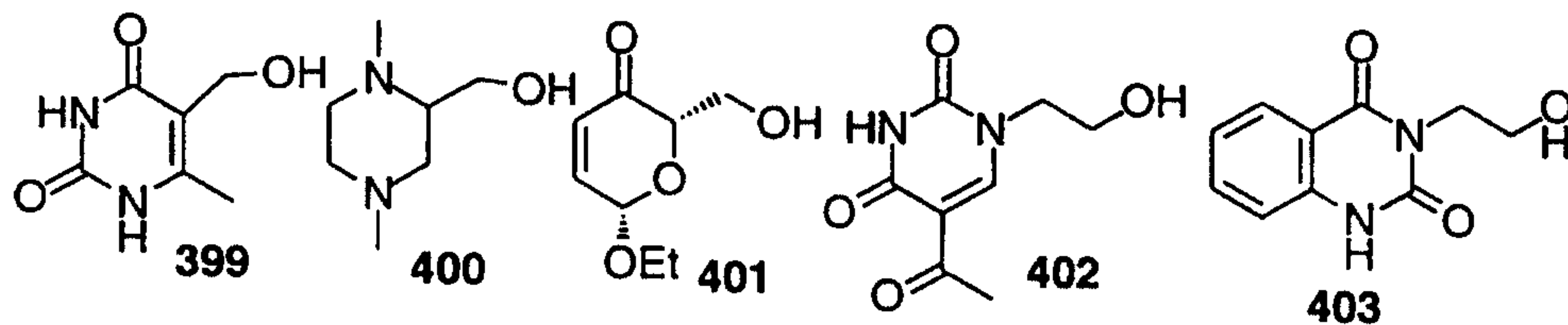
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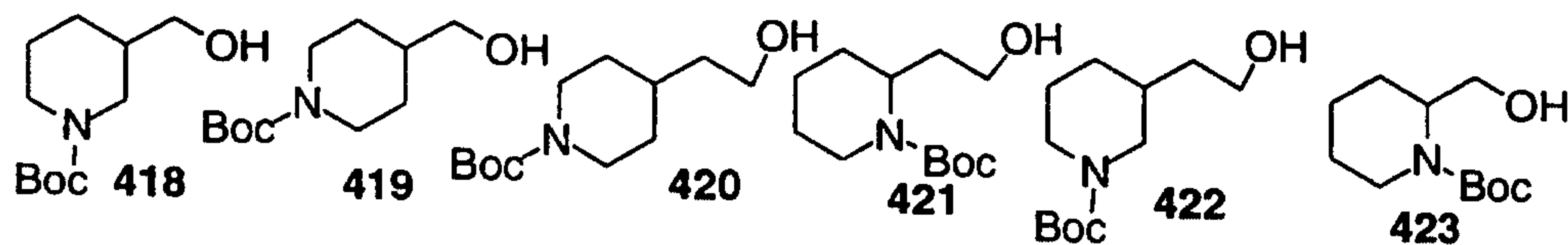
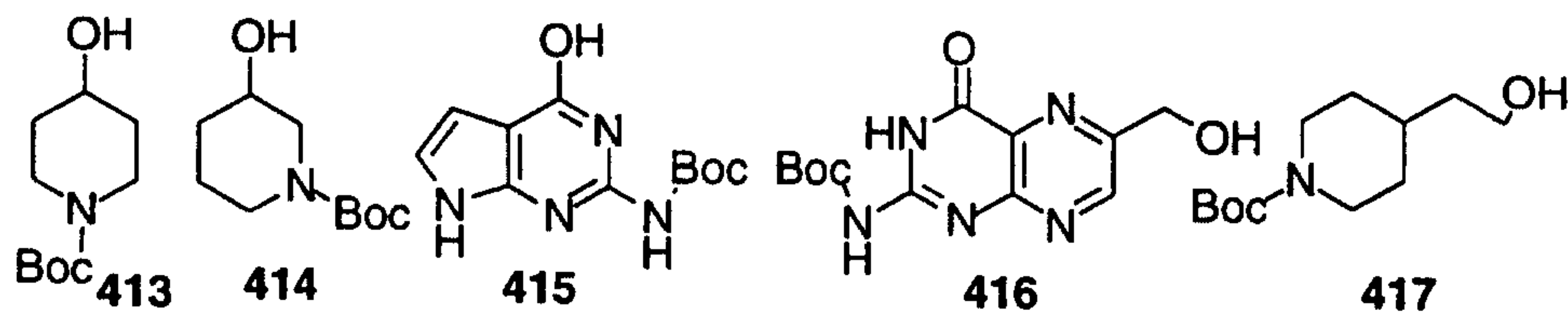




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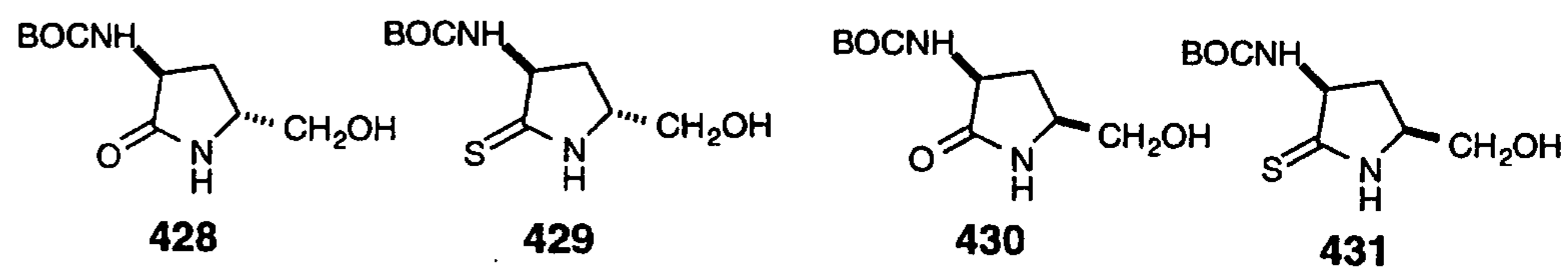
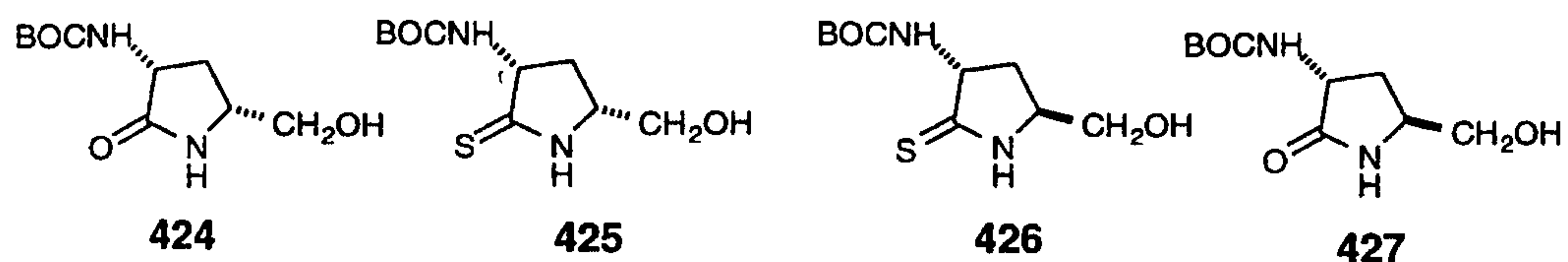
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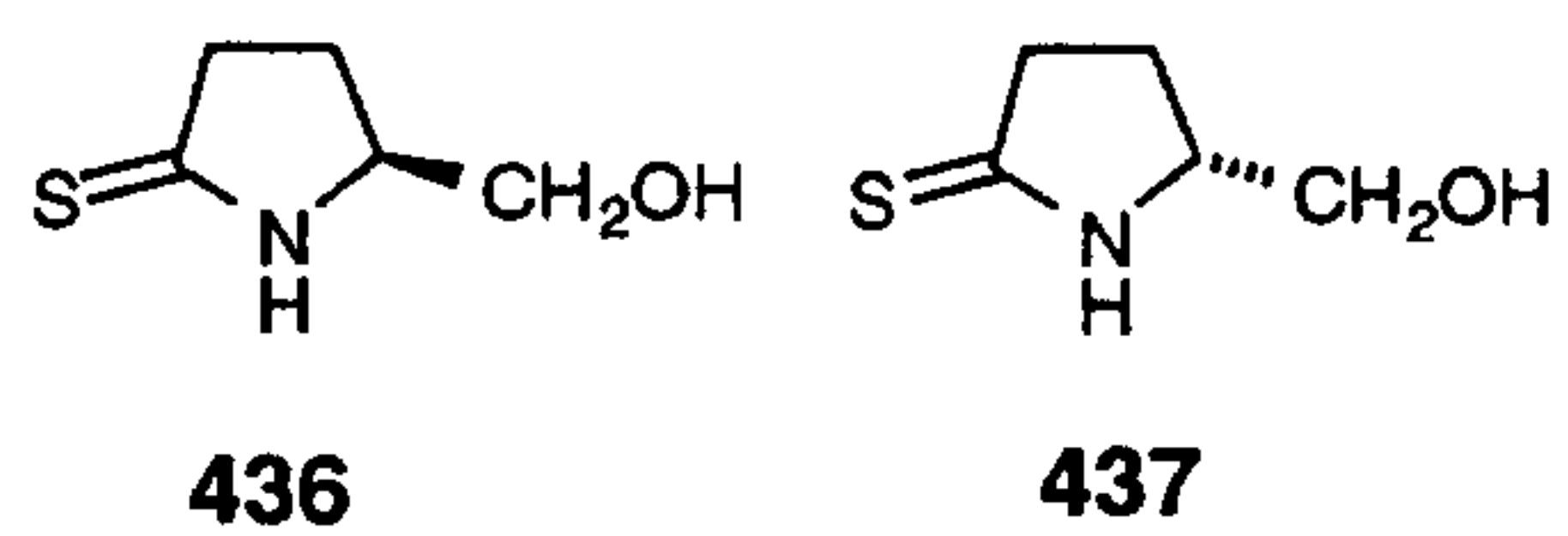
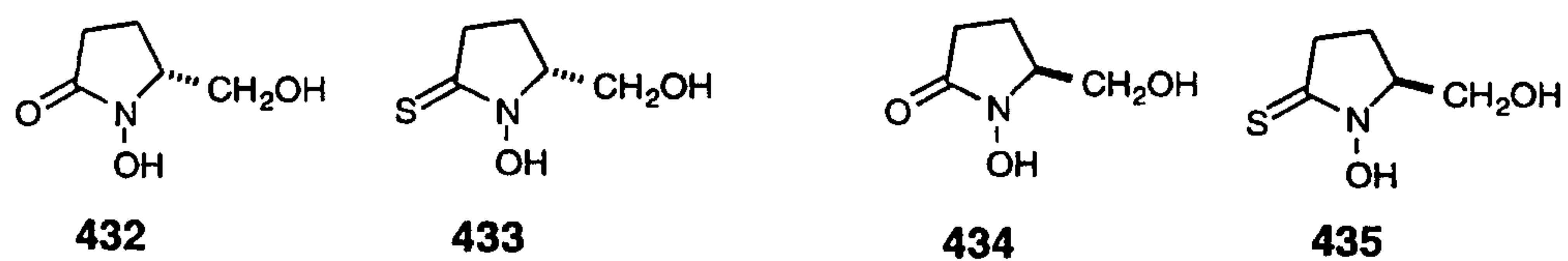
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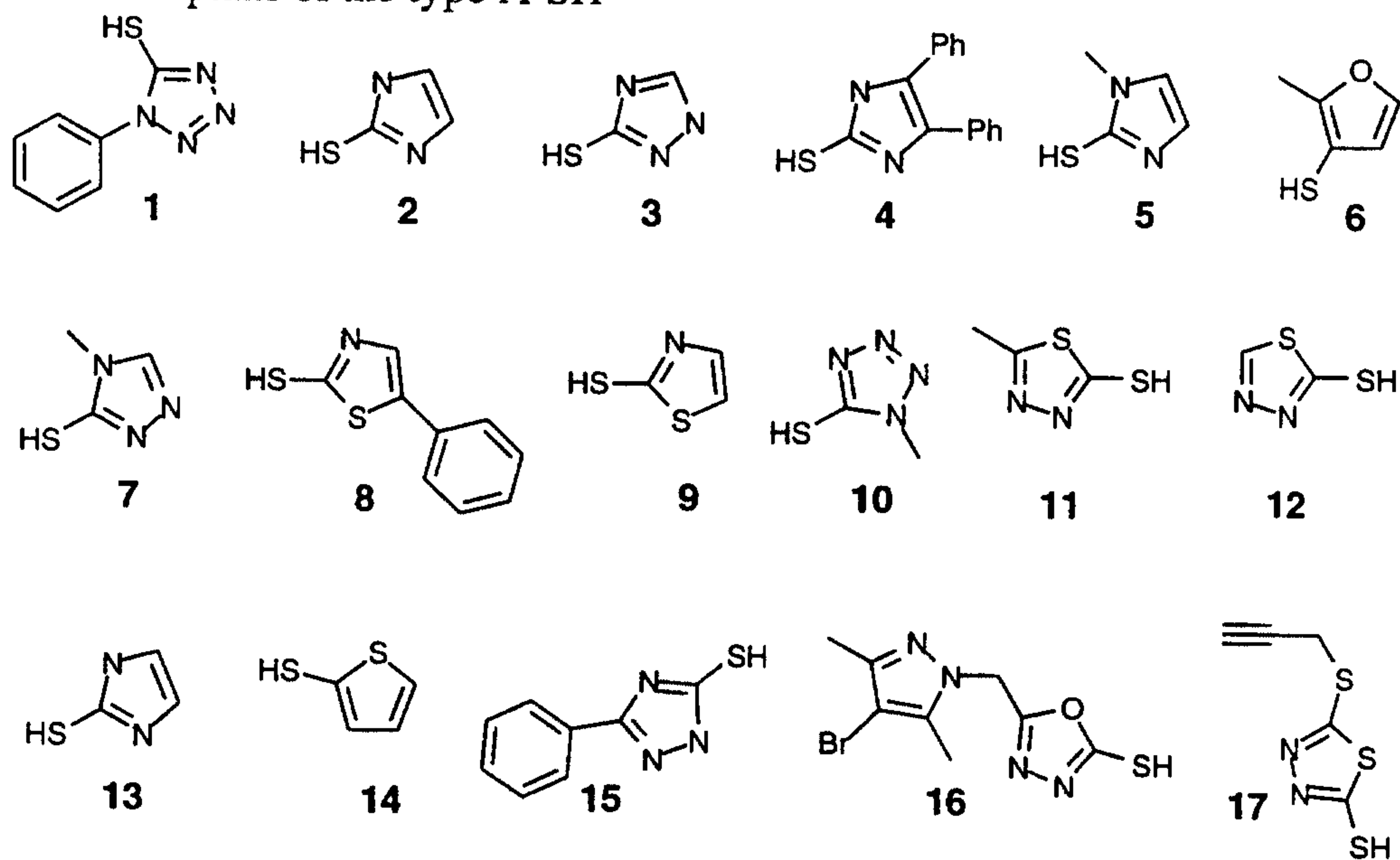
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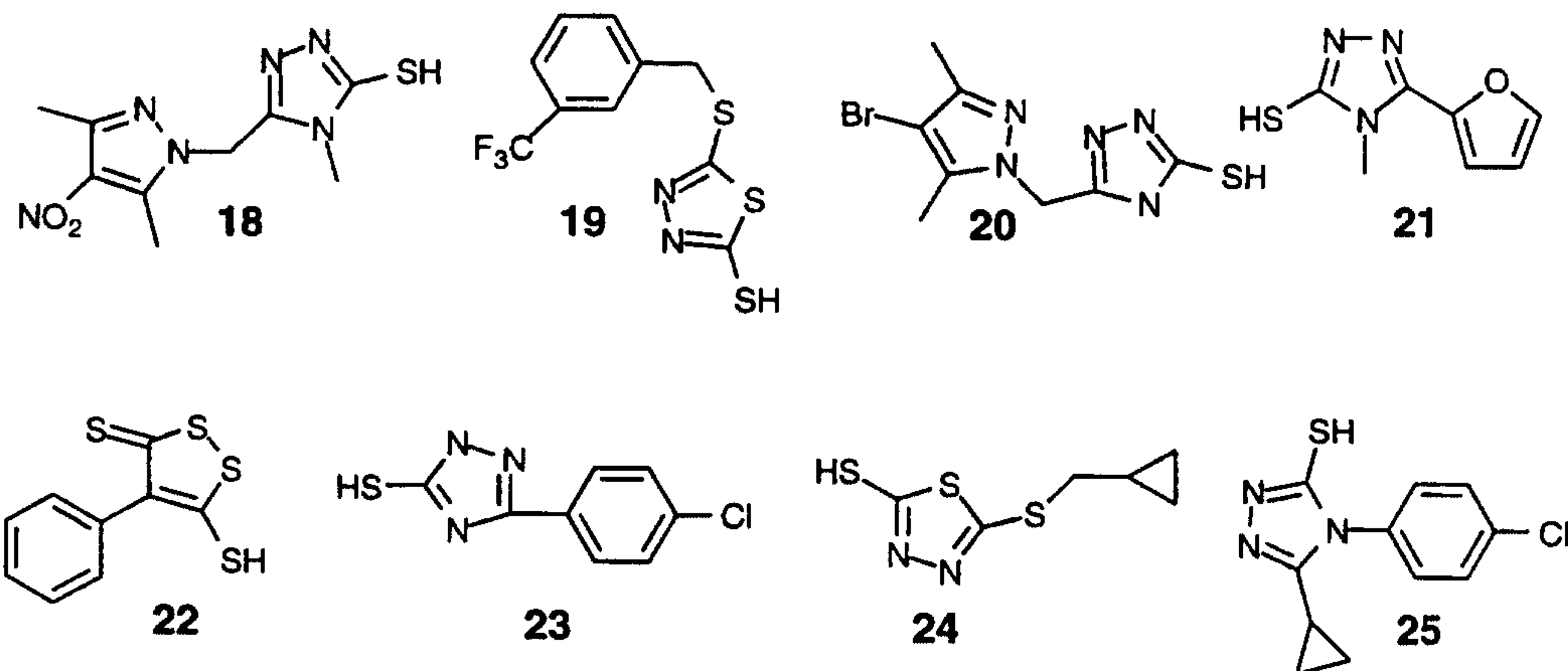
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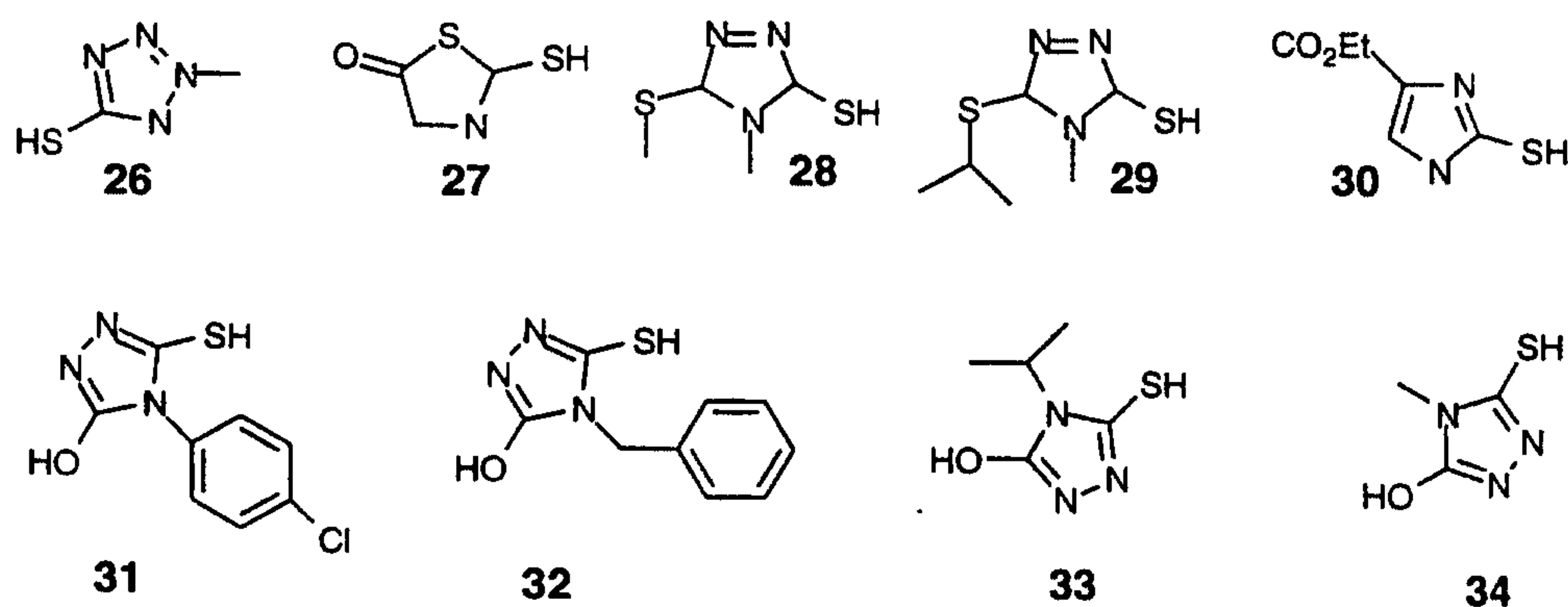
3205 Table 16. Mercaptans of the type A-SH



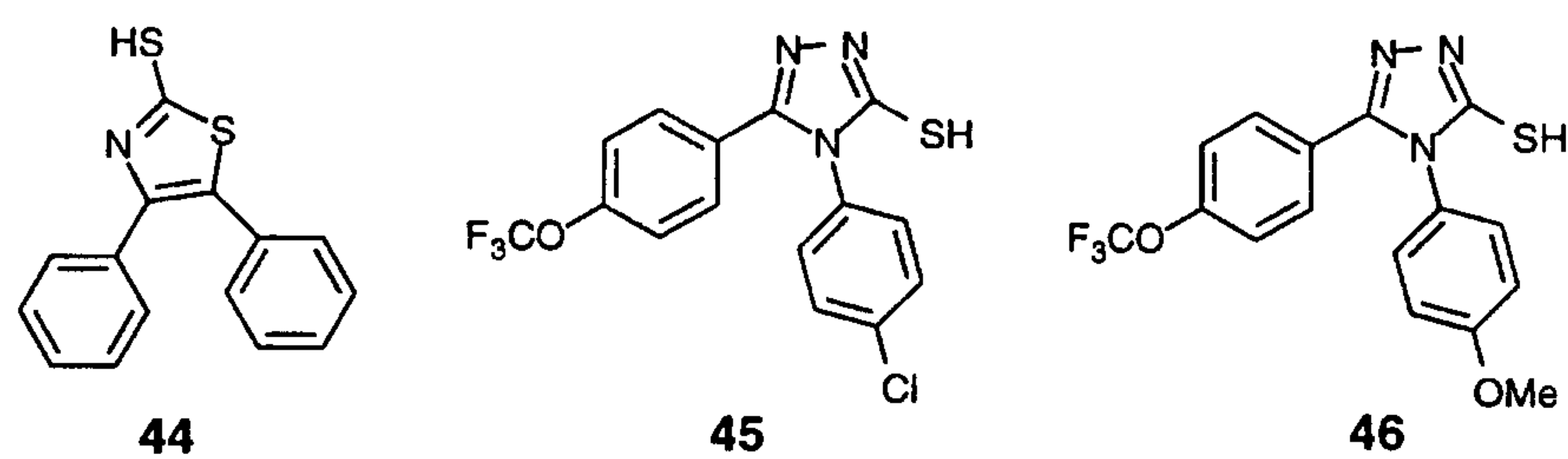
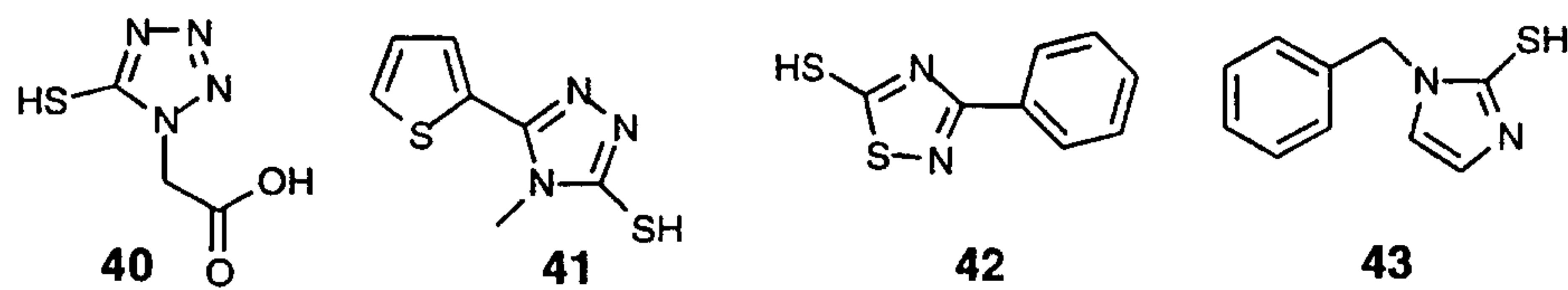
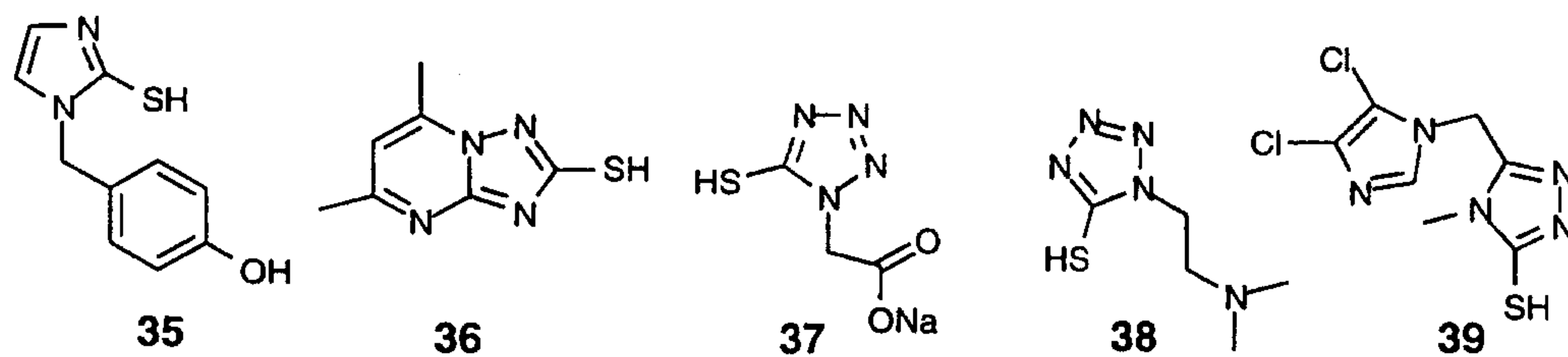
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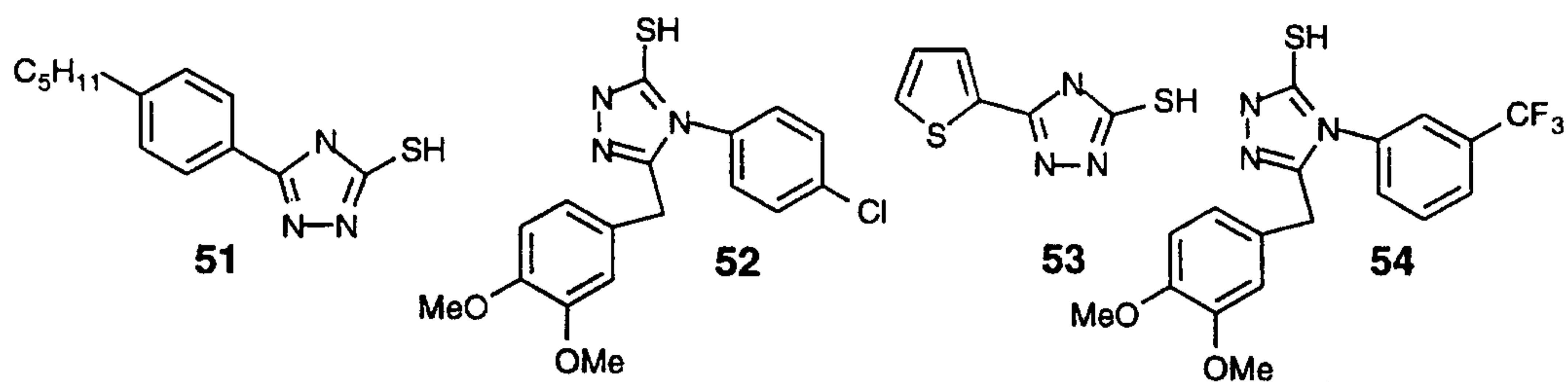
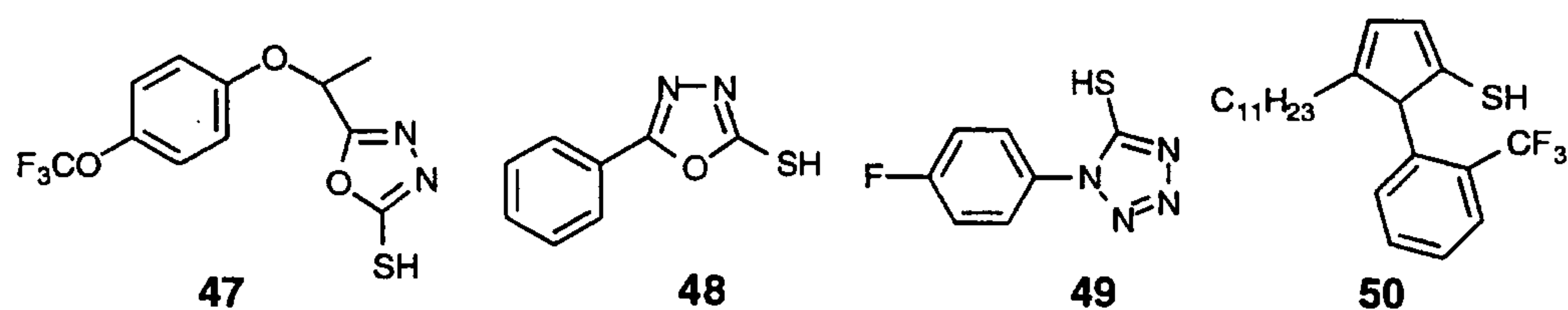
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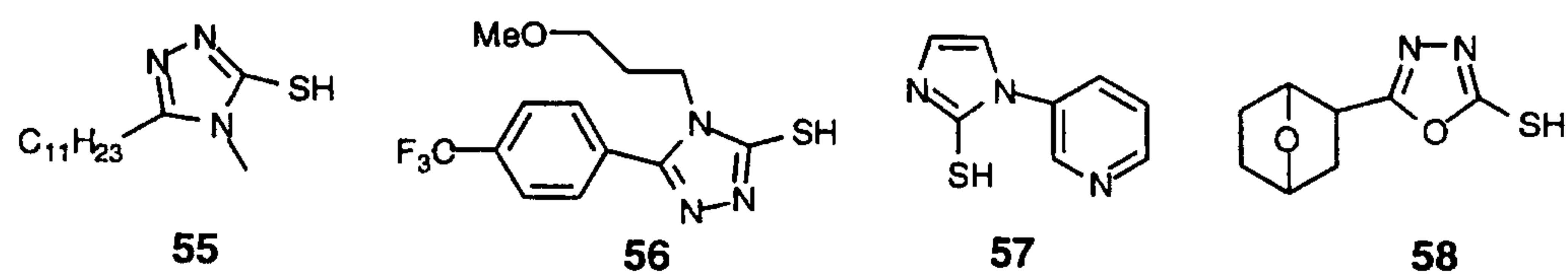
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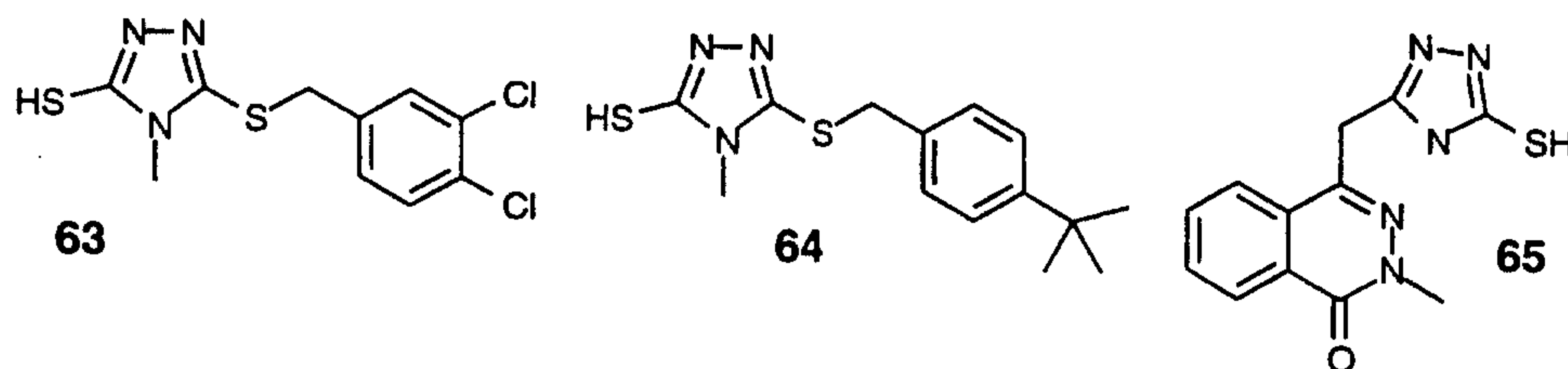
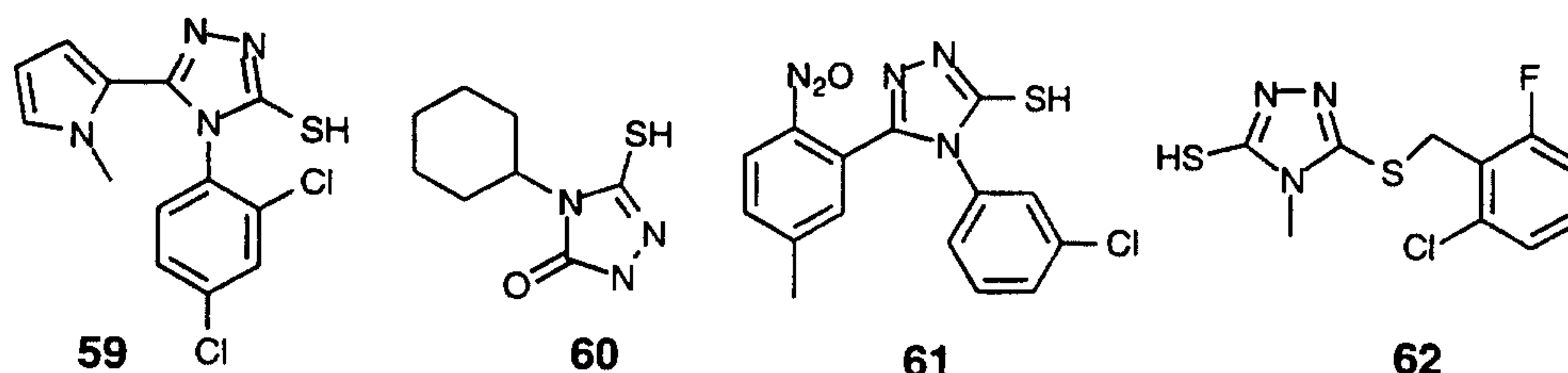


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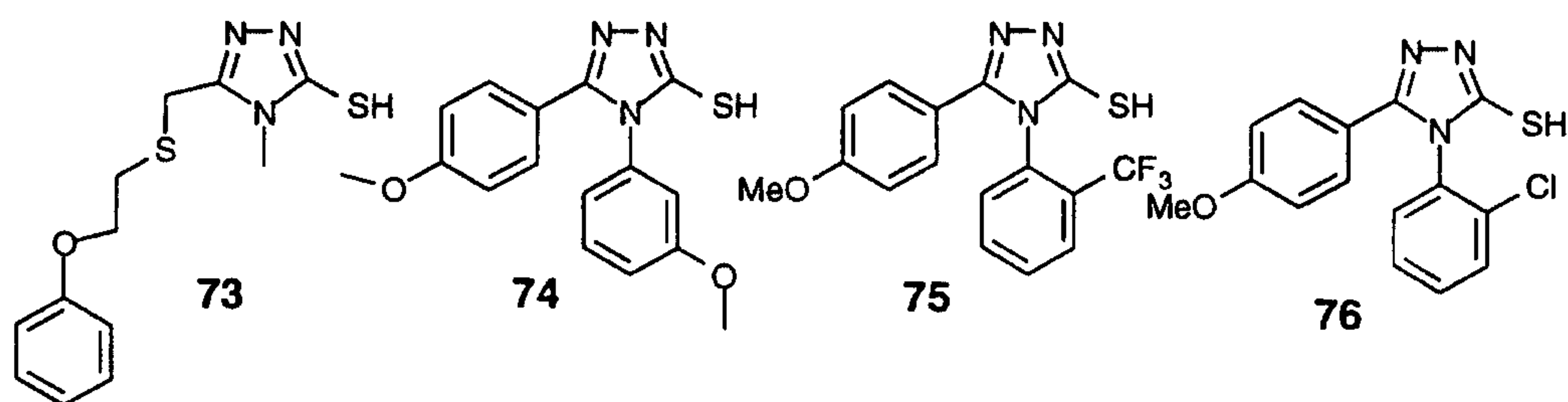
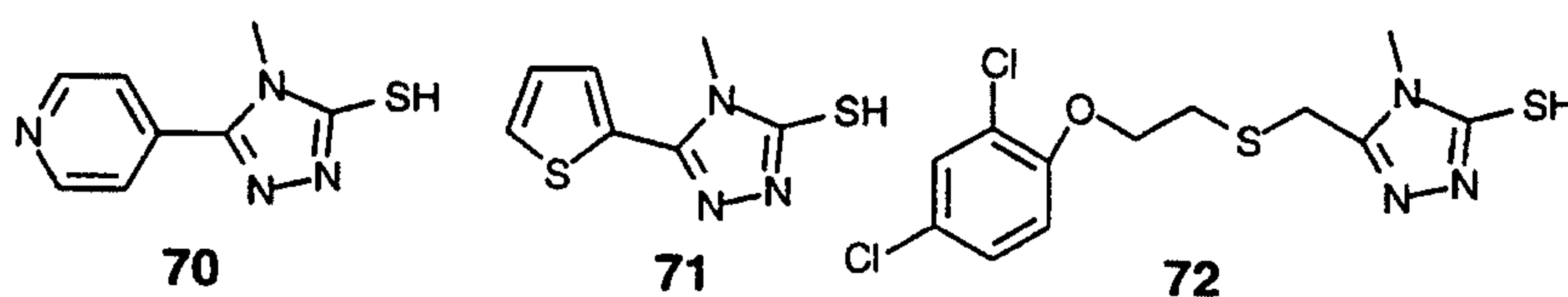
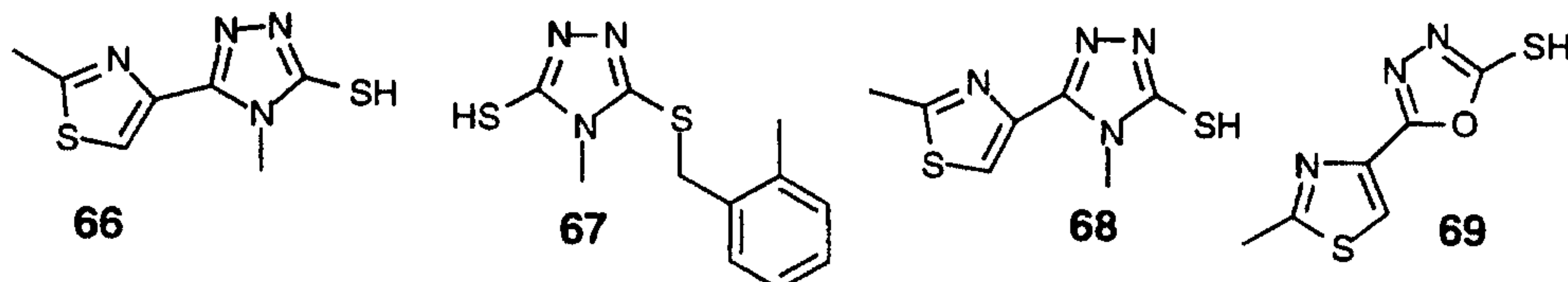


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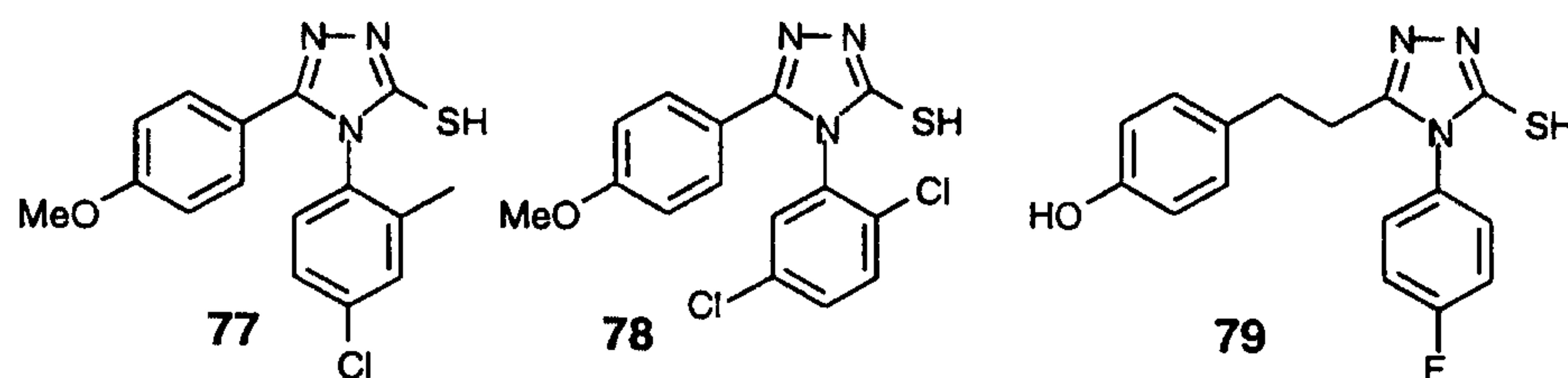
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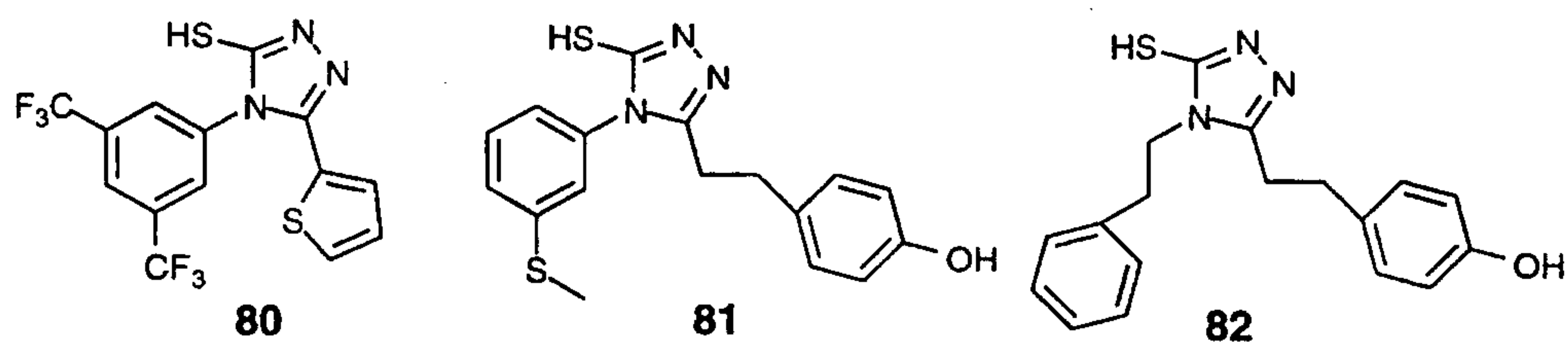


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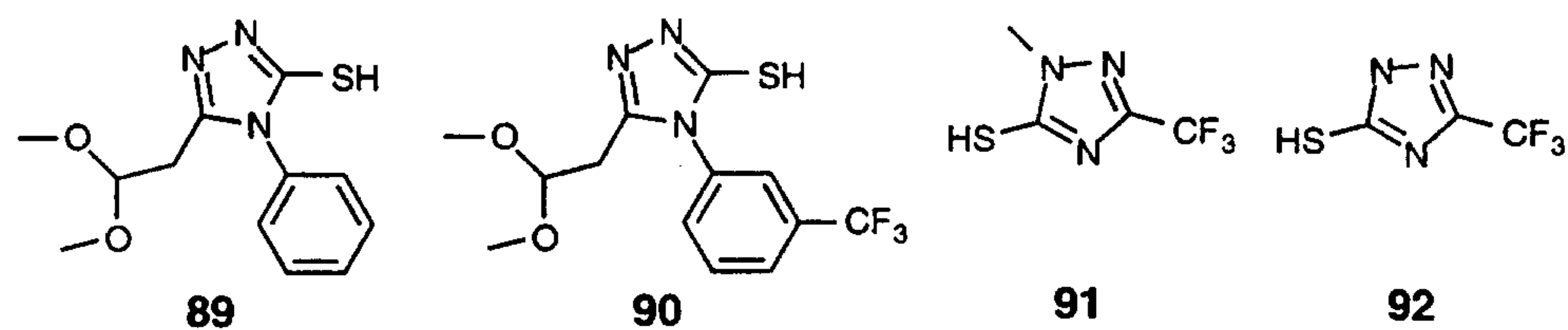
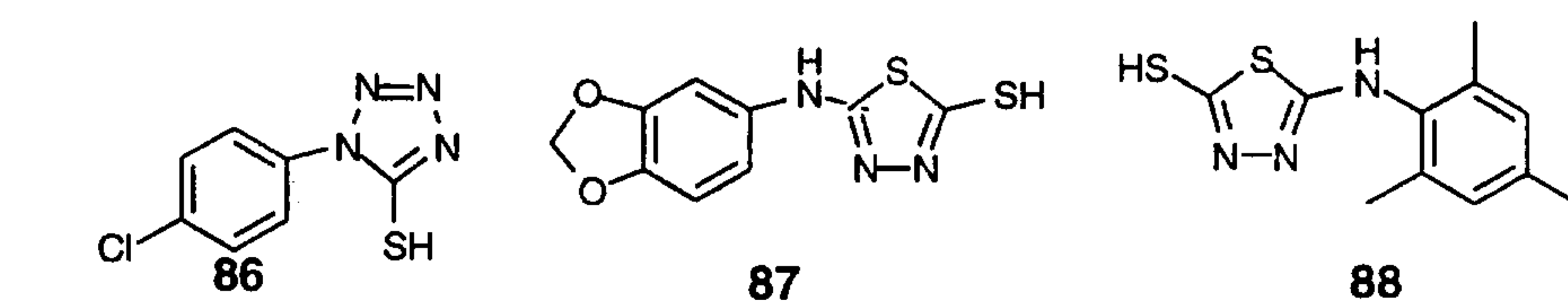
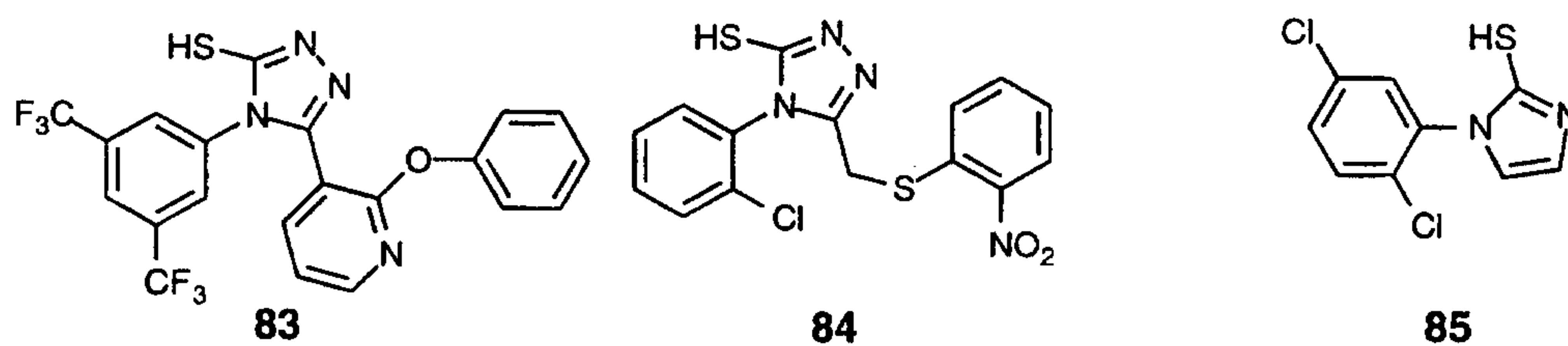


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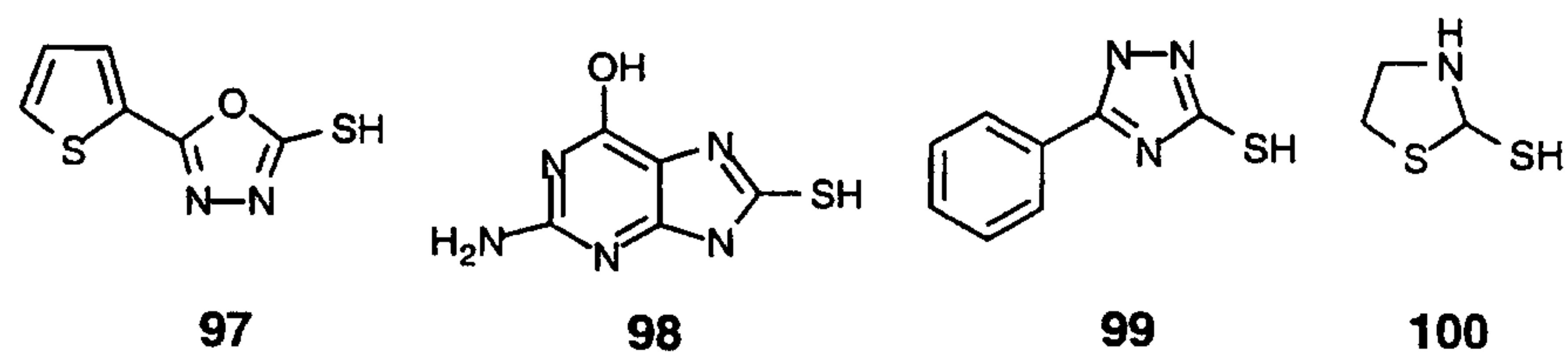
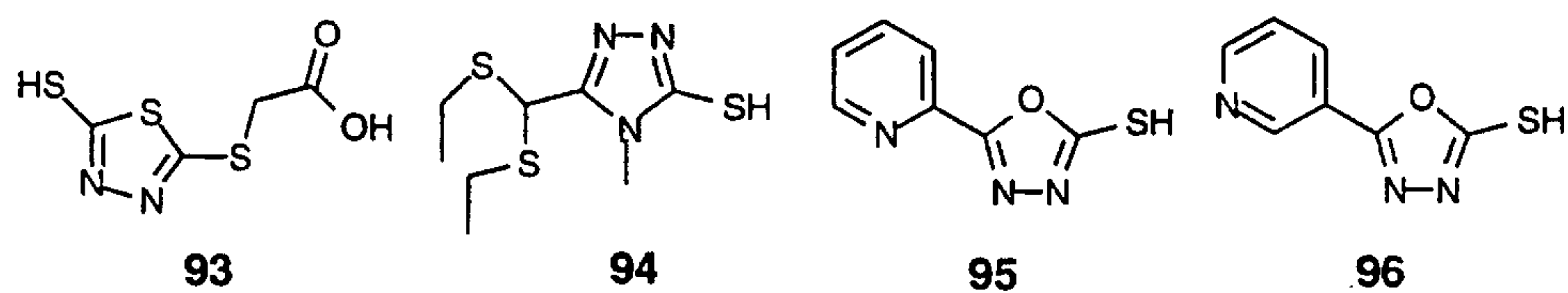
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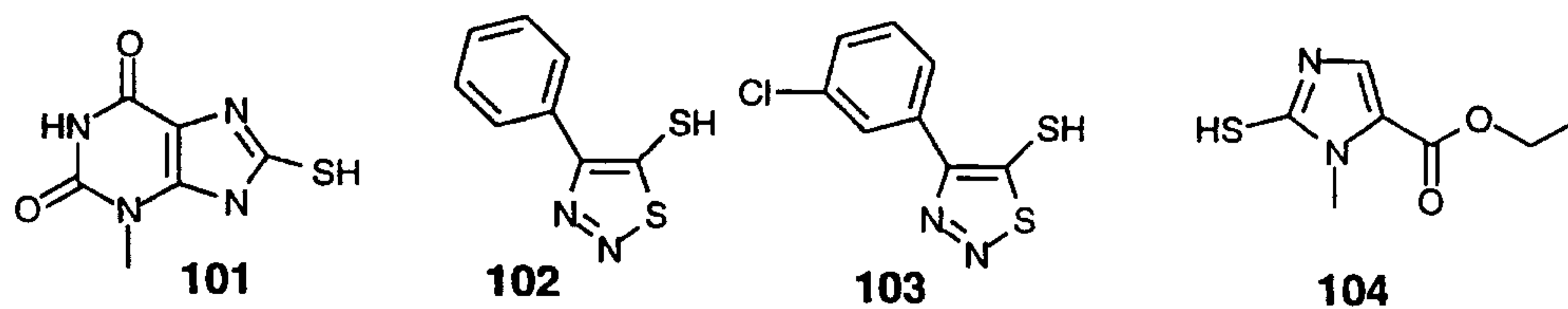
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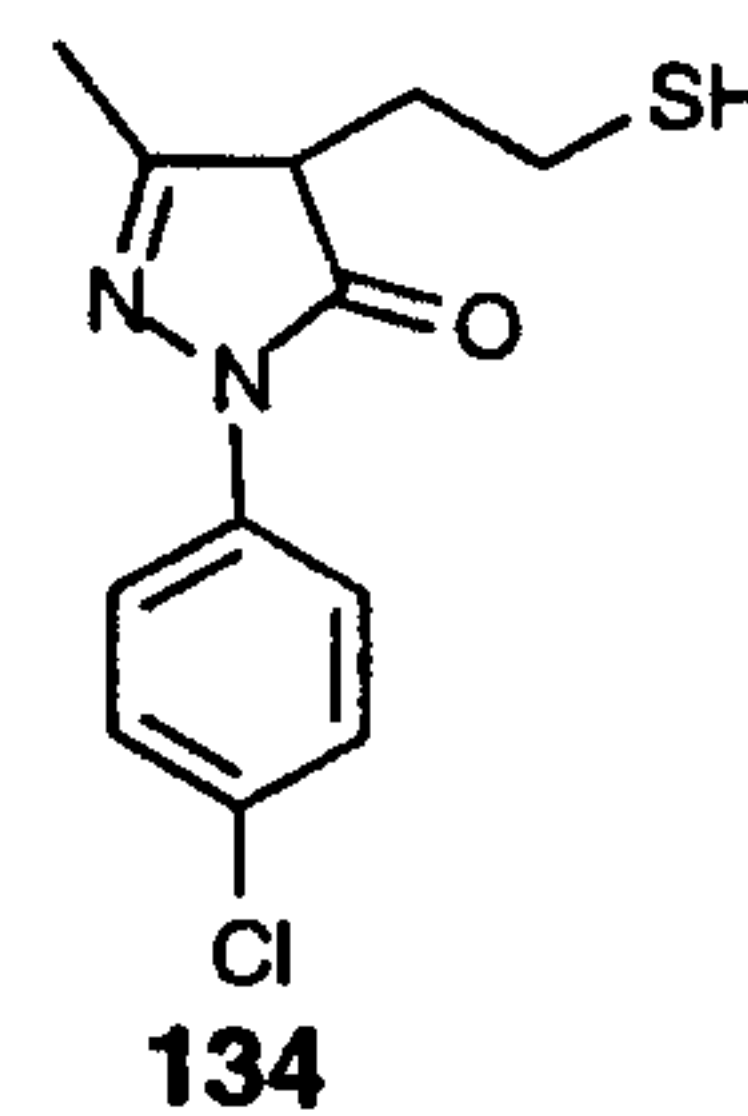
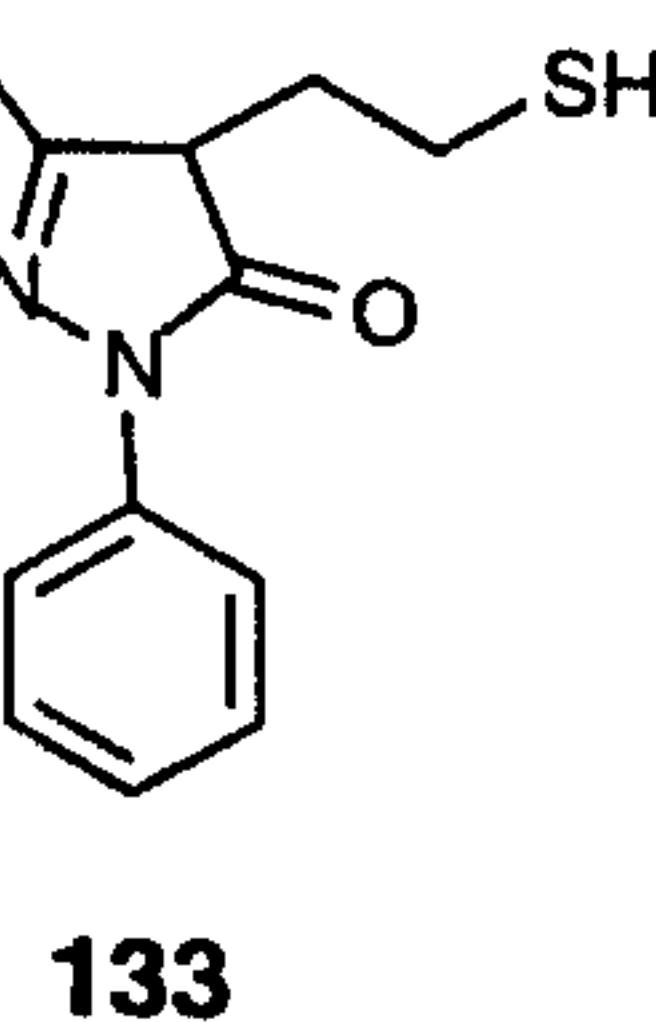
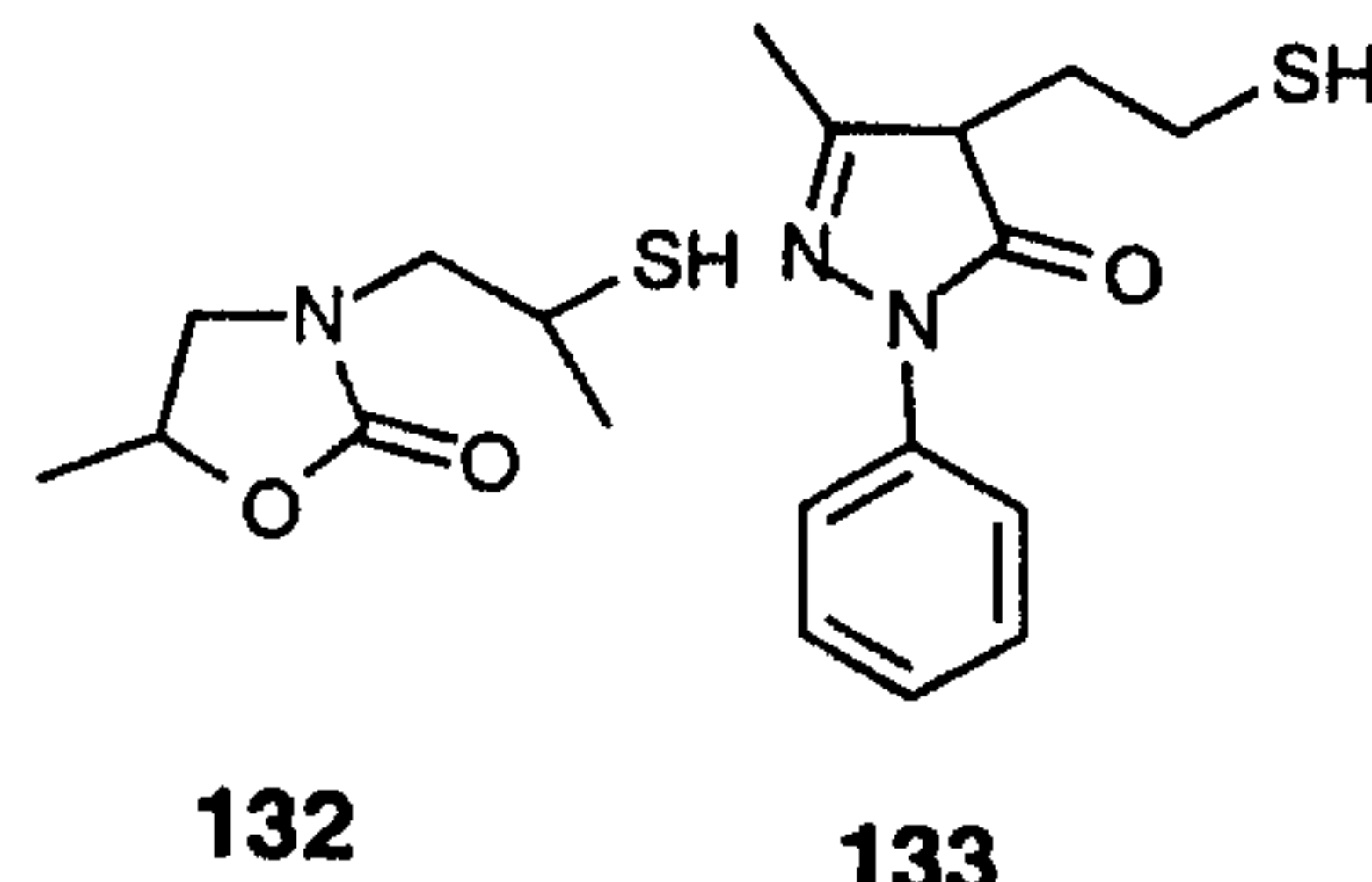
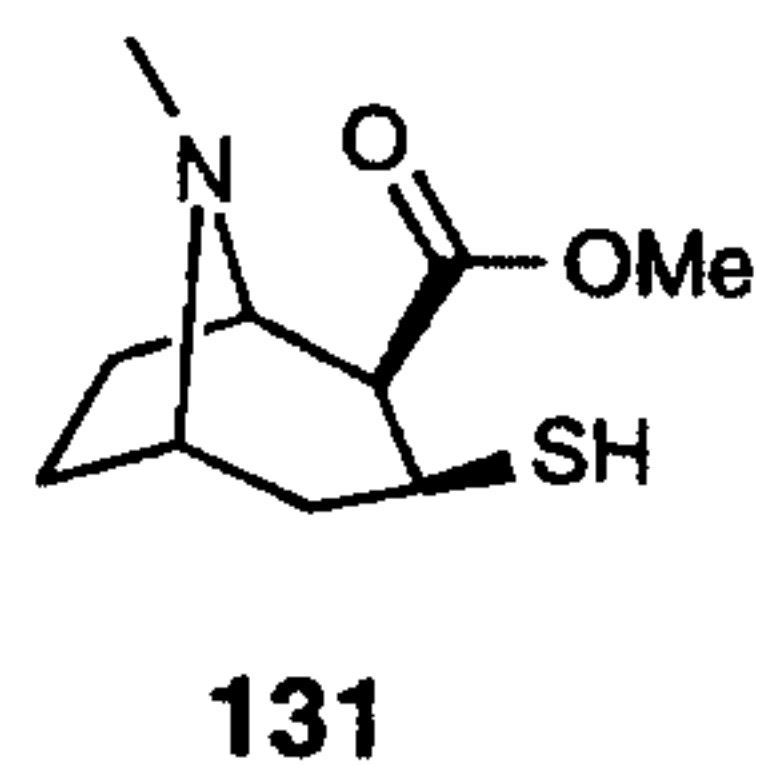
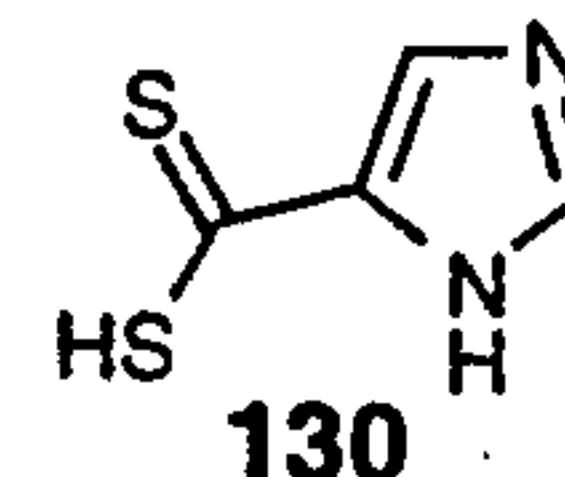
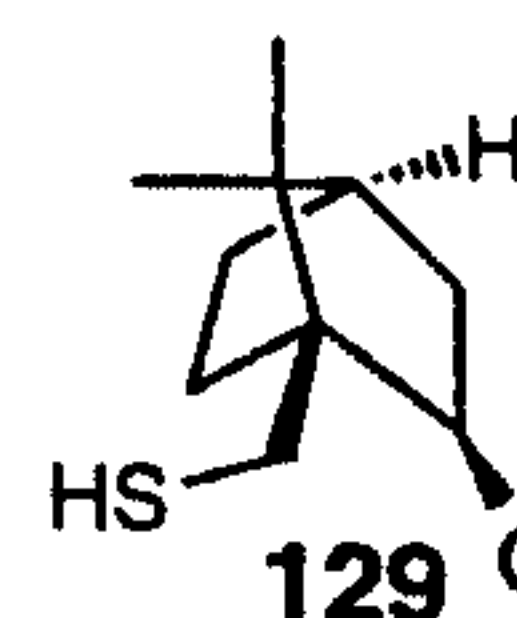
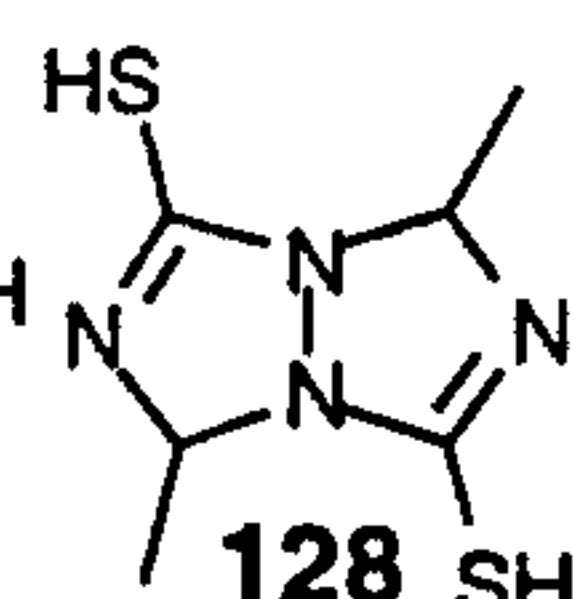
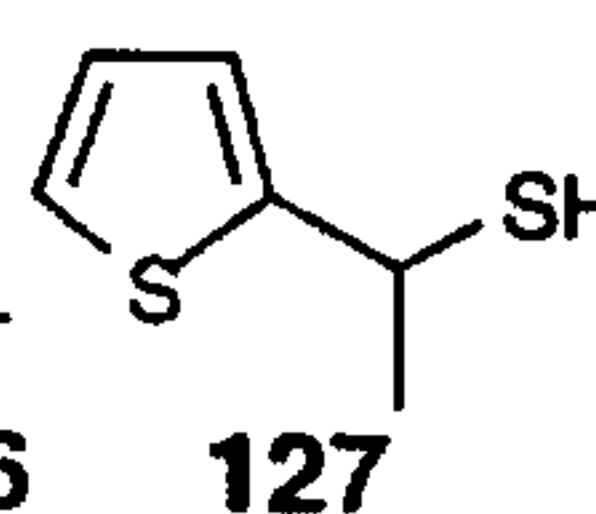
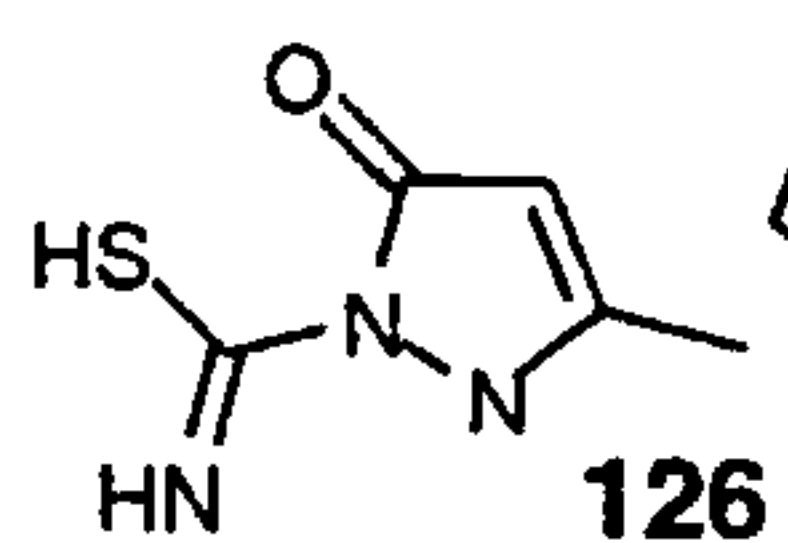
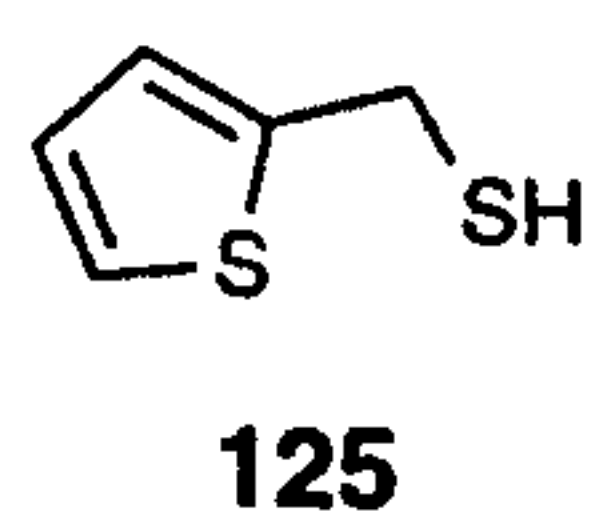
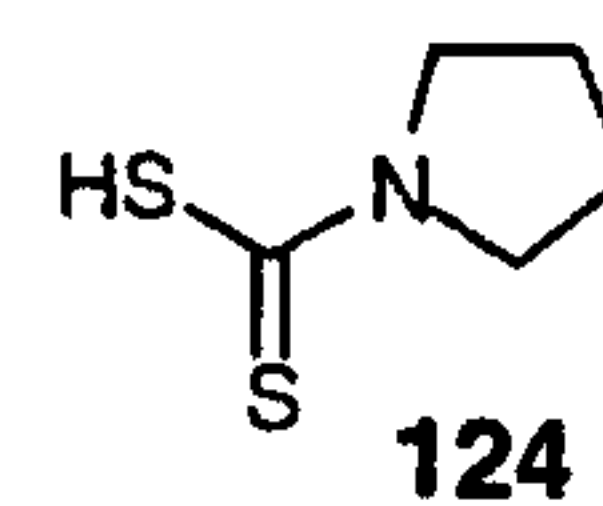
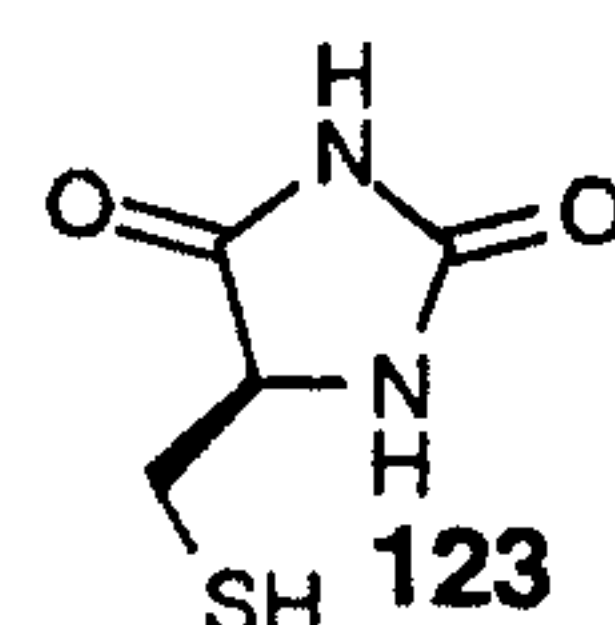
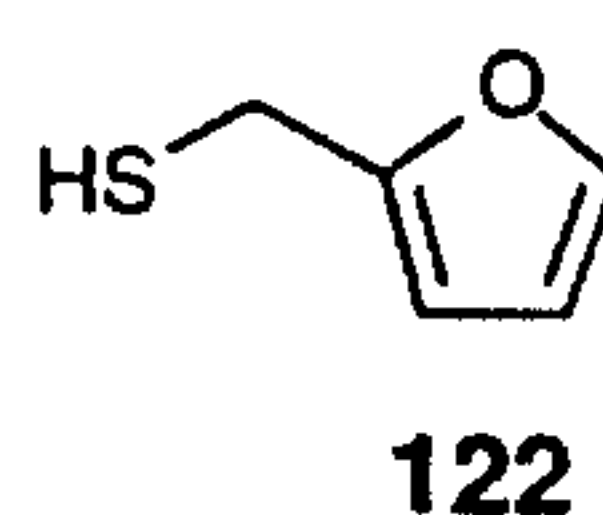
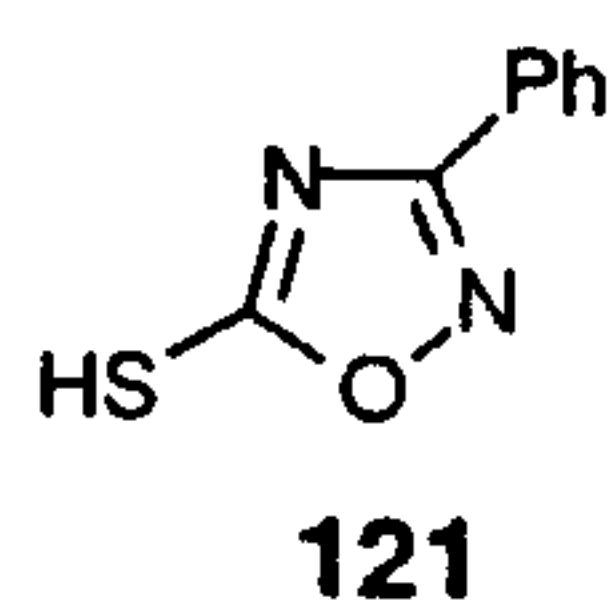
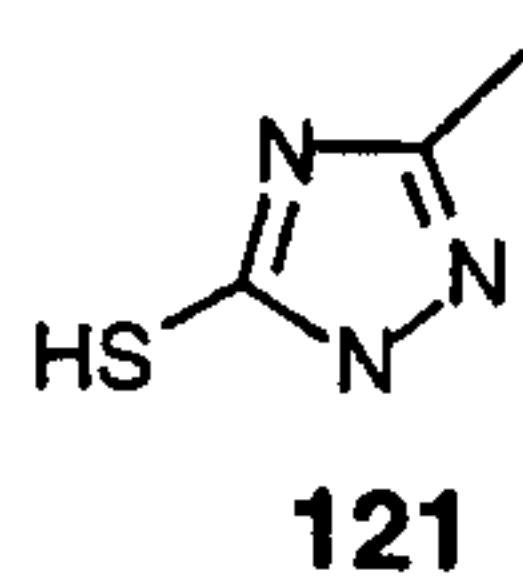
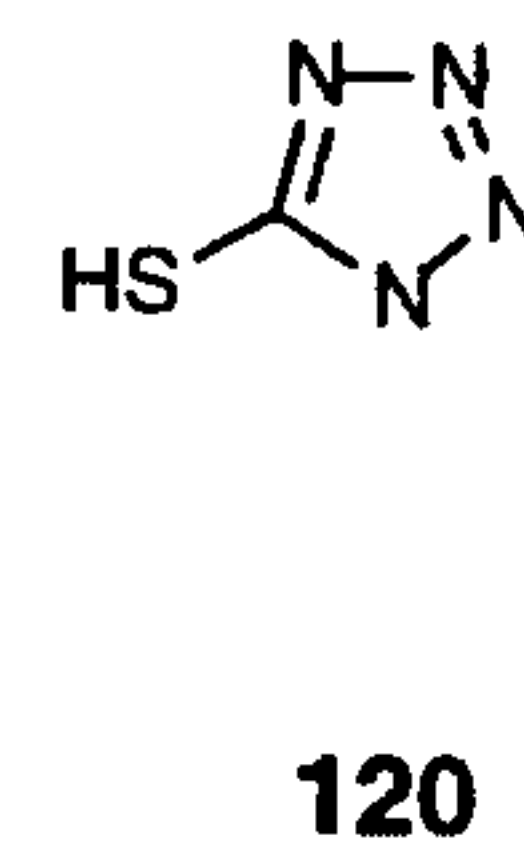
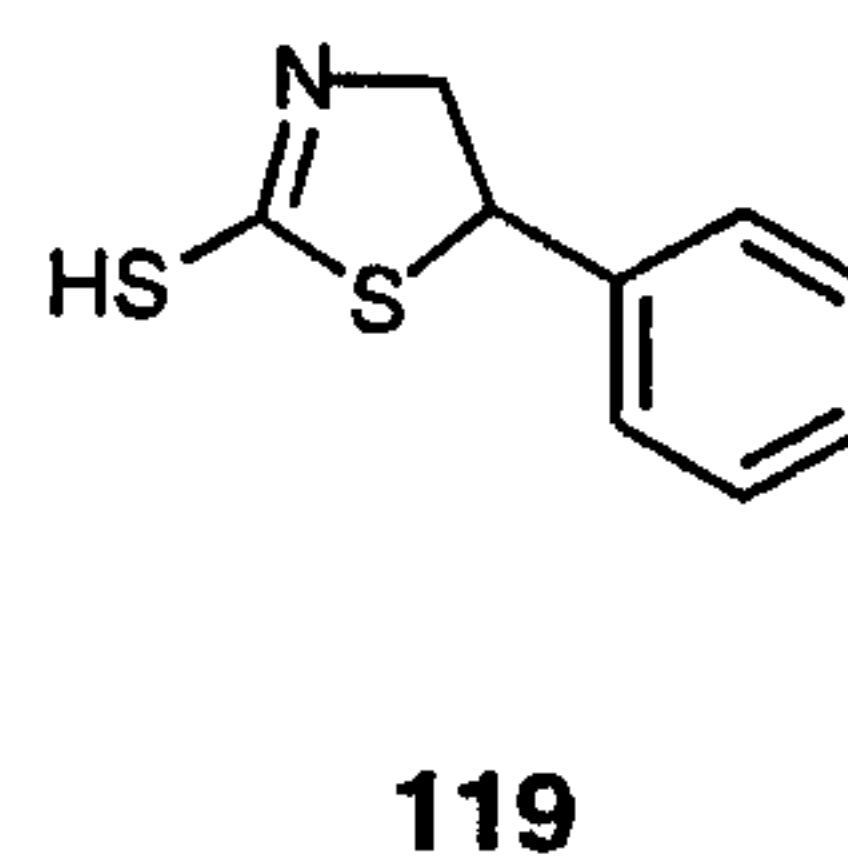
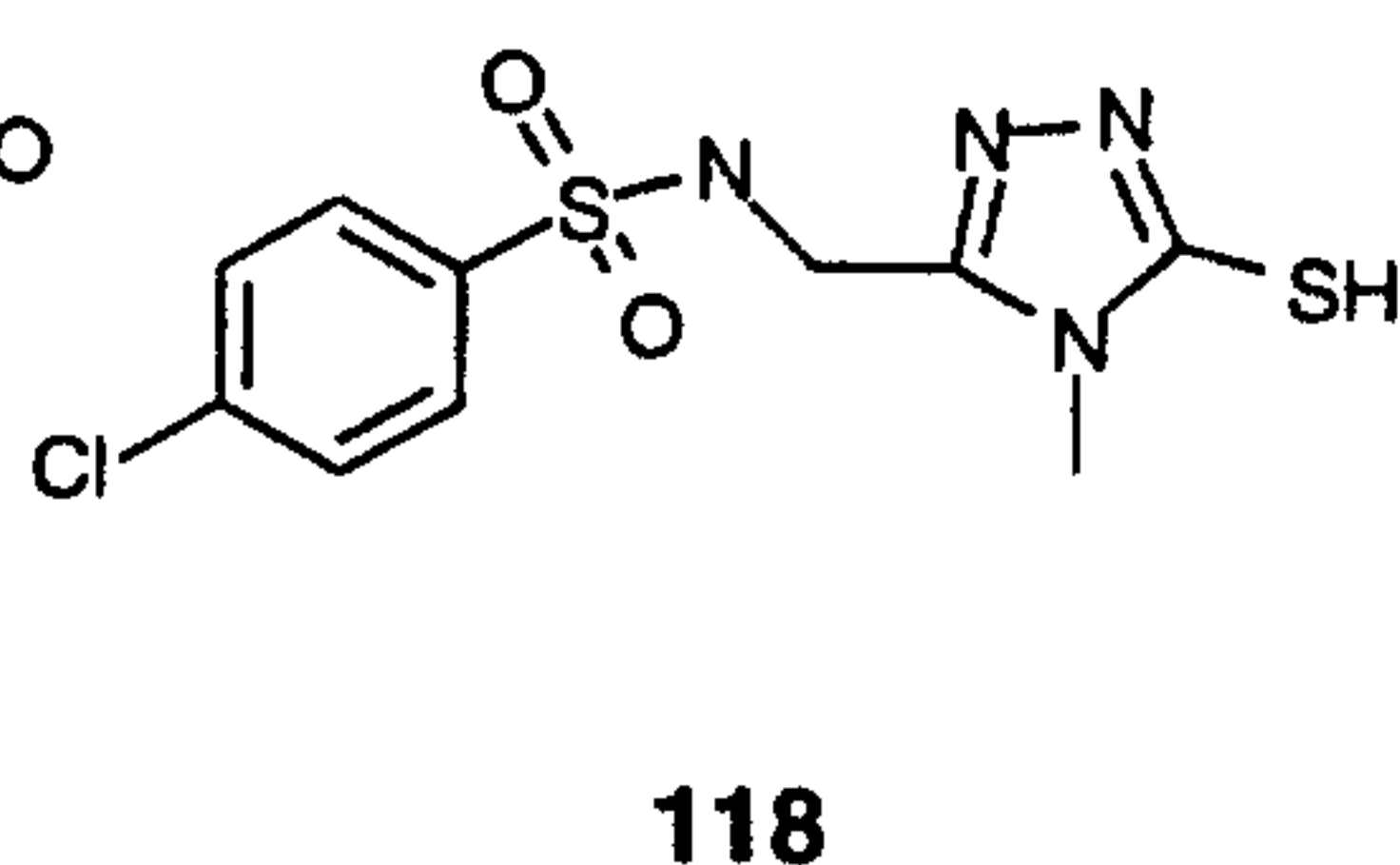
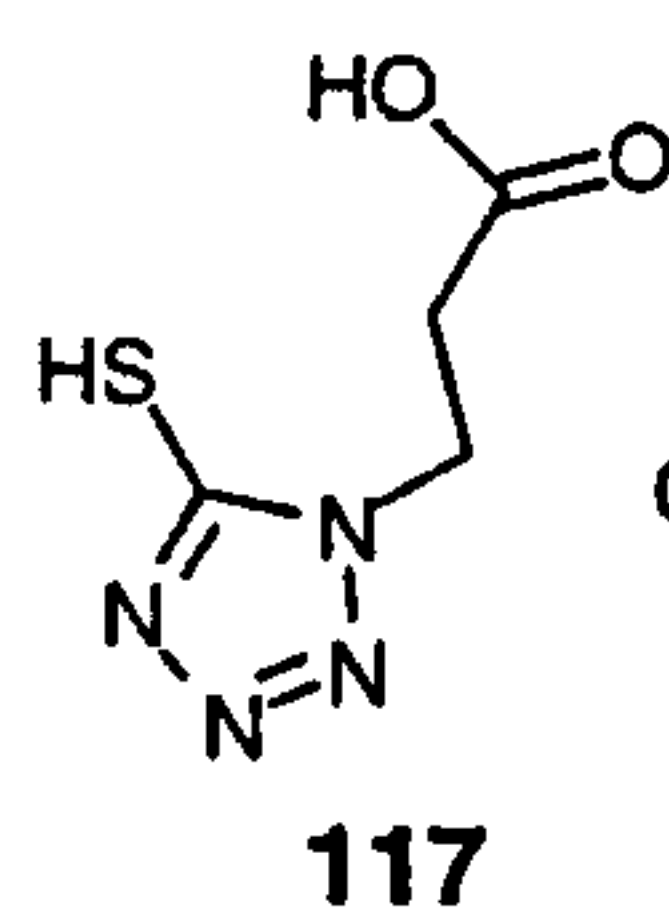
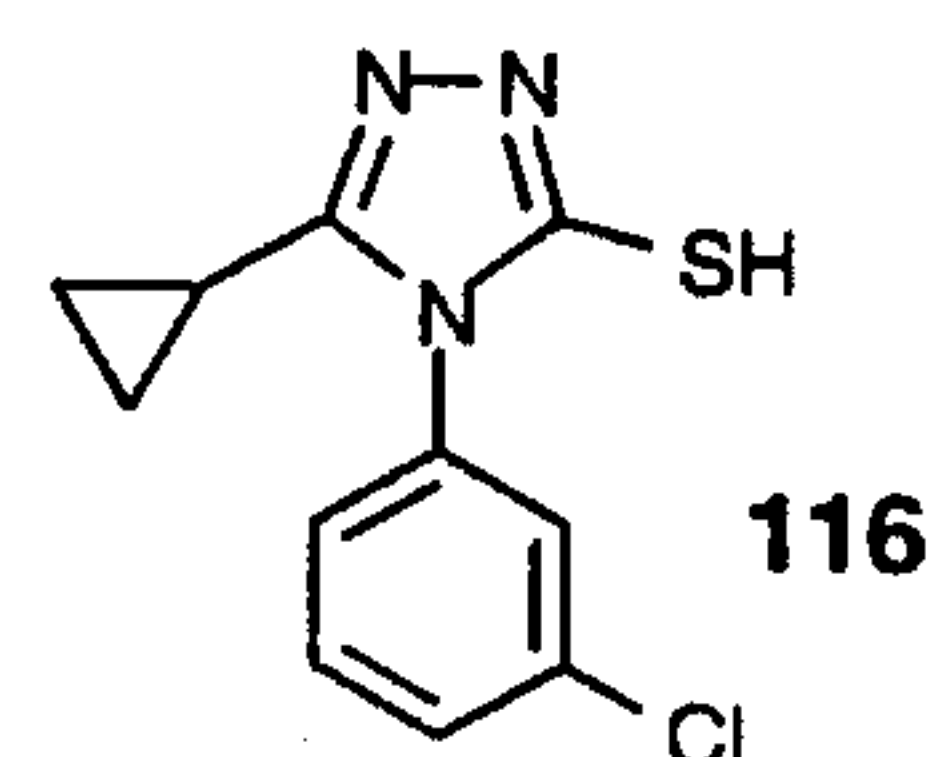
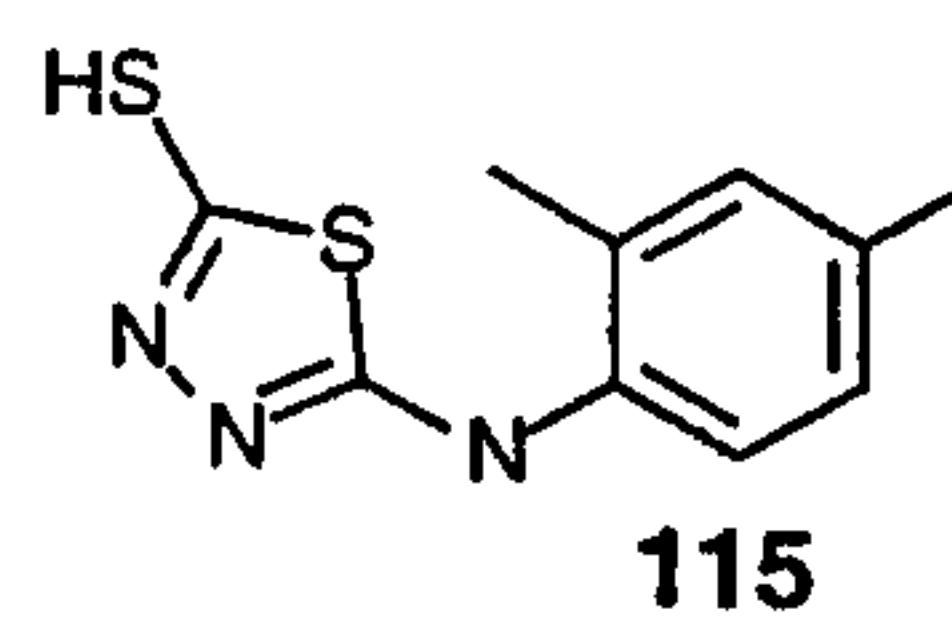
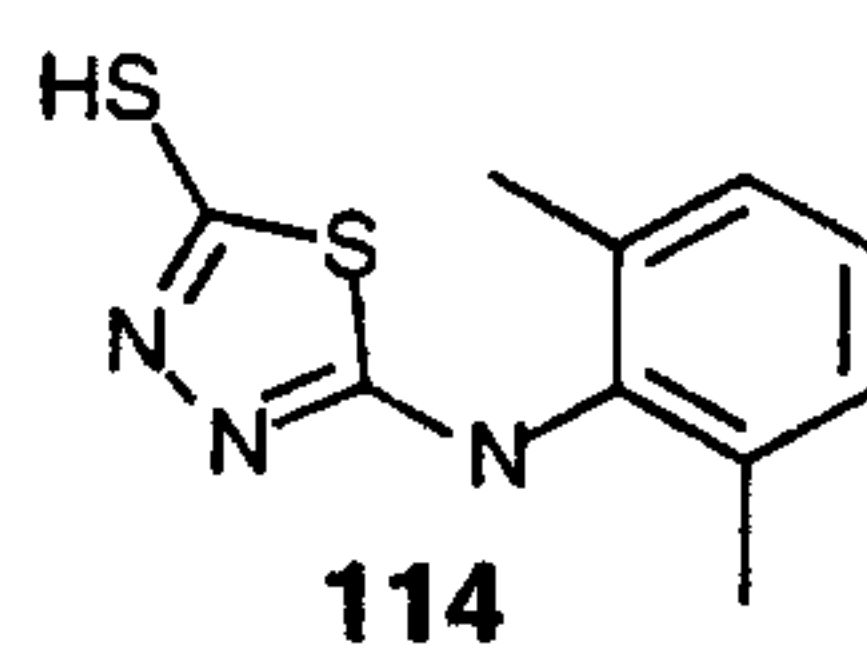
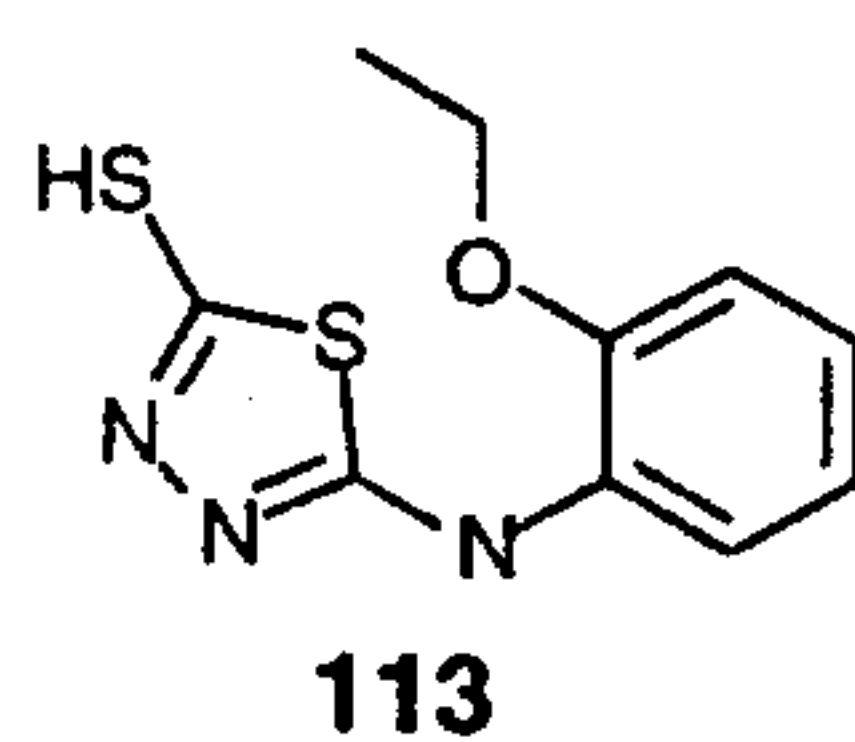
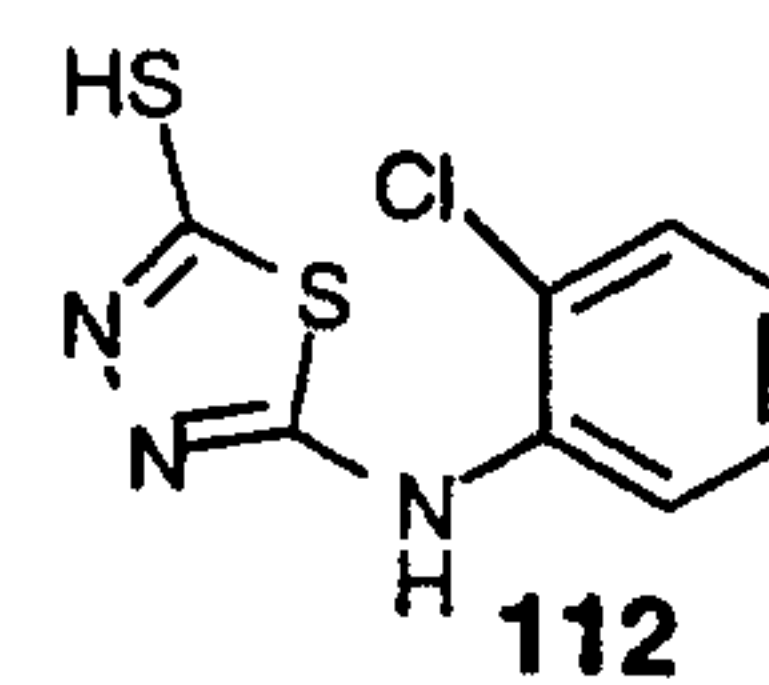
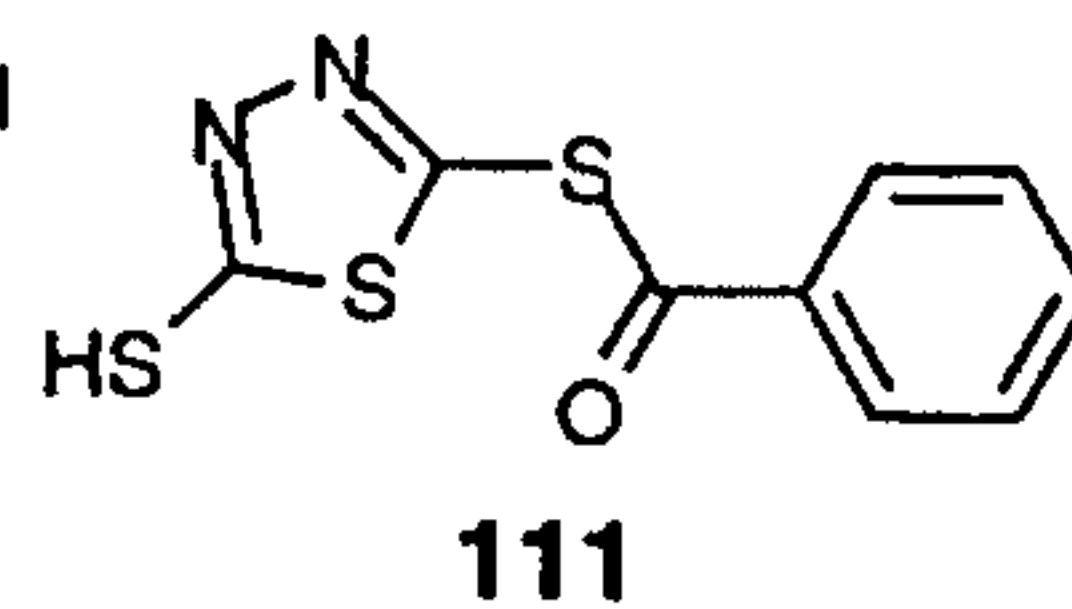
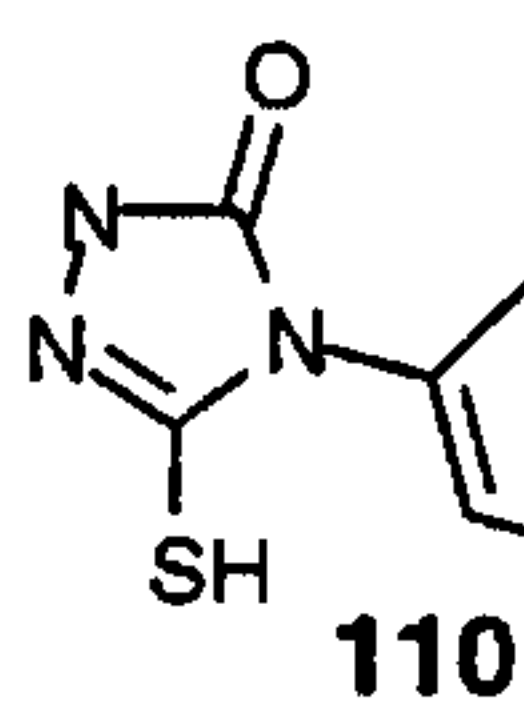
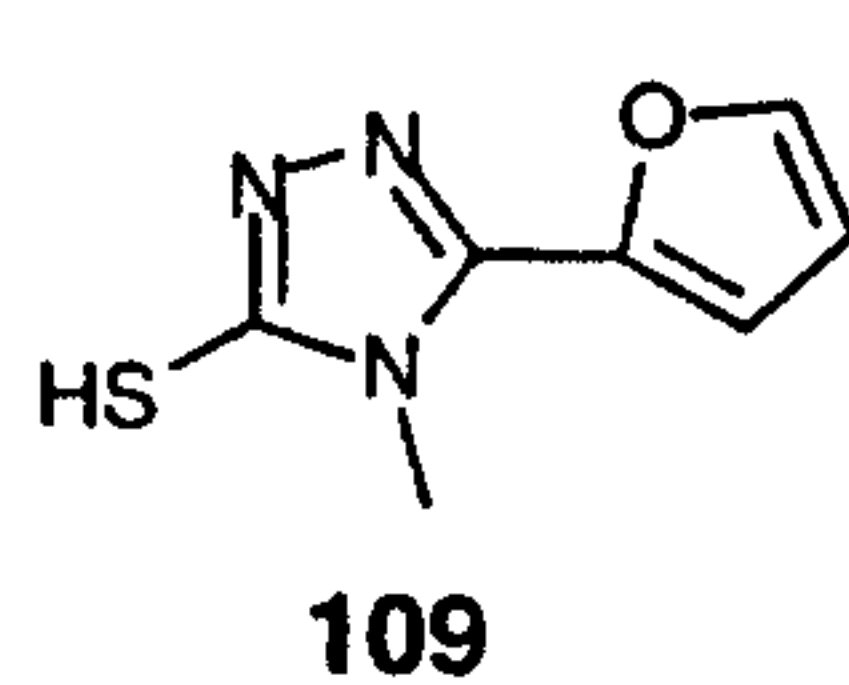
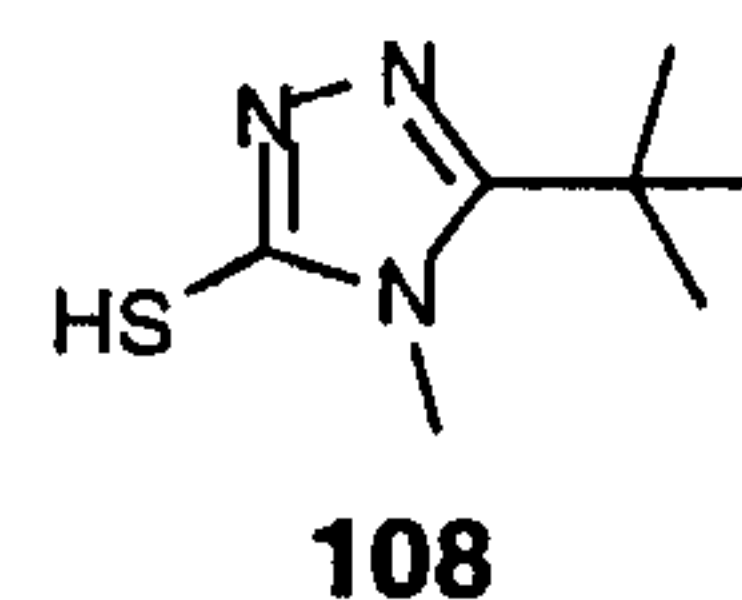
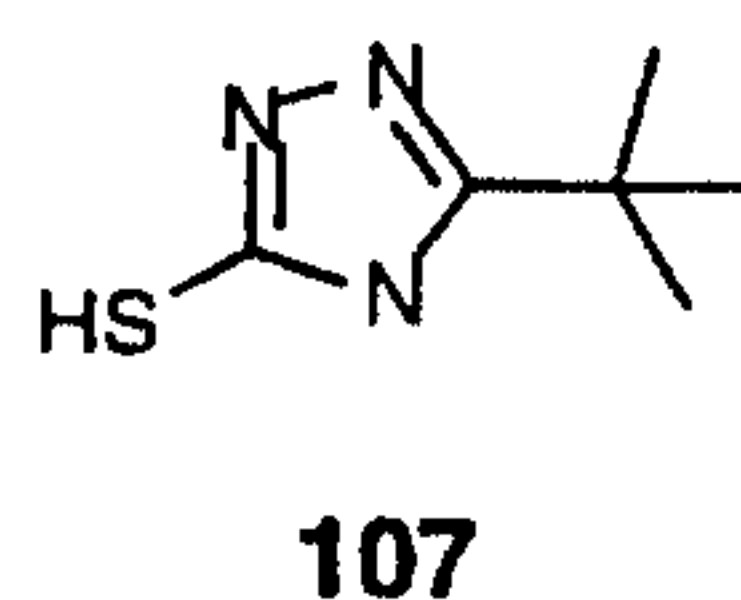
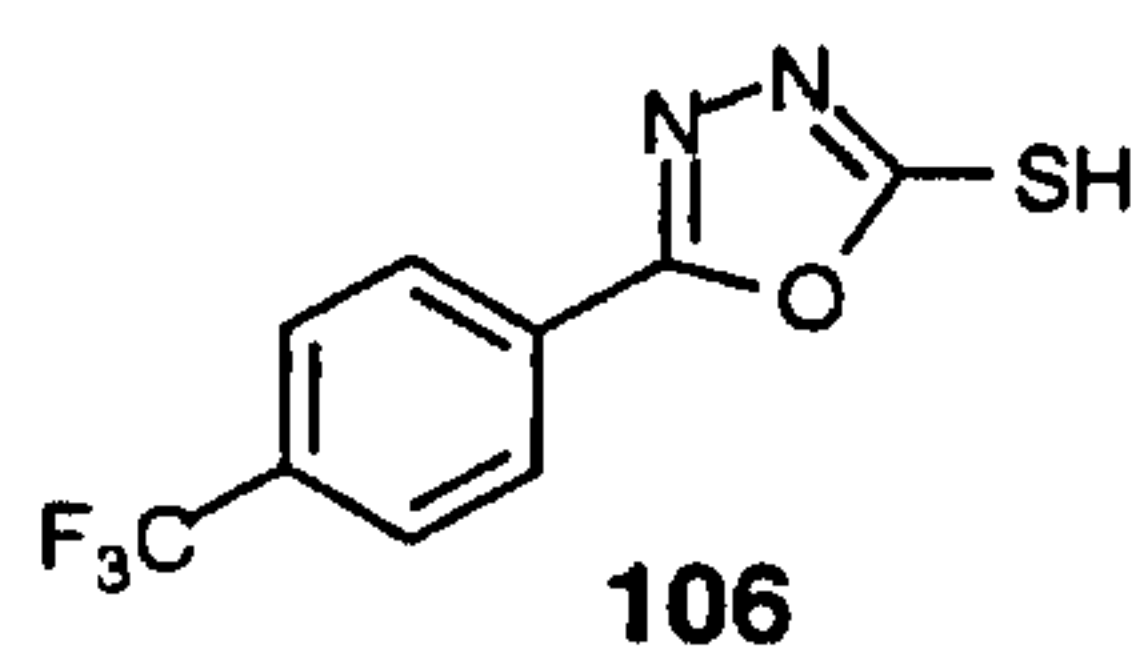
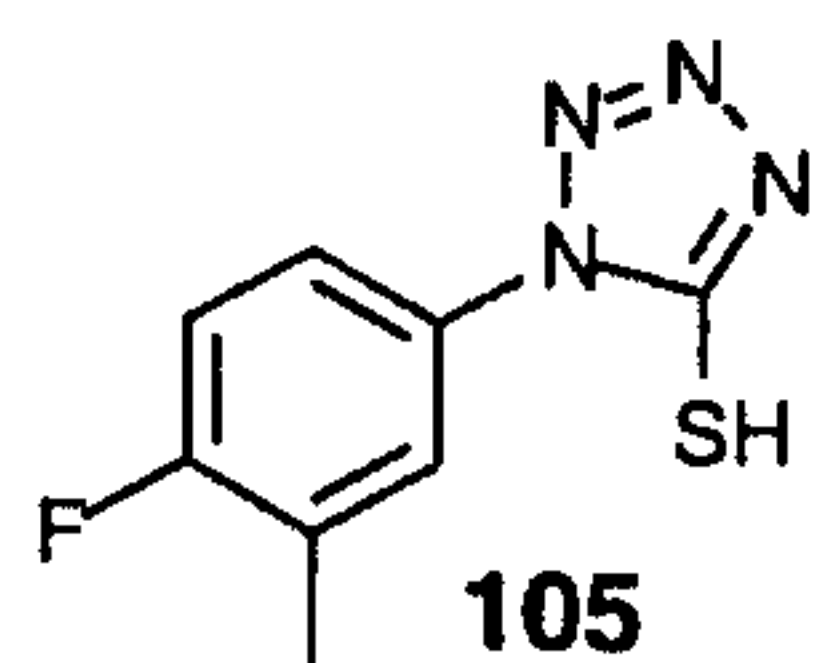


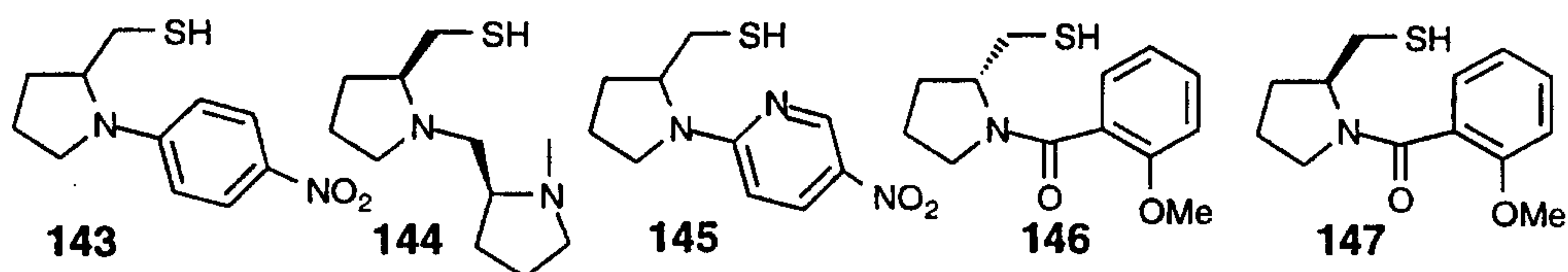
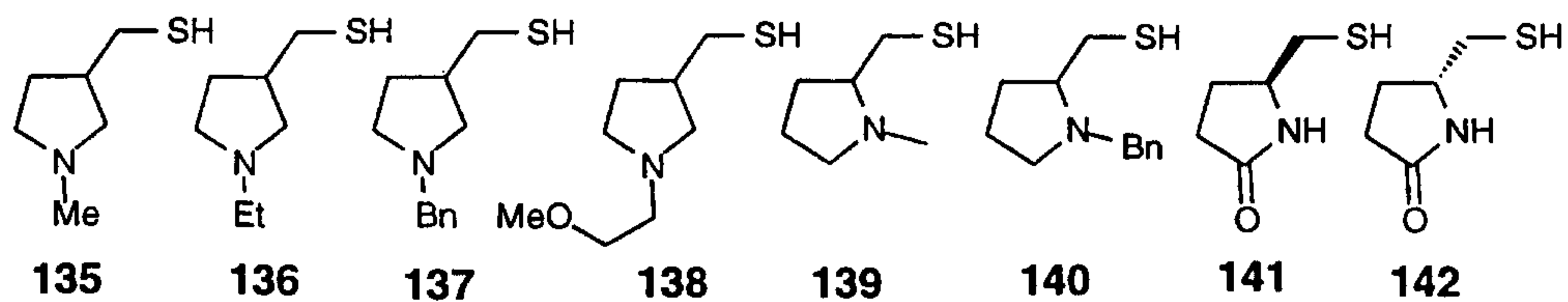
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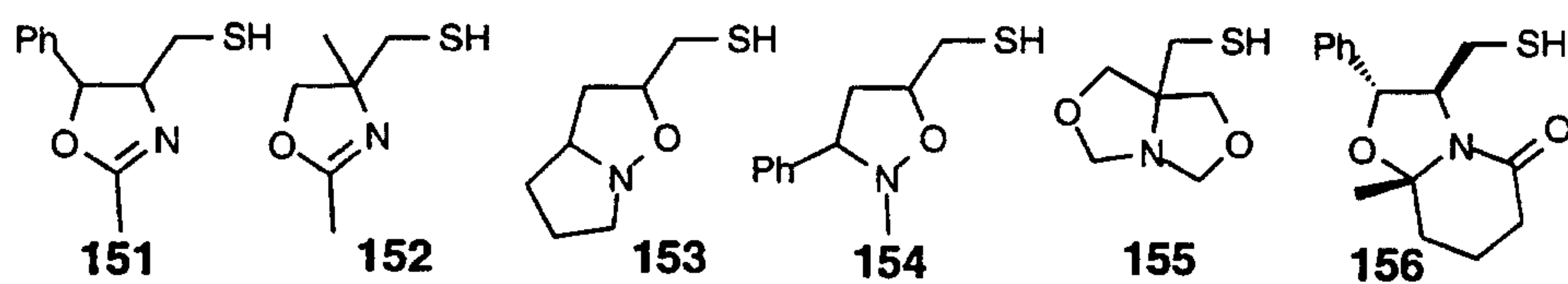
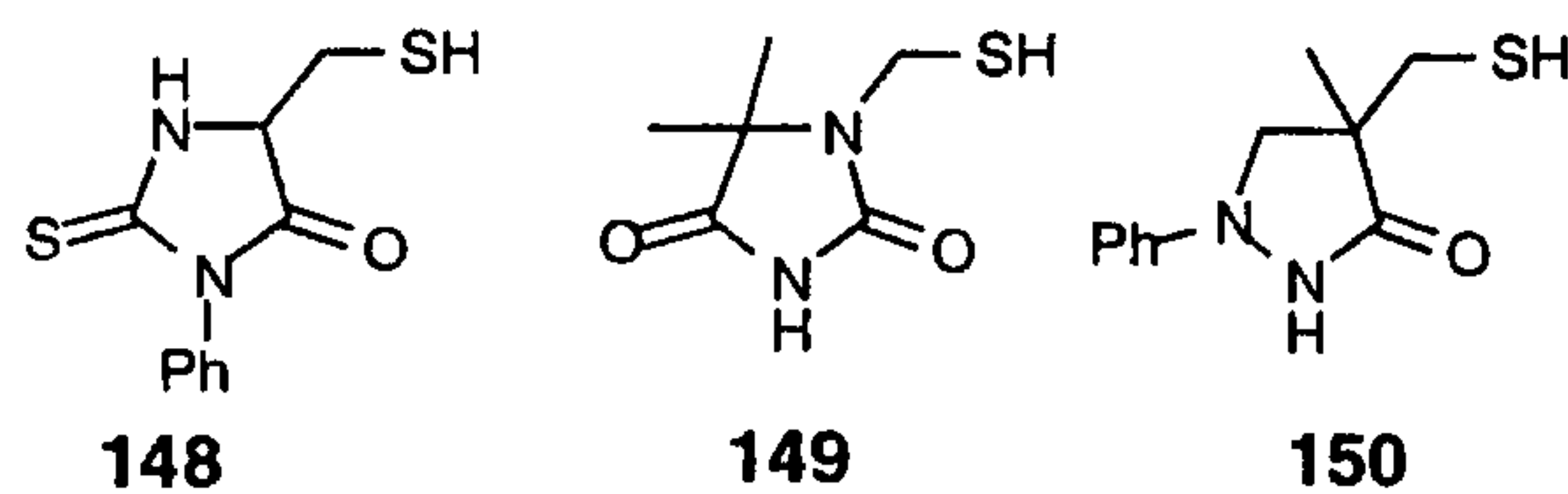
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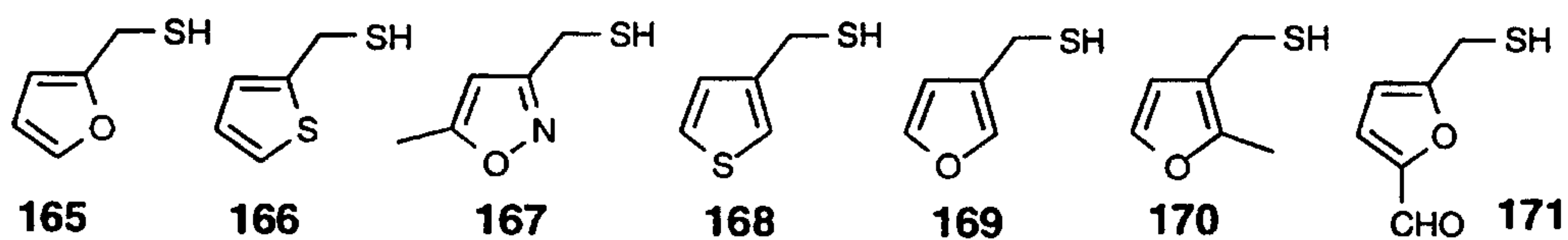
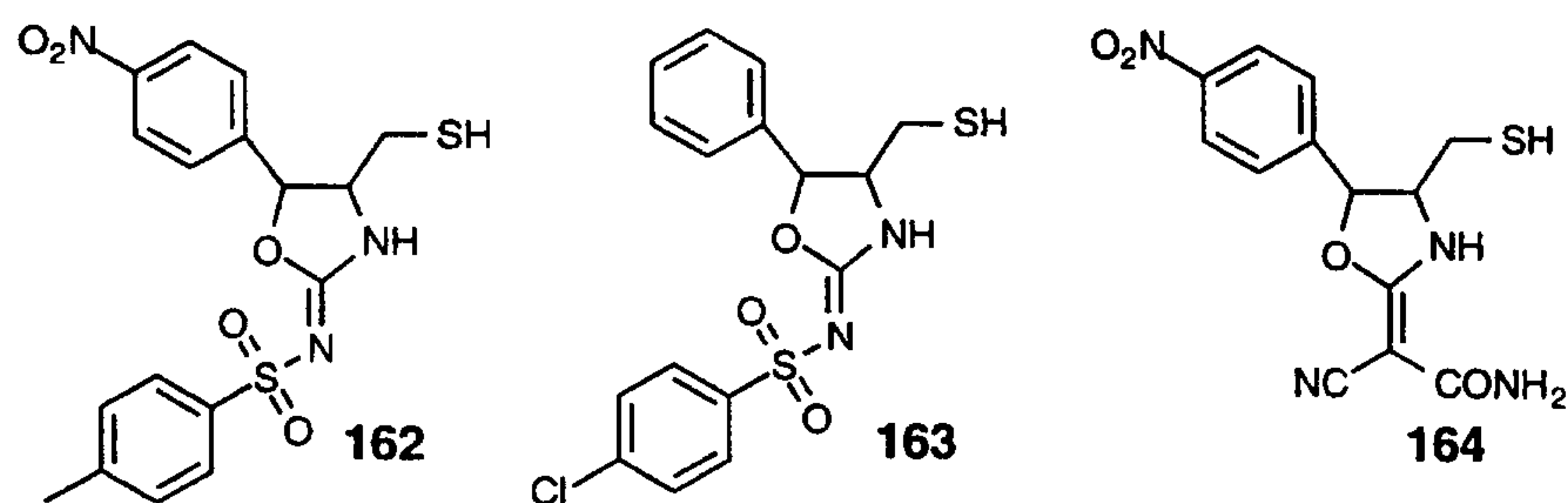
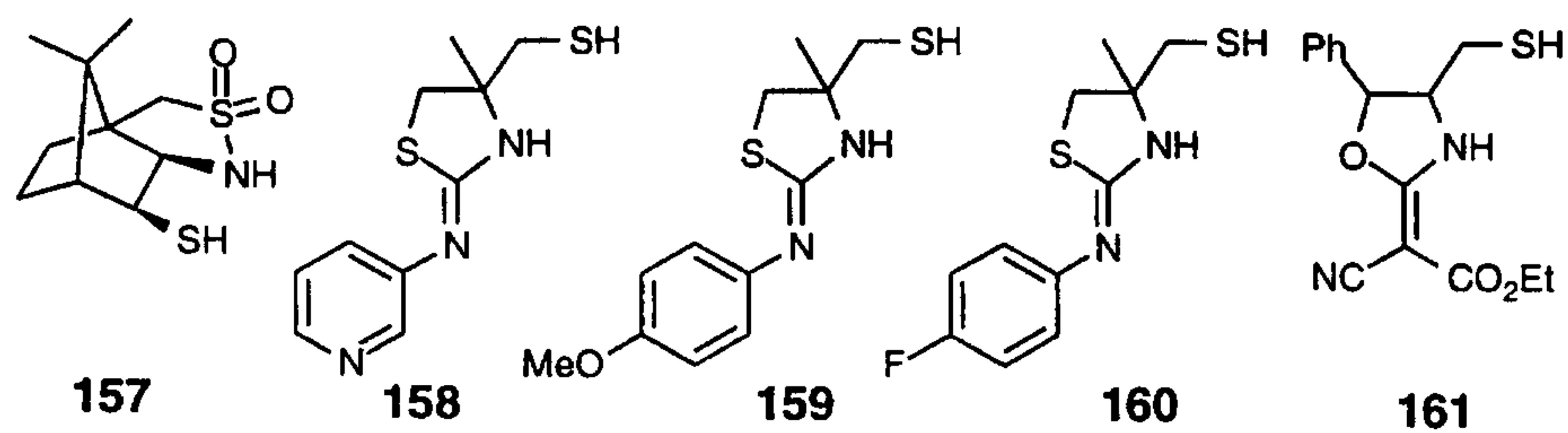




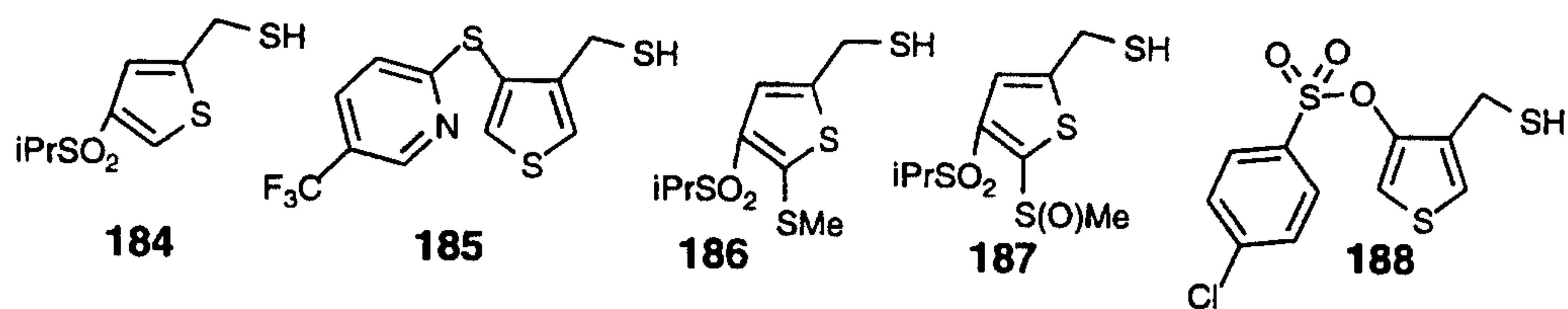
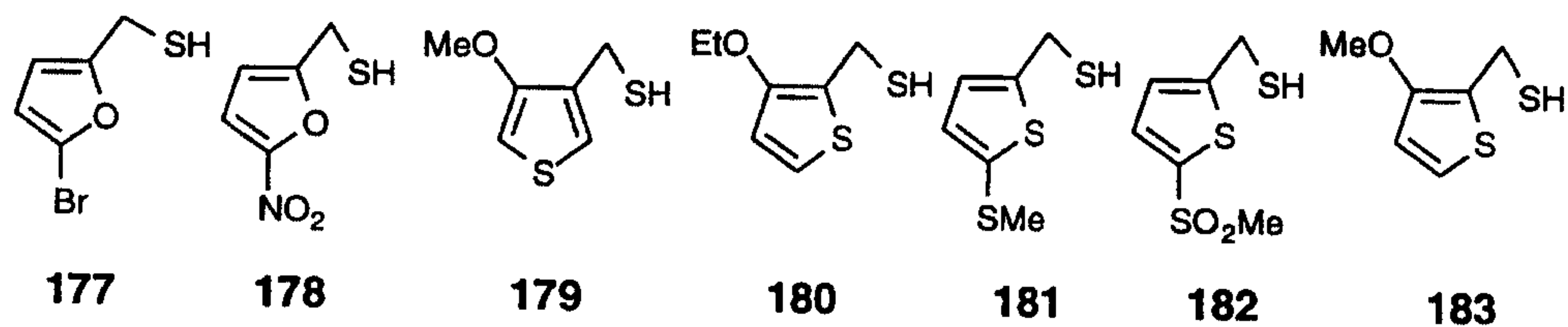
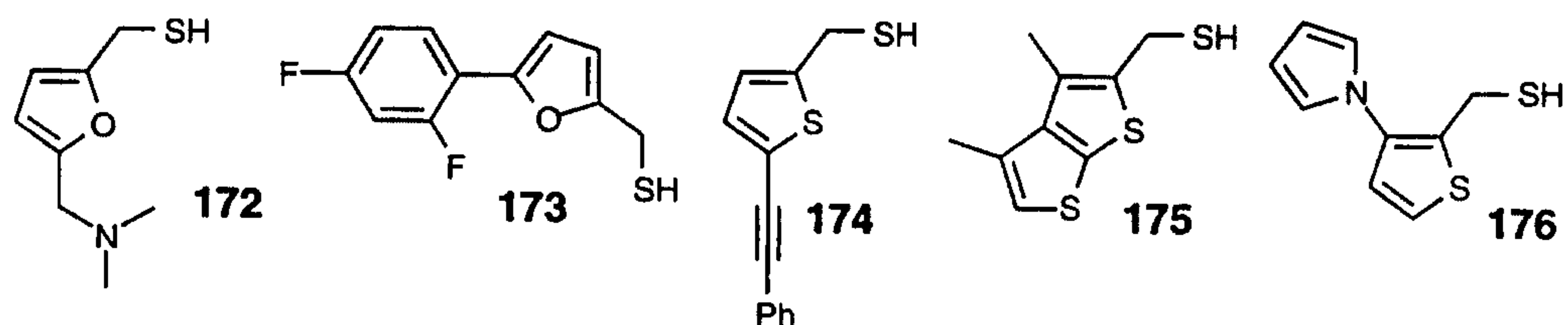
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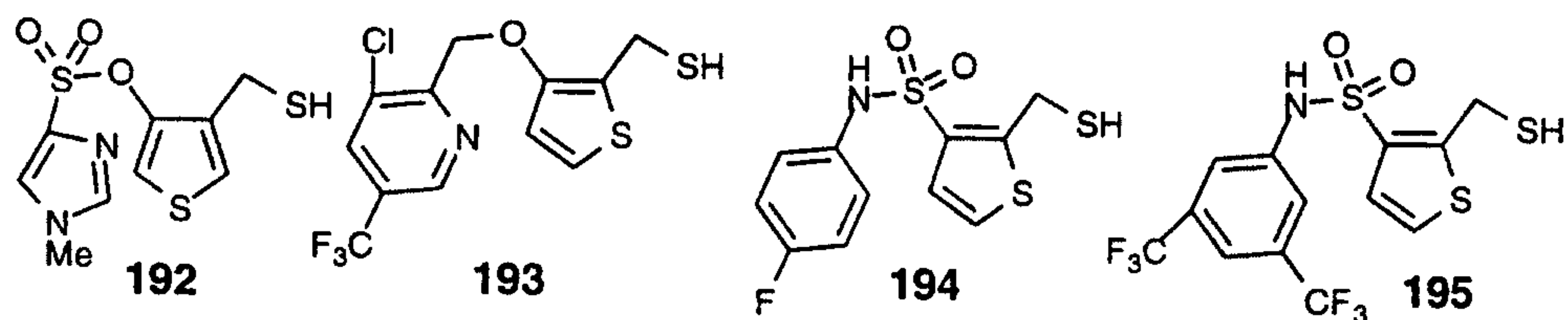
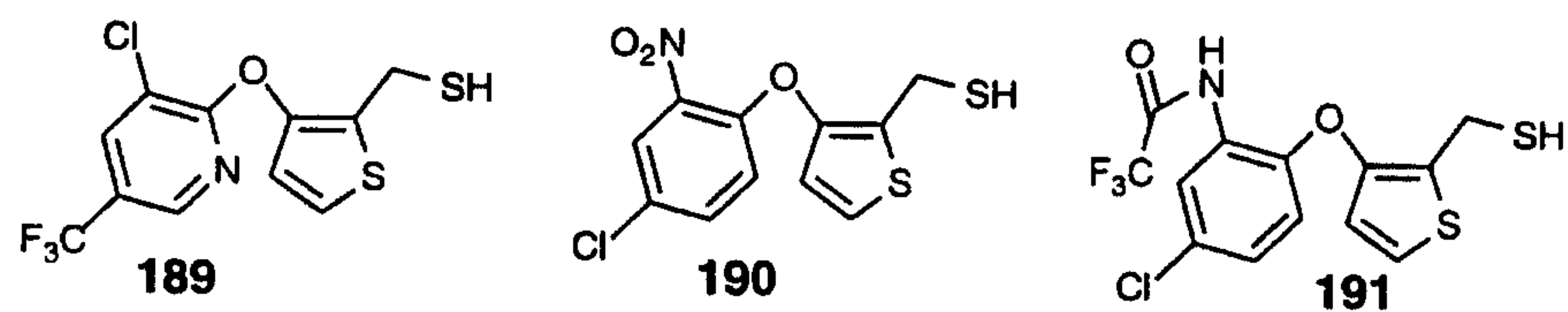
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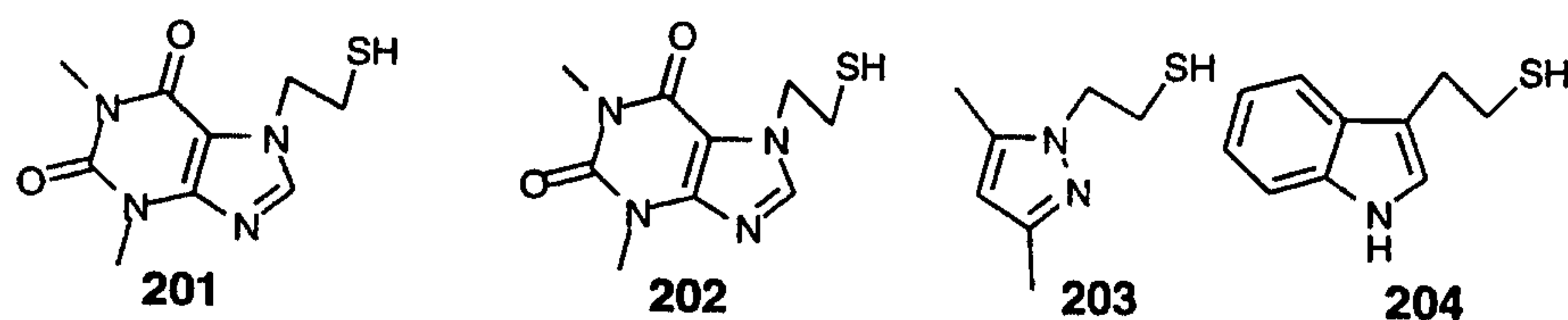
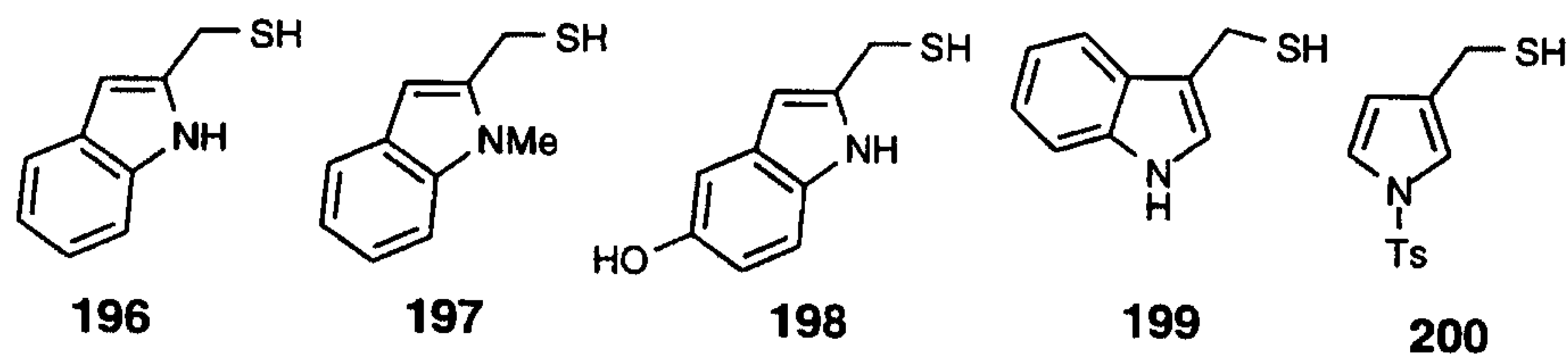
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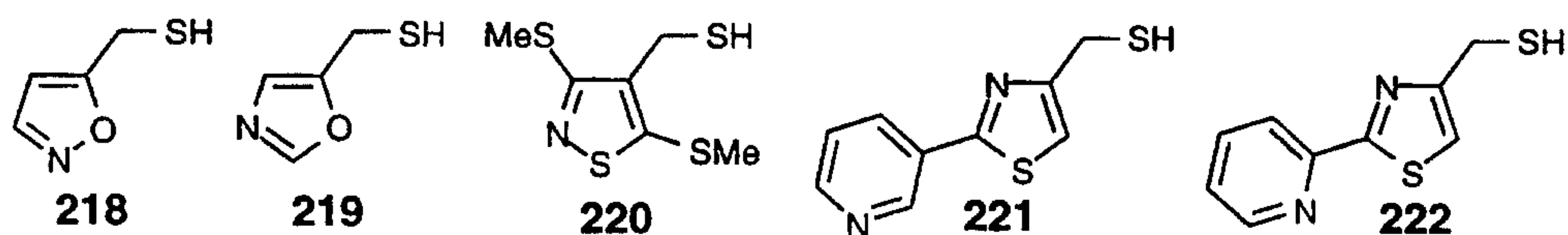
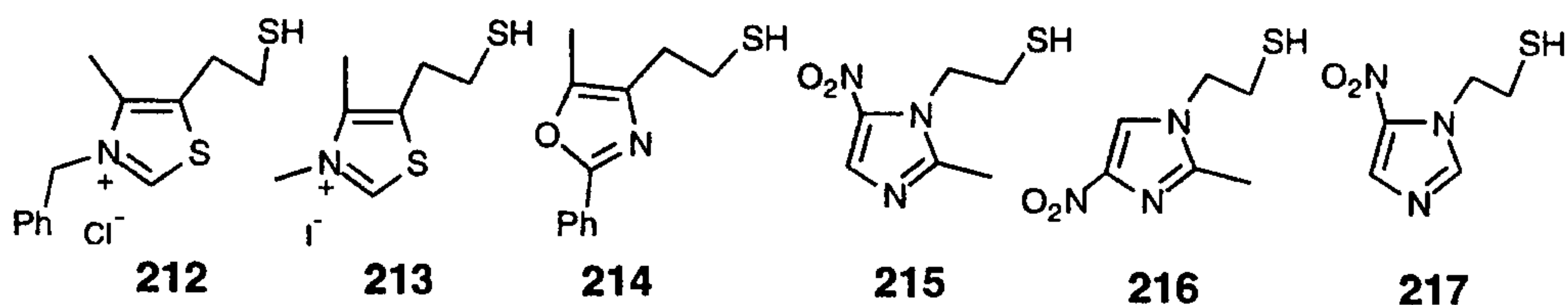
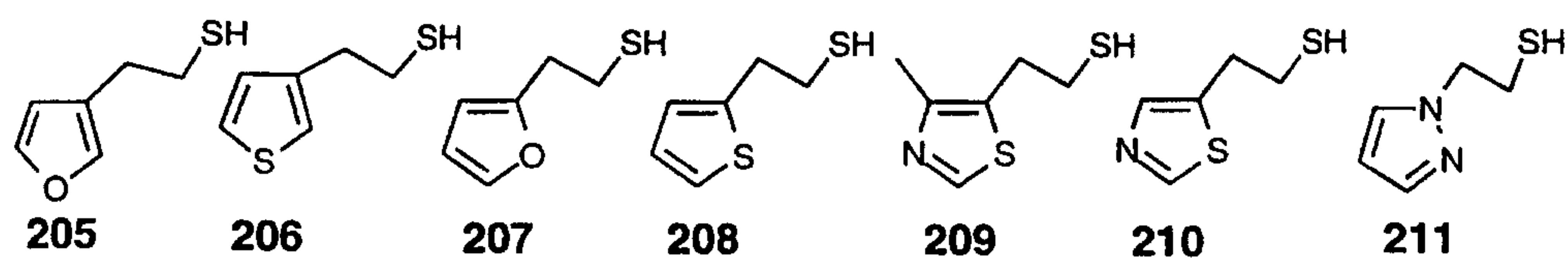
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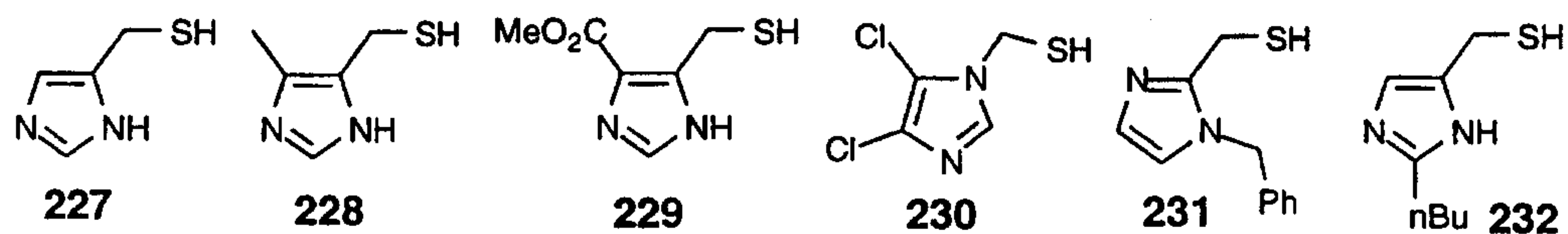
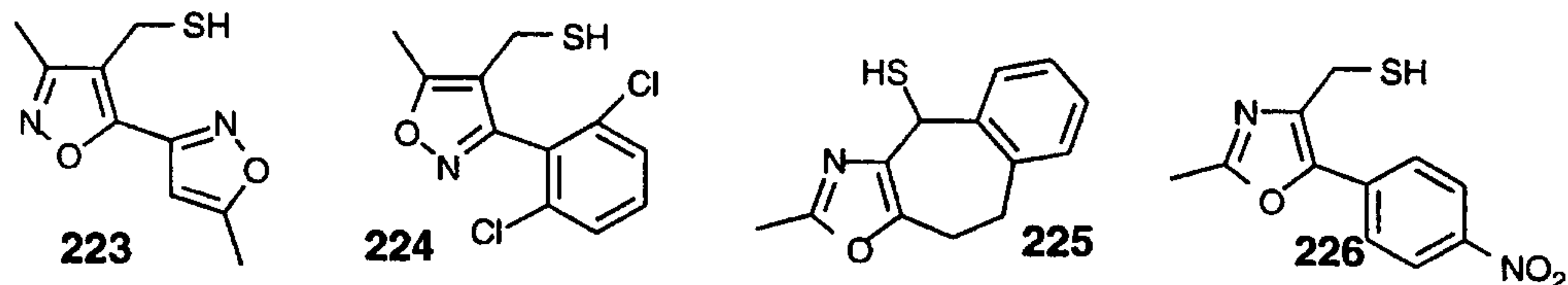
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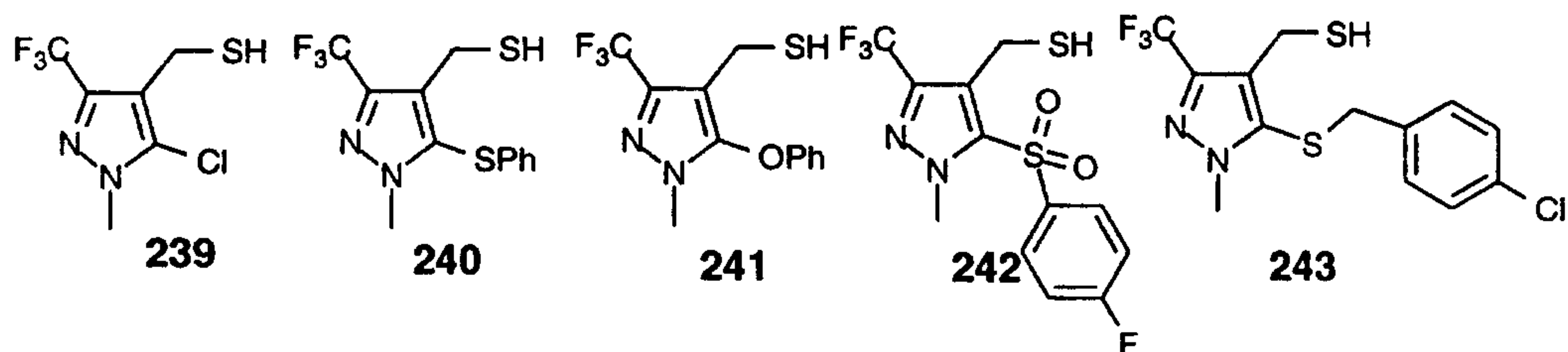
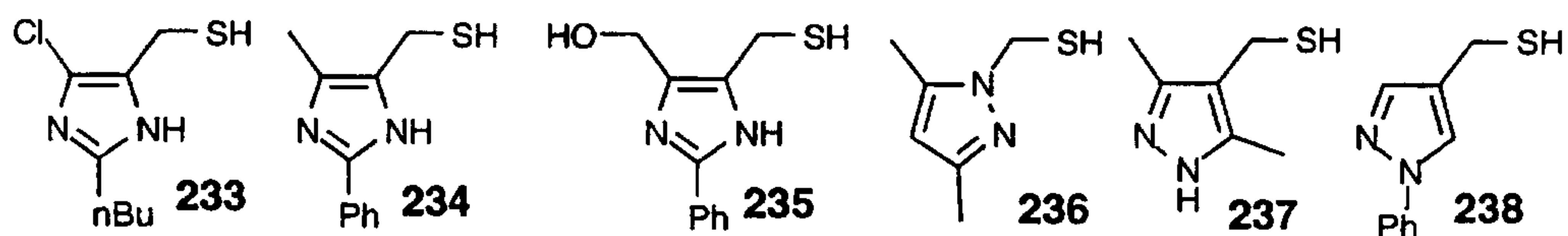
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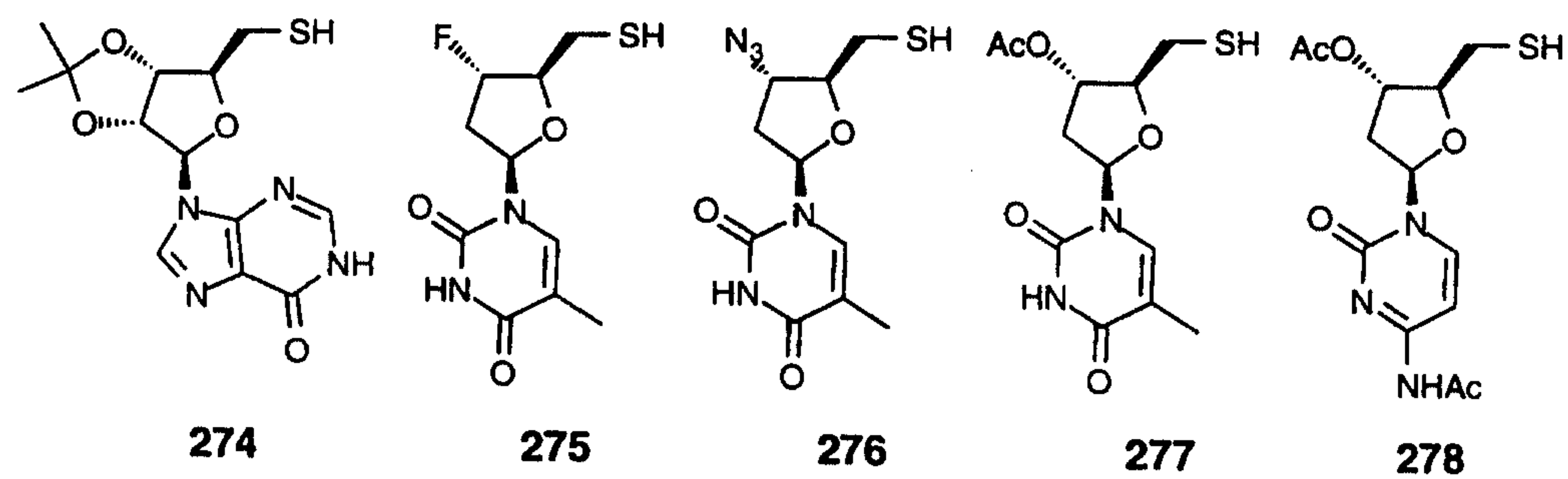
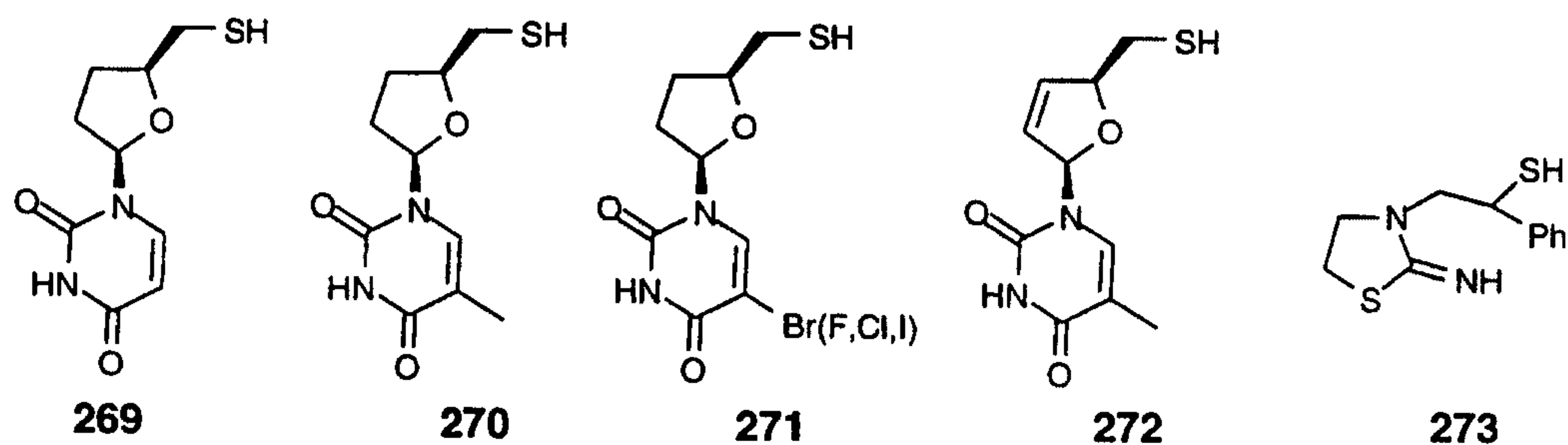
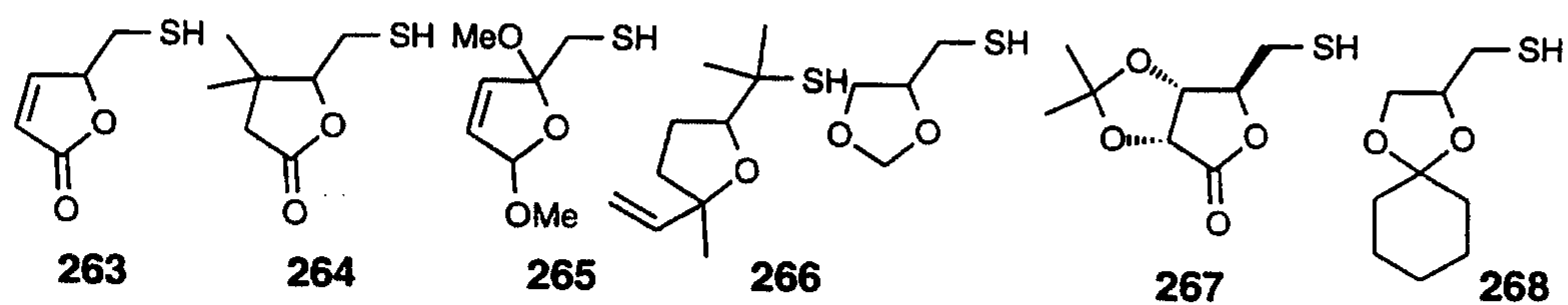
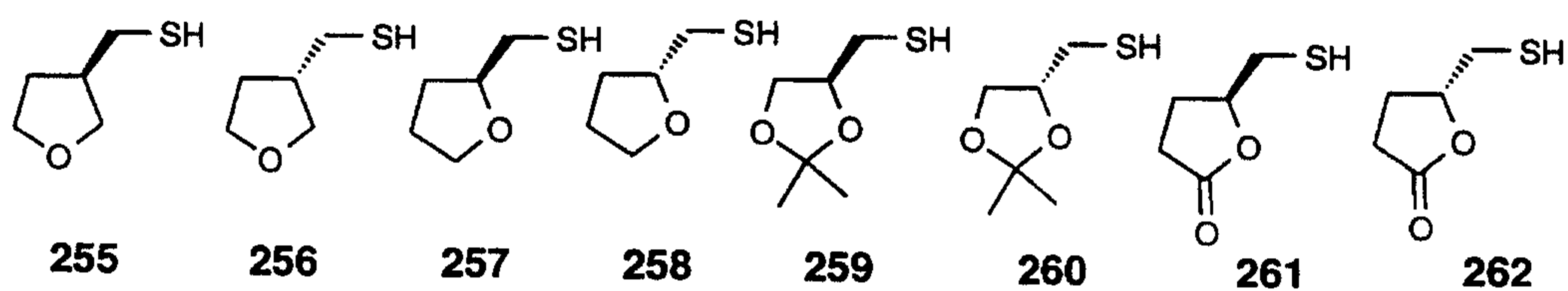
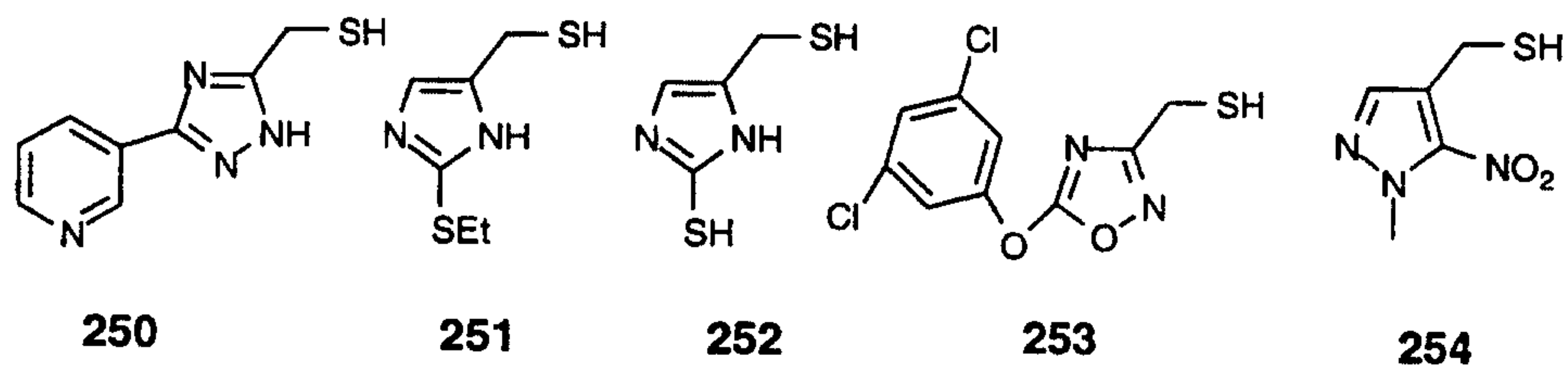
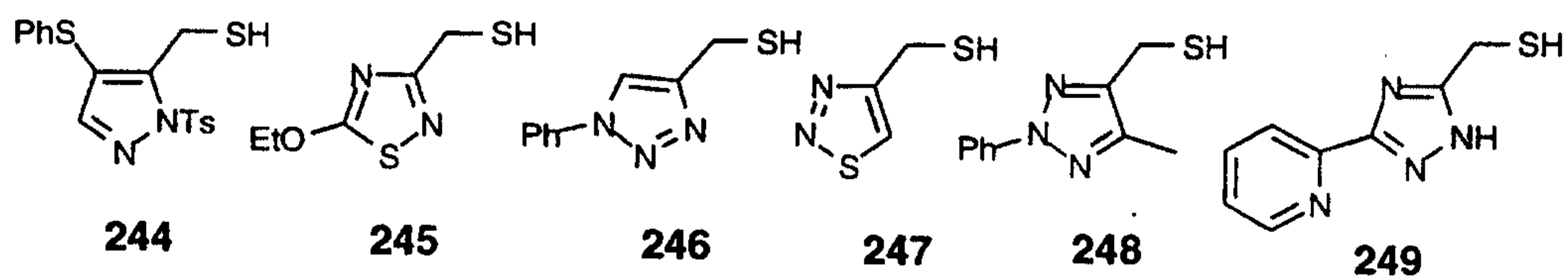


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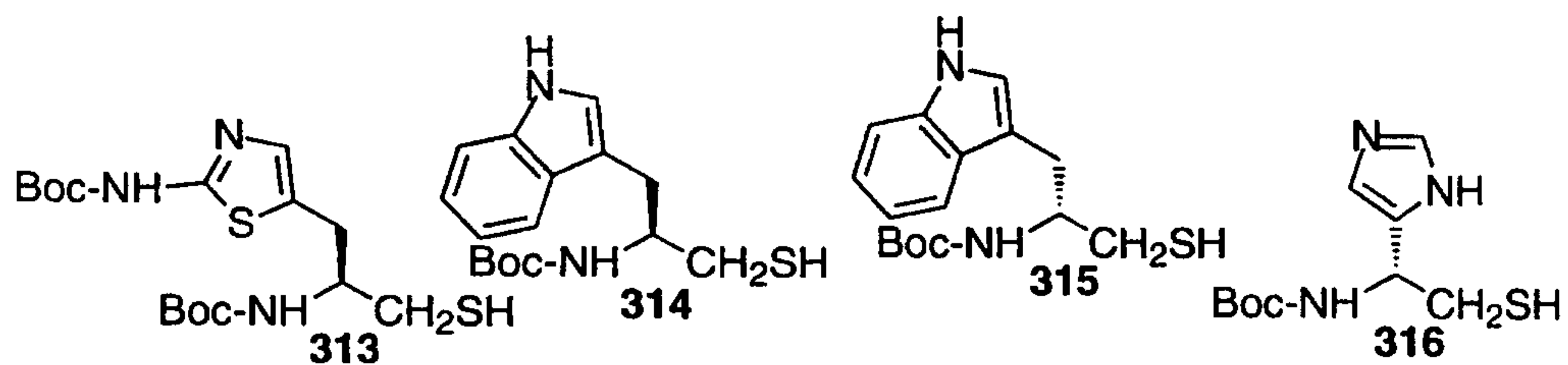
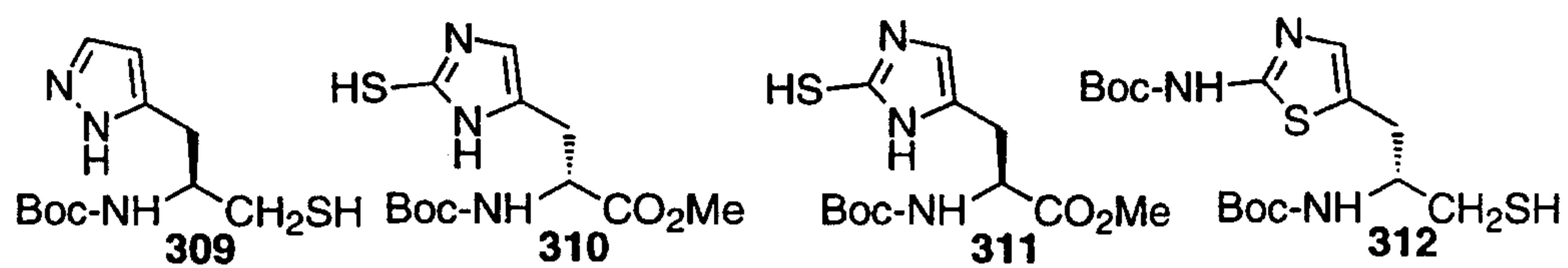
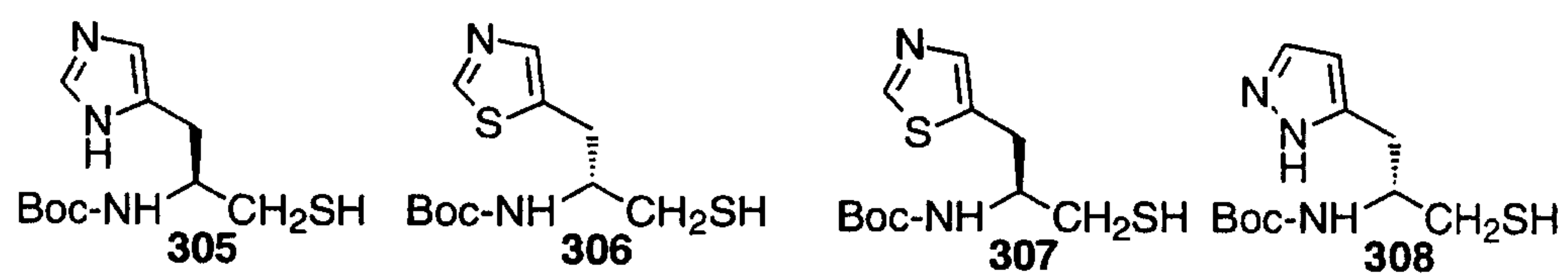
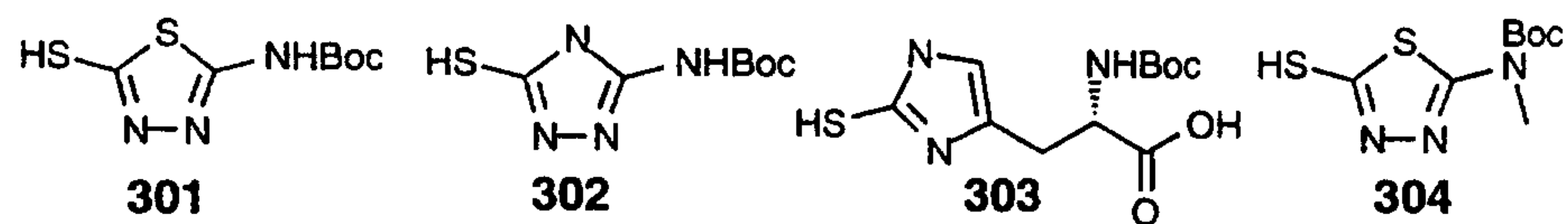
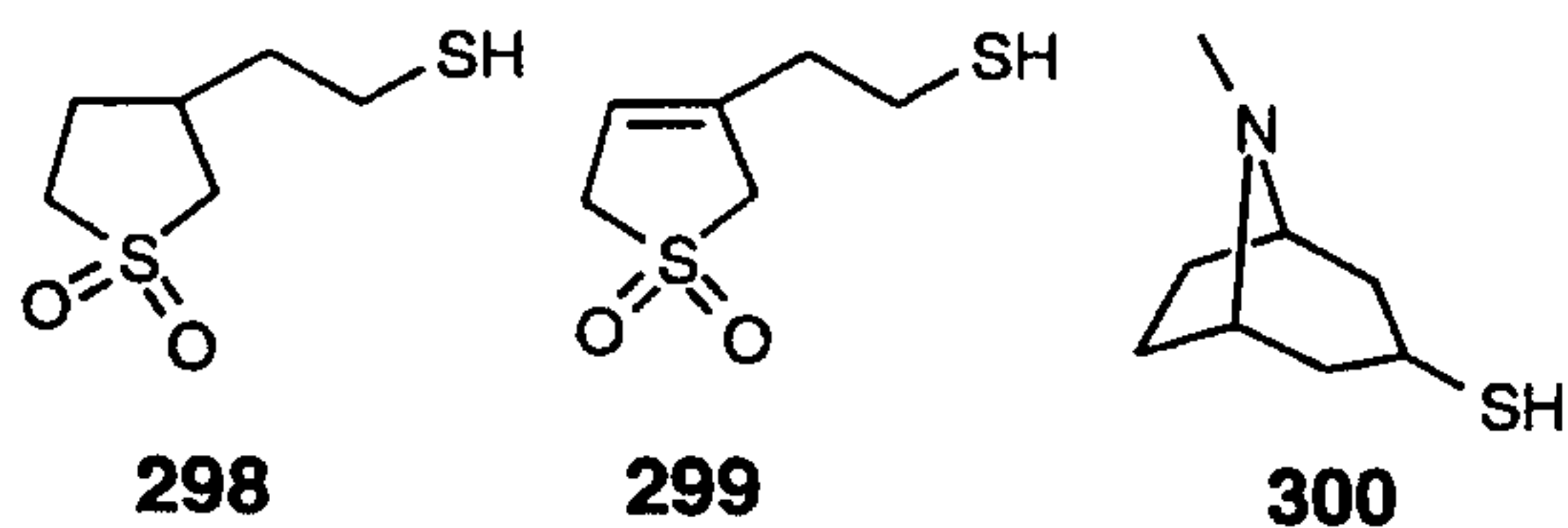
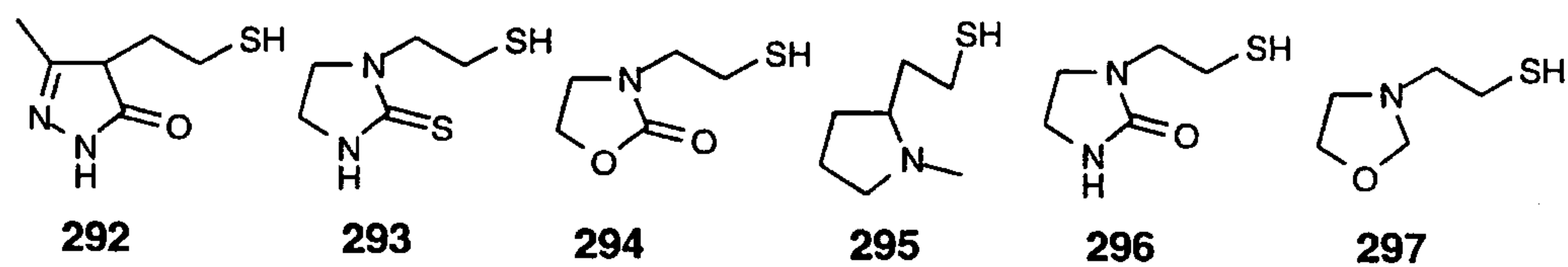
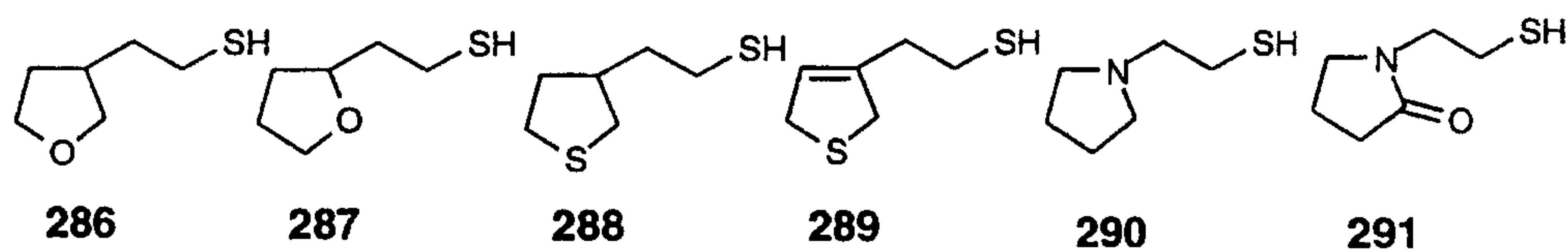
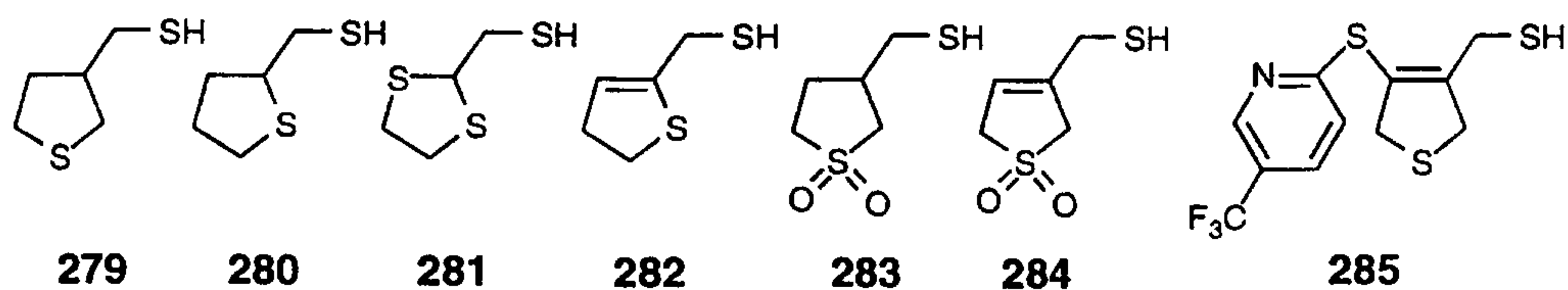
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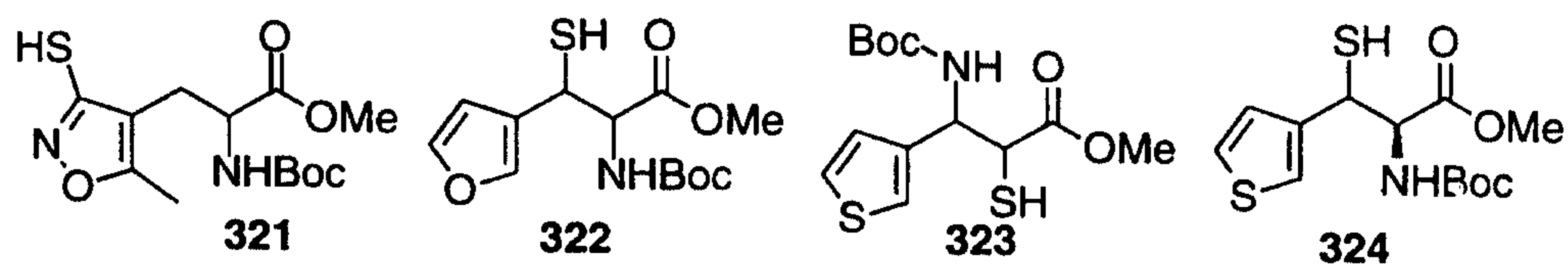
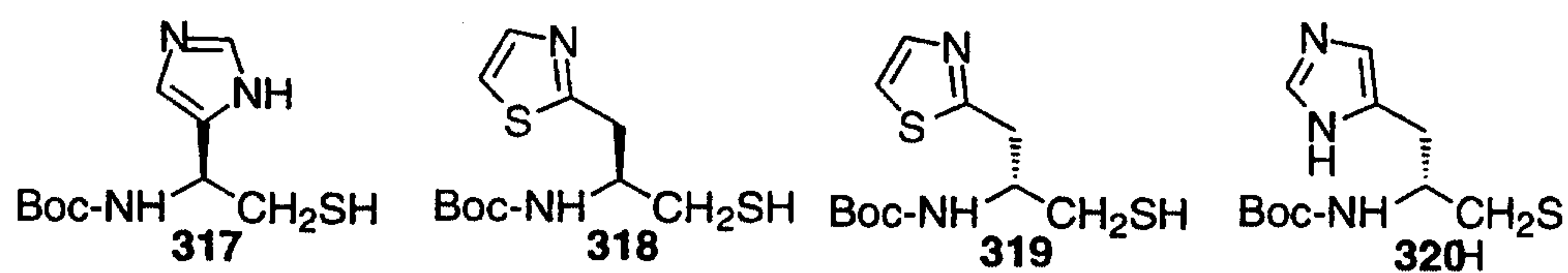




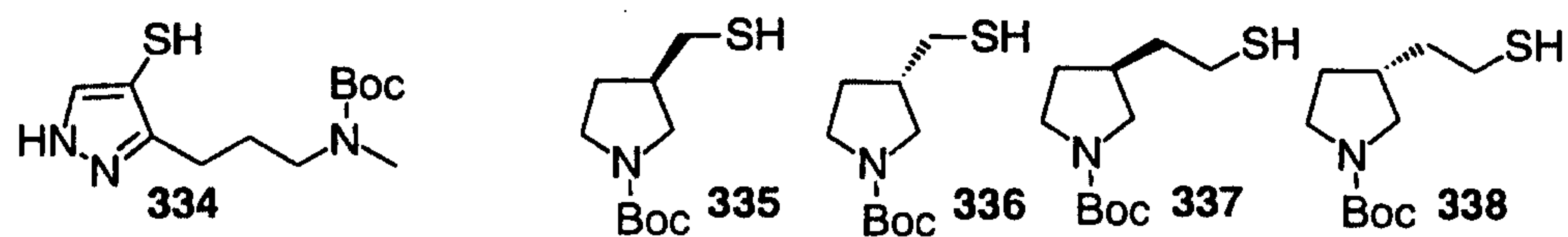
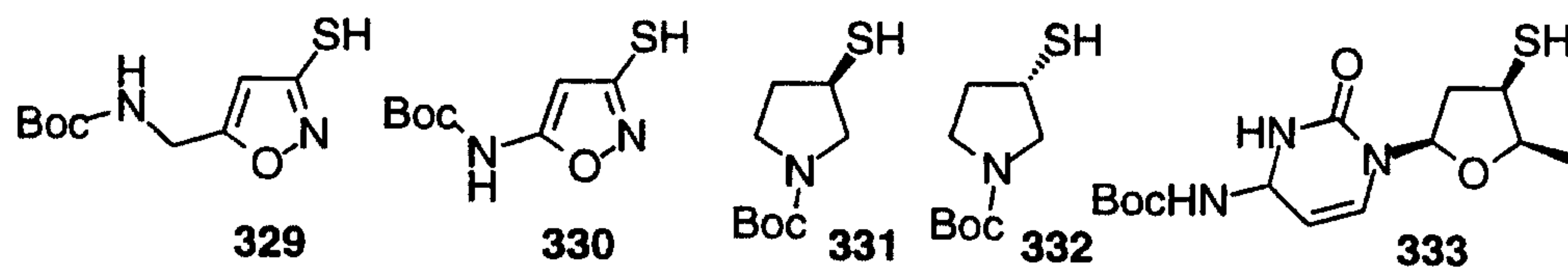
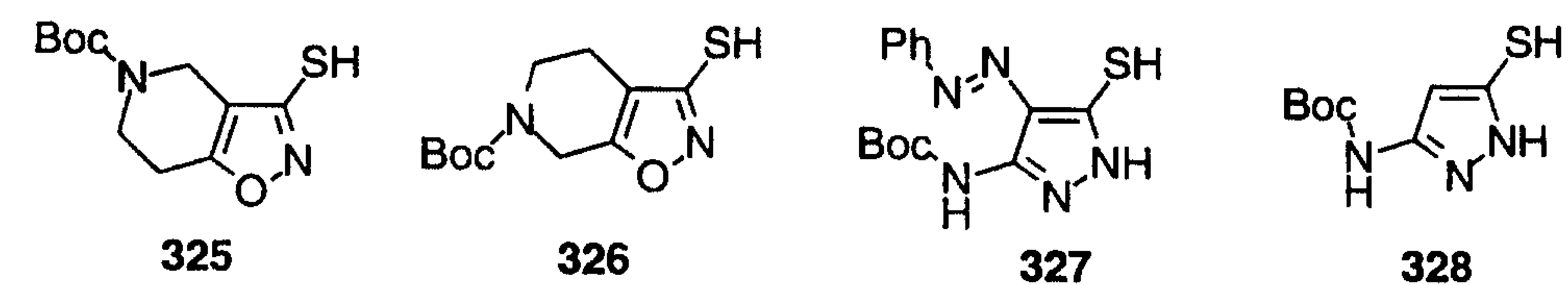
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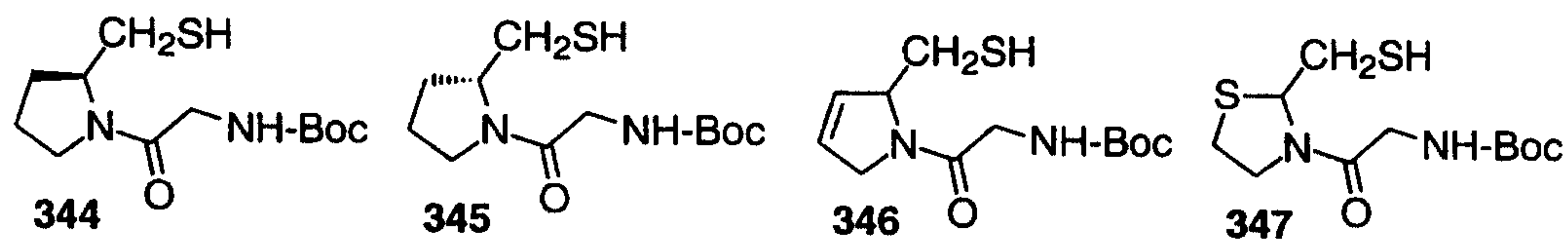
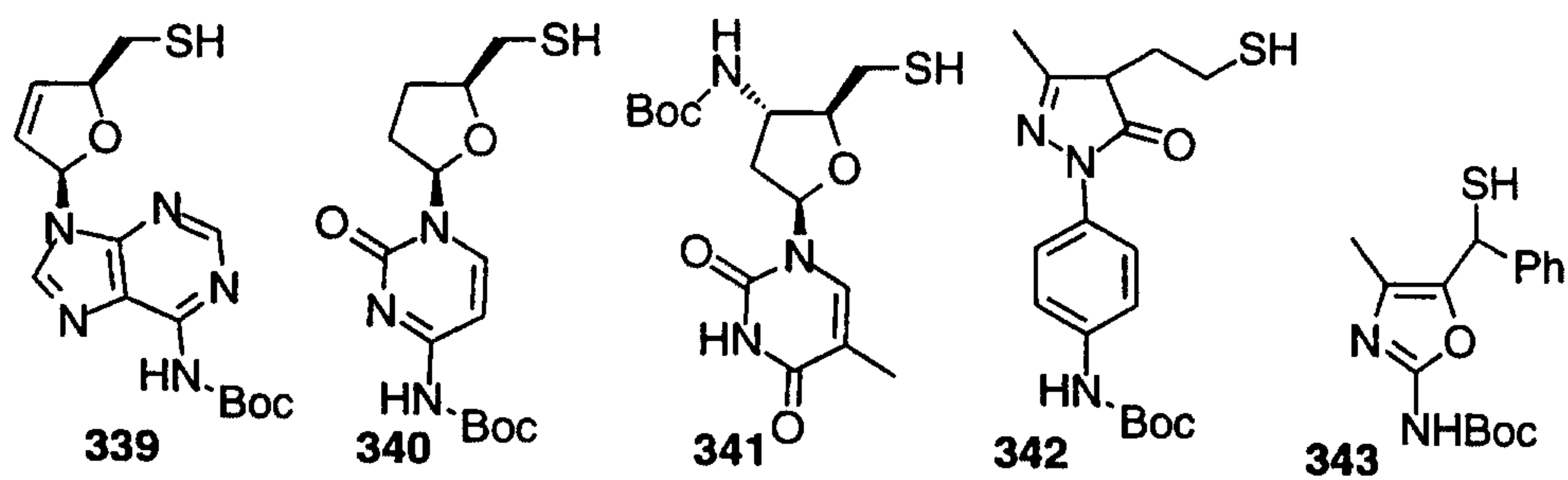




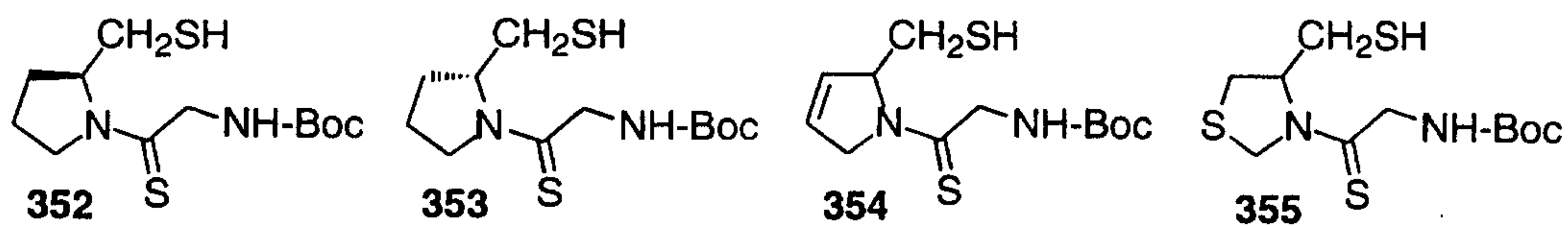
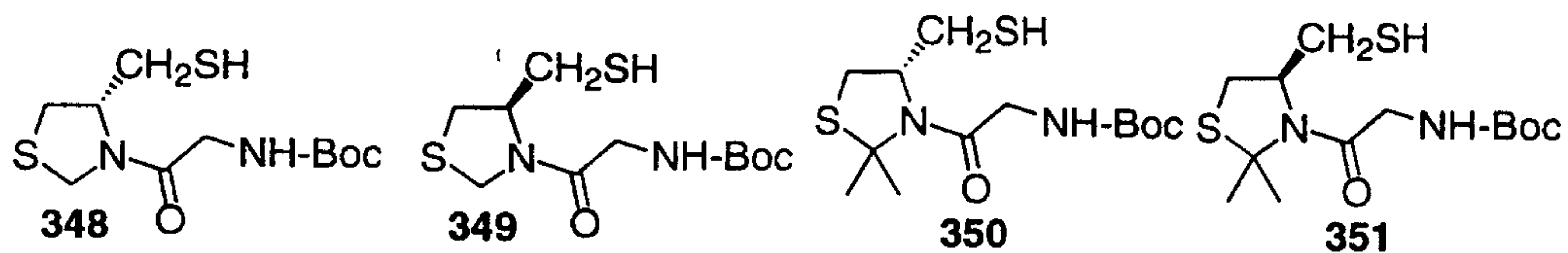
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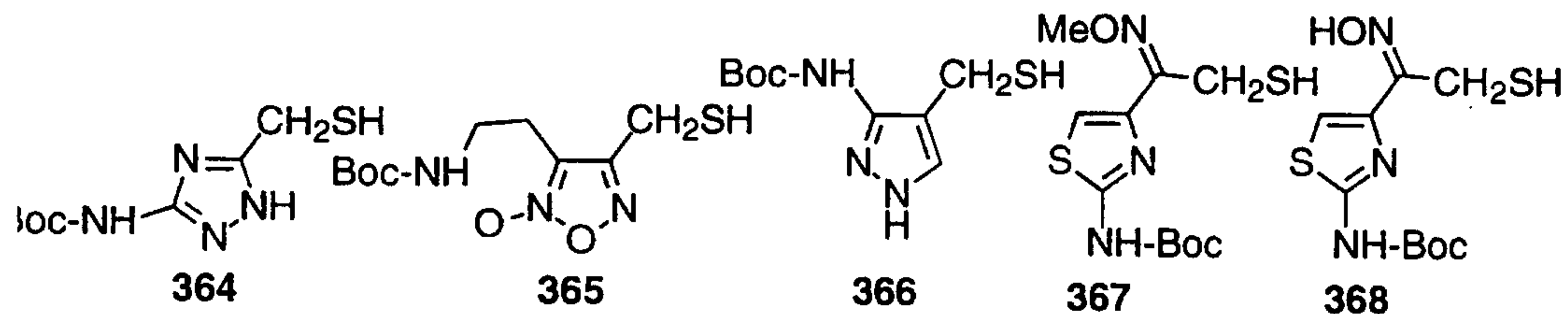
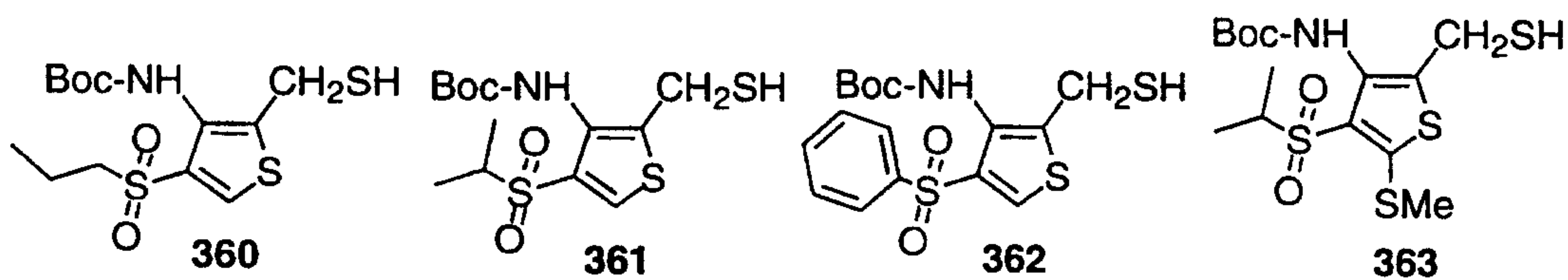
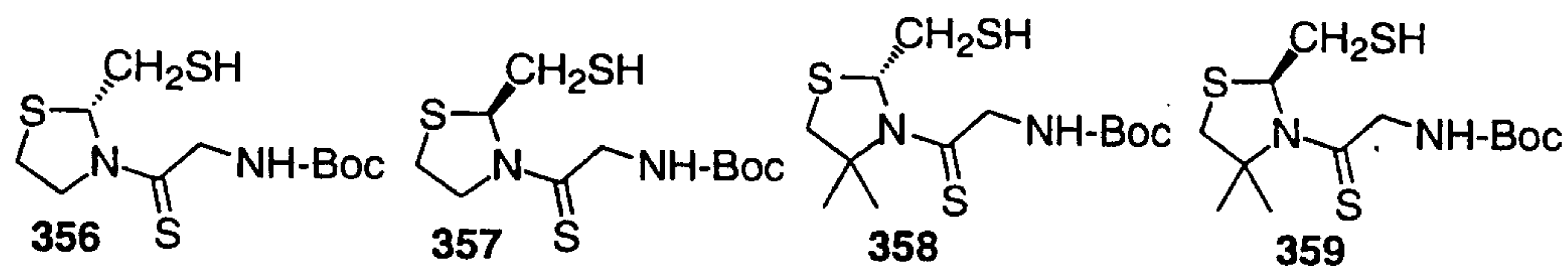
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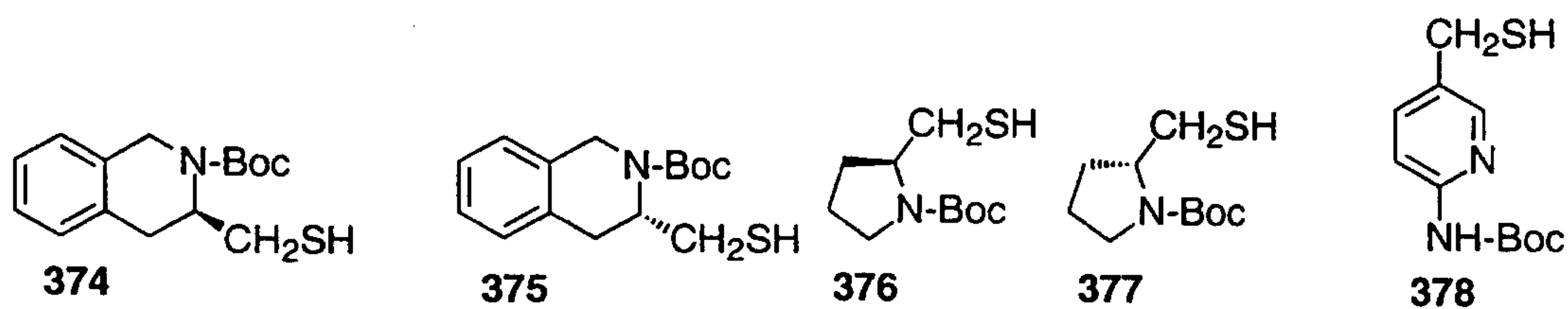
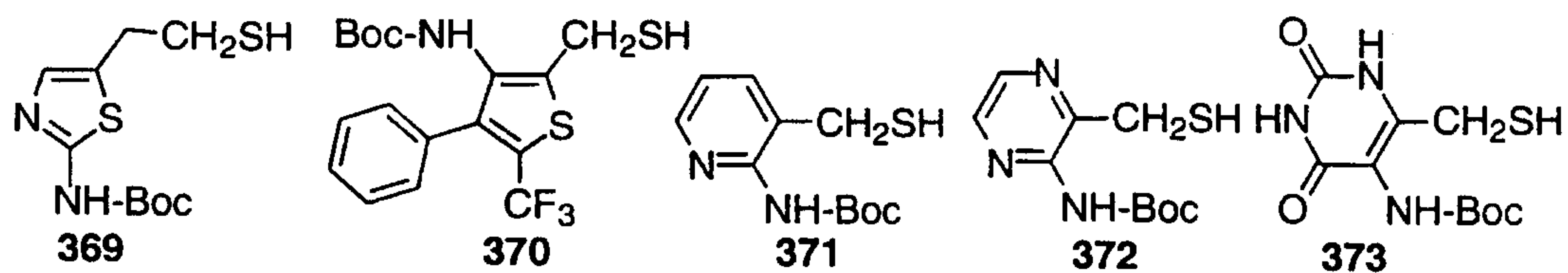
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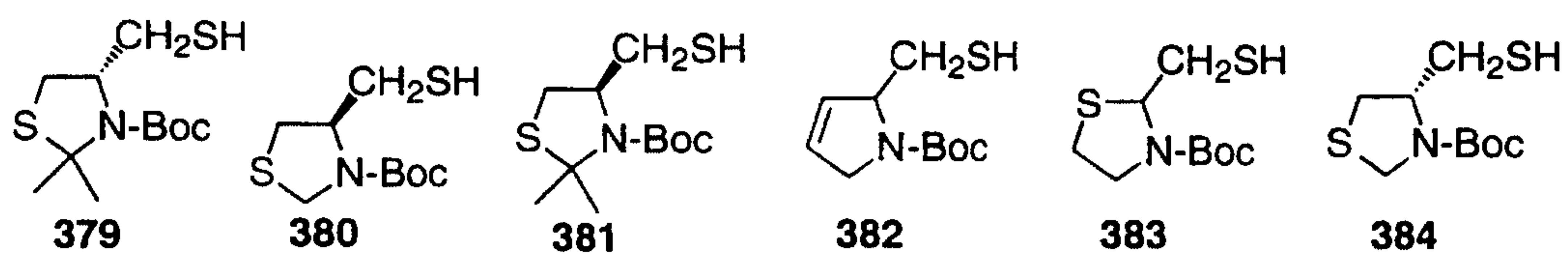
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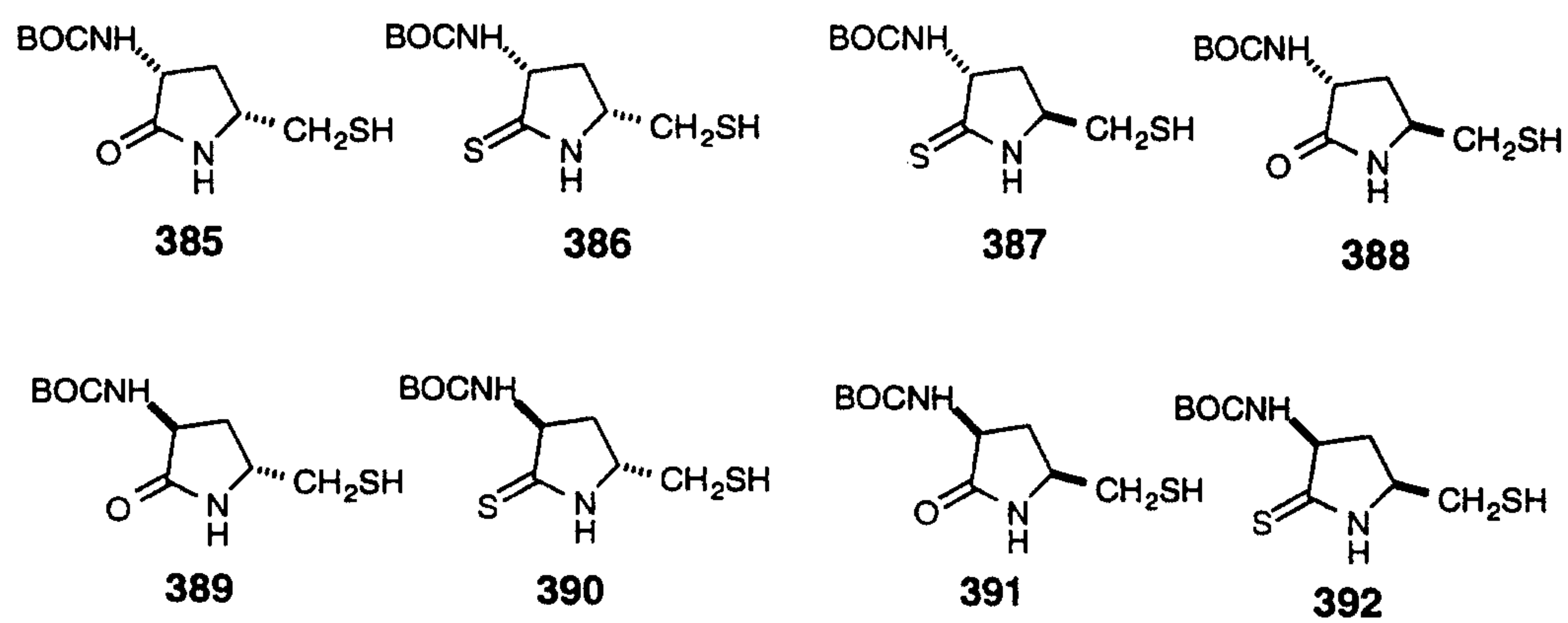
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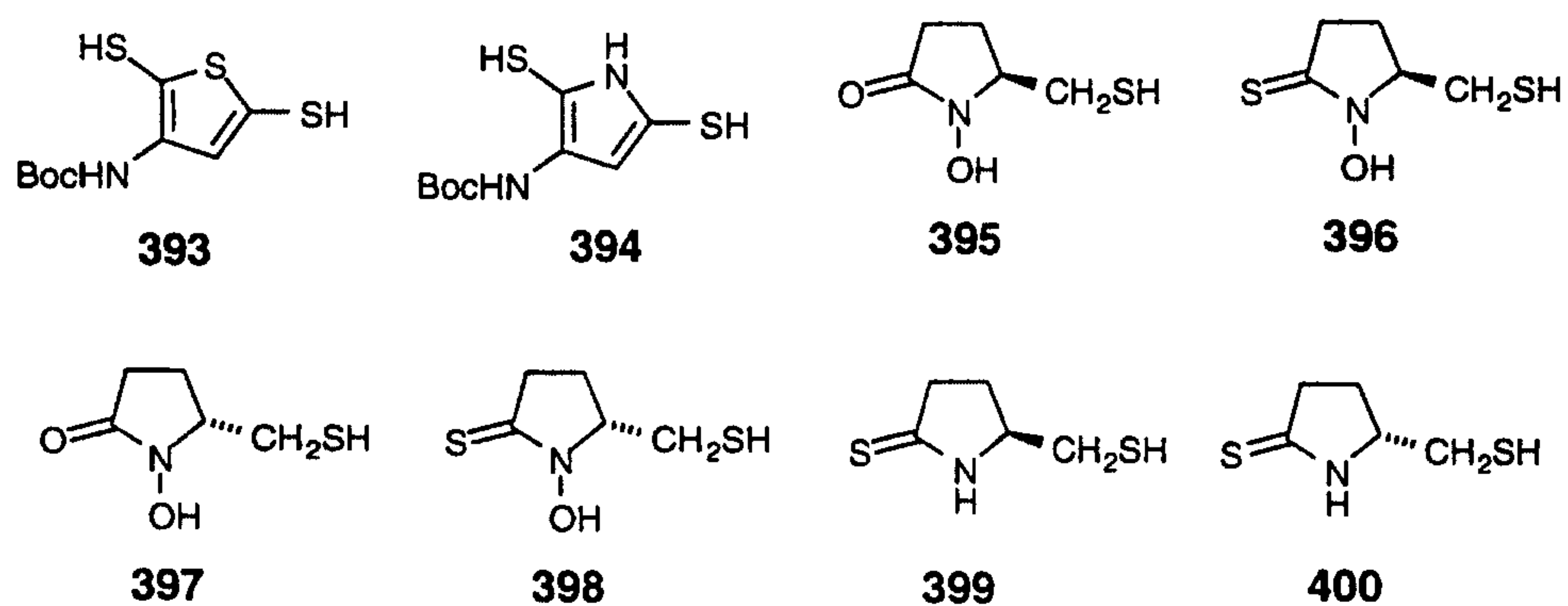
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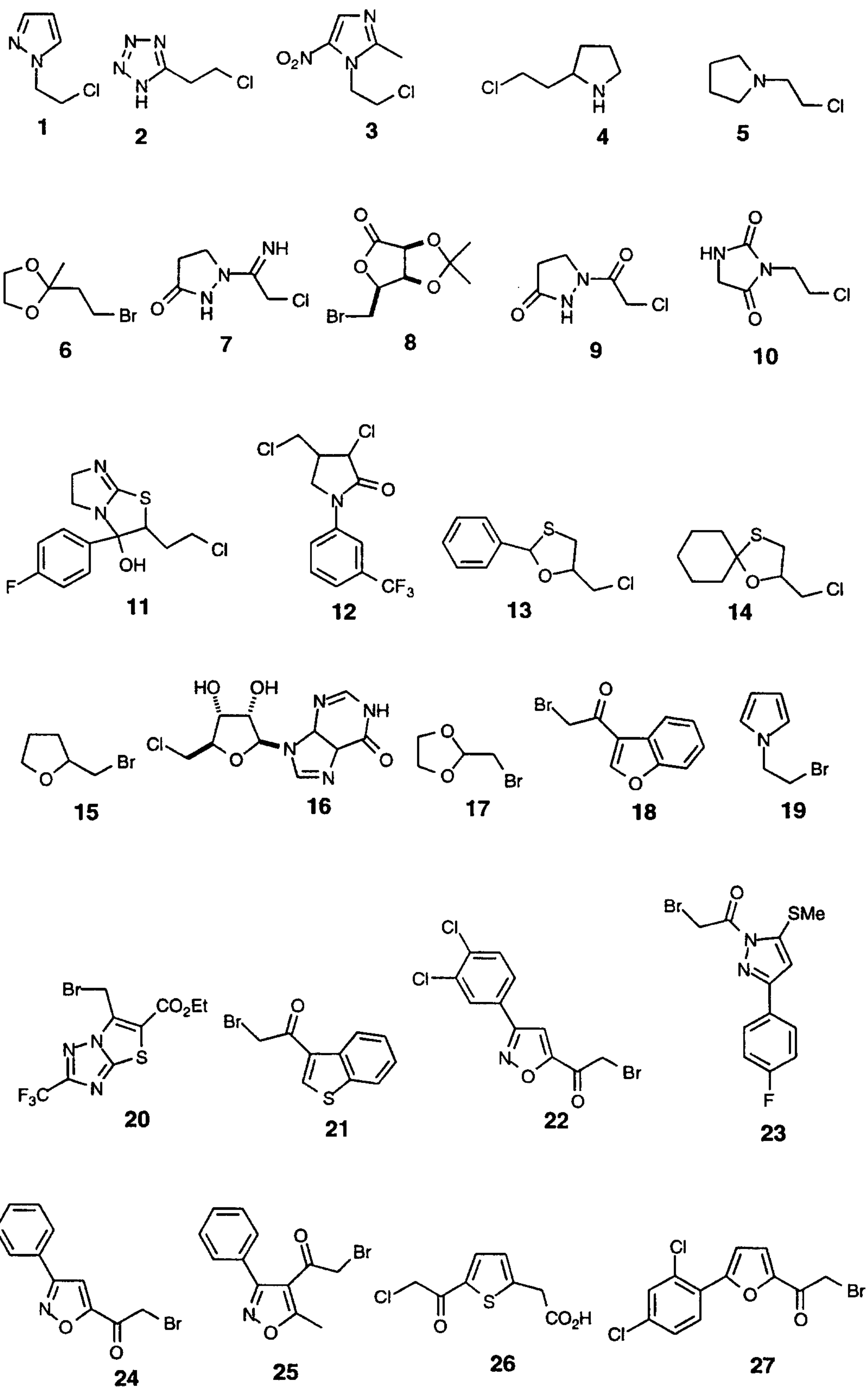
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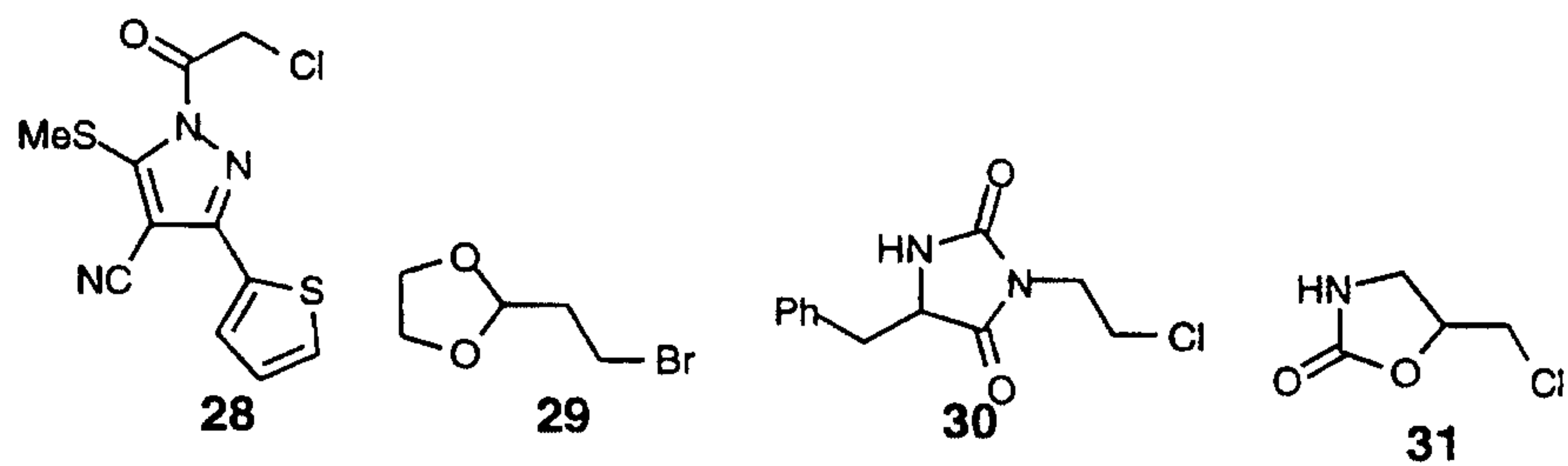


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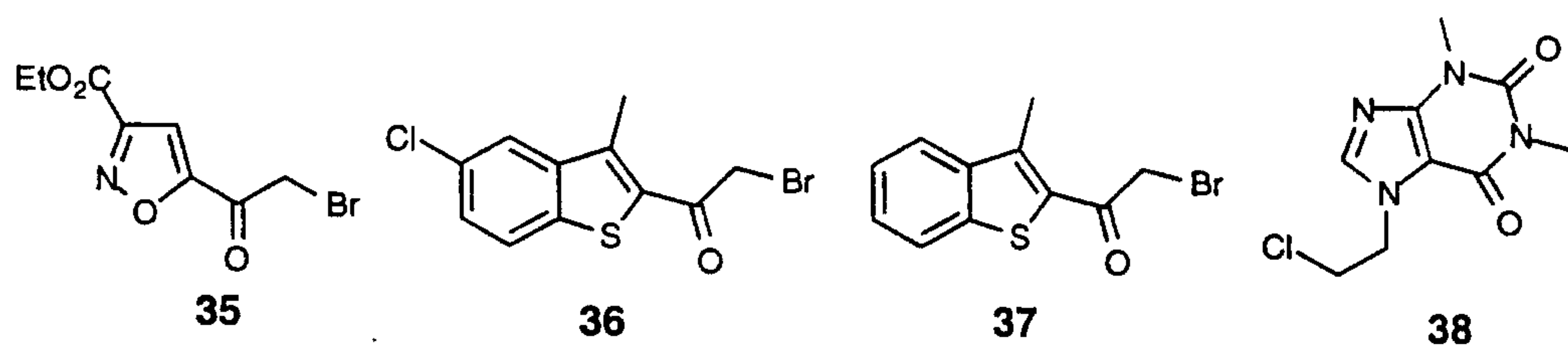
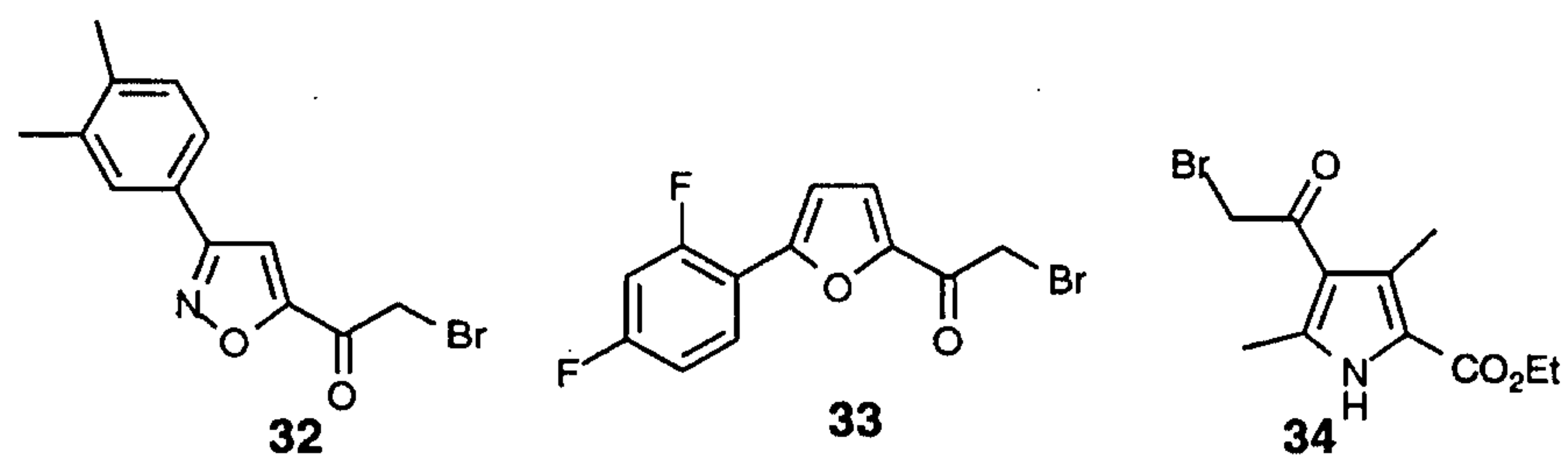
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Table 17. Halides of the type A-Cl, A-Br, and A-I

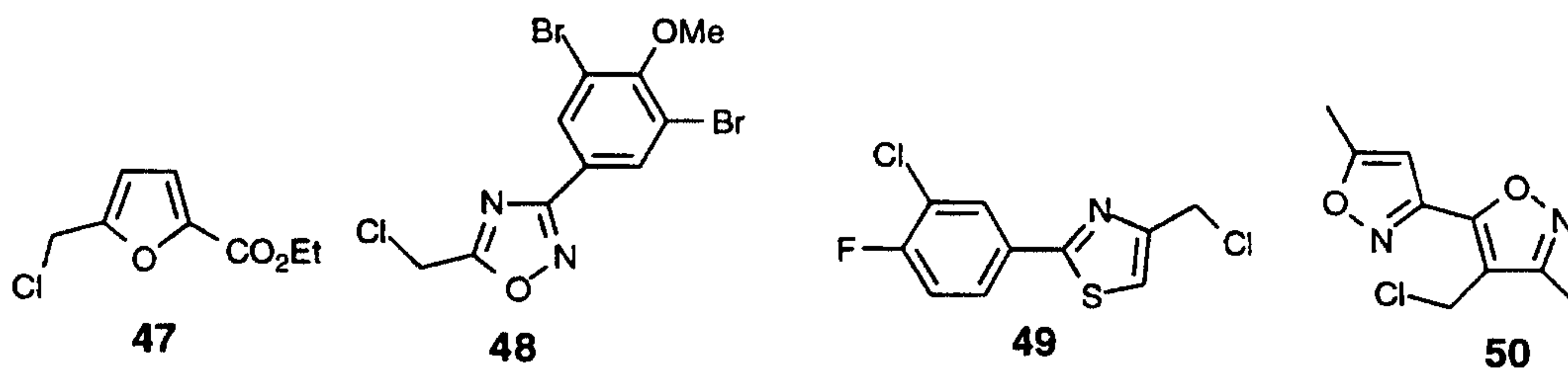
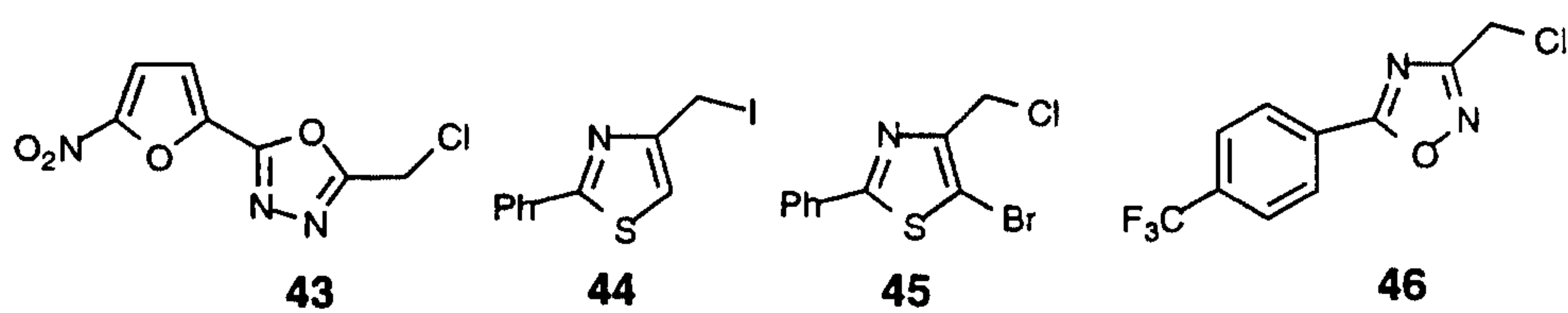
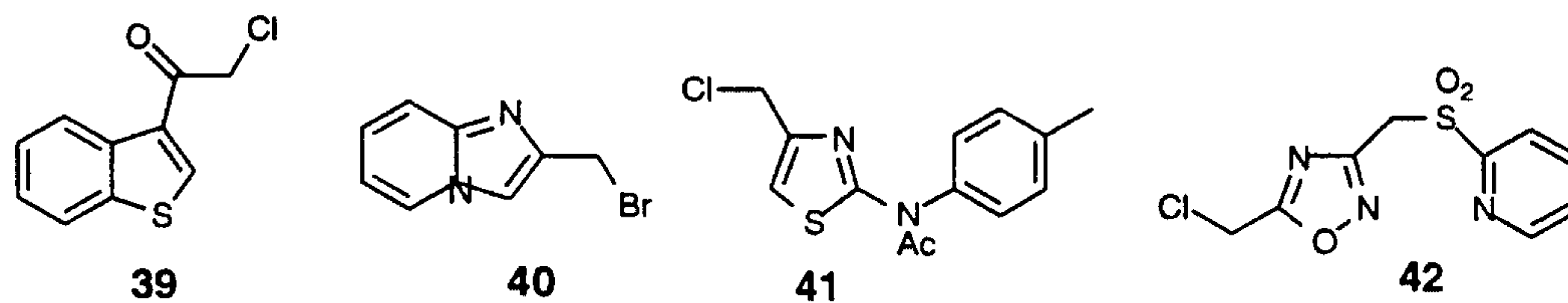




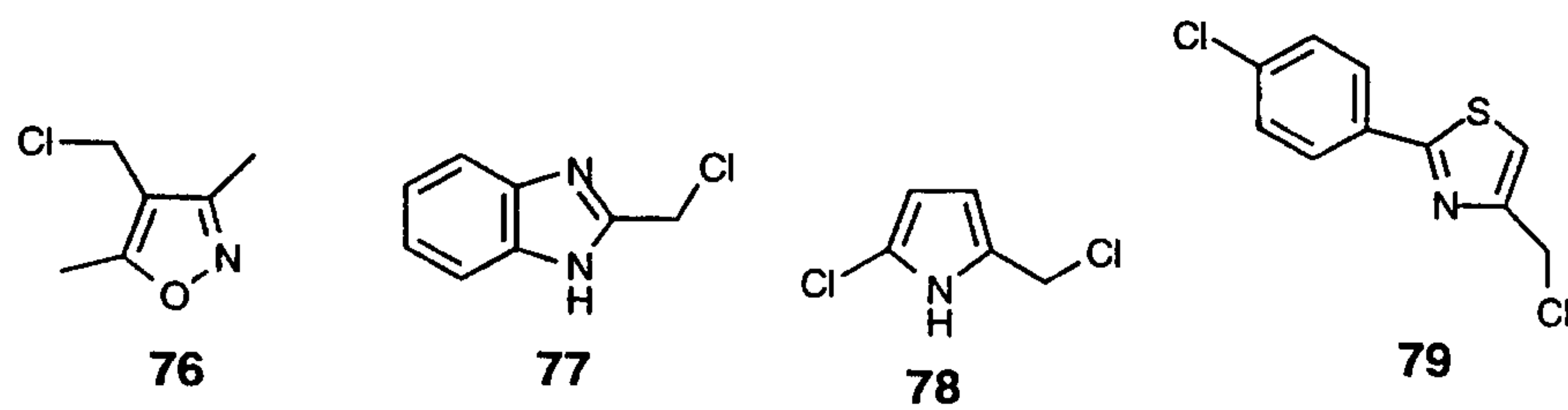
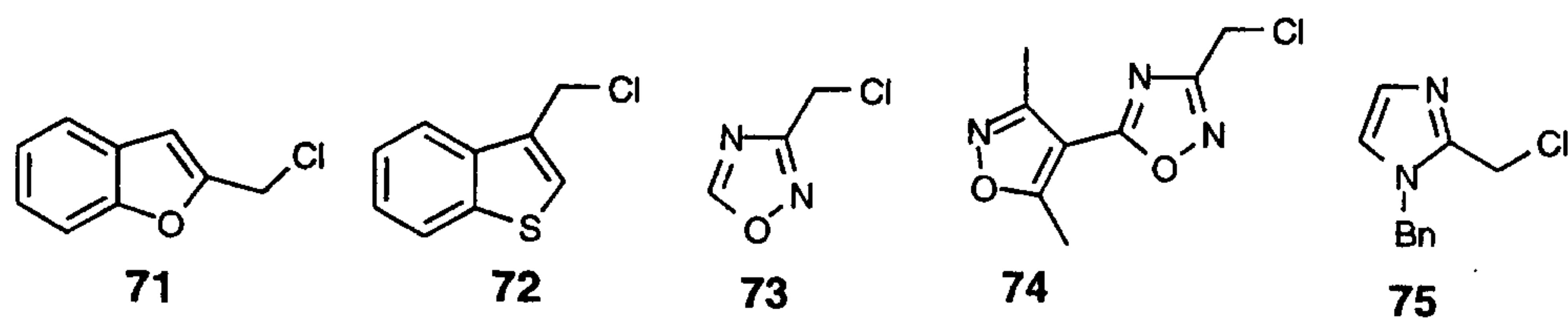
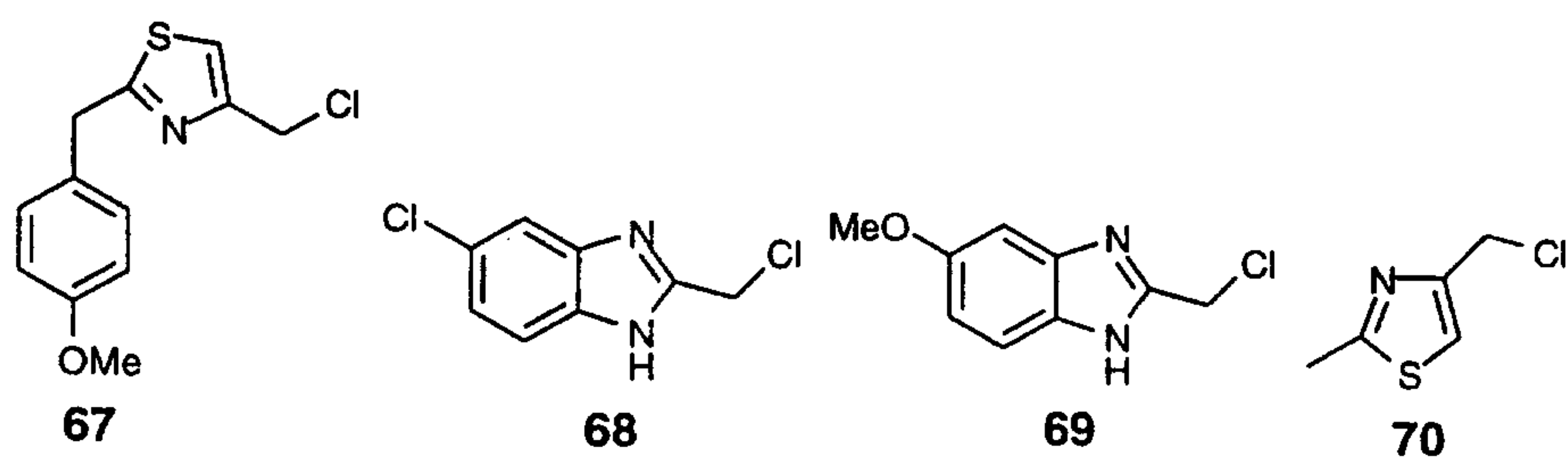
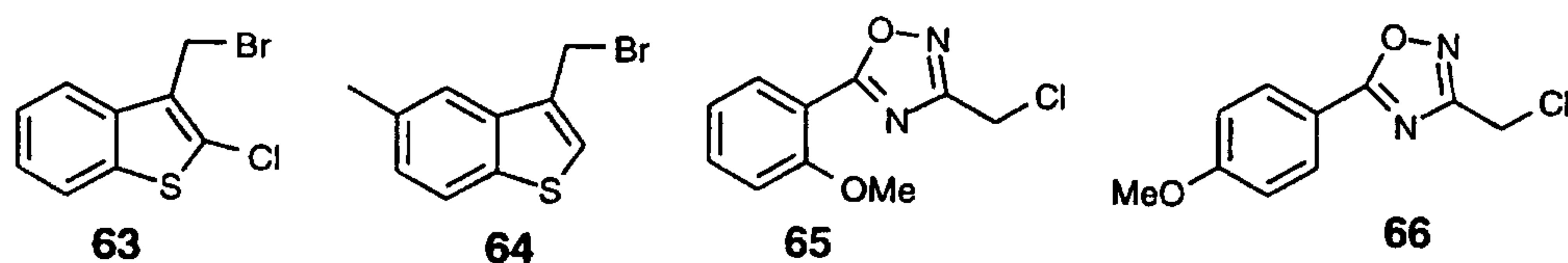
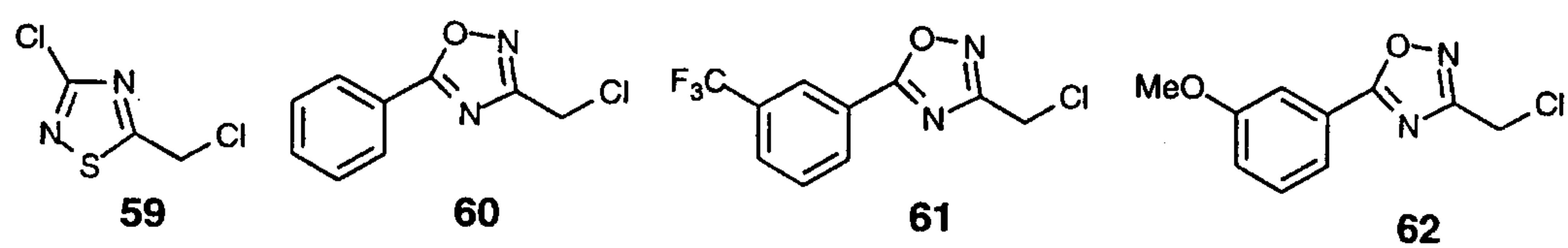
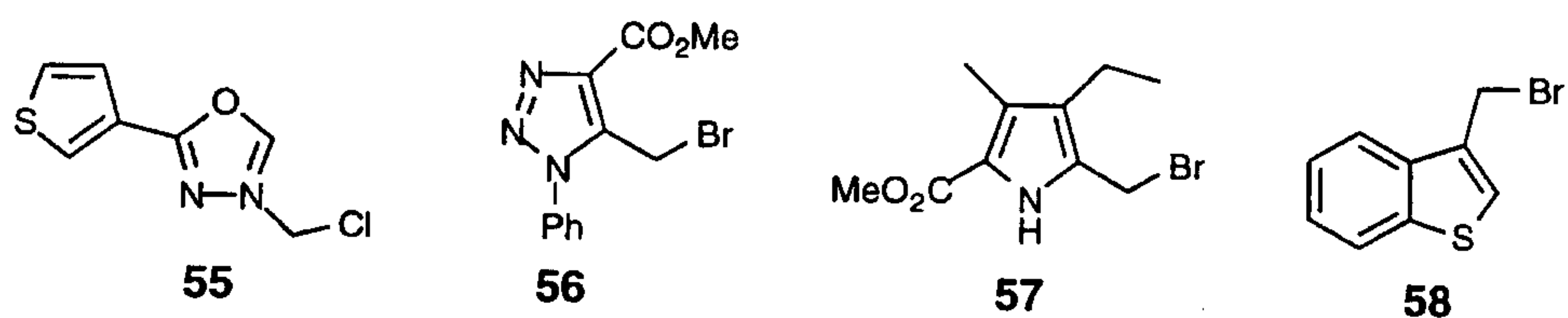
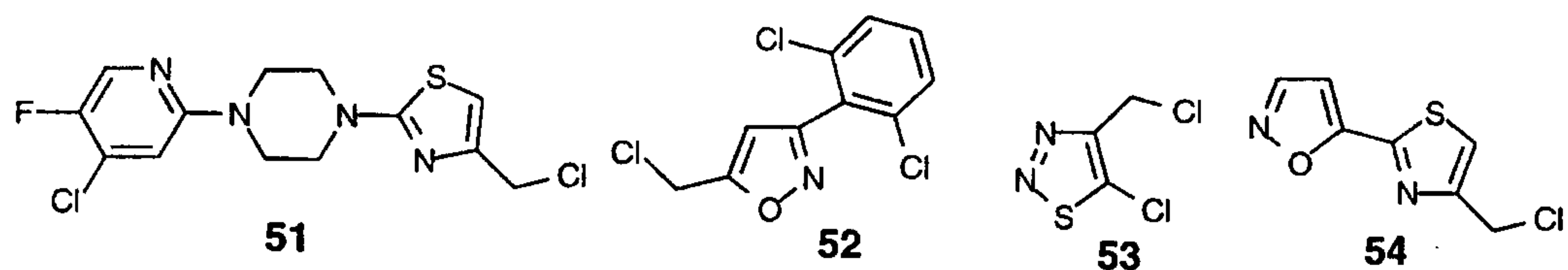
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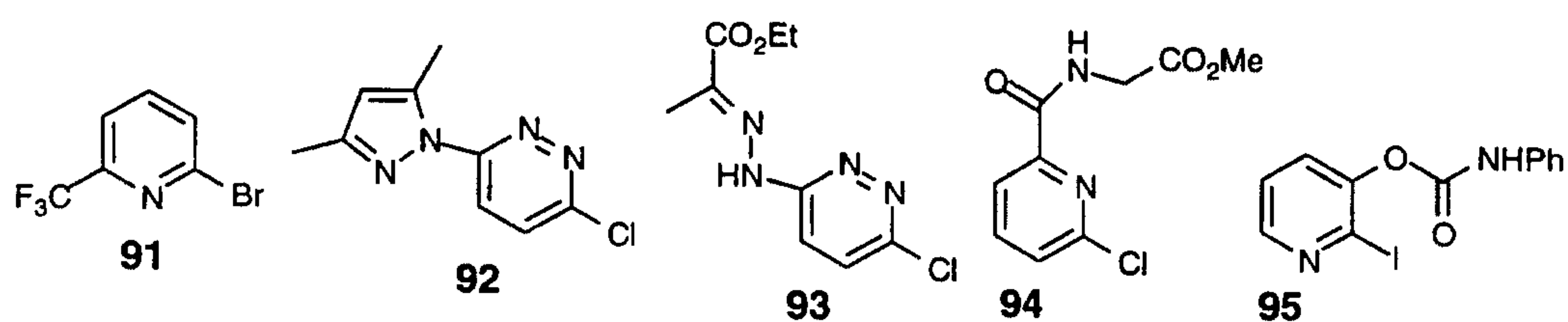
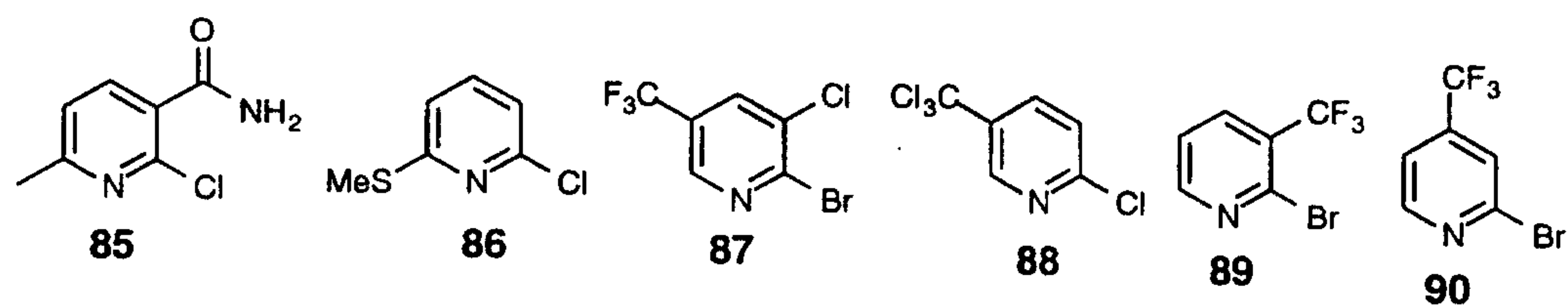
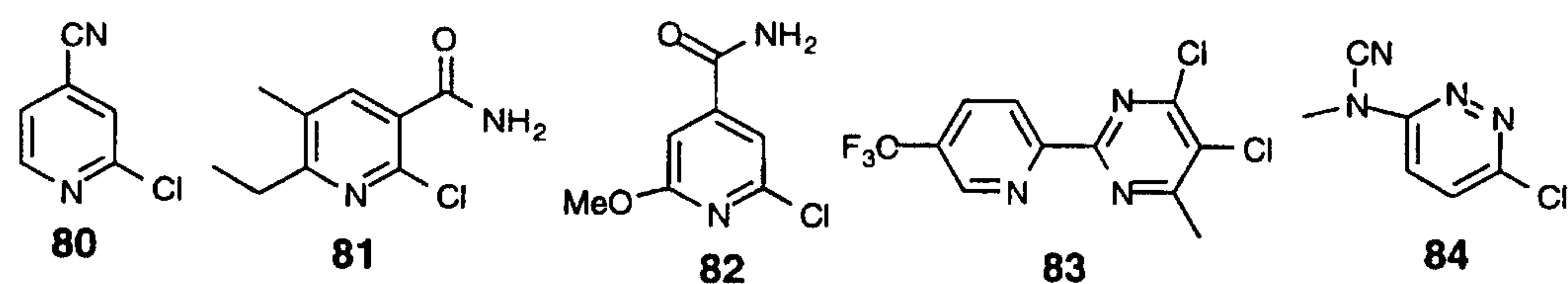
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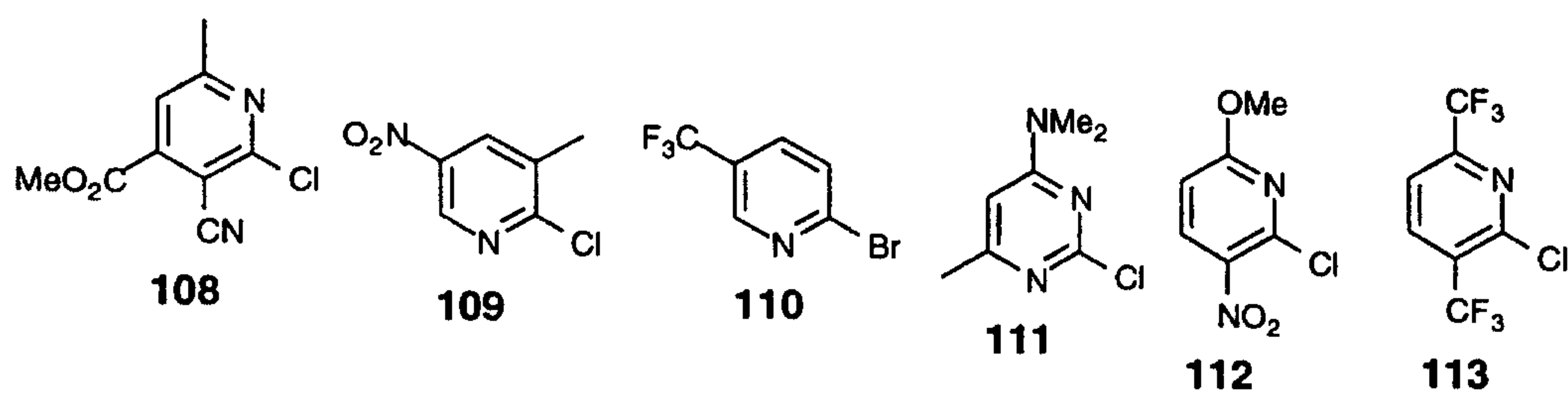
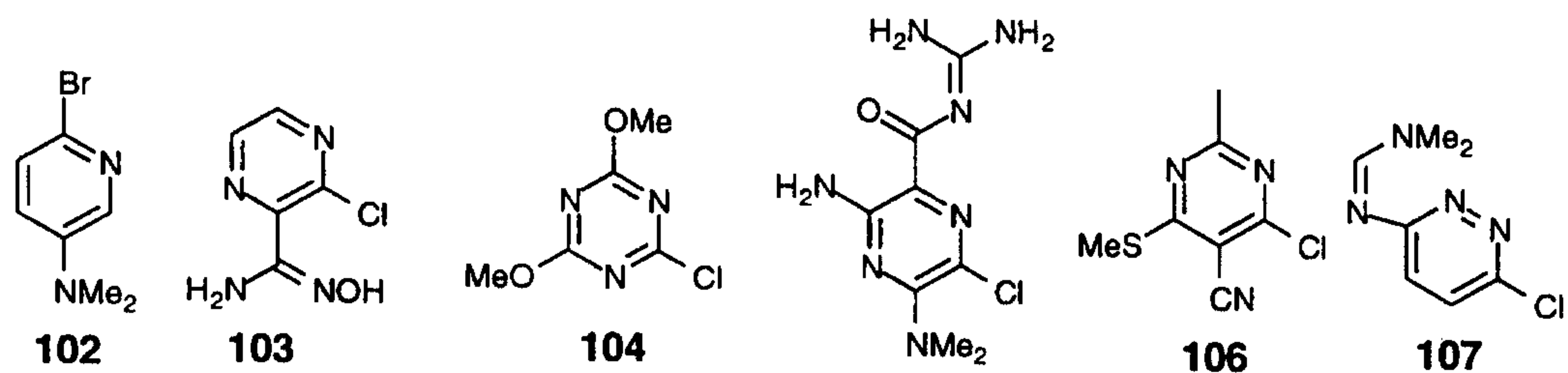
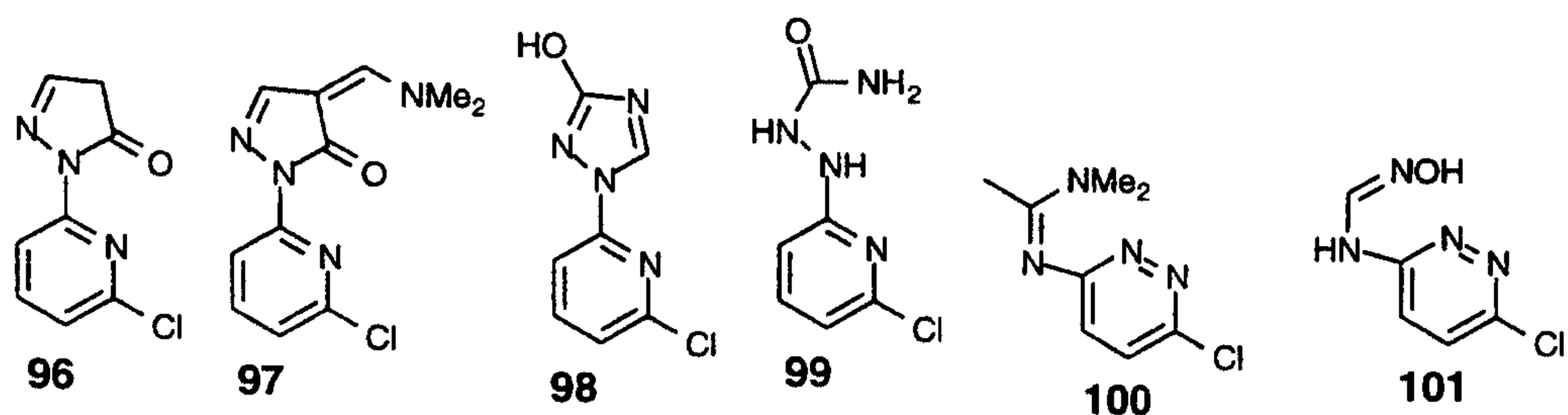
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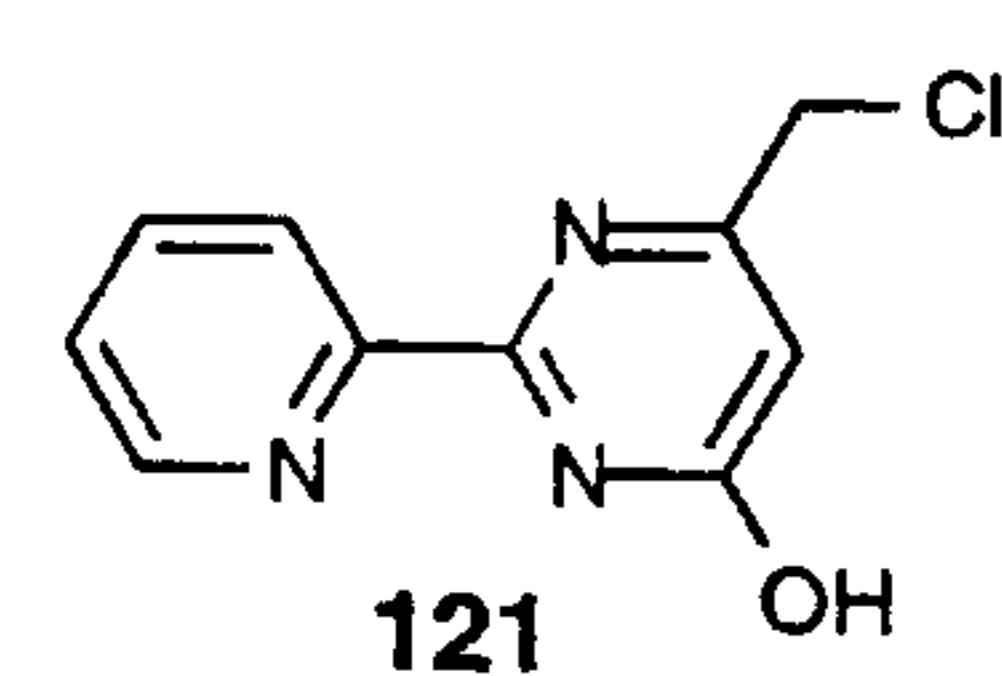
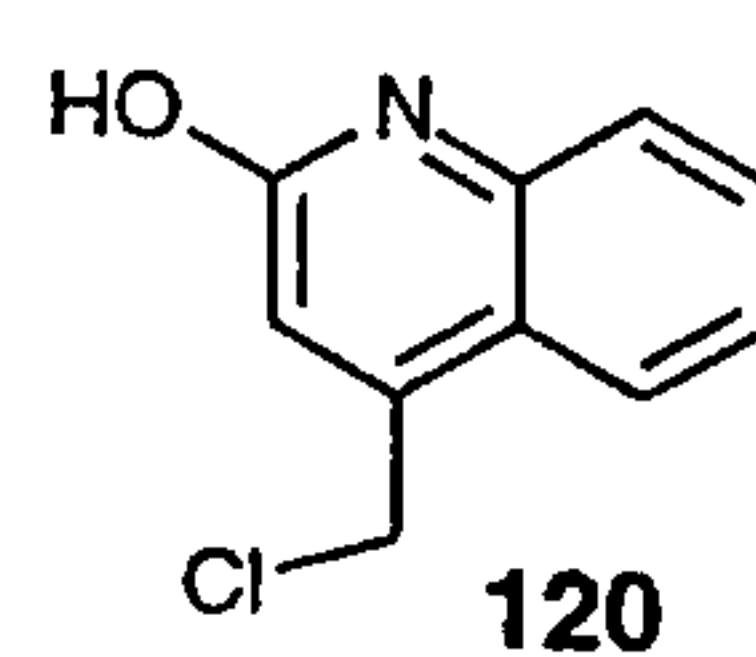
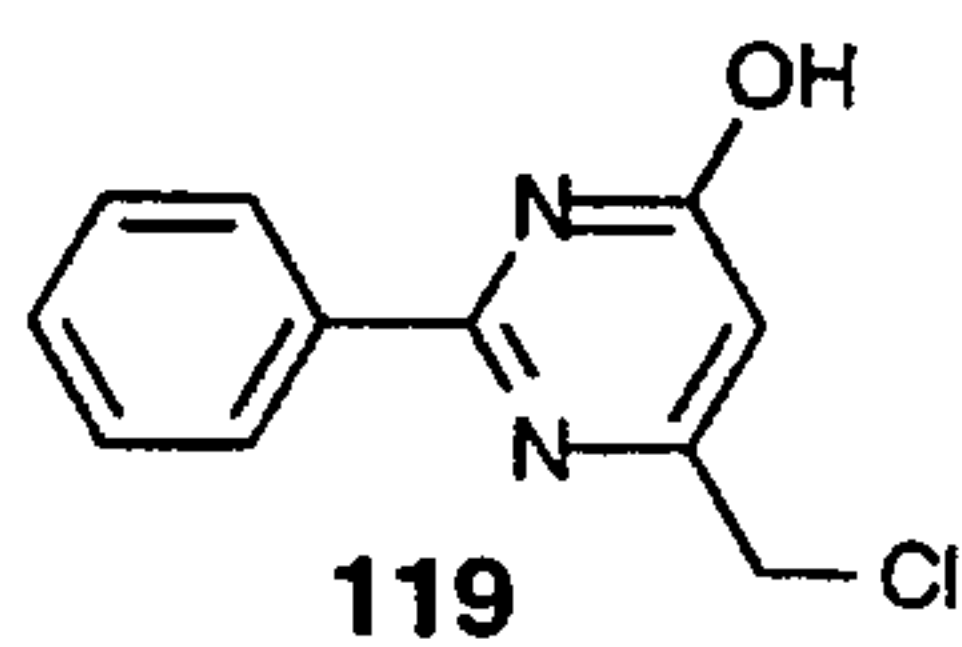
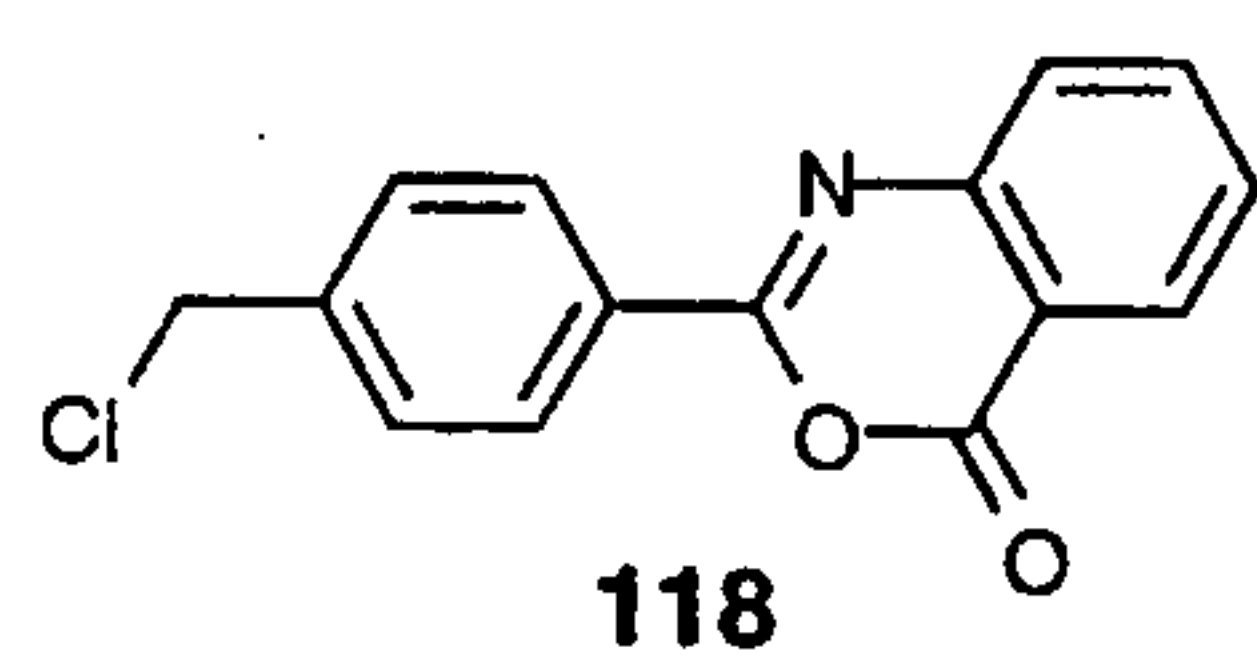
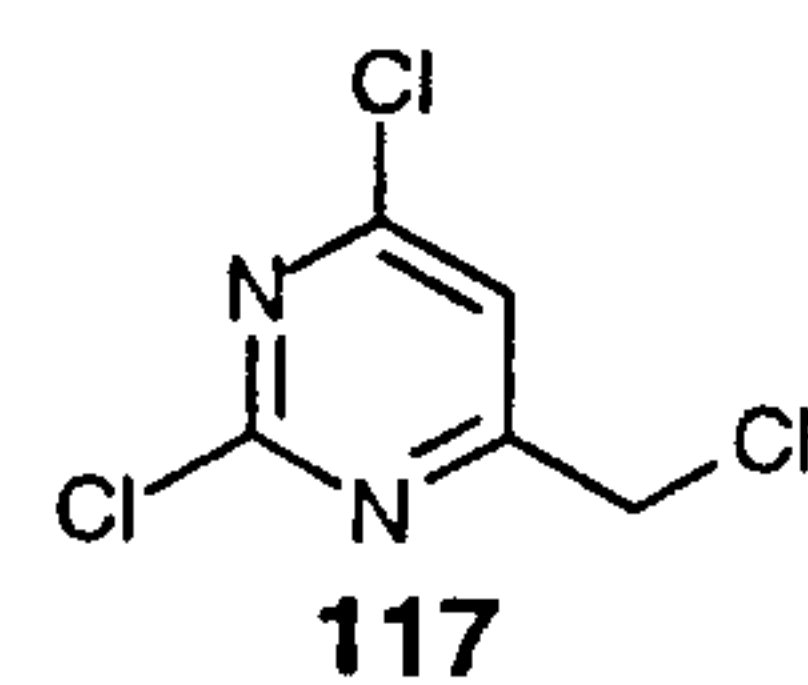
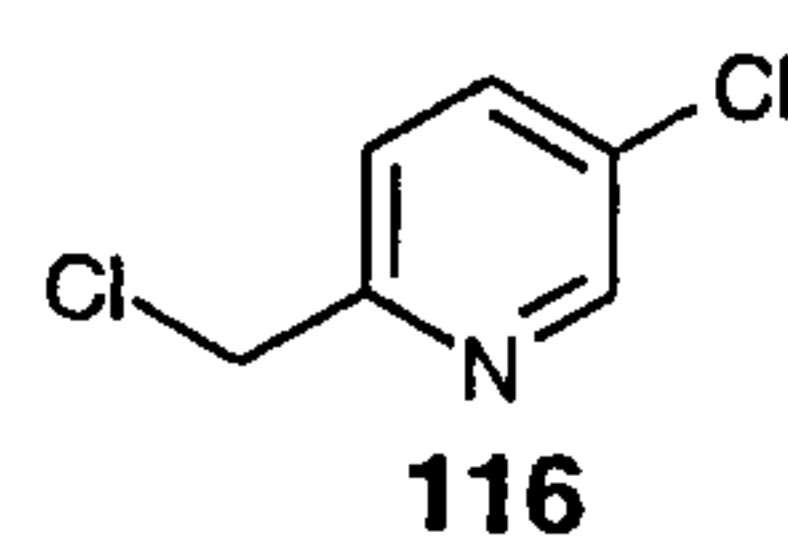
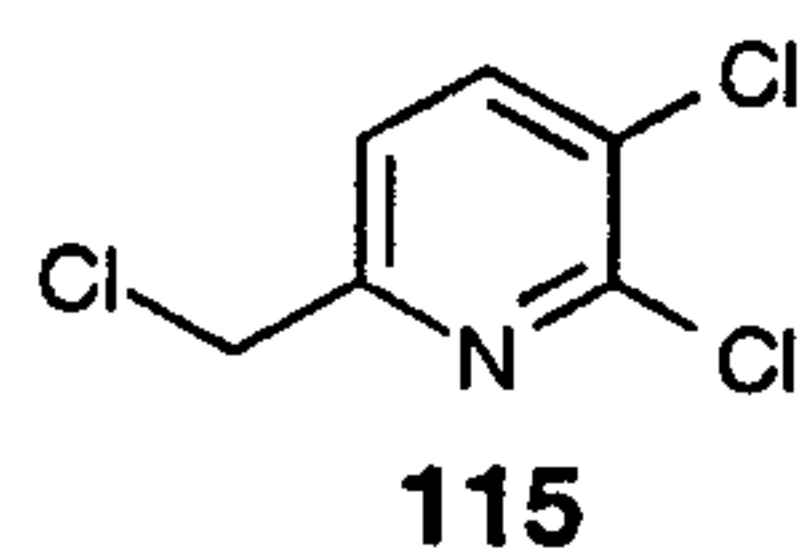
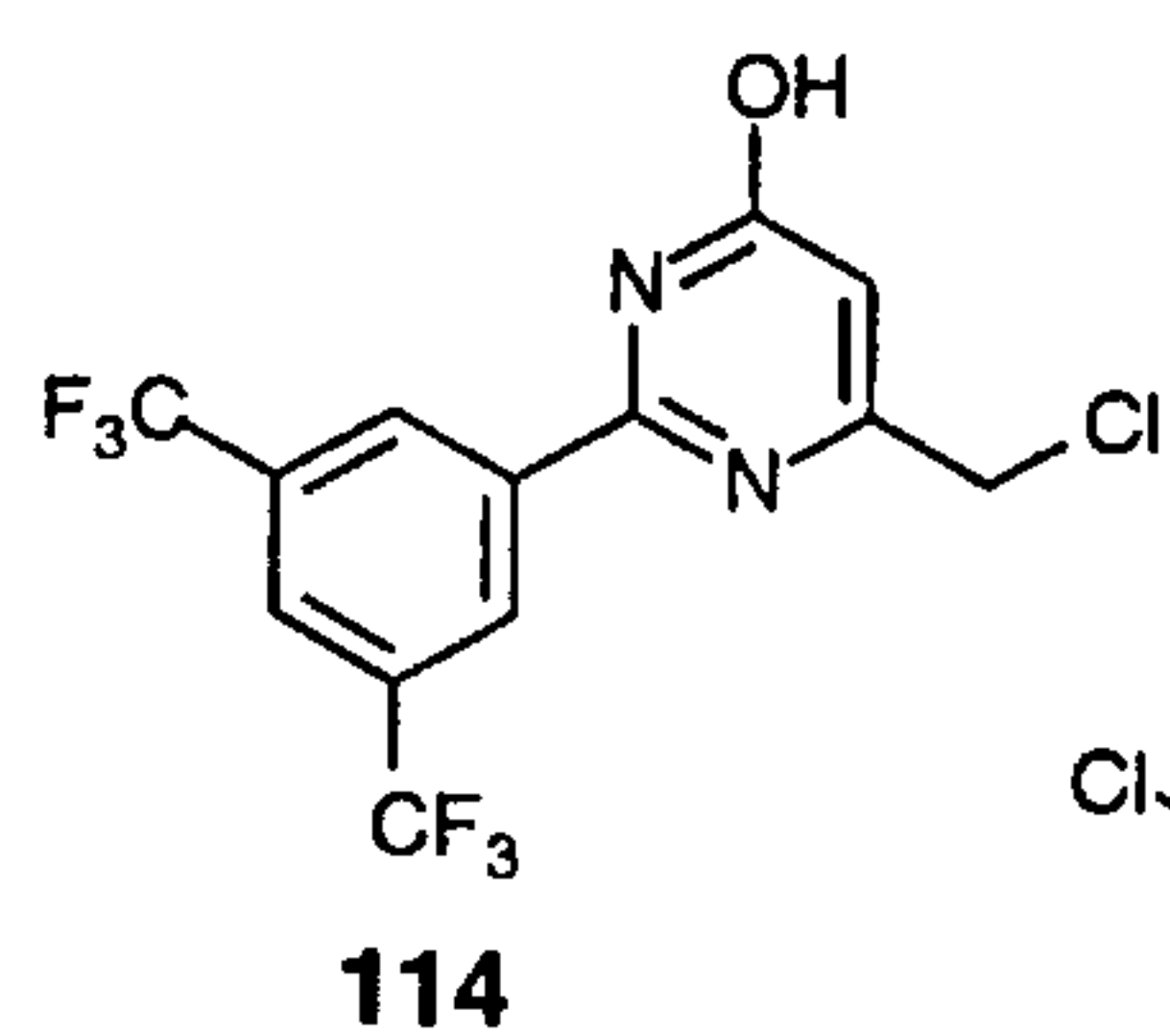
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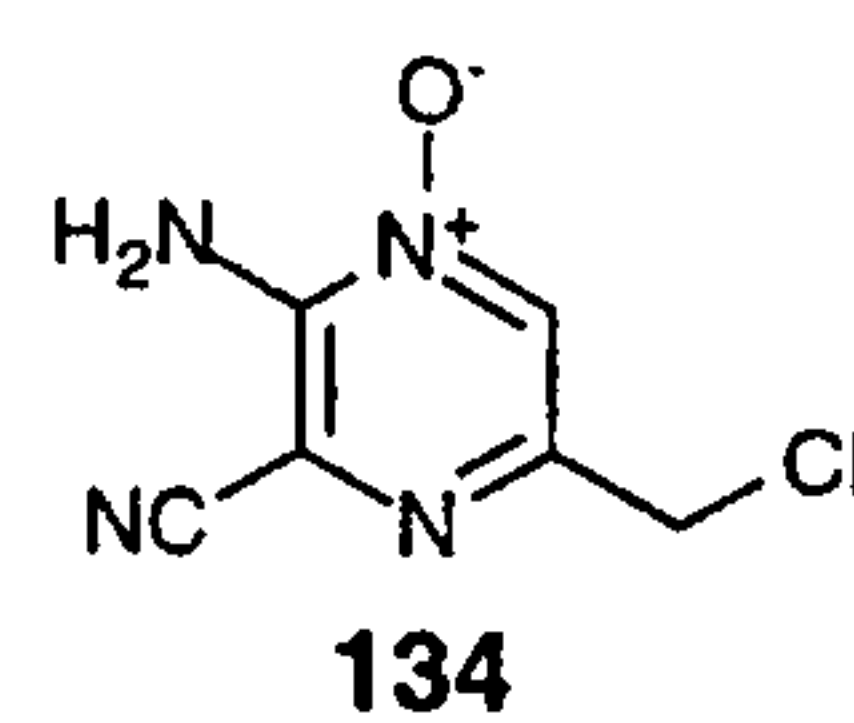
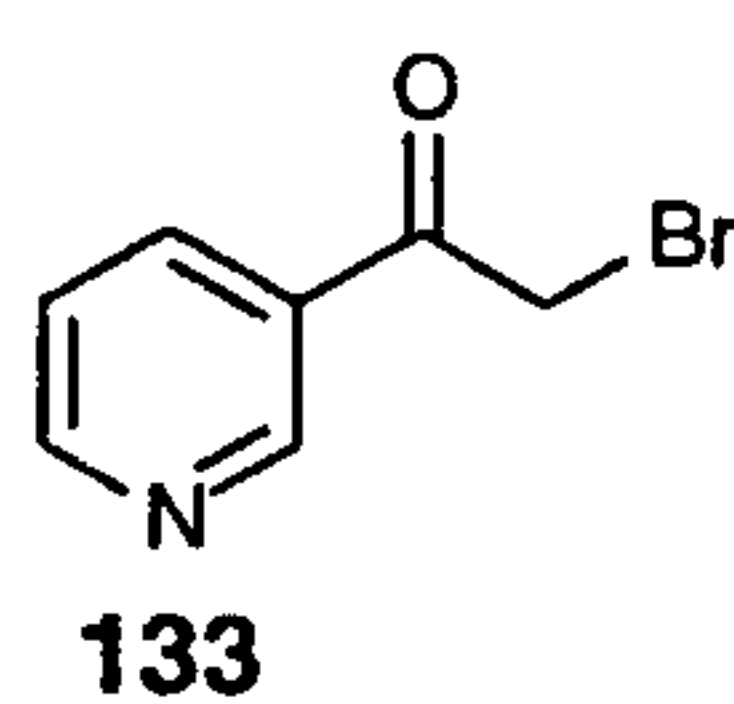
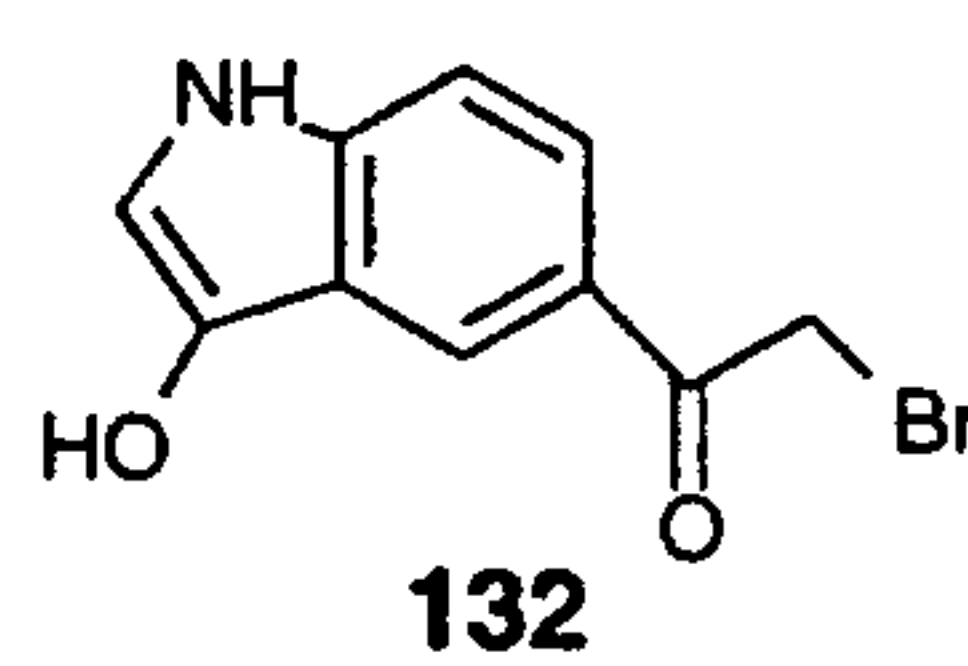
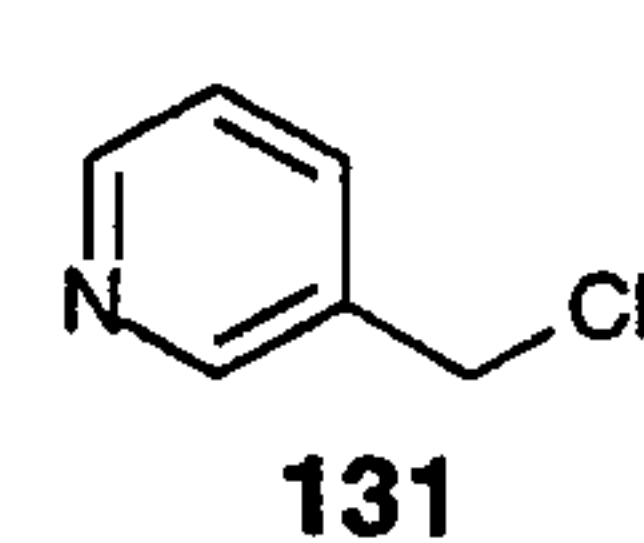
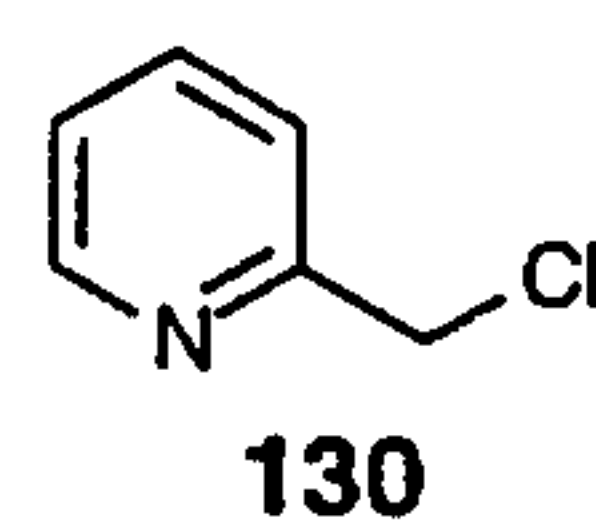
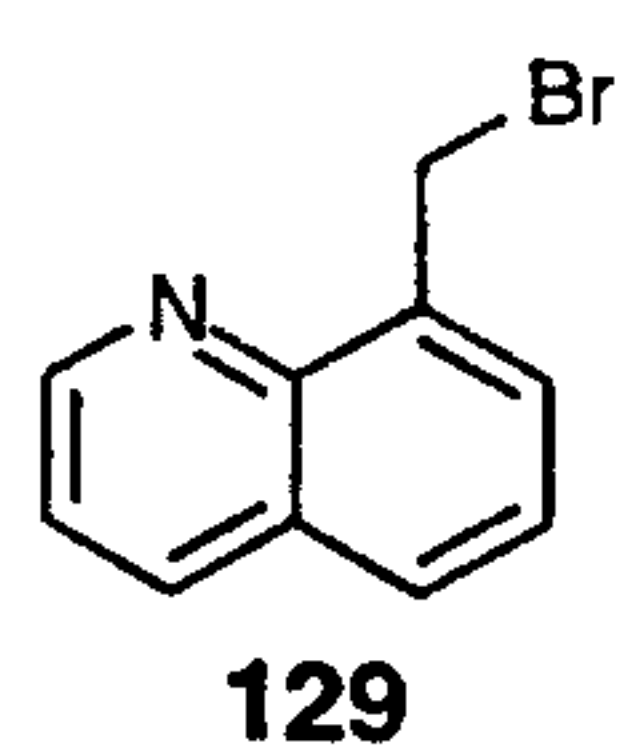
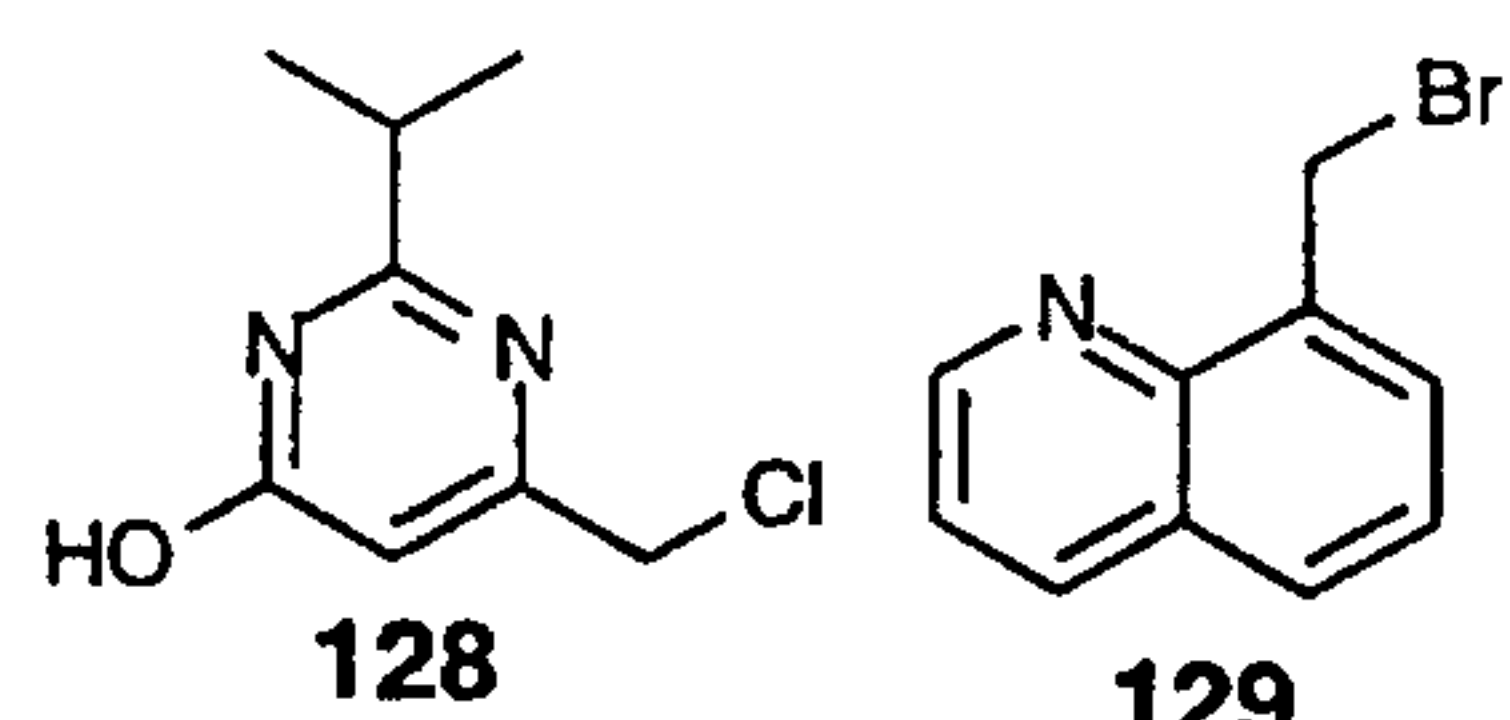
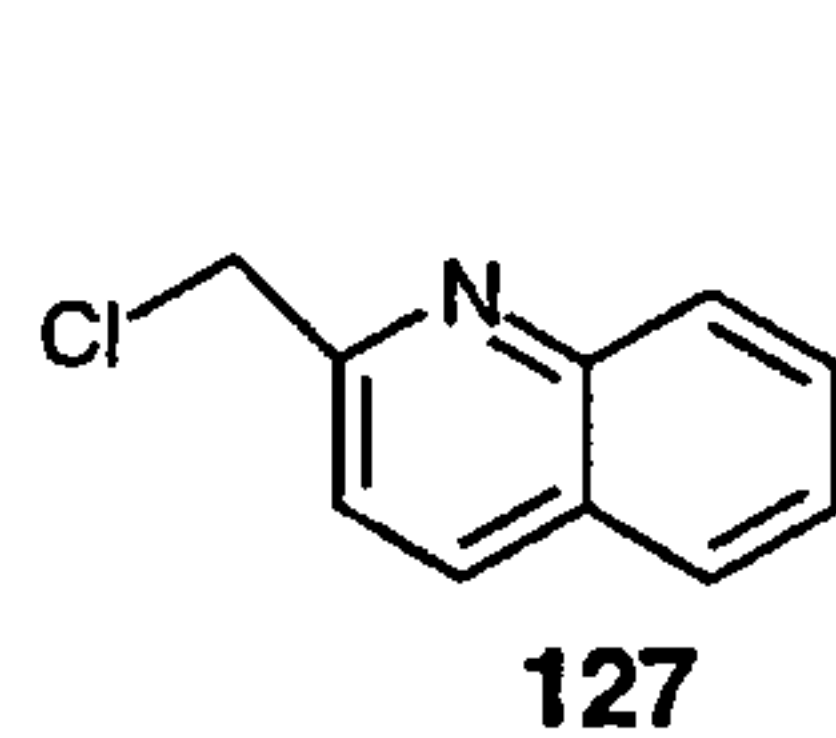
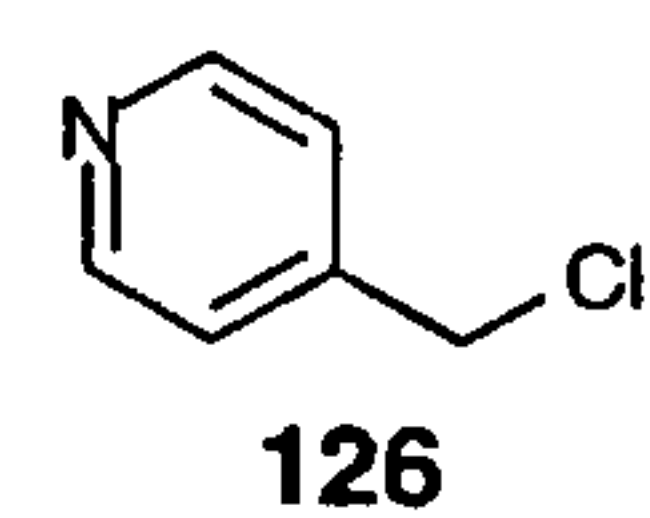
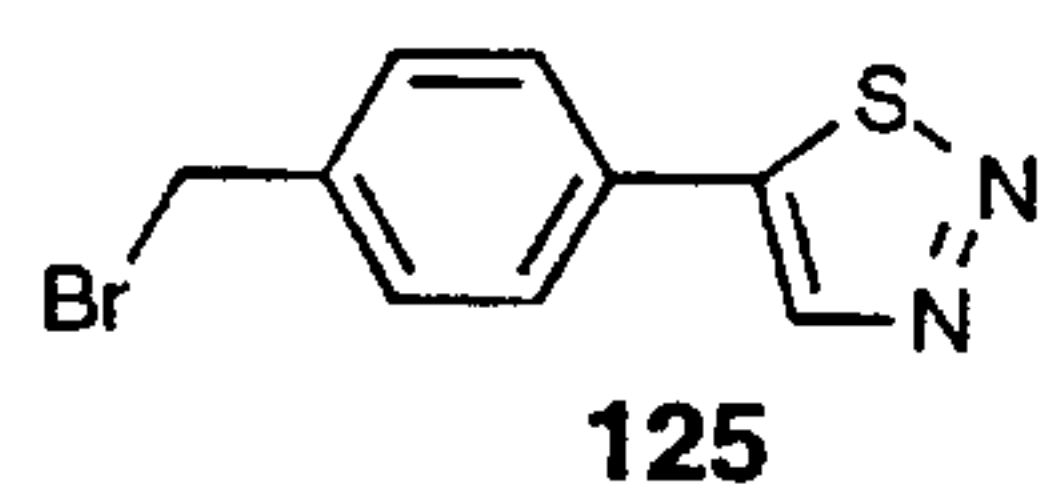
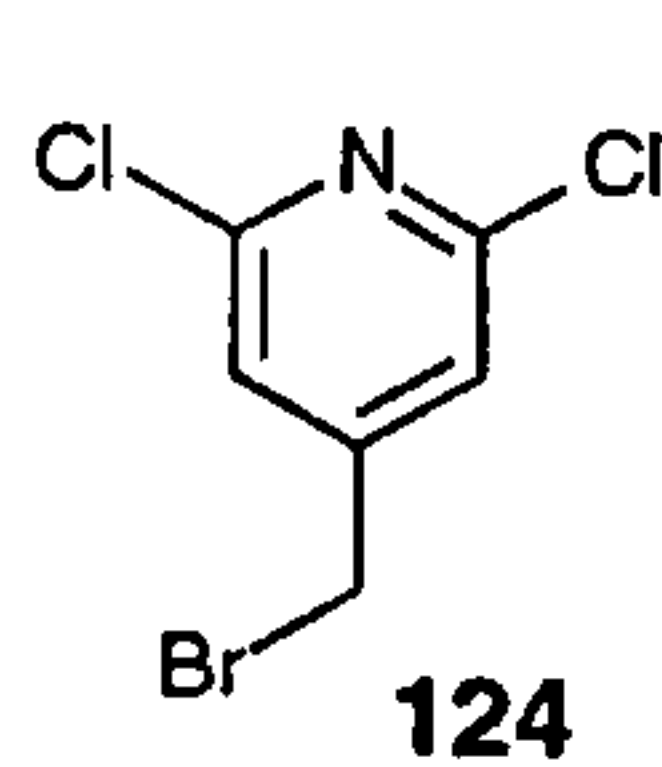
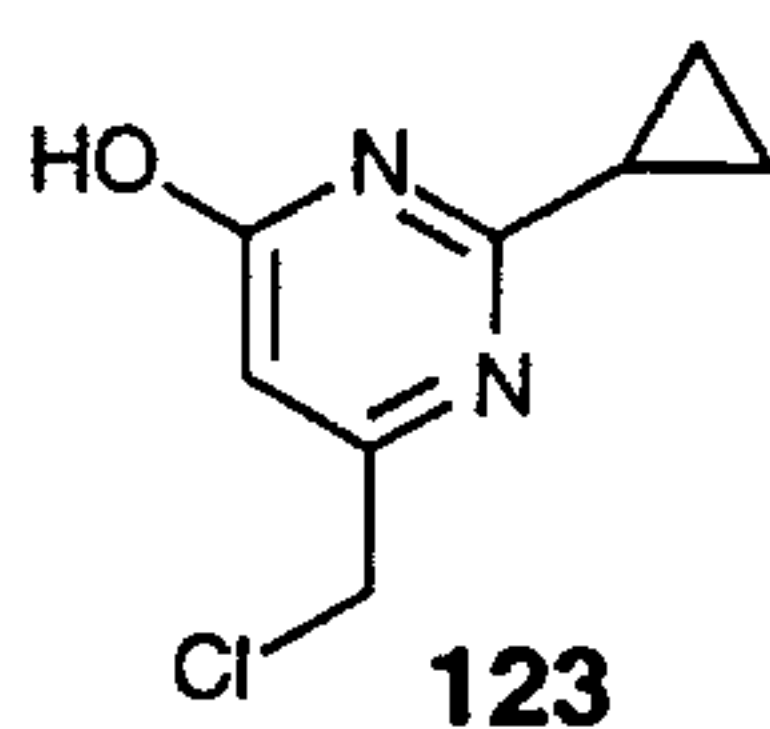
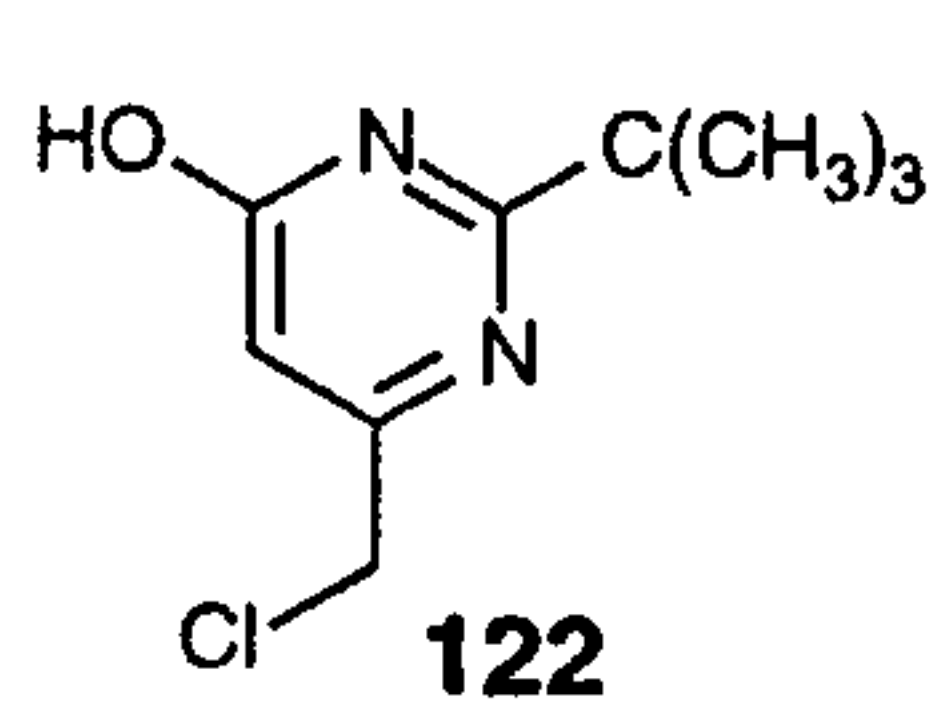
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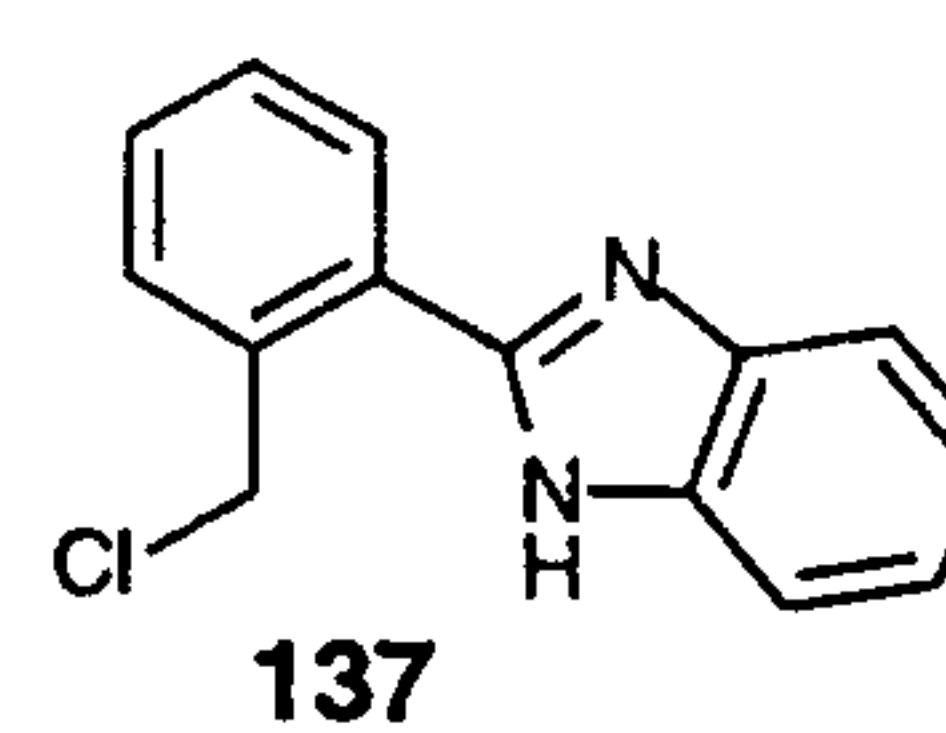
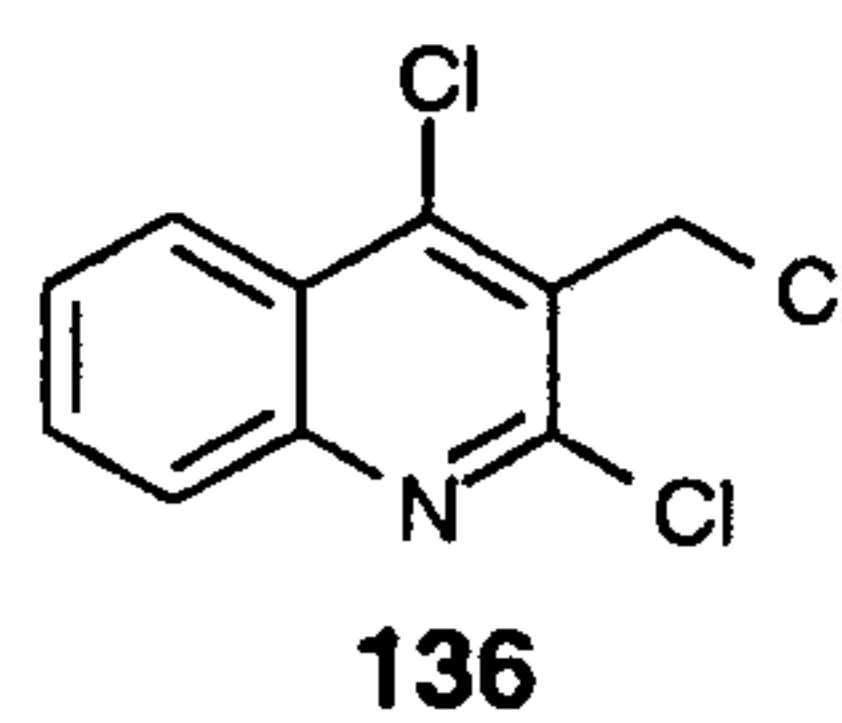
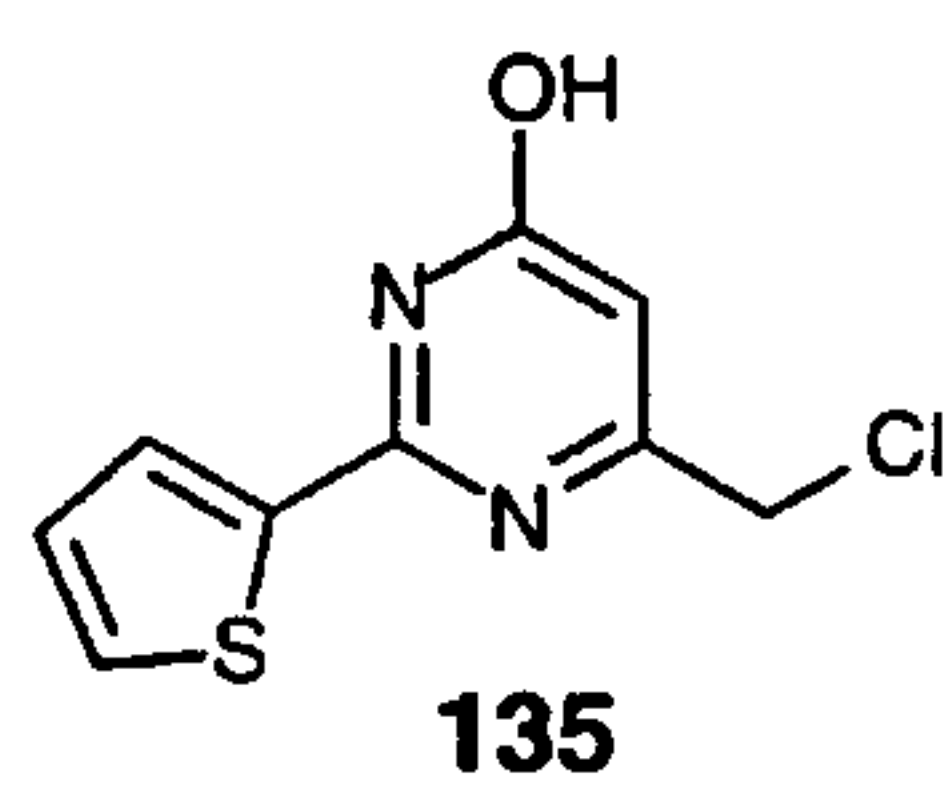
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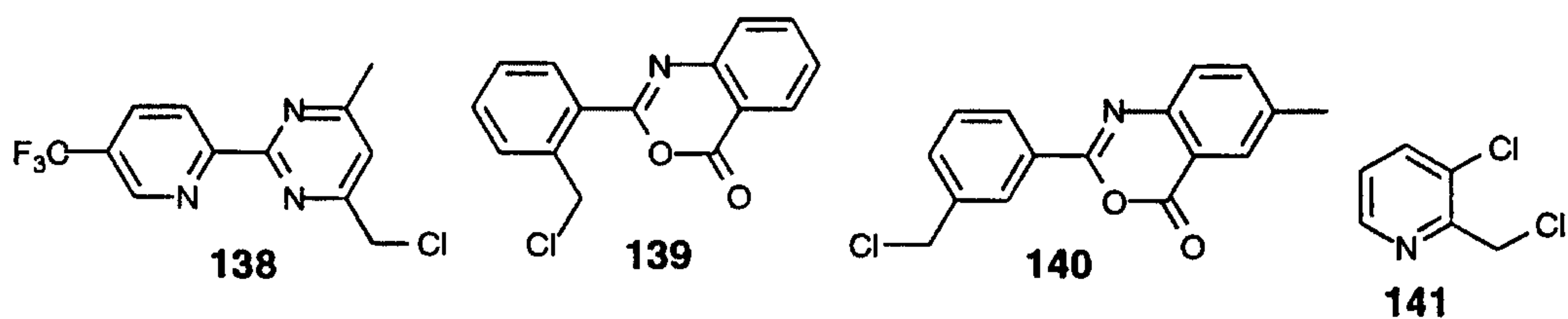


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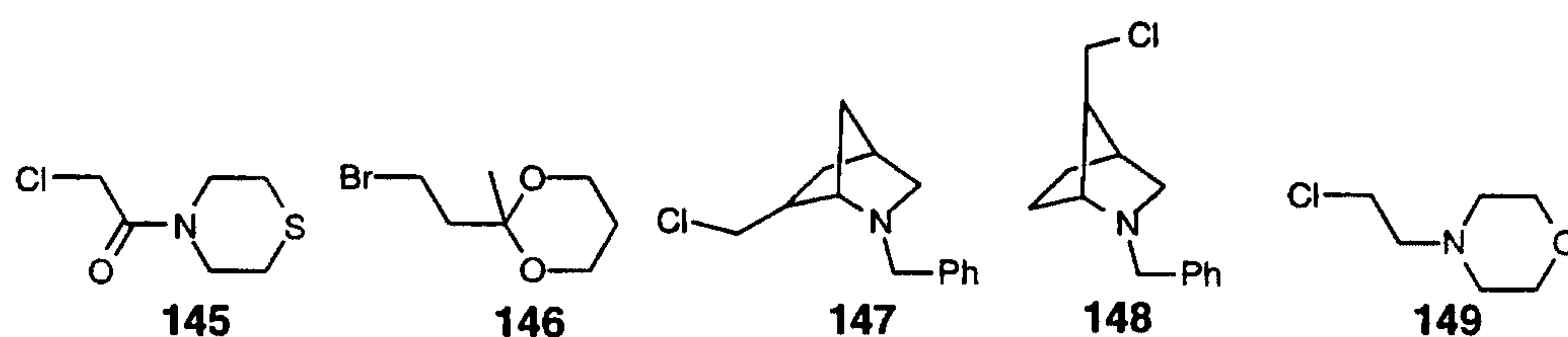
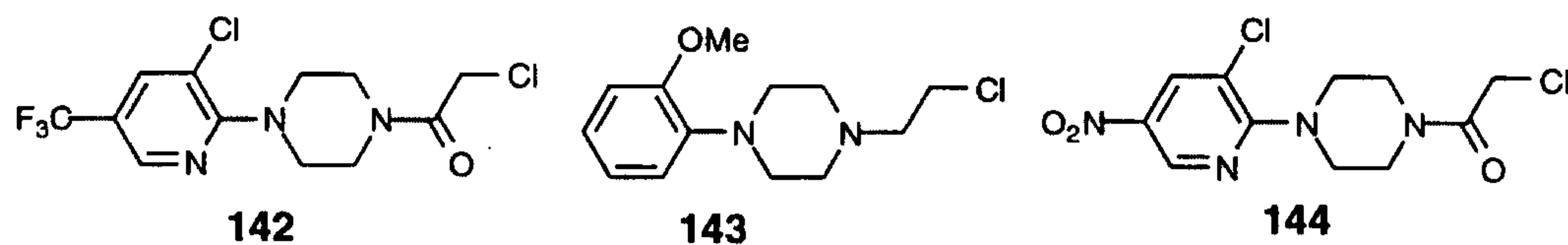


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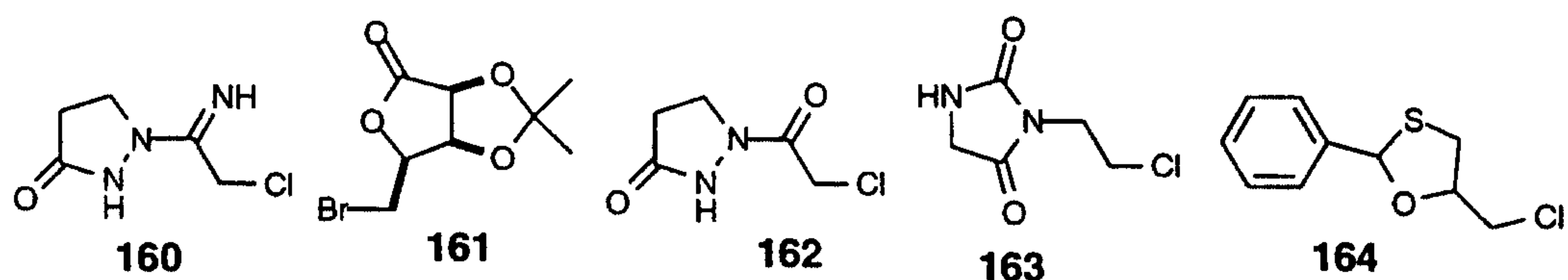
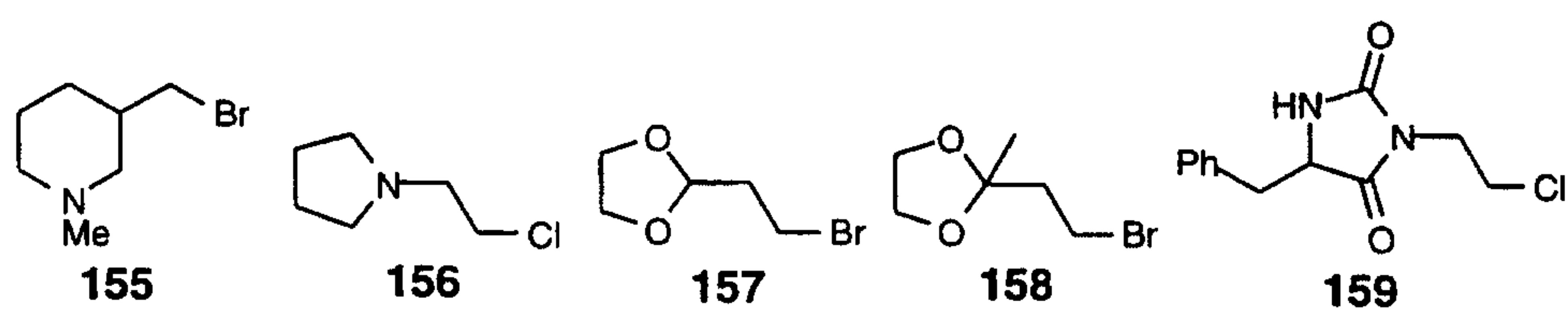
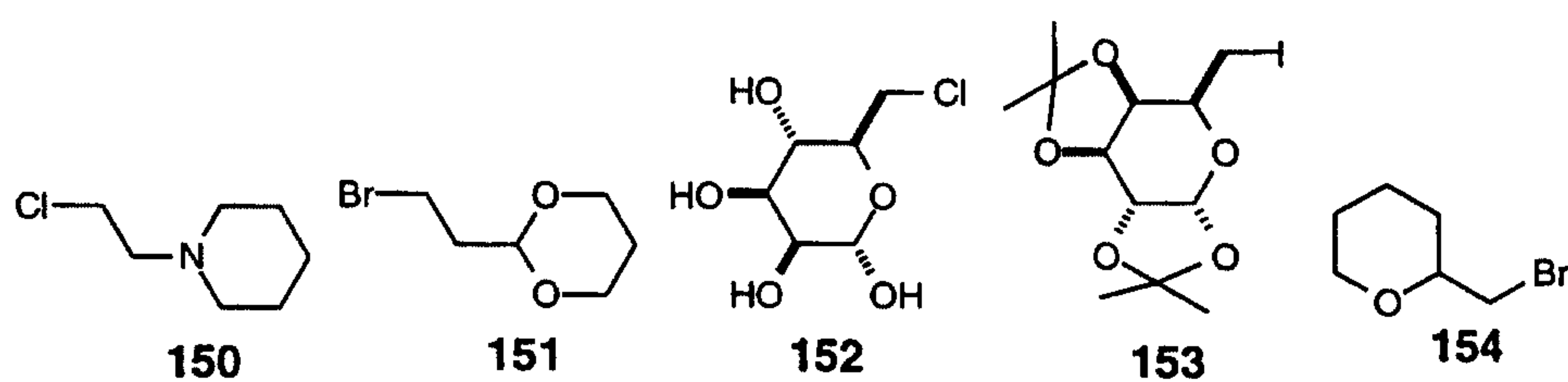




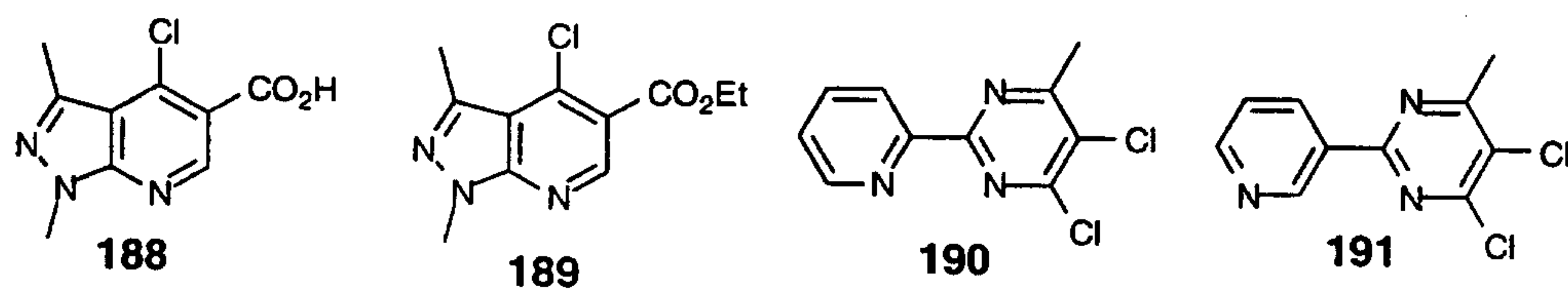
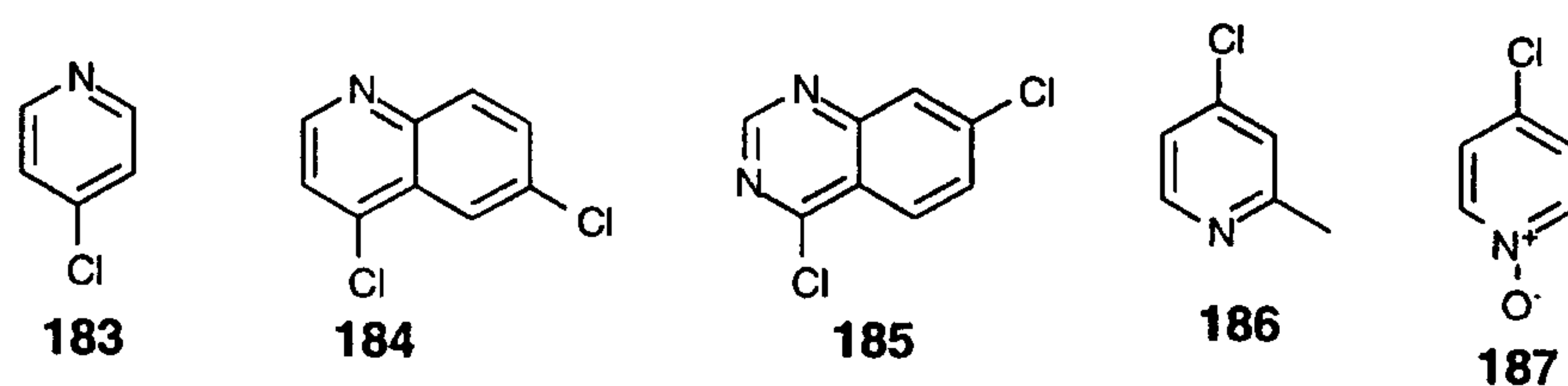
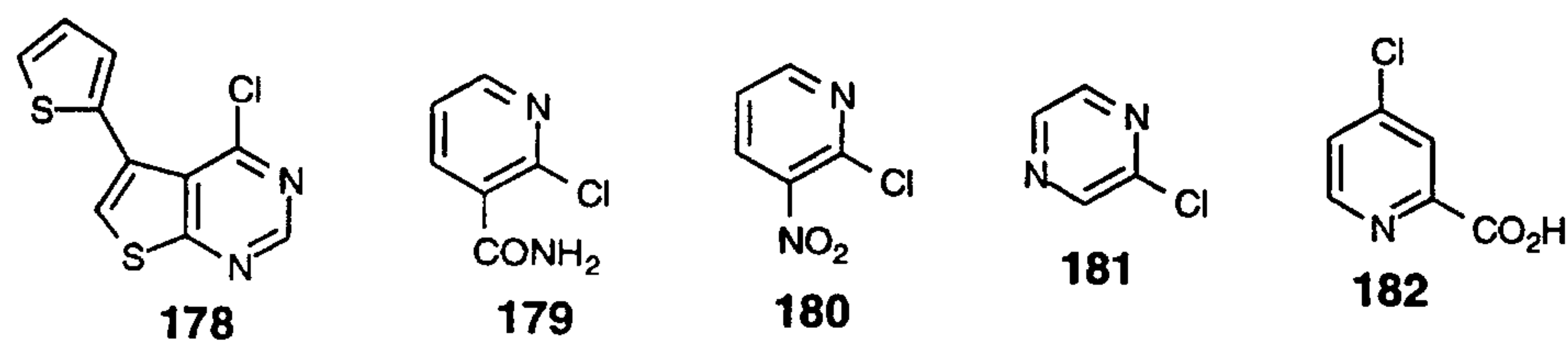
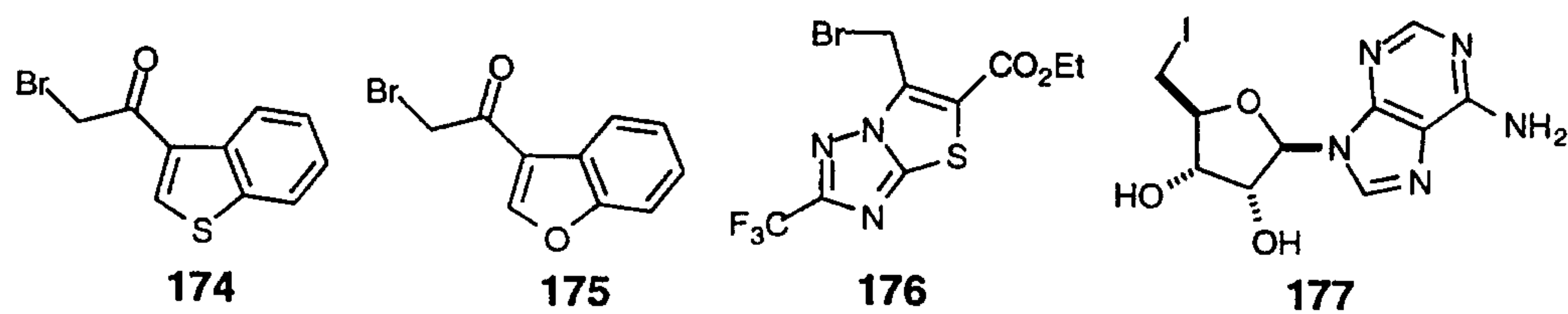
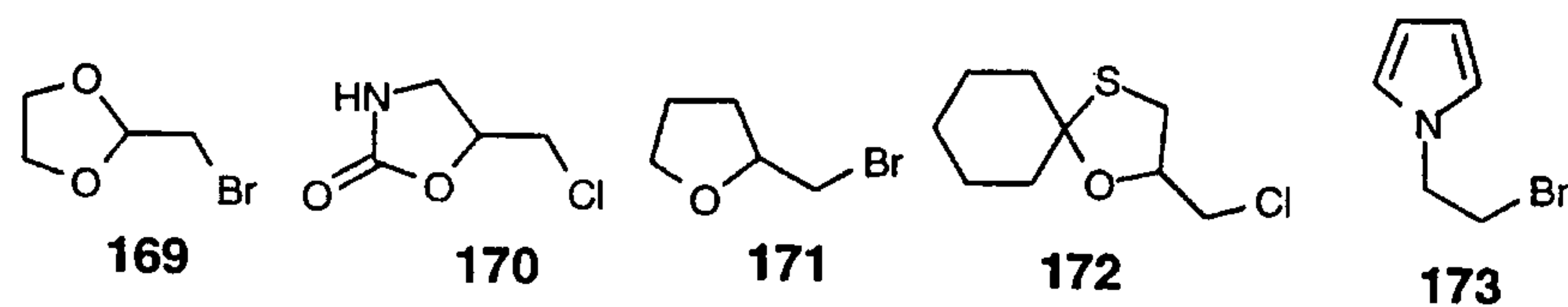
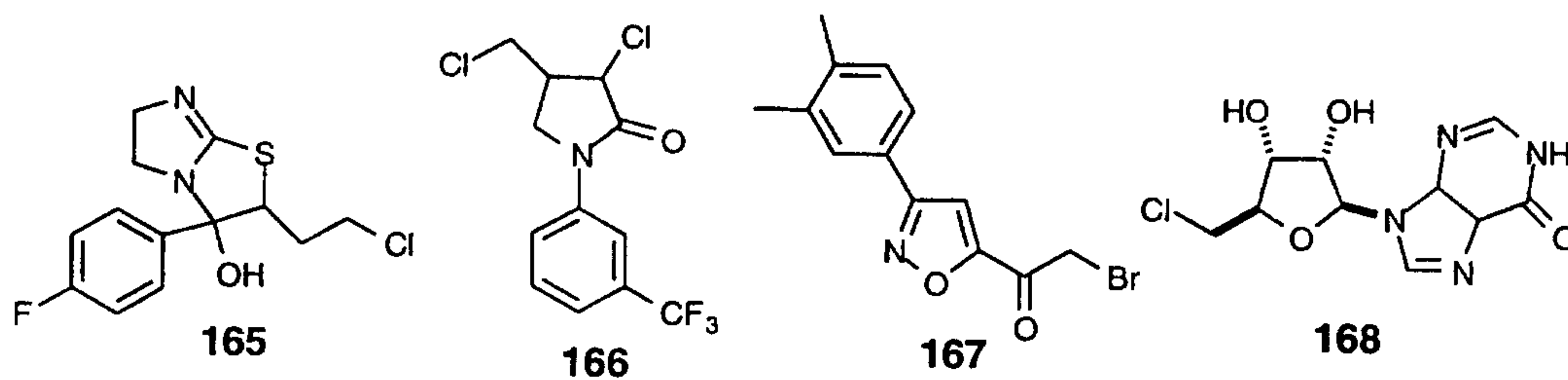
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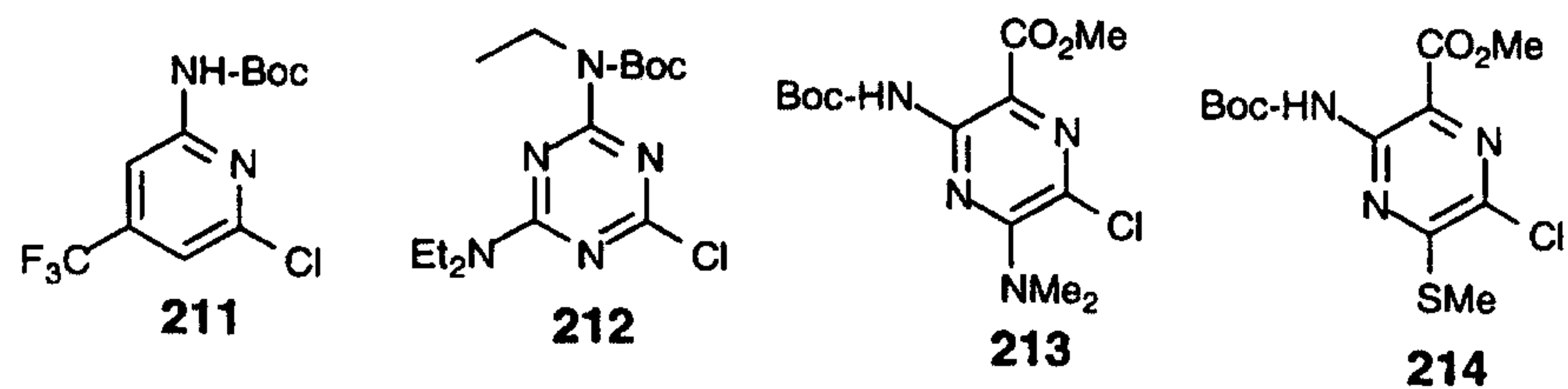
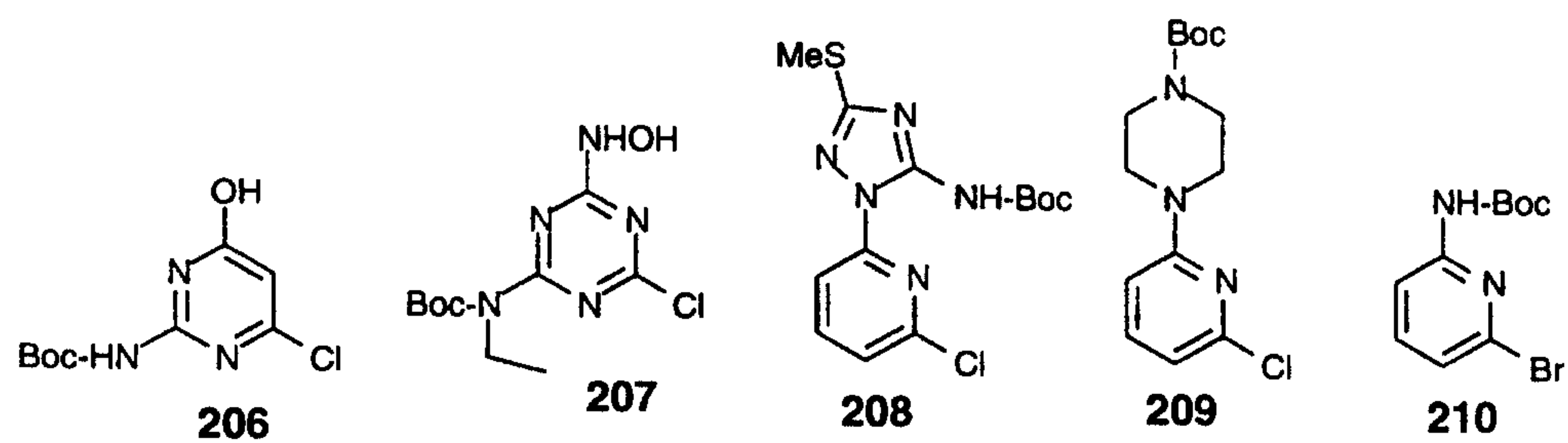
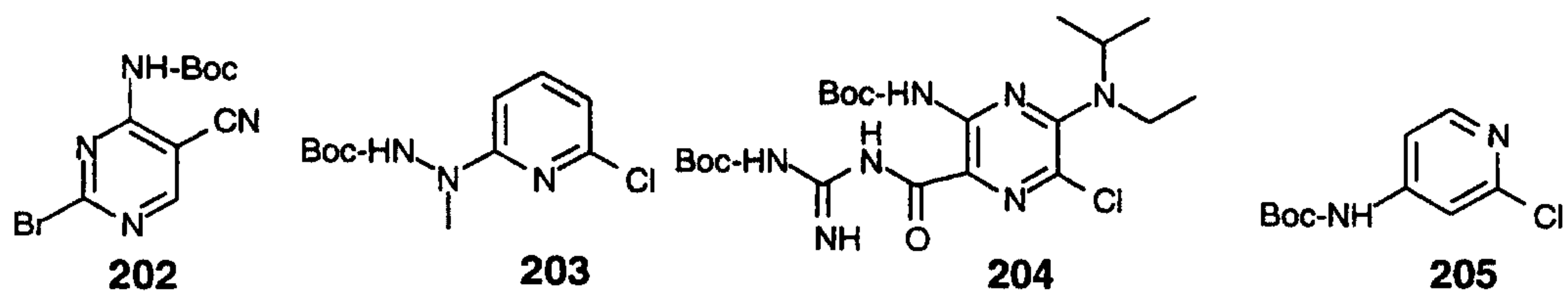
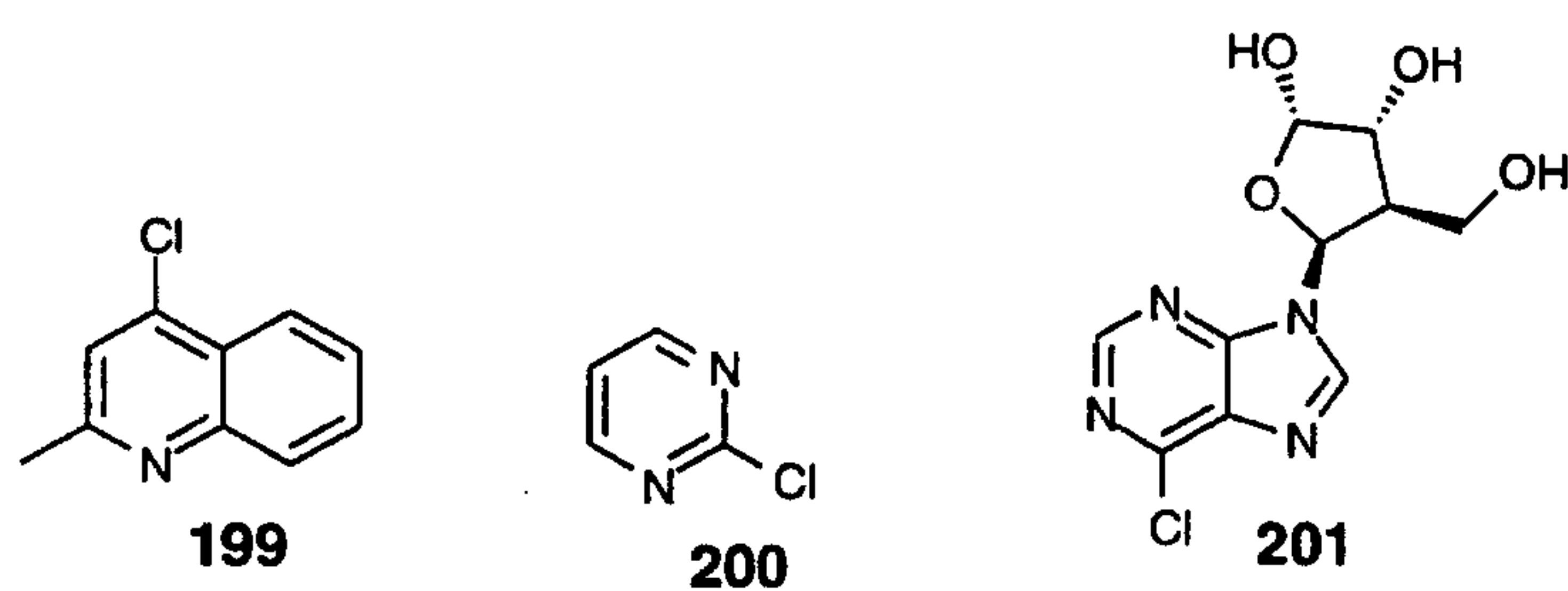
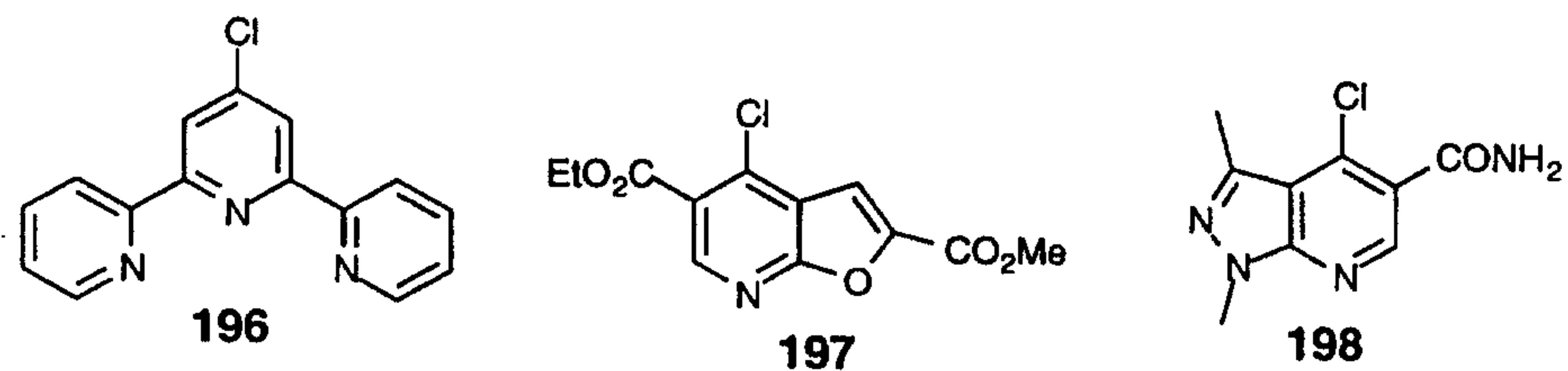
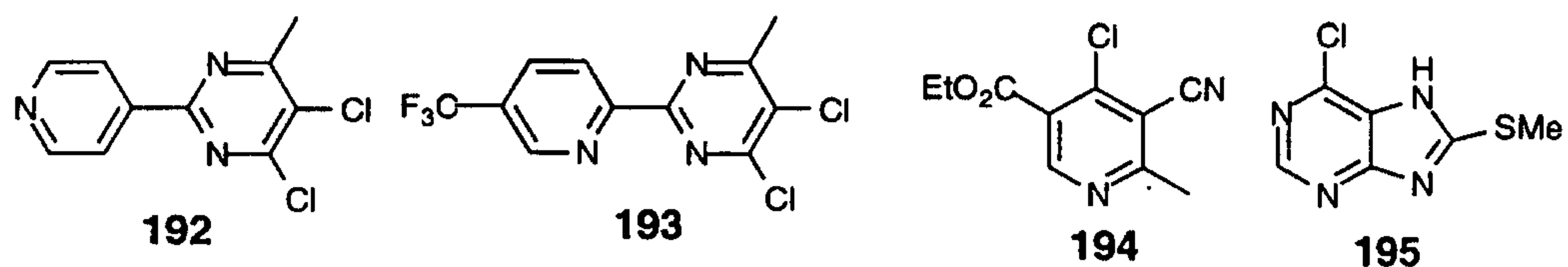


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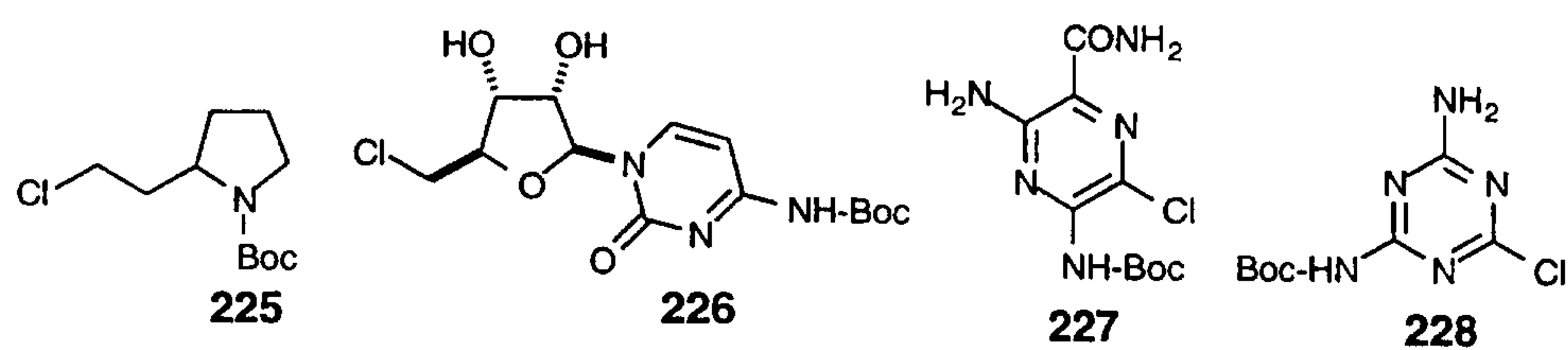
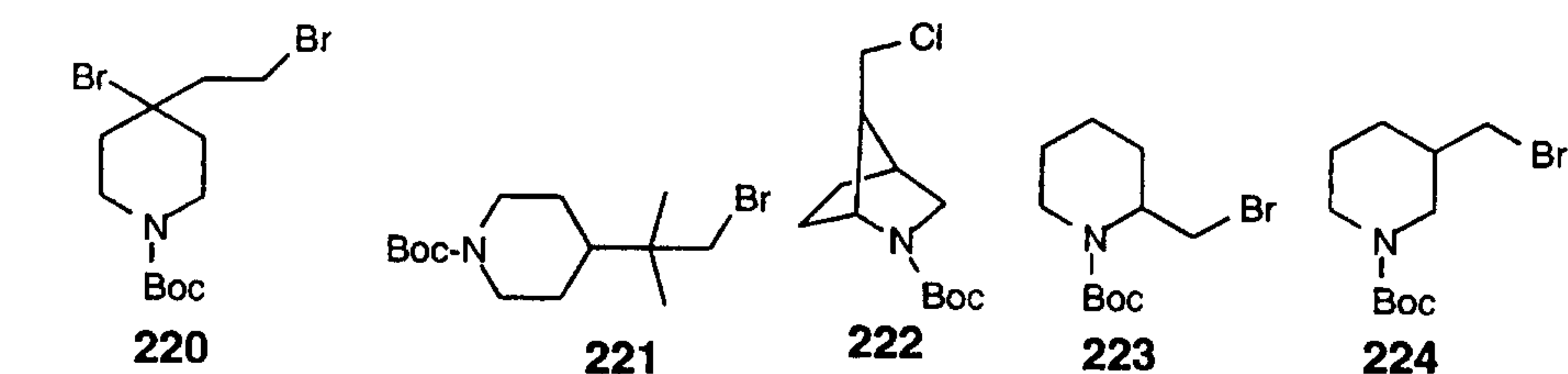
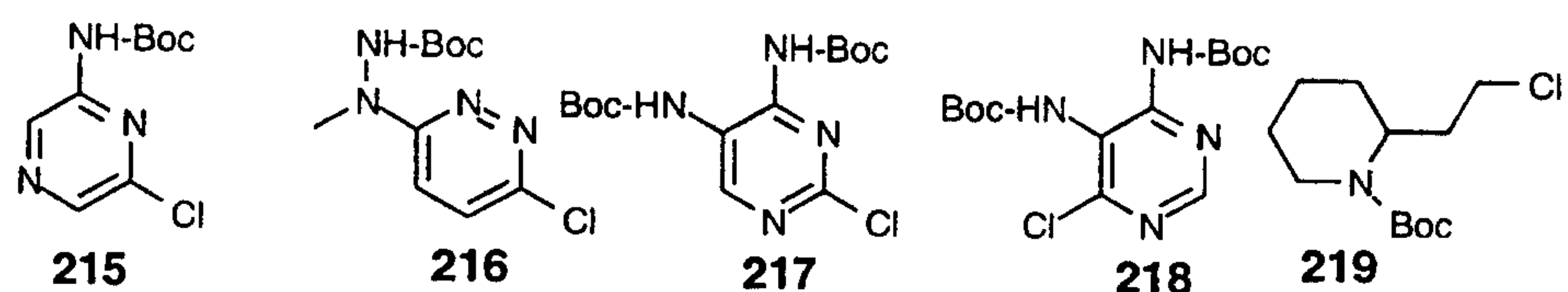




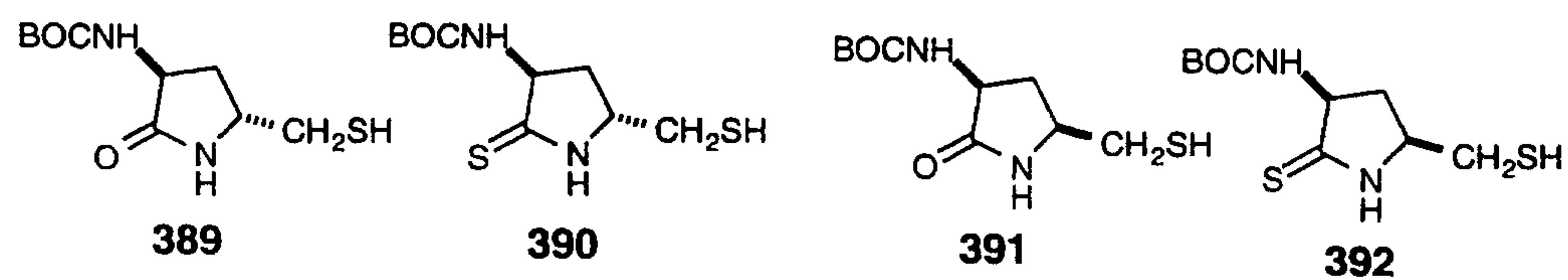
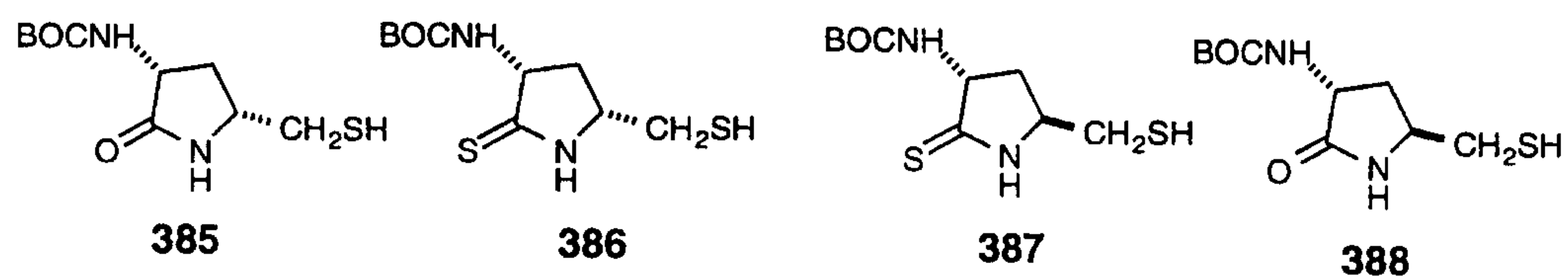
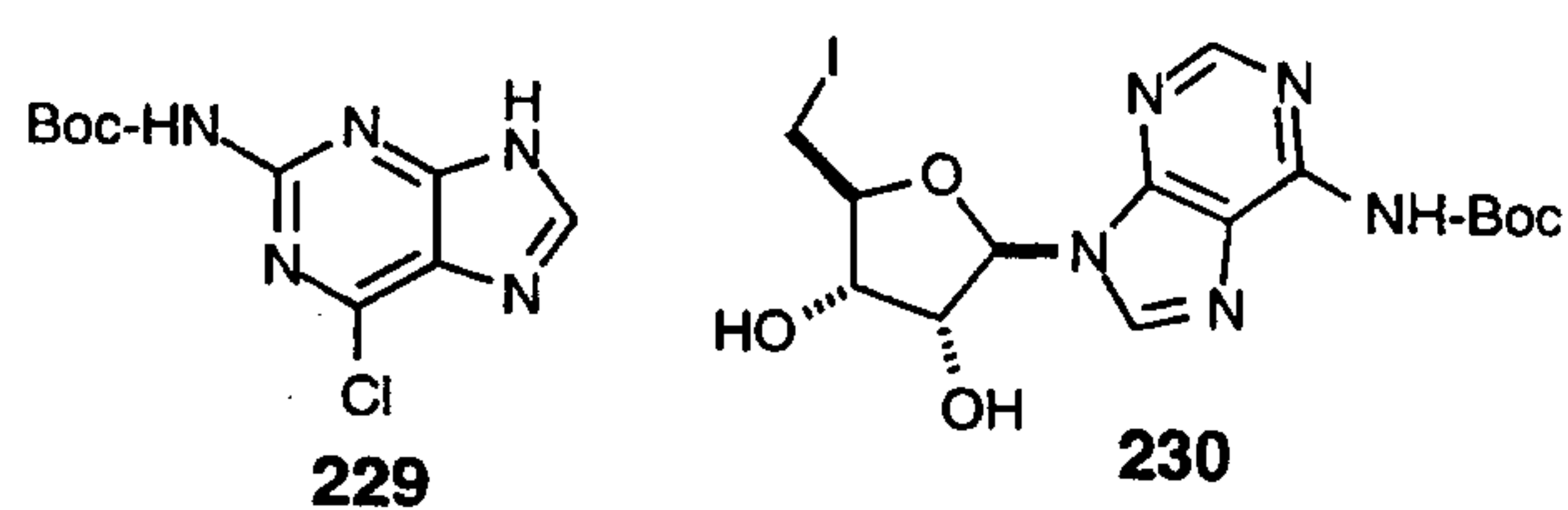
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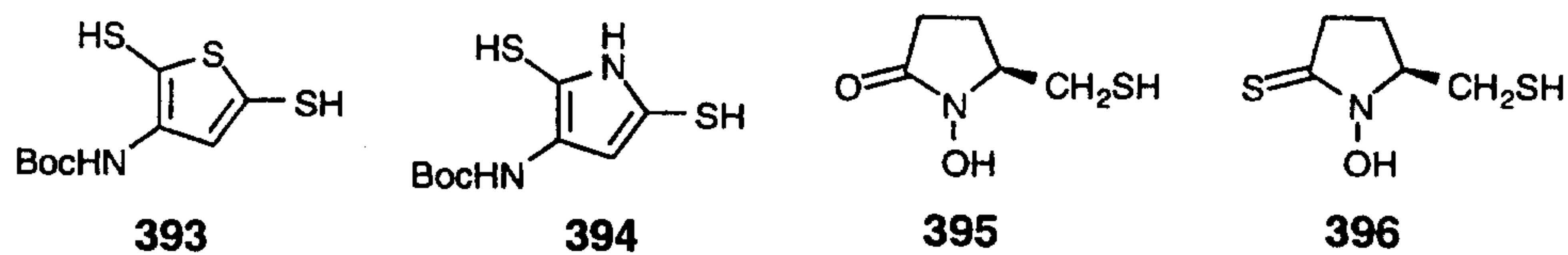
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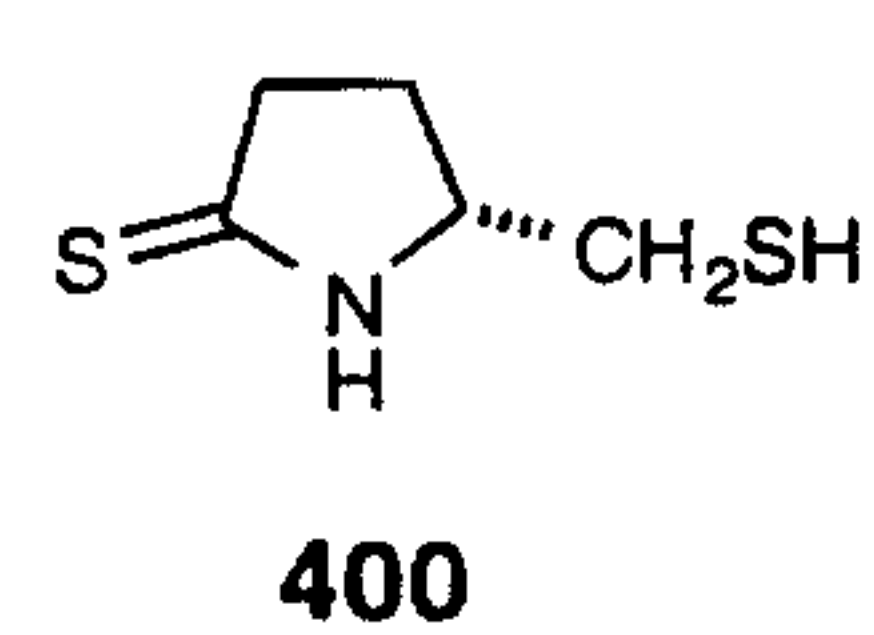
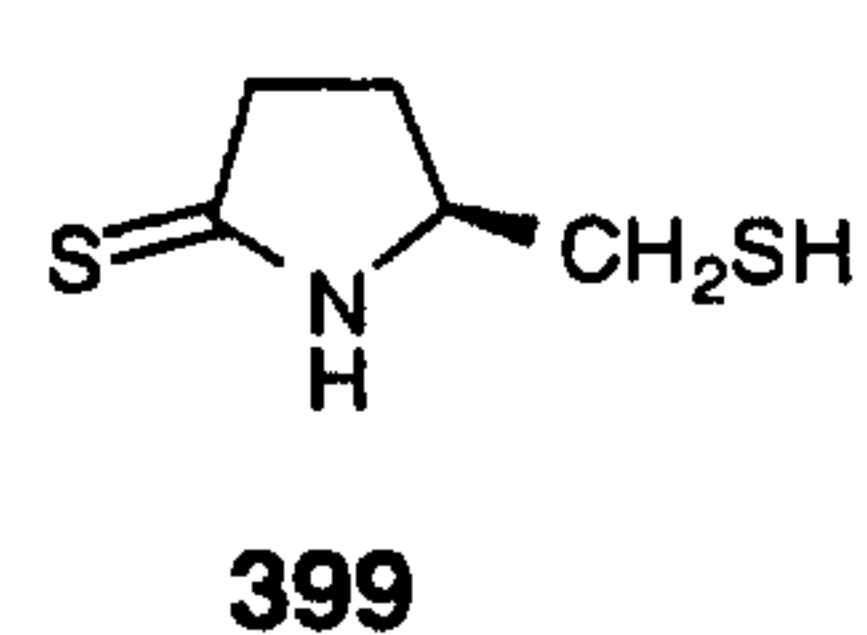
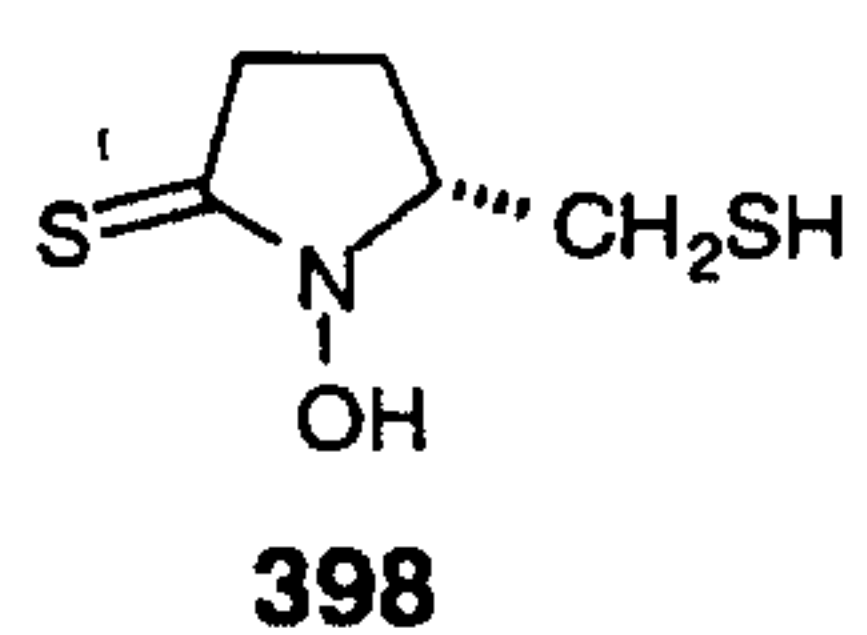
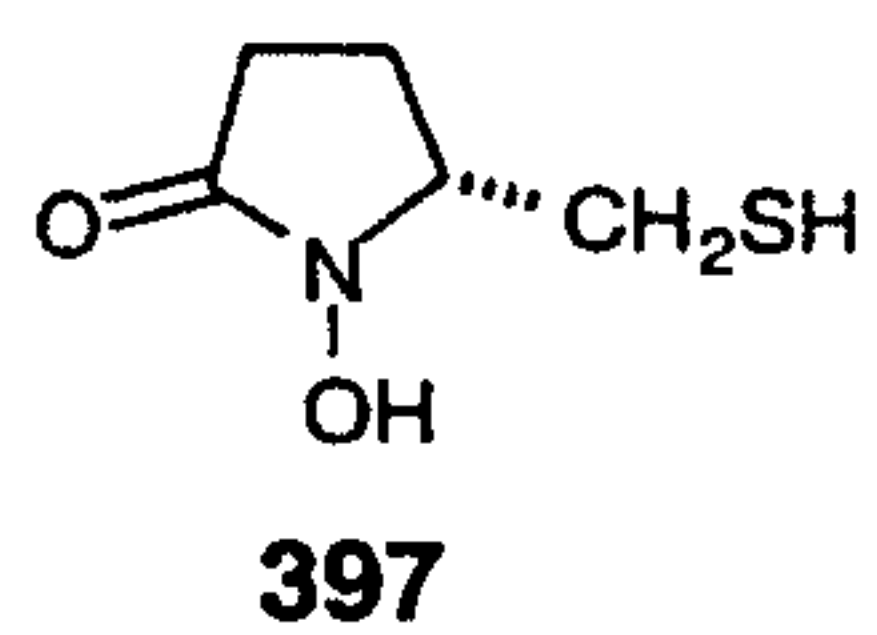


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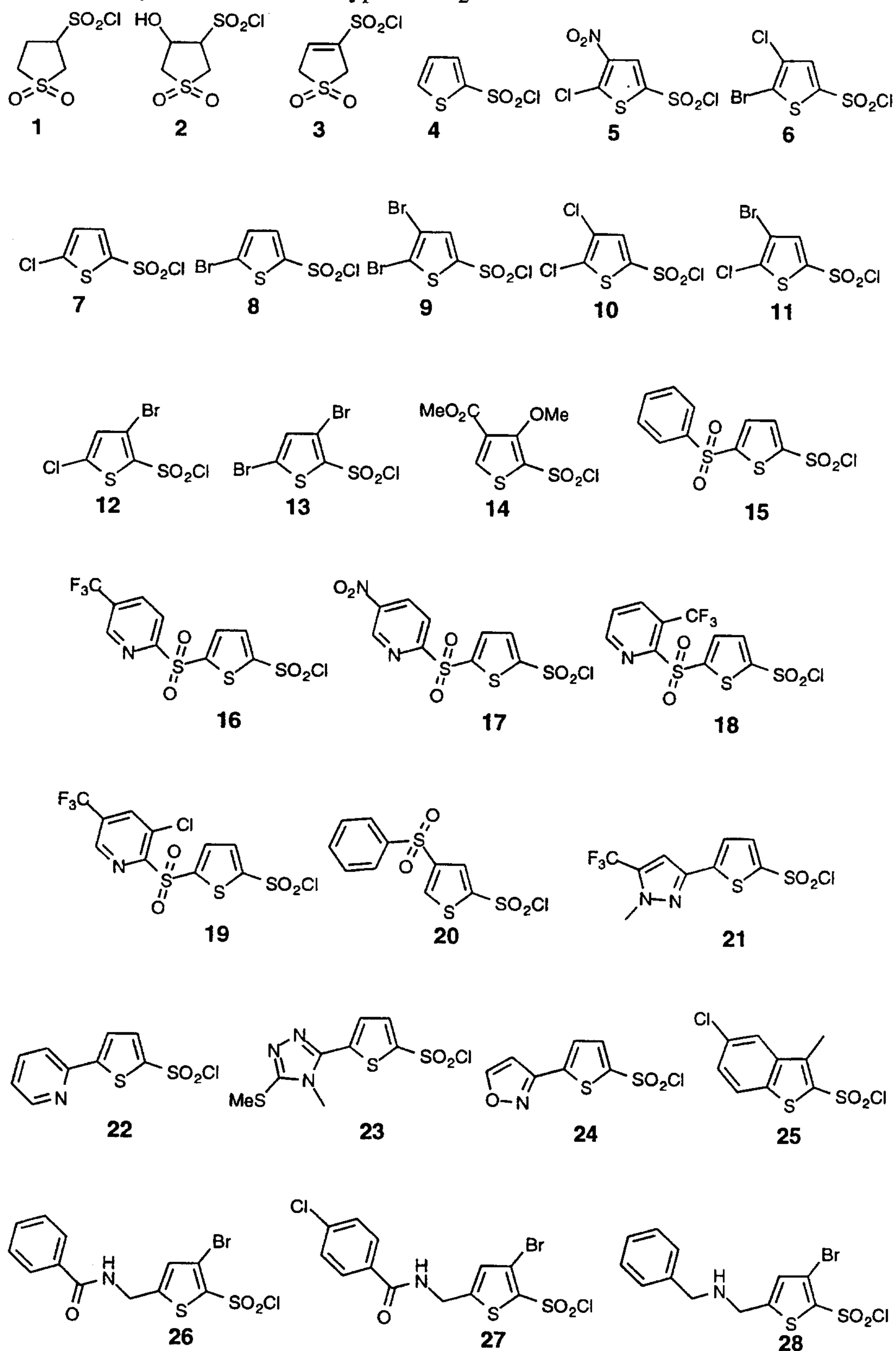
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Table 18. Sulfonyl chlorides of the type A-SO₂Cl

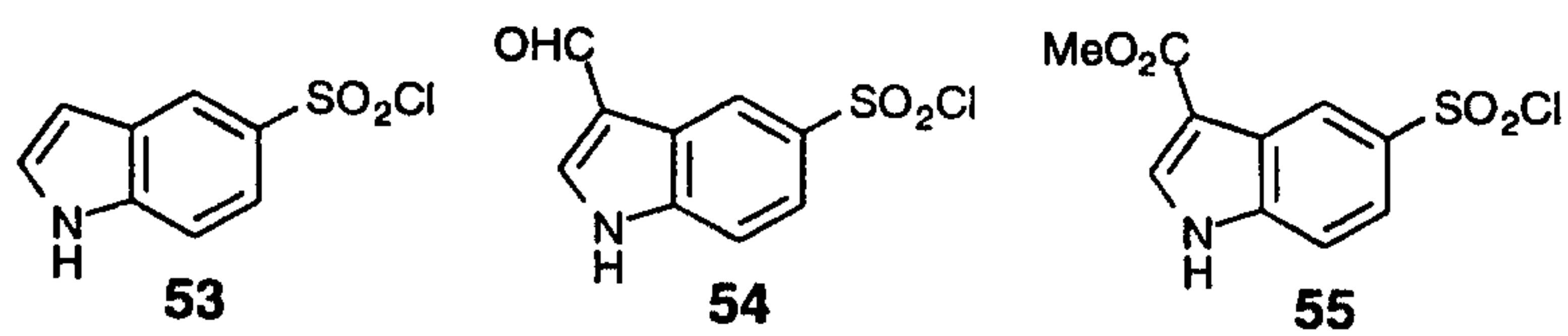
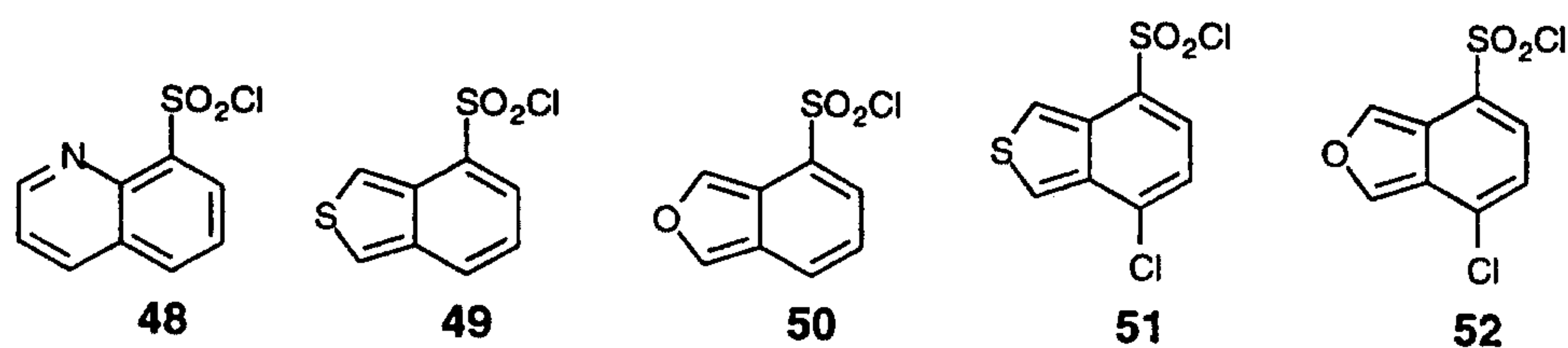
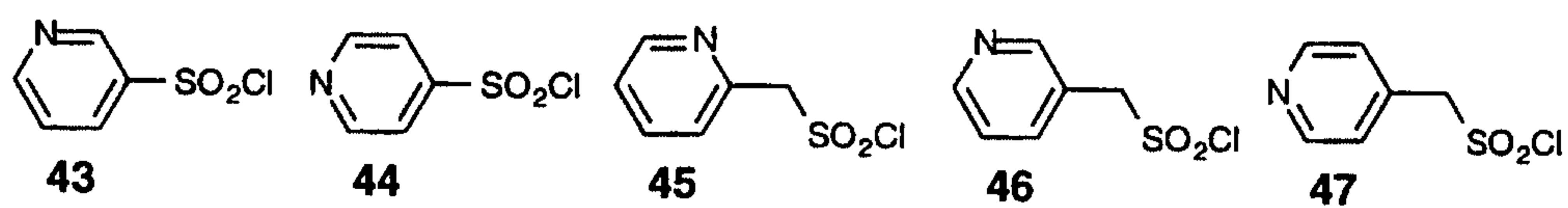
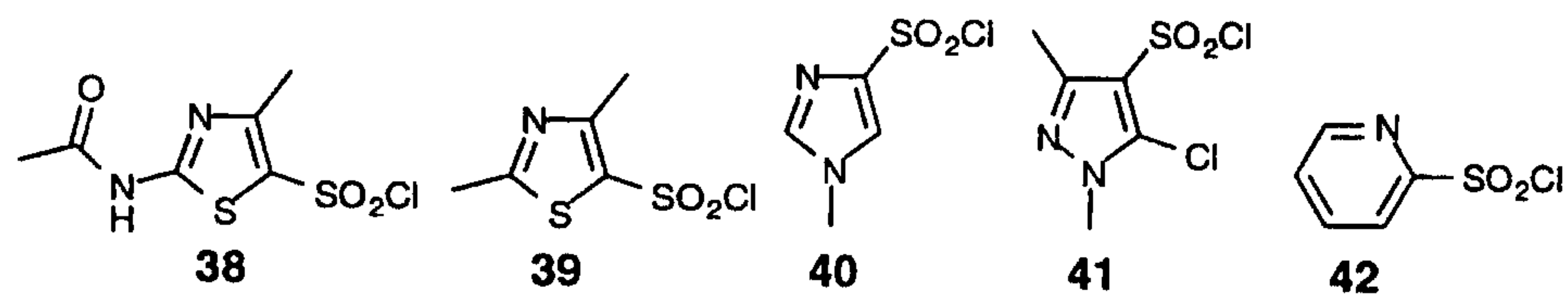
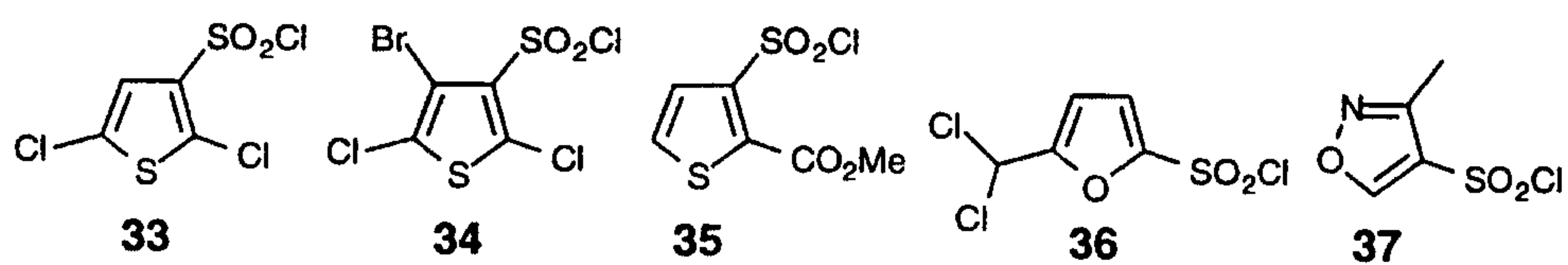
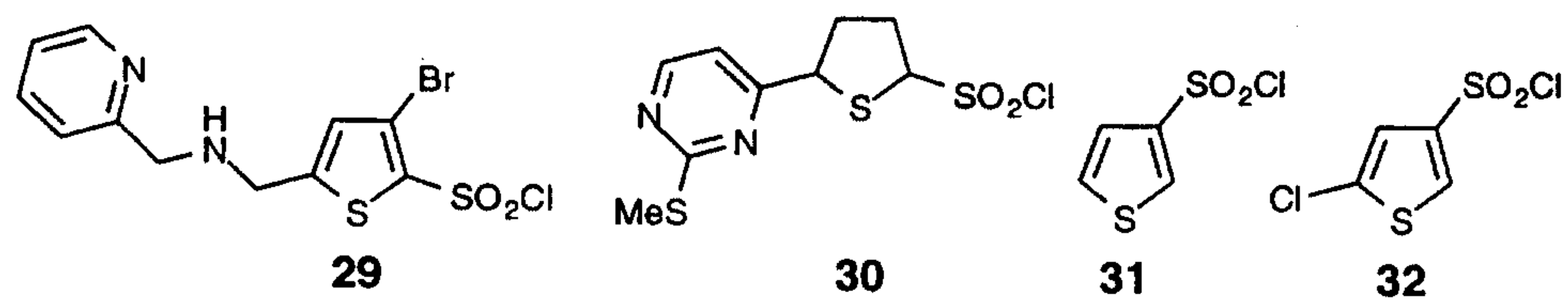
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The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

3525 In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butyloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH₃

3530

Step A

(3-(Chloromethyl)benzoyl)-Met-OCH₃

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C; ¹H NMR (CDCl₃) δ 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6 Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59 (2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1 Hz), 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); ¹³C NMR (CDCl₃) δ 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

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Step B

(3-(Azidomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH₃ (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; ¹H NMR (CDCl₃) δ 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H, s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); ¹³C NMR (CDCl₃) δ 177.50, 166.54, 135.97, 134.06, 131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00, 15.30.

Step C

(3-(Aminomethyl)benzoyl)-Met-OCH₃

3560 A suspension of (3-(azidomethyl)benzoyl)-Met-OCH₃ (1.29 g, 4.0 mmol) and 5%
palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere
(1 atm) for two days at room temperature. The catalyst was removed by filtration through
celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water
(5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. ¹H NMR
3565 (CDCl₃) δ 7.81 (1H, s), 7.68 (1H, d, *J*=7.4 Hz), 7.45 (1H, d, *J*=6.5 Hz), 7.36 (1H, t,
J=7.4 Hz), 4.91 (1H, ddd, *J*=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br
s), 2.59 (2H, t, *J*=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).

Compound 2

3570 (4-(Aminomethyl)benzoyl)-Met-OCH₃

The title compound is prepared according to the procedure used to prepare Compound 1 but
replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3

3575 (3-Aminobenzoyl)-Met-OCH₃

The title compound was prepared according to the procedure described in J. Biol. Chem.
269 12410-12413 (1994).

Compound 4

3580 (4-Aminobenzoyl)-Met-OCH₃

Step AN-BOC-4-Aminobenzoic acid

3585 4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL)
and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-*t*-butyl dicarbonate
(23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room
temperature and stirred overnight. The next day, the dioxane was removed, the residue was
made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and
washed with 1N HCl to remove any unreacted starting material. The solution was dried
3590 over Na₂SO₄ and the solvent was removed in vacuo. The crude material was recrystallized
from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; ¹H
NMR (CD₃OD) δ 1.52 (9H, s), 7.49 (2H, d, *J*=8.6 Hz), 7.91 (2H, d, *J*=8.6 Hz), 9.28
(1H, s); ¹³C NMR (CD₃OD) δ 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00,

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169.80; Anal. Calc. for $C_{12}H_{15}NO_4$, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H: 6.43, N: 5.83; HRMS Calc. for $C_{12}H_{15}NO_4$, 237.0961, Found, 237.1001.

Step B(N-BOC-4-Aminobenzoyl)-Met-OCH₃

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M NaHCO₃ and water. The methylene chloride was dried over MgSO₄ and the solvent was removed in vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, *J*=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, *J*=8.7 Hz), 7.77 (2H, d, *J*=8.7 Hz); ¹³C NMR (CDCl₃) δ 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75; Anal. Calc. for $C_{18}H_{26}N_2O_5S$, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; *m/z* (EI) 382 (M).

Step C(4-Aminobenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-aminobenzoyl-Met-OCH₃ (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO₂ (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; ¹H NMR (CDCl₃) δ 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, *J*=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, *J*=8.6 Hz), 7.55 (2H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) δ 15.23, 31.43, 31.53, 52.91, 52.43, 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for $C_{13}H_{18}N_2O_3S$, 282.1038, Found 282.1009.

Compound 5(4-Amino-3-methylbenzoyl)-Met-OCH₃

Step AN-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same
 3635 procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The
 resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide
 the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; ¹H NMR (CD₃OD)
 d 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s);
¹³C NMR (CD₃OD) d 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99,
 3640 142.45, 155.33, 168.70; Anal. Calc. for C₁₃H₁₇NO₄, C: 62.15, H: 6.82, N: 5.58; Found
 C: 62.07, H: 6.86, N: 5.46; m/z (EI) 251; HRMS Calc. for C₁₃H₁₇NO₄, 251.1158;
 Found, 251.1153.

Step B

3645 (N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH₃

N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with
 methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI
 (1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBT, 1.18 g, 8.76 mmol) in dry
 methylene chloride (31.8 mL) according to the procedure described for the preparation of N-
 3650 BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl
 acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; ¹H NMR (CDCl₃) d
 1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H,
 s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66
 (1H, s), 8.05 (1H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) d 15.47, 17.61, 28.22, 30.03,
 3655 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58,
 172.66.

Step C(4-Amino-3-methylbenzoyl)-Met-OCH₃ hydrochloride

3660 N-BOC-4-Amino-3-methylbenzoyl-Met-OCH₃ (0.99 g, 2.59 mmol) was dissolved in
 methylene chloride (15-20 mL) and precipitated with 3M HCl/Et₂O (20.7 mL). A pale
 orange precipitate was obtained, washed with ether and dried overnight on the vacuum
 pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; ¹H NMR
 (CD₃OD) d 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H,
 3665 s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s);
¹³C NMR (CD₃OD) d 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85,

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131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for $C_{14}H_{21}N_2O_3S$, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

3670

Compound 6(4-Amino-3-methoxybenzoyl)-Met-OCH₃Step AN-BOC-4-Amino-3-methoxybenzoic acid

3675 4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired product (1.5 g) as tan crystals: m.p. 176-178°C; ¹H NMR (CD₃OD) δ 1.52 (9H, s), 3.92 (3H, s), 7.56 (1H, s), 7.62 (1H, d, *J*=8.4 Hz), 7.96 (1H, s), 8.03 (1H, d, *J*=8.4 Hz); ¹³C NMR (CD₃OD) δ 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84, 149.04, 154.20, 169.60; HRMS Calc. for $C_{13}H_{17}NO_5$, 267.1107; Found, 267.1103.

3680

Step B(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH₃

3685 N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH₃.

The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (0.36 g): m.p. 163-165°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.09-2.18 (4H, m), 2.23-2.35 (1H, m), 2.60 (2H, t, *J*=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s), 6.93 (1H, d, *J*=7.6 Hz), 7.25 (1H, m), 7.31 (1H, d, *J*=10.2 Hz), 7.44 (1H, s), 8.15 (1H, d, *J*=8.5 Hz); ¹³C NMR (CDCl₃) δ 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81, 80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; *m/z* (FAB) 413 (*M* + 1).

3695

Step C(4-Amino-3-methoxybenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH₃ (0.71 g, 1.79 mmol) was dissolved in methylene chloride (4 mL) and precipitated with 3M HCl/Et₂O (12 mL). A reddish precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.55 g: m.p. 176-177°C; ¹H NMR (CD₃OD) δ 2.08 (3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50

3700

(1H, d, $J=8.2$ Hz), 7.57 (1H, d, $J=4.1$ Hz), 7.67 (1H, s); ^{13}C NMR (CD_3OD) δ 15.26, 31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67, 168.79, 173.81.

Compound 7
(4-Amino-1-naphthoyl)-Met-OCH₃

Step A

4-Amino-1-naphthoic acid

4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; ^1H NMR (CD_3OD) δ 6.69 (1H, d, $J=8.2$ Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, $J=8.5$ Hz), 8.13 (1H, d, $J=8.2$ Hz), 9.09 (1H, d, $J=8.5$ Hz); ^{13}C NMR (CD_3OD) δ 107.39, 114.61, 122.99, 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for $\text{C}_{11}\text{H}_7\text{NO}_2$, 187.0633; Found, 187.0642.

Step B

N-BOC-4-Amino-1-naphthoic acid

4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-*t*-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; ^1H NMR (CD_3OD) δ 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, $J=8.1$ Hz), 8.12 (1H, d, $J=8.0$ Hz), 8.22 (1H, d, $J=8.18$ Hz), 9.02 (1H, d, $J=8.9$ Hz); ^{13}C NMR (CD_3OD) δ 26.68, 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_4$, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for $\text{C}_{16}\text{H}_{17}\text{NO}_4$, 287.1158; Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃

- 3740 N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH₃. After workup and recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as
- 3745 pale pink crystals: m.p. 131-132°C; ¹H NMR (CDCl₃) δ 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, *J*=7.1 Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, *J*=8.0 Hz), 7.02 (1H, s), 7.56-7.59 (2H, m) 7.69 (1H, d, *J*=7.9 Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, *J*=7.9 Hz), 8.44-8.48 (1H, m); ¹³C NMR (CDCl₃) δ 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53,
- 3750 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for C₂₂H₂₈N₂O₅S, 432.1719; Found, 432.1702; *m/z* (FAB) 433 (*M*+1).

Step D(4-Amino-1-naphthoyl)-Met-OCH₃ hydrochloride

- 3755 (N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃ (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; ¹H NMR (CD₃OD) δ 2.08-2.16 (4H, m), 2.20-2.30 (1H, m) 2.57-2.75 (2H, m) 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, *J*=7.5 Hz), 7.67 (1H, d, *J*=7.5 Hz) 7.71-7.80 (2H, m), 8.03 (1H, dd, *J*=7.1, 2.0 Hz), 8.35 (1H, dd, *J*=6.8, 1.8 Hz); ¹³C NMR (CD₃OD) δ 15.23,
- 3760 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41, 127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; *m/z* (FAB), 369 (*M*+1).

Compound 8(4-Amino-2-phenylbenzoyl)-Met-OCH₃

3765

Step A4-Nitro-2-phenyltoluene

- 2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added
- 3770 Pd(Ph₃P)₄ (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et₂O. The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; ¹H NMR (CDCl₃) δ 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); ¹³C NMR (CDCl₃)

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3775 d 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for $C_{13}H_{11}NO_2$, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; m/z (EI) 213; HRMS Calc. for $C_{13}H_{11}NO_2$, 213.0790; Found, 213.0793.

3780

Step B4-Nitro-2-phenylbenzoic acid

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and $KMnO_4$ (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several
 3785 times with boiling water. The aqueous solution was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C, ^1H NMR (CD_3OD) d 7.38-7.48 (5H, m), 7.96 (1H, d, $J=8.5$ Hz), 8.21 (1H, d, $J=2.3$ Hz), 8.28 (1H, dd, $J=8.48, 2.37$ Hz); ^{13}C NMR (CD_3OD) d 122.95, 126.09, 129.27, 129.42,
 3790 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

Step C(4-Nitro-2-phenylbenzoyl)-Met-OCH₃

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride
 3795 salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH₃. After recrystallization of the product from ethyl acetate hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C; ^1H NMR ($CDCl_3$) d 1.62-1.73 (1H, m), 1.79-1.88 (1H, m),
 3800 1.91 (3H, s), 1.99 (2H, t, $J=7.2$ Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d, $J=7.8$ Hz), 7.33-7.40 (5H, m), 7.67 (1H, d, $J=8.3$ Hz), 8.07-8.12 (2H, m); ^{13}C NMR ($CDCl_3$) d 14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

3805

Step D(4-Amino-2-phenylbenzoyl)-Met-OCH₃

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃ (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added $SnCl_2 \cdot 2H_2O$ (1.02 g, 4.5 mmol) and the reaction mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice,
 3810 the solution was made basic using $NaHCO_3$ and the product was extracted into ethyl acetate several times (7-8). The ethyl acetate solutions were combined, washed with brine and

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dried over Na₂SO₄. The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid: ¹H NMR (CDCl₃) δ 1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t, *J*=7.7 Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d, *J*=7.7 Hz), 6.50 (1H, s), 6.61 (1H, d, *J*=8.4 Hz) 7.29-7.42 (5H, m), 7.58 (1H, d, *J*=8.3 Hz); ¹³C NMR (CDCl₃) δ 15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

Compound 9

3820 (4-Amino-2-(2-thienyl)benzoyl)-Met-OCH₃

The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10

3825 (4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH₃

The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 11

3830 4-Amino-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 12

3835 4-Amino-4'-biphenyl carboxylic acid

Step A

4-Nitro-4'-methylbiphenyl

3840 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

Step B

4-Nitro-4'-biphenyl carboxylic acid

3845 The title compound was prepared by KMnO₄ oxidation of 4-nitro-4'-methylbiphenyl.

Step C

4-Amino-4'-biphenyl carboxylic acid

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The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

3850

Compound 13

4-Amino-3'-biphenyl carboxylic acid

Step A

3855

4-Nitro-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B

3860

4-Nitro-3'-biphenyl carboxylic acid

The title compound was prepared by KMnO_4 oxidation of 4-nitro-3'-methylbiphenyl.

Step C

4-Amino-3'-biphenyl carboxylic acid

3865

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 14

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

3870

Step A

2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

3875

Step B

2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by KMnO_4 oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

3880

Step C

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

3885

Compound 154-Amino-2-isopropoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3890

Compound 164-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3895

Compound 17(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃Step A

3900

2-Bromo-4-nitrobenzoic acid

2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and KMnO₄ (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na₂SO₄ and the solvent was removed in vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na₂SO₄ and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; ¹H NMR (CD₃OD) δ 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); ¹³C NMR (CD₃OD) δ 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for C₇H₄BrNO₄ • 0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

3905

3910

Step B

3915

3,5-Dimethylphenylboronic acid

Magnesium turnings (1.44 g, 59.43 mmol) were covered with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reaction mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The reaction mixture was then cooled and transferred to an addition funnel fitted to an nitrogen

3920

filled flask containing triisopropyl borate (24.9 mL) at -70°C . The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow.

3925 The solution was extracted with Et_2O and the Et_2O fractions were combined, dried over MgSO_4 and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p. $249-251^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); ^{13}C NMR (CD_3OD) δ 21.36, 133.28, 134.39, 137.48.

3930

Step C4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Cs_2CO_3 (1.66 g, 5.08 mmol) followed by $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.12 g, 5%).

3935 The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et_2O . It was dried over MgSO_4 and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g): ^1H NMR (CDCl_3) δ 2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d, $J=9.0$ Hz), 8.23-8.25 (2H, m); ^{13}C NMR (CDCl_3) δ 21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21, 144.74, 170.75.

3940

Step D(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

3945 4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBt (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)-Met-OCH₃ as described above. After recrystallization from ethyl acetate and hexanes, the desired product

3950 was obtained (0.13 g): m.p. $122-124^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.2-1.84 (1H, m), 1.85-1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t, $J=7.7$ Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d, $J=7.9$ Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m) 8.23-8.26 (2H, m); ^{13}C NMR (CDCl_3) δ 15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56,

3955 148.41, 167.14, 171.53.

Step E(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

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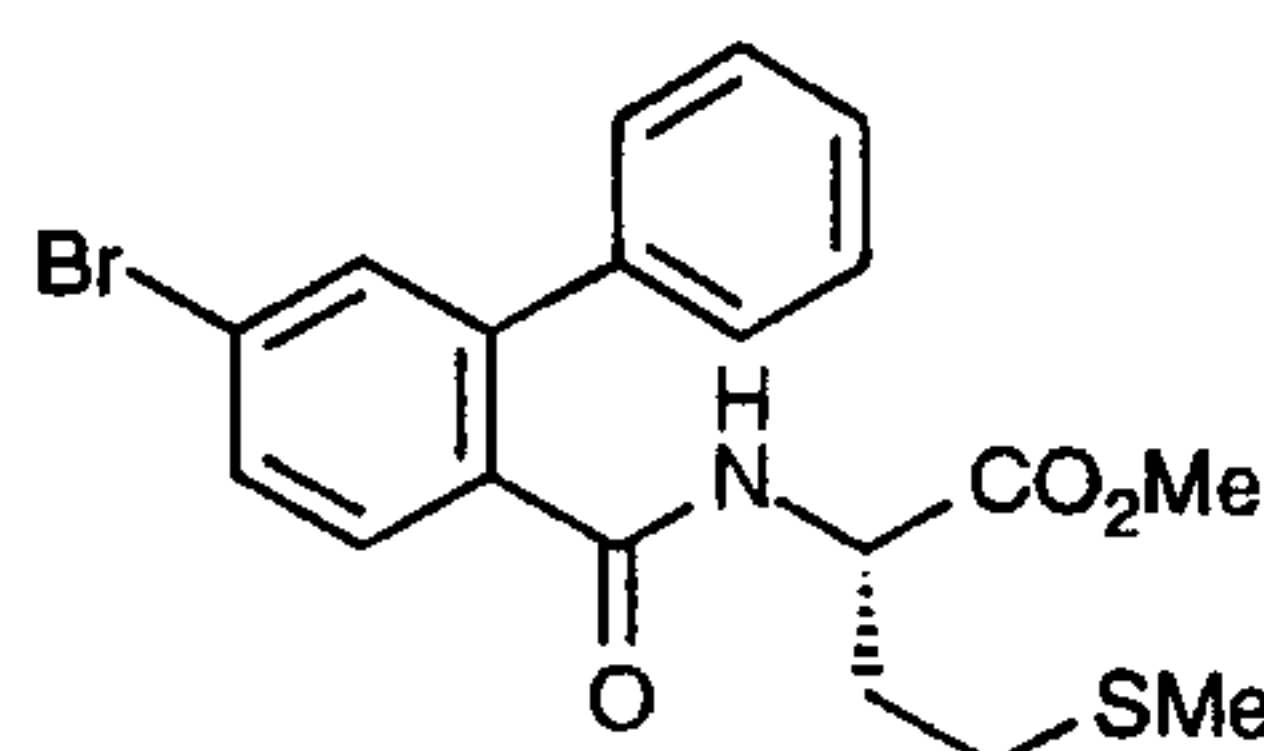
3960 (4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃ (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added SnCl₂ · 2H₂O (0.3 g, 1.30 mmol) and the reaction was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH₃ to give the desired product (0.15 g): ¹H NMR (CDCl₃) δ 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t, *J*=7.6 Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d, *J*=7.7 Hz), 6.49 (1H, d, *J*=2.3 Hz), 6.62 (1H, dd, *J*=8.4, 2.4 Hz), 6.98 (2H, s), 7.00 (1H, s), 7.65 (1H, d, *J*=8.3 Hz); ¹³C NMR (CDCl₃) δ 15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

3970

Preparation 1Anilines of the formula B-NH₂

The anilines from Table 1, entries 10-126 (B-NH₂) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.

3980

Preparation 24-Bromo-2-phenylbenzoyl methionine methyl esterPreparation 2A

3985

4-Bromo-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

3990

Preparation 2B4-Bromo-2-phenylbenzoic acid

3995 To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

4000

Preparation 2C4-Bromo-2-phenylbenzoyl methionine methyl ester

4005 To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

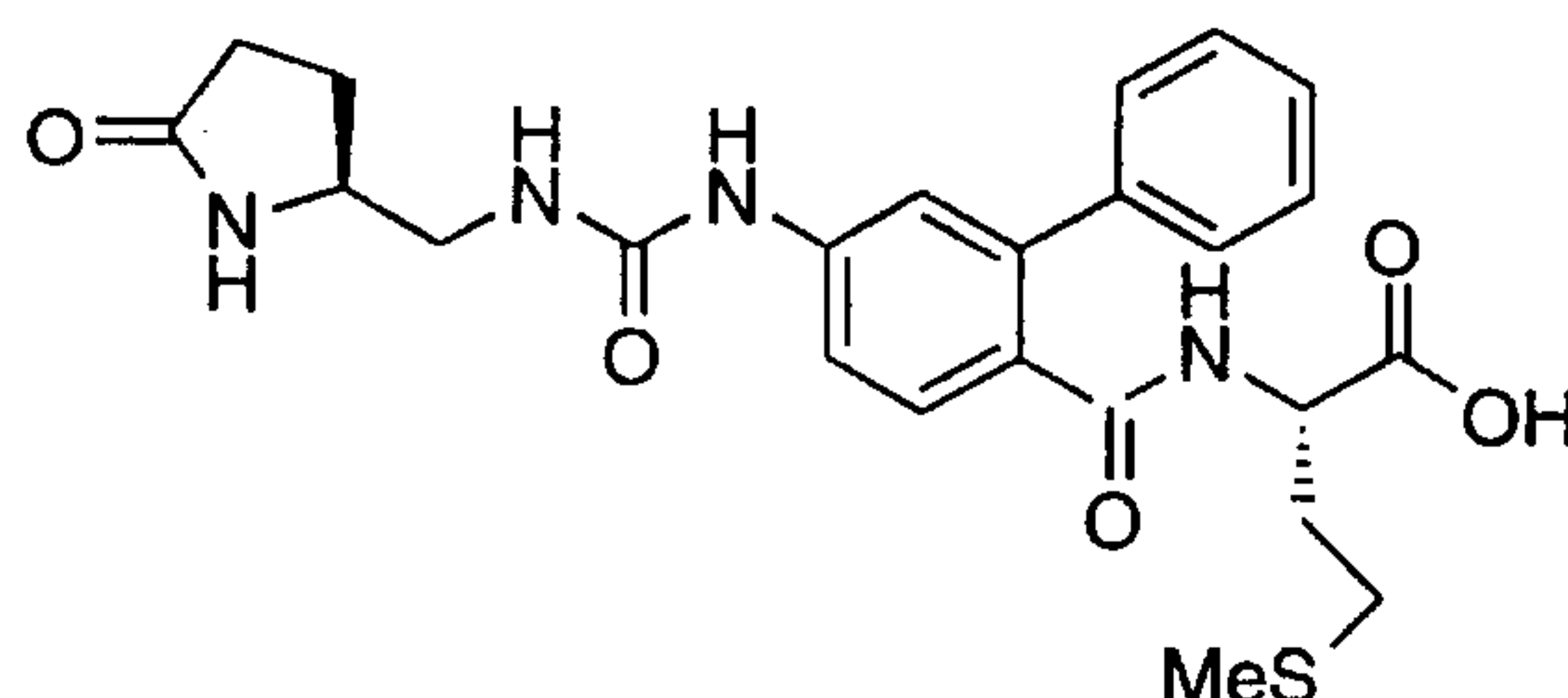
4010

Preparation 2D4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

4015 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3Arylbromides of the formula B-Br

4020 The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Preparation 2 to provide the arylbromides listed in Table 2.



4025

Example 14-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionineExample 1AMethyl 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate

4030 To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until judged complete by TLC analysis. The intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with

4035 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1B4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

4040 To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

4045

Example 1C4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

4050 To a solution of the resultant compound from Example 1B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

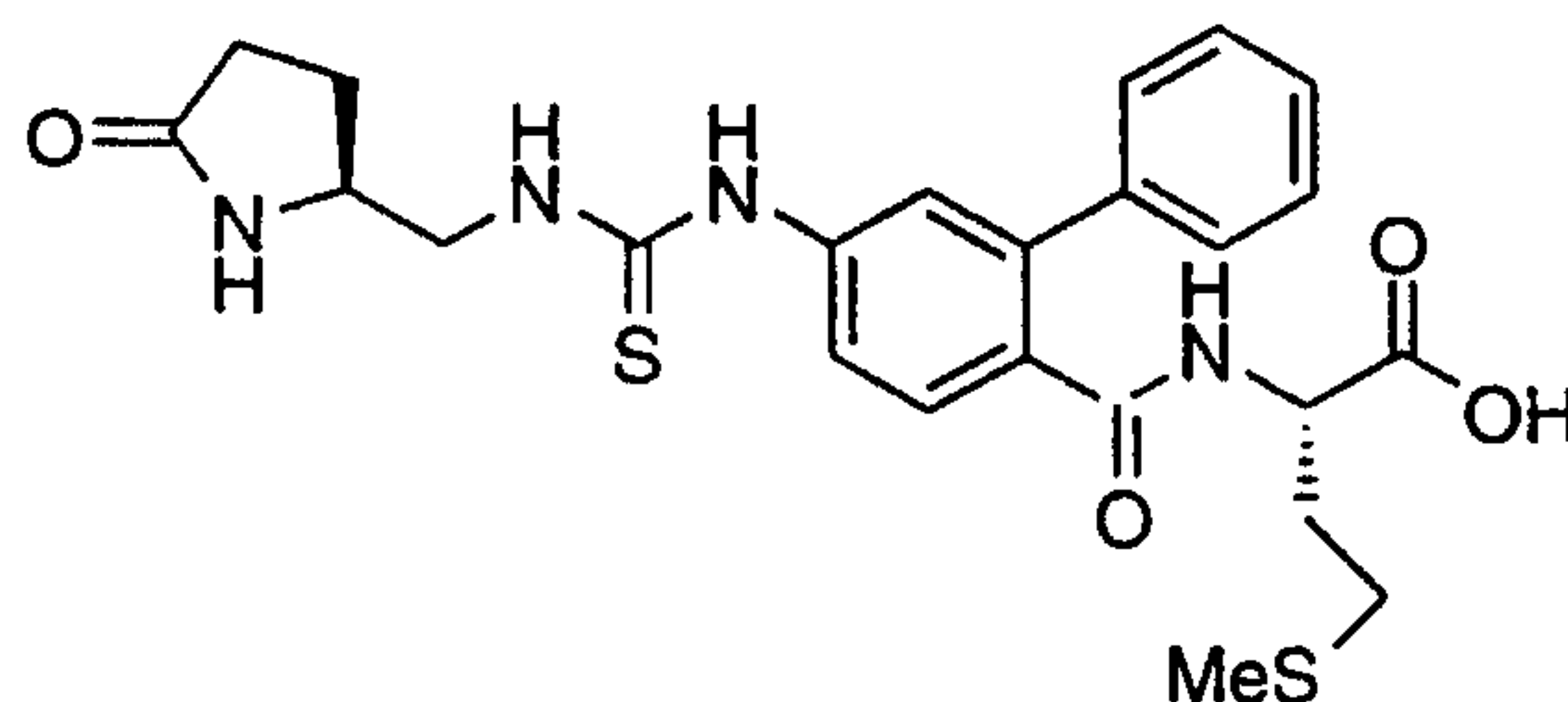
4055

Example 1D4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

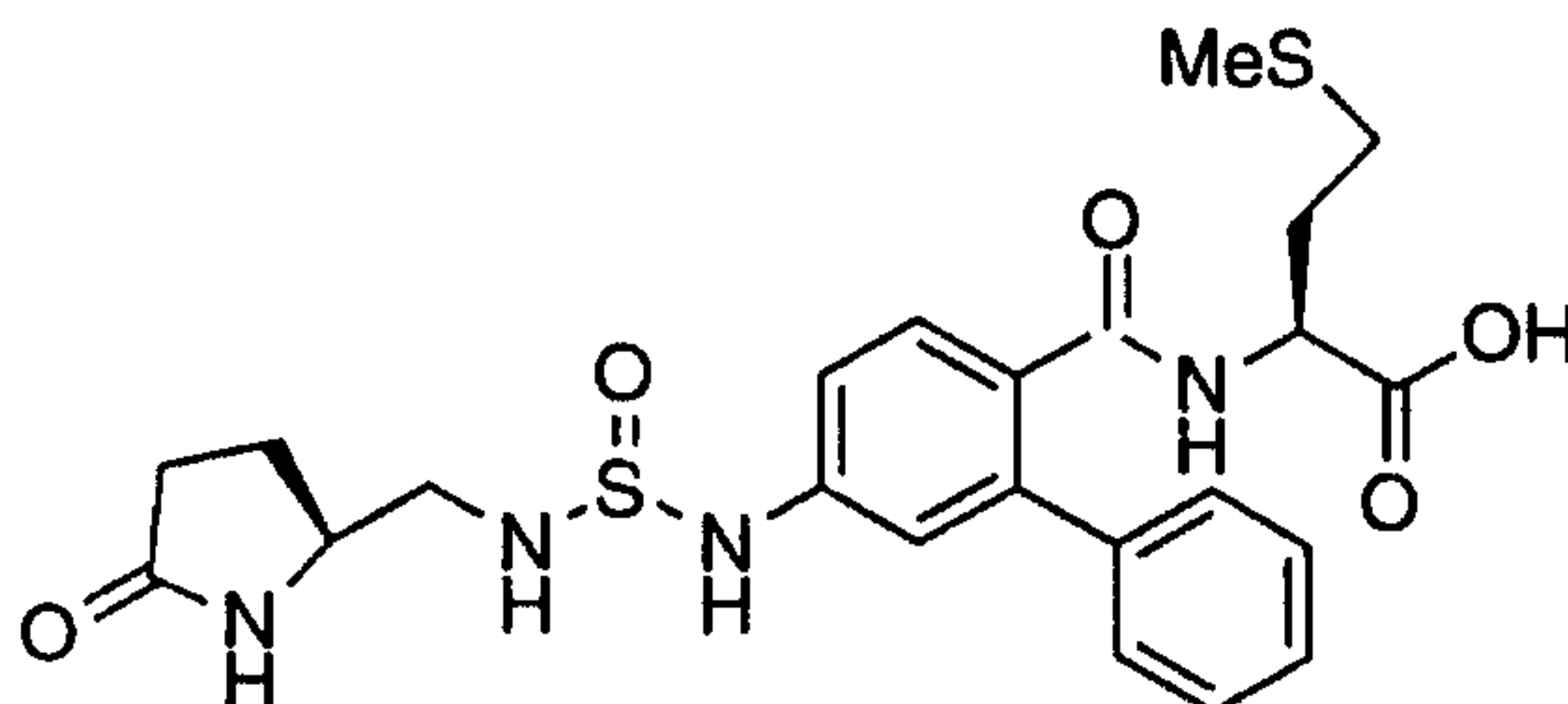
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and triethylamine (2.0 equivalents). The intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 24-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 3

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4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

4085

Example 3A4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

4090

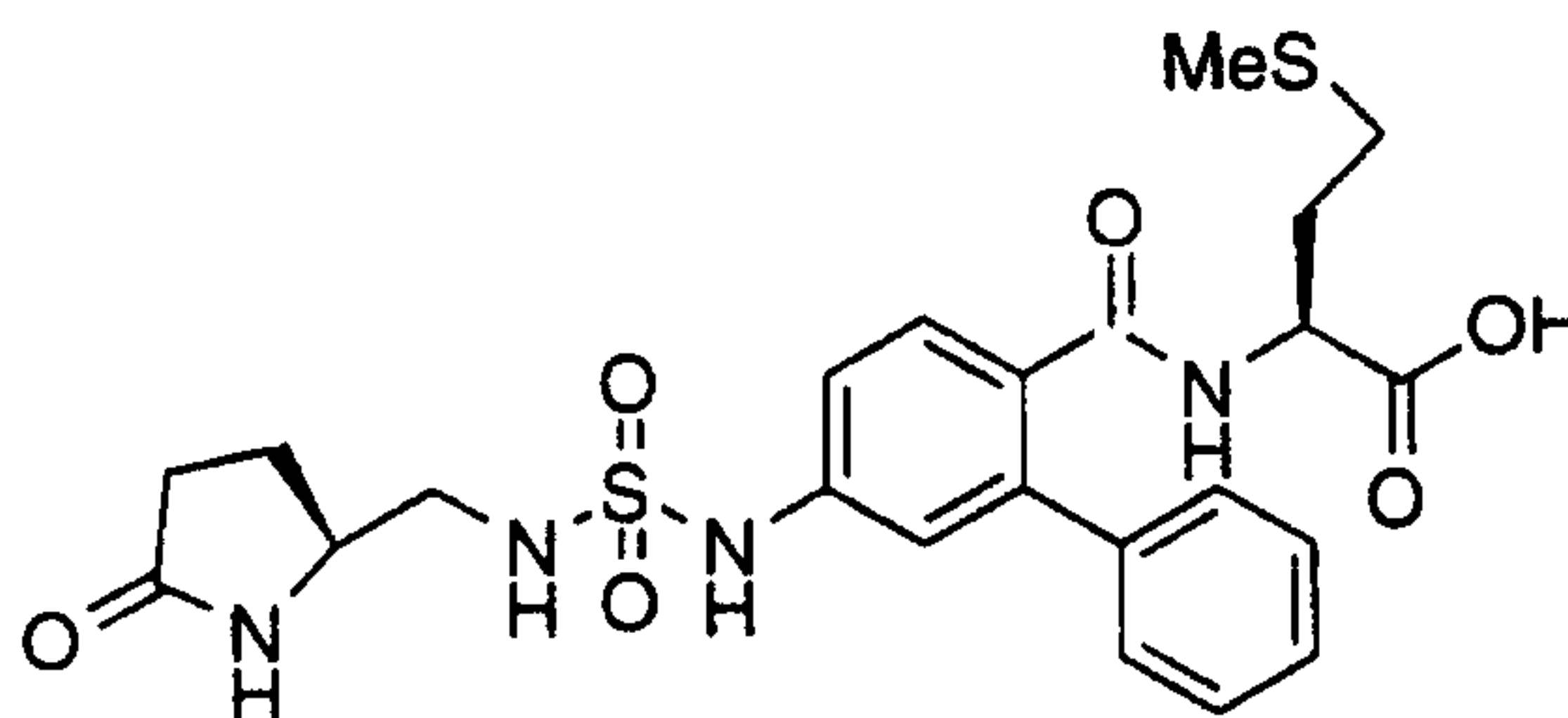
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

4095

Example 3B4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

4100

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



4105

Example 44-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionineExample 4A4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

4110

4115

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfuryl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4B4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

4120 A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfuryl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent and (S)-

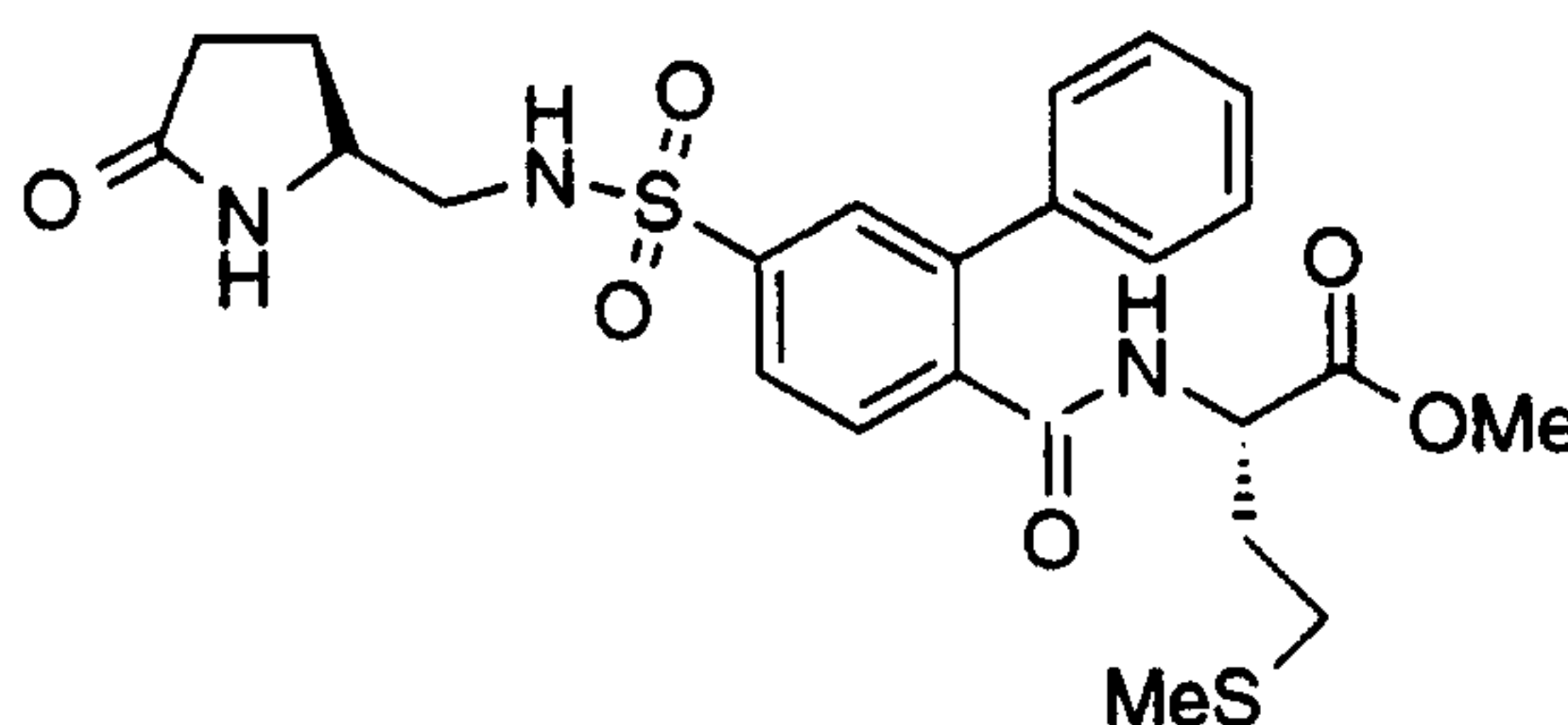
4125 5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4C

4130 4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.

4135

Example 54-((S)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

4140

Example 5A4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper

4145 (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

Example 5B

4150 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

4155

Example 5C

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

4160

Example 5D

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

4170

Example 5E

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

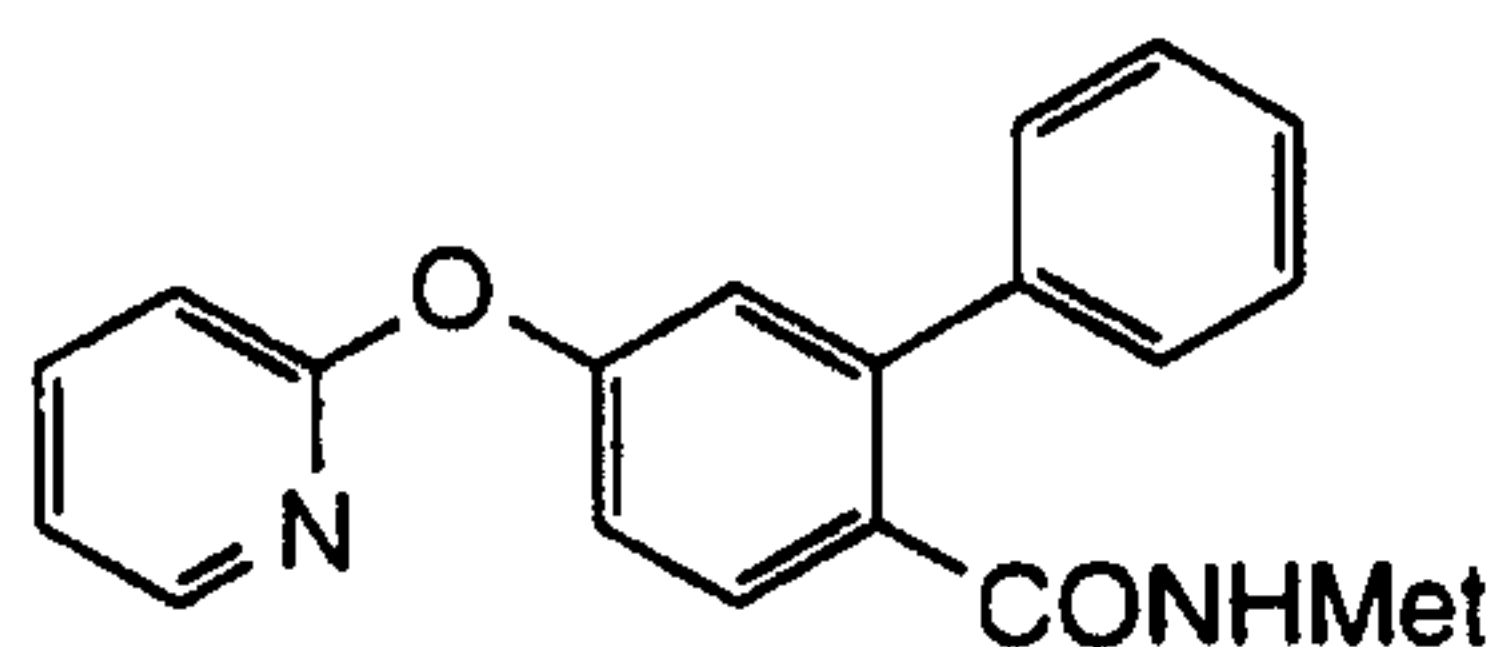
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

4180

Example 5F

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 6

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

4195

Example 6A

4-Hydroxy-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 6B

4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4210

Example 6C

4-(2-Pyridyloxy)-2-phenylbenzoic acid

A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.

Example 6D

4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

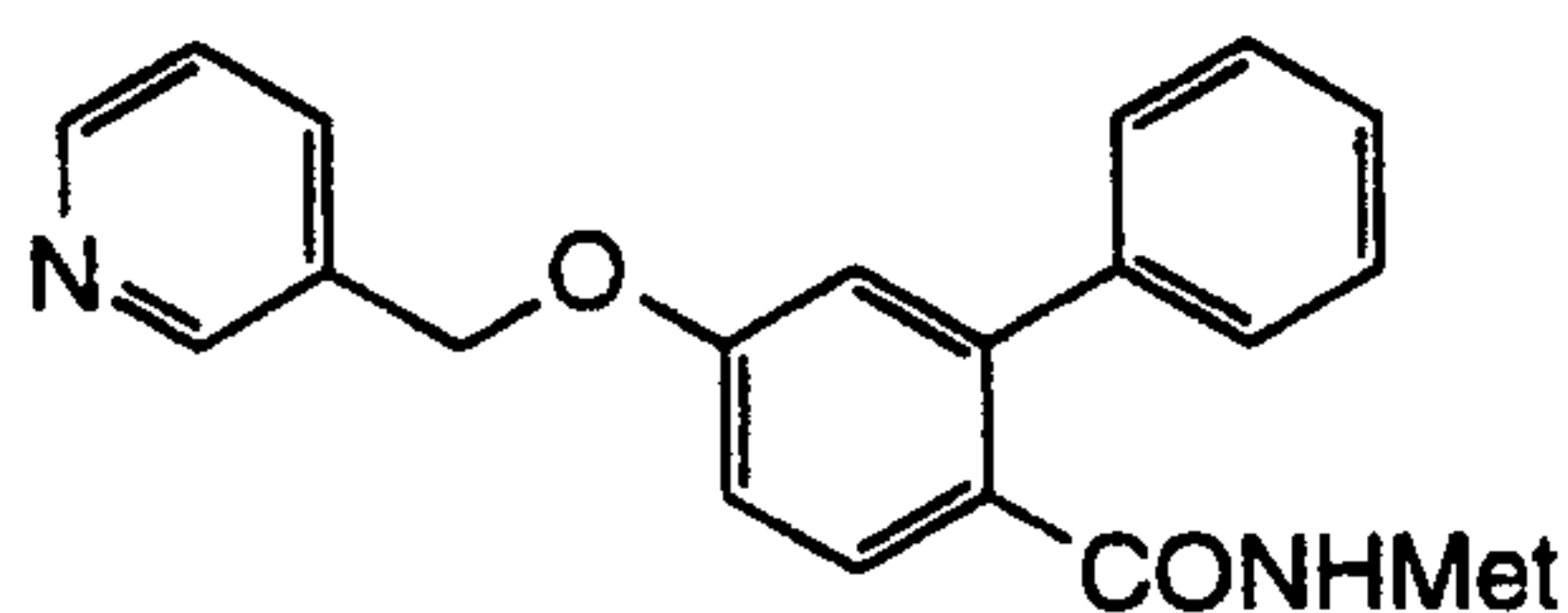
4220 The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 6E4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

4225 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or
4230 pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6F4-(2-pyridyloxy)-2-phenylbenzoylmethionine

4235 The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.

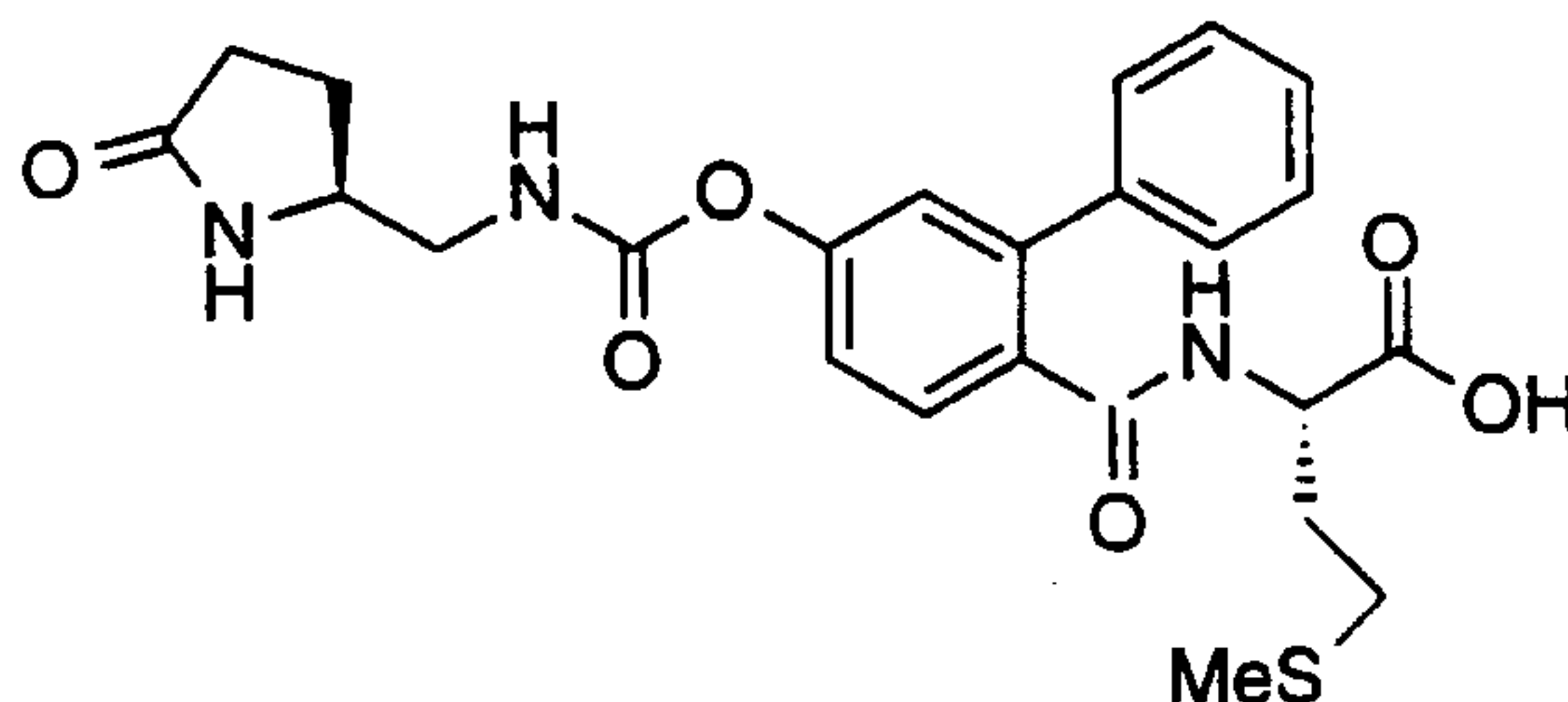


4240

Example 74-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.

4245



Example 8

4250 4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

Example 8A

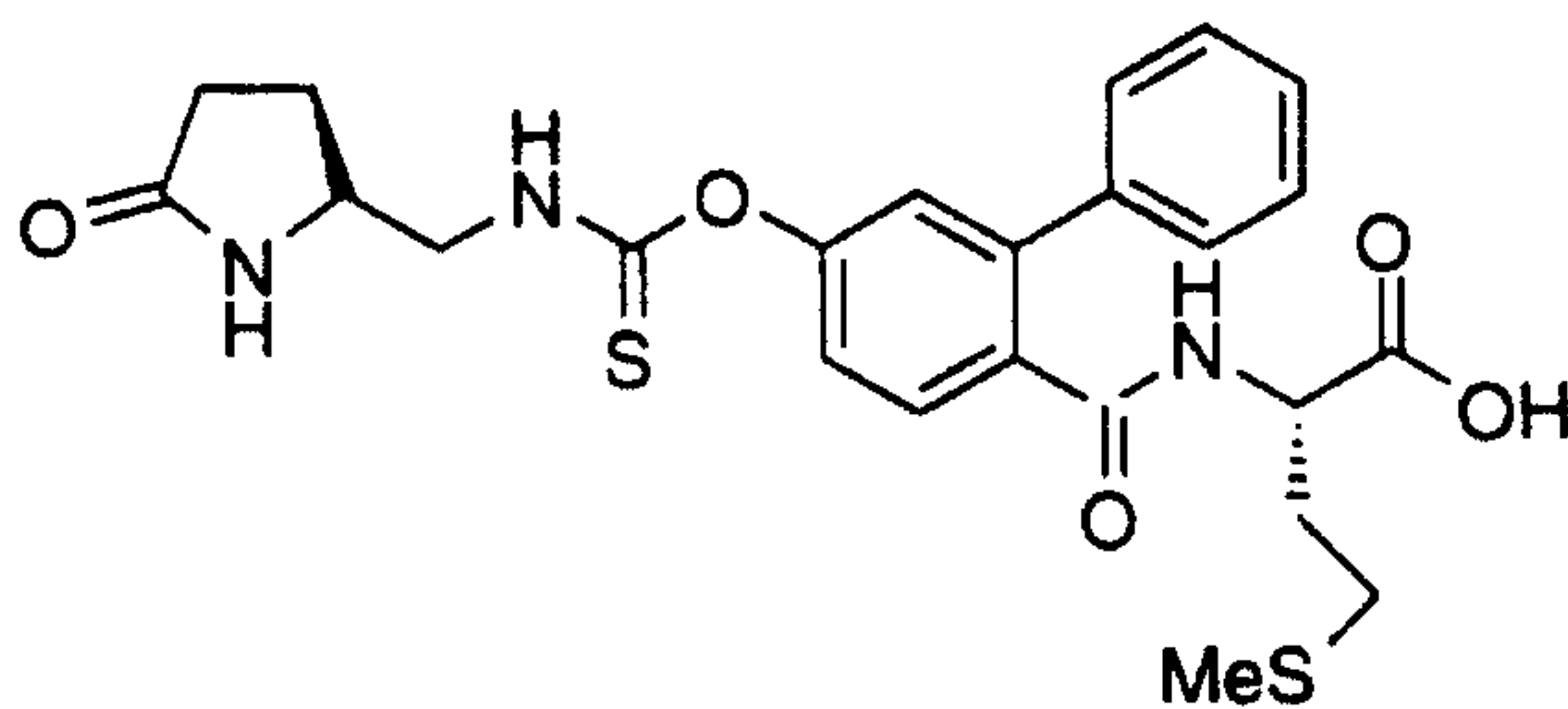
4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from
 4255 Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0
 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged
 complete by TLC analysis, the solvent is evaporated with toluene chasers. The
 chloroformate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone
 (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged
 4260 complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl
 and brine, evaporated, and purified by chromatography on silica gel.

Example 8B

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

4265 The resultant compound from Example 8A is hydrolyzed according to the procedure of
 Example 1B to give the title product.

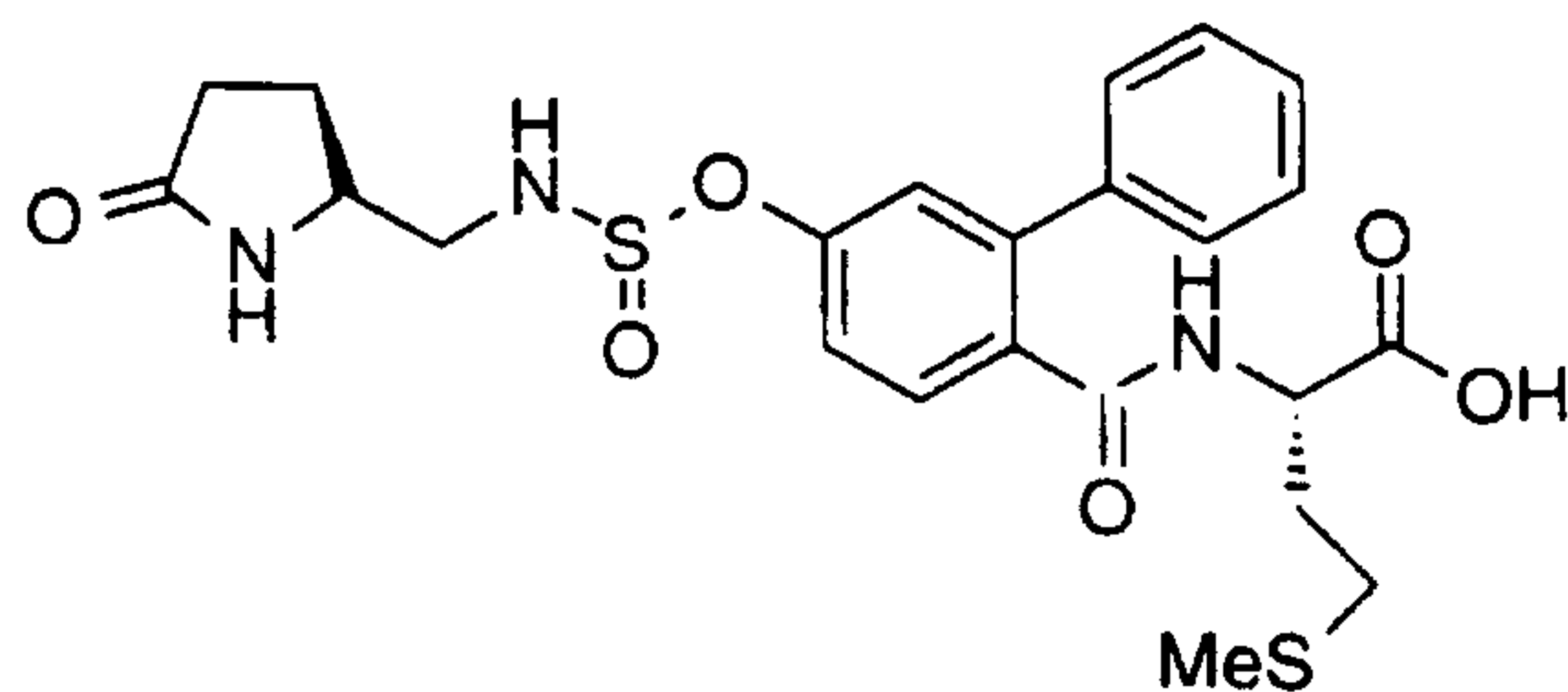


4270

Example 9

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

The title compound is prepared as described in Example 8 with the exception that phosgene
 4275 in toluene is replaced by thiophosgene.

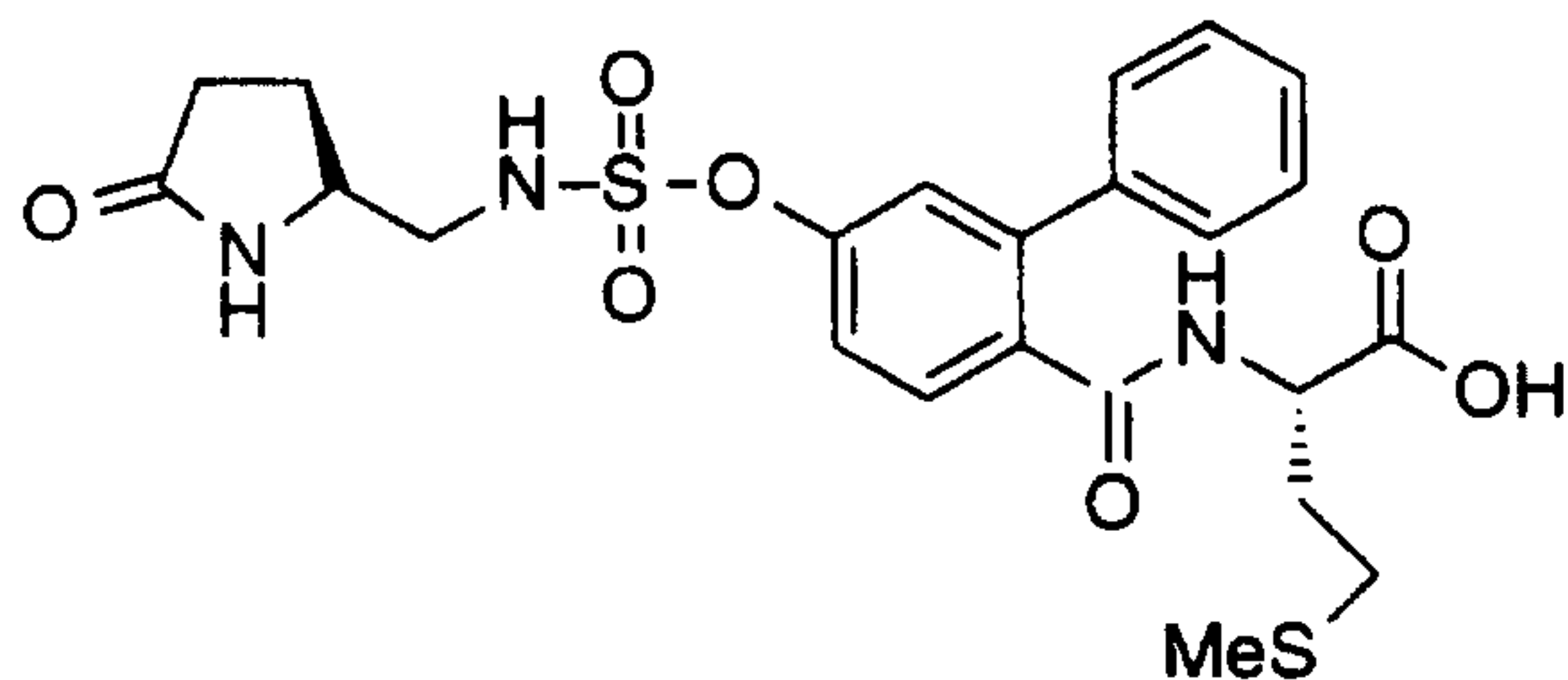


4280

Example 104-((S)-2-Pyrrolidone-5-aminomethyl)sulfinyloxy)-2-phenylbenzoyl methionine

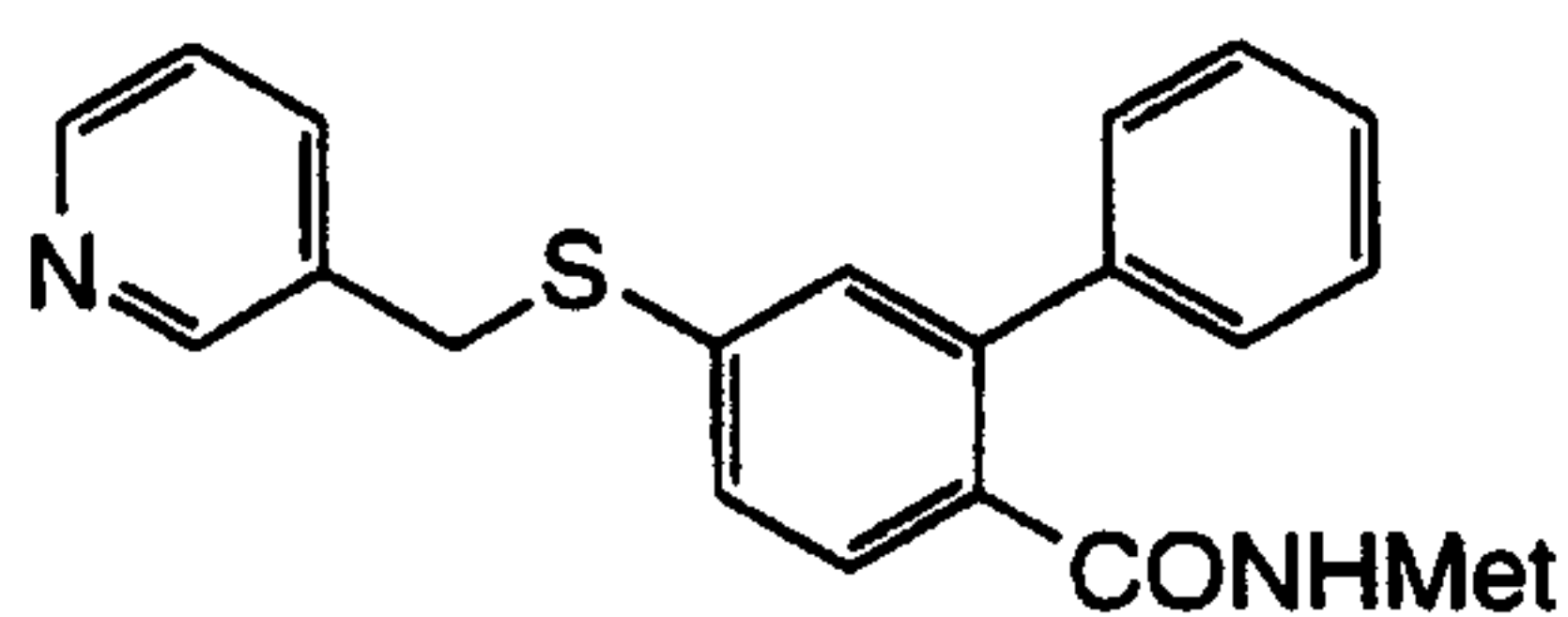
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.

4285

Example 114-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy)-2-phenylbenzoyl methionine

4290

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by sulfonyl chloride.



4295

Example 124-(3-Pyridylmethylthio)-2-phenylbenzoylmethionineExample 12A

4300

4-Mercapto-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The reaction is

4305 treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel.

Example 12B

4-(2-Pyridylmethylenethio)-2-phenylbenzoic acid methyl ester

4310 A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4315

Example 12C

4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

4320

Example 12D

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

4325 The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 12E

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

4330 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this
4335 thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4340

Example 12F4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2

Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10 °C. Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M NaOH aqueous solution). After completion of the addition, the reaction mixture is refluxed until judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained is dissolved in methanol and water, followed by addition of lithium hydroxide (200 mmol), and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride, followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent) and 1-hydroxybenzotriazol (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

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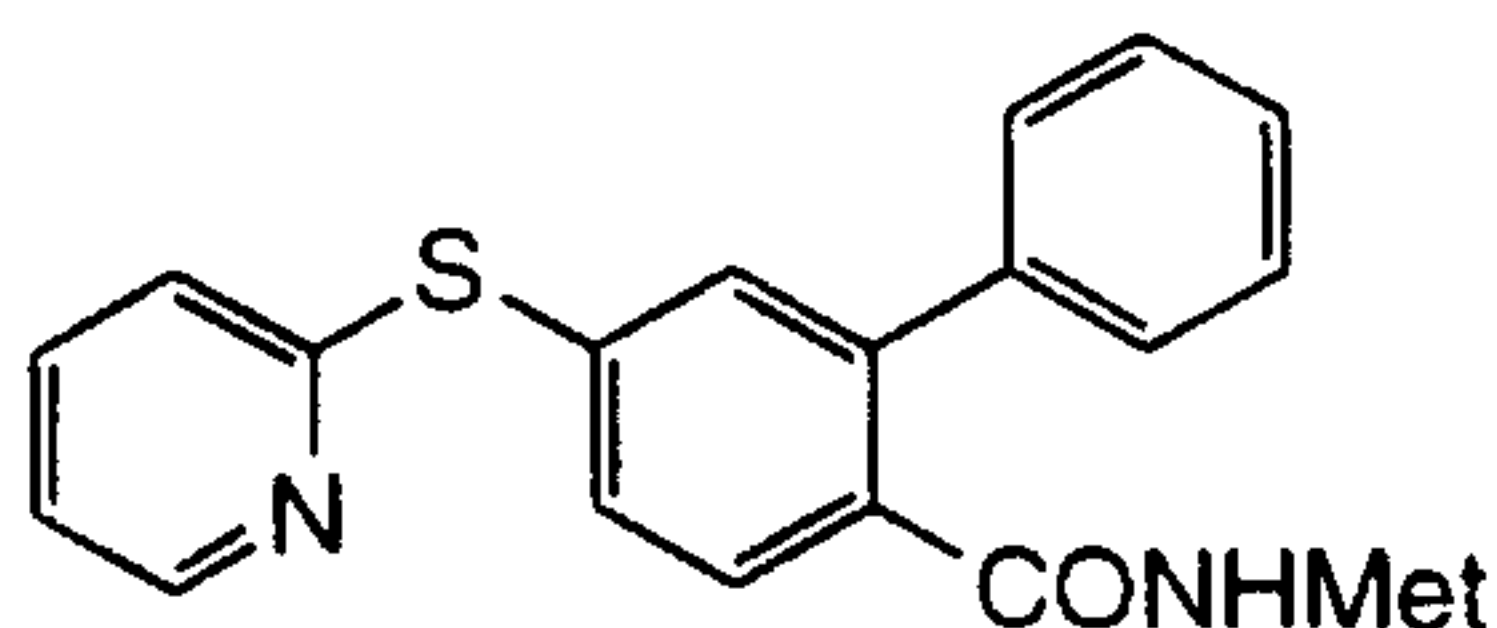
Example 12G4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

WO 98/50029

PCT/US98/09296

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.

4380

Example 134-(2-Pyridylthio)-2-phenylbenzoylmethionine

4385

Example 13A4-Fluoro-2-phenyl benzoic acid methyl ester

4390 A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous HBF_4 is treated with NaNO_2 (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 13B4-Fluoro-2-phenyl benzoic acid

4395 The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 13C4-Fluoro-2-phenyl benzoyl methionine methyl ester

4400 The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13D4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

4405 A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with K_2CO_3 (2.0 equivalents) or NaH (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

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Example 13E4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The

4415 reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and
 4420 chromatography on silica gel.

Example 13F

4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

4425 A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

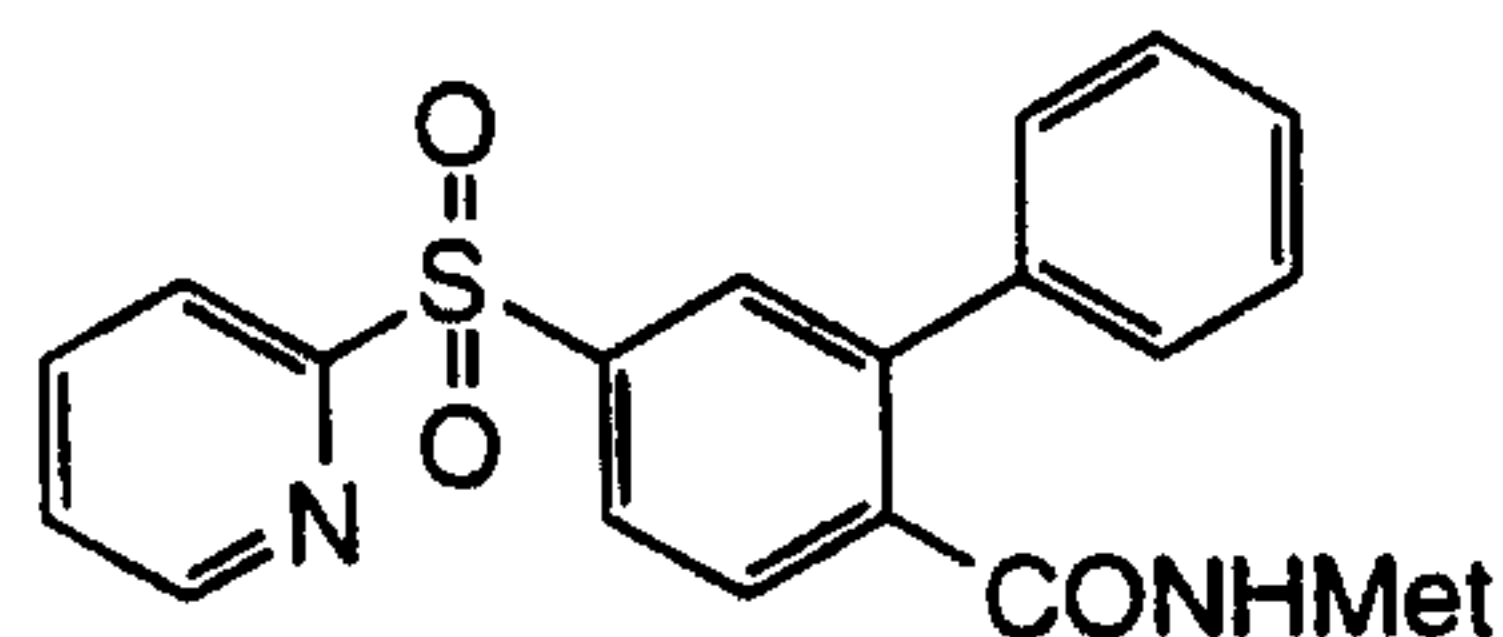
4430

Example 13G

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.

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Example 14

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4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

Example 14A

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

4445 A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na₂SO₃ when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous NaHCO₃ to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

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Example 14B

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

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Example 14C

4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

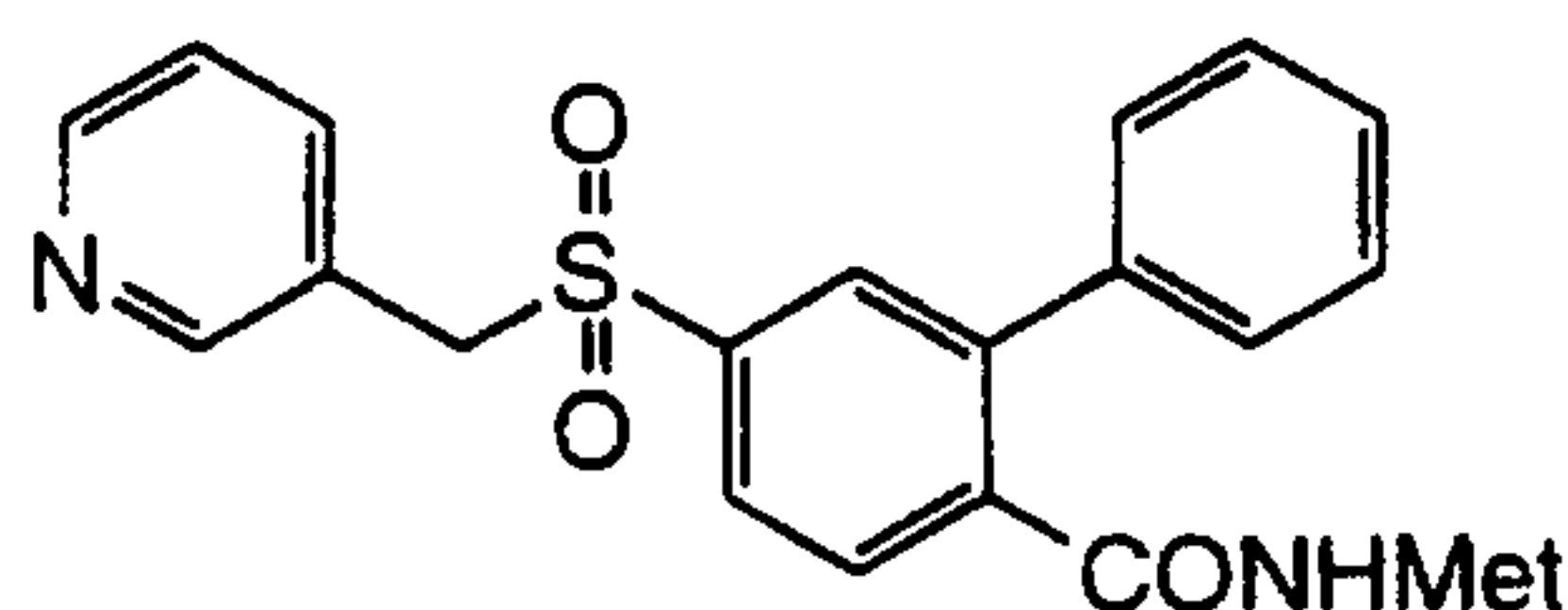
4460

Example 14D

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.

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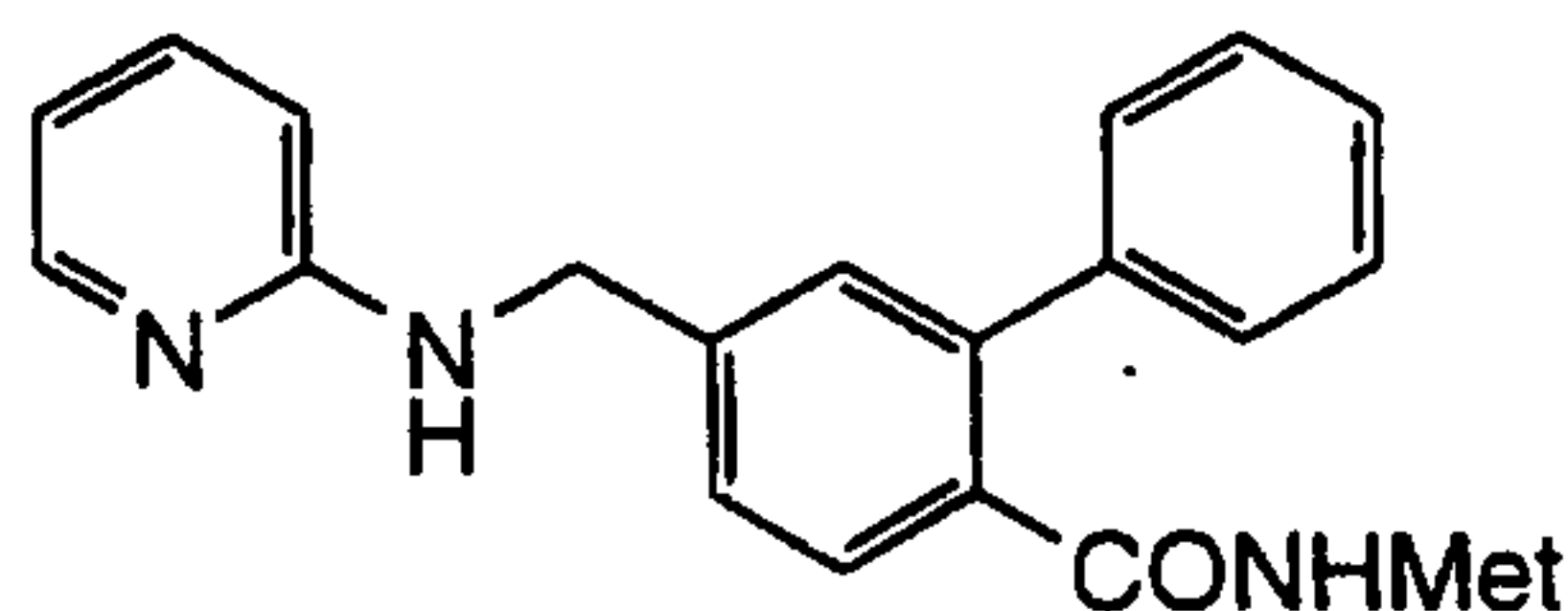


Example 15

4470

4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



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Example 16

4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

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Example 16A2-Phenylterephthalic acid mono methyl ester

A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

4485

Example 16B4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with NaBH₄ (1.0 equivalent) and aqueous NaHCO₃ and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

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Example 16C4-(Hydroxymethyl)-2-phenylbenzoic acid

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

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Example 16D4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

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Example 16E4-formyl-2-phenylbenzoyl methionine methyl ester

A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH₂Cl₂/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO₂. The product is purified by chromatography on silica gel.

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Example 16F4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

4520 A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica
4525 gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetroxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by
4530 column chromatography on silica gel to afford the title product.

Example 16G4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

4535 To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel
4540 to afford the title product.

Example 16H4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

4545 A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and NaCNBH₃ (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

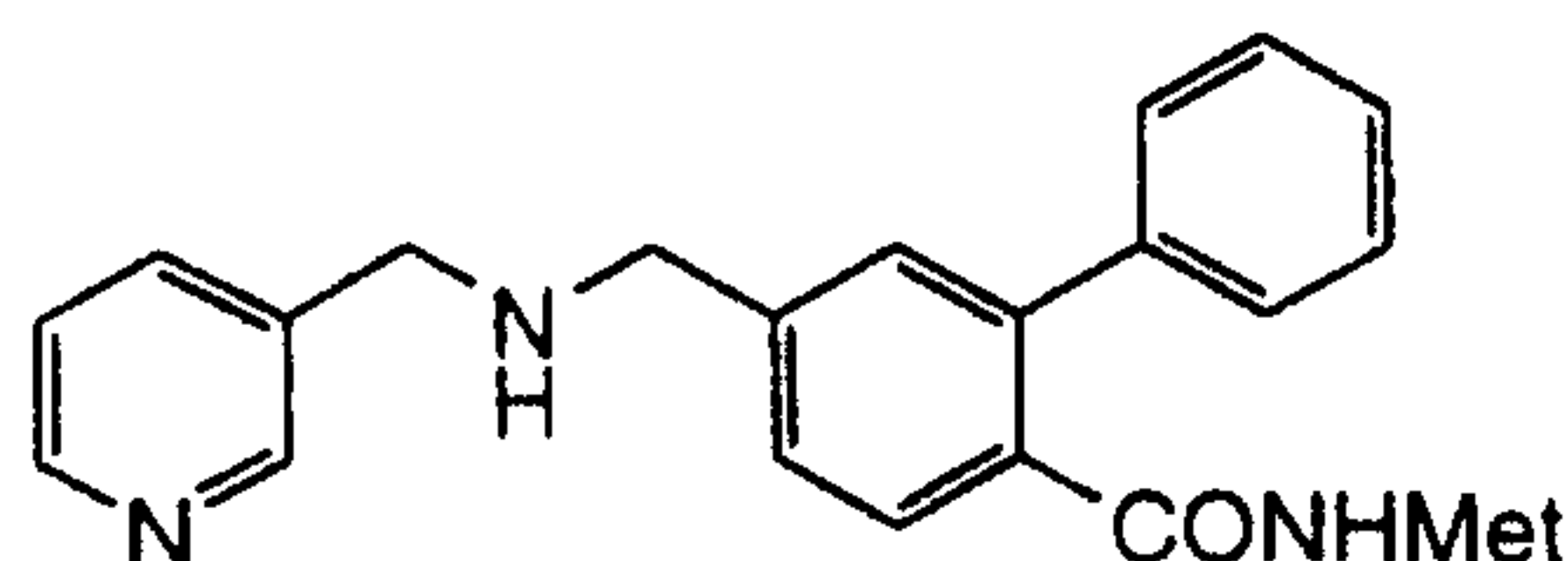
4550

Example 16I4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

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The resultant compound from Example 16H is hydrolyzed according to the procedure of
 4555 Example 1B to give the title product.

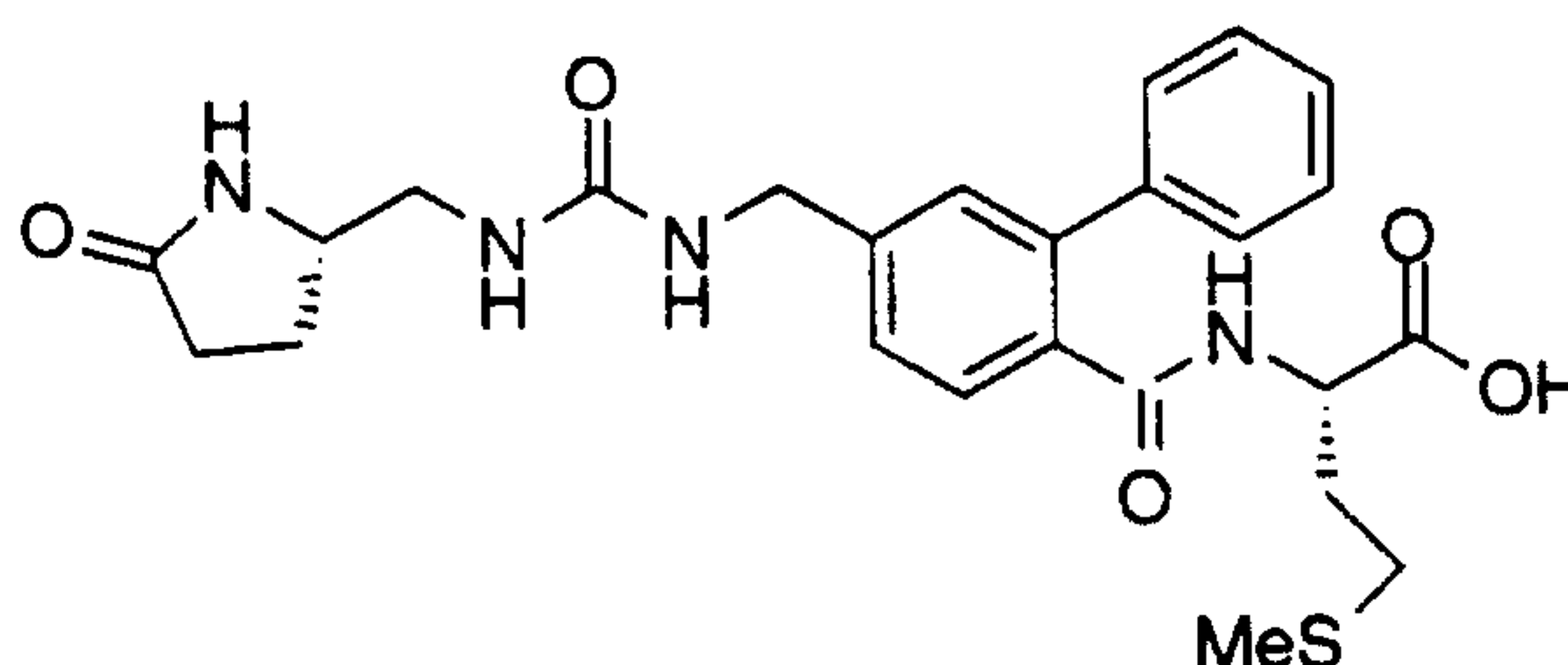


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Example 174-[(3-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.

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Example 184-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

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Example 18A4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at -78° C is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

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Example 18B4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on
 4585 silica gel provides the title product.

Example 18C

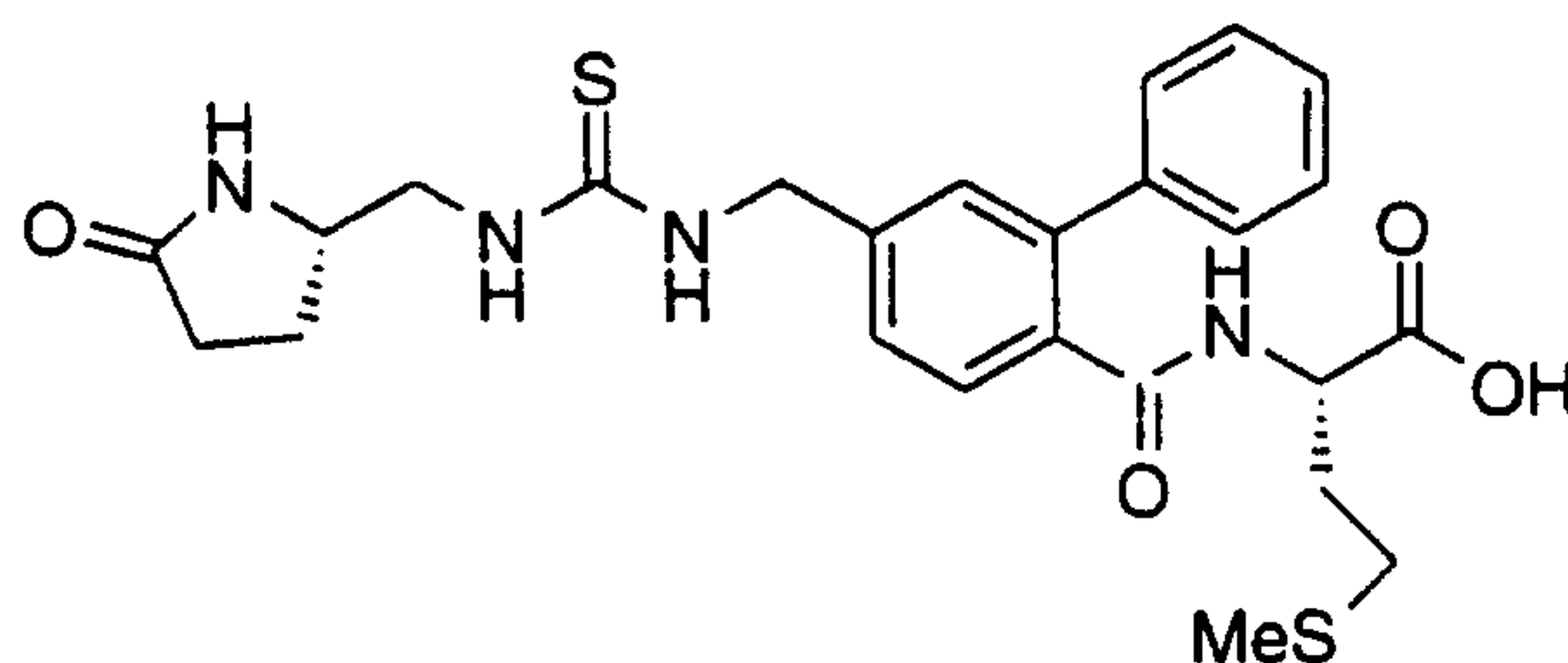
4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

4590 To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine,
 4595 evaporated, and purified by chromatography on silica gel.

Example 18D

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

The resultant compound from Example 18C is hydrolyzed according to the procedure of
 4600 Example 1B to give the title product.



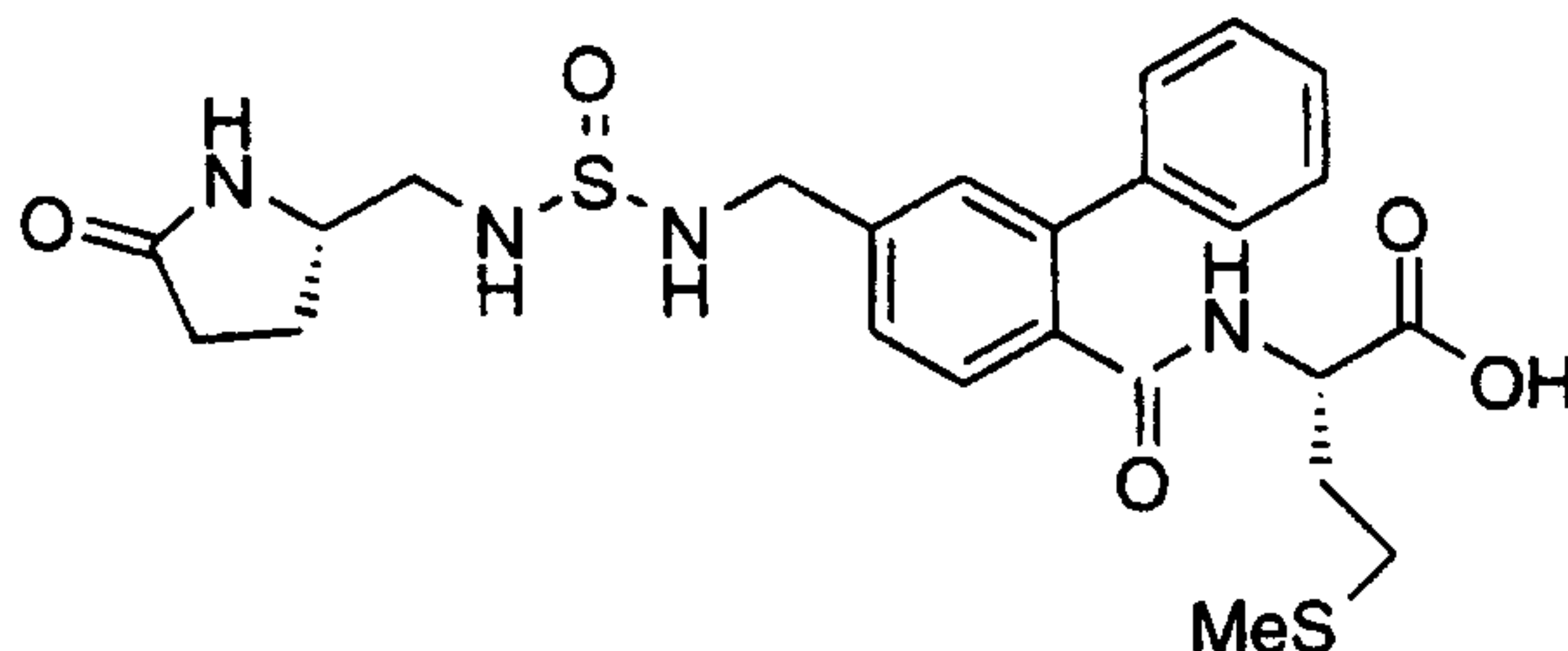
4605

Example 19

4-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

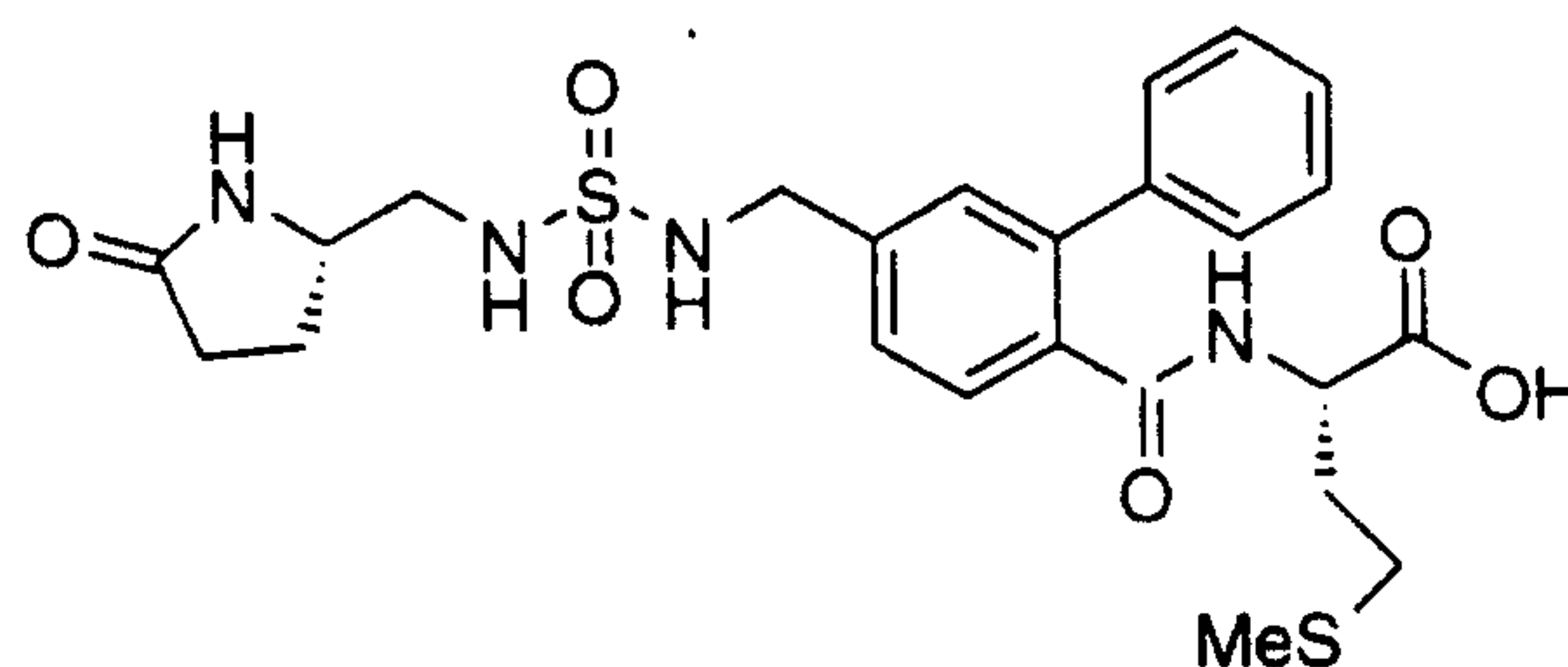
The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

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Example 204-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

4615 The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).

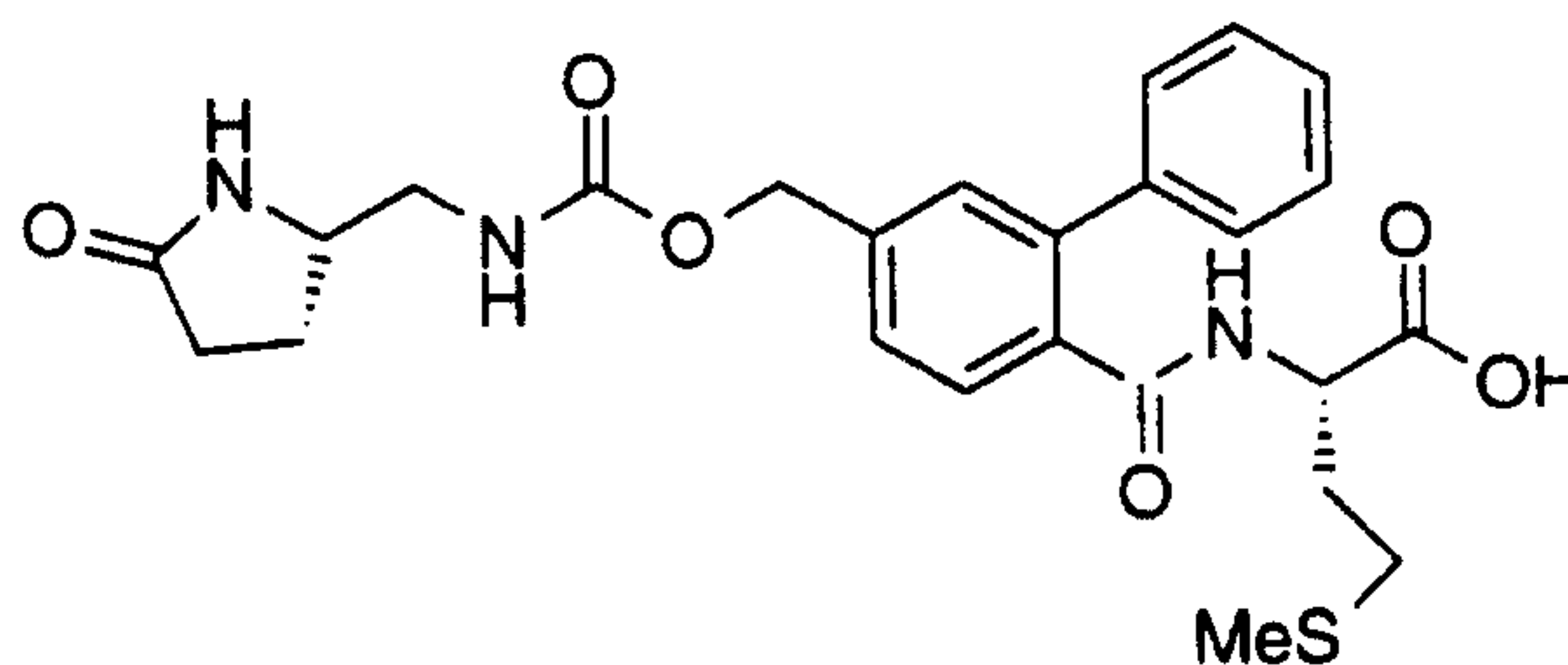


4620

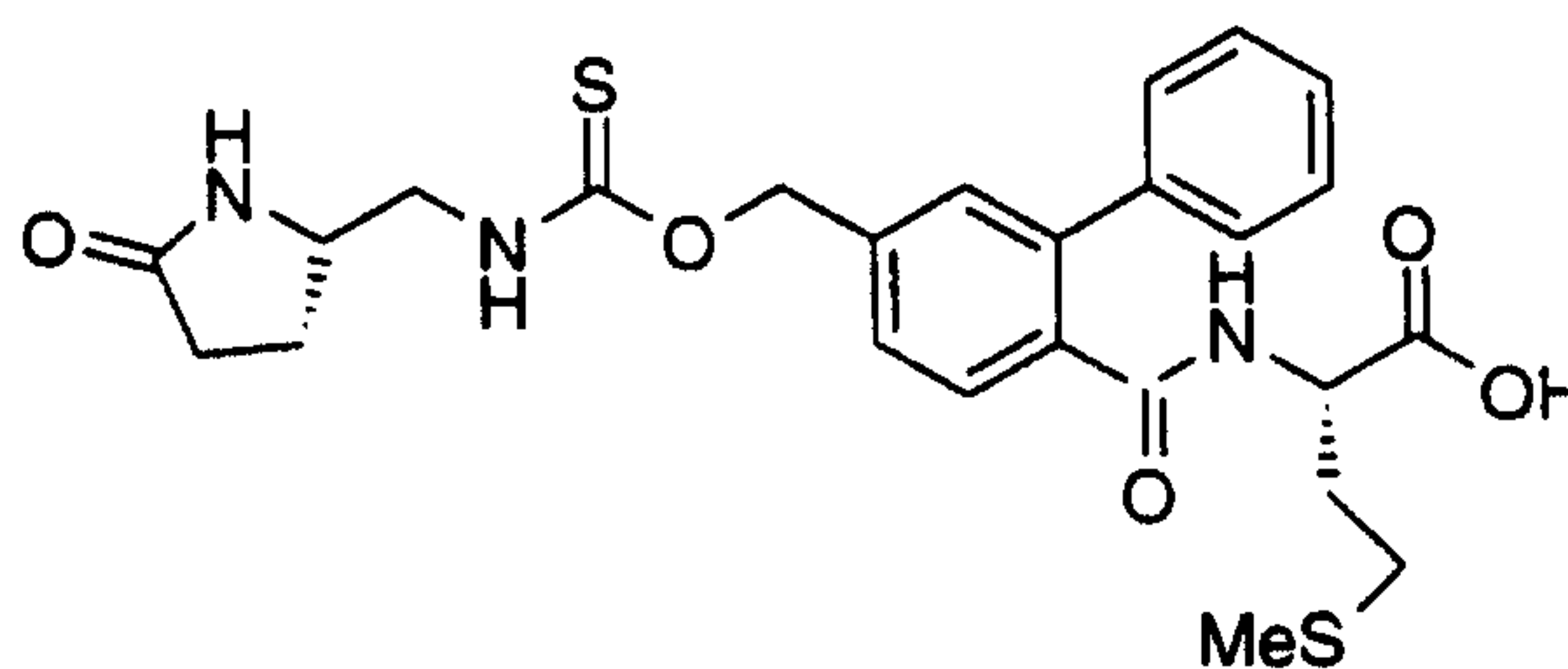
Example 214-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

Using the Procedure of Example 4 with the resultant compound from Example 18B affords the title product.

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Example 224-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxymethylene)-2-phenylbenzoyl methionine

Using the procedure of Example 8 with the resultant compound from Example 16D provides the title product.

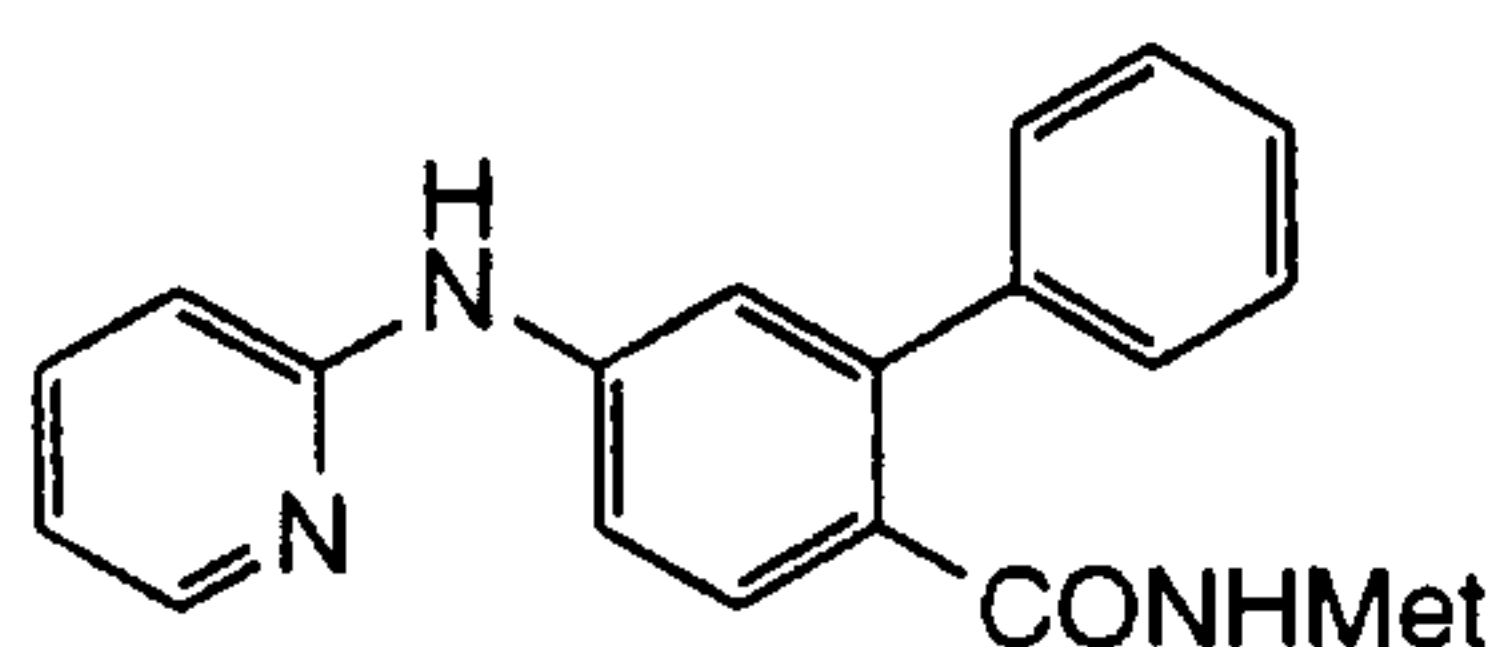


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Example 23

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl
methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

Example 24A

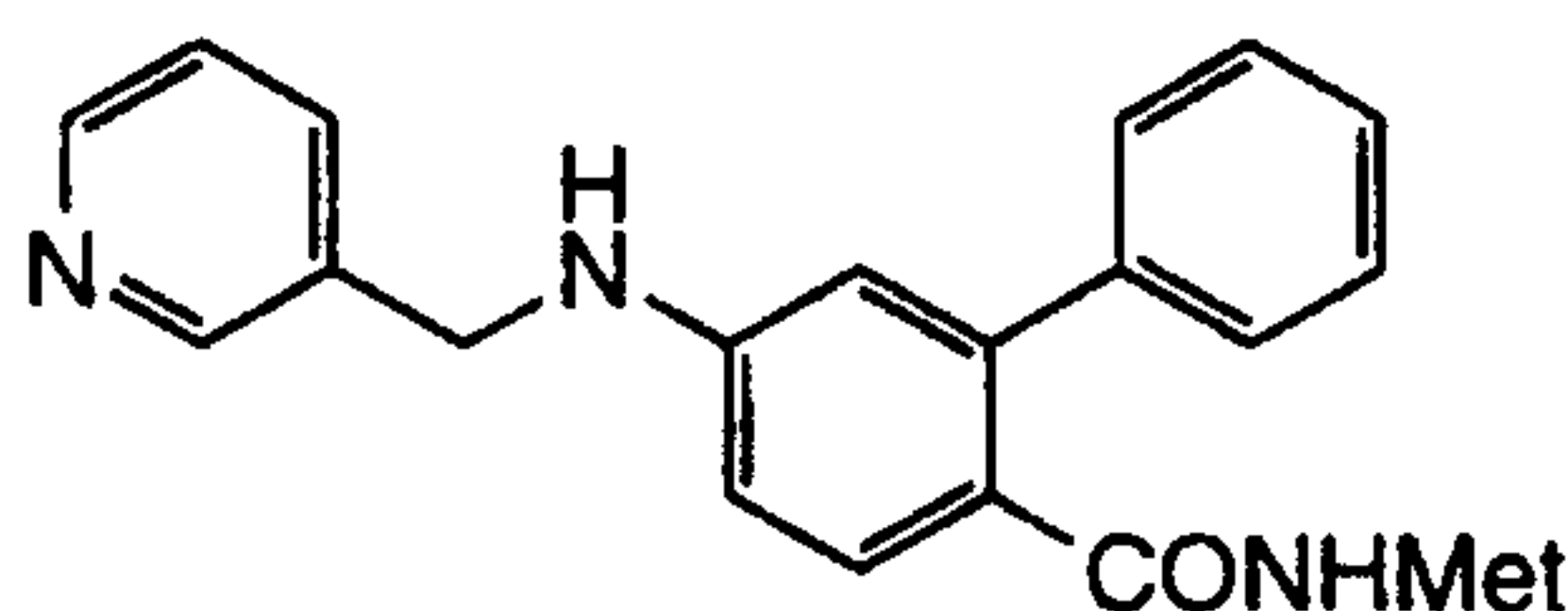
4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

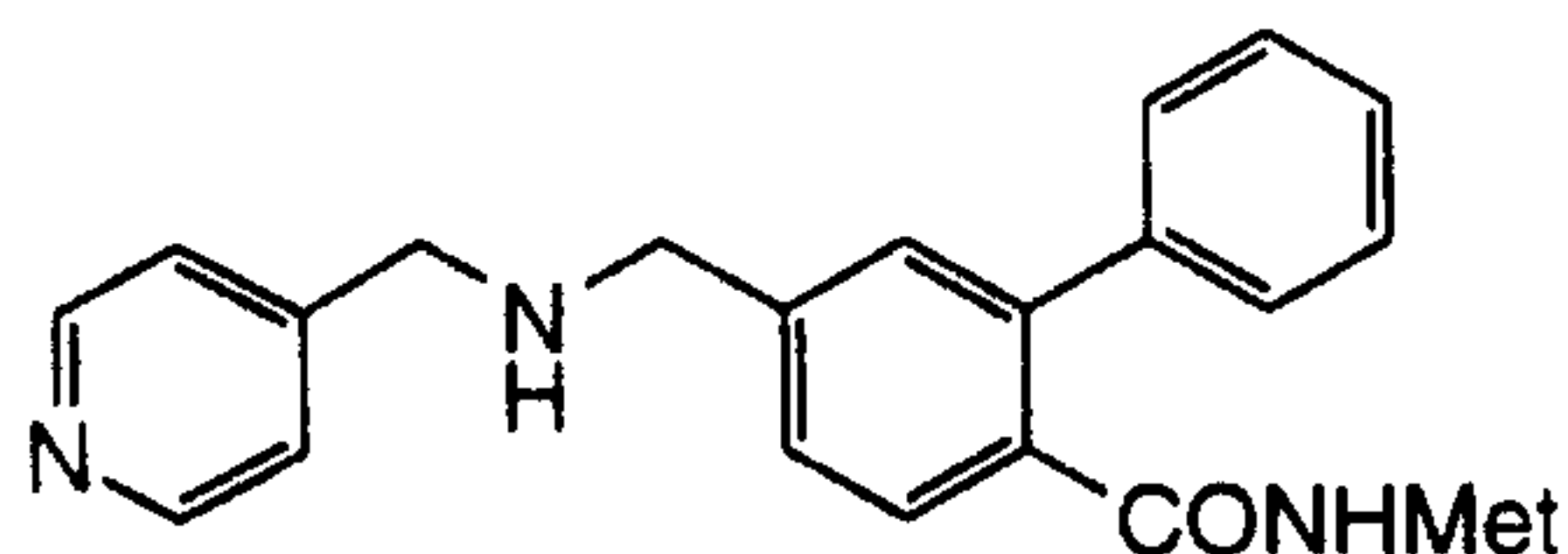
4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and NaCNBH₃ (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

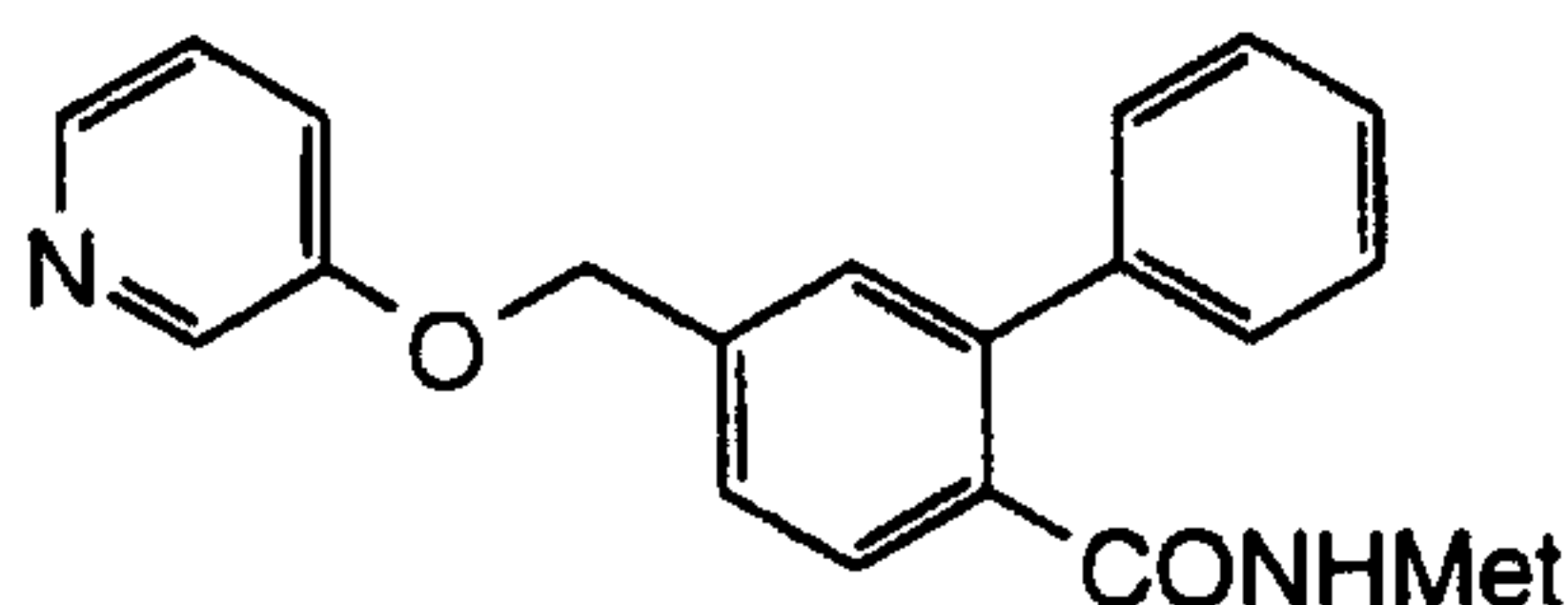
The resultant compound from Example 25A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

Example 27A

4-(p-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

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Example 27B4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

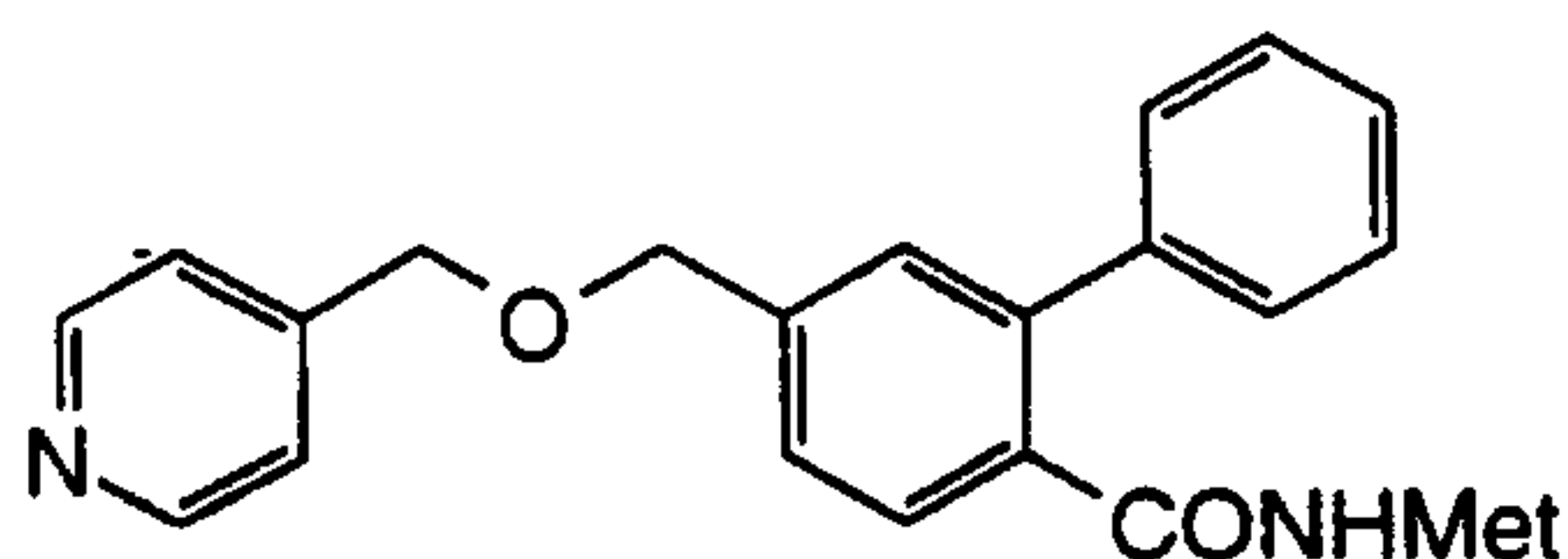
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3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 27C4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

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The resultant compound from Example 27B is hydrolyzed according to the procedure of Example 1B to give the title product.



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Example 284-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionineExample 28A4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

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Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-hydroxymethylpyridine affords the title compound.

Example 28B4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate procedure

4725

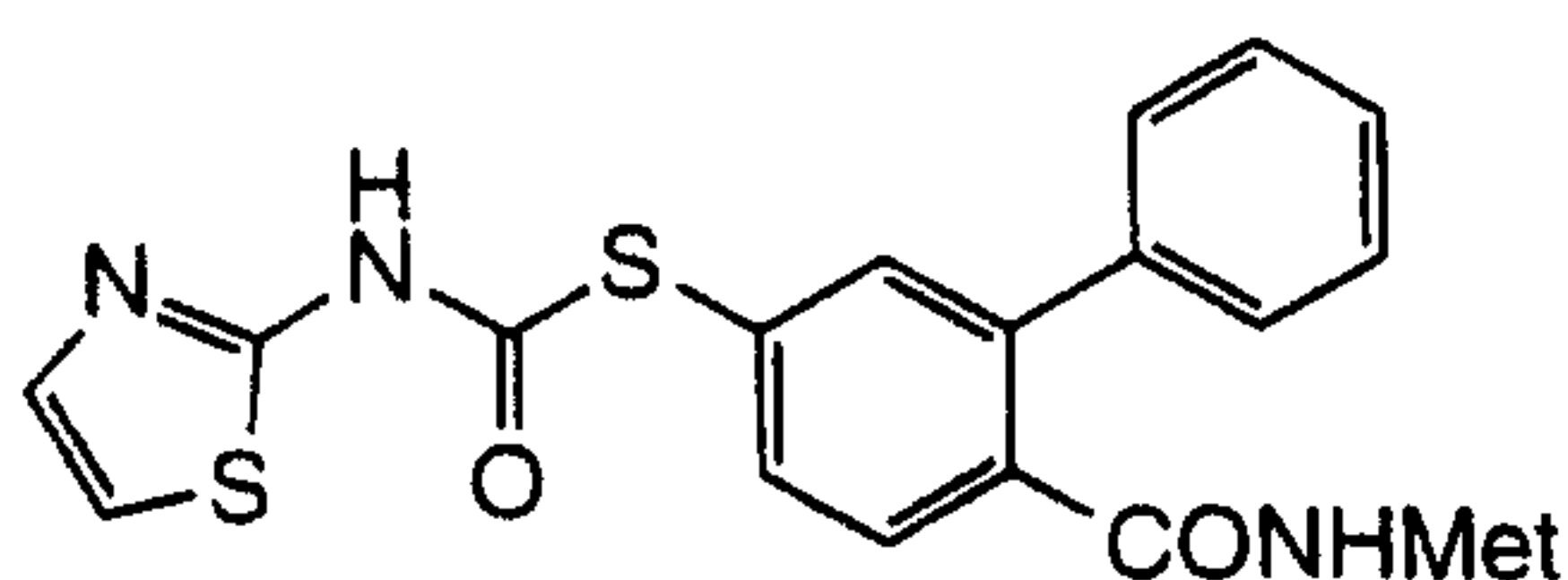
The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

4730

Example 28C

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 28A is hydrolyzed according to the procedure of
 4735 Example 1B to give the title product.

Example 29{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionineExample 29AThiazol-2-ylisocyanate

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0
 4745 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

Example 29B{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester

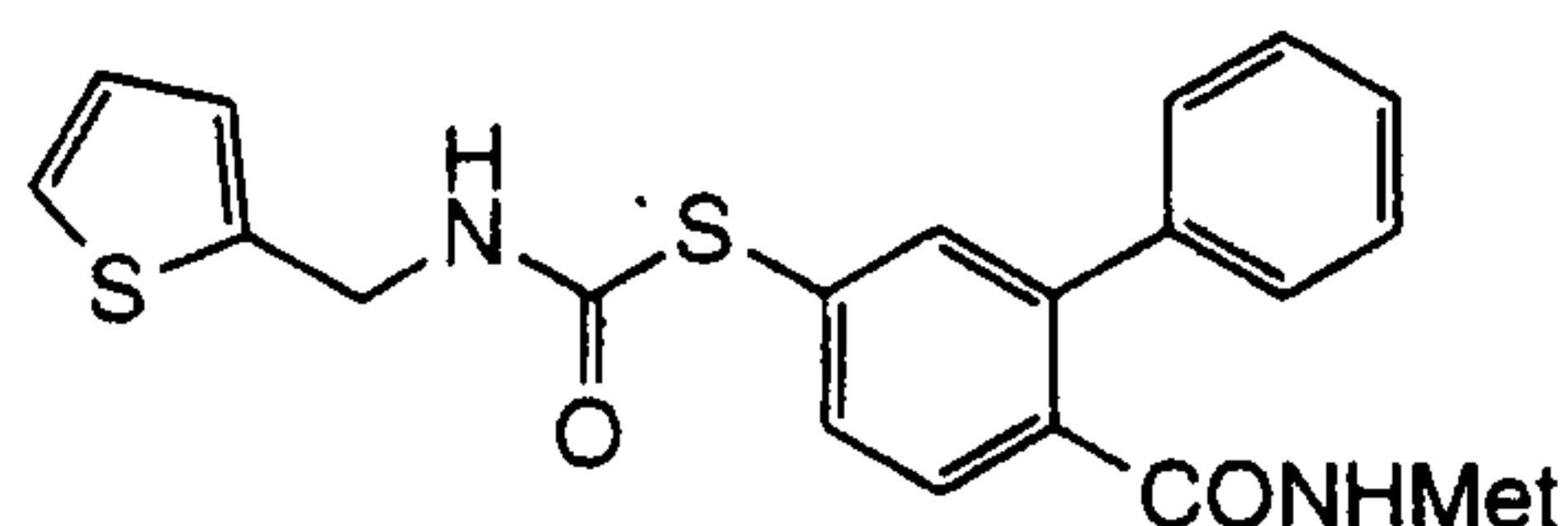
A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or
 4750 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 29C{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester, alternate procedure

To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or
 4760 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiochloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and
 4765 brine, evaporated, and purified by chromatography on silica gel.

Example 29D{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

The resultant compound from Example 29B is hydrolyzed according to the procedure of
 4770 Example 1B to give the title product.

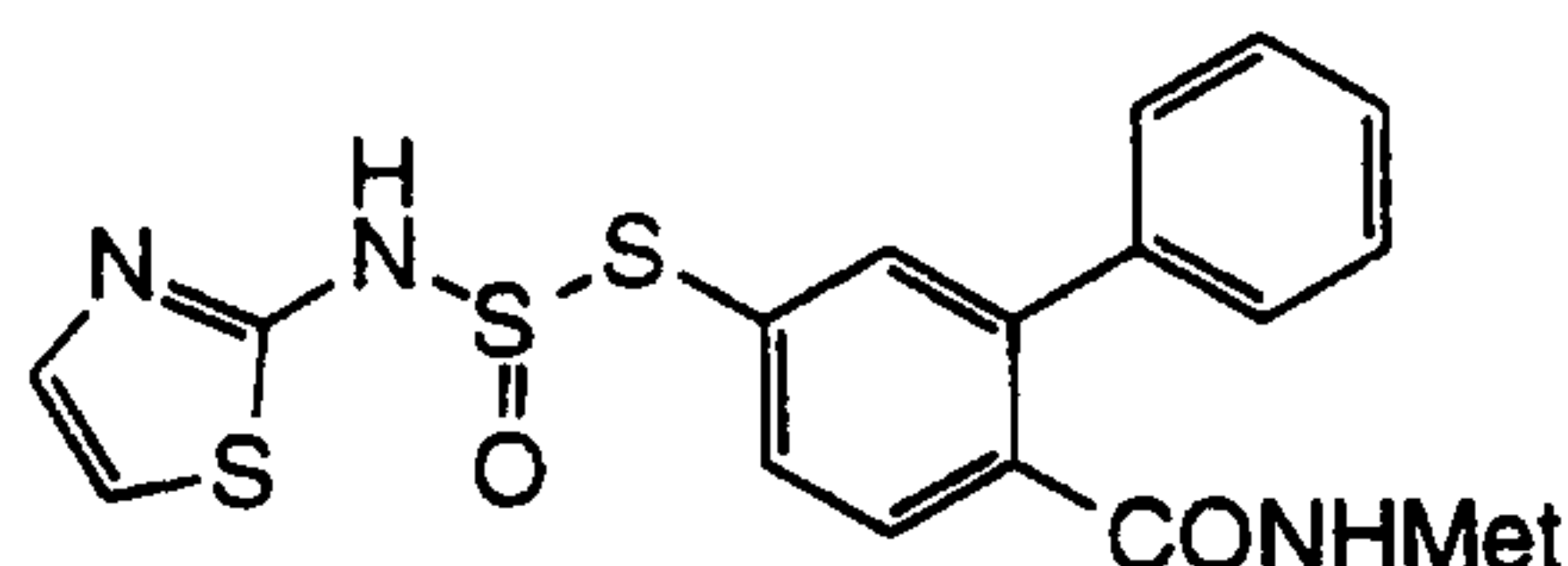


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Example 30{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-
 ylmethylamine affords the title product.

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Example 31{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

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Example 31A(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the
 reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is
 distilled out in vacuo. The resulting material is used without further purification.

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Example 31B{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A
 with the resultant product from Example 31A affords the title compound.

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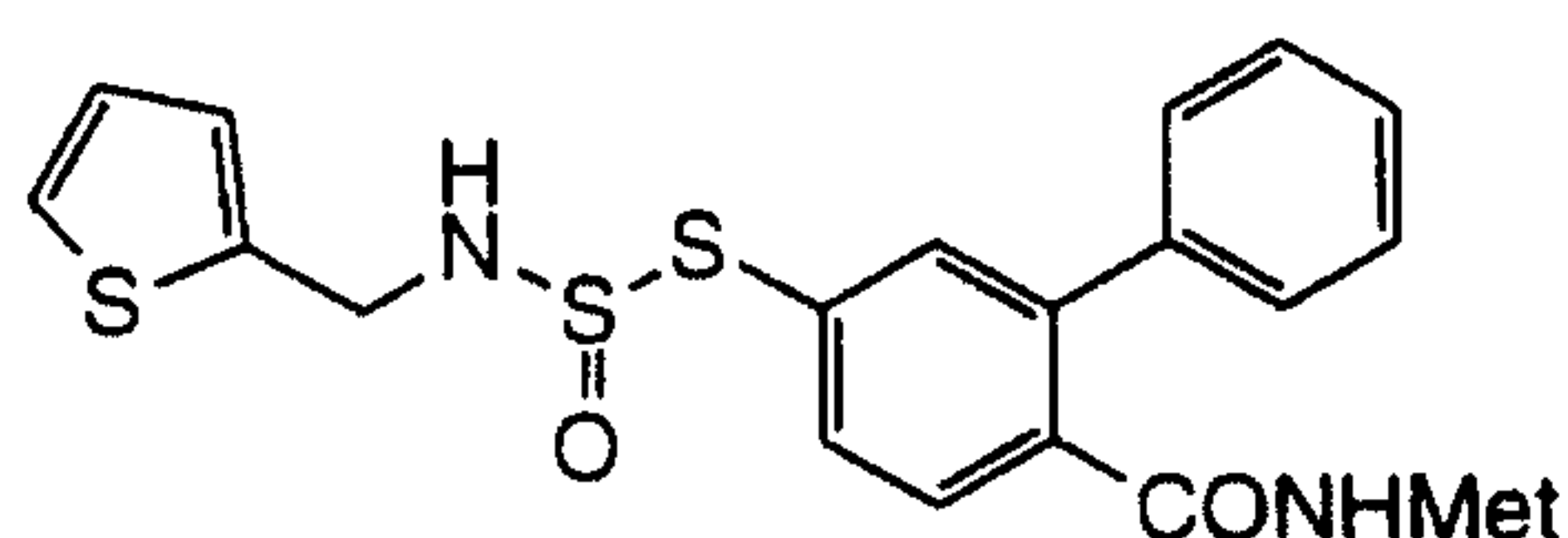
Example 31C{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate
 procedure

Using the procedure of Example 29C but replacing phosgene in toluene with thionyl
 4800 chloride affords the title compound.

Example 31D

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

The resultant compound from Example 31B is hydrolyzed according to the procedure of
 4805 Example 1B to give the title product.



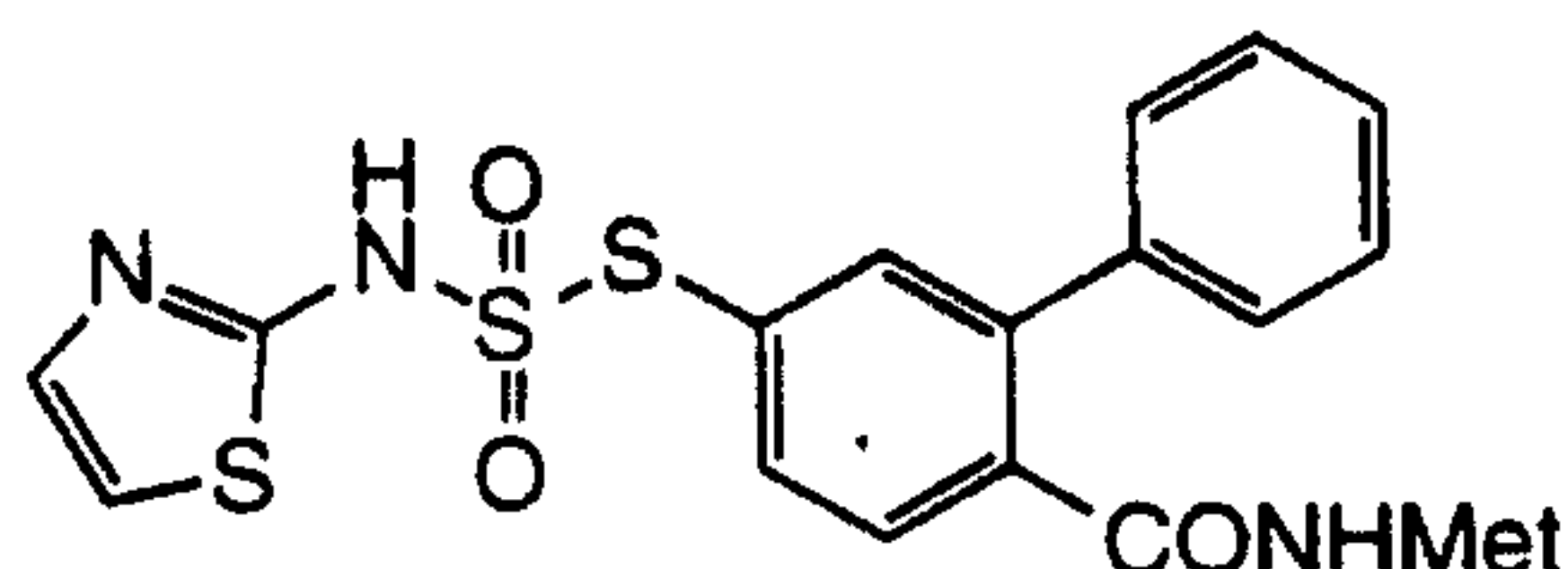
4810

Example 32

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-
 ylmethylamine affords the title product.

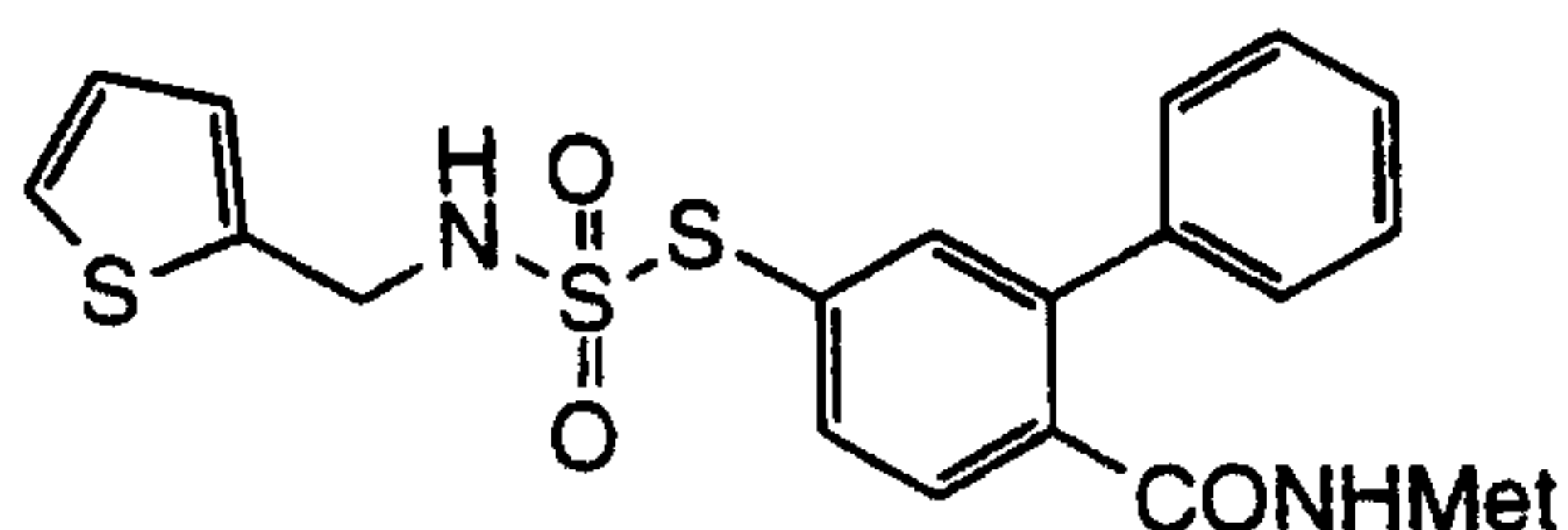
4815



Example 33

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

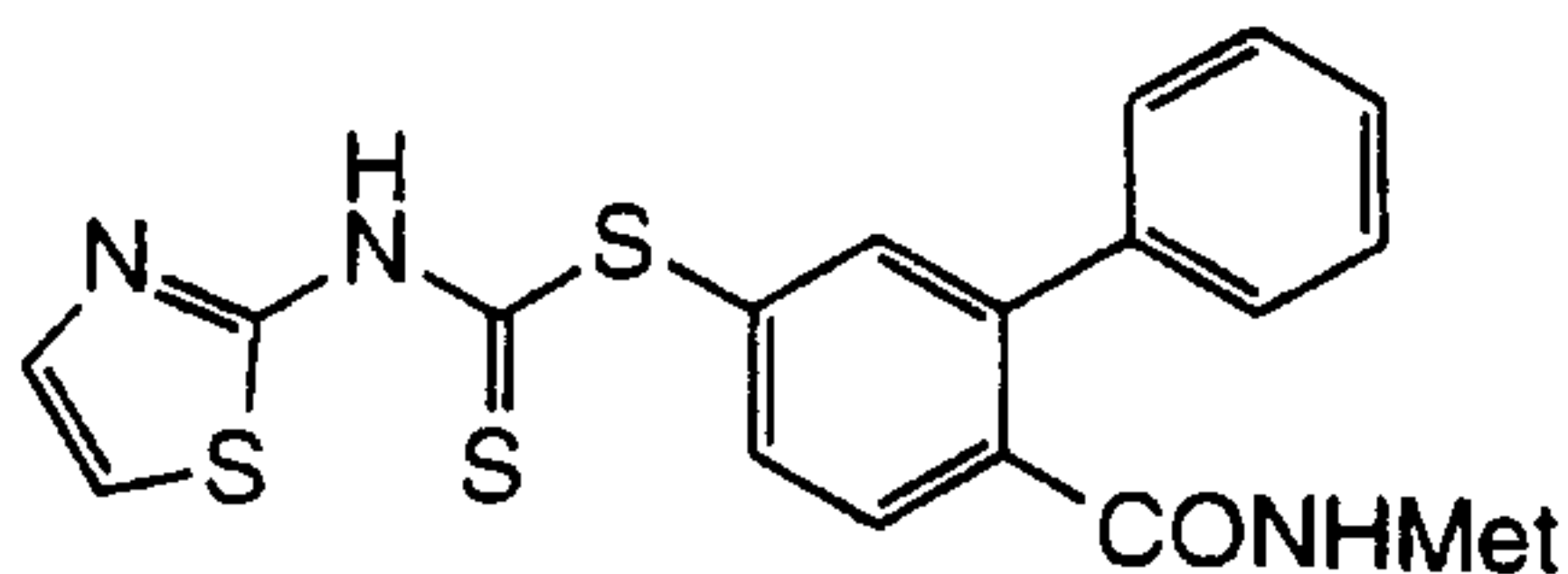
Using the procedure of Example 31 but replacing thionyl chloride with sulfonyl chloride
 4820 affords the title product.



Example 34

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

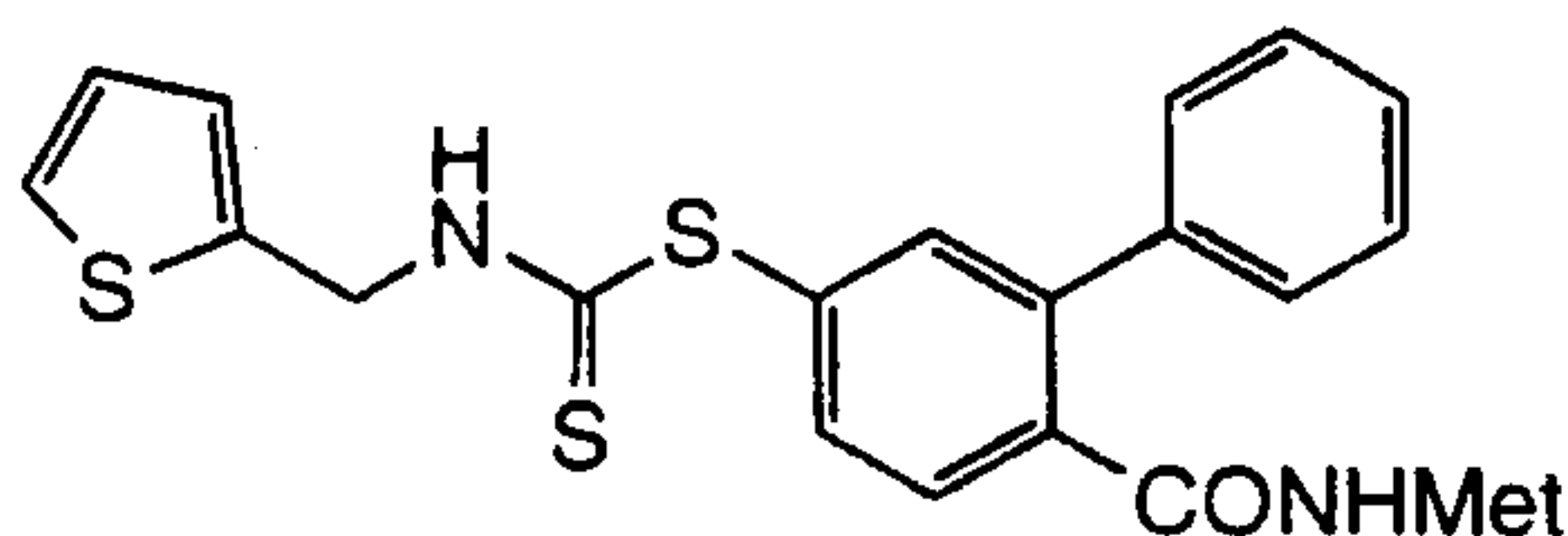
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-
 4825 ylmethylamine and replacing thionyl chloride with sulfonyl chloride affords the title product.



4830

Example 35{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

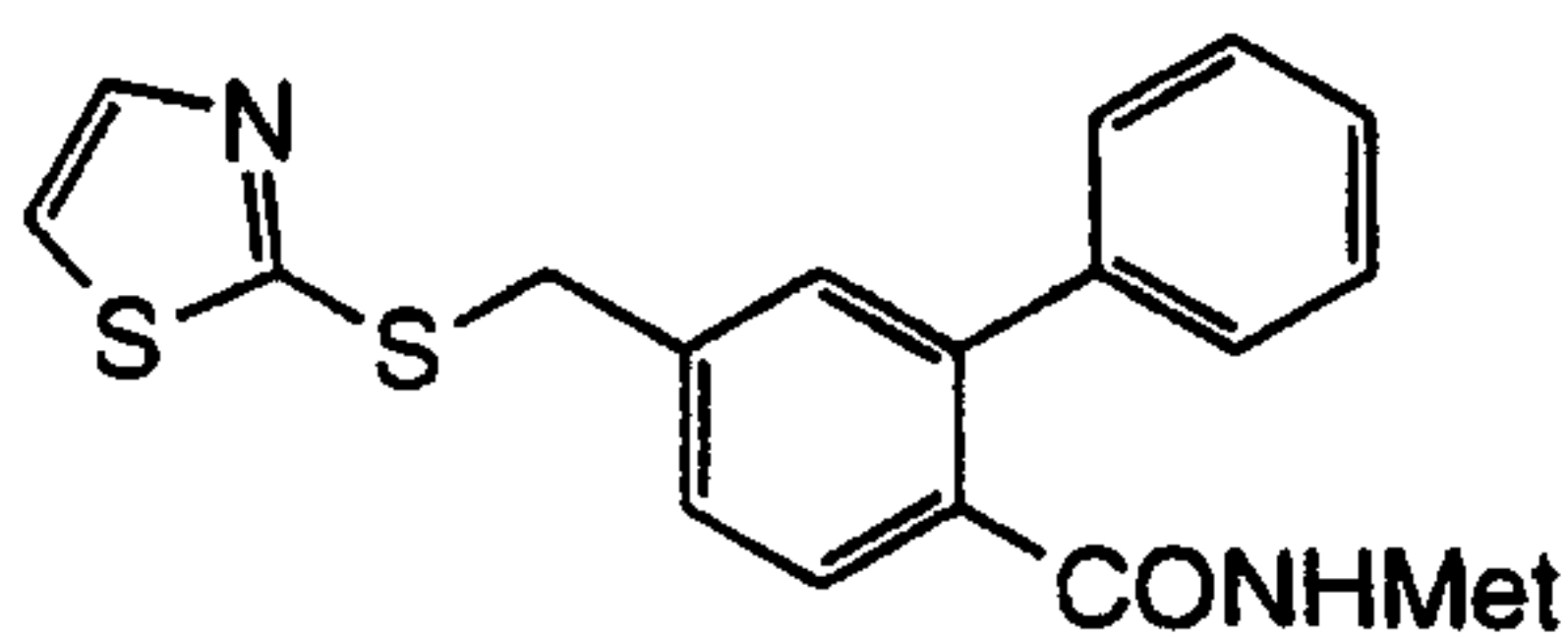


4835

Example 36{2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4840



4845

Example 37{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionineExample 37A{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

4850

4855

Example 37B{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester, alternate procedure

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added
 4860 followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on
 4865 silica gel to afford the title product.

Example 37C

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine methyl ester

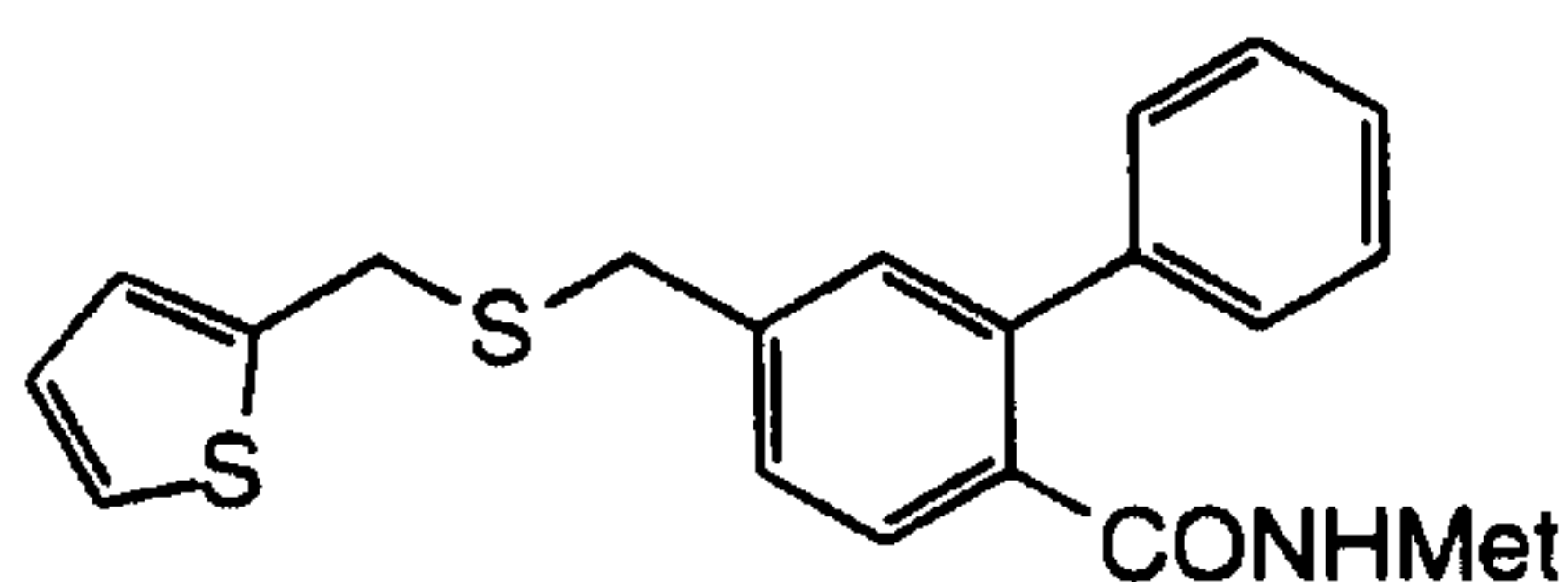
A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol),
 4870 and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

4875

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.

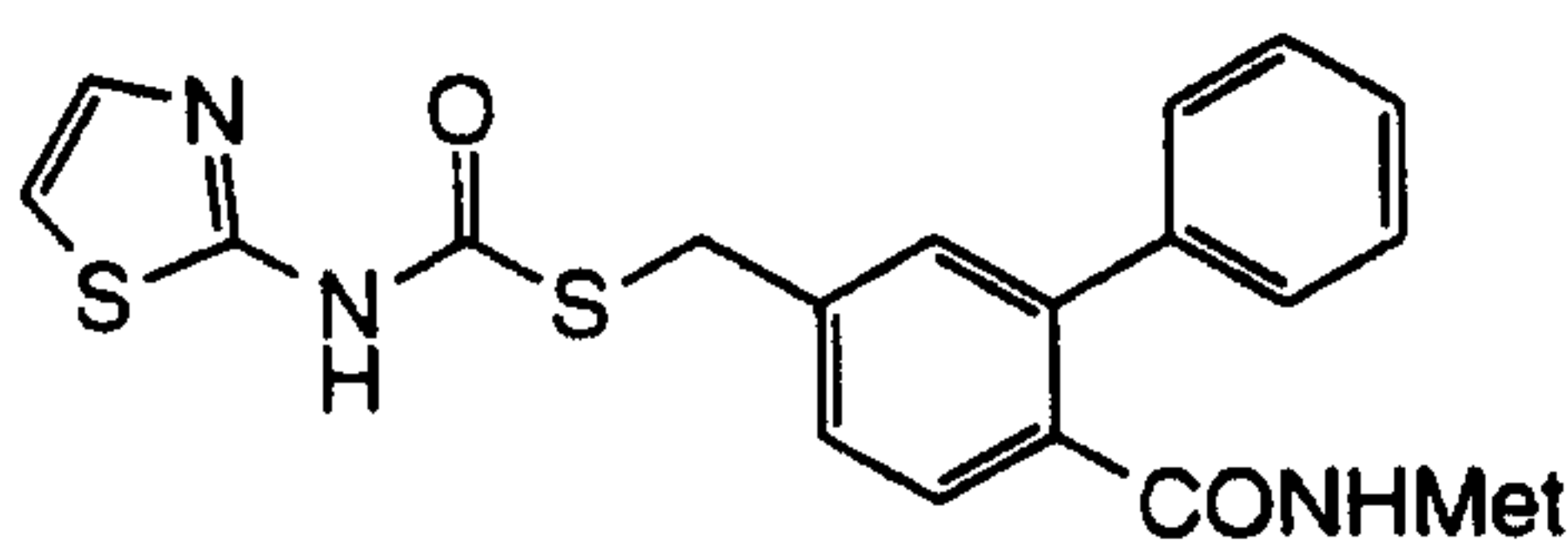
4880



Example 38

{2-Phenyl-4-[(thien-2-ylmethyl)thiomethyl]benzoyl}-methionine

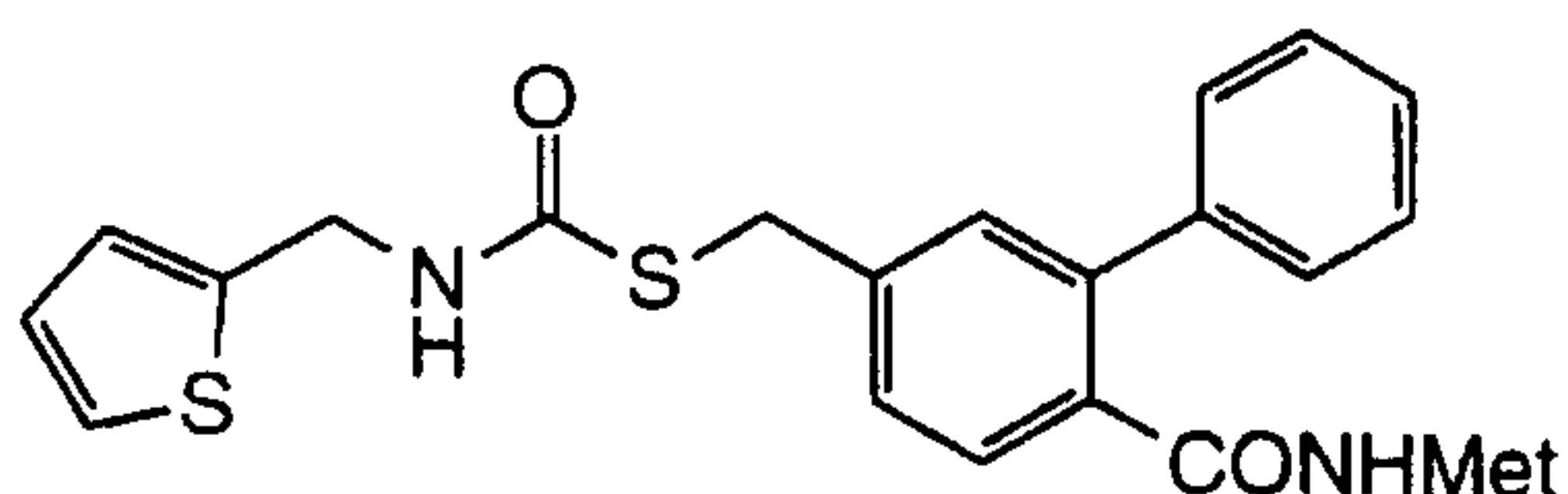
Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.
 4885



Example 39

4890 {2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.



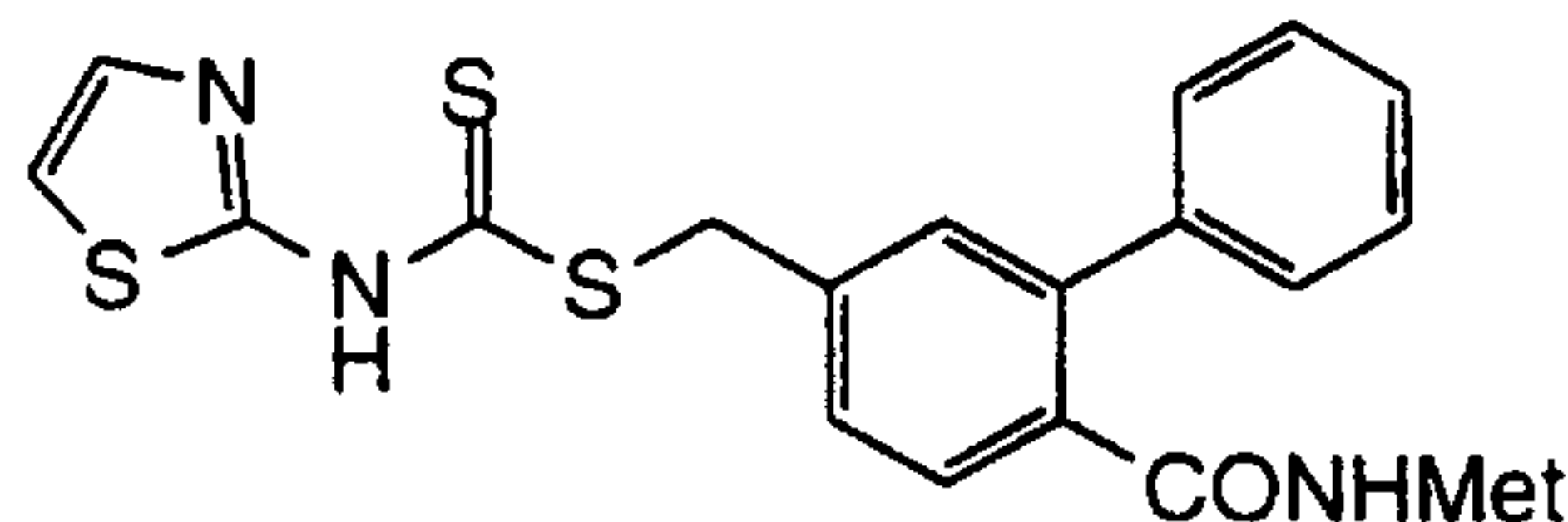
4895

Example 40

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

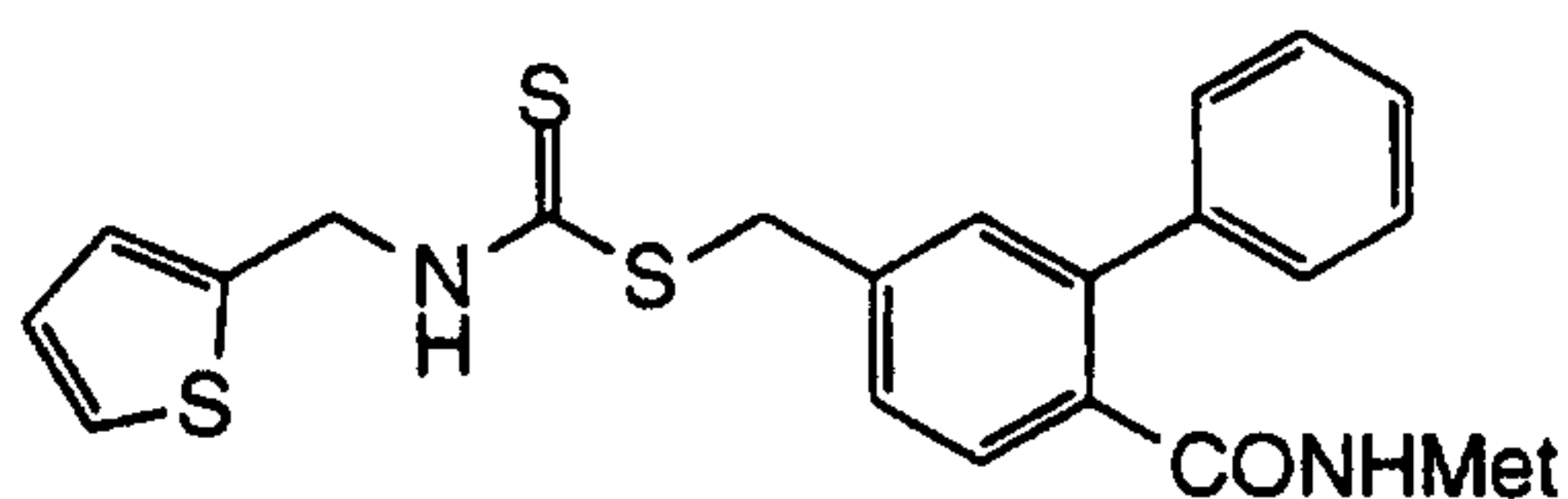
4900



Example 41

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

4905 Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.



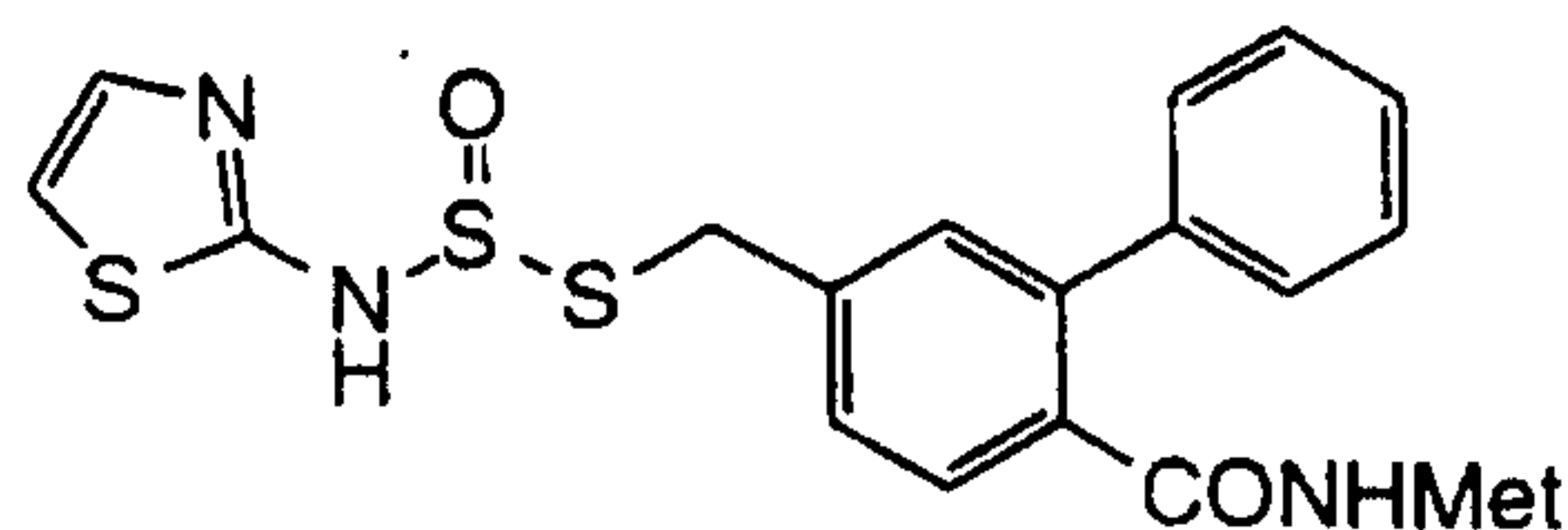
4910

Example 42

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

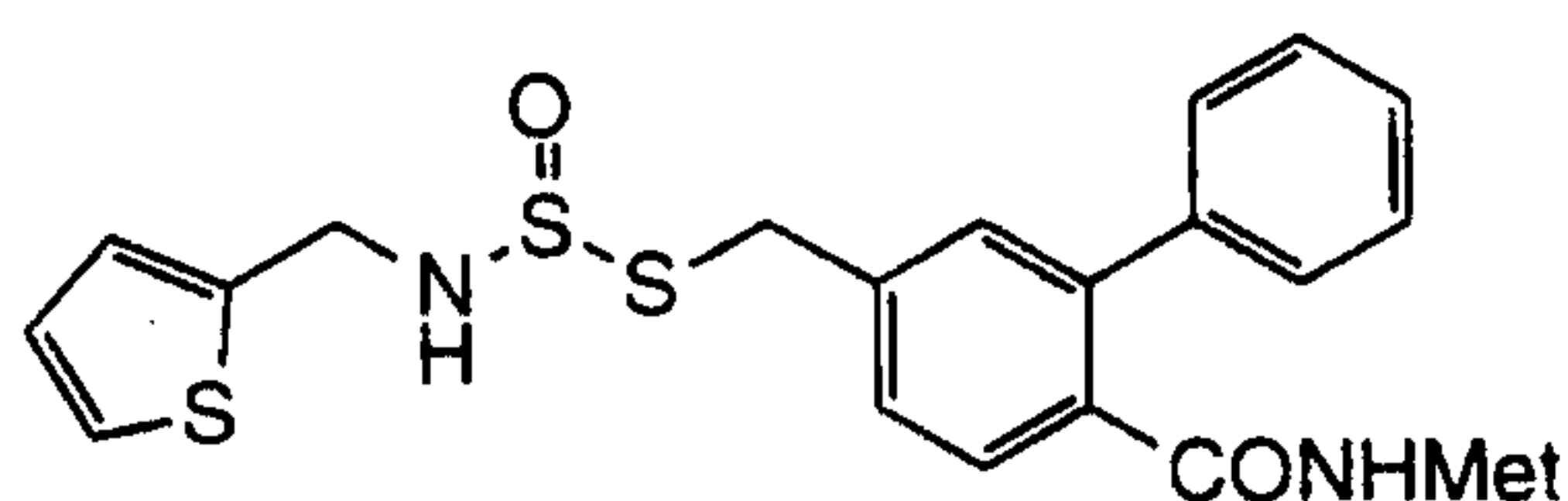
Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4915

**Example 43**

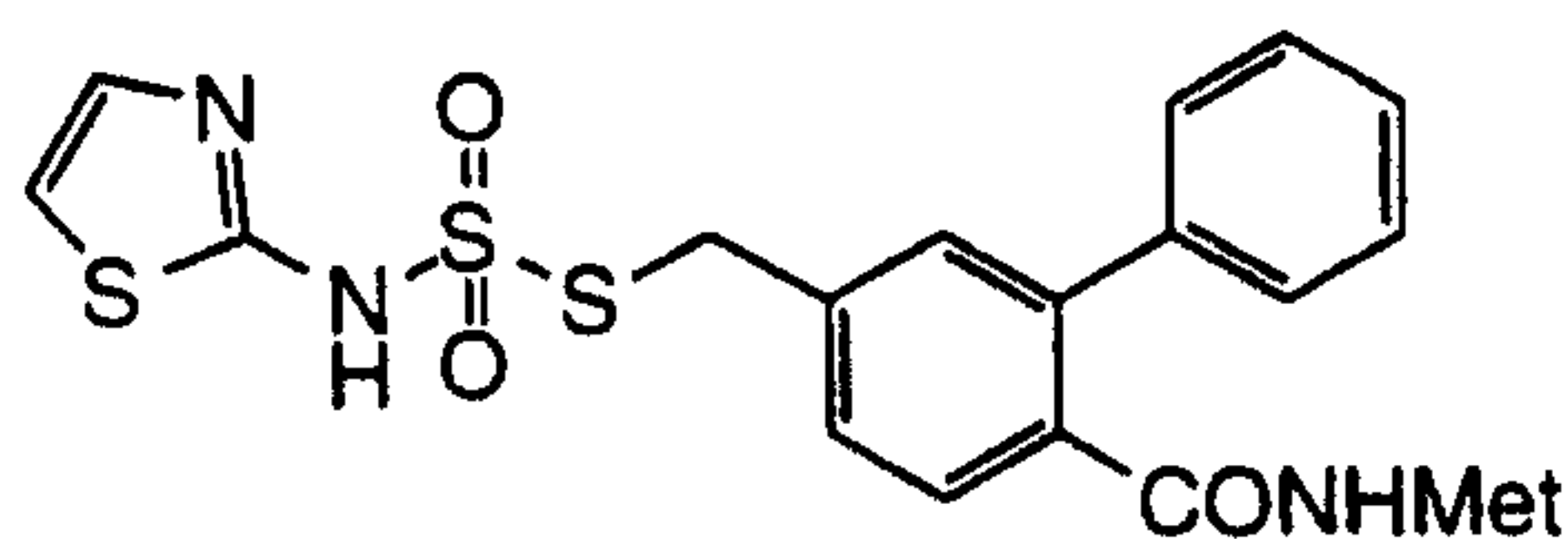
{2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.

**Example 44**

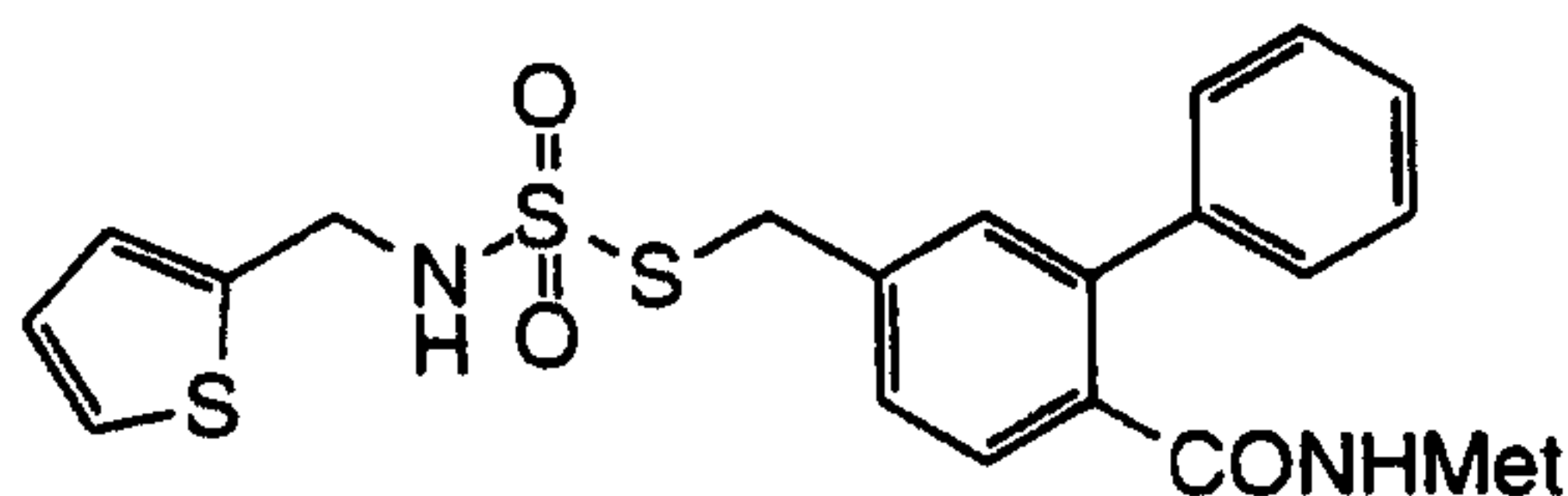
{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl}methionine

Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

**Example 45**

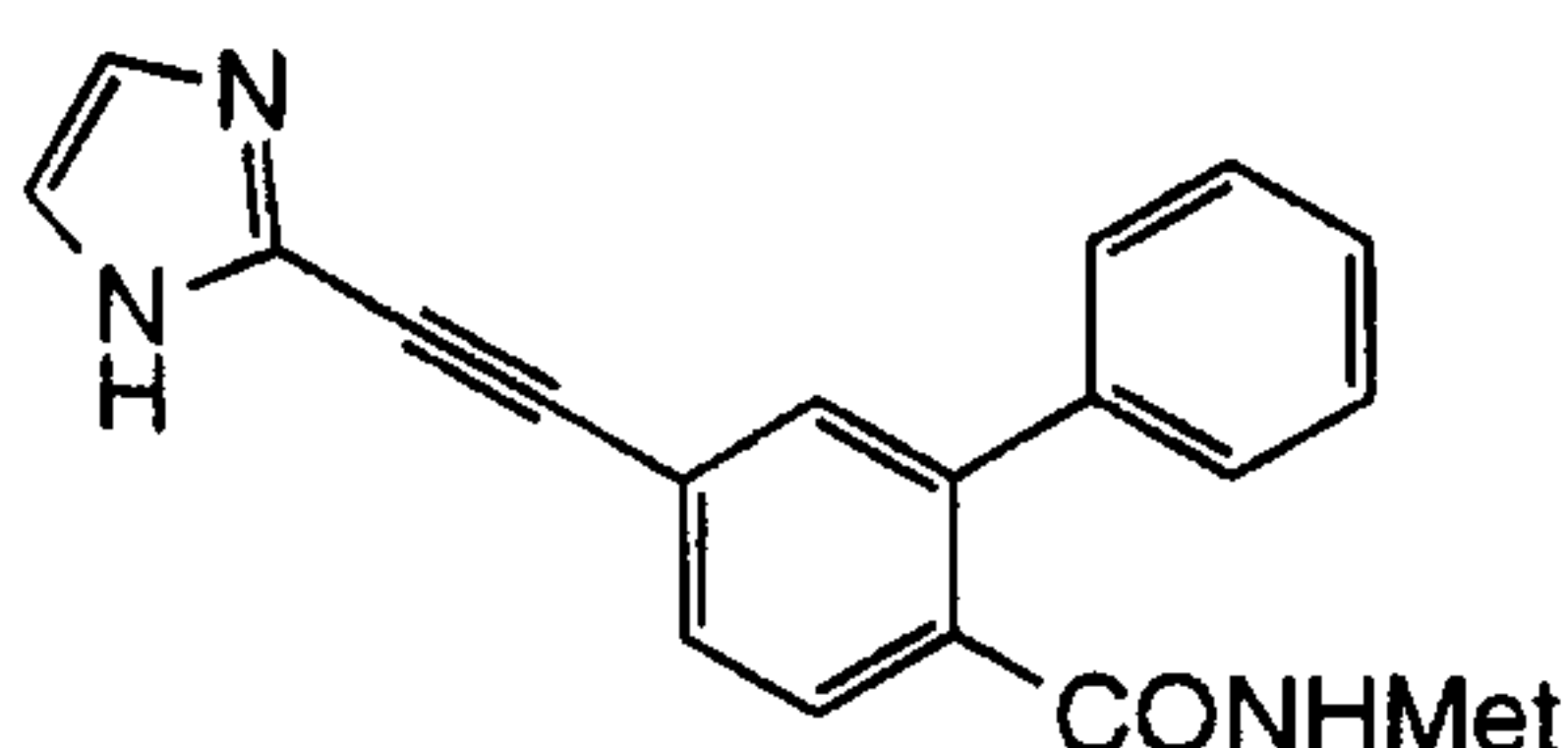
{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfonyl chloride affords the title product.

**Example 46**

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl}-methionine

4945 Using the procedure of Example 31 with the resultant product from Example 37A, replacing thionyl chloride with sulfuryl chloride, and replacing 2-aminothiazol with thien-2-ylmethanamine affords the title product.



4950

Example 47{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}methionineExample 47A(4-Ethynyl-2-phenylbenzoyl)methionine methyl ester

4955 A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol), diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine) palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated.

4960 The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified with column chromatography on silica gel to give the title product.

4965

Example 47B{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and

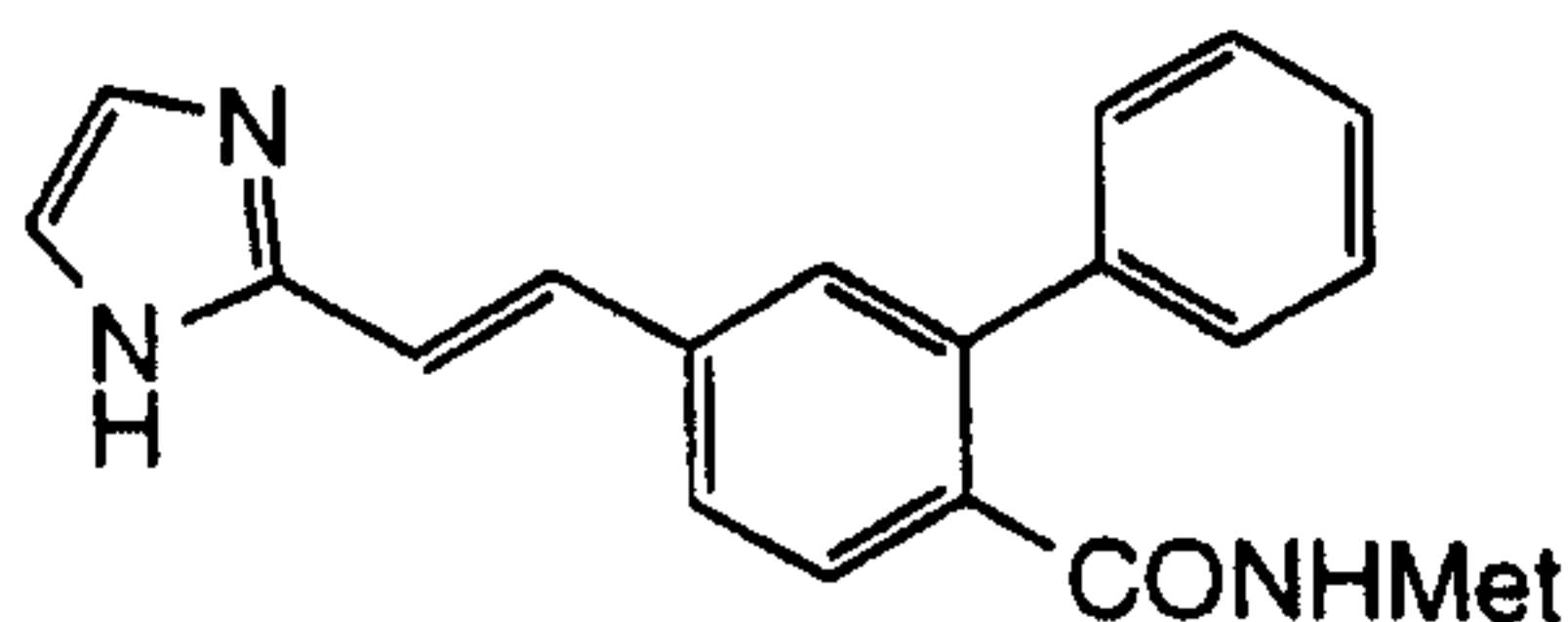
4970 copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the residue is purified with column chromatography on silica gel to give the title product.

Example 47C

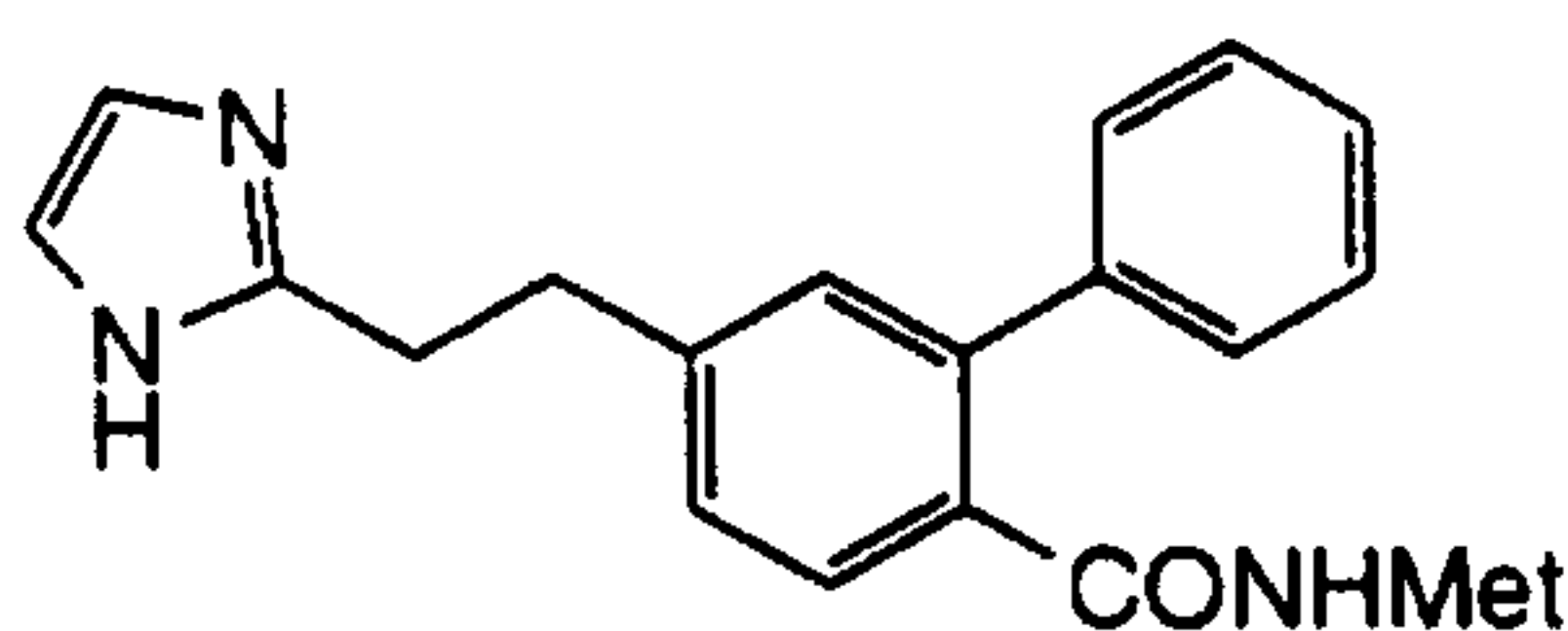
4975

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine

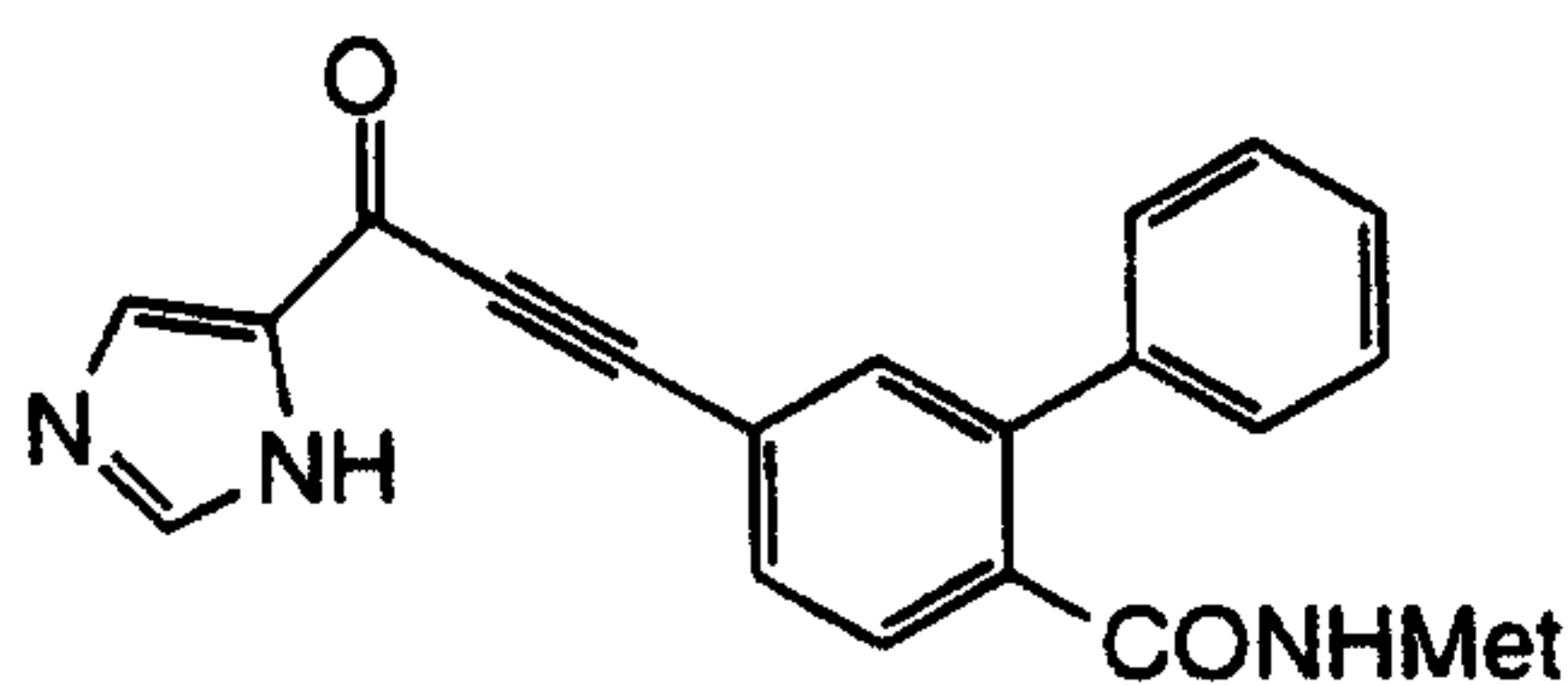
The resultant compound from Example 47B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 48{4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl}-methionine

The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.

Example 49{4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl}-methionine

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.

Example 50{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionineExample 50A{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

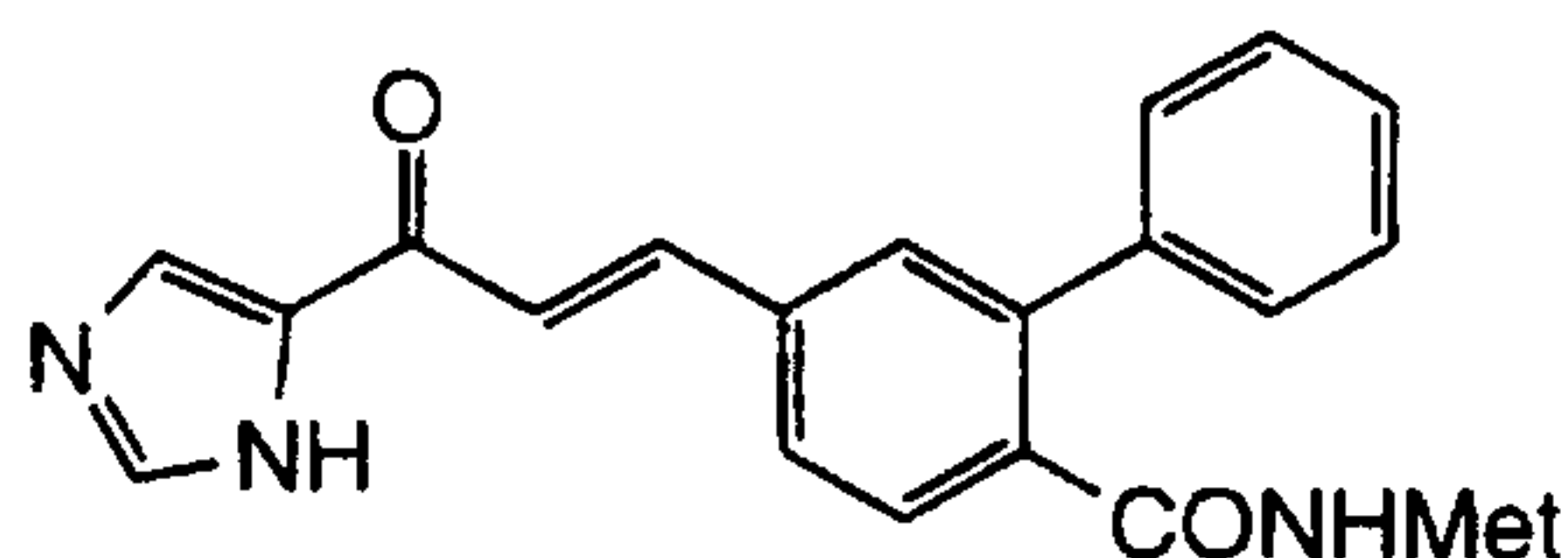
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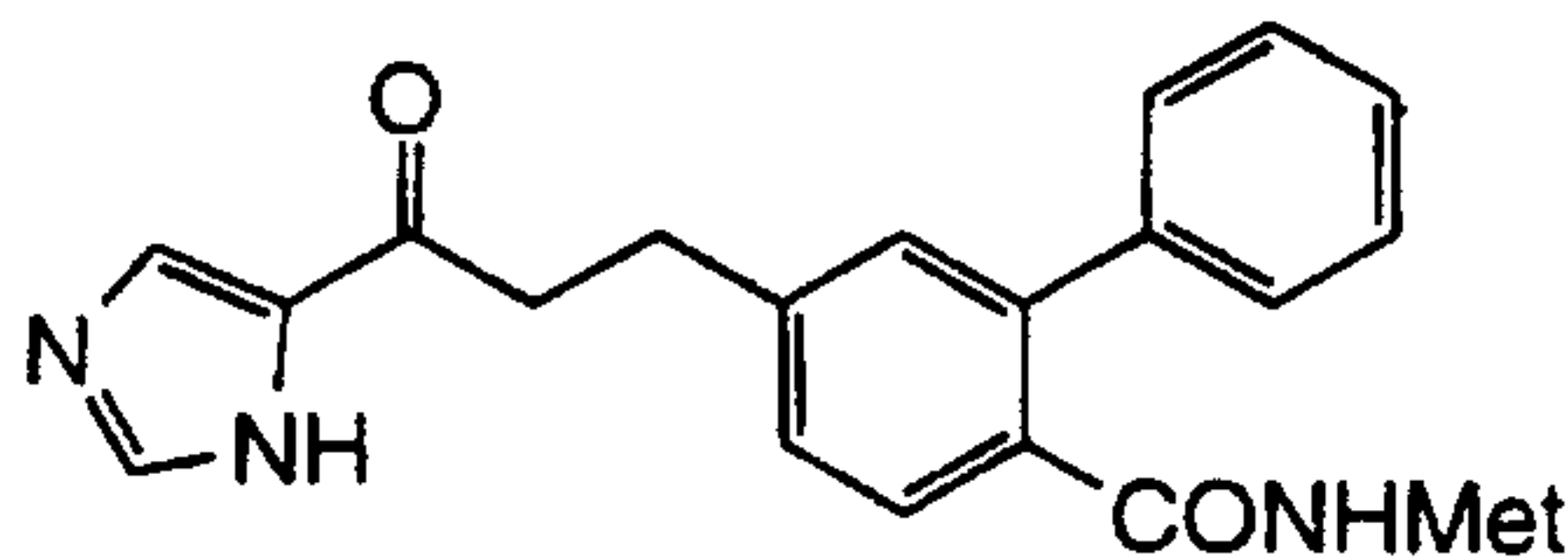
A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 50B{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

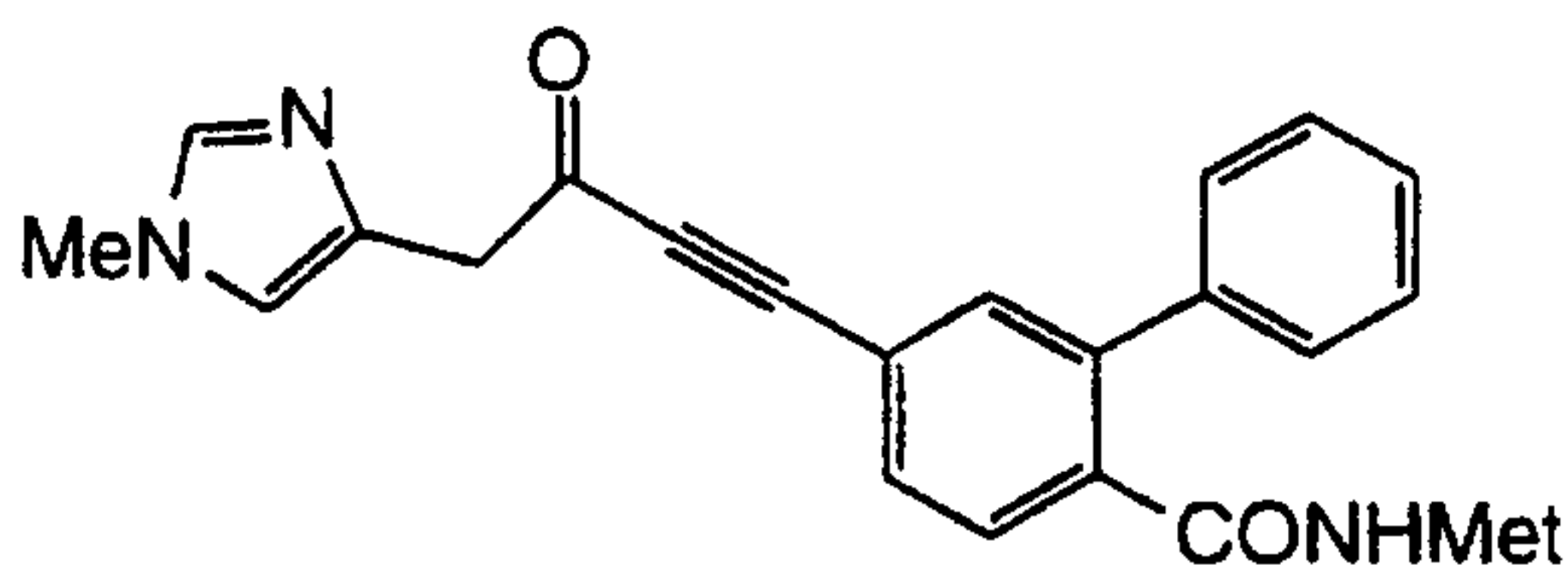
The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 51{4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.

Example 52{4-[2-(Imidazol-4-ylcarbonyl)ethyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.

Example 53

5035 {4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

Example 53A

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine methyl ester

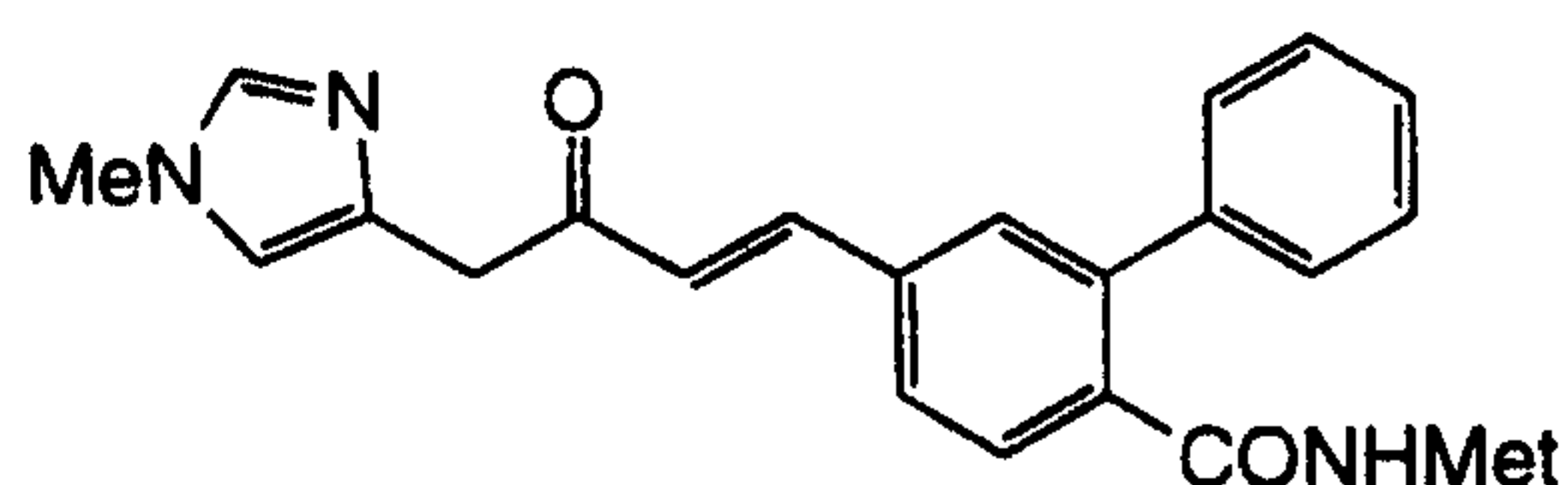
5040 To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates
5045 no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

5050 Example 53B

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.

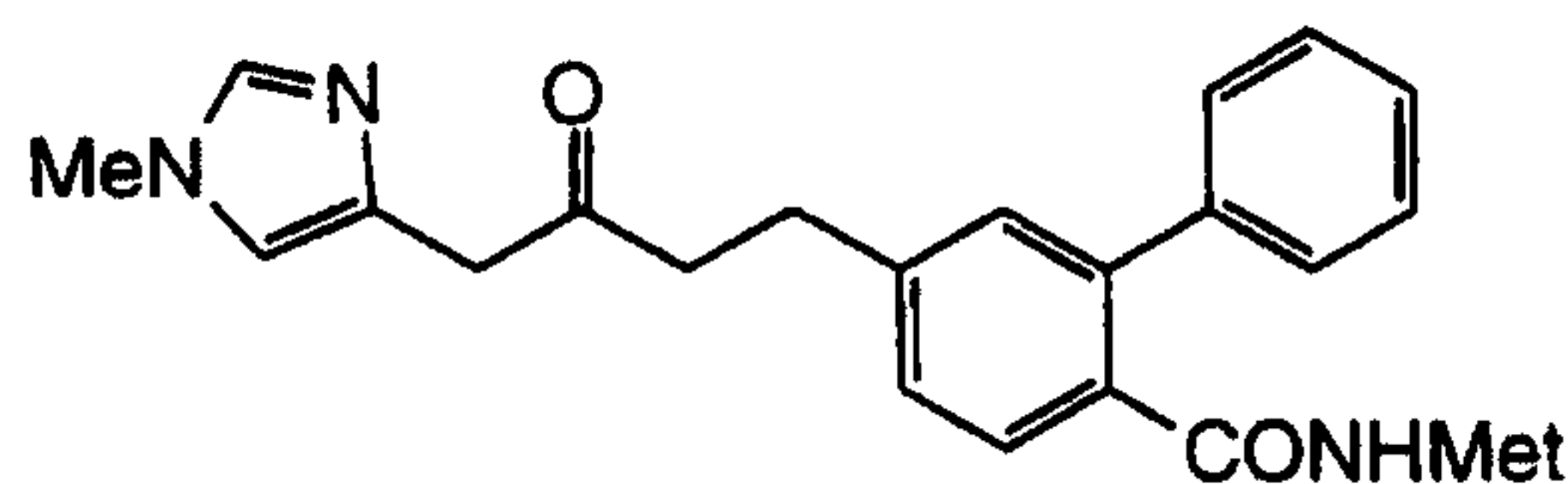
5055



Example 54

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 53 affords
5060 the title product.



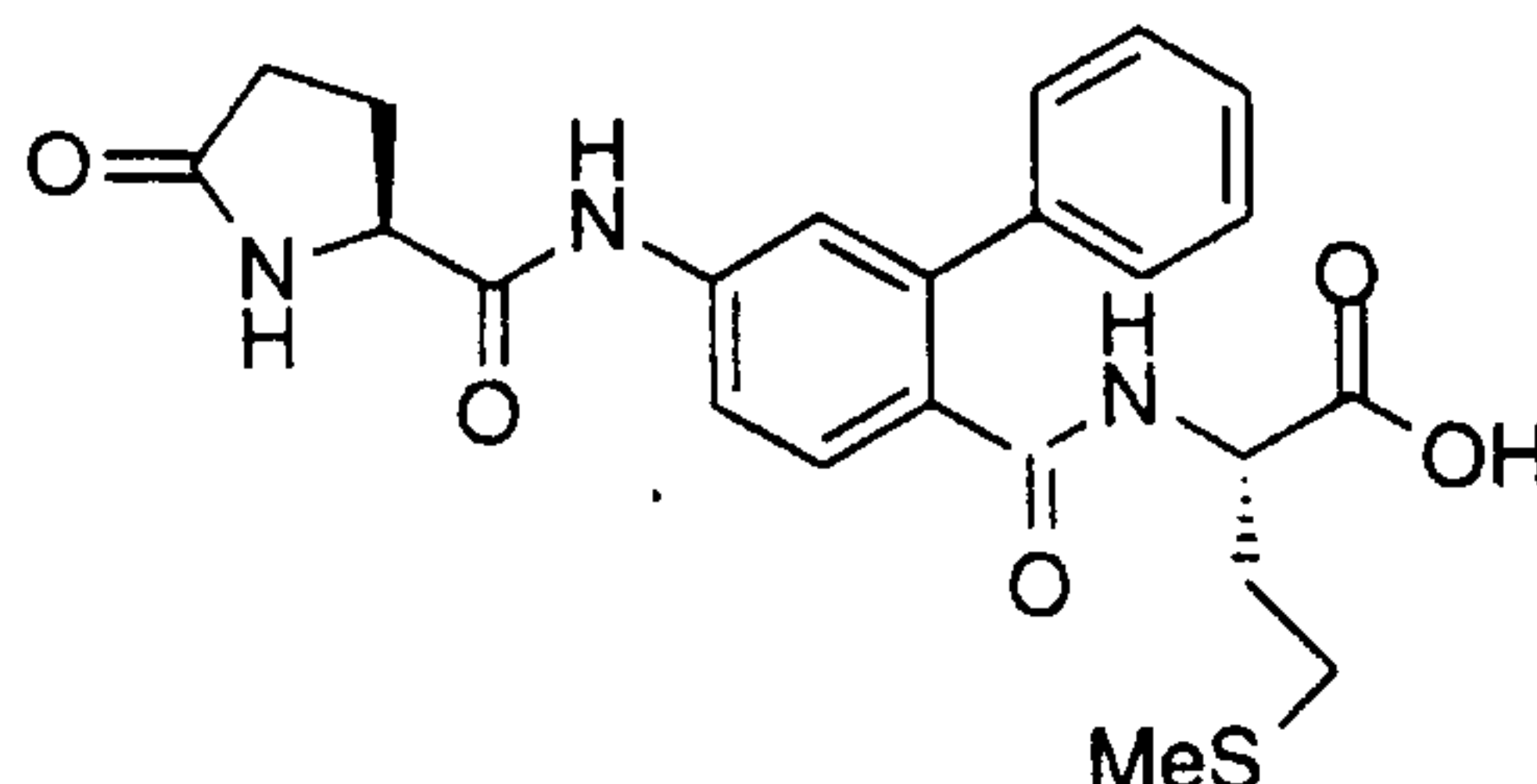
Example 55

5065 {4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyl]-2-phenylbenzoyl}-methionine

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Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



5070

Example 56(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionineExample 56A

5075

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

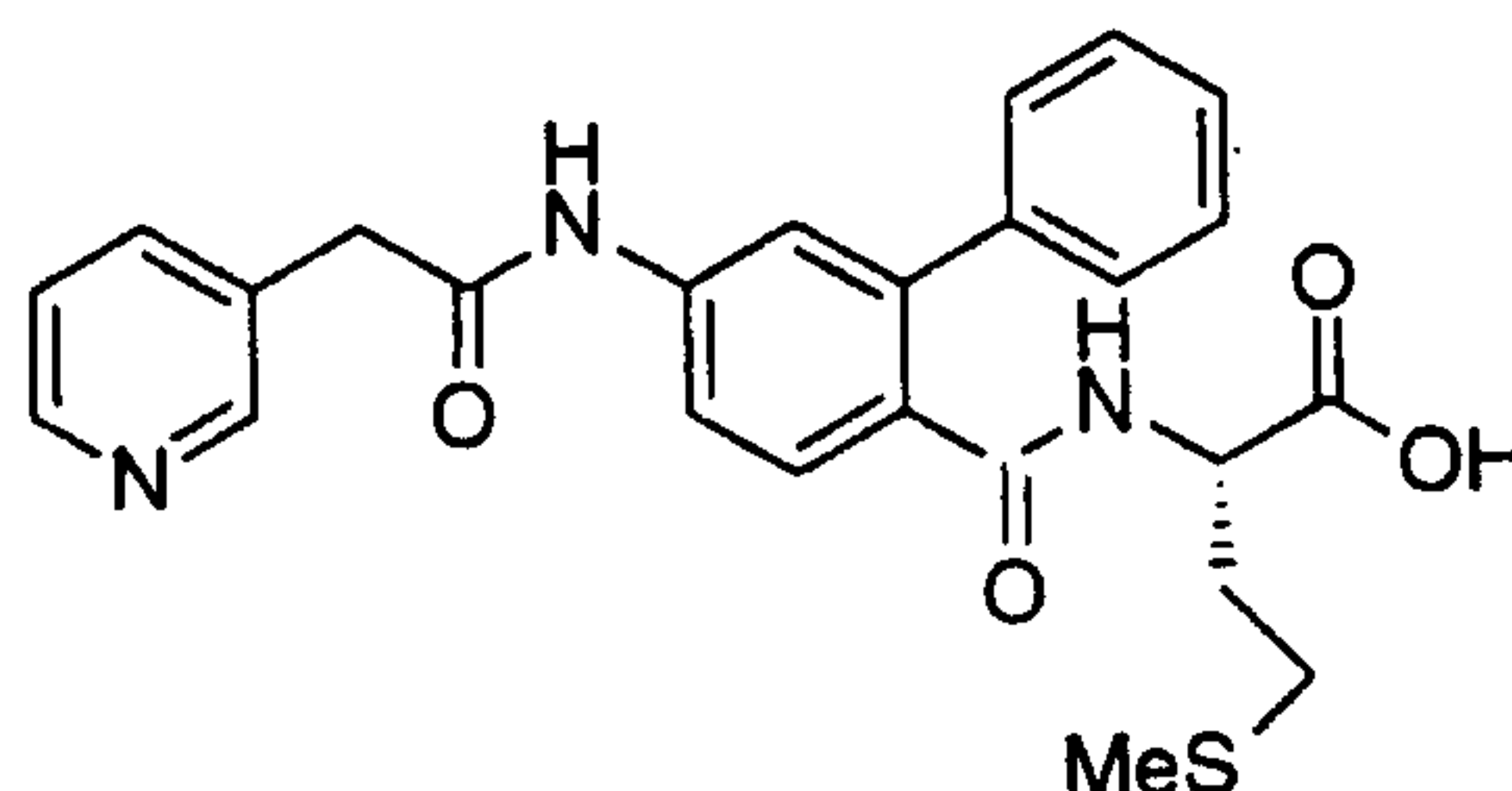
5080

Example 56B

5085

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.



5090

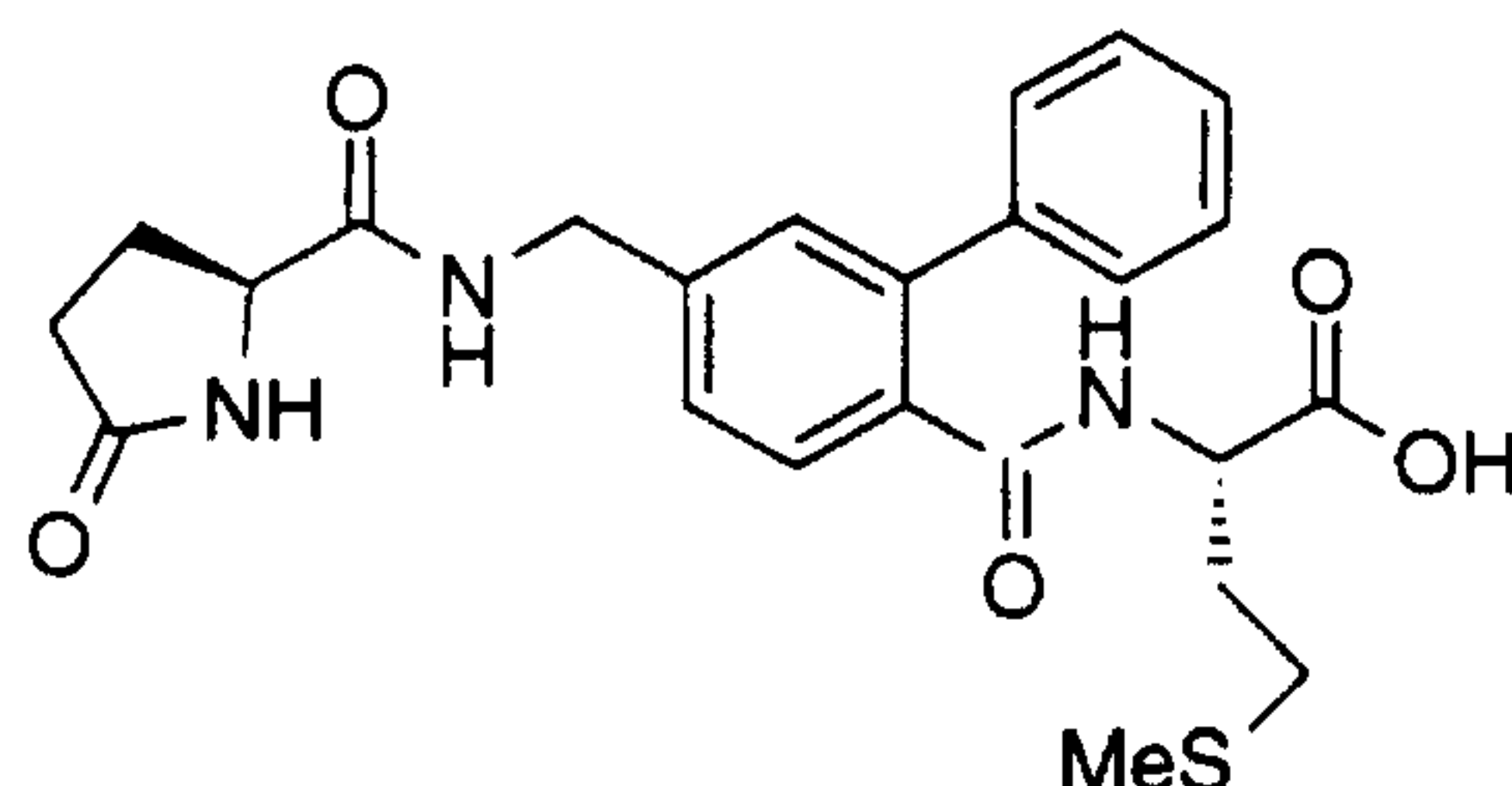
Example 57(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

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Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.

5095

Example 58(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

5100

Example 58A(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

5105

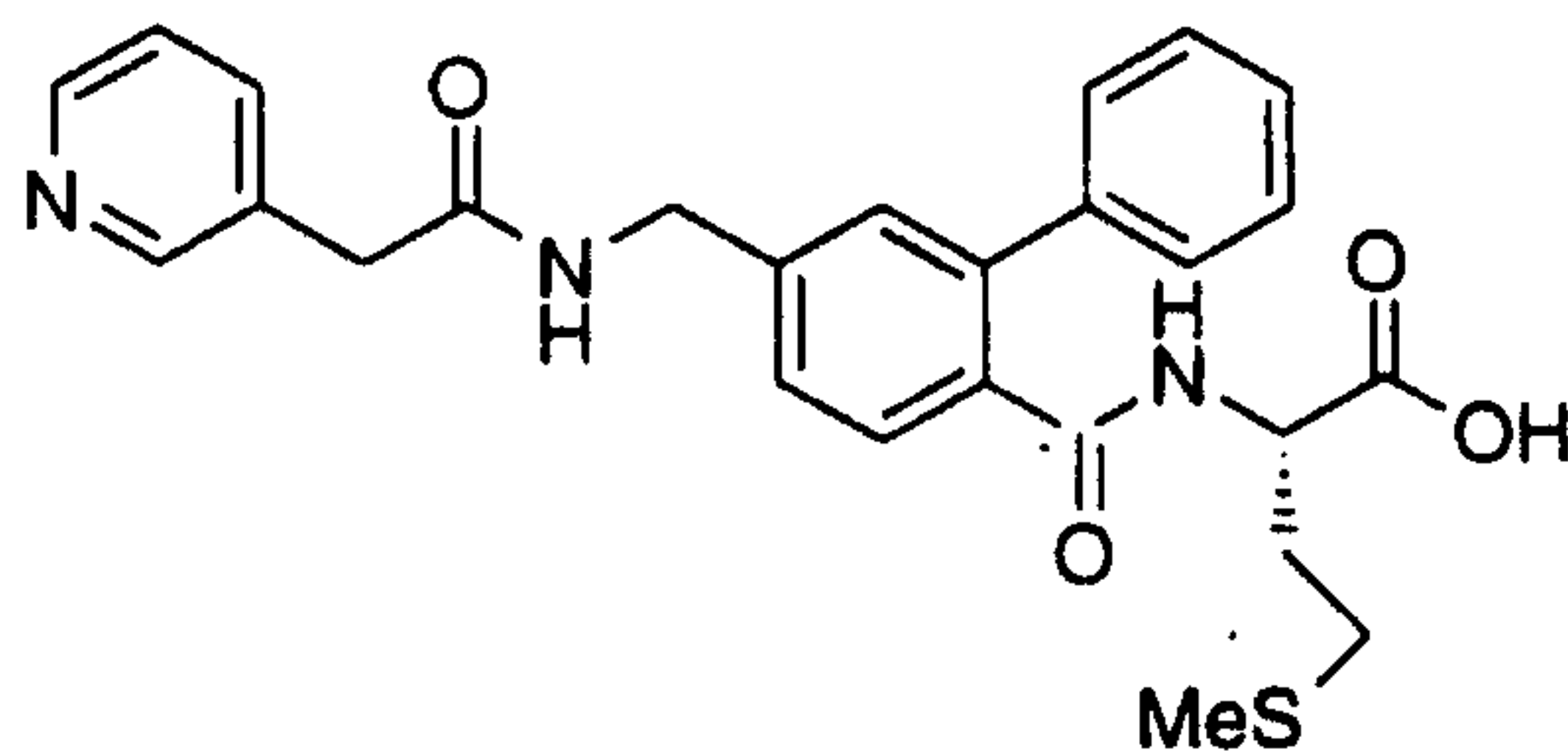
To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

5110

Example 58B(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.

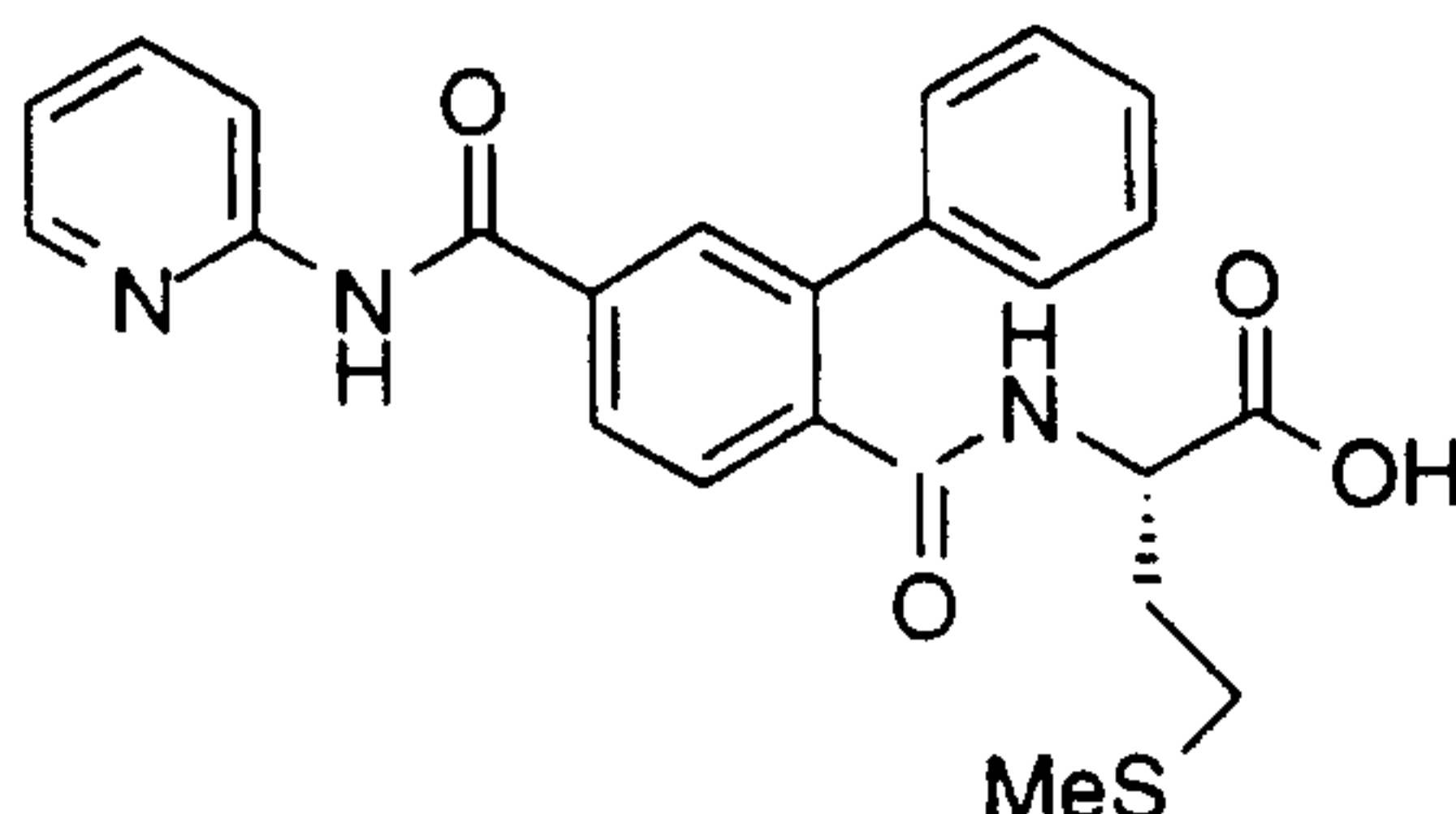
5115

Example 59naming error((S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine)

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- 5120 Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



5125

Example 604-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionineExample 60A4-Carboxy-2-phenylbenzoyl methionine methyl ester

- 5130 A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

5135

Example 60B4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

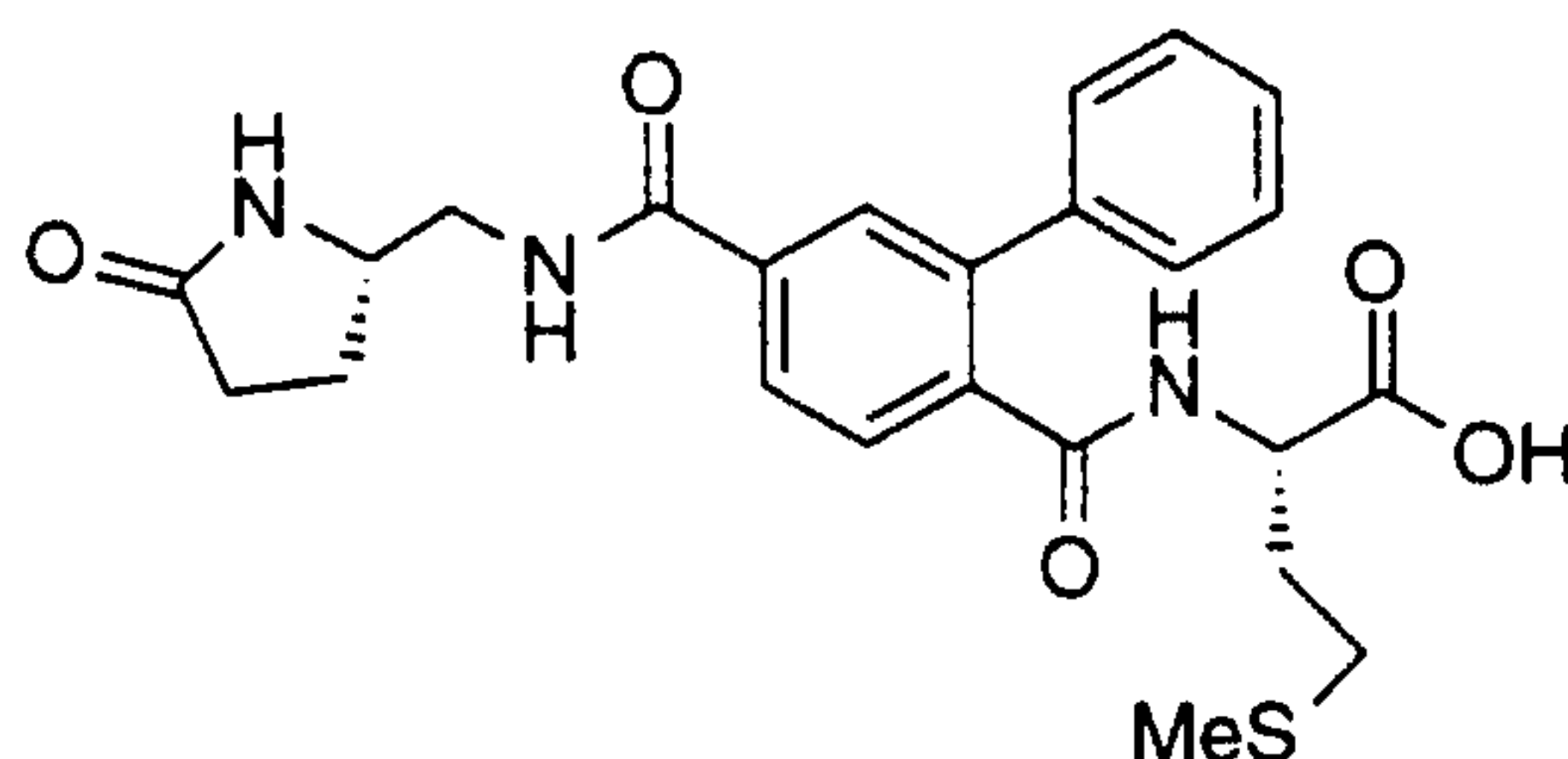
- 5140 To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

5145

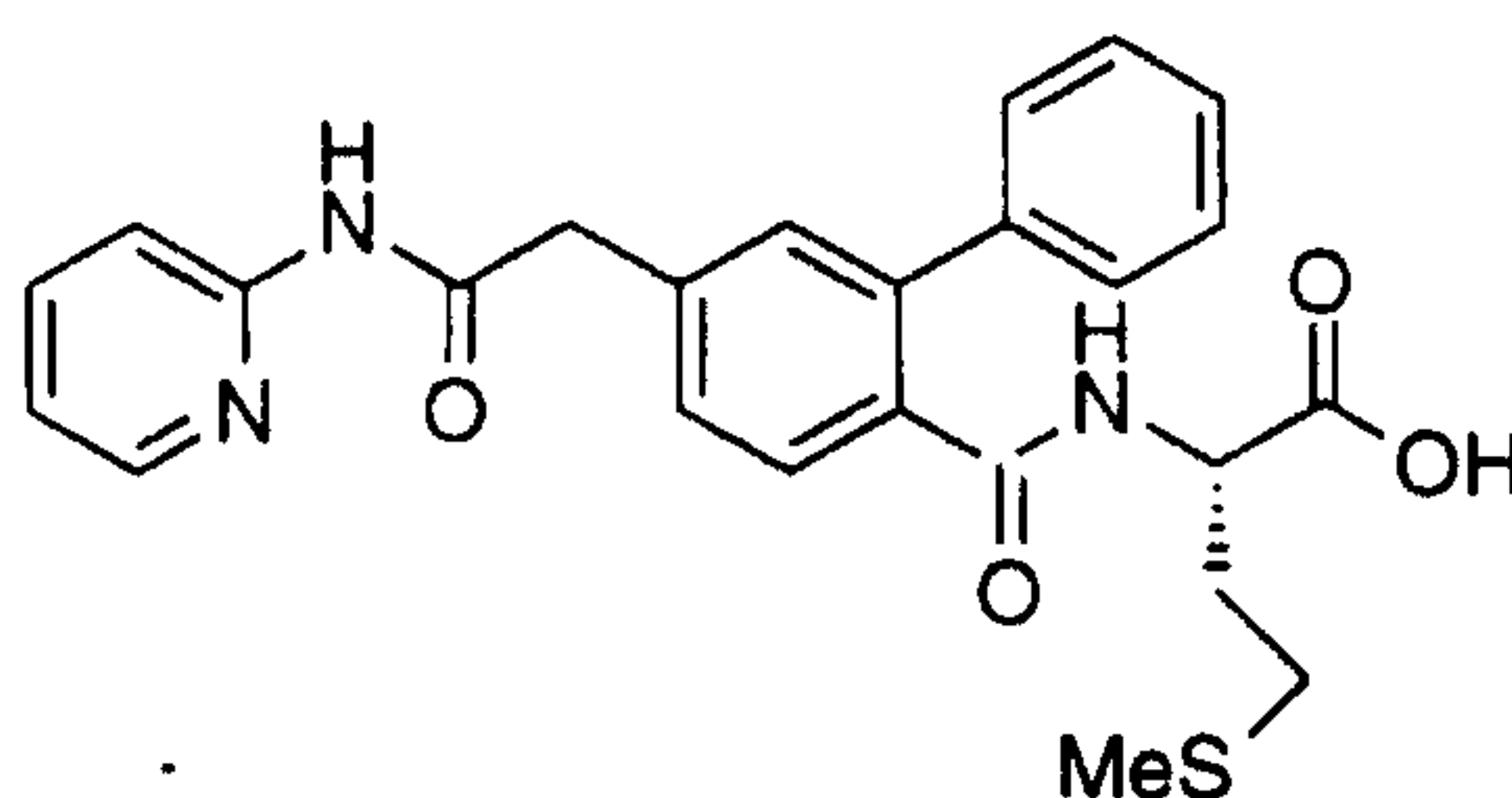
Example 60C4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.

5150

Example 614-((S)-2-Pyrrolidone-5-aminomethyl)carbonyl)-2-phenylbenzoyl methionine

Using the procedure of Example 60 and replacing 2-aminopyridine with (S)-5-aminomethyl-
 5155 2-pyrrolidone affords the title product.

Example 62

5160 4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

Example 62A4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with
 5165 oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased,
 the acid chloride solution is added to an ether solution of diazomethane. The reaction is
 stirred until judged complete by TLC analysis, and then is concentrated to give the crude title
 compound which is purified by chromatography on silica gel.

5170

Example 62B4-carboxymethyl-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of
 sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The
 reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted
 5175 into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica
 gel affords the title product.

Example 62C

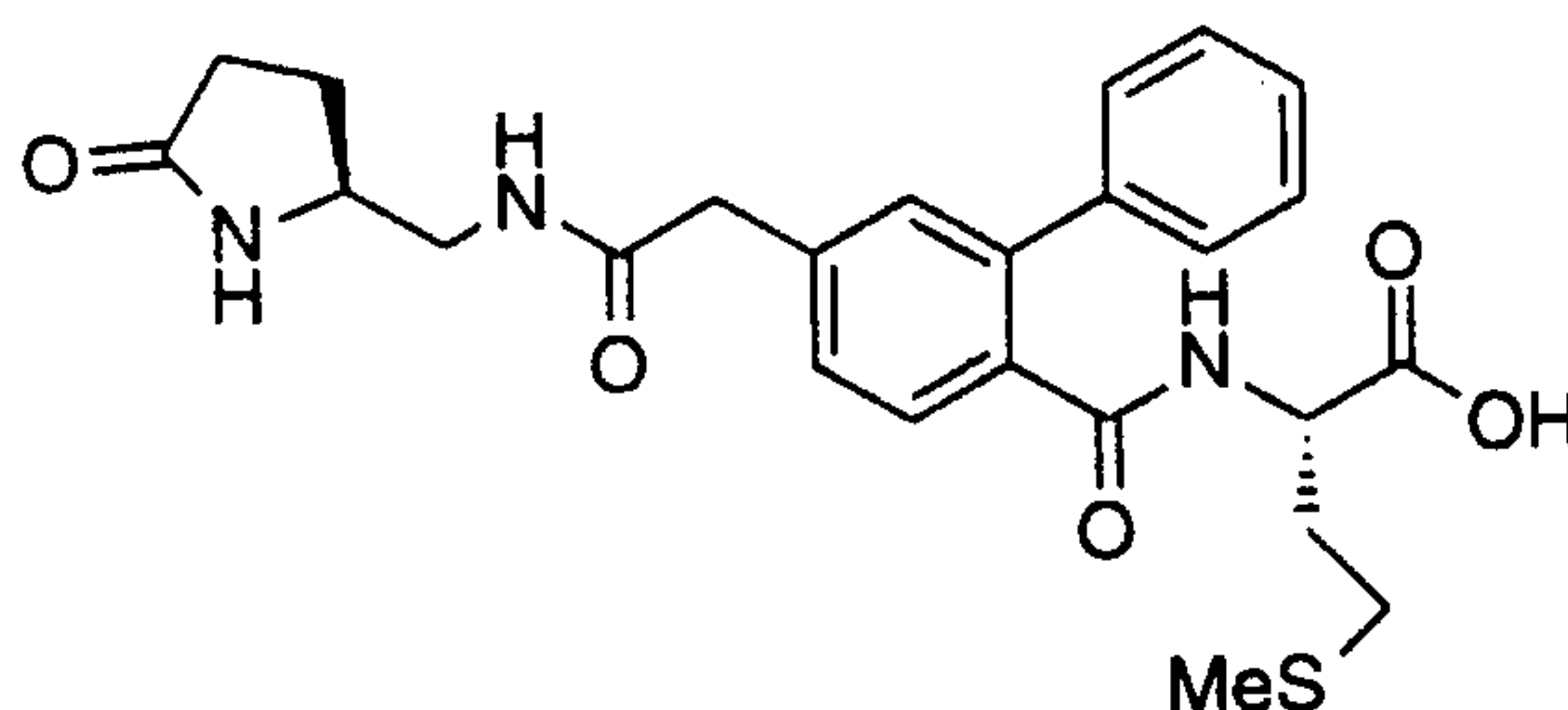
4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

5180 To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried

5185 and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

5190 The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.

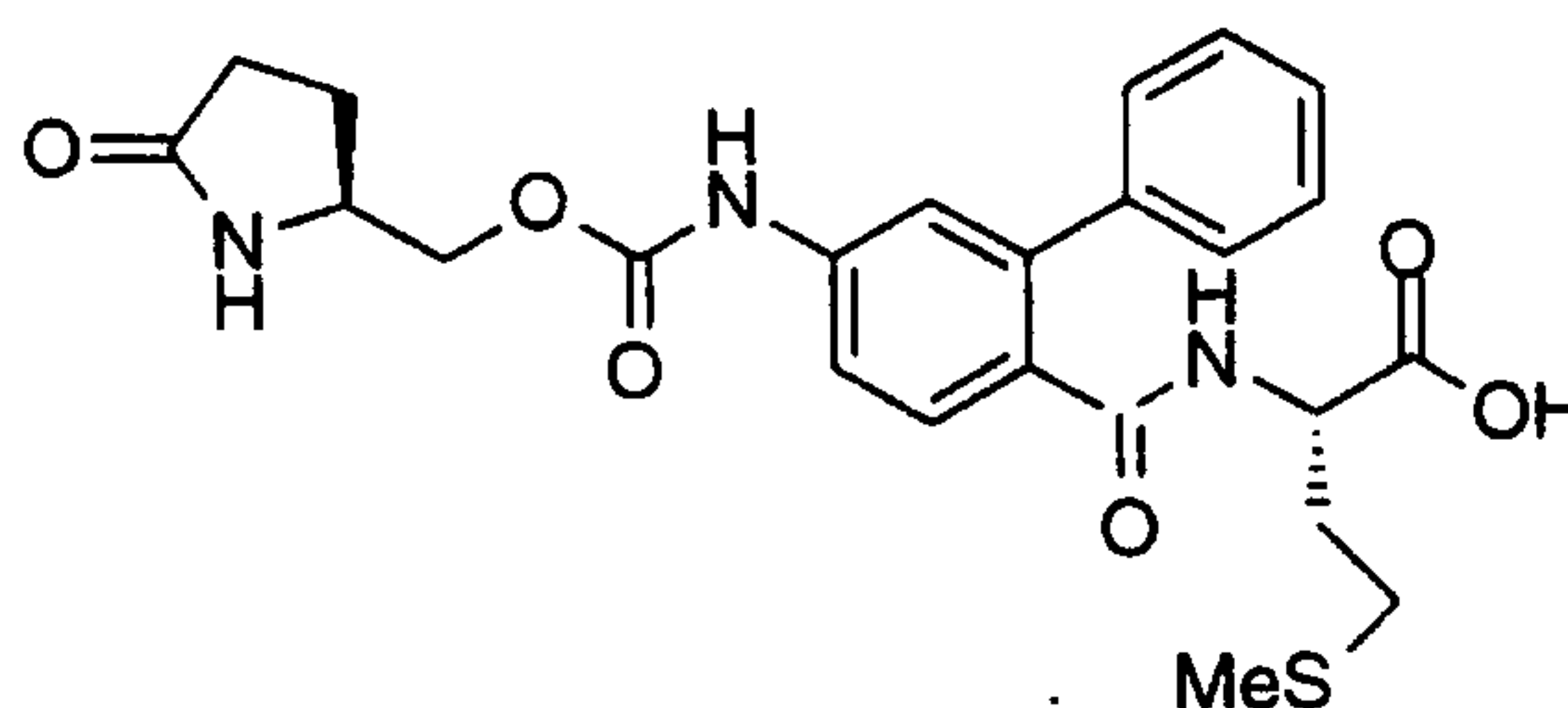


5195

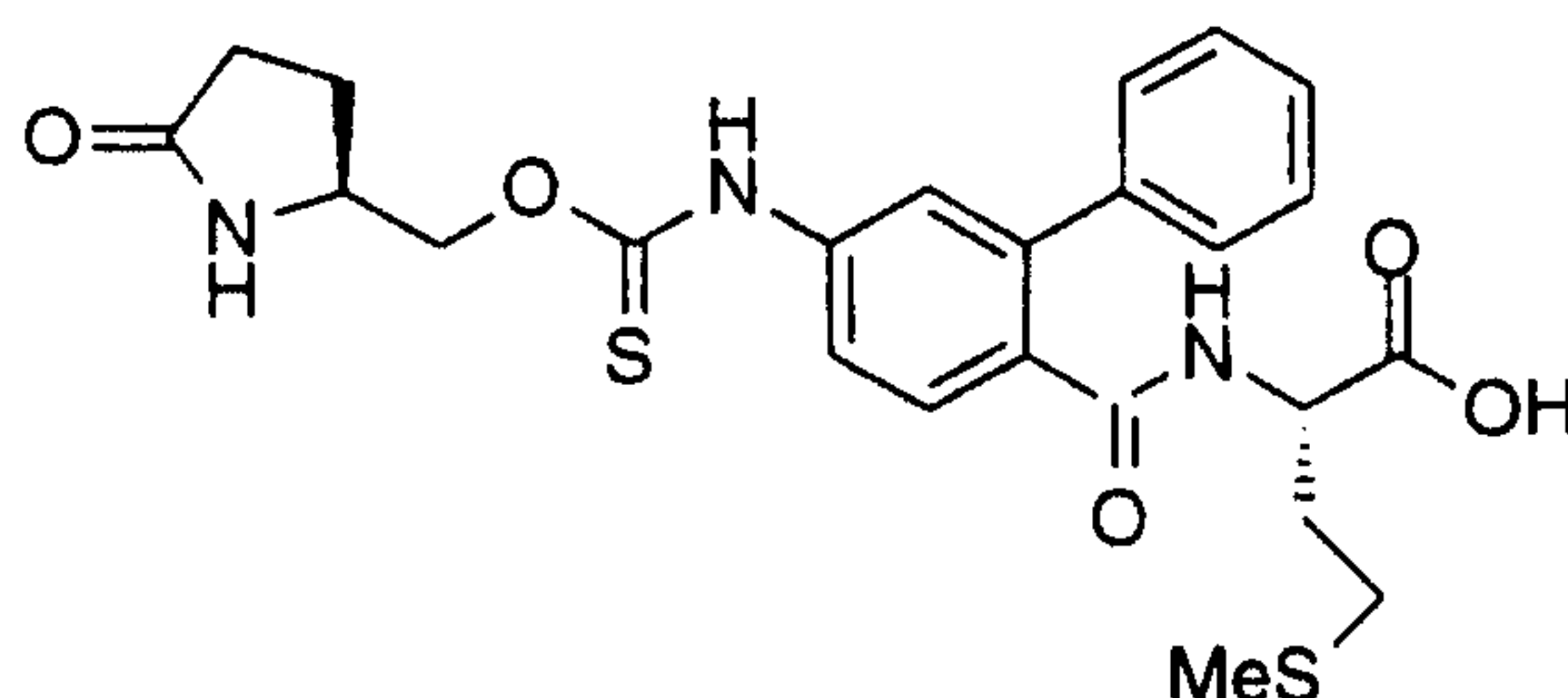
Example 634-((S)-2-Pyrrolidone-5-aminomethyl)carbonylmethyl)-2-phenylbenzoyl methionine

Using the procedure of Example 62 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

5200

Example 644-((S)-2-Pyrrolidone-5-methoxycarbonyl)amino-2-phenylbenzoyl methionine

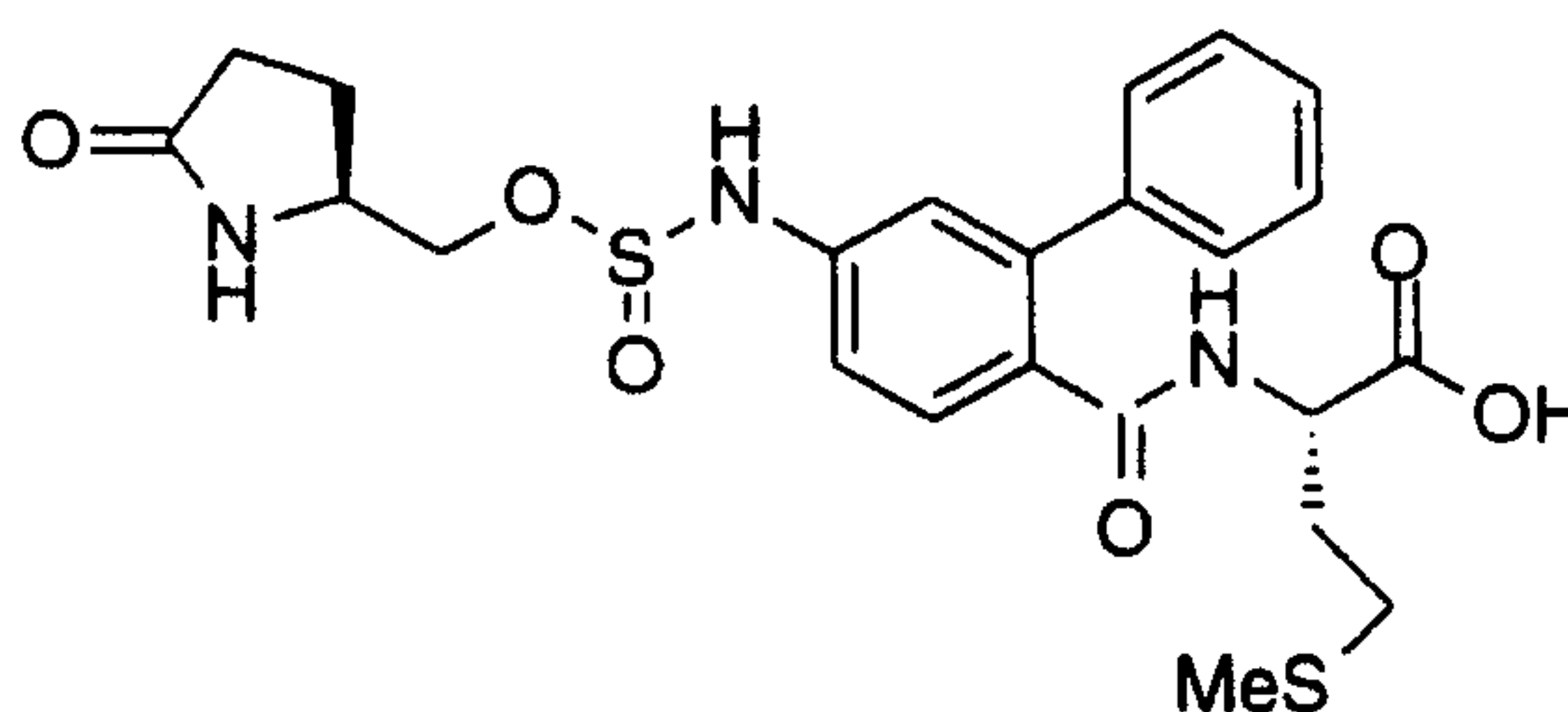
5205 The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 65

4-((S)-2-Pyrrolidone-5-methoxythiocarbonyl)amino-2-phenylbenzoyl methionine

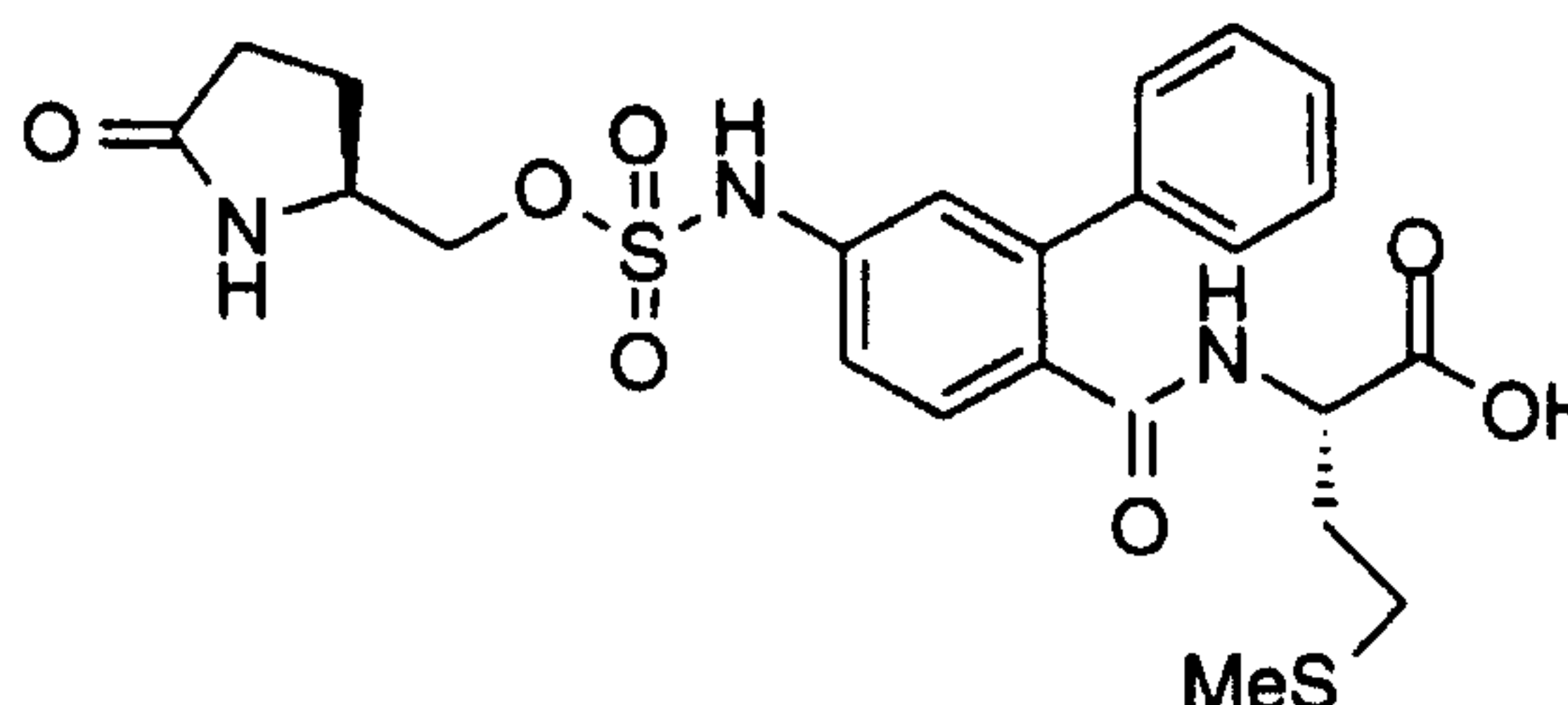
The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 66

4-((S)-2-Pyrrolidone-5-methoxysulfinyl)amino-2-phenylbenzoyl methionine

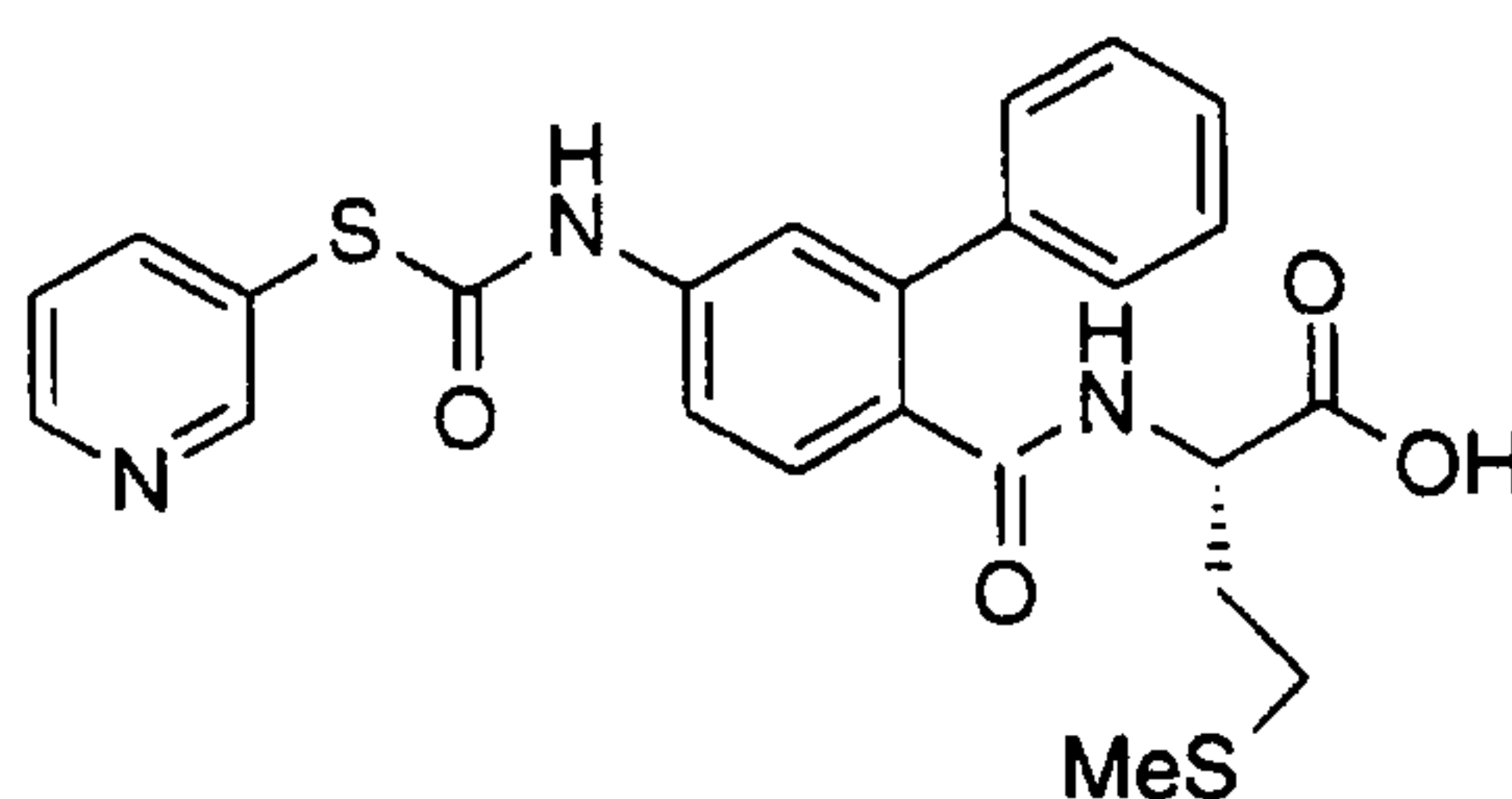
The title compound is prepared as described in Example 3 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 67

4-((S)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

5230 The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

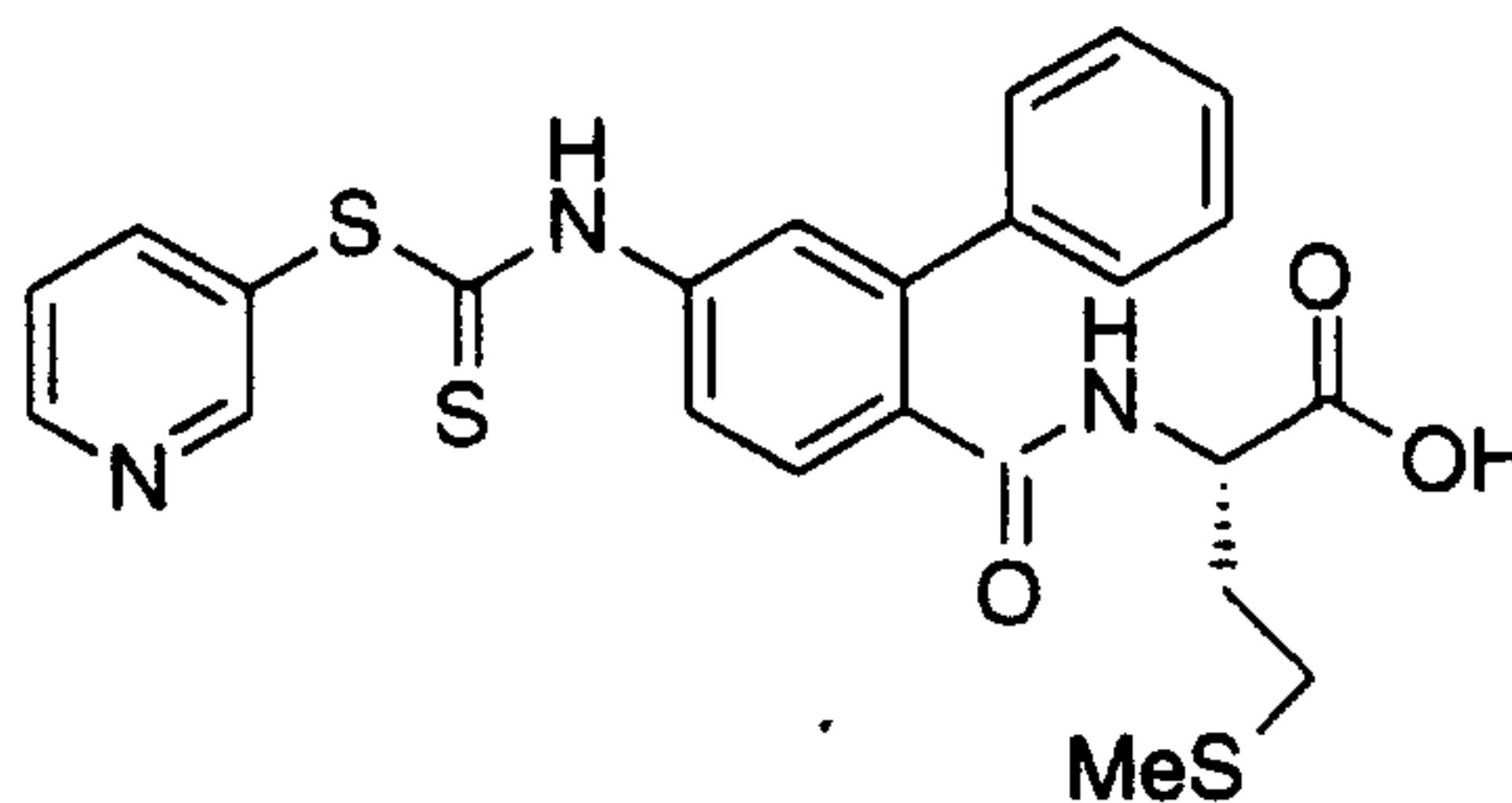


5235

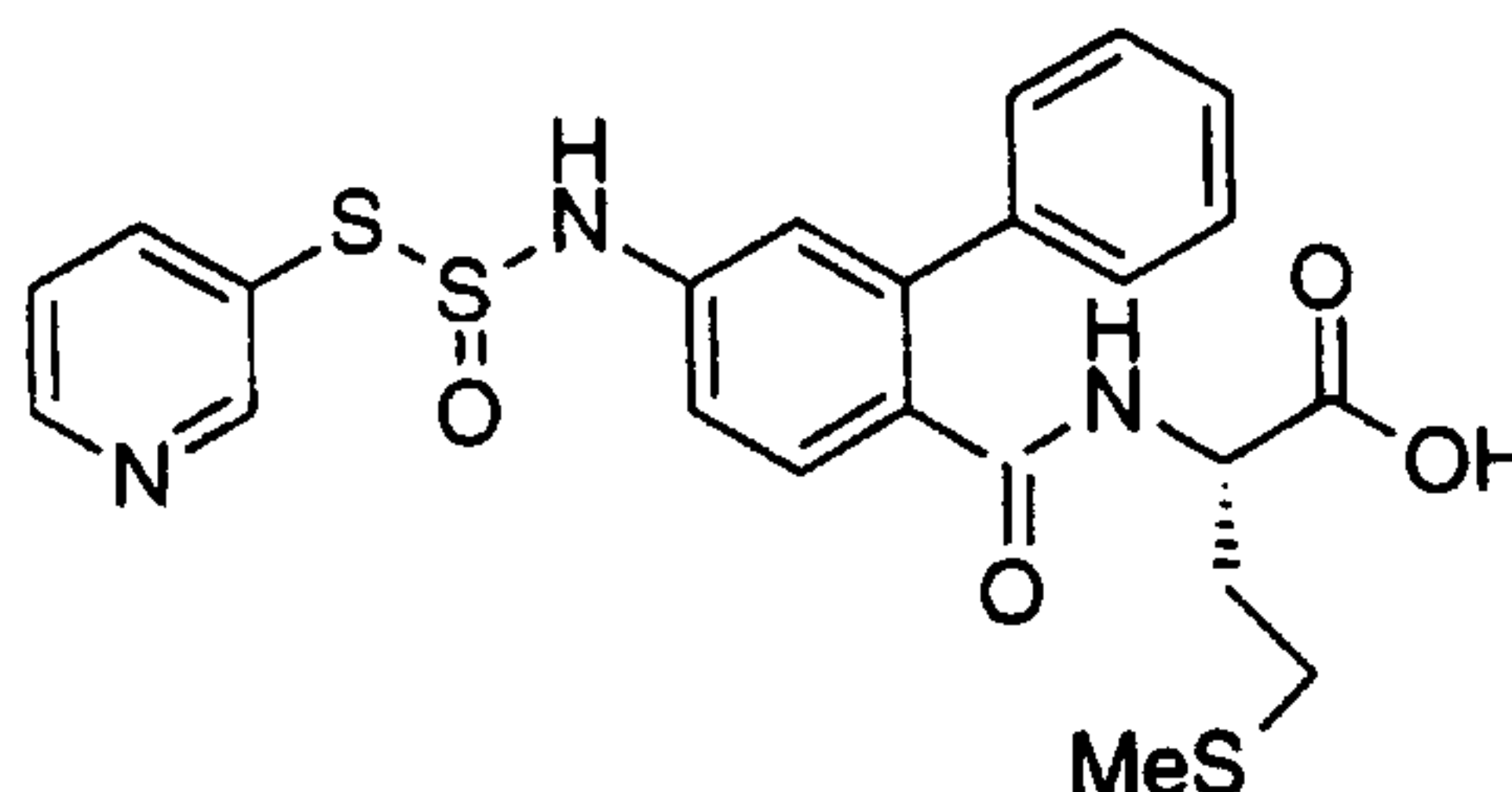
Example 684-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5240

Example 694-(Pyridin-3-ylmercaptothiacyl)amino-2-phenylbenzoyl methionine

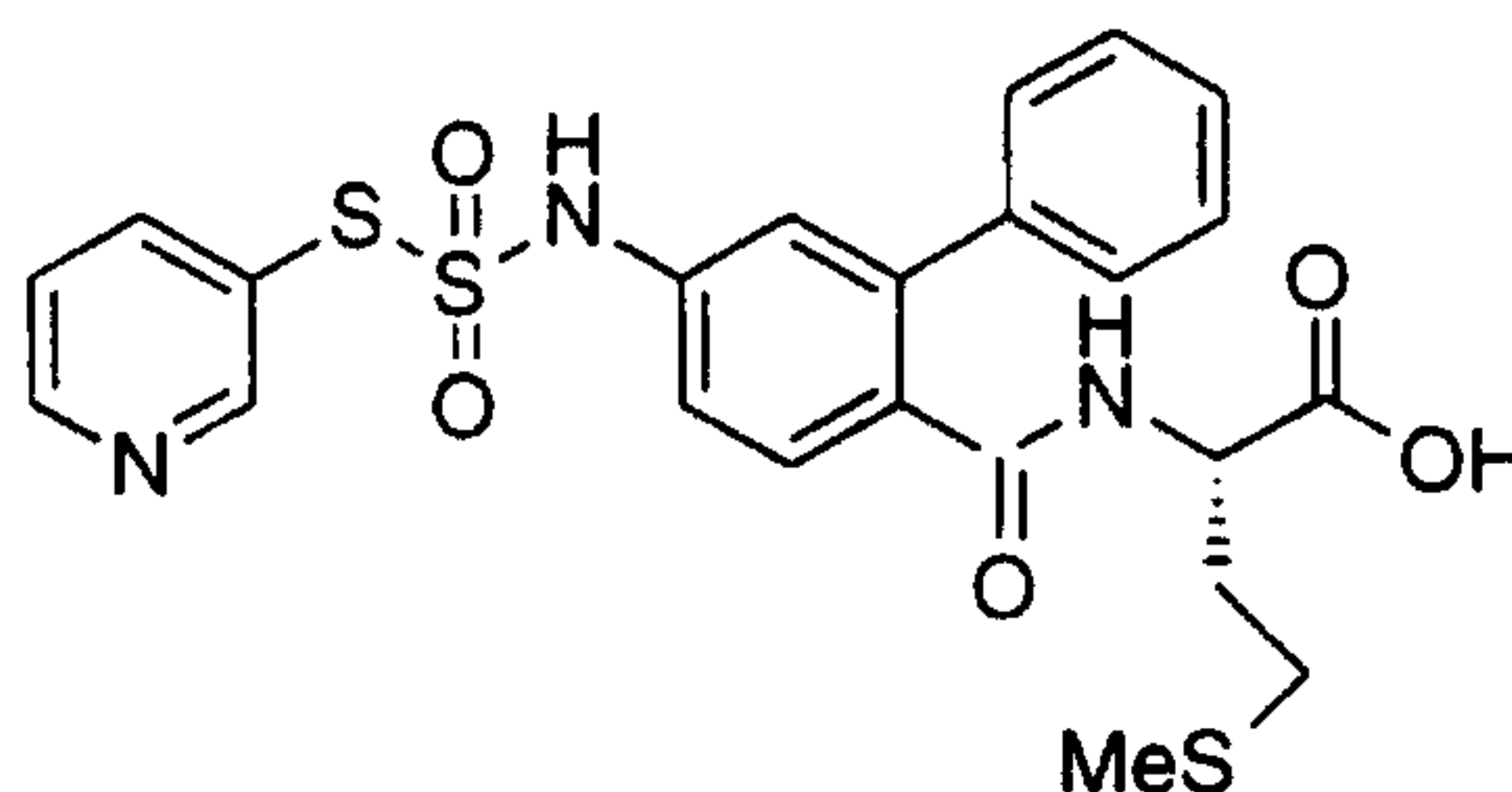
5245 The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



5250

Example 704-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

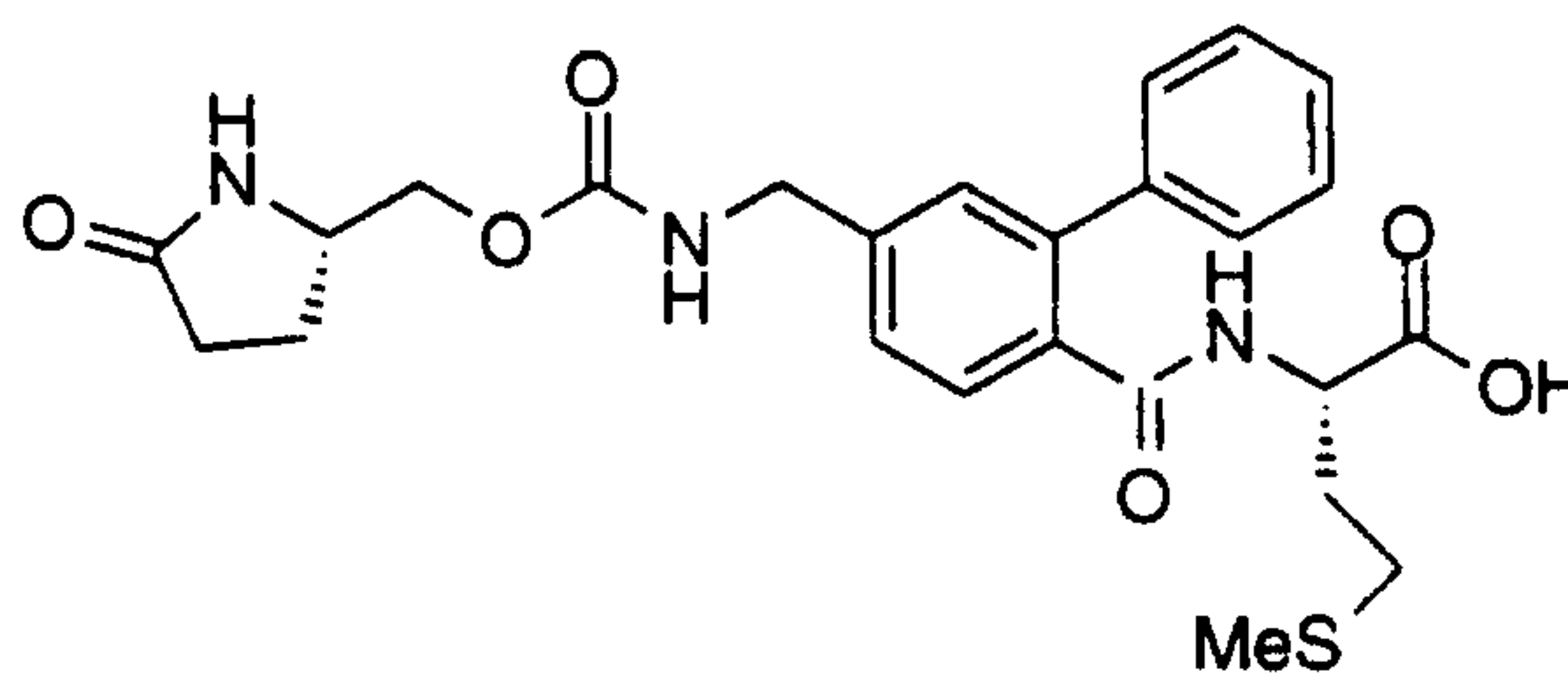
The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 71

4-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

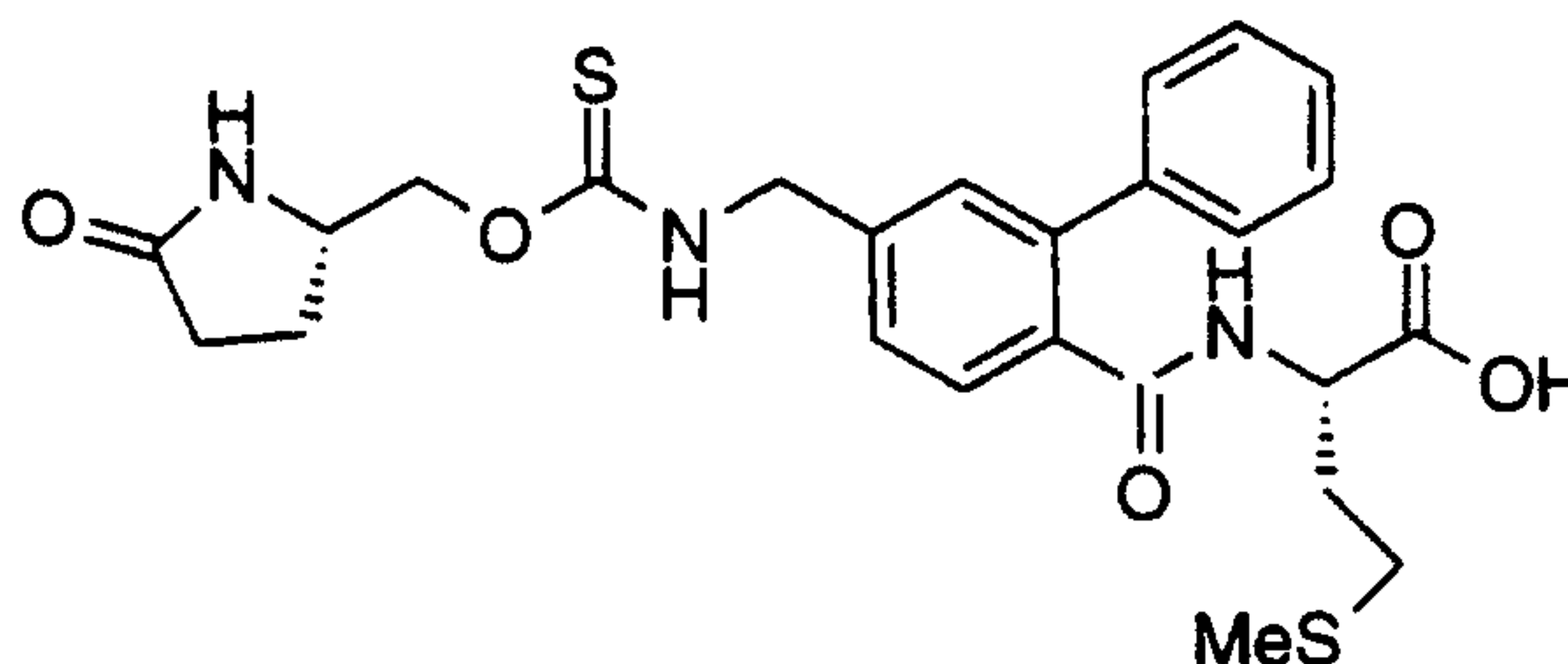
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 72

4-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



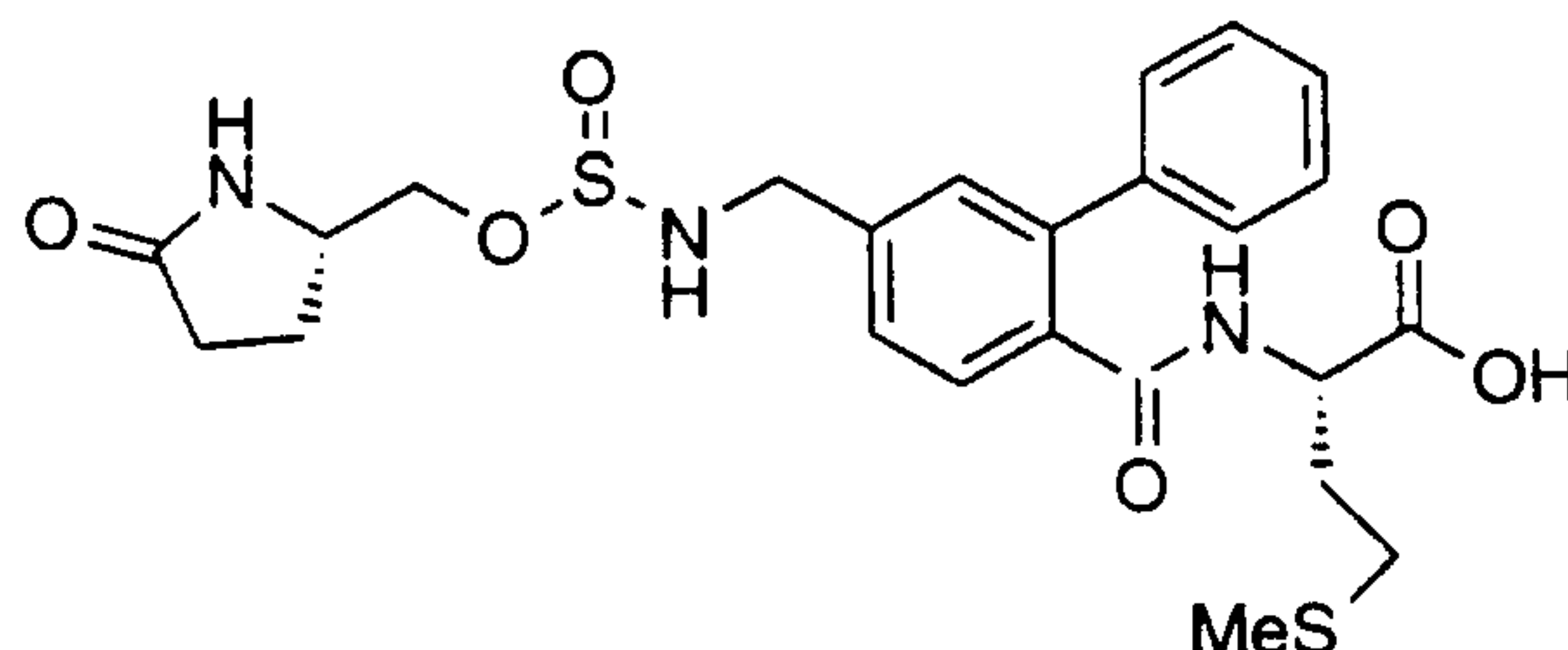
Example 73

4-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

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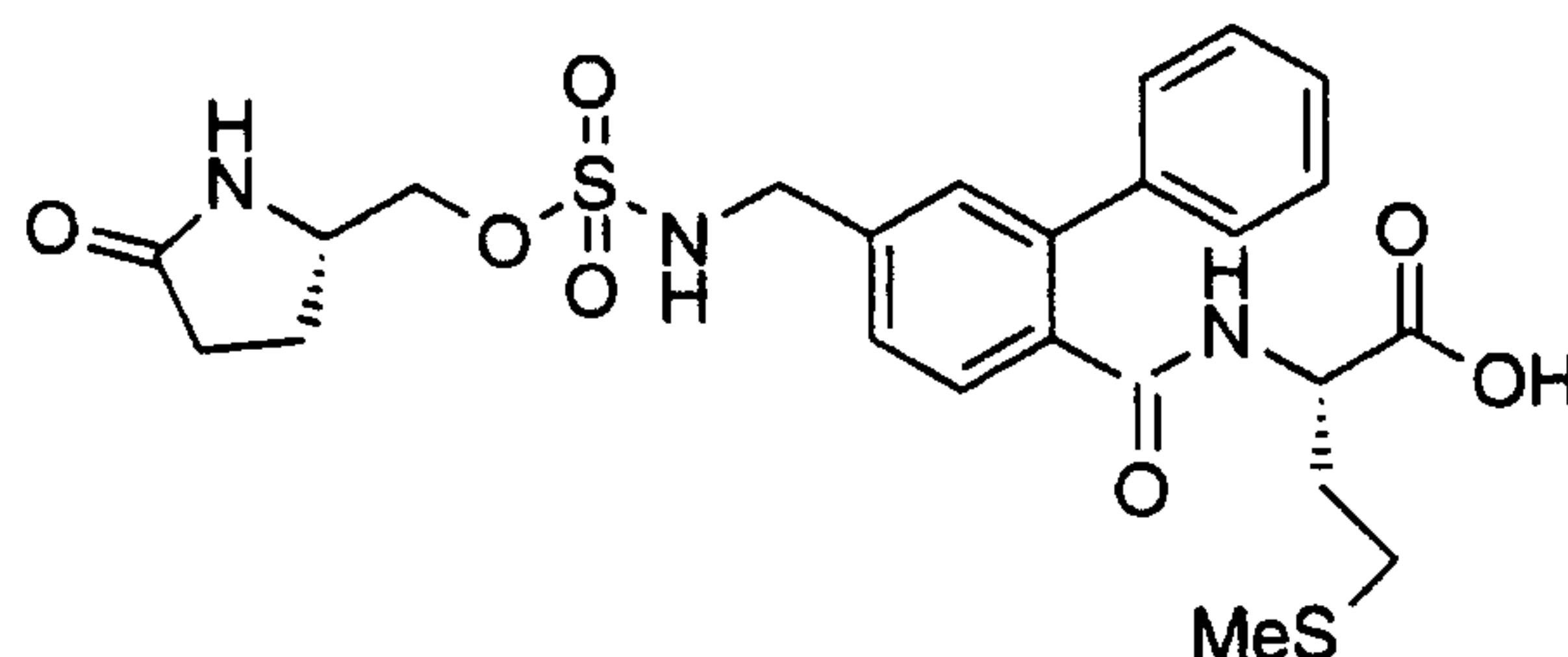
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The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 74

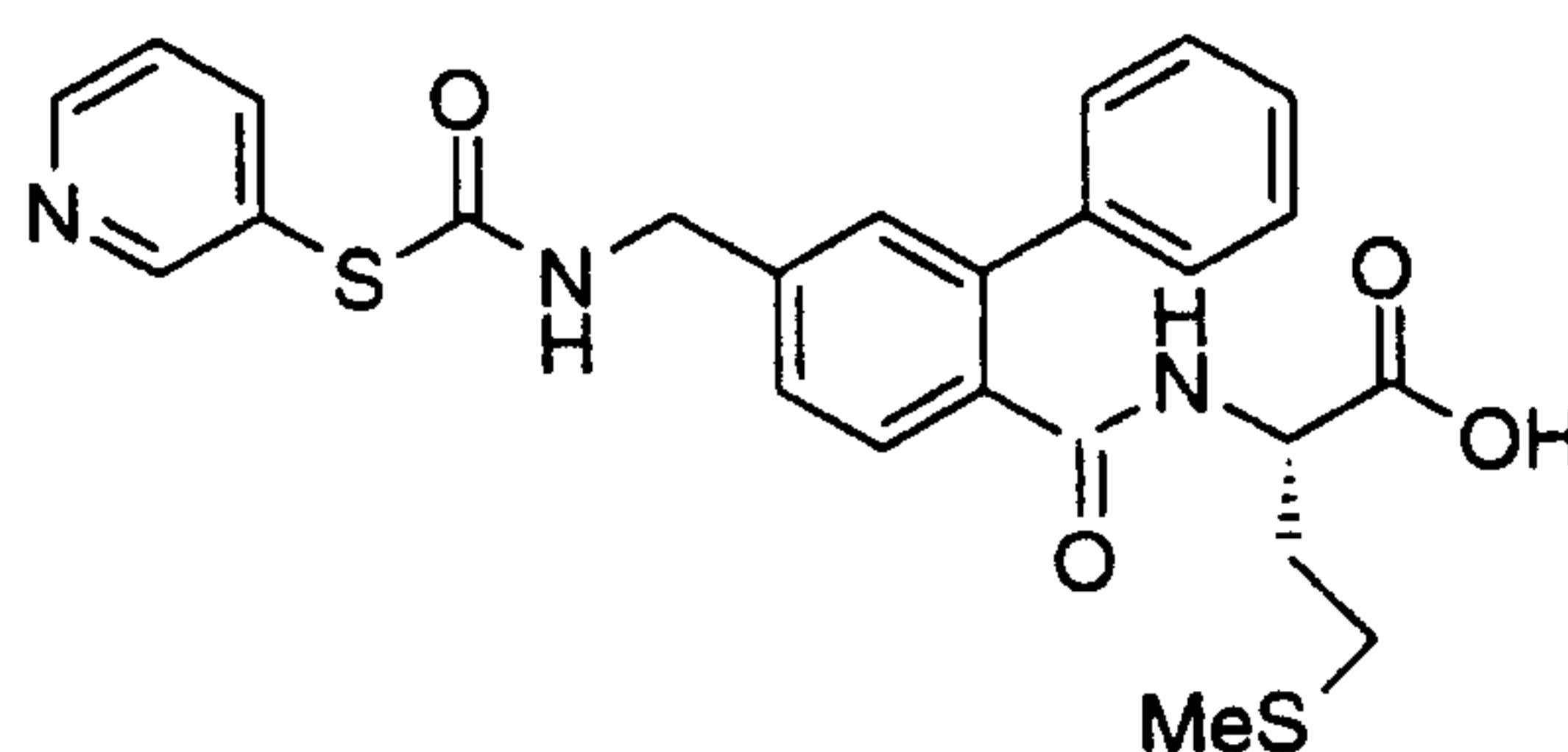
4-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 75

4-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

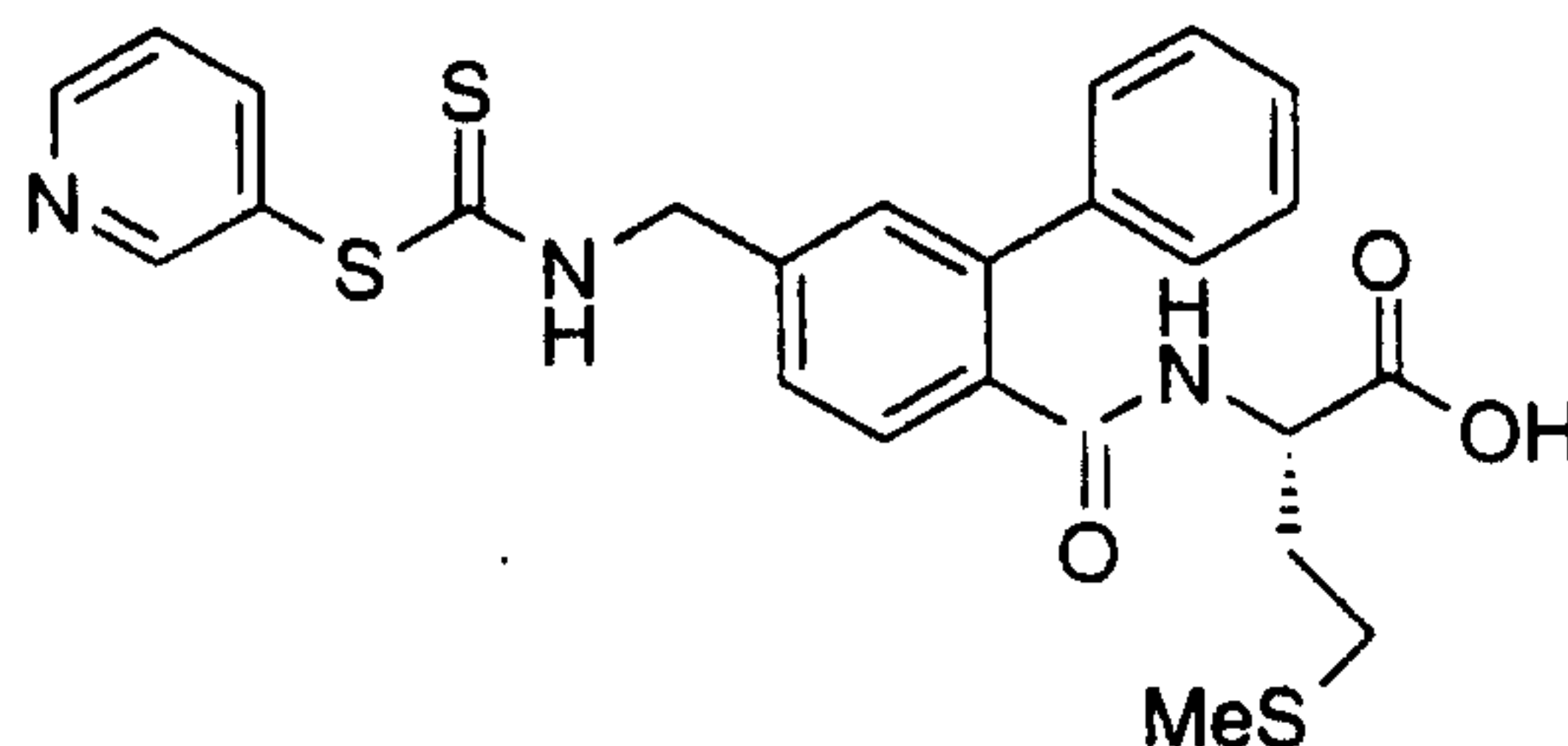
The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 76

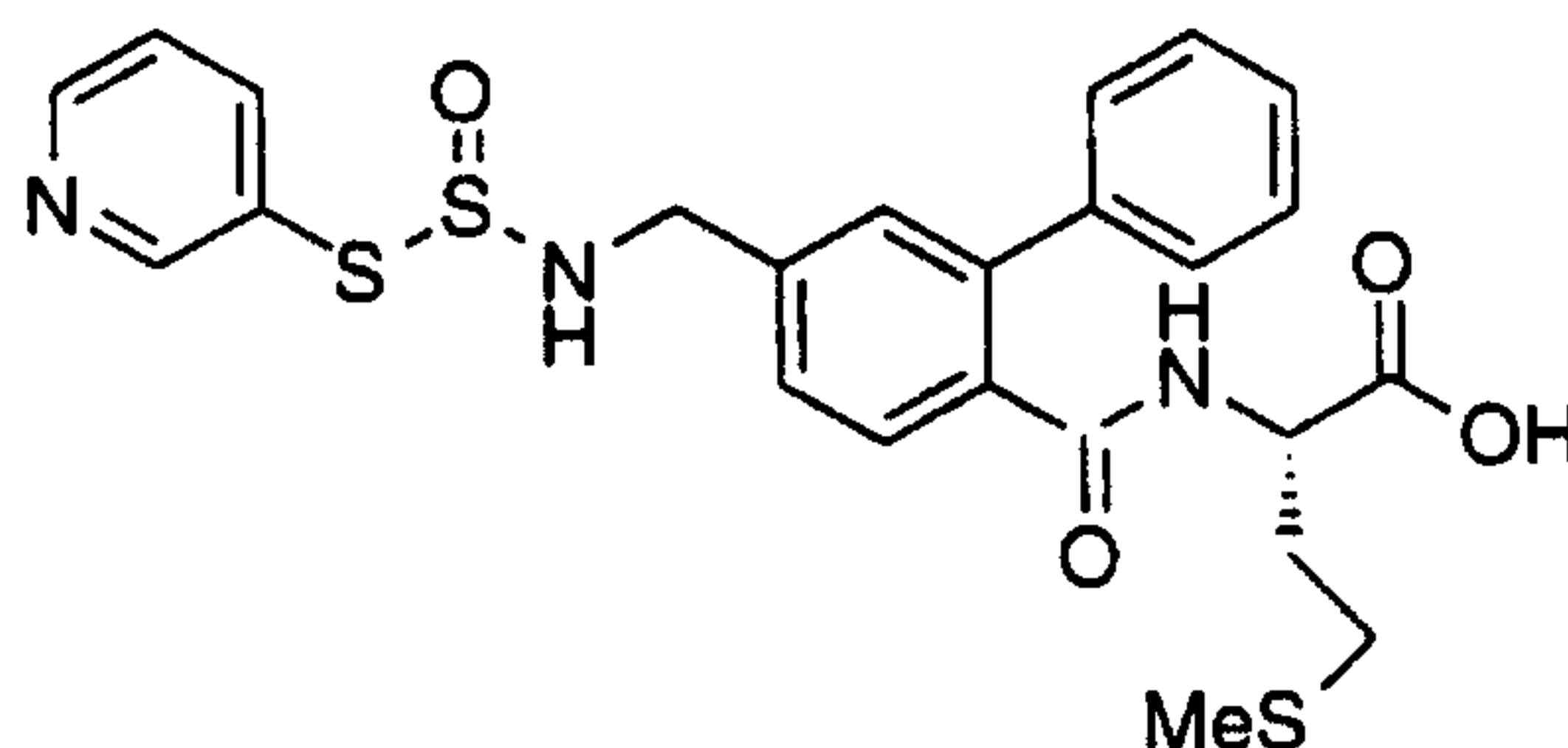
4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5305

Example 774-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

5310 The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

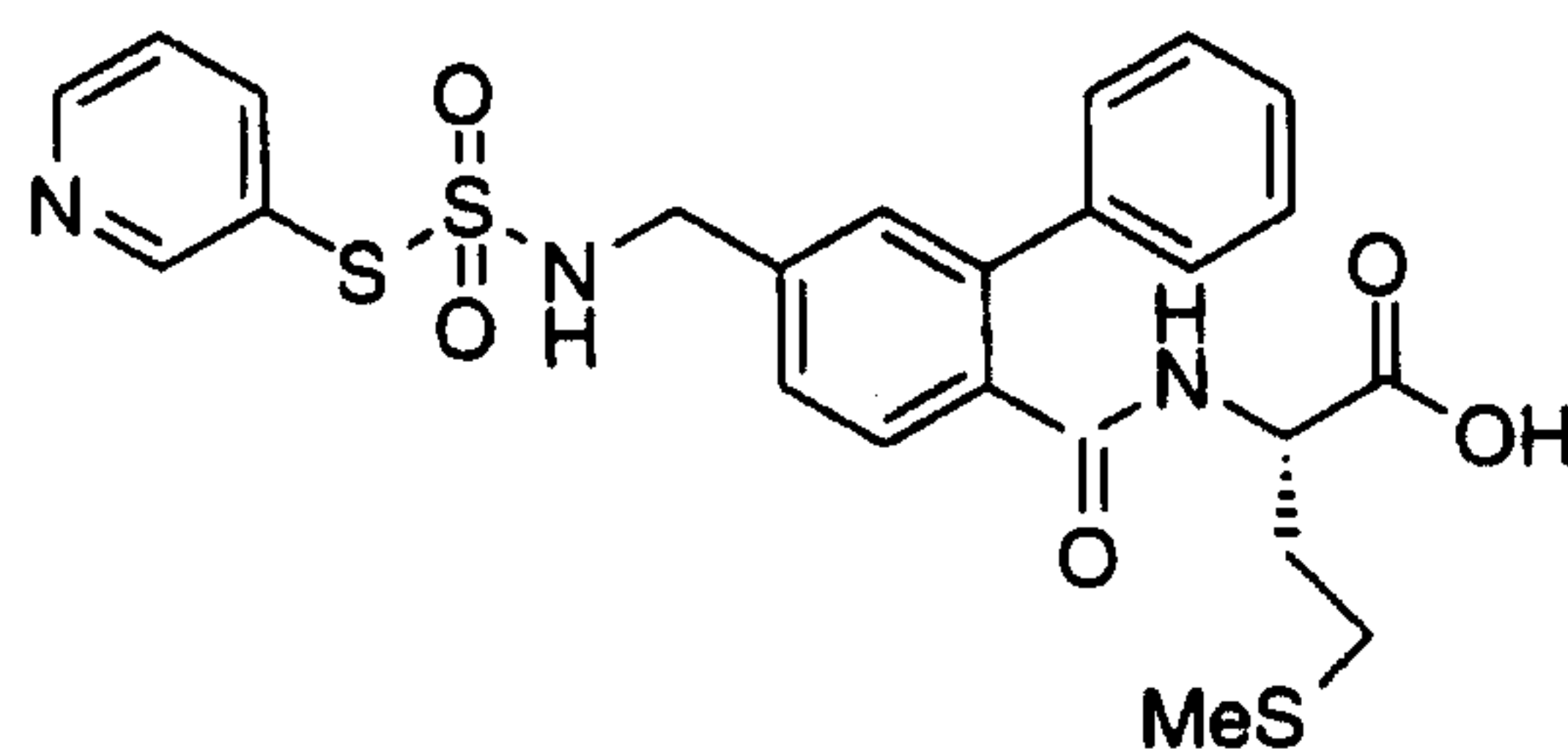


5315

Example 784-(Pyridin-3-ylmercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5320

Example 79

5325 4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5330

Example 80

A-NH-CO-NH-B

5335 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5340 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 81

A-NH-CS-NH-B

5345

The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206

5350 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5355 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 82

A-NH-SO-NH-B

5360

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-

aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5365 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5370

Example 83

A-NH-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and
5375 (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5380 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5385

Example 84

A-NH-SO₂-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
5390 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5395 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 85

A-NH-CO-O-B

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The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E.

5400 The resultant phenols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5405 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5410

Example 86

A-NH-CS-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-

5415 aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5420 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 87

A-NH-SO-O-B

5425

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E.

The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from

5430 amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-

5435 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 88A-NH-SO₂-O-B

5440 The anilines from Table 1 (B-NH₂) are reacted according to the procedure of
Example 6E. The resultant phenols are reacted according to the procedure of Example 8
with the exception that phosgene in toluene is replaced by sulfuryl chloride and (S)-5-
aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes
5445 the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety,
in which case the final LiOH step is eliminated and the amino acid methyl esters used to
prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl,
butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5450

Example 89A-NH-CH₂-B

The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-
5455 methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine
is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206
from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of
the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5460 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5465

Example 90A-NH-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of
Example 16F-G. The resultant alcohols are reacted according to the procedure of Example
18 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from
5470 Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH
hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is
derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to
5475 prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 91

5480

A-NH-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For
5485 products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
5490 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 92

A-NH-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For
5495 products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also
5500 hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
5505 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 93

A-NH-SO₂-NH-CH₂-B

5510 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also
5515 hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl,
5520 butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 94

A-NH-CO-O-CH₂-B

5525 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from
5530 amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5535

Example 95

A-NH-CS-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the
5540 exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5545 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

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bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

5550

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis

5555 step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-

5560 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 97

A-NH-CS-S-B

5565

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on

5570 the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5575

Example 98

A-NH-SO-S-B

5580

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from

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amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5585 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5590

Example 99

A-NH-SO₂-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of
5595 Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5600 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5605

Example 100

A-NH-CO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the
5610 procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5615 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5620

Example 101A-NH-CS-S-CH₂-B

5625

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5630

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5635

Example 102A-NH-SO-S-CH₂-B

5640

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5645

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5650

Example 103A-NH-SO₂-S-CH₂-B

5655

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl

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NOTE: Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

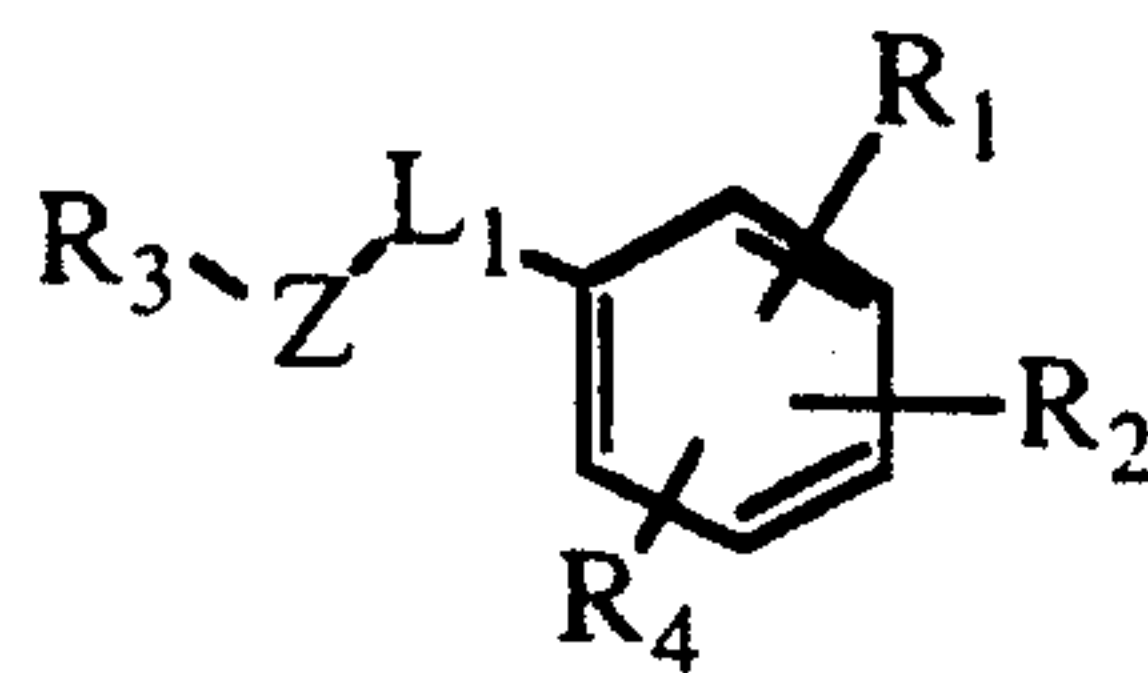
THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE
THAN ONE VOLUME

THIS IS VOLUME 1 OF 2

NOTE: For additional volumes please contact the Canadian Patent Office

WHAT IS CLAIMED IS:

- 17220 1. A compound having Formula I

**I**

or a pharmaceutically acceptable salt thereof, wherein

- 17225 **R₁** is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 17230 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl-L₂- wherein aryl is selected from the group consisting of

- 17235 (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 17240 (f) indenyl

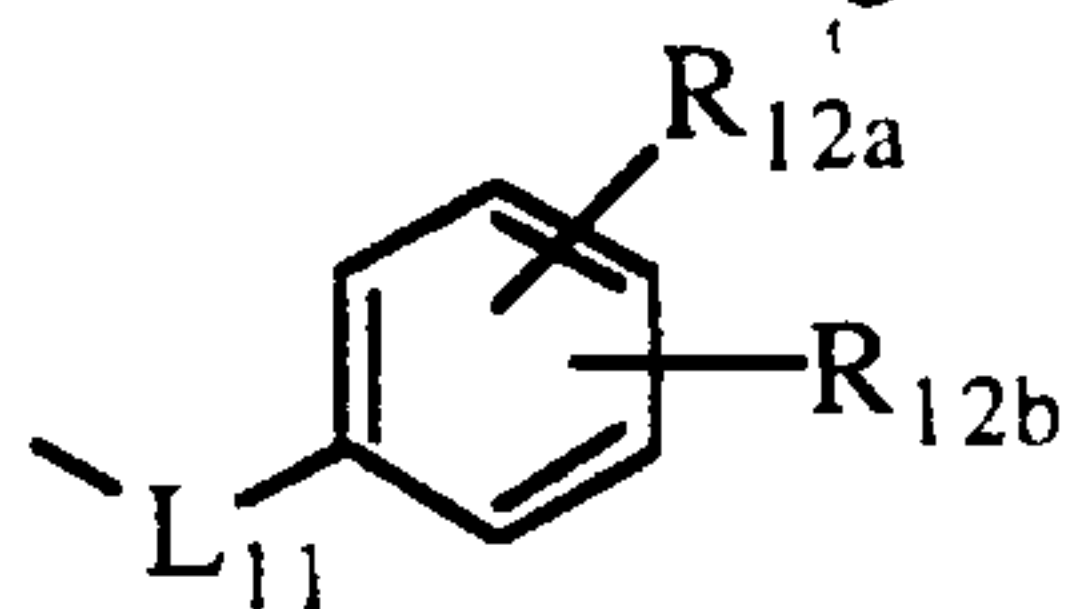
wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

- or Z wherein X, Y, and Z are independently selected from the group consisting of

- 17245 alkenyl,
- alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 17250 halogen,
- haloalkyl,

- hydroxy,
hydroxyalkyl,
loweralkyl,
17255 nitro,
N-protected amino, and
-NRR' wherein R and R' are independently selected
from the group consisting of
hydrogen and
17260 loweralkyl,
oxo (=O), and
thioalkoxy and
L₂ is absent or is selected from the group consisting of
17265 -CH₂-,
-CH₂CH₂-,
-CH(CH₃)-,
-O-,
-C(O)-,
-S(O)_q wherein q is 0, 1 or 2, and
17270 -N(R)-, and
(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
unsubstituted or substituted with 1, 2, 3 or 4 substituents
independently selected from the group consisting of
17275 (a) loweralkyl,
(b) hydroxy,
(c) hydroxyalkyl,
(d) halogen
(e) cyano,
(f) nitro,
17280 (g) oxo (=O),
(h) -NRR',
(i) N-protected amino,
(j) alkoxy,
(k) thioalkoxy,
17285 (l) haloalkyl,
(m) carboxy, and
(n) aryl;

R_2 is selected from the group consisting of



17290

(1)

wherein L_{11} is selected from the group

consisting of

- (a) a covalent bond,
- (b) $-C(W)N(R)-$ wherein R is defined previously and W is selected from the group consisting of O and S ,
- (c) $-C(O)-$,
- (d) $-N(R)C(W)-$,
- (e) $-CH_2O-$,
- (f) $-C(O)O-$, and
- (g) $-CH_2N(R)-$,

17295

17300

R_{12a} is selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl, and
- (c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group

consisting of

hydrogen and

a carboxy-protecting group, and

R_{12b} is selected from the group consisting of

- (a) hydrogen and
- (b) loweralkyl,

17305

17310

with the proviso that R_{12a} and R_{12b} are not both hydrogen,

(2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,

R_v is selected from the group consisting of

- (a) hydrogen and
- (b) loweralkyl,

17315

R_{15} is selected from the group consisting of

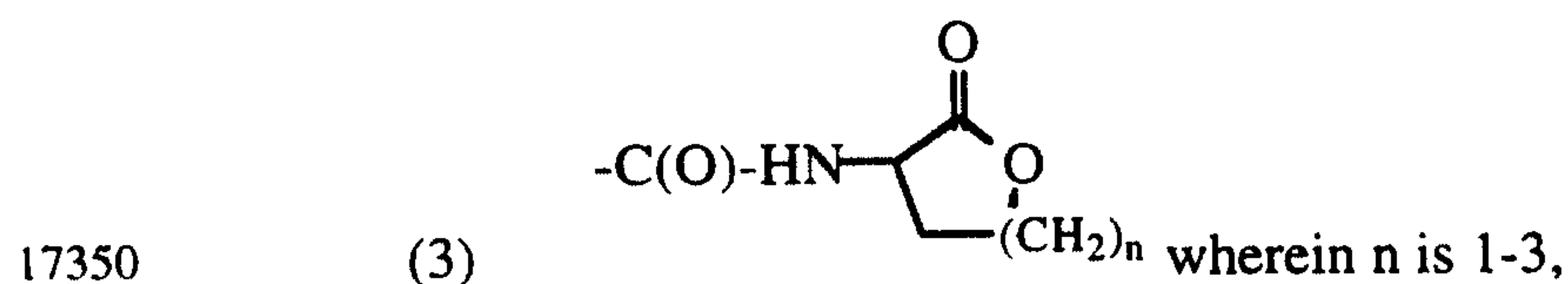
- (a) hydrogen,
- (b) alkanoyloxyalkyl,
- (c) loweralkyl, and
- (b) a carboxy-protecting group, and

17320

R_{14} is selected from the group consisting of

- (a) alkoxyalkyl,

- 17325 (b) alkoxyarylalkyl,
(c) alkoxycarbonylalkyl,
(d) alkylsulfinylalkyl,
(e) alkylsulfonylalkyl,
(f) alkynyl,
(g) aminoalkyl,
(h) aminocarbonylalkyl,
17330 (i) aminothiocarbonylalkyl,
(j) aryl,
(k) arylalkyl,
(l) carboxyalkyl,
(m) cyanoalkyl,
17335 (n) cycloalkyl,
(o) cycloalkylalkoxyalkyl,
(p) cycloalkylalkyl,
(q) (heterocyclic)alkyl,
(r) hydroxyalkyl,
17340 (s) hydroxyarylalkyl,
(t) loweralkyl,
(u) sulfhydrylalkyl,
(v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
unsubstituted or substituted with 1, 2, 3, or 4
17345 substituents selected from the group consisting of
halogen,
(w) thioalkoxyalkylamino, and
(x) thiocycloalkyloxyalkyl,



- (4) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_{14} is defined previously
and R_{16} is selected from the group consisting of
17355 (a) loweralkyl,
(b) haloalkyl,
(c) aryl wherein the aryl is unsubstituted or substituted with

- 17360 1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
17365 oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
17370 haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
17375 selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
17380 cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
17385 alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;
- 17390 (5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted
or substituted with loweralkyl or haloalkyl,

- 17395 (6) $-L_{11}$ -heterocycle,
- (7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously and R_{17} and R_{18} are independently selected from the group consisting of
- 17400 (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,
- 17405 (8) $-C(O)OR_{15}$, and
- (9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;
- 17410 L_1 is absent or is selected from the group consisting of
- (1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group consisting of
- 17415 (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,
- wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of
- 17420 alkenyl,
- alkenyloxy,
- alkenyloxyalkyl,
- alkenyl[S(O)_q]alkyl,
- alkoxy,
- alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or
- 17425 substituted with 1 or 2 hydroxyl substituents,
- with the proviso that no two hydroxyls are attached to the same carbon,
- alkoxycarbonyl wherein the alkoxycarbonyl is
- 17430 unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the

- group consisting of
halogen and
cycloalkyl,
alkylsilyloxy,
17435 alkyl[S(O)_q],
alkyl[S(O)_q]alkyl,
aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
17440 alkoxy wherein the alkoxy is unsubstituted or
substituted with substituents selected
from the group consisting of cycloalkyl,
aryl,
arylalkyl,
17445 aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of,
halogen,
17450 nitro, and
-NRR',
cycloalkyl,
halogen,
loweralkyl,
17455 hydroxyl,
nitro,
-NRR', and
-SO₂NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or
substituted with substituents selected from the
group consisting of alkoxy,
arylalkyl,
arylalkyl[S(O)_q]alkyl,
aryl[S(O)_q],
17465 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents independently selected from

- alkoxy and
loweralkyl,
- 17470 arylalkoxyalkyl wherein the arylalkoxyalkyl is
unsubstituted or substituted with substituents
selected from the group consisting of
alkoxy, and
halogen,
- 17475 aryloxy,
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
carboxyl,
- 17480 $-C(O)NR_C R_D$ wherein R_C and R_D are independently
selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or
- 17485 R_C and R_D together with the nitrogen to which
they are attached form a ring selected
from the group consisting of
morpholine,
piperidine,
pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R_C and R_D
- 17490 together is unsubstituted or
substituted with 1 or 2
substituents independently
selected from the group consisting
of alkoxy and alkoxyalkyl,
- 17495
- 17500 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
cyclolalkoxy,
cycloalkoxycarbonyl,

- 17505 cyclolalkoxyalkyl,
cyclolalkyl wherein the cycloalkyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting
of aryl,
17510 loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
17515 cycloalkylalkyl,
cyclolalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
17520 substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
17525 independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
unsubstituted or substituted with 1 or 2
substituents independently selected from
17530 the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2
17535 substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or
17540 substituted with 1, 2, 3, 4, or 5
substituents independently selected from

- the group consisting of
 alkanoyl,
 alkoxy,
 17545 carboxaldehyde,
 haloalkyl,
 halogen,
 loweralkyl,
 nitro,
 17550 -NRR', and
 thioalkoxy,
 arylalkyl,
 aryloxy,
 cycloalkoxyalkyl,
 17555 cycloalkyl,
 cycloalkylalkyl,
 halogen,
 heterocycle,
 hydroxyl,
 17560 loweralkyl wherein the loweralkyl is
 unsubstituted or substituted with 1, 2, or
 3 substituents independently selected
 from the group consisting of
 heterocycle,
 17565 hydroxyl,
 with the proviso that no two hydroxyls
 are attached to the same carbon,
 and
 -NRR³R^{3'} wherein R³ and R^{3'} are
 17570 independently selected from the
 group consisting of
 hydrogen
 aryl,
 loweralkyl,
 17575 aryl,
 arylalkyl,
 heterocycle,
 (heterocyclic)alkyl,

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- 17580 cycloalkyl, and
cycloalkylalkyl, and
sulfhydryl,
(heterocyclic)alkoxy,
(heterocyclic)alkyl,
(heterocyclic)alkyl[S(O)_q]alkyl,
17585 (heterocyclic)oxy,
(heterocyclic)alkoxyalkyl,
(heterocyclic)oxyalkyl,
heterocycle[S(O)_q]alkyl,
hydroxyl,
17590 hydroxyalkyl,
imino,
N-protected amino,
=N-O-aryl, and
=N-OH,
17595 =N-O-heterocycle wherein the heterocycle is
unsubstituted or substituted with 1, 2, 3, or 4
substituents independently selected from the
group consisting of
loweralkyl,
17600 hydroxy,,
hydroxyalkyl,
halogen,
cyano,
nitro,
17605 oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
17610 haloalkyl,
carboxy, and
aryl,
=N-O-loweralkyl,
-NRR³R^{3'},
17615 -NHNR_CR_D,

-OG wherein G is a hydroxyl protecting group,

-O-NH-R,

$\text{-O-N}=\begin{matrix} \text{J}' \\ \text{J} \end{matrix}$ wherein J and J' are independently selected

from the group consisting of

17620

loweralkyl and

arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

17625

oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

17630

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

17635

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

17640

sulfhydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

17645

(b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R₅ is selected from the group consisting of

hydrogen,

17650

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

- group consisting of aryl,
alkoxy,
alkoxyalkyl,
17655 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2 or 3
substituents independently selected from the
group consisting of
aryl and
17660 halogen,
alkylaminocarbonylalkyl wherein the
alkylaminocarbonylalkyl is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group consisting
17665 of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or
17670 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group
consisting of
alkoxy,
aryl,
17675 carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
17680 nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
17685 group consisting of halogen,
aryloxycarbonyl,
carboxaldehyde,
-C(O)NRR',

- 17690 cycloalkoxycarbonyl,
cycloalkylaminocarbonyl,
cycloalkylaminothiocarbonyl,
cyanoalkyl,
cycloalkyl,
cycloalkylalkyl wherein the cycloalkylalkyl is
- 17695 unsubstituted or substituted with 1 or 2 hydroxyl
substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,
(cycloalkyl)oyl,
- 17700 (9,10-dihydroanthracenyl)alkyl wherein the
(9,10-dihydroanthracenyl)alkyl is unsubstituted
or substituted with 1 or 2 oxo substituents,
haloalkyl,
heterocycle,
- 17705 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents selected from the group consisting of
loweralkyl,
(heterocyclic)oyl,
- 17710 loweralkyl, wherein the loweralkyl is unsubstituted
or substituted with substituents selected from the
group consisting of -NRR',
-SO₂-A, and
thioalkoxyalkyl;
- 17715
- (2) -L₄-O-L₅-,
- (3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
or 2,
- 17720
- (4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
R₆ is selected from the group consisting of
- (a) hydrogen,
- (b) loweralkyl,
- 17725 (c) aryl,

- 17730 (d) arylalkyl,
 (e) heterocycle,
 (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 (h) cycloalkylalkyl, and
 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R_6)- wherein R_6 is selected from the group
- 17735 consisting of
 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 heterocycle,
 17740 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- 17745 (5) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,
 (6) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,
 (7) $-L_4-N(R_5)-C(W)-L_7-L_5-$ wherein L_4 , R_5 , W , and L_5 are
 17750 defined previously and L_7 is absent or is selected from the group
 consisting of -O- and -S-,
 (8) C_1-C_{10} -alkylene wherein the alkylene group is unsubstituted or
 17755 substituted with 1 or 2 substituents independently selected from
 the group consisting of
 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 17760 (e) cyclolakyl,
 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and

(h) hydroxy,

17765 (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

(a) aryl,

(b) arylalkyl,

17770 (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

(d) heterocycle,

17775 (e) (heterocycle)alkyl,

(f) hydroxyalkyl,

(g) cyclolalkyl,

(h) cycloalkylalkyl,

(i) alkylthioalkyl, and

17780 (j) hydroxy,

(10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

17785 (a) aryl,

(b) arylalkyl,

(c) heterocycle,

(d) (heterocyclic)alkyl,

(e) cyclolalkyl,

17790 (f) cycloalkylalkyl,

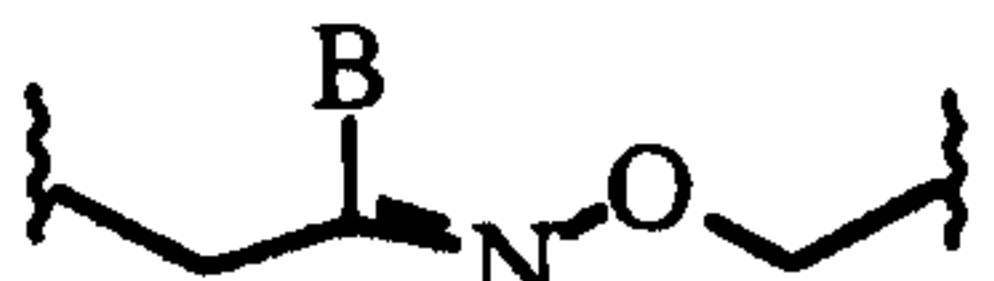
(g) alkylthioalkyl, and

(h) hydroxy,

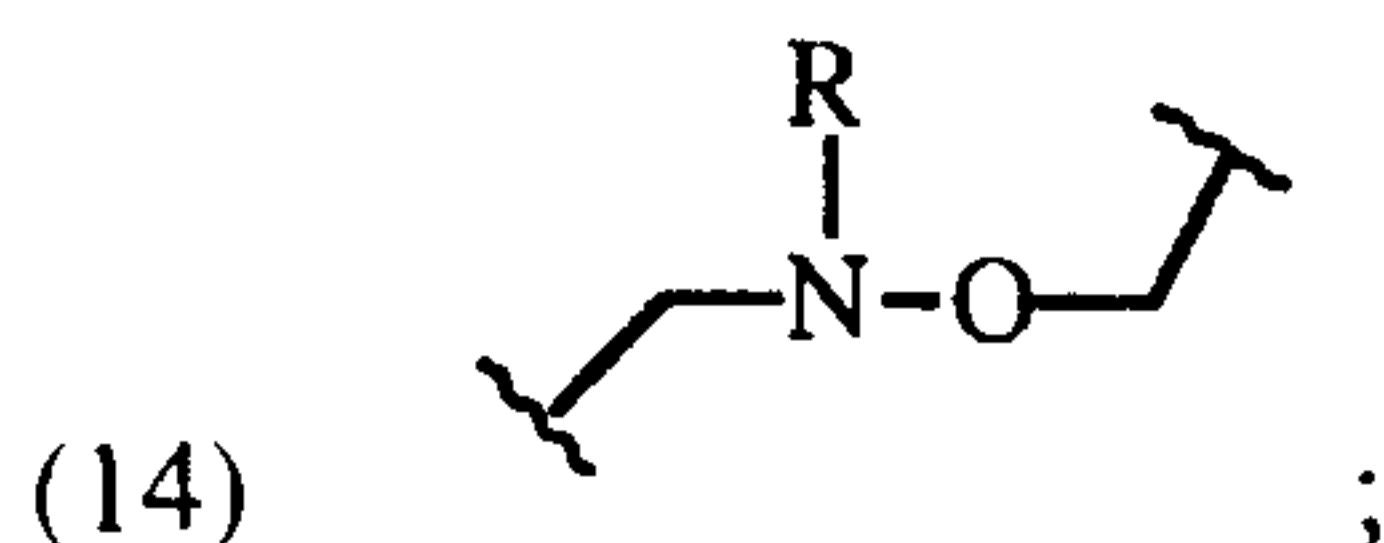
(11) -L₄-heterocycle-L₅-,

17795

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of

loweralkyl and
arylalkyl, and



Z is selected from the group consisting of

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)_q-, and
- (4) -NR_z- wherein R_z is selected from the group consisting of
 - (a) hydrogen
 - (b) loweralkyl,
 - (c) aryl,
 - (d) arylalkyl,
 - (e) heterocycle,
 - (f) (heterocyclic)alkyl,
 - (g) cyclolalkyl, and
 - (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,
- (4) heterocycle,

with the proviso that the heterocycle is other than imidazole and pyridine,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5

substituents independently selected from the group consisting of

- (a) alkanoyl,
- (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

halogen,
aryl, and
cycloalkyl,
- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents

- 17835 independently selected from the group consisting of
aryl and
cycloalkyl,
- (d) 17840 alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of
aryl, and
cycloalkyl,
- (e) 17845 alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) 17850 aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3,
4, or 5 substituents independently selected from the
group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted
with 1 or 2 substituents selected from the group
consisting of cycloalkyl,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
17855 nitro,
-NRR', and
thioalkoxy,
- (h) arylalkyl,
- (i) 17860 aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
- (j) 17865 (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) 17870 -C(O)NRR" wherein R is defined previously and R" is
selected from the group consisting of

- hydrogen,
loweralkyl, and
carboxyalkyl,
- 17875 (o) cyano,
(p) cyanoalkyl,
(q) cycloalkyl,
(r) cycloalkylalkyl,
(s) cycloalkoxyalkyl,
(t) halogen,
- 17880 (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,
- 17885 (v) heterocycle,
(w) hydroxyl,
(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,
- 17890 (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
with substituents selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,
- 17895 -NR^{R3}R^{R3'}, and
-P(O)(OR)(OR'),
- (z) nitro,
(aa) -NRR',
(bb) oxo,
- 17900 (cc) -SO₂NR_A'R_B' wherein R_A' and R_B' are independently selected
from the group consisting of
hydrogen,
(aryl)oyl,
loweralkyl, and
- 17905 heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, or 3 substituents
independently selected from the group consisting

of loweralkyl,

(dd) sulfhydryl, and

17910

(ee) thioalkoxy,

(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from the group consisting of

17915

(a) alkoxy,

(b) aryl,

(c) arylalkoxy

(d) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

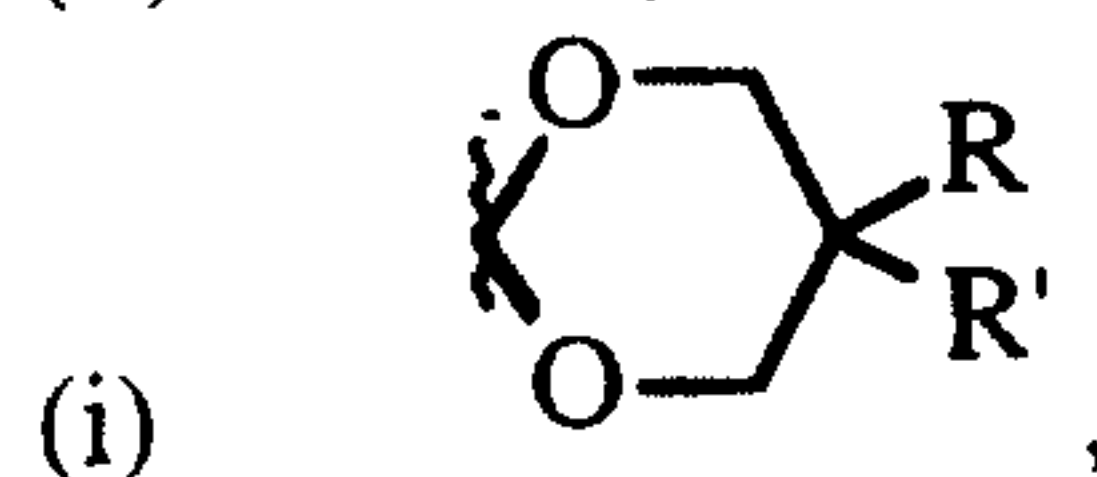
17920

(e) loweralkyl,

(f) halogen,

(g) $\text{NR}^3\text{R}^{3'}$,

(h) oxo, and



17925

(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

17930

(a) loweralkyl,

(b) alkoxy,

(c) halogen,

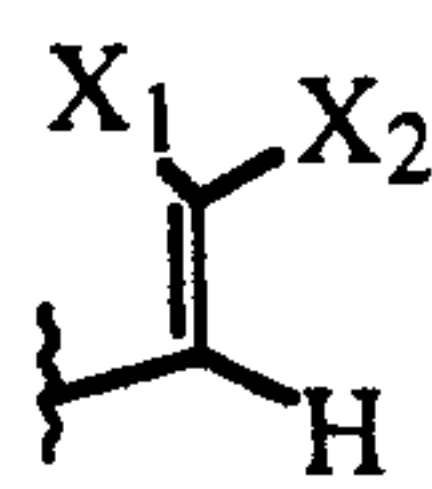
(d) aryl,

(e) aryloxy,

(f) alkanoyl, and

17935

(g) $\text{NR}^3\text{R}^{3'}$,

(7)  wherein X_1 and X_2 together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

17940

(8) $-\text{P}(\text{W})\text{R}^3\text{R}^{3'}$; and

R₄ is selected from the group consisting of

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl
- (4) halogen,
- (5) aryl,
- (6) arylalkyl,
- (7) heterocycle,
- (8) (heterocyclic)alkyl
- (9) alkoxy, and
- (10) -NRR'; or

L₁, Z, and R₃ together are selected from the group consisting of

- (1) aminoalkyl,
- (1) haloalkyl,
- (2) halogen,
- (3) carboxaldehyde, and
- (4) (carboxaldehyde)alkyl, and
- (5) hydroxyalkyl,

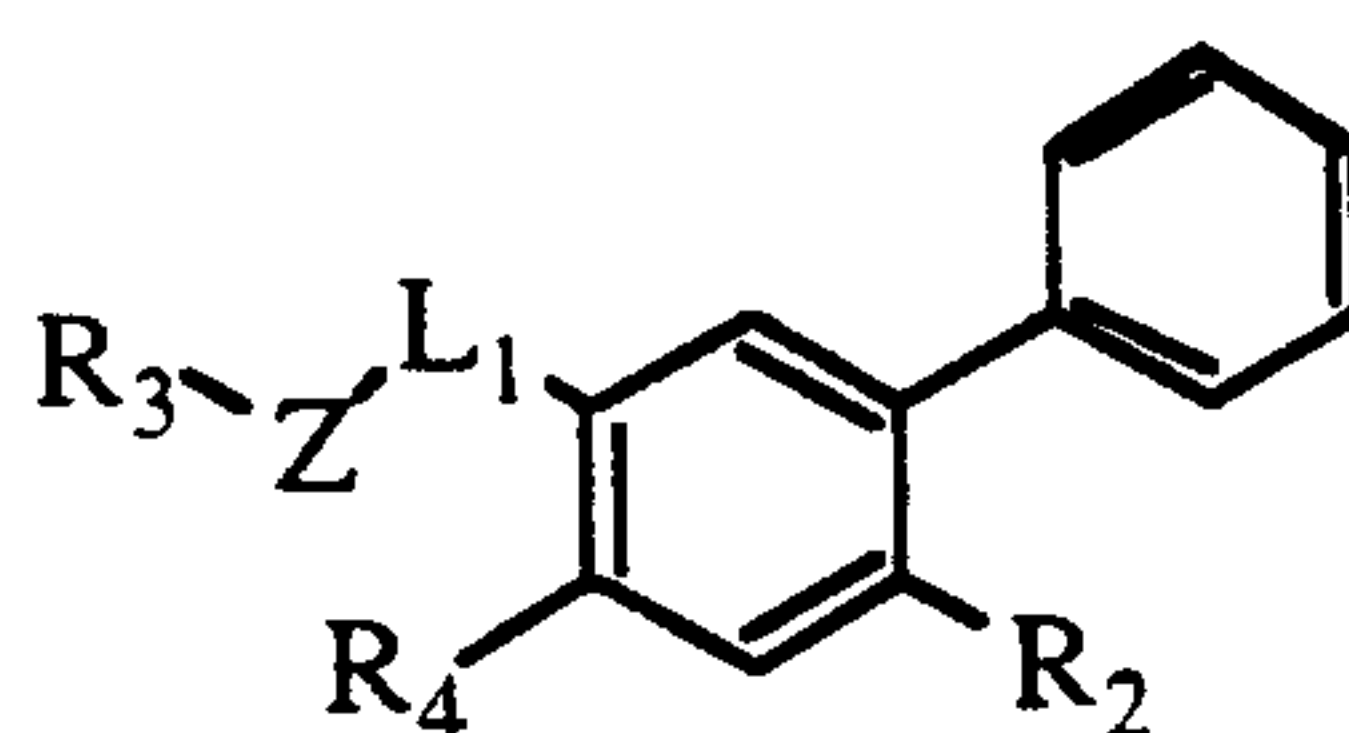
with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

2. A compound according to claim 1 wherein **L₁** is selected from the group consisting of

- (1) -L₄-N(R₅)-L₅-,
- (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
- (3) -L₄-N(R₅)-C(W)-L₇-L₅- and

Z is a covalent bond or -O-.

3. A compound according to claim 1 of formula



wherein

R₃ is selected from the group consisting of

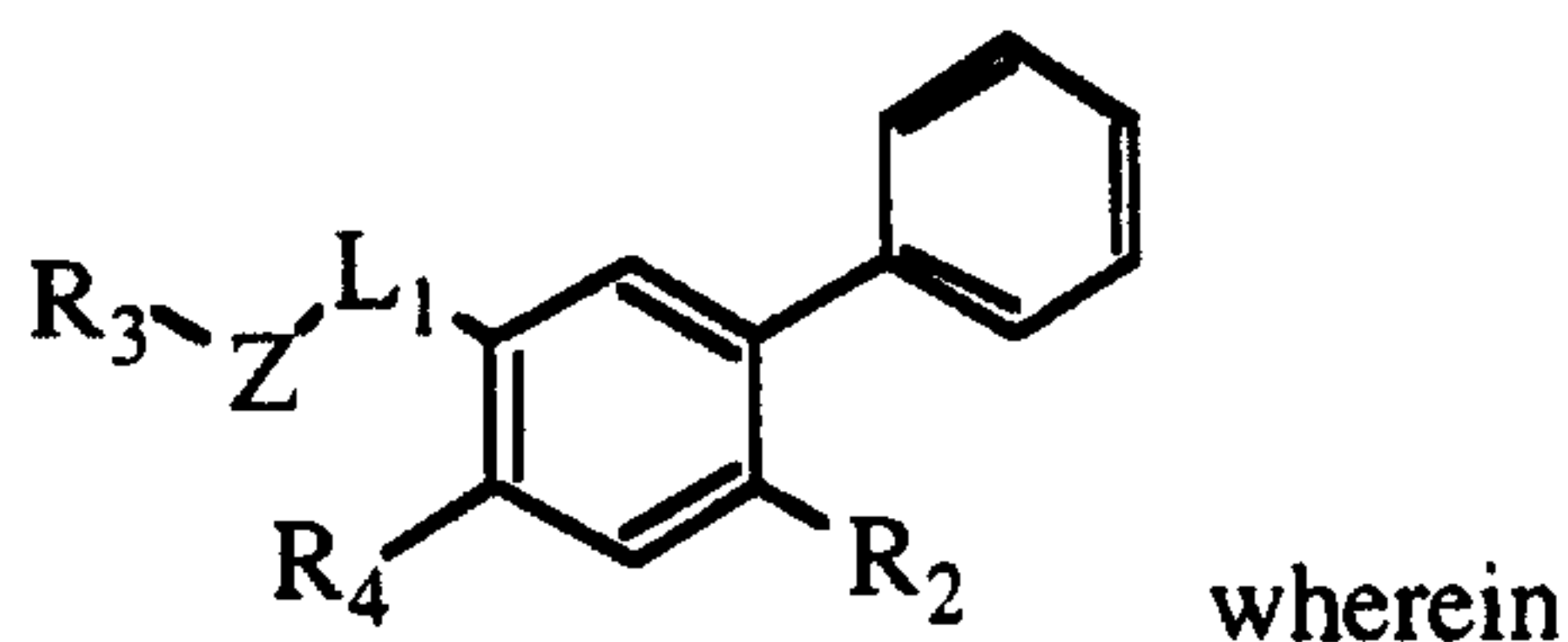
- (1) hydrogen,
 - (2) aryl,
 - (3) heterocycle,
 - (3) fluorenyl,
- wherein (2)-(4) are unsubstituted or substituted as defined previously,
- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
 - (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) -L₄-N(R₅)-L₅-,
- (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
- (3) -L₄-N(R₅)-C(W)-L₇-L₅-, and

Z is a covalent bond or -O-.

4. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- (1) hydrogen,
 - (2) aryl,
 - (3) fluorenyl,
- wherein (2) and (3) are unsubstituted or substituted as defined previously,
- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
 - (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) -L₄-N(R₅)-L₅-,
- (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and

(3) $-L_4-N(R_5)-C(W)-L_7-L_5-$; and

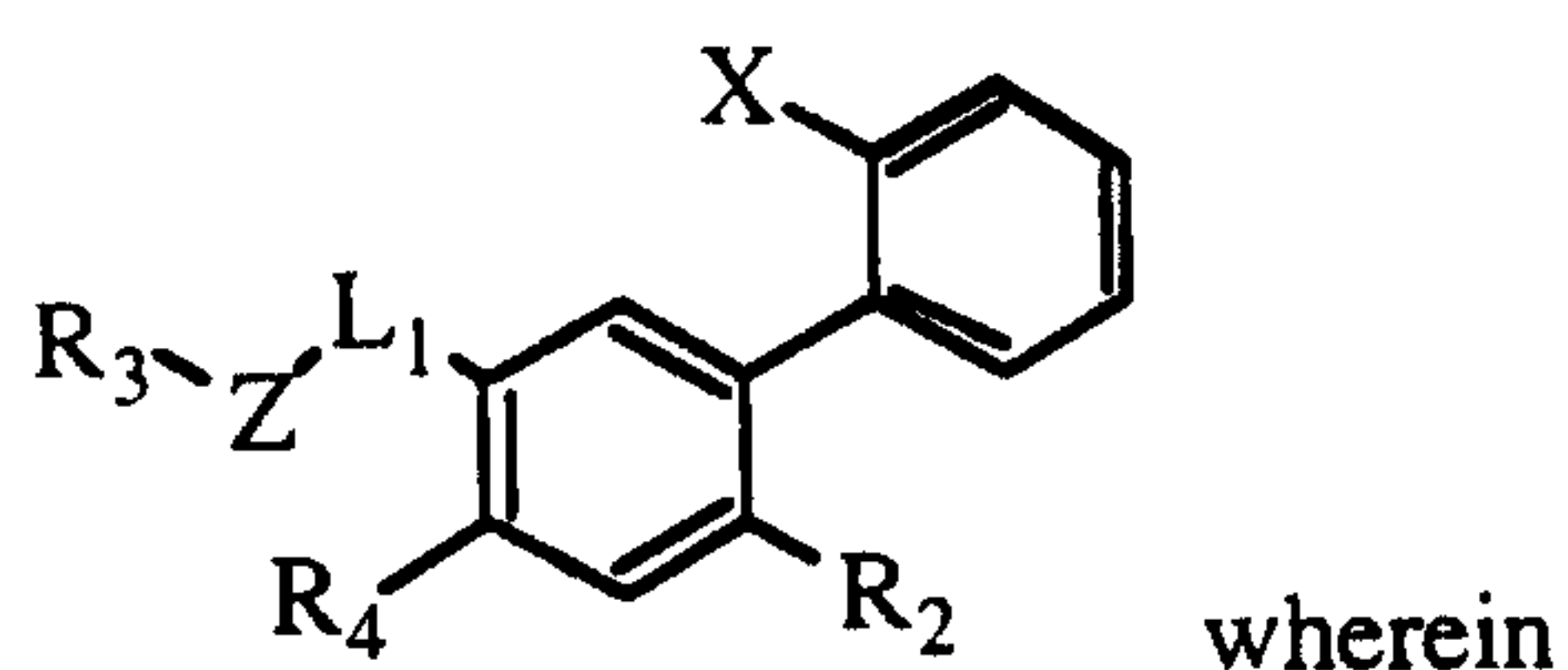
Z is a covalent bond or $-O-$.

20

5. A compound according to claim 4 selected from the group consisting of
 [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 5 methyl ester, hydrochloride,
 [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine,
 hydrochloride,
 [4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine, trifluoroacetate,
 10 [4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]-
 methionine, trifluoroacetate,
 [4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]-
 methionine, hydrochloride,
 [4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]-methionine,
 15 hydrochloride,
 [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine,
 trifluoroacetate,
 [4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine,
 hydrochloride,
 20 [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine,
 [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine,
 [4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine,
 hydrochloride,
 [4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-
 25 phenylbenzoyl]methionine, sodium salt,
 [4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine,
 [4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt,
 N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine,
 N-[4-(N-2-amino-3-benzyloxypropionyl)amino-2-phenylbenzoyl]methionine,
 30 N-[4-N-phenyl-N-benzylaminomethyl-2-phenylbenzoyl]methionine,
 N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl-2-
 phenylbenzoyl]methionine, lithium salt,

N-[4-N-(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
 N-[4-N,N-dibenzylaminomethyl-2-phenylbenzoyl]methionine, lithium salt,
 35 N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl-2-phenylbenzoyl]-
 methionine,
 N-[4-(N-benzylaminomethyl)-2-phenylbenzoyl]methionine, hydrochloride salt,
 N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine,
 N-[4-((2S,4S)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine,
 40 N-[4-((2S,4R)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine, and
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]-
 methionine, lithium salt.

6. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- 5 (1) hydrogen,
 (2) aryl,
 (3) fluorenyl,
 (4) heterocycle
 wherein (2)-(4) are unsubstituted or substituted as defined previously,
 10 (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as
 defined previously, and
 (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as
 defined previously;

15 **L₁** is selected from the group consisting of

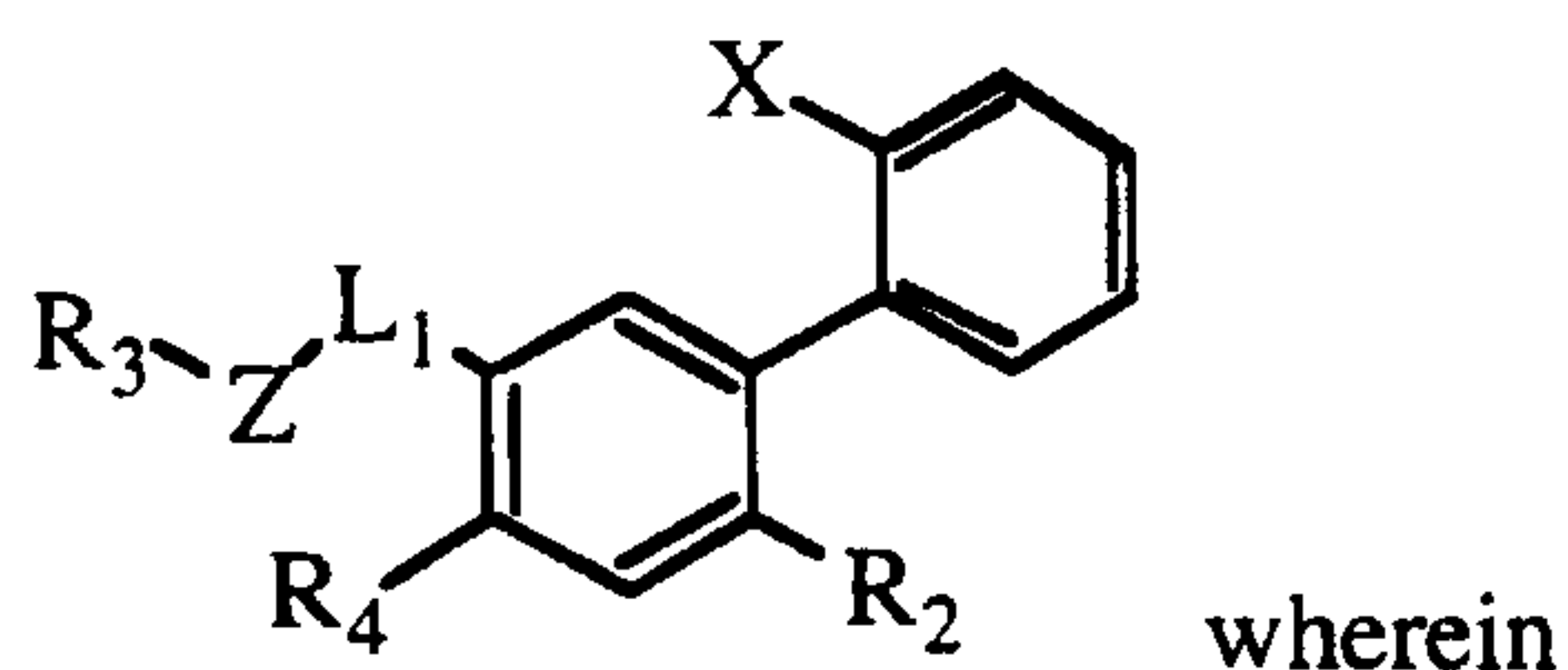
- (1) -L₄-N(R₅)-L₅-,
 (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
 (3) -L₄-N(R₅)-C(W)-L₇-L₅-;

20 **Z** is a covalent bond or -O-; and

X is selected from the group consisting of
 alkoxy,

25 aryl,
 carboxy,
 cyano,
 halogen,
 haloalkyl,
 hydroxy,
 30 hydroxyalkyl,
 loweralkyl,
 nitro,
 N-protected amino,
 -NRR,
 35 oxo (=O), and
 thioalkoxy.

7. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- 5 (1) hydrogen,
 (2) aryl,
 (3) fluorenyl,
 wherein (2) and (3) are unsubstituted or substituted as defined previously,
 (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as
 10 defined previously, and
 (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as
 defined previously;

L₁ is selected from the group consisting of

- 15 (1) -L₄-N(R₅)-L₅-,
 (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
 (3) -L₄-N(R₅)-C(W)-L₇-L₅-;

Z is a covalent bond or -O-; and

20

X is selected from the group consisting of

alkoxy,
 aryl,
 carboxy,
 25 cyano,
 halogen,
 haloalkyl,
 hydroxy,
 hydroxyalkyl,
 30 loweralkyl,
 nitro,
 N-protected amino,
 -NRR,
 oxo (=O), and
 35 thioalkoxy.

8. A compound according to claim 6 wherein X is selected from the group consisting of loweralkyl, halogen, and haloalkyl.
9. A compound according to claim 8 selected from the group consisting of
 [4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 4-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine,
 5 N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-
 methionine, sodium salt,
 N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-
 methionine, sodium salt,
 N-[4-N-(2-cyclohexylmethyl-3-hydroxypropyl)amino-2-(2-methylphenyl)-
 10 benzoyl]methionine,
 N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(2-phenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 15 methionine,
 N-[4-N-(3-phenyl)propyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine,
 N-[4-N-(2,2-diphenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)-

- benzoyl]methionine,
 20 N-[4-N-(adamantan-1-ylmethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 25 lithium salt,
 N-[4-N-(2-phenylethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 30 N-[4-N-methyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(2-phenylethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)-
 35 benzoyl]methionine, lithium salt,
 N-[4-N-(2-indol-3-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 40 N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(1-cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methyl-
 45 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(1-cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-
 2-(2-methylphenyl)benzoyl]methionine,
 50 N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-
 2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-
 55 benzoyl]methionine, methyl ester,

- N-[4-N-phenylacetyl-amino-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
- N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
- 60 N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
- N-[4-N-(3-phenylpropionoyl)amino-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
- 65 N-[4-N-(3-(2-methoxyphenyl)propionoyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
- N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
- N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
- 70 N-[4-(2-cyclohexylethan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
- N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, trifluoroacetate salt,
- 75 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- 80 N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethyl)-
aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-benzenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine lithium salt,
- 85 N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
- N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
- 90 N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-

- methionine, lithium salt,
 N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
 95 methionine,
 N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, trifluoroacetate salt,
 N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 100 N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]-2-amino-4-methanesulfonylbutanoic acid, lithium salt,
 N-[4-(3-cyclohexyl-1-t-butylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-
 105 benzoyl]methionine, lithium salt,
 N-[4-(3-cyclohexyl-1-phenylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-benzoyl-N-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 110 N-[4-N-t-butyloxycarbonyl-N-2-cyclohexylethylaminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 pivaloyloxymethyl N-[4-N-(3-cyclohexyl-1-ethylthioprop-2-yl)-N-methyl-
 aminomethyl-2-(2-methylphenyl)benzoyl]methionine, hydrochloride salt,
 N-[4-N-(3-cyclohexyl-1-ethylthioprop-2-yl)-N-methylaminomethyl-2-
 115 (2-methylphenyl)benzoyl]-N-methylmethionine, lithium salt,
 N-[4-N-(3-cyclohexyl-1-cyclohexylthioprop-2-yl)-N-methylamino-
 methyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(3-cyclohexyl-1-(2-methylphenyl)thioprop-2-yl)-N-methyl-
 aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 120 N-[4-N-(N-phenyl-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-
 125 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,

- 130 N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 135 N-[4-(N-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]-methionine,
N-[4-N-(furan-2-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(furan-3-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 140 N-[4-N-benzyl-N-3-methoxyphenylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(2-phenylethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 145 N-[4-N-benzyl-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyridizin-2-ylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 150 N-[4-(N-benzyl-N-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 155 N-[4-(N-benzyl-N-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-benzyl-N-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-benzyl-N-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]-methionine, lithium salt,
- 160 N-[4-N-(N-benzyl-N-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 165 N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,

- N-[4-N-(N-benzyl-N-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 170 N-[4-N-(N-benzyl-N-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-benzyl-N-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- N-[4-(N-benzyl-N-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 175 N-[4-(N-benzyl-N-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-benzyl-N-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 180 N-[4-(N-benzyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(4-piperidin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
- N-[4-N-(4-morpholin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
- 185 N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
- N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
- N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 190 N-[4-N-(methanesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(N-2-cyclohexylethyl-N-cyclopropylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine,
- 195 N-[4-(N-tetrahydrothiopyran-4-yl-N-thiazol-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-t-butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(3-cyclohexyl-1-oxo-1-piperidin-1-ylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 200 N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine,
- N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)-N-methylaminomethyl)-2-(2-

- methoxyphenyl)benzoyl]methionine,
 205 N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-acetyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 210 N-[4-(N-benzoyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-benzenesulfonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 215 N-[4-(N-(N,N-dibutylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(N,N-dibutylacetamido)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(N,N-dibenzylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 220 N-[4-(N-(2-cyclohexylethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-butanefulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 225 N-[4-(N,N-dibutylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-butanefulfonyl-N-(3-phenylpropyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 230 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-2-(2-methylphenyl)benzoyl]methionine, hydrochloride,
 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-isobutylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-formylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 235 N-[4-N-acetyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-t-butyloxycarbonyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 240 N-[4-N-benzoyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-

- methylphenyl)-benzoyl]methionine,
 N-[4-N-butanefulfoyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
 methyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-benzenesulfonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
 methyl-2-(2-methylphenyl)benzoyl]methionine,
 245 N-[4-(N-5-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 250 N-[4-(N-methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-
 methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(N-2-cyclohexylethyl-N-thiazol-5-ylmethylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)-benzoyl]-
 255 methionine,
 N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 260 N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 265 N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2-yl)phenyl)aminomethyl-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 270 N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
 275 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,

- N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 280 N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)-aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 285 N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-3,5-difluorobenzyl-N-(4-(2-tert-butyl dimethylsiloxyethyl)phenyl)-aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)amino-methyl-2-(2-methylphenyl)benzoyl]methionine,
- 290 N-[4-(2-N-piperidin-1-ylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(4-trans-pentafluorophenoxy cyclohexyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 295 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]glutamine, trifluoroacetic acid salt,
- N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]homocysteine, lithium salt,
- 300 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]histidine, trifluoroacetic acid salt,
- N-[4-(N-cyclohexylmethylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 305 N-[4-(N-cyclohexylmethyl-N-phenylacetylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-1-adamantanoylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 310 N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-

- 315 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-adamantyloxycarbonylaminoethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
- 320 N-[4-(N-cyclohexylmethyl-N-phenoxy carbonylaminoethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
- 325 N-[4-(N-cyclohexylmethyl-N-adamant-1-aminothiocarbonylaminoethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]glutaminitrile, lithium salt,
- 330 N-[4-(N-p-toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(N-(4-benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)-
 aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
- 335 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt,
 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-
 methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
- 340 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]norleucine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]amino-4-methylsulfenylbutanoate, lithium salt,
- 345 N-[4-(N-(2-cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
- 350 N-[4-(N-(2-cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,

- N-[4-(N-(2-cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 355 N-[4-(N-(2-cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 360 N-[4-(3-cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 (2S)-2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt,
 365 N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 370 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt,
 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt,
 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt,
 375 2-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt,
 N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 380 N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-ylmethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylamino-methyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 385 N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methyl-

- phenyl)benzoyl]methionine,
- 390 N-[4-(N-(2-cyclohexylethyl)-N-2,2,2-trifluoroethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
- 395 N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
- N-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(N-(2-cyclohexylethyl)-N-2-N,N-dimethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
- 400 N-[4-(N-(1-benzyloxymethyl-2-(S)-ethylthioethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
- N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]ornithine, trifluoroacetate salt,
- N-[4-(N-(2-cyclohexylethyl)-N-2-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]thien-2-ylalanine,
- 405 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methyl-phenyl)benzoyl]methionine,
- N-[4-(N-butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 410 N-[4-(N-butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 415 N-[4-(N-cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 420 N-[4-(N-cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine lithium salt,
- N-[4-(N-cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexyl-N-propanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine,
- 425 N-[4-(N-cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]-

- methionine, lithium salt,
N-[4-(N-cyclohexyl-N-methylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexyl-N-butylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
430 methionine, lithium salt,
N-[4-(N,N-dicyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-1-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
435 N-[4-(N-adamant-2-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-1-ylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-mytanylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
440 methionine, lithium salt,
N-[4-(N-cyclooctanylaminocarbonylethyl)-2-(2-methylphenyl)-benzoyl]-methionine,
lithium salt,
3-[4-(N-cyclohexyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoylmethyl]-
4-methylthiobutyric acid,
445 N-[4-(N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(N-(2,2,4,4-tetramethylbutylamino)carbonylethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N,N-dibutylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium
450 salt,
N-[4-N-(2-ethylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-propylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(4-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
455 N-[4-N-(2-butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-(2,6-diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(2-butylphenyl)-N-(cyclohexylmethyl)aminomethyl-2-(2-methylphenyl)-
460 benzoyl]methionine, lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-(3-methylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,

- N-[4-N-(2-butylphenyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 465 N-[4-N-butyl-N-(2-(3,5-difluoro)phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-butanefonyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt,
- N-[4-N-(2-cyclohexylethyl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]-3-aminotetrahydrofuran-2-one,
- 470 N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine 4-methylphenylsulfonimide,
- 475 N-[4-N-butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-t-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 480 N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(2-cyclohexylethyl)-N-propyloxyaminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 485 N-[4-N-(2-cyclohexylethyl)-N-propanesulfonylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(3-chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(2-cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt,
- 490 N-[4-N-(2-cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 495 N-[4-N-(4-cyclohexyl-1-ethylthiobutan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-butyl-N-quinolin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-

- 500 methionine,
N-[4-(N-butyl-N-(2-piperidin-1-ylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-((1-norpholinocarbonyl)butyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
- 505 N-[4-N-butyl-N-(2-morpholin-4-ylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-butyl-N-(fluoren-9-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(2-cyclohexylethyl)-N-(furan-2-ylmethyl)aminomethyl-2-(2-methyl-
- 510 henyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-pyrrolidin-1-ylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
- 515 N-[4-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-butyl-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
- 520 methionine p-tolylsulfonimide, hydrochloride salt,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine 4-(aminomethyl)phenylsulfonimide, dihydrochloride salt,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, isopropylsulfonimide,
- 525 N-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(n-butanesulfonyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-nitrobenzenesulfonyl)aminomethyl)-2-(2-methyl-
- 530 phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
- 535 N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,

- N-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 540 N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 545 N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 550 N-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 555 N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
- 560 N-[4-N-(N-phenyl-N-(4-phenylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
- 565 N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2-methyl-anthraquinone-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 570 N-[4-N-(N-phenyl-N-(2,3-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-

- benzoyl]methionine, lithium salt,
- 575 N-[4-N-(N-phenyl-N-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2-methyl-4-methylemethiazolyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
- 580 N-[4-N-(N-3,5-difluorophenyl-N-(5-thiazolylmethyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-(5-thiazolylmethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- 585 N-[4-N-(N-(4-acetonitrilephenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-(4-nitrophenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- 590 N-[4-N-(N-butyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-(4,4,4-trifluorobutyl-N-(3,5-difluorobenzyl)aminomethyl)-
2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 595 N-[4-N-(N-cyclohexyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-(4-cyclohexanonyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-N-(3,5-
difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium
- 600 salt,
- N-[4-N-(N-cyclohexylmethyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-cyclohexylmethyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- 605 N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-(3,5-difluorobenzyl)-N-(4-N-carboxymethionine)benzyl)-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
- 610 N-[4-N-(N-(2-cyclohexylethyl-N-(3,5-difluorobenzyl)aminomethyl)-2-

- (2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-cyclopropyl-N-(2-(3,5-difluorophenyl)ethyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 615 [4-N-(N-2-methylbutyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 [4-N-(N-butyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 620 N-[4-N-(N-(4-methyltetrahydropyran-yl)-N-(3,5-difluorobenzyl)-
 aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-methyltetrahydrothiopyran-yl)-N-(3,5-difluorobenzyl)-
 aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
 625 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-methyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, p-tolylsulfonimide,
 630 N-[4-N-(N-(trans-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(cis-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)-aminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 (2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-
 635 methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt,
 N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]thioglutamine, lithium salt,
 640 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-
 methylphenyl)benzoyl]methionine,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N'N'-dimethyl-
 amino-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(6-fluorobenzothiazol-2-yl)aminomethyl-2-(2-methylphenyl)-
 645 benzoyl]methionine, and
 N-[4-N-butyl-N-(furan-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine.

10. A compound selected from the group consisting of
- [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine, methyl ester, hydrochloride,
 - [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine, hydrochloride,
 - [4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine, trifluoroacetate,
 - [4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]-methionine, trifluoroacetate,
 - [4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]-methionine, hydrochloride,
 - [4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]-methionine, hydrochloride,
 - [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine, trifluoroacetate,
 - [4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine, hydrochloride,
 - [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine,
 - [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine,
 - [4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine, hydrochloride,
 - [4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine, sodium salt,
 - [4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine,
 - [4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt,
 - N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine,
 - N-[4-(N-2-amino-3-benzyloxypropionyl)amino-2-phenylbenzoyl]methionine,
 - N-[4-N-phenyl-N-benzylaminomethyl-2-phenylbenzoyl]methionine,
 - N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl-2-phenylbenzoyl]methionine, lithium salt,
 - N-[4-N-(t-butylcarbazonocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
 - N-[4-N,N-dibenzylaminomethyl-2-phenylbenzoyl]methionine, lithium salt,
 - N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl-2-phenylbenzoyl]-methionine,

N-[4-(N-benzylaminomethyl)-2-phenylbenzoyl]methionine, hydrochloride salt,
N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine,
N-[4-((2S,4S)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine,
N-[4-((2S,4R)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]-
methionine, lithium salt,
[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
4-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine,
N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, sodium salt,
N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, sodium salt,
N-[4-N-(2-cyclohexylmethyl-3-hydroxypropyl)amino-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-phenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(3-phenyl)propyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(2,2-diphenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(adamantan-1-ylmethyl)-N-phenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-N-(2-phenylethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-methyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-

methionine, lithium salt,
 N-[4-N-(2-phenylethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(2-indol-3-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(1-cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(1-cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-
 2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-
 2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, methyl ester,
 N-[4-N-phenylacetyl-amino-2-(2-methylphenyl)benzoyl]methionine,
 lithium salt,
 N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine,
 lithium salt,
 N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-(3-phenylpropionoyl)amino-2-(2-methylphenyl)benzoyl]methionine,
 lithium salt,
 N-[4-N-(3-(2-methoxyphenyl)propionoyl)amino-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,

N-[4-(2-cyclohexylethan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, trifluoroacetate salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-benzenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt,
N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, trifluoroacetate salt,
N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methanesulfonylbutanoic acid, lithium salt,
N-[4-(3-cyclohexyl-1-t-butylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-phenylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-

benzoyl]methionine, lithium salt,
 N-[4-N-benzoyl-N-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-N-t-butyloxycarbonyl-N-2-cyclohexylethylaminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 pivaloyloxymethyl N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methyl-
 aminomethyl-2-(2-methylphenyl)benzoyl]methionine, hydrochloride salt,
 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-
 (2-methylphenyl)benzoyl]-N-methylmethionine, lithium salt,
 N-[4-N-(3-cyclohexyl-1-cyclohexylthiopropyl)-N-methylamino-
 methyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(3-cyclohexyl-1-(2-methylphenyl)thiopropyl)-N-methyl-
 aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-
 methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
 N-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(N-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]-
 methionine,
 N-[4-N-(furan-2-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(furan-3-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-benzyl-N-3-methoxyphenylaminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(2-phenylethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-

benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyrimidin-5-ylaminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyridizin-2-ylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]-
methionine, lithium salt,
N-[4-N-(N-benzyl-N-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,

N-[4-N-(4-piperidin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
 N-[4-N-(4-morpholin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
 N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
 N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(methanesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-2-cyclohexylethyl-N-cyclopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-tetrahydrothiopyran-4-yl-N-thiazol-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-t-butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(3-cyclohexyl-1-oxo-1-piperidin-1-ylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-acetyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-benzoyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-benzenesulfoyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(N,N-dibutylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine,
 N-[4-(N-(N,N-dibutylacetamido)-N-methylaminomethyl)-2-(2-methylphenyl)-

benzoyl]methionine,
 N-[4-(N-(N,N-dibenzylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-(N-butanesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-(N,N-dibutylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-butanesulfonyl-N-(3-phenylpropyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine,
 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-
 (2-methylphenyl)benzoyl]methionine, hydrochloride,
 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-isobutylaminomethyl-
 2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-formylaminomethyl-2-
 (2-methylphenyl)benzoyl]methionine,
 N-[4-N-acetyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-
 methylphenyl)benzoyl]methionine,
 N-[4-N-t-butyloxycarbonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
 methyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-benzoyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-
 methylphenyl)-benzoyl]methionine,
 N-[4-N-butanesulfonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
 methyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-benzenesulfonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
 methyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-5-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-
 methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(N-2-cyclohexylethyl-N-thiazol-5-ylmethylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)-benzoyl]-

methionine,
N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2yl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(2-tert-butyl dimethylsiloxyethyl)phenyl)-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,

N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-N-(4-trans-pentafluorophenoxy)cyclohexyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]glutamine, trifluoroacetic acid salt,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]homocysteine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]histidine, trifluoroacetic acid salt,
 N-[4-(N-cyclohexylmethylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-phenylacetylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-1-adamantanoylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-adamantyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-phenoxy carbonylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-adamant-1-aminothiocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-

benzoyl]glutaminitrile, lithium salt,
 N-[4-(N-p-toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(N-(4-benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)-
 aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-
 methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]norleucine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-(3-cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(1-ethylsulfonyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 (2S)-2-N-[4-(1-ethylsulfonyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methyl-
 phenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,

N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt,
 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt,
 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt,
 2-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt,
 N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-yl)methyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-2,2,2-trifluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-2-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(1-benzyloxymethyl-2-(S)-ethylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-

benzoyl]ornithine, trifluoroacetate salt,
 N-[4-(N-(2-cyclohexylethyl)-N-2-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]thien-2-ylalanine,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-(N-butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-
 methionine lithium salt,
 N-[4-(N-cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-cyclohexyl-N-propanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-
 methionine,
 N-[4-(N-cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-cyclohexyl-N-methylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-cyclohexyl-N-butylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N,N-dicyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-adamant-1-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-adamant-2-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-adamant-1-ylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
 methionine, lithium salt,
 N-[4-(N-myrtanylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-

methionine, lithium salt,
N-[4-(N-cyclooctanylaminocarbonylethyl)-2-(2-methylphenyl)-benzoyl]-methionine,
lithium salt,
3-[4-(N-cyclohexyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoylmethyl]-
4-methylthiobutyric acid,
N-[4-(N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(N-(2,2,4,4-tetramethylbutylamino)carbonylethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N,N-dibutylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium
salt,
N-[4-N-(2-ethylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-propylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(4-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-(2,6-diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(2-butylphenyl)-N-(cyclohexylmethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-(3-methylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-(3,5-difluoro)phenylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-butanefonyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-methylaminomethyl-2-(2-methylphenyl)-
benzoyl]-3-aminotetrahydrofuran-2-one,
N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine 4-methylphenylsulfonimide,
N-[4-N-butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,

N-[4-N-t-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-(2-cyclohexylethyl)-N-propyloxyaminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(2-cyclohexylethyl)-N-propanesulfonylaminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-N-(3-chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-
 methylphenyl)benzoyl]methionine,
 N-[4-N-(2-cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl-2-(2-
 methylphenyl)benzoyl]methionine lithium salt,
 N-[4-N-(2-cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)amino-
 methyl-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(4-cyclohexyl-1-ethylthiobutan-2-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-(butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-butyl-N-quinolin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine,
 N-[4-(N-butyl-N-(2-piperidin-1-ylethyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-((1-norpholinocarbonyl)butyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-butyl-N-(2-morpholin-4-ylethyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-butyl-N-(fluoren-9-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-
 methionine,
 N-[4-N-(2-cyclohexylethyl)-N-(furan-2-ylmethyl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-N-butyl-N-(2-pyrrolidin-1-ylethyl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-(2-butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methyl-

phenyl)benzoyl]methionine,
 N-[4-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-N-butyl-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methyl-
 phenyl)benzoyl]methionine,
 N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine p-tolylsulfonimide, hydrochloride salt,
 N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine 4-(aminomethyl)phenylsulfonimide, dihydrochloride salt,
 N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, isopropylsulfonimide,
 N-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(n-butanesulfonyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(3-nitrobenzenesulfonyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methyl-
 phenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(2-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,
 N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine, lithium salt,

N-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
N-[4-N-(N-phenyl-N-(4-phenylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-methyl-anthraquinone-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2,3-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-methyl-4-methylemethiazolyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-3,5-difluorophenyl-N-(5-thiazolylmethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(5-thiazolylmethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-acetonitrilephenyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-

methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-nitrophenyl)-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-butyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4,4,4-trifluorobutyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-cyclohexyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-cyclohexanonyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-cyclohexylmethyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-cyclohexylmethyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(3,5-difluorobenzyl)-N-(4-N-carboxymethionine)benzyl)-aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
 N-[4-N-(N-(2-cyclohexylethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-cyclopropyl-N-(2-(3,5-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 [4-N-(N-2-methylbutyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 [4-N-(N-butyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-methyltetrahydropyran-yl)-N-(3,5-difluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-methyltetrahydrothiopyran-yl)-N-(3,5-difluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-

methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-methyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, p-tolylsulfonimide,
 N-[4-N-(N-(trans-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(cis-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 (2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thioglutamine, lithium salt,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(6-fluorobenzothiazol-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, and
 N-[4-N-butyl-N-(furan-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine.

11. A compound according to claim 10 selected from the group consisting of [4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt, and N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt.
12. A method of inhibiting protein isoprenyl transferases in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
13. A composition for inhibiting protein isoprenyl transferases comprising a

pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.

14. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
15. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
16. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 17. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 18. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
19. A composition for treating or preventing restenosis in a mammal comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier.