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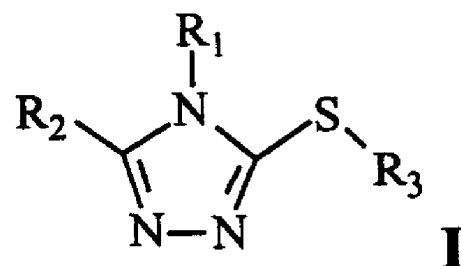
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[54] 发明名称 5-硫烷基-4H-1,2,4-三唑衍生物及其作为药物的应用

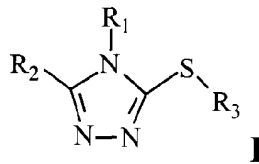
[57] 摘要

本发明涉及式(I)的新5-硫烷基-4-1,2,4-三唑衍生物,其中R<sub>1</sub>、R<sub>2</sub>和R<sub>3</sub>代表不同的基团,本发明还涉及采用平行的液相合成方法制备这些化合物的方法。这些化合物对生长激素的某些受体亚型具有良好的亲合性,因此,可以用于治疗涉及一种或多种生长激素受体的病变或疾病。本发明还涉及含有所述化合物的药物组合物,以及它们在制备药物中的应用。



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## 1. 下述通式化合物:



该化合物呈外消旋形式、对映异构体形式或这些形式的组合, 其中:

5  $R_1$ 、 $R_2$  或  $R_3$  基团中的一个代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  或  $-(CH_2)_n-W$  的基团, 其中:

$W$  代表含有至少一个氮原子的杂环烷基;

$Q$  代表  $-O-$ 、 $-S-$ 、 $-C(O)-NH-$ 、 $-C(Z_q)(Z_q')$ 、芳基或  $(C_3-C_7)$  环烷基;

10  $Z_q$  和  $Z_q'$  独立地代表氢原子、任选地被芳基取代的芳基、 $(C_3-C_7)$  环烷基-烷基、芳烷基、 $-C(O)O-R$  或  $-C(O)-NH-R'$ ;

$R$  代表  $(C_1-C_6)$  烷基、芳基或芳烷基, 这些芳基和芳烷基任选地被一个或多个选自  $(C_1-C_6)$  烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基) 氨基的相同或不同取代基取代;

15  $R'$  代表  $(C_1-C_6)$  烷基、芳基、芳烷基、杂芳基或杂芳基-烷基, 这些芳基、芳烷基、杂芳基和杂芳基-烷基任选地被一个或多个选自  $(C_1-C_6)$  烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基) 氨基的相同或不同取代基取代;

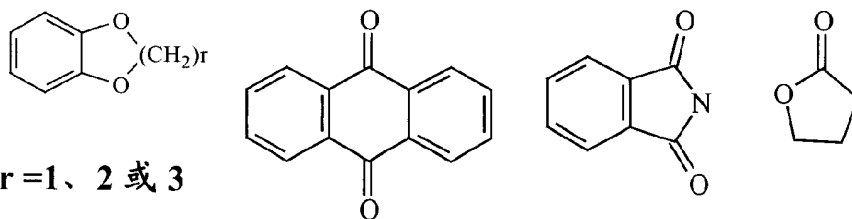
20  $X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$  烷基、 $(C_1-C_6)$  烷氧基-羰基或杂芳基-烷基, 或  $X$  和  $Y$  与它们连接的氮原子一起构成杂环烷基, 它任选地被  $(C_1-C_6)$  烷基取代;

$p$  代表 0 或 1; 且  $n$  和  $m$  独立地代表 0-6 中的一个整数;

并且两个其它基团独立地代表式  $-(CH_2)_n-[Q']_p-[C(X')(Y')]_m-Z'$  的基团, 其中:

$Q'$  代表  $-O-$ 、 $-S-$ 、 $-C(O)-$ 、 $-NH-$ 、 $-CH=CH-$  或  $-C\equiv C-$ ;

25  $X'$ 、 $Y'$  和  $Z'$  独立地代表氢原子、 $(C_1-C_6)$  烷基、 $(C_1-C_6)$  烷氧基、 $(C_1-C_6)$  烷氧基-羰基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基) 氨基、 $(C_3-C_7)$  环烷基、杂环烷基、芳基或杂芳基, 或下式的基团:



这些(C<sub>3</sub>-C<sub>7</sub>)环烷基、杂环烷基、芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-S-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键;

- 5 Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基; 或芳基或杂芳基, 它们任选地被一个或多个选自(C<sub>1</sub>-C<sub>6</sub>)烷氧基、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

p'代表0或1, n'、m'和q'独立地代表0-6中的一个整数;

- 10 下述化合物除外, 其中:

i) R<sub>1</sub>代表(CH<sub>2</sub>)<sub>2</sub>-W, W代表吗啉基或哌嗪基, R<sub>2</sub>代表苯基、m-氟苯基或4-哌啶基, 且R<sub>3</sub>代表氢原子;

ii) R<sub>1</sub>代表(CH<sub>2</sub>)<sub>2</sub>-W, W代表吡咯烷基, R<sub>2</sub>代表p-氟苯基, 且R<sub>3</sub>代表氢原子;

- 15 或它们与药学上可接受的无机或有机酸的加成盐。

2. 根据权利要求1所述的通式I化合物, 其特征在于:

R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团;

Q代表芳基或(C<sub>3</sub>-C<sub>7</sub>)环烷基;

- 20 X和Y独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基, 或X和Y与它们连接的氮原子一起构成杂环烷基, 它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代;

p代表0或1, 且n和m独立地代表0-6中的一个整数;

R<sub>2</sub>代表式-(CH<sub>2</sub>)<sub>n'</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团;

Q'代表-O-;

X'代表氢原子;

Y'和Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、氰基、氨基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、芳基或杂芳基;

5 这些芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-S-或一个共价键;

Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基,或任选地被一个或多个相同或不同卤素基团取代的芳基;

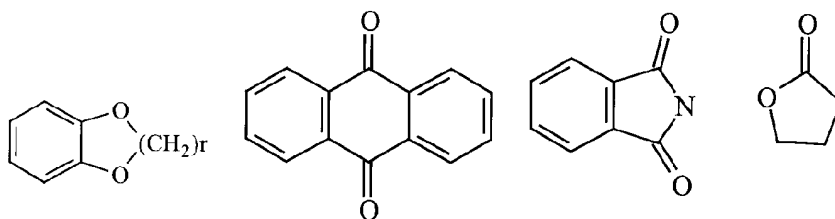
p'代表0或1; n'代表0、1或2; 且m'代表0-6中的一个整数;

10 R<sub>3</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团;

Q'代表-O-、-C(O)-、-CH=CH-或-C≡C-;

X'代表氢原子;

Y'和Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、芳基或杂芳基,或下式的基团:



r=1、2或3

15 这些芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、卤素、硝基、氰基、二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键;

Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基,或芳基;

20 p'代表0或1; 且n'和m'代表0-6中的一个整数。

3. 根据权利要求2所述的通式I化合物, 其特征在于:

Q代表的芳基是苯基; Q代表的(C<sub>3</sub>-C<sub>7</sub>)环烷基是环己基;

X和Y与它们连接的氮原子一起构成的杂环烷基选自吡咯烷、哌啶、哌嗪和吗啉基;

Y'和 Z'独立地代表的(C<sub>3</sub>-C<sub>7</sub>)环烷基是环己基;

Y'和 Z'独立地代表的芳基选自苯基、萘基和茚基;

R<sub>2</sub>基团的 Y'和 Z'独立地代表的杂芳基选自噻吩基、呋喃基、苯并噻吩基、吡啶基、吲哚基、噻二唑基、喹啉基、异喹啉基、喹喔啉基、咕吨基和萘啶基;

R<sub>3</sub>基团的 Y'和 Z'独立地代表的杂芳基选自苯并噻吩基、呋喃基、吲哚基和异噻唑基; 和

Y''代表的芳基是苯基。

4. 根据权利要求 1 所述的通式 I 化合物, 其特征在于:

R<sub>1</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p</sub>[C(X')(Y')]<sub>m</sub>Z'的基团;

X'代表氢原子;

Y'和 Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基, 或任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、卤素和氨基的相同或不同取代基取代的芳基;

X''代表一个共价键;

Y'' 代表芳基;

p'代表 0, n'代表 0 或 1, 且 m'代表 0-6 中的一个整数;

R<sub>2</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY 或-(CH<sub>2</sub>)<sub>n</sub>-W 的基团;

W 代表含有至少一个氮原子的杂环烷基;

Q 代表-C(Z<sub>q</sub>)(Z<sub>q</sub>')-;

Z<sub>q</sub> 代表氢原子;

Z<sub>q</sub>'代表氢原子、任选地被芳基取代的芳基、(C<sub>3</sub>-C<sub>7</sub>)环烷基-烷基或芳烷基;

X 和 Y 独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基或(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基;

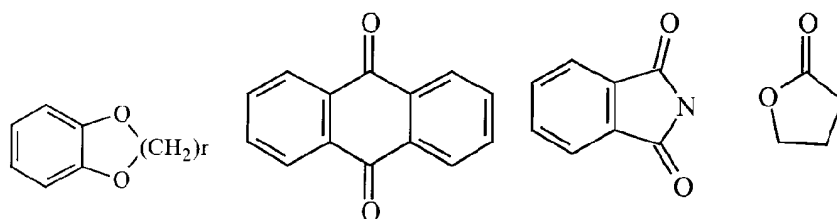
p 代表 0 或 1, n 代表 0 或 1, 且 m 代表 0-6 中的一个整数;

R<sub>3</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p</sub>[C(X')(Y')]<sub>m</sub>Z'的基团;

Q'代表-O-、-C(O)-、-CH=CH- 或-C≡C-;

X'代表氢原子;

Y'和 Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、芳基或杂芳基, 或下式的基团:



这些芳基和杂芳基任选地被一个或多个选自 $-(\text{CH}_2)_q-\text{X}''-\text{Y}''$ 、卤素、硝基、氰基、二 $((\text{C}_1-\text{C}_6)$ 烷基)氨基的相同或不同取代基取代;

$\text{X}''$ 代表 $-\text{O}-$ 、 $-\text{C}(\text{O})-$ 、 $-\text{C}(\text{O})-\text{O}-$ 、 $-\text{SO}_2-$ 或一个共价键;

$\text{Y}''$ 代表任选地被一个或多个相同或不同卤素基团取代的 $(\text{C}_1-\text{C}_6)$ 烷基, 5 或芳基;

$r$  代表 1、2 或 3;  $p'$  代表 0 或 1; 且  $n'$  和  $m'$  代表 0-6 中的一个整数。

5. 根据权利要求 4 所述的通式 I 化合物, 其特征在于:

$\text{R}_1$  基团的  $\text{Y}'$  和  $\text{Z}'$  独立地代表的芳基选自苯基和萘基;

$\text{W}$  代表的杂环烷基是哌啶或吡咯烷环;

10  $\text{Z}_q'$  代表的芳基是苯基或萘基;

$\text{Z}_q'$  代表的芳基的芳基取代基是苯基;

$\text{Z}_q'$  代表的芳烷基是苄基;

$\text{Z}_q'$  代表 $-(\text{C}_3-\text{C}_7)$ 环烷基-烷基的 $(\text{C}_3-\text{C}_7)$ 环烷基是环己基;

$\text{Y}'$  和  $\text{Z}'$  独立地代表的 $(\text{C}_3-\text{C}_7)$ 环烷基是环己基;

15  $\text{R}_3$  基团的  $\text{Y}'$  和  $\text{Z}'$  独立地代表的芳基选自苯基、萘基和茛基;

$\text{R}_3$  基团的  $\text{Y}'$  和  $\text{Z}'$  独立地代表的杂芳基选自苯并噻吩基、呋喃基、吡啶基和异噻唑基; 且

$\text{Y}''$  代表的芳基是苯基。

6. 根据权利要求 1 所述的通式 I 化合物, 其特征在于:

20  $\text{R}_1$  代表式 $-(\text{CH}_2)_n[\text{Q}']_p[\text{C}(\text{X}')(\text{Y}')]_m\text{Z}'$ 的基团;

$\text{X}'$  代表氢原子;

$\text{Y}'$  和  $\text{Z}'$  独立地代表氢原子、 $(\text{C}_1-\text{C}_6)$ 烷基, 或任选地被一个或多个选自 $-(\text{CH}_2)_q-\text{X}''-\text{Y}''$ 、卤素和氨基的相同或不同取代基取代的芳基;

$\text{X}''$  代表一个共价键;

Y''代表芳基;

p'代表0, n'代表0或1, 且m'代表0-6中的一个整数;

R<sub>2</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团;

Q'代表-O-;

5 X'代表氢原子;

Y'和Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、氰基、氨基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、芳基或杂芳基;

10 这些芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-S-或一个共价键;

Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基, 或任选地被一个或多个相同或不同卤素基团取代的芳基;

p'代表0或1; n'代表0、1或2; 且m'代表0-6中的一个整数;

15 R<sub>3</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团或-(CH<sub>2</sub>)<sub>n</sub>-W的基团,

W代表含有至少一个氮原子的杂环烷基;

Q代表-C(O)-NH-;

X和Y独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基或杂芳基-烷基, 或X和Y与它们连接的氮原子一起构成杂环烷基, 它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代;

20 p代表0或1, n代表0或1, 且m代表0-6中的一个整数。

7. 根据权利要求6所述的通式I化合物, 其特征在于:

R<sub>1</sub>基团的Y'和Z'独立地代表的芳基选自苯基和萘基;

W代表的杂环烷基是哌啶环;

Y'和Z'独立地代表的(C<sub>3</sub>-C<sub>7</sub>)环烷基是环己基;

25 R<sub>2</sub>基团的Y'和Z'独立地代表的芳基选自苯基、萘基和苊基;

X和Y独立地代表杂芳基-烷基的杂芳基是吡啶环;

X和Y与它们连接的氮原子一起构成的杂环烷基选自哌嗪基和吡咯烷基;

30 R<sub>2</sub>基团的Y'和Z'独立地代表的杂芳基选自噻吩基、呋喃基、苯并噻吩基、吡啶基、吲哚基和噻二唑基; 和

Y''代表的芳基是苯基。

8. 根据权利要求 1-3 中任一项权利要求所述的通式 I 化合物, 其特征在于:

R<sub>1</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY 的基团,

5 Q 代表环己基;

X 和 Y 独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基, 或 X 和 Y 与它们连接的氮原子一起构成吡啶环;

n 代表 0 或 1、p 代表 0 或 1, 且 m 代表 1-6 中的一个整数;

R<sub>2</sub> 代表式-(CH<sub>2</sub>)<sub>n'</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团;

10 Q'代表-O-;

X'代表氢原子;

Y'代表氢原子或苯基;

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、氨基、环己基、苯基、萘基、苄基、噻吩基、咪唑基、苯并噻吩基、噻二唑基、吡啶基、喹啉基、喹喔啉基、异喹啉基、吡嗪基、咕吨基或萘啶基; 这些苯基、萘基、喹啉基和噻二唑基  
15 任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-S-或一个共价键;

Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基,  
20 或任选地被卤素基团取代的苯基;

p'代表 0 或 1; n'代表 0-4 中的一个整数; 且 m'代表 0-4 中的一个整数;

R<sub>3</sub> 代表式-(CH<sub>2</sub>)<sub>n'</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团;

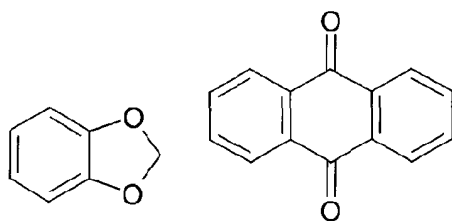
Q' 代表-C(O)-;

X'代表氢原子;

25 Y'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基或苯基;

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、苯基、萘基、苄基、咪唑基, 苯并噻吩基, 或下式的基团:





这些苯基、苯并噻吩基和呋喃基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、 $(C_1-C_6)$ 烷氧基、卤素、硝基、氰基、二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代;

$X''$ 代表 $-O-$ 、 $-C(O)-$ 、 $-C(O)-O-$ 、 $-SO_2-$ 或一个共价键;

5  $Y''$ 代表任选地被一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基, 或苯基;

$p'$ 代表0或1; 且 $n'$ 和 $m'$ 代表0-6中的一个整数。

9. 根据权利要求1、4和5中任一项权利要求所述的通式I化合物, 其特征在于:

10  $R_1$ 代表式 $-(CH_2)_n-[Q']_p-[C(X')(Y')]_m-Z'$ 的基团;

$X'$ 代表氢原子;

$Y'$ 代表氢原子或苯基;

$Z'$ 代表氢原子、 $(C_1-C_6)$ 烷基、任选地被一个或多个相同或不同卤素基团取代的苯基, 或萘基;

15  $p$ 代表0,  $n'$ 代表0或1, 且 $m'$ 代表0-6中的一个整数;

$R_2$ 代表吡咯烷基或式 $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$ 的基团, 其中:

$Q$ 代表 $-C(Z_q)(Z_q')$ ;

$Z_q$ 代表氢原子,  $Z_q'$ 代表氢原子、任选地被苯基取代的苯基、环己基-甲基或苄基;

20  $X$ 和 $Y$ 代表氢原子;

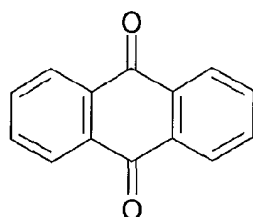
$p$ 代表0或1, 和 $n$ 代表0或1, 且 $m$ 代表0-6中的一个整数;

$R_3$ 代表式 $-(CH_2)_n-[Q']_p-[C(X')(Y')]_m-Z'$ 的基团;

$X'$ 代表氢原子;

$Y'$ 代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基;

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、苯基、萘基或茚基，  
或下式的基团：



该苯基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''Y''、卤素、硝基、氰基的  
相同或不同取代基取代；

5 X''代表-O-、-C(O)-、-C(O)-O-或一个共价键；

Y''代表任选地被一个或多个相同或不同卤素基团取代的烷基，或苯  
基；

p'代表0，n'和m'代表0-6中的一个整数。

10 10. 根据权利要求1、6和7中任一项权利要求所述的通式I化合物，  
其特征在于：

R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n'</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团；

X'代表氢原子；

Y'代表氢原子或苯基；

15 Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、萘基，或任选地被一个或多个选自卤素、  
氨基或苯基的相同或不同取代基取代的苯基；

p'代表0，n'代表0或1，和m'代表0-6中的一个整数；

R<sub>2</sub>代表式-(CH<sub>2</sub>)<sub>n'</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团；

X'和Y'代表氢原子；

20 Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、苯基、萘基、吡啶或苯并噻吩基，

该苯基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q'</sub>-X''-Y''的相同或不同取代基  
取代；

X''代表-O-或一个共价键；

Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基，  
或苯基；

25 p'代表0，n'代表0或1，且m'代表0-6中的一个整数；

$R_3$  代表哌啶环或式 $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$ 的基团, 其中:

Q 代表 $-C(O)-NH-$ ;

X 代表氢原子或 $(C_1-C_6)$ 烷基;

Y 代表氢原子、 $(C_1-C_6)$ 烷基或吡啶-乙基, 或 X 和 Y 与它们连接的氮原子一起构成哌嗪环, 它任选地被 $(C_1-C_6)$ 烷基取代;

p 代表 0 或 1, n 代表 0 或 1, 且 m 代表 0-6 中的一个整数。

11. 根据权利要求 1 所述的通式 I 化合物, 其特征在于  $R_1$  和  $R_3$  基团中的一个代表式 $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  或 $-(CH_2)_n-W$ 的基团, 其中:

W 代表含有至少一个氮原子的杂环烷基;

Q 代表 $-O-$ 、 $-S-$ 、 $-C(O)-NH-$ 、 $-C(Z_q)(Z_q')$ 、芳基或 $(C_3-C_7)$ 环烷基;

$Z_q$  和  $Z_q'$  独立地代表氢原子、任选地被芳基取代的芳基、 $(C_3-C_7)$ 环烷基-烷基、芳烷基、 $-C(O)O-R$  或 $-C(O)-NH-R'$ ;

R 代表 $(C_1-C_6)$ 烷基、芳基或芳烷基, 这些芳基和芳基-烷基任选地被一个或多个选自 $(C_1-C_6)$ 烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代;

R' 代表 $(C_1-C_6)$ 烷基、芳基、芳烷基、杂芳基或杂芳基-烷基, 这些芳基、芳烷基、杂芳基和杂芳基-烷基任选地被一个或多个选自 $(C_1-C_6)$ 烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代;

X 和 Y 独立地代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基或杂芳基-烷基, 或 X 和 Y 与它们连接的氮原子一起构成杂环烷基, 它任选地被 $(C_1-C_6)$ 烷基取代;

p 代表 0 或 1; 且 n 和 m 独立地代表 0-6 中的一个整数。

12. 根据权利要求 11 所述的通式 I 化合物, 其特征在于:

$R_1$  代表式 $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$ 的基团, 其中:

Q 代表芳基或 $(C_3-C_7)$ 环烷基;

X 和 Y 独立地代表氢原子、 $(C_1-C_6)$ 烷基, 或 X 和 Y 与它们连接的氮原子一起构成杂环烷基, 它任选地被 $(C_1-C_6)$ 烷基取代;

p 代表 0 或 1, 且 n 和 m 独立地代表 0-6 中的一个整数。

13. 根据权利要求 11 所述的通式 I 化合物, 其特征在于:

$R_3$  代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  或  $-(CH_2)_n-W$  的基团，其中：

$W$  代表含有至少一个氮原子的杂环烷基；

$Q$  代表  $-C(O)-NH-$ ；

$X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$ 烷基或杂芳基-烷基，或  $X$  和  $Y$  与它们连接的氮原子一起构成杂环烷基，它任选地被  $(C_1-C_6)$ 烷基取代；

$p$  代表 0 或 1， $n$  代表 0 或 1，且  $m$  代表 0-6 中的一个整数。

14. 根据权利要求 11-13 中任一项权利要求所述的通式 I 化合物，其特征在于  $R_2$  代表式  $-(CH_2)_{n'}[Q']_{p'}[C(X')(Y')]_{m'}Z'$  的基团，其中：

$Q'$  代表  $-O-$ ；

$X'$  代表氢原子；

$Y'$  和  $Z'$  独立地代表氢原子、 $(C_1-C_6)$ 烷基、氰基、氨基、 $(C_3-C_7)$ 环烷基、芳基或杂芳基；

这些芳基和杂芳基任选地被一个或多个选自  $-(CH_2)_q-X''-Y''$ 、羟基、卤素、硝基、氨基、 $(C_1-C_6)$ 烷基氨基和二  $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；

$X''$  代表  $-O-$ 、 $-S-$  或一个共价键；

$Y''$  代表任选地被一个或多个相同或不同卤素基团取代的  $(C_1-C_6)$ 烷基，或任选地被一个或多个相同或不同卤素基团取代的芳基；

$p'$  代表 0 或 1； $n'$  代表 0、1 或 2；且  $m'$  代表 0-6 中的一个整数。

15. 根据权利要求 11-14 中任一项权利要求所述的通式 I 化合物，其特征在于  $R_1$  代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  的基团，其中：

$X$  和  $Y$  独立地代表氢原子或  $(C_1-C_6)$ 烷基；

$p$  和  $n$  代表 0，且  $m$  代表 2-6 中的一个整数。

16. 根据权利要求 11-15 中任一项权利要求所述的通式 I 化合物，其特征在于在通式 I 中， $R_2$  代表任选被取代的芳基或杂芳基，特别是萘基、苯基、苯并噻吩基、喹啉基、喹啉基、异喹啉基或吲哚基，这些苯基、萘基和喹啉基任选地被一个或多个相同或不同的  $(C_1-C_6)$ 烷氧基、卤素、硝基、羟基、 $(C_1-C_6)$ 烷基取代，而该  $(C_1-C_6)$ 烷基本身任选地被一个或多个相同或不同卤素基团取代。

17. 根据权利要求 11-16 中任一项权利要求所述的通式 I 化合物, 其特征在于  $R_3$  代表式  $-(CH_2)_n-[Q']_p-[C(X')(Y')]_mZ'$  的基团, 其中:

$X'$  和  $Y'$  代表氢原子;

$Z'$  代表吡啶基或苯并噻吩基; 该吡啶基任选地被一个或多个选自  $-(CH_2)_q-X''-Y''$ 、 $(C_1-C_6)$  烷氧基或卤素的相同或不同取代基取代;

$X''$  代表  $-SO_2-$  或一个共价键;

$Y''$  代表苯基或任选地被一个或多个相同或不同卤素基团取代的烷基;

$q'$  代表 0 或 1;  $p'$  代表 0;  $n'$  代表 0 或 1; 且  $m'$  代表 0 或 1。

18. 根据权利要求 1 所述的通式 I 化合物, 其特征在于  $R_1$  代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  的基团,

$Q$  代表环己基;

$X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$  烷基, 或  $X$  和  $Y$  与它们连接的氮原子一起构成吡啶环;

$n$  代表 0 或 1,  $p$  代表 0 或 1, 且  $m$  代表 1-6 中的一个整数。

19. 根据权利要求 1 或 18 所述的通式 I 化合物, 其特征在于  $R_2$  代表式  $-(CH_2)_n-[Q']_p-[C(X')(Y')]_mZ'$  的基;

$Q'$  代表  $-O-$ ;

$X'$  代表氢原子;

$Y'$  代表氢原子或苯基;

$Z'$  代表氢原子、 $(C_1-C_6)$  烷基、氨基、环己基、苯基、萘基、茚基、噻吩基、呋喃基、苯并噻吩基、噻二唑基、吡啶基、喹啉基、喹喔啉基、异喹啉基、吡嗪基、咕吨基或萘啶基; 这些苯基、萘基、喹啉基和噻二唑基任选地被一个或多个选自  $-(CH_2)_q-X''-Y''$ 、羟基、卤素、硝基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基) 氨基的相同或不同取代基取代;

$X''$  代表  $-O-$ 、 $-S-$  或一个共价键;

$Y''$  代表  $(C_1-C_6)$  任选地被一个或多个相同或不同卤素基团取代的烷基, 或任选地被卤素基团取代的苯基;

$p'$  代表 0 或 1;  $n'$  代表 0、1 或 2; 且  $m'$  代表 0-4 中的一个整数。

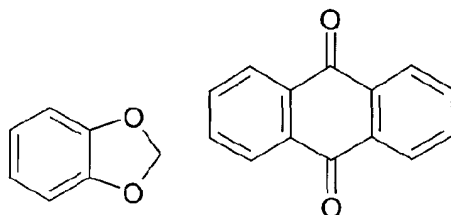
20. 根据权利要求 1、18 或 19 所述的通式 I 化合物, 其特征在于  $R_3$  代表式  $-(CH_2)_n-[Q']_p-[C(X')(Y')]_mZ'$  的基团;

Q'代表-C(O)- ;

X'代表氢原子;

Y'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基或苯基;

- 5 Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、苯基、萘基、苄基、  
 吲哚基、苯并噻吩基, 或下式的基团:



这些苯基、苯并噻吩基和吲哚基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、(C<sub>1</sub>-C<sub>6</sub>)烷氧基、卤素、硝基、氰基、二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键;

- 10 Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基,  
 或苯基;

p'代表0或1; n'代表0、1或2; 且m'代表0-6中的一个整数。

21. 根据权利要求18-20中任一项权利要求所述的通式I化合物, 其特征在于:

- 15 R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团, 其中:

X和Y独立地代表氢原子或(C<sub>1</sub>-C<sub>6</sub>)烷基;

p和n代表0, m代表2-6中的一个整数,

R<sub>2</sub>代表喹啉基、喹啉基或萘基, 这些喹啉基和萘基任选地被一个或多个相同或不同的(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基、卤素取代;

- 20 R<sub>3</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>'[Q']<sub>p</sub>'[C(X')(Y')]<sub>m</sub>'Z'的基团, 其中:

X'和Y'代表氢原子;

Z'代表吲哚基, 它任选地一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、(C<sub>1</sub>-C<sub>6</sub>)烷氧基或卤素的相同或不同取代基取代;

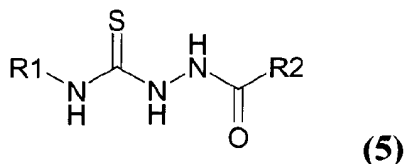
X''代表一个共价键;

- 25 Y''代表任选地被一个或多个相同或不同卤素基团取代的烷基;

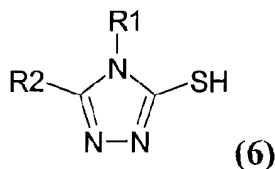
q'代表0或1; p'代表0; n'代表0或1; 且 m'代表0或1。

22. 如权利要求1所限定的通式I化合物的液相制备方法,其特征在于该方法包括:

使式  $R_1-NCS$  的异硫氰酸酯与式  $R_2-C(O)-NH-NH_2$  的酰肼反应, 其中  
5  $R_1$  和  $R_2$  具有权利要求2中指出的意义, 得到下式(5)的化合物:



对式(5)化合物进行碱处理, 得到相应的式(6)化合物:



使式(6)化合物与下述化合物进行反应:

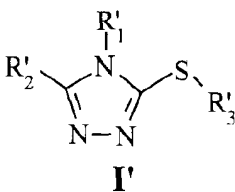
10 A) 式  $\text{Br}-(\text{CH}_2)_n[\text{Q}']_p[\text{C}(\text{X}')(\text{Y}')]_m\text{Z}'$  的化合物, 其中  $n'=1$ ,  $p'=m'=0$ , 且  $Z'$  具有权利要求1中指出的意义, 在该分子上存在的胺官能去保护后得到相应的式(I)化合物, 或

B) 式  $\text{Br}-(\text{CH}_2)_n[\text{Q}']_p[\text{C}(\text{X}')(\text{Y}')]_m\text{Z}'$  的化合物, 其中  $n'=1$ ,  $\text{Q}' = -\text{C}(\text{O})-$ ,  $m'=0$ , 且  $Z'$  具有权利要求1中指出的意义, 在该分子上存在的  
15 胺官能去保护后, 得到相应的式(I)化合物, 或

C) 式  $\text{Br}-(\text{CH}_2)_n[\text{Q}']_p[\text{C}(\text{X}')(\text{Y}')]_m\text{Z}'$  的化合物, 其中  $\text{Q}'$ 、 $\text{X}'$ 、 $\text{Y}'$ 、 $\text{Z}'$ 、 $n'$ 、 $p'$ 和  $m'$ 具有权利要求1中指出的意义, 在该分子上存在的胺官能去保护后, 得到相应的式(I)化合物。

23. 药物组合物, 它含有至少一种如权利要求1-21中任一项权利要求  
20 所限定的化合物作为活性组分, 并且还含有药学上可接受的载体。

24. 药物组合物, 它含有与药学上可接受的载体并用的至少一种下述通式的化合物作为活性组分:



该化合物呈外消旋形式、对映异构体形式或这些形式的组合，其中：

$R_1$ 、 $R_2$  或  $R_3$  基团中的一个代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  或  $-(CH_2)_n-W$  的基团，其中：

$W$  代表含有至少一个氮原子的杂环烷基；

5  $Q$  代表  $-O-$ 、 $-S-$ 、 $-C(O)-NH-$ 、 $-C(Z_q)(Z_q')$ 、芳基或  $(C_3-C_7)$  环烷基；

$Z_q$  和  $Z_q'$  独立地代表氢原子、任选地被芳基取代的芳基、 $(C_3-C_7)$  环烷基-烷基、芳烷基、 $-C(O)O-R$  或  $-C(O)-NH-R'$ ；

$R$  代表  $(C_1-C_6)$  烷基、芳基或芳烷基，这些芳基和芳烷基任选地被一个或多个选自  $(C_1-C_6)$  烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基)氨基的相同或不同取代基取代；

$R'$  代表  $(C_1-C_6)$  烷基、芳基、芳烷基、杂芳基或杂芳基-烷基，这些芳基、芳烷基、杂芳基和杂芳基-烷基任选地被一个或多个选自  $(C_1-C_6)$  烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基)氨基的相同或不同取代基取代；

15  $X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$  烷基、 $(C_1-C_6)$  烷氧基-羰基或杂芳基-烷基，或  $X$  和  $Y$  与它们连接的氮原子一起构成杂环烷基，它任选地被  $(C_1-C_6)$  烷基取代；

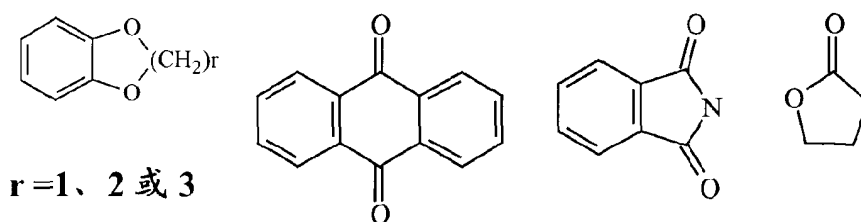
$p$  代表 0 或 1；且  $n$  和  $m$  独立地代表 0-6 中的一个整数；

并且两个其它基团独立地代表式  $-(CH_2)_n'[Q']_p'[C(X')(Y')]_m'Z'$  的基团，其中：

20  $Q'$  代表  $-O-$ 、 $-S-$ 、 $-C(O)-$ 、 $-NH-$ 、 $-CH=CH-$  或  $-C\equiv C-$ ；

$X'$ 、 $Y'$  和  $Z'$  独立地代表氢原子、 $(C_1-C_6)$  烷基、 $(C_1-C_6)$  烷氧基、 $(C_1-C_6)$  烷氧基-羰基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基)氨基、 $(C_3-C_7)$  环烷基、杂环烷基、芳基或杂芳基，或下式的基团：





这些(C<sub>3</sub>-C<sub>7</sub>)环烷基、杂环烷基、芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-S-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键;

- 5 Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基; 或任选地被一个或多个选自(C<sub>1</sub>-C<sub>6</sub>)烷氧基、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代的芳基或杂芳基;

p'代表 0 或 1, n'、m'和 q'独立地代表 0-6 中的一个整数。

### 5-硫烷基-4H-1,2,4-三唑衍生物及其作为药物的应用

5 本申请的目的是新的 5-硫烷基-4H-1,2,4-三唑衍生物与采用平行液相合成方法制备这些衍生物的方法。这些化合物对生长激素受体的某些亚型具有良好的亲合性，在治疗涉及一种或多种生长激素受体的病变或疾病时，它们具有特别重要的意义。本发明还涉及含有所述化合物的药物组合物，以及它们在制备药物中的应用。

10 生长激素(SST)是一种环十四肽，人们首先从下丘脑中作为生长激素抑制物质分离出这种环十四肽(Brazeau P.等人, *Science* 1973, 179, 77-79)。它还在脑中作为神经递质起作用(Reisine T.等人, *Neuroscience*, 1995, 67, 777-790; Reisine T.等人, *Endocrinology* 1995, 16, 427-442)。对生长激素生物功能的不均一性与其肽类似物的结构-活性关系研究导致人们发现了与膜结合的 5 个受体亚型(Yamada 等人, *Proc. Natl. Acad. Sci. U.S.A.*, 89, 251-255, 1992; Raynor, K.等人, *Mol. Pharmacol.*, 44, 385-392, 1993)。分子克隆技术证明，生长激素的生物活性直接地取决于这 5 个受体亚型。

目前人们正积极地研究这些受体的功能作用。第 2 和第 5 亚型的优先活化作用与分泌这些激素的腺瘤中的生长激素 GH (肢端肥大症)、TSH 激素和促乳激素抑制相关；但每个亚型的确切作用还有待确定。

在与生长激素相关的病理病症中，可以列举与过量激素，例如生长激素，胰岛素或高血糖素相关的内分泌疾病(Moreau J.P. 等人, *Life Sciences*, 1987, 40, 419; Harris A.G. 等人, *The European Journal of Medicine*, 1993, 2, 97-105)。因此表明，本发明的化合物可治疗疾病，如肢端肥大症、垂体腺瘤、库欣病、gonadotrophinomas 和泌乳素瘤，糖尿病及其并发症，糖尿病型视网膜病、糖尿病型肾病、甲状腺功能亢进、巨人症。还包括胃肠疾病，与外分泌或内分泌的胃或胰腺分泌过多相关的疾病，还包括与胃肠道各种肽的释放相关的疾病。已表明，本发明的化合物可治疗所述疾病，例如内分泌的胃肠胰腺肿瘤，其中包括类癌综合征、VIPoma、胰岛瘤、成

胰岛细胞瘤、高胰岛素血症、高血糖素瘤、胃泌素瘤和 Zollinger-Ellison 氏综合征, GRFoma 以及急性食管静脉曲张出血、胃食管返流、胃与十二指肠返流、胰腺炎、肠皮肤和胰腺瘘管, 也可以治疗腹泻, 与胃泌素肽释放相关的疾病, 肠移植的继发性病理学, 门静脉高血压以及肝硬化病人的静脉曲张出血、胃肠出血、胃十二指肠溃疡出血、局限性回肠炎、全身性硬皮症、倾倒综合征(dumping syndrome)、小肠综合征、低血压、硬皮病和髓性甲状腺癌。本发明的化合物可以治疗与细胞过度增殖相关的疾病, 例如癌, 更特别地是乳腺癌、前列腺癌、甲状腺癌, 以及胰腺癌和结直肠癌、脑癌、肺癌、纤维组织化, 更特别是肾纤维化、肝纤维化、肺纤维化、皮肤纤维化, 还有中枢神经系统纤维化以及鼻纤维化和由化疗引起的纤维组织形成。其它的治疗领域包括, 例如头痛, 其中包括与垂体瘤相关的头痛, 疼痛, 心理变化, 例如焦虑, 抑郁和精神分裂症, 化疗, 伤口结疤, 延缓发育造成的肾机能不全, 肥胖症和与肥胖症相关的延缓发育, 延缓子宫发育, 骨骼发育不良, 努南氏综合征, 睡眠窒息综合征, 格雷夫斯病, 卵巢多囊疾病, 胰腺假囊肿和腹水, 白血病, 脑脊膜瘤, 癌性恶病质, 幽门螺杆菌抑制, 牛皮癣以及神经变性疾病, 例如痴呆、癫痫症或阿尔茨海默氏病, 还包括骨质疏松症。

本申请人发现下述通式化合物对生长激素受体具有亲合性和选择性。作为生长激素及其肽类似物, 口服的生物利用率往往很低, 选择性也低 (Robinson, C., 《*Drugs of the Future*》, 1994, 19, 992; Reubi, J.C. 等人, *TIPS*, 1995, 16, 110), 所述化合物, 作为生长激素的非肽激动剂或拮抗剂可以用于治疗如前面指出的病变或疾病, 以及涉及一种或多种生长激素受体的病变或疾病。优选地, 所述化合物可以用于治疗肢端肥大症、垂体腺瘤、胃或胰腺分泌过多、胃肠胰腺肿瘤、乳腺癌、前列腺癌、甲状腺、肺癌和纤维组织形成。

本发明的化合物也是硬骨鱼紧张肽 II 的类似物, 因此可用于治疗涉及硬骨鱼紧张肽 II 的病变或疾病。

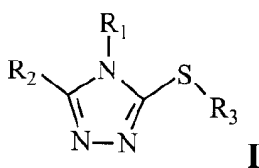
从几种鱼和两栖动物中分离出不同形式的硬骨鱼紧张肽 II(U-II), 20 多年前已测序的环肽。这些肽具有使平滑肌收缩的能力, 以及重要的血管

收缩能力。最近,在不同种的哺乳动物(包括人)中克隆了硬骨鱼紧张肽 II。人的硬骨鱼紧张肽(hU-II)是一种环十一肽,发现它保留了在其它动物蛋白质形态中也存在的环六肽部分(P.Grieco 等人 *Bioorg.Med. Chem.* 2002, 10, 3731-3739)。在体外, U-II 对人静脉和动脉显示出显著的血管收缩作用。

- 5 此外, U-II 及其受体还存在于鼠的脑中, 因此给人这样一种启示, 即该物质在中枢神经系统中可能具有一种神经递质或神经调节物质的作用(J.J. Maguire, A.P. Davenport *Br J. Pharmacol* 2002, 579-588)。

下面描述的通式化合物, 作为硬骨鱼紧张肽 II 的类似物, 可以用于治疗与高血压(门静脉、肺、肾、脑的)、与心脏血管疾病(心脏肥大、心律失常、咽峡炎)、与肺病症(哮喘)以及与动脉粥样硬化和与中风相关的病变。  
10 此外, 由于 U-II 及其受体还存在于哺乳动物的中枢神经系统中, 所以本发明的化合物还可以用于治疗焦虑、应激反应、精神分裂症、抑郁症和神经肌肉功能的变化。

因此, 本发明的主题是下述通式化合物:



- 15 该化合物呈外消旋形式、对映异构体形式或这些形式的组合, 其中:  
R<sub>1</sub>、R<sub>2</sub> 或 R<sub>3</sub> 基团中的一个代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY 或-(CH<sub>2</sub>)<sub>n</sub>-W 的基团,

W 代表含有至少一个氮原子的杂环烷基;

Q 代表-O-、-S-、-C(O)-NH-、-C(Z<sub>q</sub>)(Z<sub>q</sub>')-、芳基或(C<sub>3</sub>-C<sub>7</sub>)环烷基;

- 20 Z<sub>q</sub> 和 Z<sub>q</sub>'独立地代表氢原子、任选地被芳基取代的芳基、(C<sub>3</sub>-C<sub>7</sub>)环烷基-烷基、芳烷基、-C(O)O-R 或-C(O)-NH-R';

R 代表(C<sub>1</sub>-C<sub>6</sub>)烷基、芳基或芳烷基; 这些芳基和芳烷基任选地被一个或多个选自(C<sub>1</sub>-C<sub>6</sub>)烷氧基、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

$R'$ 代表 $(C_1-C_6)$ 烷基、芳基、芳烷基、杂芳基或杂芳基-烷基；这些芳基、芳烷基、杂芳基和杂芳基-烷基任选地被一个或多个选自 $(C_1-C_6)$ 烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；

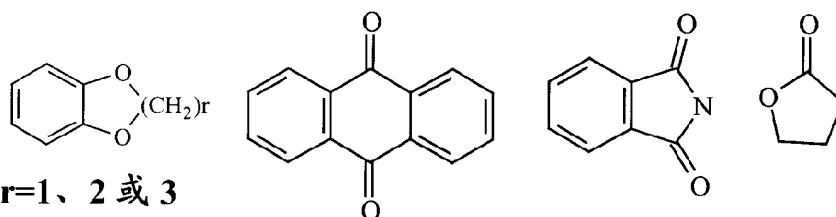
- 5  $X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基或杂芳基-烷基，或  $X$  和  $Y$  与它们连接的氮原子一起形成的杂环烷基，它任选地被 $(C_1-C_6)$ 烷基取代；

$p$  代表 0 或 1； $n$  和  $m$  独立地代表 0-6 中的一个整数；

并且两个其它基团独立地代表 $-(CH_2)_n[Q']_p[C(X')(Y')]_mZ'$ 的基团，

- 10  $Q'$  代表 $-O-$ 、 $-S-$ 、 $-C(O)-$ 、 $-NH-$ 、 $-CH=CH-$ 或 $-C\equiv C-$ ；

$X'$ 、 $Y'$ 和 $Z'$ 独立地代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基、 $(C_1-C_6)$ 烷氧基-羰基、氰基、氨基、 $(C_1-C_6)$ 烷基氨基、二 $((C_1-C_6)$ 烷基)氨基、 $(C_3-C_7)$ 环烷基、杂环烷基、芳基或杂芳基，或下式的基团：



- 15 这些 $(C_3-C_7)$ 环烷基、杂环烷基、芳基和杂芳基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；

$X''$ 代表 $-O-$ 、 $-S-$ 、 $-C(O)-$ 、 $-C(O)-O-$ 、 $-SO_2-$ 或一个共价键；

- 20  $Y''$  代表任选地被一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基；或芳基或杂芳基，它们任选地被一个或多个选自 $(C_1-C_6)$ 烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；

$p'$ 代表 0 或 1，且  $n'$ 、 $m'$ 和  $q'$ 独立地代表 0-6 中的一个整数；

但下述化合物除外，其中：

- 25 i)  $R_1$  代表 $(CH_2)_2-W$ ，而  $W$  代表吗啉基或哌嗪基， $R_2$  代表苯基、 $m$ -氯苯基或 4-吡啶基，和  $R_3$  代表氢原子；

ii)  $R_1$  代表  $(CH_2)_2-W$ ，而  $W$  代表吡咯烷基， $R_2$  代表  $p$ -氯苯基和  $R_3$  代表氢原子；

或这些化合物与药学上可接受的无机或有机酸的加成盐。

在上面指出的定义中，术语卤素代表氟、氯、溴或碘，优选氯、氟或溴基。术语烷基(除非另外特别指出)优选地代表有 1-6 个碳原子的直链或支链烷基，例如甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基和叔丁基、戊基(pentyle)或戊基(amyly)、异戊基、新戊基、己基或异己基。另外，在本申请中  $-(CH_2)_n-$  基团代表  $n$  个碳原子的含烃链，它们可以是直链或支链的；因此，这个  $-(CH_2)_n-$  基团可以代表如前面定义的烷基。

术语  $(C_3-C_7)$  环烷基表示含有 3-7 个碳原子的单环含碳系统，优选环丙基、环丁基、环戊基或环己基环。术语杂环烷基表示含有 2-7 个碳原子和至少一个杂原子的饱和环烷基。这个基团可以含有几个相同或不同的杂原子。优选地，这些杂原子选自氧、硫或氮。作为杂环烷基实例，可以列举含有至少一个氮原子的环，例如吡咯烷、吡咯烷酮、咪唑烷、吡唑烷、异噻唑烷、噻唑烷、异噁唑烷、吡啶、吡嗪或吗啉，或四氢呋喃或四氢噻吩。

烷氧基可以对应于前面指出的烷基，例如像甲氧基、乙氧基、丙氧基或异丙氧基，也还像直链的仲或叔丁氧基、戊氧基。术语烷氧基羰基优选地表示其中烷氧基如前面所定义的这些基，例如像甲氧基羰基、乙氧基羰基。

术语芳基代表由环或稠合环构成的芳族基，例如像苯基、萘基或茚基。术语杂芳基表示由环或稠合环构成的芳族基，其中至少一个环含有一个或多个选自硫、氮或氧的相同或不同杂原子。作为杂芳基实例，可以列举噻吩基、呋喃基、吡咯基、咪唑基、吡唑基、异噻唑基、噻唑基、异噁唑基、噁唑基、三唑基、噻二唑基、吡啶基、吡唑基(pyrazyle)、嘧啶基、喹啉基、异喹啉基、喹喔啉基、萘啶基(naphthyridyl)、咕吨基、苯并噻吩基、苯并呋喃基、吲哚基和苯并噁二唑基。术语芳烷基(芳基烷基)、环烷基-烷基和杂芳基-烷基优选地表示其中芳基、环烷基和杂芳基以及烷基分别地如前面所定义的基团；作为芳基烷基实例，可以列举苄基和苯乙基。

术语烷基氨基和二烷基氨基优选地代表其中烷基如前面所定义的基, 例如像甲氨基、乙氨基、二甲氨基、二乙氨基或(甲基)(乙基)氨基。

优选地, 本发明涉及如前面定义的式 I 化合物, 并且其中:

$R_1$  代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  的基团,

5  $Q$  代表芳基或  $(C_3-C_7)$  环烷基;

$X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$  烷基, 或  $X$  和  $Y$  与它们连接的氮原子一起形成杂环烷基, 该杂环烷基任选地被  $(C_1-C_6)$  烷基取代;

$p$  代表 0 或 1,  $n$  和  $m$  独立地代表 0-6 中的一个整数;

$R_2$  代表式  $-(CH_2)_n'[Q']_{p'}[C(X')(Y')]_{m'}Z'$  的基团,

10  $Q'$  代表  $-O-$ ;

$X'$  代表氢原子,

$Y'$  和  $Z'$  独立地代表氢原子、 $(C_1-C_6)$  烷基、氰基、氨基、 $(C_3-C_7)$  环烷基、芳基或杂芳基;

15 这些芳基和杂芳基任选地被一个或多个选自  $-(CH_2)_q''-X''-Y''$ 、羟基、卤素、硝基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基)氨基的相同或不同取代基取代;

$X''$  代表  $-O-$ 、 $-S-$  或一个共价键;

$Y''$  代表任选地被一个或多个相同或不同卤素基团取代的  $(C_1-C_6)$  烷基, 或任选地被一个或多个相同或不同卤素基团取代的芳基;

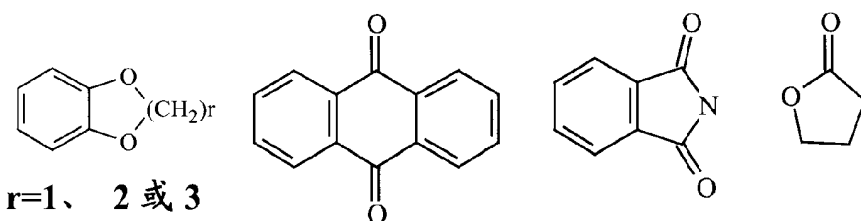
20  $p'$  代表 0 或 1;  $n'$  代表 0、1 或 2;  $m'$  和  $q'$  代表 0-6 中的一个整数;

$R_3$  代表式  $-(CH_2)_n'[Q']_{p'}[C(X')(Y')]_{m'}Z'$  的基团,

$Q'$  代表  $-O-$ 、 $-C(O)-$ 、 $-CH=CH-$  或  $-C\equiv C-$ ;

$X'$  代表氢原子;

25  $Y'$  和  $Z'$  独立地代表氢原子、 $(C_1-C_6)$  烷基、 $(C_1-C_6)$  烷氧基-羰基、 $(C_3-C_7)$  环烷基、芳基或杂芳基, 或下式的基团:



$r=1, 2$  或  $3$

这些芳基和杂芳基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、卤素、硝基、氰基、二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代;

$X''$ 代表 $-O-$ 、 $-C(O)-$ 、 $-C(O)-O-$ 、 $-SO_2-$ 或一个共价键;

$Y''$ 代表任选地被一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基,

5 或芳基;

$p'$ 代表 0 或 1;  $n'$ 、 $m'$ 和  $q'$ 代表 0-6 中的一个整数。

更特别优选,

$Q$  代表的芳基是苯基;  $Q$  代表的 $(C_3-C_7)$ 环烷基是环己基;

$X$  和  $Y$  与它们连接的氮原子一起形成的杂环烷基选自吡咯烷、哌啶、

10 哌嗪和吗啉基;

$Y'$ 和  $Z'$ 独立地代表的 $(C_3-C_7)$ 环烷基是环己基;

$Y'$ 和  $Z'$ 独立地代表的芳基选自苯基、萘基和茛基;

$R_2$ 基团的  $Y'$ 和  $Z'$ 独立地代表的杂芳基选自噻吩基、呋喃基、苯并噻吩基、吡啶基、吲哚基、噻二唑基、喹啉基、异喹啉基、喹喔啉基、咕吨基

15 和萘啶基;

$R_3$ 基团的  $Y'$ 和  $Z'$ 独立地代表的杂芳基选自苯并噻吩基、呋喃基、吲哚基和异噻唑基; 和

$Y''$ 代表的芳基是苯基。

优选地, 本发明还涉及如前面定义的式 I 化合物, 并且其中:

20  $R_1$ 代表式 $-(CH_2)_n'[Q']_p'[C(X')(Y')]_m'Z'$ 的基团,

$X'$ 代表氢原子;

$Y'$ 和  $Z'$ 独立地代表氢原子,  $(C_1-C_6)$ 烷基或芳基,

该芳基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、卤素和氨基的相同或不同取代基取代;

25  $X''$ 代表共价键;



Y''代表芳基;

p'代表 0, n'代表 0 或 1, m'代表 0-6 中的一个整数;

R<sub>2</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NX<sub>1</sub>Y 或-(CH<sub>2</sub>)<sub>n</sub>-W 的基团,

W 代表含有至少一个氮原子的杂环烷基;

5 Q 代表-C(Z<sub>q</sub>)(Z<sub>q</sub>')-;

Z<sub>q</sub> 代表氢原子;

Z<sub>q</sub>'代表氢原子、任选地被芳基取代的芳基、(C<sub>3</sub>-C<sub>7</sub>)环烷基-烷基或芳烷基;

X 和 Y 独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基或(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基;

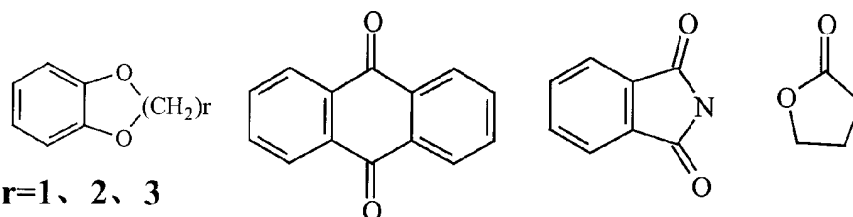
10 p 代表 0 或 1, n 代表 0 或 1, m 代表 0-6 中的一个整数;

R<sub>3</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p</sub>[C(X')(Y')]<sub>m</sub>Z'的基团, 其中:

Q' 代表 -O-、-C(O)-、-CH=CH-或-C≡C-;

X'代表氢原子;

15 Y'和 Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、芳基或杂芳基, 或下式的基团:



r=1、2、3

这些芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、卤素、硝基、氰基、二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键;

20 Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基, 或芳基;

p'代表 0 或 1; n'和 m'代表 0-6 中的一个整数;

更特别优选,

R<sub>1</sub> 基团的 Y'和 Z'独立地代表的芳基选自苯基和萘基;

W 代表的杂环烷基是哌啶或吡咯烷环;

25 Z<sub>q</sub>'代表的芳基是苯基或萘基;

- $Z_q'$ 代表的芳基的芳基取代基是苯基；  
 $Z_q'$ 代表的芳烷基是苄基；  
 $Z_q'$ 代表的 $-(C_3-C_7)$ 环烷基-烷基的 $(C_3-C_7)$ 环烷基是环己基；  
 $Y'$ 和 $Z'$ 独立地代表的 $(C_3-C_7)$ 环烷基是环己基；
- 5  $R_3$ 基团的 $Y'$ 和 $Z'$ 独立地代表的芳基选自苯基、萘基和茚基；  
 $R_3$ 基团的 $Y'$ 和 $Z'$ 独立地代表的杂芳基选自苯并噻吩基、咪唑基、吲哚基和异噁唑基；和  
 $Y''$ 代表的芳基是苯基。
- 优选地，本发明还涉及如前面定义的式I化合物，其中：
- 10  $R_1$ 代表式 $-(CH_2)_n-[Q']_{p'}[C(X')(Y')]_{m'}Z'$ 的基团，  
 $X'$ 代表氢原子；  
 $Y'$ 和 $Z'$ 独立地代表氢原子、 $(C_1-C_6)$ 烷基、或任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、卤素和氨基的相同或不同取代基取代的芳基；  
 $X''$ 代表一个共价键；
- 15  $Y''$ 代表芳基；  
 $p'$ 代表0， $n'$ 代表0或1，且 $m'$ 代表0-6中的一个整数；
- $R_2$ 代表式 $-(CH_2)_n-[Q']_{p'}[C(X')(Y')]_{m'}Z'$ 的基团，  
 $Q'$ 代表-O-；  
 $X'$ 代表氢原子；
- 20  $Y'$ 和 $Z'$ 独立地代表氢原子、 $(C_1-C_6)$ 烷基、氰基、氨基、 $(C_3-C_7)$ 环烷基、芳基或杂芳基；  
 这些芳基和杂芳基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、羟基、卤素、硝基、氨基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；
- 25  $X''$ 代表-O-、-S-或一个共价键；  
 $Y''$ 代表被一个或多个相同或不同卤素基团任选取代的 $(C_1-C_6)$ 烷基，或被一个或多个相同或不同卤素基团任选取代的芳基；  
 $p'$ 代表0或1； $n'$ 代表0、1或2；且 $m'$ 代表0-6中的一个整数；
- $R_3$ 代表式 $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$ 或 $-(CH_2)_n-W$ 的基团，

W 代表含有至少一个氮原子的杂环烷基;

Q 代表-C(O)-NH-;

X 和 Y 独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基或杂芳基-烷基, 或 X 和 Y 与它们连接的氮原子一起形成杂环烷基, 它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代;

5 p 代表 0 或 1, n 代表 0 或 1, 且 m 代表 0-6 中的一个整数;  
更特别优选,

R<sub>1</sub> 基团的 Y' 和 Z' 独立地代表的芳基选自苯基和萘基;

W 代表的杂环烷基是哌啶环;

Y' 和 Z' 独立地代表的(C<sub>3</sub>-C<sub>7</sub>)环烷基是环己基;

10 R<sub>2</sub> 基团的 Y' 和 Z' 独立地代表的芳基选自苯基、萘基和苊基;

X 和 Y 独自代表的杂芳基-烷基的杂芳基是吡啶环;

X 和 Y 与它们连接的氮原子一起构成的杂环烷基选自哌嗪基和吡咯烷基;

15 R<sub>2</sub> 基团的 Y' 和 Z' 独立地代表杂芳基选自噻吩基、呋喃基、苯并噻吩基、吡啶基、吲哚基和噻二唑基; 和

Y'' 代表的芳基是苯基。

本发明更特别的目的是如前面定义的通式 I 化合物, 其中:

R<sub>1</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY 的基团, 其中:

Q 代表环己基;

20 X 和 Y 独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基, 或 X 和 Y 与它们连接的氮原子一起构成哌啶环;

n 代表 0 或 1, p 代表 0 或 1, 且 m 代表 1-6 中的一个整数;

R<sub>2</sub> 代表式-(CH<sub>2</sub>)<sub>n'</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z' 的基团;

Q' 代表-O-;

25 X' 代表氢原子;

Y' 代表氢原子或苯基;

Z' 代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、氨基、环己基、苯基、萘基、苊基、噻吩基、呋喃基、苯并噻吩基、噻二唑基、吲哚基、喹啉基、喹喔啉基、异喹啉基、哌嗪基、咕吨基或萘啶基;

这些苯基、萘基、喹啉基和噻二唑基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、羟基、卤素、硝基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代;

$X''$ 代表-O-、-S-或一个共价键;

- 5  $Y''$ 代表任选地被一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基,或任选地被卤素基团取代的苯基;

$p'$ 代表0或1;  $n'$ 代表0-4中的一个整数;且 $m'$ 和 $q'$ 代表0-4中的一个整数;

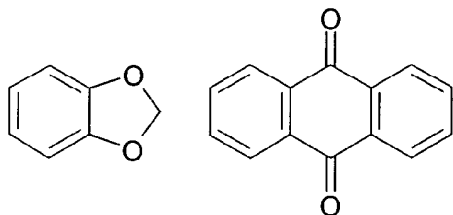
$R_3$ 代表式 $-(CH_2)_{n'}[Q']_{p'}[C(X')(Y')]_{m'}Z'$ 的基团;

- 10  $Q'$ 代表-C(O)-;

$X'$ 代表氢原子;

$Y'$ 代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基或苯基;

$Z'$ 代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基、苯基、萘基、茚基、吲哚基、苯并噻吩基或下式的基团:



- 15 这些苯基、苯并噻吩基和吲哚基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、 $(C_1-C_6)$ 烷氧基、卤素、硝基、氰基、二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代;

$X''$ 代表-O-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键;

- 20  $Y''$ 代表任选地被取代一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基,或苯基;

$p'$ 代表0或1;  $n'$ 、 $m'$ 、 $q'$ 和 $m'$ 代表0-6中的一个整数。

更特别地,本发明的目的是如前面定义的通式I化合物,其中:

$R_1$ 代表式 $-(CH_2)_{n'}[Q']_{p'}[C(X')(Y')]_{m'}Z'$ 的基团;

$X'$ 代表氢原子;

- 25  $Y'$ 代表氢原子或苯基;

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、任选地被一个或多个相同或不同卤素取代基取代的苯基，或萘基；

p'代表0，n'代表0或1，且m'代表0-6中的一个整数；

R<sub>2</sub>代表吡咯烷基(pyrrolydiny)或式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团；

5 Q代表-C(Z<sub>q</sub>)(Z<sub>q</sub>')-；

Z<sub>q</sub>代表氢原子，Z<sub>q</sub>'代表氢原子、任选地被苯基取代的苯基、环己基-甲基或苄基；

X和Y代表氢原子；

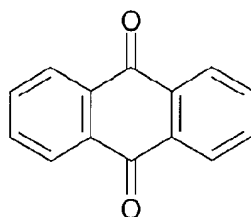
p代表0或1，n代表0或1，且m代表0-6中的一个整数；

10 R<sub>3</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m</sub>Z'的基团；

X'代表氢原子；

Y'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基；

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、苯基、萘基或苄基，或下式基：



15 该苯基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>X''Y''、卤素、硝基、氰基的相同或不同取代基取代；

X''代表-O-、-C(O)-、-C(O)-O-或一个共价键；

Y''代表任选地被一个或多个相同或不同卤素基团取代的烷基，或苯基；

20 p'代表0，且n'和m'代表0-6中的一个整数。

更特别地，本发明的目的是如前面定义的通式I化合物，其中：

R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m</sub>Z'的基团；

X'代表氢原子；

Y'代表氢原子或苯基；

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、萘基，或任选地被一个或多个选自卤素、氨基或苯基的相同或不同取代基取代的苯基；

p'代表0，n'代表0或1，且m'代表0-6中的一个整数；

R<sub>2</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p'</sub>[C(X')(Y')]<sub>m'</sub>Z'的基团；

5 X'和Y'代表氢原子；

Z'代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、苯基、萘基、吡啶或苯并噻吩基，该苯基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>X''Y''的相同或不同取代基取代；

X''代表-O-或一个共价键；

10 Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基，或苯基；

p'代表0，n'代表0或1，且m'代表0-6中的一个整数；

R<sub>3</sub>代表哌啶环或式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团，

Q代表-C(O)-NH-；

15 X代表氢原子或(C<sub>1</sub>-C<sub>6</sub>)烷基；

Y代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、或(吡啶)-乙基，或

X和Y与它们连接的氮原子一起构成哌嗪环，它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代；

p代表0或1，n代表0或1，和m代表0-6中的一个整数。

20 优选地，本发明的一个目的是如前面定义的通式I的产品，其特征在于R<sub>1</sub>或R<sub>3</sub>基团中的一个代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY或-(CH<sub>2</sub>)<sub>n</sub>-W的基团，其中：

W代表含有至少一个氮原子的杂环烷基；

Q代表-O-、-S-、-C(O)-NH-、-C(Z<sub>q</sub>)(Z<sub>q</sub>')-、芳基或(C<sub>3</sub>-C<sub>7</sub>)环烷基；

25 Z<sub>q</sub>和Z<sub>q</sub>'独立地代表氢原子、任选地被芳基取代的芳基、(C<sub>3</sub>-C<sub>7</sub>)环烷基-烷基、芳烷基、-C(O)O-R或-C(O)-NH-R'；

R代表(C<sub>1</sub>-C<sub>6</sub>)烷基、芳基或芳烷基，这些芳基和芳烷基任选被一个或多个选自(C<sub>1</sub>-C<sub>6</sub>)烷氧基、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代；

R'代表(C<sub>1</sub>-C<sub>6</sub>)烷基、芳基、芳烷基、杂芳基或杂芳基-烷基, 这些芳基、芳烷基、杂芳基和杂芳基-烷基任选地被一个或多个选自(C<sub>1</sub>-C<sub>6</sub>)烷氧基、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

- 5 X和Y独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基或杂芳基-烷基, 或X和Y与它们连接的氮原子一起构成杂环烷基, 它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代;

p代表0或1; n和m独立地代表0-6中的一个整数;  
更优选地,

- 10 R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团, 其中:

Q代表芳基或(C<sub>3</sub>-C<sub>7</sub>)环烷基;

X和Y独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基, 或X和Y与它们连接的氮原子一起构成杂环烷基, 它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代;

p代表0或1, n和m独立地代表0-6中的一个整数; 或

- 15 R<sub>3</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY或-(CH<sub>2</sub>)<sub>n</sub>-W的基团, 其中:

W代表含有至少一个氮原子的杂环烷基;

Q代表-C(O)-NH-;

X和Y独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基或杂芳基-烷基, 或X和Y与它们连接的氮原子一起构成杂环烷基, 它任选地被(C<sub>1</sub>-C<sub>6</sub>)烷基取代;

- 20 p代表0或1, n代表0或1, 和m代表0-6中的一个整数。

优选地, 本发明的目的是如前面定义的通式I的产品, 其特征在于R<sub>2</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q']<sub>p</sub>-[C(X')(Y')]<sub>m</sub>-Z'的基团, 其中:

Q'代表-O-;

X'代表氢原子,

- 25 Y'和Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、氰基、氨基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、芳基或杂芳基;

该芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代;

X''代表-O-、-S-或一个共价键;

Y''代表任选地被一个或多个相同或不同卤素基团取代的(C<sub>1</sub>-C<sub>6</sub>)烷基,或任选地被一个或多个相同或不同卤素基团取代的芳基;

p'代表0或1; n'代表0、1或2; 且m'代表0-6中的一个整数。

5 非常优选地, R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>-[Q]<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团, 其中:

X和Y独立地代表氢原子或(C<sub>1</sub>-C<sub>6</sub>)烷基;

p和n代表0, 且m代表2-6中的一个整数。

非常优选地, R<sub>2</sub>代表任选地取代的芳基或杂芳基, 更特别地是萘基、萘基、苯并噻吩基、喹啉基、喹啉基、异喹啉基或吲哚基; 该萘基、萘基和喹啉基任选地被一个或多个相同或不同的(C<sub>1</sub>-C<sub>6</sub>)烷氧基、卤素、硝基、羟基、(C<sub>1</sub>-C<sub>6</sub>)烷基取代、该(C<sub>1</sub>-C<sub>6</sub>)烷基本身任选地被一个或多个相同或不同卤素基团取代。

非常优选地, R<sub>3</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p</sub>[C(X')(Y')]<sub>m</sub>Z'的基团, 其中:

X'和Y'代表氢原子;

15 Z'代表吲哚基或苯并噻吩基, 该吲哚基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、(C<sub>1</sub>-C<sub>6</sub>)烷氧基或卤素的相同或不同取代基取代、X''代表-SO<sub>2</sub>-或一个共价键;

Y''代表萘基或任选地被一个或多个相同或不同卤素基团取代的烷基;

q'代表0或1; p'代表0; n'代表0或1; 且m'代表0或1。

20 更特别地, 本发明的一个目的还是如前面定义的通式I化合物, 其中:

R<sub>1</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q]<sub>p</sub>[(CH<sub>2</sub>)<sub>m</sub>-NXY的基团;

Q代表环己基;

X和Y独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基, 或X和Y与它们连接的氮原子一起构成吡啶环;

25 n代表0或1, p代表0或1, 且m代表1-6中的一个整数;

R<sub>2</sub>代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p</sub>[C(X')(Y')]<sub>m</sub>Z'的基团;

Q'代表-O-;

X'代表氢原子;

Y'代表氢原子或萘基;



$Z'$ 代表氢原子、 $(C_1-C_6)$ 烷基、氨基、环己基、苯基、萘基、茚基、噻吩基、呋喃基、苯并噻吩基、噻二唑基、吡啶基、喹啉基、喹喔啉基、异喹啉基、吡嗪基、咕吨基或萘啶基；这些苯基、萘基、喹啉基和噻二唑基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、羟基、卤素、硝基、 $(C_1-C_6)$ 烷基氨基和二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；

$X''$ 代表-O-、-S-或一个共价键；

$Y''$ 代表任选地被一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基，或任选地被卤素基团取代的苯基；

$p'$ 代表0或1； $n'$ 代表0、1或2；且 $m'$ 代表0-4中的一个整数；

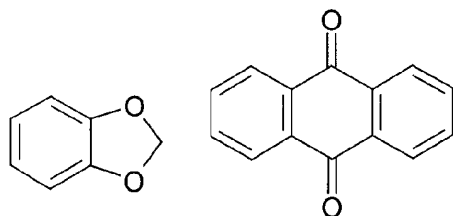
10  $R_3$ 代表式 $-(CH_2)_n[Q']_{p'}[C(X')(Y')]_{m'}Z'$ 的基团；

$Q'$ 代表-C(O)-；

$X'$ 代表氢原子；

$Y'$ 代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基或苯基；

15  $Z'$ 代表氢原子、 $(C_1-C_6)$ 烷基、 $(C_1-C_6)$ 烷氧基-羰基、苯基、萘基、茚基、吡啶基、苯并噻吩基，或下式的基团：



这些苯基、苯并噻吩基和吡啶基任选地被一个或多个选自 $-(CH_2)_q-X''-Y''$ 、 $(C_1-C_6)$ 烷氧基、卤素、硝基、氰基、二 $((C_1-C_6)$ 烷基)氨基的相同或不同取代基取代；

$X''$ 代表-O-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键；

20  $Y''$ 代表任选地被一个或多个相同或不同卤素基团取代的 $(C_1-C_6)$ 烷基，或苯基；

$p'$ 代表0或1； $n'$ 代表0、1或2；且 $m'$ 代表0-6中的一个整数。

非常优选地，

$R_1$ 代表式 $-(CH_2)_n-[Q]_{p'}-(CH_2)_m-NXY$ 的基团，其中：

X 和 Y 独立地代表氢原子或(C<sub>1</sub>-C<sub>6</sub>)烷基;

p 和 n 代表 0, m 代表 2-6 中的一个整数。

R<sub>2</sub> 代表喹喔啉基、喹啉基或萘基, 这些喹啉基和萘基任选地被一个或多个相同或不同的(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基、卤素基团取代;

5 R<sub>3</sub> 代表式-(CH<sub>2</sub>)<sub>n</sub>[Q']<sub>p</sub>[C(X')(Y')]<sub>m</sub>Z'的基团, 其中:

X'和 Y' 代表氢原子;

Z'代表任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、(C<sub>1</sub>-C<sub>6</sub>)烷氧基或卤素的相同或不同取代基取代的吡啶基;

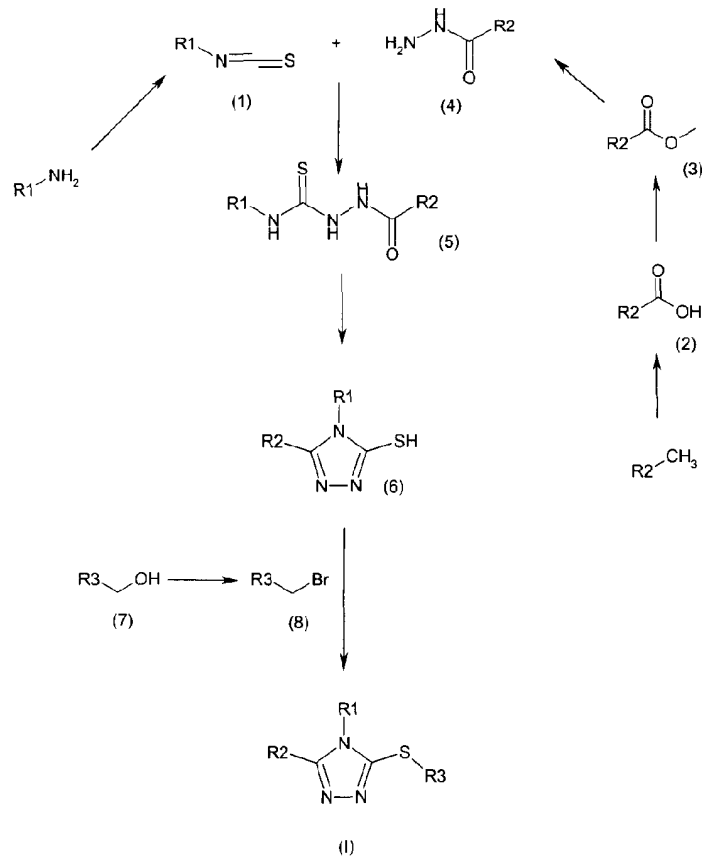
X''代表一个共价键;

10 Y''代表任选地被一个或多个相同或不同卤素基团取代的烷基;

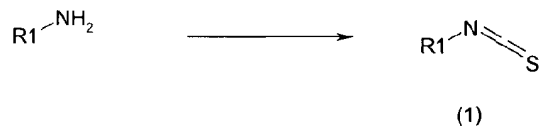
q'代表 0 或 1; p'代表 0; n'代表 0 或 1; 且 m'代表 0 或 1。

在本申请中, 符号->\*相应于基的连接点。没有指出在基上连接位置时, 这意味着这样一种连接是这种基在可达到的其中一个位置进行这种连接。

可以按照下述的一般流程图以液相方式制备本发明的化合物:



### 1. 异硫氰酸酯(1)的制备:



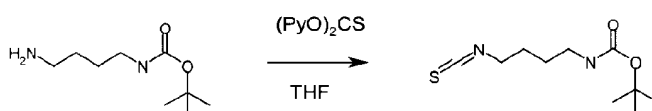
5

可以采用两种方法, 使用相应的伯胺制备通式(1)的异硫氰酸酯:

#### 1.1 方法 A:

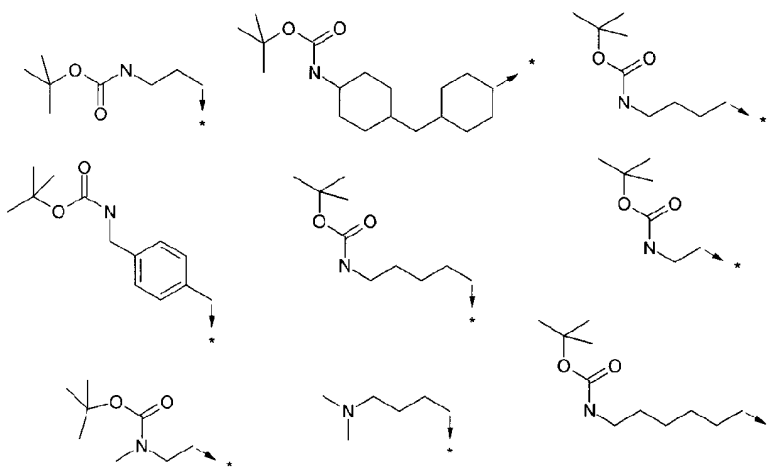
10 在无水的质子惰性溶剂(例如二氯甲烷、四氢呋喃或二甲基甲酰胺)中, 通过 O,O-二(2-吡啶基)硫代碳酸酯(1 当量)的作用, 可将伯胺转化成异硫氰酸酯(Kim, S.; Lee, J.I. *Tetrahedron Lett.*, 1985, 26 (13), 1661-1664)。在室温下将该反应混合物搅拌 1-4 小时, 然后蒸去溶剂, 该残留物无须纯化便可用于后续的步骤。

制备 1: 4-异硫氰酸根合丁基氨基甲酸叔丁酯(C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S, M=230.33)



4-氨基丁基氨基甲酸叔丁酯(3.2 ml; 17 mmol)加到 O,O-二(2-吡啶基)硫代碳酸酯(3.9 g; 17 mmol)溶于四氢呋喃的溶液中。在室温下将该溶液搅拌 2 小时。蒸去溶剂, 得到的固体可立刻用于后续步骤。

- 5 按照这种操作方式合成通式  $R_1NCS$  的异硫氰酸酯, 其中具有下述  $R_1$  基团, 其伯胺和仲胺用叔丁氧基羰基基团保护:



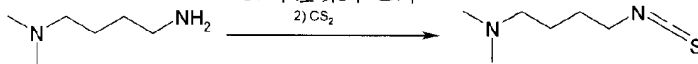
## 1.2 方法 B:

- 在质子惰性溶剂, 例如二氯甲烷或四氢呋喃中预溶胀的 N-环己基碳化二亚胺、N-甲基聚苯乙烯树脂(Novabiochem; 容量高于 1.5 mmol/g, 1.1 当量)存在下, 通过二硫代甲烷(10 当量)的作用, 可将伯胺转化成异硫氰酸酯。该反应混合物在室温下搅拌 1-4 小时, 然后蒸发滤液, 并且无须其它纯化便可用于后续步骤。

### 制备 2: N,N-二甲基-4-异硫氰酸根合丁胺( $C_7H_{14}N_2S$ , $M=158.27$ )

1) N-环己基碳化二亚胺

N-甲基聚苯乙烯

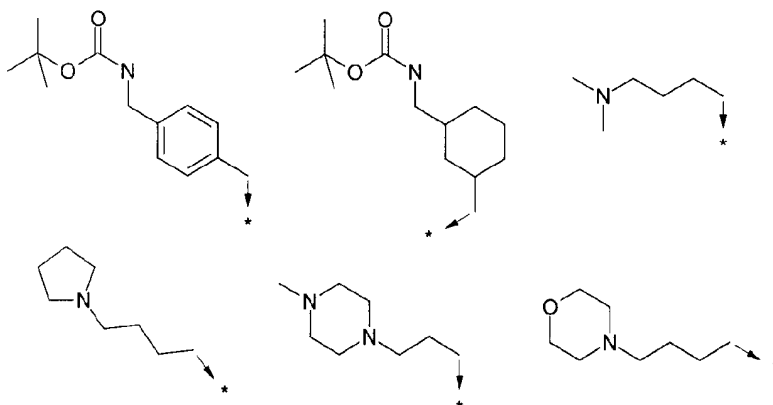


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二硫代甲烷(1 ml; 16.6mmol)加到在二氯甲烷(15ml)中的 N-环己基碳化二亚胺、N-甲基聚苯乙烯树脂(1 g; 1.69 mmol/g; Novabiochem)里。该悬浮液搅拌 30 分钟, 然后添加 N,N-二甲基-1,4-丁烷二胺(0.19 ml; 1.5

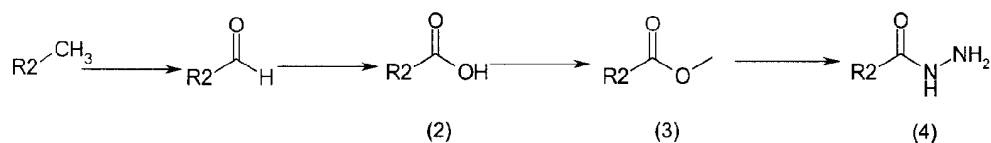
mmol)。该反应混合物搅拌 3 小时，然后过滤。蒸发滤液，并立刻用于下一个步骤。

根据这种方法合成通式  $R_1NCS$  的异硫氰酸酯，其中具有下述  $R_1$  基团，其伯胺用叔丁氧基羰基基团保护：



5

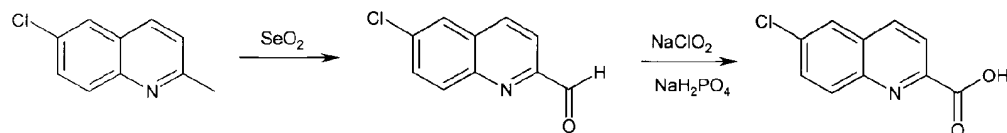
## 2. 酰肼(4)的制备:



### 2.1 羧酸(2)的制备:

10 当它们不能获自商业时，可使用相应的甲基化衍生物，通过例如用二氧化硒氧化成醛，接着用例如次氯酸钠再氧化成羧酸，这样制备通式(2)的羧酸，其中  $R_2$  是芳基或杂芳基类的基团(Bu, X.; Deady, L. W.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* 2001, 44, 2004-2014)。

### 制备 3: 6-氯喹啉-2-甲酸( $C_{10}H_6ClNO_2$ , $M=207.62$ )



15

在  $80^\circ\text{C}$ ，6-氯-2-甲基喹啉(500 mg; 2.8 mmol)加到二氧化硒(1.87 g; 16.9 mmol; 6 当量)在二氧杂环己烷(25 ml)中的悬浮液里。该反应混合物在

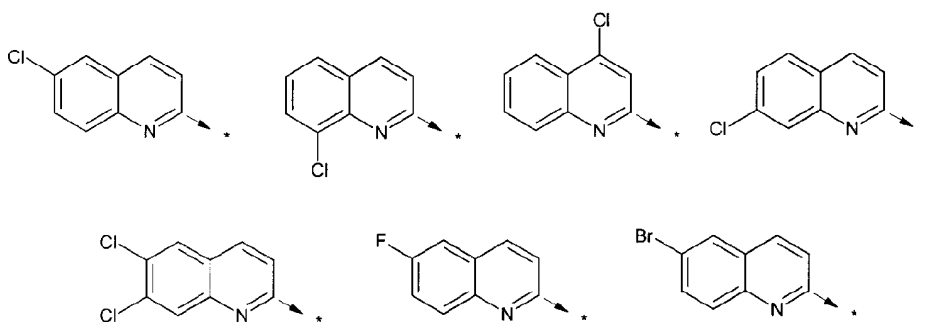
回流下搅拌 3 小时，然后趁热过滤不溶物。减压蒸去二氧杂环己烷，得到的醛不经纯化便可用于下面的步骤。

NMR  $^1\text{H}$  (DMSO- $d_6$ , 400MHz):  $\delta$  10.09 (s, 1H, CHO); 8.57-8.54 (m, 1H, 芳族 H); 8.27-8.21 (m, 2H, 芳族 H); 8.02-8.00 (m, 1H, 芳族 H); 7.91-7.88 (m, 1H, 芳族 H).

在 5 分钟时间内，将次氯酸钠(2.4 g)和磷酸二氢钠(2.4 g)在水(24ml)中的溶液添加到 6-氯喹啉-2-甲醛(536 mg; 2.8 mmol)在叔丁醇(56 ml)和 2-甲基丁-2-烯(14 ml)中的溶液里。得到的混合物在室温下搅拌 4 小时。在减压下蒸去这些有机溶剂，再往残留物添加水(30 ml)。得到的沉淀过滤后用水洗涤，然后在  $\text{P}_2\text{O}_5$  存在下真空干燥。得到 6-氯喹啉-2-甲酸，白色粉末状(505 mg; 产率= 87%)。MS/LC:  $m/z = 208.01(\text{M} + \text{H})$   $t_r = 8.55$  min(条件 1)。

NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  8.41-8.39(m, 1H, 芳族 H); 8.20-8.11 (m, 3H, 芳族 H); 7.82-7.79(m, 1H, 芳族 H)。

根据这种方法合成出通式  $\text{R}_2\text{COOH}$  的羧酸，其中具有如下  $\text{R}_2$  基团：



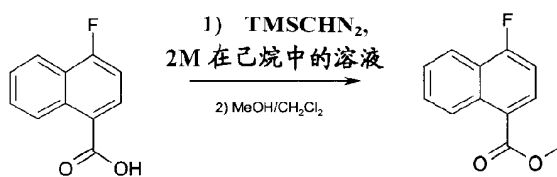
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## 2.2 甲酯(3)的制备:

首先，在甲醇中，在有或没有质子惰性溶剂，例如乙醚或二氯甲烷的存在下，例如通过过量的重氮甲烷或重氮甲烷替代物，例如三甲基甲硅烷基重氮甲烷的作用，可将一种甲酸转化成甲酯(Caturla, F.; Najera, C.; Varea, M. *Tetrahedron Lett*, 1999, 40 (32), 5957-5960)。添加羧酸，例如像乙酸中和过量的重氮甲烷。提取与洗涤后分离出这些甲酯，并且无须纯化便可用于下面的步骤中。

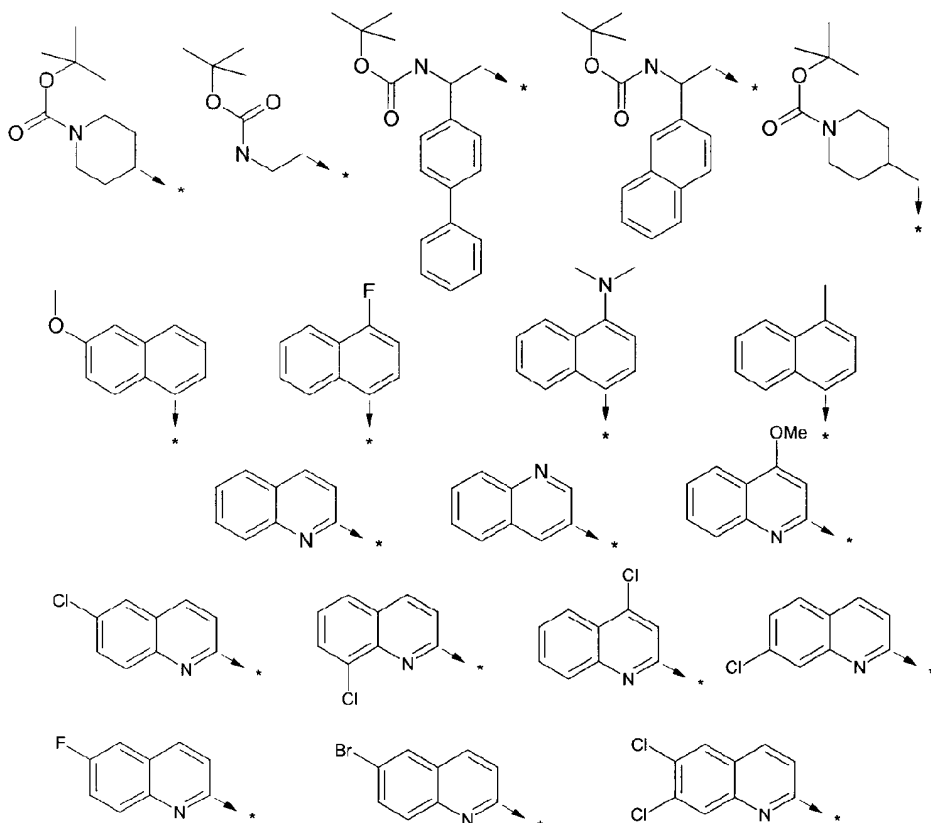
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制备 4: 4-氟-1-萘甲酸甲酯( $\text{C}_{12}\text{H}_9\text{FO}_2$ ,  $\text{M}=204.20$ )



5 (三甲基甲硅烷基)重氮甲烷的己烷(6 ml, 2 mol/l)溶液添加到 4-氟-1-萘甲酸(1g; 5.3 mmol)溶于二氯甲烷(10 ml)和甲醇(15 ml)混合物的溶液中, 直到该溶液保持浅黄色, 也不再脱气。添加几滴乙酸中和过量的(三甲基甲硅烷基)重氮甲烷直到溶液无色。该反应混合物蒸发后溶于乙酸乙酯(20 ml)中, 再用蒸馏水(10 ml), 然后用饱和氯化钠溶液(10 ml)洗涤。该有机相用硫酸钠干燥, 然后蒸发与真空干燥, 得到白色粉末(0.78 g; 产率=73%)。MS/LC:  $m/z = 205.23(M + H)$ tr = 11.21min (条件 1)。

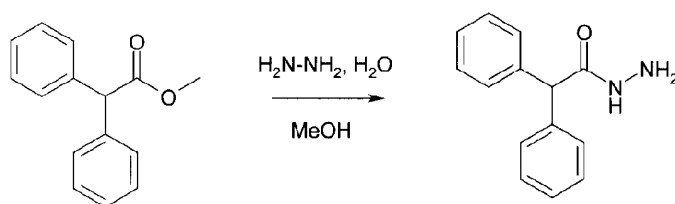
10 合成式  $R_2COOMe$  的甲酯, 其中具有伯胺和仲胺用叔丁氧基羰基基团保护的下述  $R_2$  基团:



### 2.3 酰肼(4)的制备:

在极性质子溶剂，例如乙醇或甲醇中，肼水合物(3-10 当量)与通式(3)的酯作用可以得到通式(4)的酰肼(Leung, H. K.; Phillips, B.A.; Cromwell, N. H., *J. Heterocycl. Chem.* 1976, 13, 247-252)。该反应在室温下或在 50°C 下进行 18-96 小时。蒸发后，反应介质用溶剂，例如乙酸乙酯处理，再用水洗涤。在蒸去有机溶剂与固化后得到这些酰肼。

**制备 5: 2,2-二苯基乙酰肼( $C_{14}H_{14}N_2O$ ,  $M=226.28$ )**

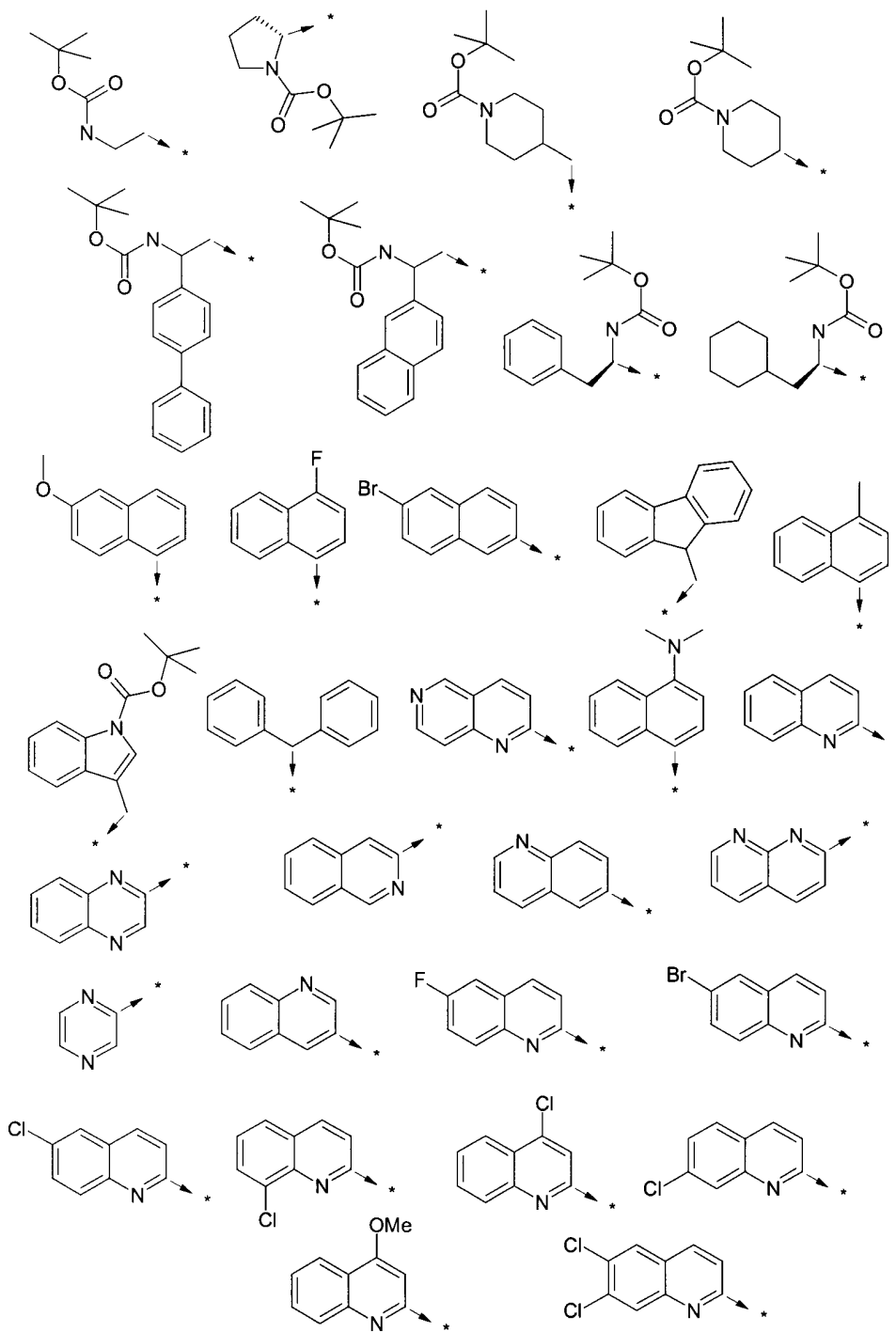


肼水合物(7 ml; 50mmol)加到二苯基乙酸甲酯(1.19g; 5mmol)溶于甲醇(15ml)中的溶液里。该反应混合物在室温下搅拌 60 小时，然后蒸去溶剂。该残留物溶于乙酸乙酯(20ml)中，接着用蒸馏水洗涤(15ml)，然后用饱和氯化钠水溶液洗涤(15ml)。有机相用硫酸镁干燥，接着蒸发与真空干燥，得到白色粉末(0.94 g; 产率=83 %)。

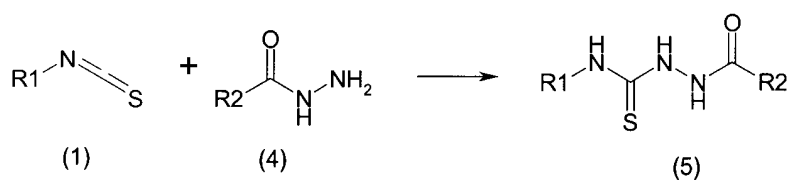
NMR  $^1H$ (DMSO- $d_6$ , 400MHz):  $\delta$  9.44(宽 s, 1H, NH); 7.33-7.20(m, 10H, 芳族的); 4.82(s, 1H, CH); 4.30(宽 s, 2H,  $NH_2$ )。MS/LC:  $m/z=227.30(M + H)$   $tr=10.19$  min(条件 1)。

制备式  $R_2CONHNH_2$  的酰肼，其中具有下述  $R_2$  基团，其伯胺和仲胺被叔丁氧基羰基基团保护：



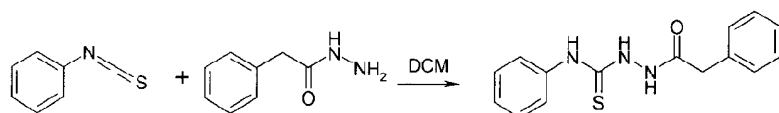


### 3. 脒硫代甲酰胺(5)的制备:



通式(1)的异硫氰酸酯(1.1 当量)加到通式(4)酰肼在例如二氯甲烷或二甲基甲酰胺的质子惰性溶剂中的溶液里, 该反应介质在室温下搅拌 18-24 小时。在过滤或蒸发反应介质后得到这些肼硫代甲酰胺(5), 它们无须纯化便可用于下面的步骤。

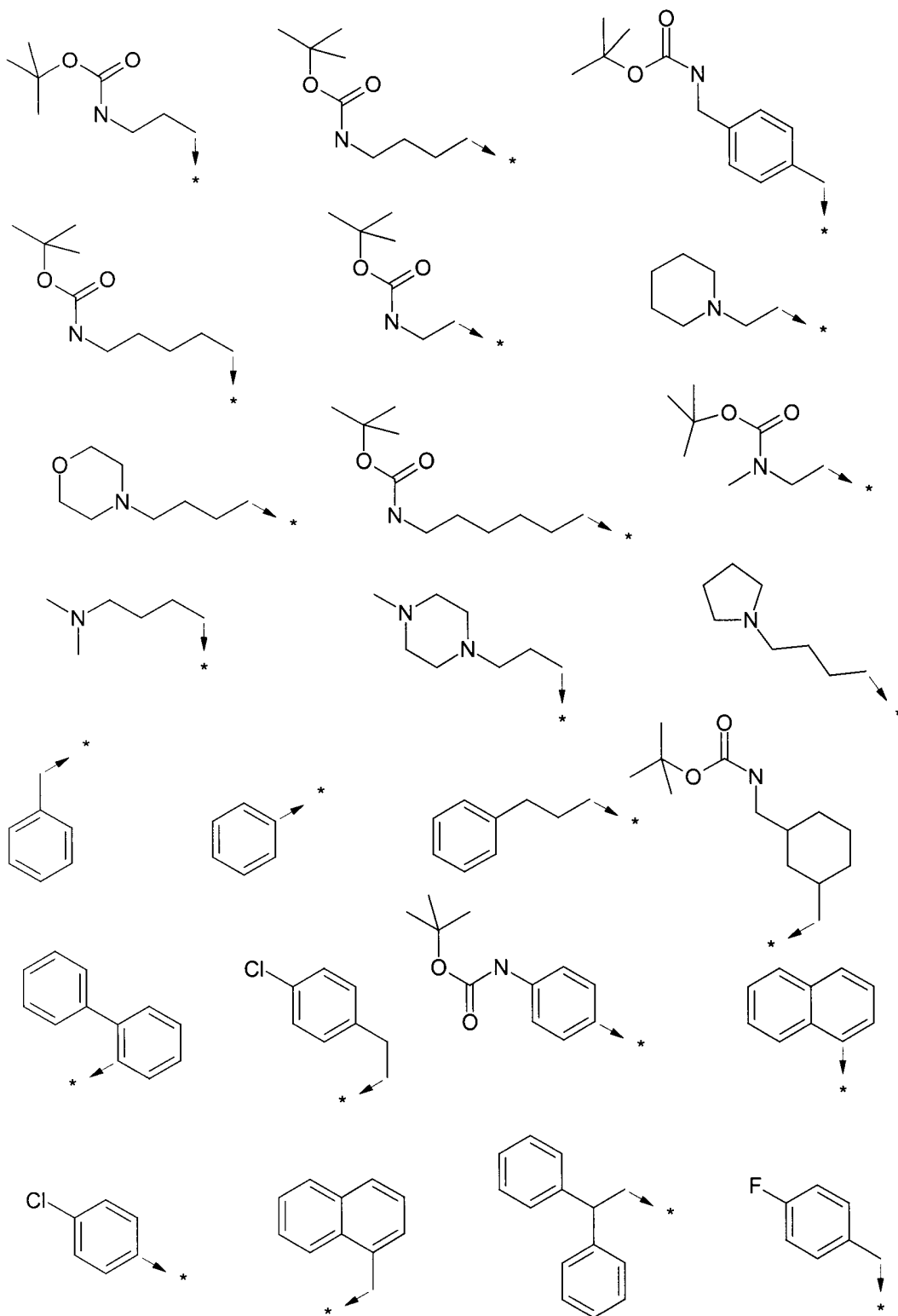
**制备 6:** N-苯基-2-(苯基乙酰基)肼硫代甲酰胺(C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>OS, M=285.37)



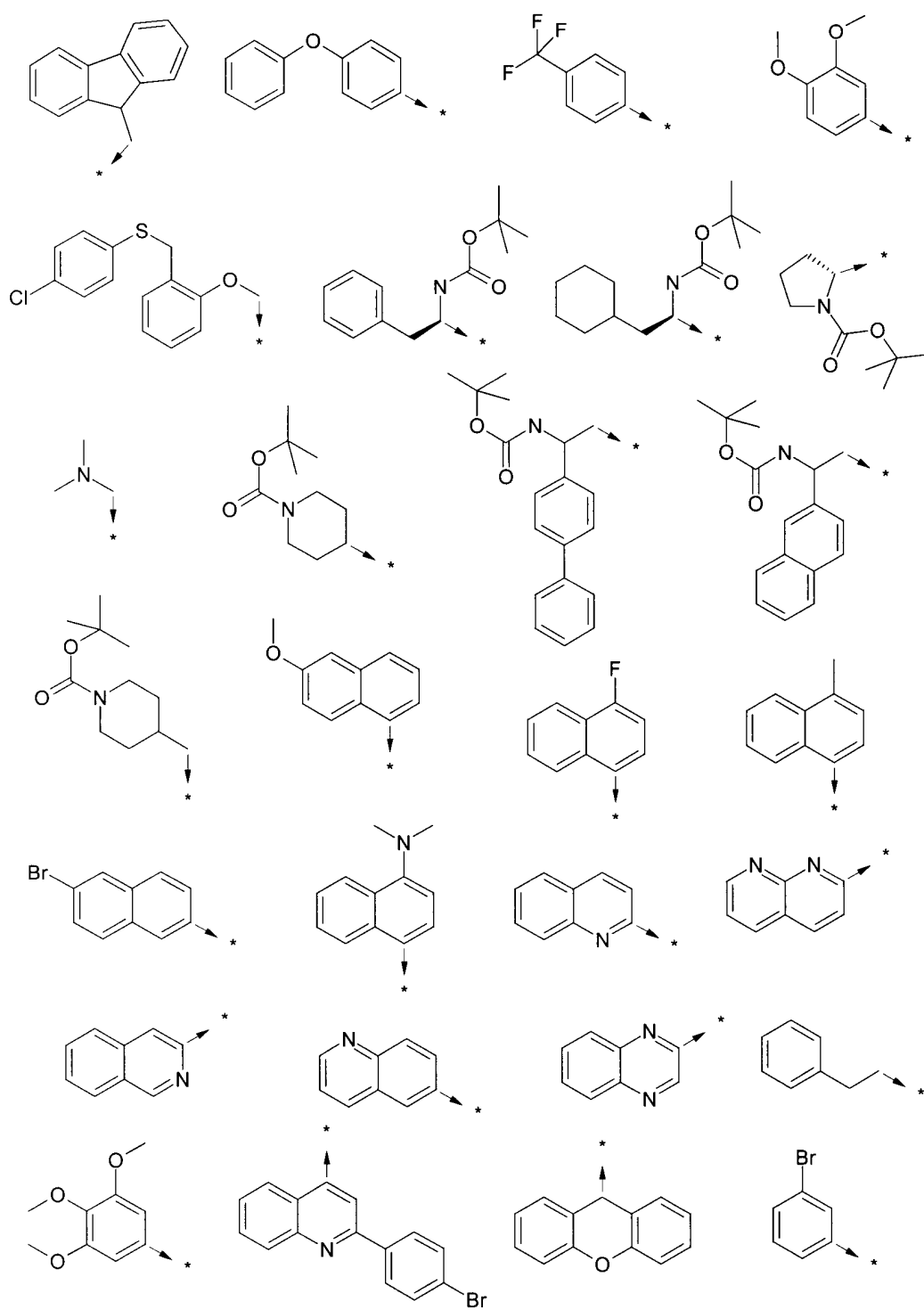
苯基异硫氰酸酯(1.3ml; 11mmol)加到 2-苯基乙酰肼(1.5 g; 10 mmol)溶于二氯甲烷(20ml)中的溶液里。该溶液在室温下进行搅拌直到产物沉淀。生成的白色固体过滤后用乙醚(10ml)洗涤, 再在真空下干燥(2.1 g; 产率=74%)。

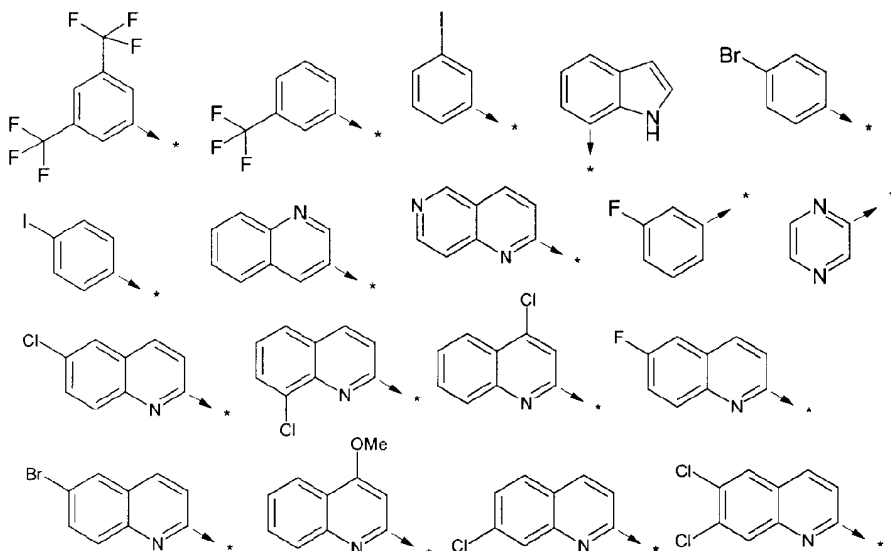
NMR <sup>1</sup>H(DMSO-d<sub>6</sub>, 400MHz): δ 10.15(宽 s, 1H, NH); 9.59(宽 s, 2H, NH<sub>2</sub>); 7.44-7.42(m, 2H, 芳族的); 7.35-7.28(m, 5H, 芳族的); 7.25-7.22(m, 2H, 芳族的); 7.18-7.14(m, 1H, 芳族的); 3.52(s, 2H, CH<sub>2</sub>)。MS/LC: m/z=286.26(M + H) tr=8.13 min(条件 1)。

合成用于制备本发明化合物的通式(5)肼硫代甲酰胺, 其中具有下述的 R<sub>1</sub> 和 R<sub>2</sub> 基团, 其伯胺和仲胺用叔丁氧基羰基基团保护:

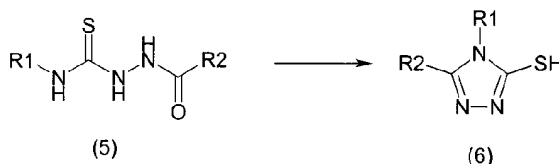
**R<sub>1</sub>:**





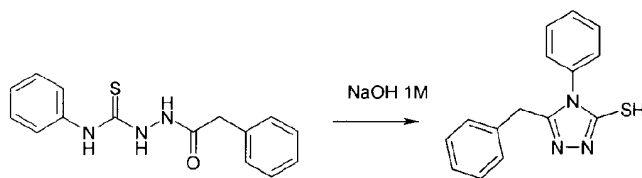


#### 4. 三唑(6)的制备:



5 通式(5)的酰肼硫代脲溶于二氧杂环己烷或甲苯类溶剂后, 在质子惰性溶剂, 例如乙醇或甲醇中, 在氢氧化钠(1M - 4M)或氢氧化钾(1M - 4M)溶液存在下进行成环步骤。该反应在 85°C 进行 4-18 小时, 再在蒸去溶剂后, 例如使用离子交换树脂, 例如 Amberlite IRN 77 树脂(H<sup>+</sup>阳离子)(Prolabo)将得到的硫醇盐转化成硫醇(6)。过滤树脂后, 浓缩滤液。可以用硅胶柱进行纯化。

10 **制备 7:** 5-苄基-4-苯基-4H-1,2,4-三唑-3-硫醇(C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>S, M=267.35)



标准氢氧化钠水溶液(20ml)加到 N-苄基-2-(苄基乙酰基)肼硫代甲酰胺(3.7 g; 13 mmol)溶于二氧杂环己烷(30ml)和甲醇(10ml)混合物中的溶液里。搅拌该溶液并在 85°C 下加热 4 小时。蒸去溶剂, 残留物溶于甲醇(25ml)中。

预先用甲醇漂洗的离子交换树脂(Amberlite IRN 77, 50 g, Prolabo)加到该溶液中,接着搅拌 15 分钟,然后过滤。蒸发滤液,再进行真空干燥(3.4 g; 产率=98%)。

NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  13.78(宽 s, 1H, SH); 7.48–7.46(m, 3H, 芳族的); 7.23–7.17(m, 5H, 芳族的); 6.92-6.90(m, 2H, 芳族的); 3.85(s, 2H,  $\text{CH}_2$ )。MS/LC:  $m/z=268.23(\text{M} + \text{H})\text{tr}=5.72 \text{ min}$ (条件 2)。

制备通式(6)的三唑,其中具有与制备上述胍硫代甲酰胺(5)时所描述的那样  $\text{R}_1$  和  $\text{R}_2$  基团。

### 5. 溴化中间产物(8)的制备:

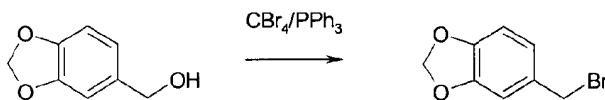
#### 5.1 苄基溴(8a)的制备:

##### 5.1.1 一般示例:



根据文献中描述的步骤,使用相应的醇(7a),例如使用含水氢溴酸回流处理(Kinoshita, T.; Okunaka, T.; Ohwada, H.; Furukawa, S. *J. Heterocycl. Chem.* 1991, 28(8), 1901-1909),或使用无机酰基卤,例如  $\text{PBr}_3$  或  $\text{SOBr}_2$  处理(Nagle, A. S.; Salvatore, R. N.; Chong, B.-D.; Jung, K. W., *Tetrahedron Lett*, 2000, 41(17), 3011-3014),或在质子惰性溶剂,例如四氢呋喃或二氯甲烷中使用 N-溴琥珀酰亚胺或  $\text{CBr}_4$  和三苯基膦的混合物处理(Amici, R.; Pevarello, P.; Colombo, M.; Varasi, M. *Synthesis* 1996, (10), 1177-1179, Campbell, J.A.; Rapoport, H. *J. Org. Chem.*, 1996, 61(18), 6313-6325),可以得到通式(8a)的苄基溴。

**制备 8:** 5-(溴甲基)-1,3-苯并间二氧杂环戊烯( $\text{C}_8\text{H}_7\text{BrO}_2$ ,  $\text{M}=215.05$ )

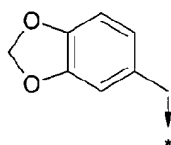


四溴化碳(3.8 g; 11.5 mmol)加到溶于二氯甲烷(30ml)的 5-(甲醇)-1,3-苯并间二氧杂环戊烯(1.5 g; 10 mmol)的溶液中;该混合物冷却到 0℃。分份添加三苯基膦(3.0 g; 11.5 mmol),该溶液在室温下搅拌 2 小时。蒸去溶

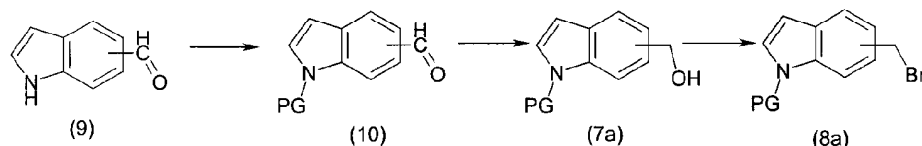
剂, 得到的固体采用硅胶柱色谱法纯化(洗脱剂: 庚烷/乙酸乙酯: 3 / 1)。这些馏分进行蒸发, 得到的固体进行真空干燥(2.1 g; 产率=97%)。

NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  7.02–6.98(m, 1H, 芳族的); 6.96–6.93(m, 1H, 芳族的); 6.88–6.86(m, 1H, 芳族的); 6.02(s, 2H,  $\text{CH}_2$ ); 4.66(s, 2H,  $\text{CH}_2$ )。

合成式  $\text{R}_3\text{Br}$  的苜基溴, 其中具有下述  $\text{R}_3$  基团:



### 5.1.2 甲基吲哚溴(8a)的具体示例:

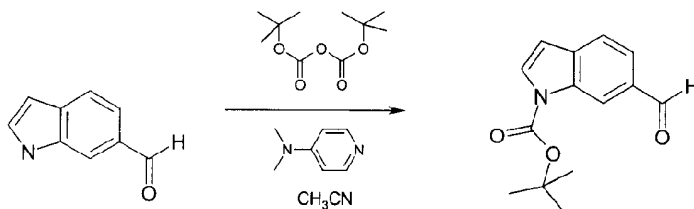


在通式(8a)的溴化中间产物是甲基吲哚类产物的情况下, 使用相应的吲哚甲醛, 分3步进行, 首先保护吲哚, 然后还原醛官能, 最后接着溴化如此得到的醇官能, 这样可以得到它们。

#### 5.1.2.1 保护吲哚:

采用本技术领域技术人员已知的方法(P. J. Kocienski, *Protecting Groups*, 192 (Georg Thiem Verlag Stuttgart, 1994)), 例如在室温下, 在乙腈或二甲基甲酰胺中, 在例如二甲氨基吡啶催化剂存在下使用二碳酸二叔丁酯, 可以往吲哚加入合适的保护基团, 例如像氨基甲酸酯类基团(例如叔丁氧基羰基基团)。

**制备 9:** 6-甲酰基-1H-吲哚-1-甲酸叔丁酯( $\text{C}_{14}\text{H}_{15}\text{NO}_3$ ,  $M=245.28$ )



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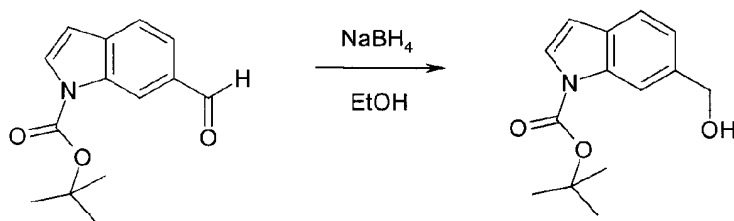
二碳酸二叔丁酯(0.827g; 3.8 mmol)和 4-*N*-二甲氨基吡啶(0.19 mmol; 21mg)加到 1*H*-吡啶-6-甲醛(0.5 g; 3.44 mmol)溶于乙腈(15ml)的溶液中。该混合物在室温下搅拌 16 小时。蒸去乙腈; 其残留物溶于乙酸乙酯(30ml)中, 再用蒸馏水(20ml)洗涤两次, 然后用饱和氯化钠水溶液洗涤(20ml)。有机相用硫酸镁干燥, 接着蒸发与真空干燥。得到期望的产物, 呈白色固体状(0.514 g; 产率=61 %)。

NMR <sup>1</sup>H(DMSO-d<sub>6</sub>, 400MHz): δ 10.06(s, 1H, CHO); 8.60(s, 1H, 芳族的); 7.92-7.91(d, J=3.7Hz, 1H, 芳族的), 7.81-7.75(m, 2H, 芳族的); 6.84-6.83(d, J=3.7Hz, 1H, 芳族的); 1.65(s, 9H, t-Bu)。MS/LC: m/z=268.23(M + H) tr=5.72 min(条件 1)。

#### 5.1.2.2 制备醇(7a):

采用本技术领域技术人员已知的方法, 例如像通过系统的作用: 在室温下, 在水/DMF 混合物中 NiCl<sub>2</sub>·6H<sub>2</sub>O-Zn(Baruah, R. N. *Tetrahedron Lett* 1992, 33(37), 5417-5418), 或在室温下, 在乙醇中使用 NaBH<sub>4</sub>(Cho, Y. J.; Lee, S. H.; Bae, J. W.; Pyun, H. J.; Yoon, C. M. *Tetrahedron Lett* 2000, 41(20), 3915-3917), 或在质子惰性溶剂, 例如像甲醇中使用 Bu<sub>3</sub>SnH (Kamiura, K.; Wada, M. *Tetrahedron Lett* 1999, 40(51), 9059-9062), 还原通式(10)的醇可以得到通式(7a)的醇。

**制备 10:** 6-(羟甲基)-1*H*-吡啶-1-甲酸叔丁酯(C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>; M=247.30)



6-甲酰基-1*H*-吡啶-1-甲酸叔丁酯(0.514 g; 2.1mmol)溶于乙醇(5ml)中, 然后缓慢添加硼氢化钠(0.159 g; 4.2mmol), 该溶液在室温下搅拌 2 小时。蒸去溶剂, 残留物溶于乙醚(20ml), 再用氢氧化钠溶液洗涤(1N; 10ml), 然后用饱和氯化钠溶液(10ml)洗涤。有机相用硫酸镁干燥, 接着蒸发与真空干燥。得到醇, 呈白色固体状(0.48 g, 产率=93 %)。

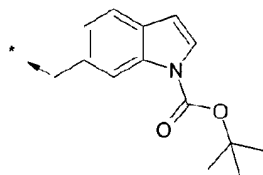
NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  8.09(s, 1H, 芳族的); 7.61-7.60(d,  $J=3.6$  Hz, 1H, 芳族的); 7.54-7.52(d,  $J=8$  Hz, 1H, 芳族的); 7.18-7.16(d,  $J=8$  Hz, 1H, 芳族的); 6.66-6.65(d,  $J=3.6$  Hz, 1H, 芳族的); 5.22-5.19(t,  $J=5.7$  Hz, 1H, OH); 4.60-4.59(d,  $J=5.7$  Hz, 2H,  $\text{CH}_2$ ); 1.62(s, 9H, t-Bu).

5 MS/LC:  $m/z$ =成碎片的;  $tr=10.28\text{min}$ (条件 1)。

### 5.1.2.3 制备甲基咪唑溴(8a):

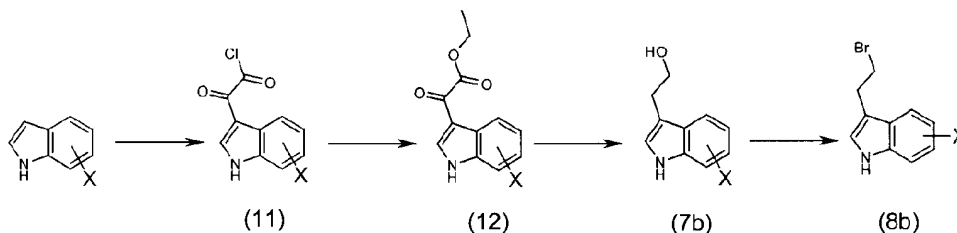
根据前面制备苄基溴时所描述的通用溴化方法,使用通式(7a)的醇可以得到通式(8a)的甲基咪唑溴。

合成式  $\text{R}_3\text{Br}$  的甲基咪唑溴,其中具有下述  $\text{R}_3$  基团:



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## 5.2 制备乙基咪唑溴(8b):



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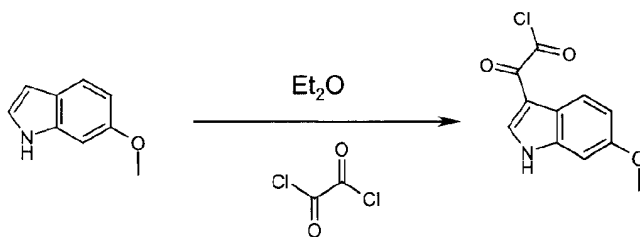
当通式(8)的溴化中间产物是乙基咪唑类的中间产物的情况时,使用相应的咪唑,分四步可以得到它们,即首先转化成 $\alpha$ -酮基酰基氯(11),接着转化成 $\alpha$ -酮基酯(12),然后还原成醇(7b),以便最后制备溴化中间产物(8b)。

### 5.2.1 得到 $\alpha$ -酮基酰基氯(11):

在室温下,在非极性的质子惰性溶剂,例如像乙醚中,通过草酰氯的作用可以得到 $\alpha$ -酮基酰基氯(11) (Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron*, 1952, 2, 1)。

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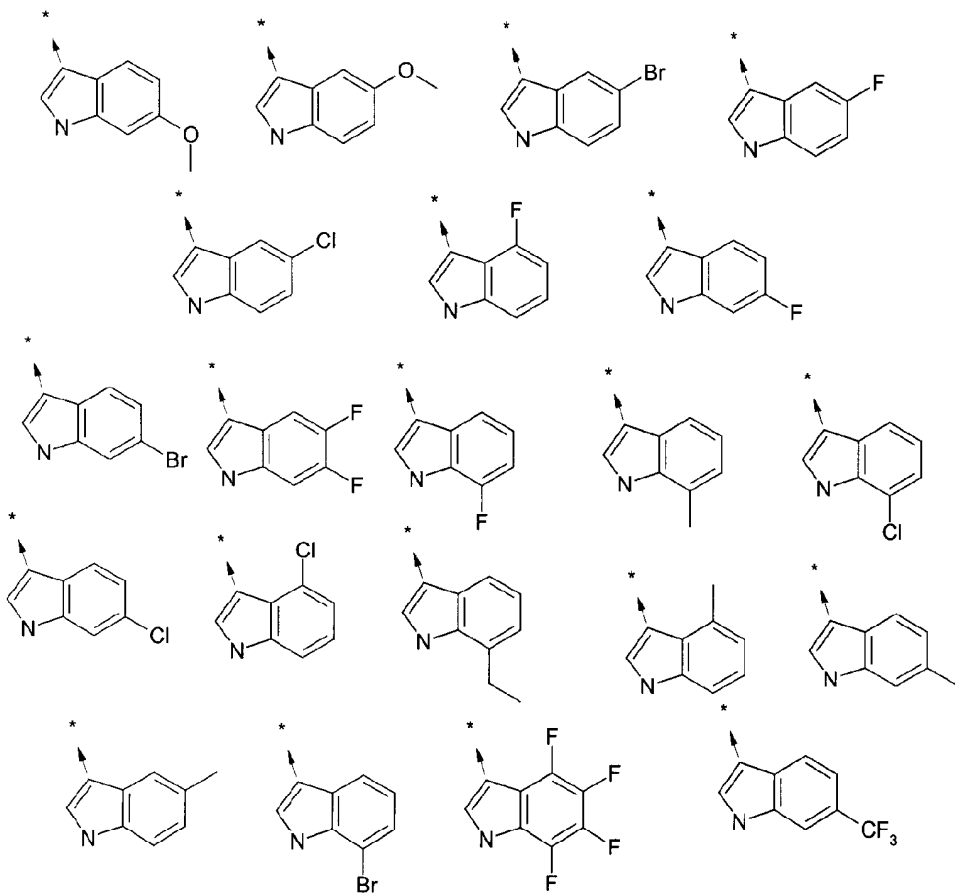
制备 11: (6-甲氧基-1H-咪唑-3-基)(氧代)乙酰基氯( $\text{C}_{11}\text{H}_8\text{ClNO}_3$ ,  $M=237.64$ )。



5-甲氧基吲哚(1g; 6.8 mmol)溶于乙醚(25ml)中的溶液冷却到 0℃。在氩气下滴加草酰氯(8.8 mmol; 0.77ml), 该混合物在室温与氩气下搅拌 3 小时。在过滤与用乙醚洗涤后得到呈黄色粉末状的期望产物(1.44 g, 产率=89%)。

NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  12.19(s, 1H, NH); 8.27(s, 1H, 芳族的); 8.01-7.99(d, J=8.7 Hz, 1H, 芳族的); 7.02(s, 1H, 芳族的); 6.90-6.87(d, J=8.7 Hz, 1H, 芳族的); 3.79(s, 1H, OCH $_3$ ).

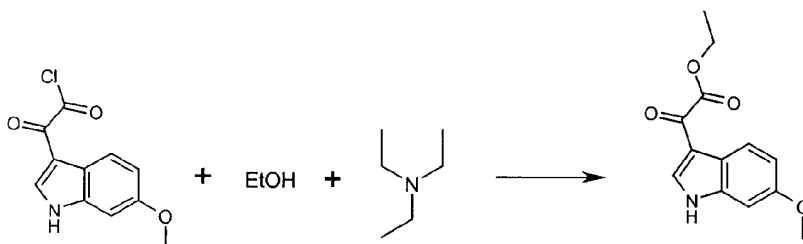
制备式  $\text{R}_3\text{C}(\text{O})\text{C}(\text{O})\text{Cl}$  的  $\alpha$ -酮基酰基氯, 其中具有下述吲哚  $\text{R}_3$  基团:



### 5.2.2 $\alpha$ -酮基酰基氯(11)酯化成 $\alpha$ -酮基酯(12):

采用本技术领域技术人员已知的经典酯化方法,例如像在有机碱,如三乙胺或二异丙基乙胺存在下,用醇(例如甲醇或乙醇)处理相应的 $\alpha$ -酮基酰氯,可以得到吲哚 $\alpha$ -酮基酯(12)。

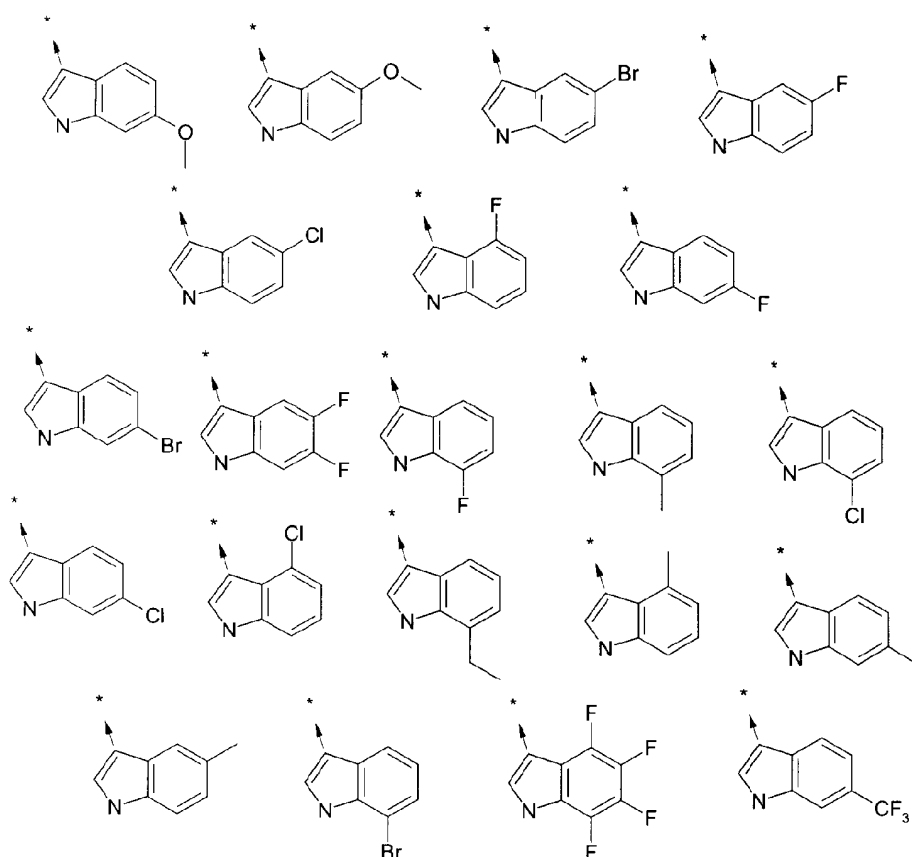
- 5 制备 12: (6-甲氧基-1*H*-吲哚-3-基)(氧代)乙酸乙酯(C<sub>13</sub>H<sub>13</sub>NO<sub>4</sub>, M=247.25)



- 10 (6-甲氧基-1*H*-吲哚-3-基)(氧代)乙酰基氯(1.44 g; 6.06mmol)溶于乙醇(15ml)中的溶液冷却到 0°C, 然后滴加三乙胺(1.04ml; 7.5mmol)。该混合物加热回流 2 小时。沉淀经过滤后,用乙醇(5ml)和乙醚(5ml)洗涤,然后进行真空干燥。得到了期望产物,呈黄色粉末状(1.36g; 产率=91%)。

- 15 NMR <sup>1</sup>H(DMSO-d<sub>6</sub>, 400MHz):  $\delta$  12.16(s, 1H, NH); 8.28(s, 1H, 芳族的); 8.00-7.98(d, J=8.6 Hz, 1H, 芳族的); 7.02(s, 1H, 芳族的); 6.91-6.88(d, J=8.6 Hz, 1H, 芳族的); 4.37-4.31(q, J=7 Hz, 2H, OCH<sub>2</sub>); 3.79(s, 3H, OCH<sub>3</sub>); 1.34-1.31(t, J=7Hz, 3H, CH<sub>3</sub>)。

制备式 R<sub>3</sub>-C(O)C(O)OEt 的 $\alpha$ -酮基酯,其中具有下述吲哚 R<sub>3</sub>基团:

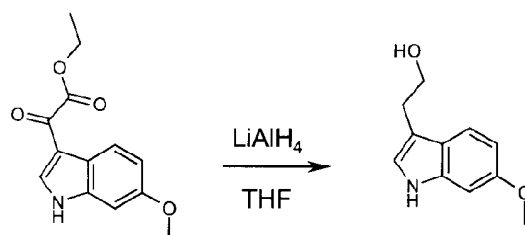


### 5.2.3 $\alpha$ -酮基酯(12)还原成乙基吲哚醇(7b):

在质子惰性溶剂, 例如四氢呋喃中, 通过例如使用氢化铝锂回流处理, 可将通式(12)的 $\alpha$ -酮基酯还原成通式(7b)的乙基醇(Feldman, P. L.;

5 Rapoport, H. *Synthesis* 1986(9), 735-737).

制备 13: 2-(6-甲氧基-1*H*-吲哚-3-基)乙醇( $C_{11}H_{13}NO_2$ ,  $M=191.23$ ).



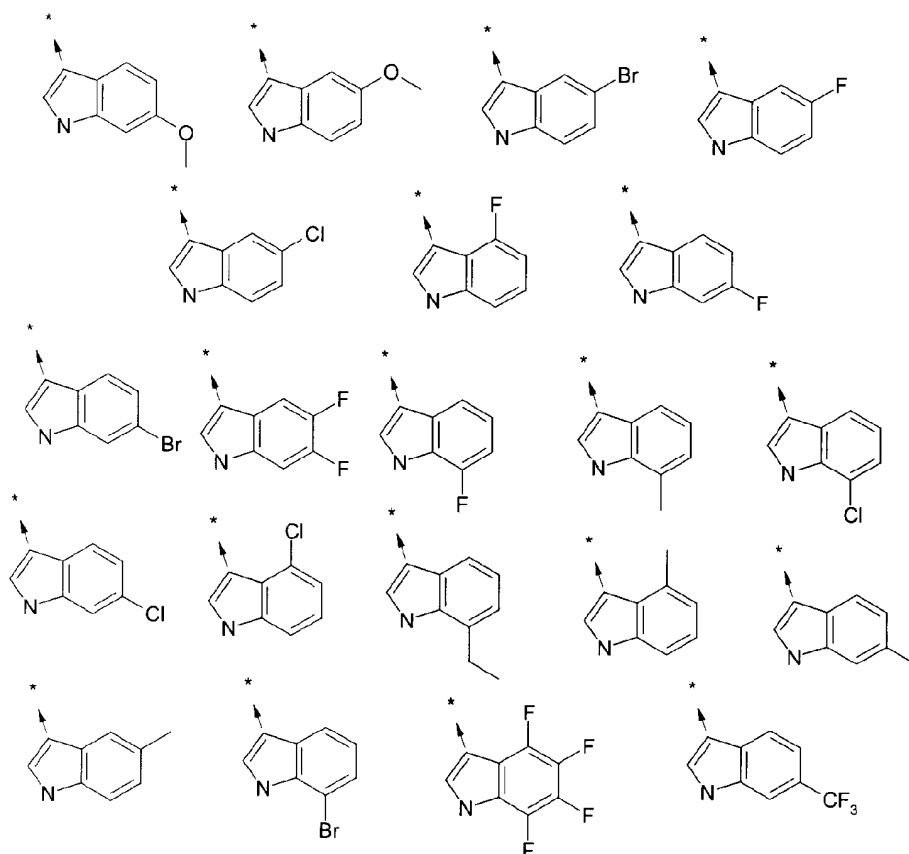
(6-甲氧基-1*H*-吲哚-3-基)(氧代)乙酸乙酯(1.36g; 5.5mmol)溶于四氢呋喃(15ml)中的溶液冷却到 0°C。这时缓慢添加氢化铝锂在四氢呋喃(1M; 16.5ml; 16.5 mmol)中的溶液。该反应混合物升温回流, 搅拌 2 小时。添加乙酸乙酯(1ml)和蒸馏水(1ml)中和过量的氢化铝锂。该反应物趁热过滤

10

后，固体用甲醇(10ml)洗涤。蒸发的滤液再溶于乙酸乙酯(25ml)中，用盐酸水溶液(0.1M; 15ml)洗涤，然后用饱和氯化钠溶液(15ml)洗涤。有机相用硫酸钠干燥，接着蒸发，然后真空干燥。得到期望的产物，呈淡黄色油状(0.815 g, 产率=78%)。

- 5 NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  10.54(s, 1H, NH); 7.36-7.34(d,  $J=8.6$  Hz, 1H, 芳族的); 6.96(s, 1H, 芳族的); 6.82(s, 1H, 芳族的); 6.63-6.60(d,  $J=8.6$  Hz, 1H, 芳族的); 4.57-5.54(t,  $J=5.4$  Hz, 1H, OH); 3.74(s, 3H,  $\text{OCH}_3$ ); 3.64-3.59(m,  $J=7.4$  Hz 和  $J'=5.4$ Hz, 2H,  $\text{CH}_2$ ); 2.80-2.76(t,  $J=7.4$ Hz, 2H,  $\text{CH}_2$ ). MS/LC:  $m/z=192.17$ (M + H)  $t_r=8.27$  min(条件 2)。
- 10

制备式  $\text{R}_3(\text{CH}_2)_2\text{OH}$  的乙基吲哚醇，其中具有下述吲哚  $\text{R}_3$  基团：

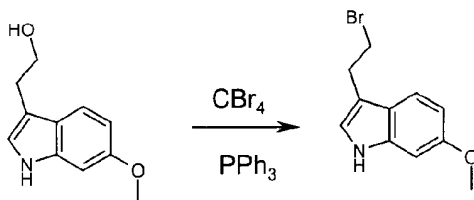


#### 5.2.4 制备乙基吲哚醇(8b):

根据前面在制备苄基溴时所描述的一般方法，通过溴化相应的醇(7b)

可以制备通式(8b)的乙基吲哚溴。

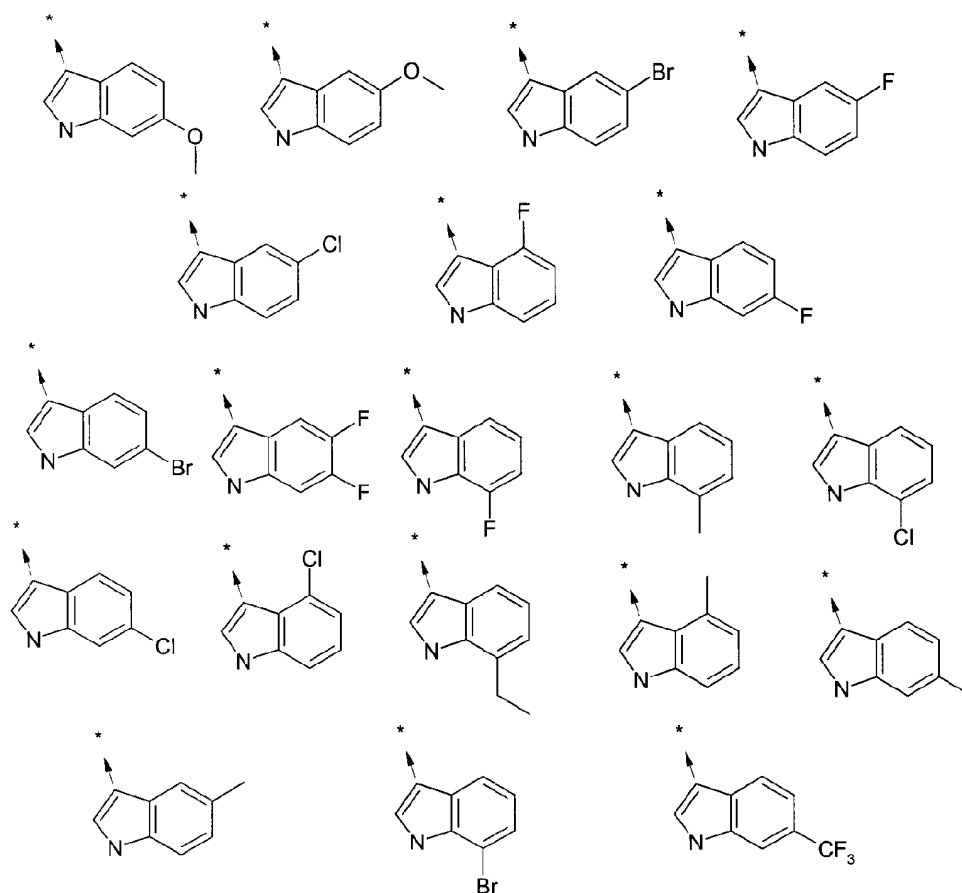
**制备 14: 3-(2-溴乙基)-6-甲氧基-1H-吲哚(C<sub>11</sub>H<sub>12</sub>BrNO, M=254.13)**



2-(6-甲氧基-1H-吲哚-3-基)乙醇(0.815 g, 4.3 mmol)和四溴化碳(1.6 g; 5 mmol)溶于二氯甲烷(25ml)中的溶液冷却到 0℃。添加三苯基膦(1.3g; 5 mmol)。该反应混合物在室温下搅拌 2 小时。蒸去二氯甲烷, 得到的残留物用硅胶纯化(洗脱剂: 庚烷/乙酸乙酯: 3/1)。这些馏分进行蒸发, 得到的固体进行真空干燥(0.69 g; 产率=63 %)。

NMR <sup>1</sup>H(DMSO-d<sub>6</sub>, 400MHz): δ 10.69(s, 1H, NH); 7.42-7.39(d, J=8.6 Hz, 1H, 芳族的); 7.08(s, 1H, 芳族的); 6.84(s, 1H, 芳族的); 6.65-6.62(d, J=8.6 Hz, 1H, 芳族的); 3.74(s, 3H, OCH<sub>3</sub>); 3.71-3.68(t, J=7.6 Hz, 2H, CH<sub>2</sub>); 3.21-3.17(t, J=7.6 Hz, 2H, CH<sub>2</sub>)。MS/LC: m/z=254.04(M + H)tr=10.56 min(条件 2)。

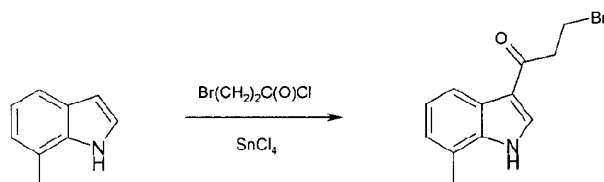
制备式 R<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>Br 的吲哚溴, 其中具有下述吲哚 R<sub>3</sub>基团:



### 5.3. 制备溴化通式(8d)衍生物:

根据本技术领域技术人员已知的方法, 例如使吲哚酰基化(O. Ottoni 等人, *Org. Lett.*, 2001, 3(7), 1005-1007), 接着或不接着还原羰基基团(E. Wenkert 等人, *J. Org. Chem.*, 1986, 51(12), 2343-2351), 可以得到通式  $\text{Br}-(\text{CH}_2)_n\text{[Q]}'_p\text{[C(X')}(Y')\text{]}'_m\text{Z}'$  的溴化衍生物, 式中  $\text{Q}'$ 代表  $\text{C(O)}$ ,  $p'$ 代表 0 或 1,  $m'$ 代表 0,  $\text{Z}'$ 代表吲哚基团,  $(\text{CH}_2)_n$ 具有前面指出的意义。

**制备 15:** 3-溴-1-(7-甲基-1H-吲哚-3-基)丙-1-酮 ( $\text{C}_{12}\text{H}_{12}\text{BrNO}$ ,  $\text{M}=266.14$ ).

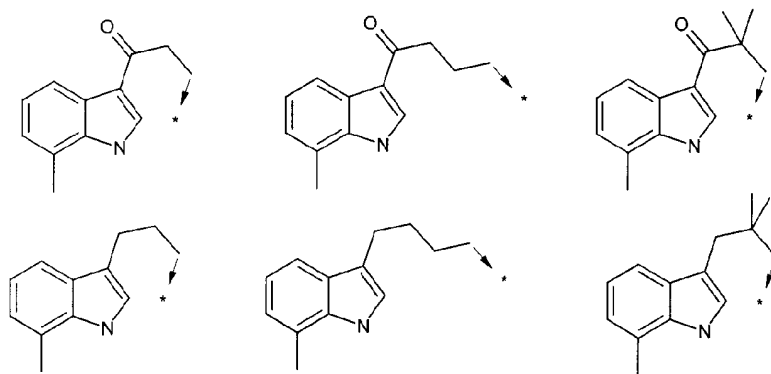




在 0°C, 7-甲基-1*H*-咪唑(131 mg; 1 mmol)在 2ml 二氯甲烷中制成溶液。在 0°C, 添加四氯化锡在二氯甲烷(1.2ml; 1.2 mmol)中的溶液, 然后, 该反应混合物在室温下搅拌 30 分钟。往这种介质添加 3-溴丙酰基氯(101  $\mu$ l; 1mmol)和硝基甲烷(1.5ml), 该反应保持搅拌 24 小时。然后添加 5ml 水, 再用乙酸乙酯提取产物 3 次, 每次 5ml。合并有机相, 用硫酸钠干燥和蒸去溶剂。得到的固体在减压下进行干燥(21.5mg; 产率=8%)。

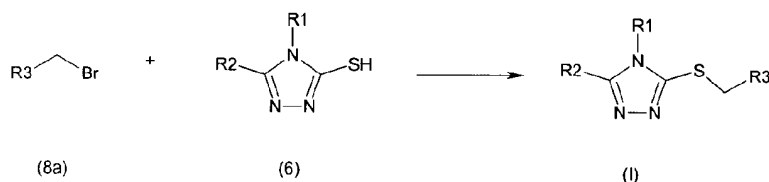
NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  8.39-8.38(m, 1H, 芳族的); 8.03-8.01(d, 1H, 芳族的); 7.09-7.07(t, 1H, 芳族的); 7.02-7.01(d, 1H, 芳族的); 3.82-3.79(t, 2H,  $\text{CH}_2$ ); 3.51-3.48(t, 2H,  $\text{CH}_2$ ); 2.43(s, 3H,  $\text{CH}_3$ )。 MS/LC:  $m/z=266.03\text{tr}=9.84$  min(条件 1)。

制备通式 (8d) 的溴化衍生物, 其中具有下述  $-(\text{CH}_2)_n\cdot[\text{Q}']_p\cdot[\text{C}(\text{X}')(\text{Y}')]_m\cdot\text{Z}'$  基团:



## 15 6. 制备通式(I)化合物:

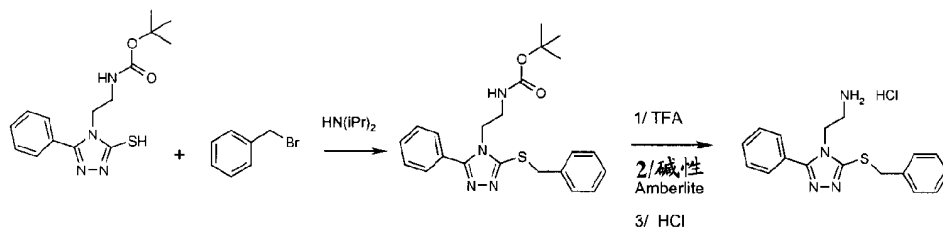
### 6.1. 用苄基溴(8a)取代硫醇(6):



在质子惰性溶剂, 例如甲醇或乙醇中, 使用碱, 例如 NaOAc, KOH,  $\text{K}_2\text{CO}_3$ (Shetgiri, N. P.; Kokitkar, S. V. *Indian J. Chem, Sect B: Org Chem*

Incl Med Chem 2001, 40(2), 163-166), 或在非极性溶剂, 例如丙酮或二氯甲烷中, 使用有机碱, 例如三乙胺或二异丙胺, 或树脂在质子惰性溶剂, 例如二氯甲烷中溶胀后, 使用这种树脂载带的碱, 例如吗啉代甲基聚苯乙烯树脂(Novabiochem)或 7-甲基-1,5,7-三氮杂双环[4,4,0]癸-5-烯聚苯乙烯树脂(Novabiochem)活化硫原子后, 可以用通式(8a)的苄基溴取代通式(6)的硫醇。该反应在室温下进行 12-36 小时。添加例如苯硫酚(thiophenol)树脂(Argonaut)和搅拌 4-8 小时可以捕获过量的通式(8a)反应物。该悬浮液过滤后, 滤液进行蒸发, 再采用硅胶柱色谱法纯化。在用氨基甲酸酯类基团(例如像叔丁氧基羰基基团)保护该分子上存在的胺官能的情况下, 残留物用酸, 例如三氟乙酸处理 10-30 分钟, 或用盐酸在乙醚中的溶液处理 16-20 小时。这时在三氟乙酸的情况下得到呈成盐形式的最后产物, 该盐用 Amberlite 类型碱性树脂处理, 然后在质子惰性溶剂, 例如乙醚、乙酸乙酯或二氧杂环己烷中, 用盐酸溶液再使其成盐。

15 实施例 A: 2-[3-(苄基-5-基)-5-苯基-4H-1,2,4-三唑-4-基]乙胺盐酸盐 (C<sub>17</sub>H<sub>19</sub>N<sub>4</sub>SCl, M=346.88)



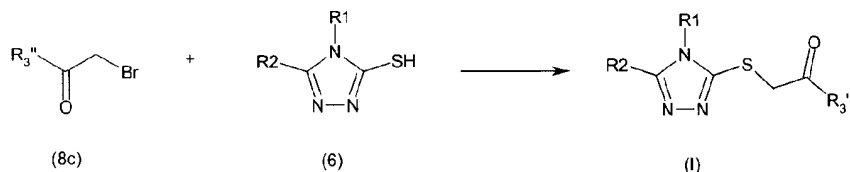
20 先将二异丙胺(0.14ml; 1mmol)、后将苄基溴(0.12ml; 1mmol)加到 2-(3-苯基-5-硫烷基-4H-1,2,4-三唑-4-基)乙基氨基甲酸叔丁酯(320 mg; 1mmol)溶于四氢呋喃(5ml)中的溶液。该溶液在室温下搅拌 24 小时, 然后蒸去溶剂。添加二氯甲烷(2ml)和三氟乙酸(2ml), 得到的溶液在室温下搅拌 10 分钟。蒸去溶剂, 再溶于甲醇中的该化合物通过碱性 Amberlite 树脂, 以便得到呈游离碱形式的胺, 接着采用硅胶柱色谱法纯化(洗脱剂: 乙酸乙酯/甲醇: 1/1)。这些馏分进行蒸发, 再使用盐酸在乙醚中的溶液(1ml; 1mmol)处理得到该胺盐酸盐。生成的沉淀经过滤后, 用乙醚洗涤, 然后进行真空干燥(80 mg; 产率=23 %)。

NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  8.22(宽 s, 3H,  $\text{NH}_3^+$ ); 7.66–7.63(m, 2H, 芳族的); 7.58–7.56(m, 3H, 芳族的) 7.41–7.40(m, 2H, 芳族的); 7.35–7.29(m, 3H, 芳族的); 4.46(s, 2H,  $\text{CH}_2$ ); 4.16(t,  $J=8.3$  Hz, 2H,  $\text{CH}_2$ ); 2.88–2.82(m,  $J=2$  和 8.3 Hz, 2H,  $\text{CH}_2$ )。MS/LC:  $m/z=311.13(\text{M} + \text{H})$   $t_r=6.51\text{min}$ (条件 1)。

使用通式  $\text{R}_3\text{Br}$  的苄基溴化物(8a), 其中具有下述  $\text{R}_3$  基团:

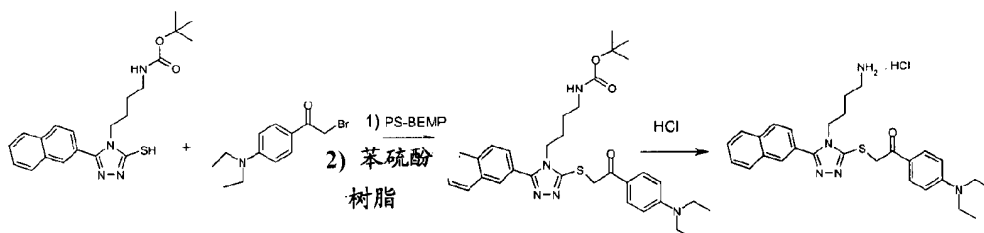


## 6.2. 用 $\alpha$ -溴代酮(8c)取代硫醇(6):



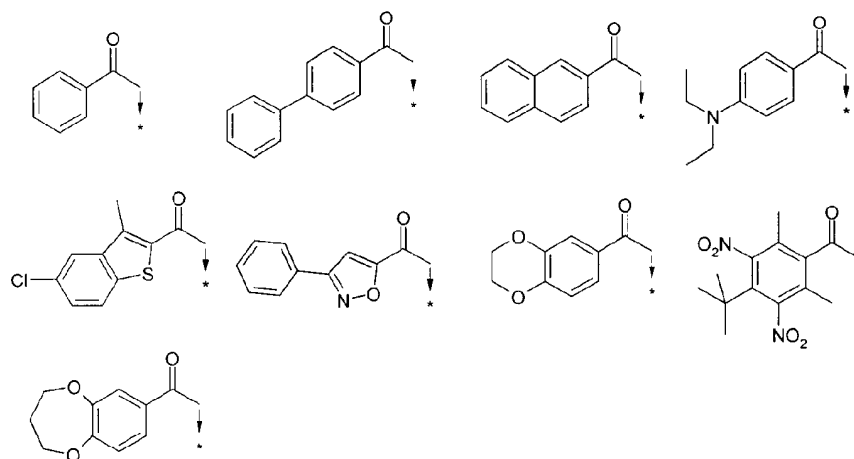
在与前面所描述的同样条件下活化硫原子后，可以用通式(8c)的  $\alpha$ -溴酮取代通式(6)的硫醇。该反应在室温下进行 12-24 小时。添加例如苯硫酚树脂(Argonaut)或氨基甲基-聚苯乙烯类树脂(Novabiochem)与搅拌 4-8 小时可以捕集过量的通式(8c)反应物。悬浮液过滤后，蒸发滤液，并用硅胶柱纯化。在用氨基甲酸酯基团(例如像叔丁氧基羰基基团)保护在该分子上存在的胺官能的情况下，其残留物用盐酸在乙醚中的溶液处理 16-20 小时。如果必要用硅胶柱纯化后，得到最后产物，呈盐酸盐形式。

**实施例 B:** 2-[4-(6-氨基己基)-5-(2-萘基)-4H-1,2,4-三唑-3-基]硫烷基-1-[4-(二乙基氨基)苯基]乙酮盐酸盐(C<sub>30</sub>H<sub>38</sub>N<sub>5</sub>O<sub>2</sub>Cl, M=552.19)

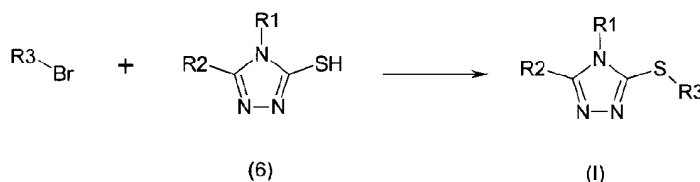


在聚苯乙烯上的 2-叔丁基亚氨基-2-二乙基氨基-1,3-二甲基-全氢-1,3,2-二氮杂磷杂苯树脂加到 6-[3-(2-萘基)-5-硫烷基-4H-1,2,4-三唑-4-基]己基氨基甲酸叔丁酯(30 mg; 0.07mmol)溶于四氢呋喃(1ml)的溶液中。该悬浮液在室温下搅拌 30 分钟，然后往该介质添加 2-溴-1-[4-(二乙基氨基)苯基]乙酮(22 mg; 0.08 mmol)。该混合物在室温下搅拌 16 小时。添加苯硫酚树脂(70 mg, 0.1mmol, Argonaut)和搅拌 6 小时捕集过量的 2-溴-1-[4-(二乙基氨基)苯基]乙酮。该悬浮液经过滤后，蒸发滤液。为了使胺官能去保护，该滤液溶于甲醇(0.5mmol)中，然后添加盐酸在乙醚中的溶液(2ml; 2 mmol)。该溶液搅拌 16 小时，然后进行蒸发。得到的固体进行真空干燥(28 mg; 产率=63%)。MS/LC: m/z=516.40(M+H) tr=8.60 min(条件 1)。

使用通式 R<sub>3</sub>Br 的溴酮(8c)，其中具有下述 R<sub>3</sub> 基团:

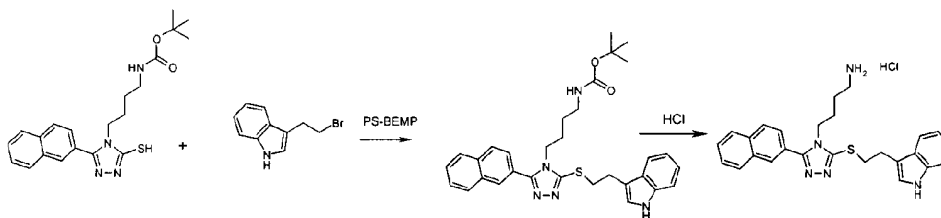


### 6.3.使用脂族卤化物，乙基吡啶溴(8b)或通式(8d)的溴化衍生物取代硫醇(6):



- 5 使用在聚苯乙烯上的 2-叔丁基亚氨基-2-二乙基氨基-1,3-二甲基-全氢-1,3,2-二氮杂磷杂苯树脂(Fluka)活化硫原子后，使用脂族卤化物，通式(8b)的乙基吡啶溴或通式(8d)的溴化衍生物取代通式(6)的硫醇(6)。该反应在室温下进行 3-6 小时。该悬浮液经过滤后，滤液进行蒸发，用硅胶柱纯化。
- 10 在用氨基甲酸酯基团(例如像叔丁氧基羰基基团)保护该分子上的胺官能的情况下，残留物用盐酸在乙醚中的溶液处理 16-20 小时。这时得到呈盐酸盐形式的最后产物。

实施例 C: 3-[3-{{2-(1H-吡啶-3-基)乙基}硫烷基}-5-(2-萘基)-4H-1,2,4-三唑-4-基]丙胺盐酸盐(C<sub>26</sub>H<sub>28</sub>N<sub>5</sub>SCl, M=478.06)



- 15 步骤 1: 3-[3-{{2-(1H-吡啶-3-基)乙基}硫烷基}-5-(2-萘基)-4H-1,2,4-三

唑-4-基]丙基氨基甲酸叔丁基酯( $C_{31}H_{35}N_5O_2S$ ,  $M=541.72$ )

在聚苯乙烯上的 2-叔丁基亚氨基-2-二乙基氨基-1,3-二甲基-全氢-1,3,2-二氮杂磷杂苯树脂(0.91 g, 2 mmol, 2.2 mmol/g, Fluka)加到 265mg (0.66mmol) 4-[3-(2-萘基)-5-硫烷基-4H-1,2,4-三唑-4-基]丁基氨基甲酸叔丁酯在无水四氢呋喃(15ml)中的悬浮液里。该悬浮液在室温下搅拌 10 分钟, 然后添加 3-(2-溴甲基)吡啶(149 mg, 0.66 mmol)。得到的反应混合物在室温下搅拌 4 小时, 然后过滤。蒸发的滤液采用硅胶闪式色谱法纯化(乙酸乙酯/庚烷 2: 1)。合并这些馏分, 接着蒸发, 白色残留物进行真空干燥(249 mg, 产率=70 %)。

10 NMR  $^1H$ (DMSO- $d_6$ , 400MHz): 8.41(宽 s, 1H, NH); 8.01(s, 1H, 芳族的); 7.99-7.96(m, 1H, 芳族的); 7.92-7.91(m, 2H, 芳族的); 7.69-7.65(m, 2H, 芳族的); 7.60-7.57(m, 2H, 芳族的); 7.39-7.37(m, 1H, 芳族的); 7.22-7.20(m, 1H, 芳族的); 7, 14-7.11(m, 2H, 芳族的); 4.44(宽 s, 1H, NH); 3.91(t,  $J=8$  Hz, 2H,  $CH_2$ ); 3.70(t,  $J=5.9$  Hz, 2H,  $CH_2$ ); 3.33(t, 15  $J=5.9$  Hz, 2H,  $CH_2$ ); 2.99-2.97(m, 2H,  $CH_2$ ); 1.61-1.57(m, 2H,  $CH_2$ ); 1.42(s, 9H,  $(CH_3)_3$ ); 1.36-1.27(m, 2H,  $CH_2$ )。MS/LC:  $m/z =542.36(M+H)$ tr= 11.07 min(条件 1)。

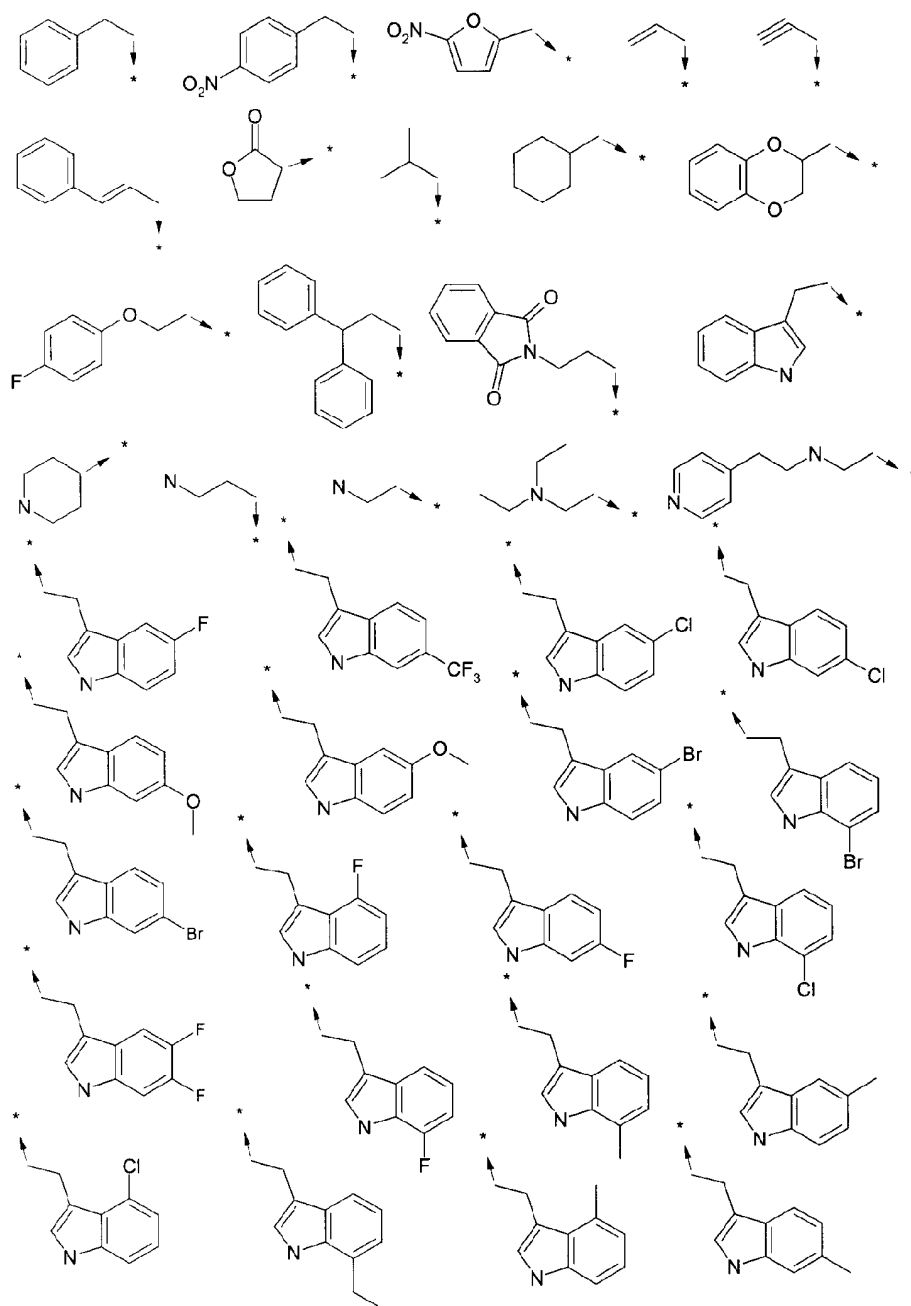
步骤 2: 3-[3-{[2-(1H-吡啶-3-基)乙基]硫烷基}-5-(2-萘基)-4H-1,2,4-三唑-4-基]丙胺盐酸盐( $C_{26}H_{28}N_5S$ ,  $M=478.06$ )

20 前面制备的 3-[3-{[2-(1H-吡啶-3-基)乙基]硫烷基}-5-(2-萘基)-4H-1,2,4-三唑-4-基]丙基氨基甲酸叔丁基酯溶于无水二氯甲烷(3ml)和甲醇(2ml)中, 然后往该溶液添加盐酸在乙醚中的溶液(3.1ml)。该混合物搅拌 45 分钟, 然后蒸发, 得到的浅褐色固体进行真空干燥(188 mg, 产率= 94 %)。

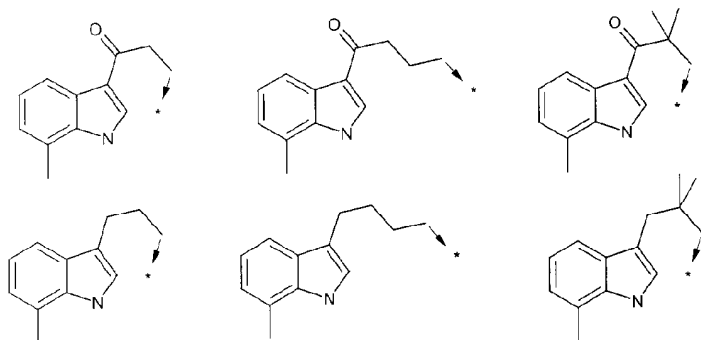
25 NMR  $^1H$ ( $D_2O$ , 77°C, 400MHz): 8.59-8.56(m, 1H, 芳族的); 8.51-8.49(m, 2H, 芳族的); 8.41(s, 1H, 芳族的); 8.19-8.16(m, 2H, 芳族的); 8.04-8.02(m, 1H, 芳族的); 7.96-7.93(m, 1H, 芳族的); 7.87-7.84(m, 1H, 芳族的); 7.68(s, 1H, 芳族的); 7.65-7.63(m, 1H, 芳族的); 7.58-7.56(m, 1H, 芳族的); 4.28(t,  $J=8.3$  Hz, 2H,  $CH_2$ ); 4.17(t,  $J=5.5$  Hz, 2H,  $CH_2$ ); 3.72(t, 30  $J=5.5$  Hz, 2H,  $CH_2$ ); 3.14(t,  $J=8.3$  Hz, 2H,  $CH_2$ ); 1.92-1.85(m,  $J=8.3$

Hz 和 7 Hz, 2H, CH<sub>2</sub>); 1.82-1.74(m, J=8.3 Hz 和 7 Hz, 2H, CH<sub>2</sub>)。 MS/LC: m/z=442.26(M + H), rt=8.14 min(条件 1)。

使用通式 R<sub>3</sub>Br 的脂族卤化物, 溴化衍生物(8b)或(8d), 其中具有下述 R<sub>3</sub> 基团:

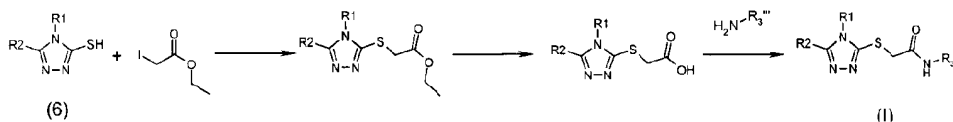






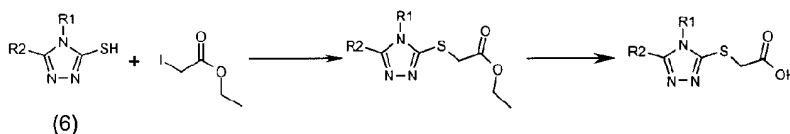
#### 6.4. R<sub>3</sub>含有酰胺官能的具体示例:

使用通式(6)的硫醇,分3步可以得到通式(I)的化合物,例如 R<sub>3</sub>是式 -CH<sub>2</sub>-C(O)-NH-(CH<sub>2</sub>)<sub>m</sub>-NXY 的基,其中 m、X 和 Y 如前面所定义。



5

##### 6.4.1. 硫的取代和酯的水解:

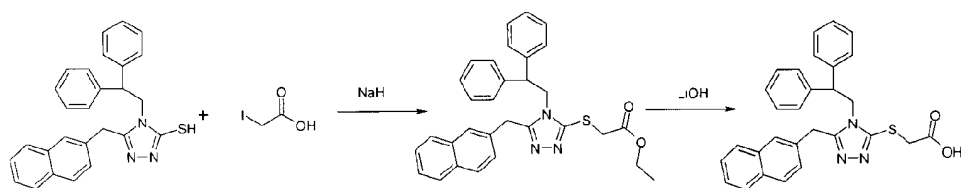


10

在质子惰性溶剂,例如二氯甲烷或二甲基甲酰胺中,使用碱,例如 NaH, 或使用在聚苯乙烯上的 2-叔丁基亚氨基-2-二乙基氨基-1,3-二甲基-全氢-1,3,2-二氮杂磷杂苯树脂(Fluka)活化硫原子后,可以用碘乙酸乙酯取代通式(6)的硫醇。该反应在室温下进行 12-24 小时,然后,该反应混合物经洗涤,再进行真空浓缩。然后,在质子惰性溶剂,例如四氢呋喃存在下,在室温下用碱,例如像 KOH 或氢氧化锂水溶液处理 3-6 小时,使这种酯水解(Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *J Chem Soc, Chem Commun* 1991 (14), 940-942)。蒸去溶剂,再用盐酸水溶液中和,使用有机溶剂,例如乙酸乙酯提取后得到相应的酸,并且无须其它纯化便可用于后面的步骤。

15

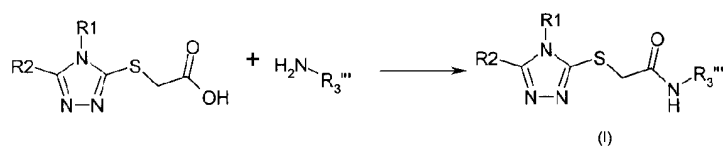
制备 16: {[4-(2,2-二苯基乙基)-5-(2-萘基甲基)-4H-1,2,4-三唑-3-基]硫烷基}乙酸(C<sub>29</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S, M=479.61)



将氢氧化钠(0.4g; 10mmol)加到 4-(2,2-二苯基乙基)-5-(2-萘基甲基)-4H-1,2,4-三唑-3-硫醇(4g; 9.5mmol)溶于二氯甲烷(100ml)的溶液中; 该溶液在室温下搅拌 30 分钟。加入碘乙酸乙酯(1.2ml; 10mmol), 该混合物在室温下搅拌 16 小时。该反应混合物用蒸馏水(50ml)洗涤, 然后用饱和氯化钠溶液(50ml)洗涤。蒸发有机相。通过水解得到这种酸: 氢氧化锂(1.1g; 27mmol)溶于蒸馏水(40ml)的溶液加到残留物溶于四氢呋喃(80ml)的溶液中, 这种混合物在室温下搅拌 4 小时。蒸去溶剂, 然后添加盐酸标准溶液, 直到 pH 微酸性。这种溶液用乙酸乙酯(50ml)提取两次, 合并有机相, 用硫酸钠干燥, 过滤, 蒸发, 得到的固体进行真空干燥(2g, 产率=44%), 然后用于后续步骤。

NMR  $^1\text{H}$ (DMSO- $d_6$ , 400MHz):  $\delta$  12.92(宽 s, 1H, C(O)-OH); 7.92-7.90(m, 1H, 芳族的); 7.83-7.81(m, 1H, 芳族的); 7.55-7.37(m, 4H, 芳族的); 7.34-7.23(m, 10H, 芳族的); 7.11-7.09(m, 1H, 芳族的); 4.64(d, J=9 Hz, 2H,  $\text{CH}_2$ ); 4.38(t, J=9 Hz, 1H, CH); 3.96(s, 2H,  $\text{CH}_2$ ); 3.92(s, 2H,  $\text{CH}_2$ )。MS/LC:  $m/z=480.28(\text{M} + \text{H})$ ,  $\text{tr}=10.75 \text{ min}$ (条件 1)。

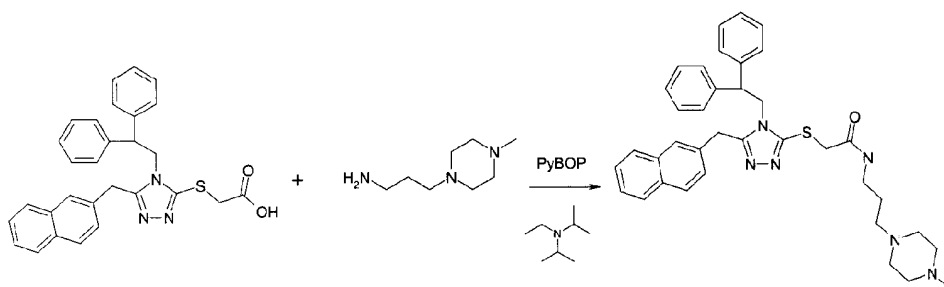
#### 6.4.2. 肽偶合:



采用经典的肽合成方法(M. Bodansky, *The Practice of Peptide Synthesis*, 145 (Springer-Verlag, 1984)), 例如在四氢呋喃、二氯甲烷或二甲基甲酰胺中, 在偶合试剂, 例如环己基碳化二亚胺(DCC)、1, 1'-羰基二咪唑(CDI)(*J, Med, Chem.* 1992, 35(23), 4464-4472)、1-(3-二甲氨基丙基)-3-乙基碳化二亚胺盐酸盐(EDC 或 WSCI)(John Jones, *the chemical synthesis of peptides*, 54 (Clarendon Press, Oxford, 1991))或六氟磷酸苯

并三唑-1-基-氧-三-吡咯烷基-磷(PyBOP)(Coste, J, ; The-Nguyen, D, ; Castro, B, ; *Tetrahedron Lett* 1990, 31, 205)的存在下,可以得到通式(I)化合物,例如 R<sub>3</sub>是式-CH<sub>2</sub>-C(O)-NH-(CH<sub>2</sub>)<sub>m</sub>-NXY的基团,其中 m、X和Y如前面所定义。用硅胶柱纯化后得到通式(I)的化合物。

5 **实施例 D:** 2-{{[4-(2,2-二苯基乙基)-5-(2-萘基甲基)-4H-1,2,4-三唑-3-基]硫烷基}-N-[3-(4-甲基-1-哌嗪基)丙基]乙酰胺(C<sub>37</sub>H<sub>42</sub>N<sub>6</sub>OS, M=618.85)

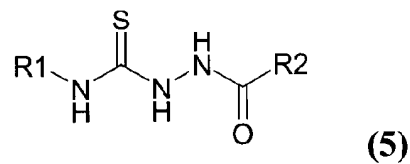


10 六氟磷酸苯并三唑-1-基-氧-三-吡咯烷基-磷(52mg; 0.1mmol)加到{{[4-(2,2-二苯基乙基)-5-(2-萘基甲基)-4H-1,2,4-三唑-3-基]硫烷基}乙酸(48mg; 0.1mmol)溶于二氯甲烷(5ml)中的溶液里。该溶液在室温下搅拌30分钟,然后添加二异丙基-乙胺(38 μl; 0.22mmol)和3-(4-甲基-1-哌嗪基)丙胺(20 μl; 0.12 mmol)。该混合物在氩气与室温下搅拌16小时。蒸去溶剂,残留物采用硅胶柱色谱法进行纯化(洗脱剂:二氯甲烷/甲醇 95/5)。馏分蒸发后,得到的固体进行真空干燥(7mg,产率=11%)。MS/LC: m/z=619.41(M + H), tr=8.37min(条件 1)。

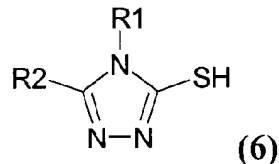
15 使用了下述 R<sub>3</sub>'''类的基团:



20 本发明还有一个目的是本发明式 I 化合物的液相制备方法,其特征在于它包括使式 R<sub>1</sub>-NCS 的异硫氰酸酯与式 R<sub>2</sub>-C(O)-NH-NH<sub>2</sub> 的酰肼反应,其中 R<sub>1</sub>和 R<sub>2</sub>具有前面指出的意义,得到下述式(5)化合物:



对式(5)化合物可以进行碱处理, 得到相应的式(6)化合物:



使式(6)化合物与下述化合物反应:

5      A) 式  $\text{Br}-(\text{CH}_2)_{n'}[\text{Q}']_{p'}[\text{C}(\text{X}')(\text{Y}')]_{m'}\text{Z}'$  化合物, 其中  $n'=1$ ,  $p'=m'=0$  和  $\text{Z}'$  具有前面指出的意义, 在该分子上存在的胺官能去保护后得到相应的式(I)化合物, 或

10      B) 式  $\text{Br}-(\text{CH}_2)_{n'}[\text{Q}']_{p'}[\text{C}(\text{X}')(\text{Y}')]_{m'}\text{Z}'$  的化合物, 其中  $n'=1$ ,  $\text{Q}'=-\text{C}(\text{O})-$ , 且  $m'=0$  和  $\text{Z}'$  具有前面指出的意义, 在该分子上存在的胺官能去保护后得到相应的式(I)化合物, 或

    C) 式  $\text{Br}-(\text{CH}_2)_{n'}[\text{Q}']_{p'}[\text{C}(\text{X}')(\text{Y}')]_{m'}\text{Z}'$  的化合物, 其中  $\text{Q}'$ 、 $\text{X}'$ 、 $\text{Y}'$ 、 $\text{Z}'$ 、 $n'$ 、 $p'$  和  $m'$  具有前面指出的意义, 在该分子上存在的胺官能去保护后得到相应的式(I)化合物。

15      本发明的化合物 I 具有有用的药理学性质。因此, 发现本发明的化合物 I 对一种或多种生长激素受体具有高亲合性。它们可以选择性或非选择性地用作生长激素的非肽激动剂或拮抗剂。

    因此, 可以在不同的治疗应用中使用本发明的化合物。它们用于治疗例如上面说明的病变或疾病, 以及涉及一种或多种生长激素受体的病变或疾病。

20      下面实验部分是对本发明化合物药理学性质所作的说明。

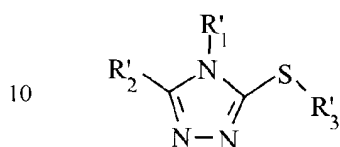
    本发明的化合物与硬骨鱼紧张肽 II 也是类似的, 并且这些化合物对其中涉及硬骨鱼紧张肽 II 的病变或疾病的治疗是特别有意义的。

25      本申请还有一个目的是药物组合物, 它们含有作为活性组分的至少一种如前面定义的式 I 的化合物, 或者所述式 I 化合物与药学上可接受的无机或有机酸的加成盐, 该组合物还包括药学上可接受的载体。

在 *Phosphorus, Sulfur and Silicon*, 2000, 第 164 卷, 第 67-81 页中描述了式 I 化合物, 其中  $R_1$  代表  $(CH_2)_2-W$ ,  $W$  代表吗啉基或哌嗪基,  $R_2$  代表苯基、*m*-氯苯基或 4-吡啶基,  $R_3$  代表氢原子, 或  $R_1$  代表  $(CH_2)_2-W$ , 而  $W$  代表吡咯烷基,  $R_2$  代表 *p*-氯苯基和  $R_3$  代表氢原子, 但它们只是作为合

5 成中间产物描述的, 没有提及这些化合物的任何治疗活性。

因此, 本发明的再一个目的是一种药物组合物, 它含有作为活性组分的至少一种如下述通式的化合物, 该组合物还包括药学上可接受的载体:



I'

该化合物呈外消旋形式、对映异构体形式或这些形式的组合, 其中:

$R_1$ 、 $R_2$  或  $R_3$  基团中的一个基团代表式  $-(CH_2)_n-[Q]_p-(CH_2)_m-NXY$  或  $-(CH_2)_n-W$  的基团, 其中:

$W$  代表含有至少一个氮原子的杂环烷基;

15  $Q$  代表  $-O-$ 、 $-S-$ 、 $-C(O)-NH-$ 、 $-C(Z_q)(Z_q')$ 、芳基或  $(C_3-C_7)$  环烷基;

$Z_q$  和  $Z_q'$  独立地代表氢原子、任选地被芳基取代的芳基、 $(C_3-C_7)$  环烷基-烷基、芳烷基、 $-C(O)O-R$  或  $-C(O)-NH-R'$ ;

$R$  代表  $(C_1-C_6)$  烷基、芳基或芳烷基, 这些芳基和芳烷基任选地被一个或多个选自  $(C_1-C_6)$  烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基)氨基的相同或不同取代基取代;

20

$R'$  代表  $(C_1-C_6)$  烷基、芳基、芳烷基、杂芳基或杂芳基-烷基, 这些芳基、芳烷基、杂芳基和杂芳基-烷基任选地被一个或多个选自  $(C_1-C_6)$  烷氧基、羟基、卤素、硝基、氰基、氨基、 $(C_1-C_6)$  烷基氨基和二  $((C_1-C_6)$  烷基)氨基的相同或不同取代基取代;

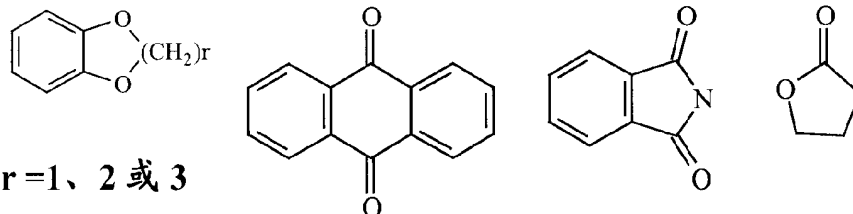
25  $X$  和  $Y$  独立地代表氢原子、 $(C_1-C_6)$  烷基、 $(C_1-C_6)$  烷氧基-羰基或杂芳基-烷基, 或  $X$  和  $Y$  与它们连接的氮原子一起构成杂环烷基, 它任选地被  $(C_1-C_6)$  烷基取代;

$p$  代表 0 或 1;  $n$  和  $m$  独立地代表 0-6 中的一个整数;

且两个其它的基团独立地代表式  $-(CH_2)_n'[Q']_p'[C(X')(Y')]_m'Z'$  的基团, 其中:

Q'代表-O-、-S-、-C(O)-、-NH-、-CH=CH- 或-C≡C-

X'、Y'和Z'独立地代表氢原子、(C<sub>1</sub>-C<sub>6</sub>)烷基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基、(C<sub>1</sub>-C<sub>6</sub>)烷氧基-羰基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基、(C<sub>3</sub>-C<sub>7</sub>)环烷基、杂环烷基、芳基或杂芳基，或下式的基团：



5 这些(C<sub>3</sub>-C<sub>7</sub>)环烷基、杂环烷基、芳基和杂芳基任选地被一个或多个选自-(CH<sub>2</sub>)<sub>q</sub>-X''-Y''、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代；

X''代表-O-、-S-、-C(O)-、-C(O)-O-、-SO<sub>2</sub>-或一个共价键；

10 Y''代表任选地被一个或多个相同或不同卤素基取代的(C<sub>1</sub>-C<sub>6</sub>)烷基；或任选地被一个或多个选自(C<sub>1</sub>-C<sub>6</sub>)烷氧基、羟基、卤素、硝基、氰基、氨基、(C<sub>1</sub>-C<sub>6</sub>)烷基氨基和二((C<sub>1</sub>-C<sub>6</sub>)烷基)氨基的相同或不同取代基取代的芳基或杂芳基；

p'代表0或1，且n'、m'和q'独立地代表0-6中的一个整数。

15 本发明的药物组合物可以为固体状，例如粉剂、颗粒剂、片剂、胶囊或栓剂。合适的固体载体例如可以是磷酸钙、硬脂酸镁、滑石、糖、乳糖、糊精、淀粉、明胶、纤维素、甲基纤维素、羧甲基纤维素钠、聚乙烯基吡咯烷和蜡。

20 含有本发明化合物的药物组合物还可以为液体，例如溶液、乳液，悬液或糖浆。合适的液体载体可以是例如水，有机溶剂，例如甘油或二元醇，以及它们的不同比例的混合物，在水中添加了药学上可接受的油或脂肪。无菌液体组合物可以用于肌肉、腹膜内或皮下注射，无菌组合物也可以采用静脉内方式用药。

25 本发明说明书中使用的所有科学技术术语及含义都具有本技术领域技术人员已知的意义。另外，所有专利(或专利申请)以及其它引用的参考书目都引入本文中。

**实验部分:**

根据前面实施例 A、B、C 和 D 所描述的步骤得到的本发明的其它化合物汇集在下面表中。

5 这些化合物可以使用用液相色谱法(LC)测定的以分表示保留时间(tr),  
用质谱法(MS)测定,以分子峰(M+H)<sup>+</sup>表征。对于质谱法,使用配备电喷雾  
源的单四极质谱仪(Micromass, Platform 型),其分辨率为在 50%谷处 0.8  
Da。

这些实施例的实施条件如下:

洗脱剂: A: 水 + 0.02%三氟乙酸; B: 乙腈

10 **条件 1(C1):**

T(min)	A(%)	B(%)
0	95	5
8.5	10	90
10.5	10	90
10.6	95	5
15	95	5

流速: 1.0ml/min

进样量: 10 μl

室温

波长(% UV): 220 nm

15 柱: Uptisphere HDO 3 μ m 75 \* 4.6 mm i.d.

**条件 2(C2):**

T(min)	A(%)	B(%)
0	100	0
6	20	80
8	20	80
8.1	100	0
10	100	0

流速: 1.0ml/min

进样量: 5  $\mu$ l

室温

波长(% UV): 220 nm

柱: Uptisphere ODS 3 m 50 \* 4.6 mm i.d

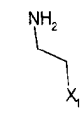
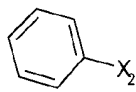
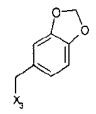
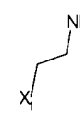
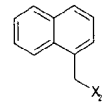
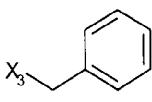

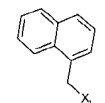
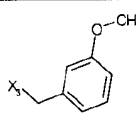
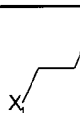
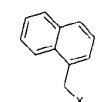
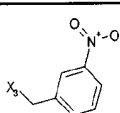

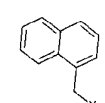
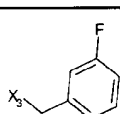
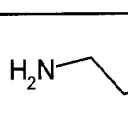
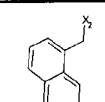
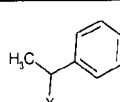
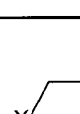
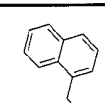
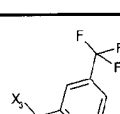

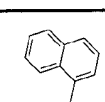
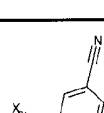

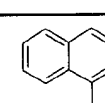
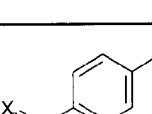

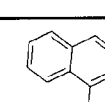
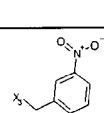
5 下述实施例的条件如下:

实施例	条件	实施例	条件	实施例	条件
1 - 15	1	163 - 164	1	374 - 466	1
16 - 30	2	165 - 191	2	467 - 489	2
31 - 45	1	192 - 210	1	490	1
46 - 59	2	211 - 213	2	491 - 495	2
60	1	214	1	496 - 533	1
61 - 81	2	215 - 234	2	534 - 537	2
82 - 98	1	235 - 236	1	538 - 551	1
99 - 145	2	237 - 260	2	552	2
146 - 151	1	261	1	553 - 582	1
152 - 153	2	262 - 269	2	583 - 638	1
155	1	270 - 368	1	639 - 708	1
155 - 162	2	369 - 373	2		

列出这些实施例以便说明上述步骤, 在任何情况下都不应该看作是对本发明保护范围的限制。

在每次说明  $R_1$ 、 $R_2$  和  $R_3$  基团时,  $X_1$ 、 $X_2$  和  $X_3$  基团分别代表通式(I)化合物的余下部分。



	R1	R2	R3	RT	MH+
1				7.46	355.23
2				7.39	375.27
3				7.11	405.33
4				7.17	420.33
5				7.29	393.21
6				7.26	389.36
7				7.70	443.21
8				7.02	400.33
9				7.30	389.29
10				7.22	450.35

11				7.72	451.36
12				7.50	425.35
13				7.14	438.32
14				7.56	505.32
15				7.75	449.37
16				3.71	311.24
17				3.84	341.21
18				3.97	325.24
19				3.86	356.20

20				3.82	356.20
21				3.82	369.21
22				3.82	329.20
23				3.62	336.22
24				3.79	329.17
25				4.60	367.20
26				3.37	389.16
27				3.99	325.25
28				3.90	386.10
29				4.36	379.18

30				3.90	371.23
31				7.31	361.28
32				7.03	391.31
33				7.09	406.32
34				7.21	379.21
35				7.11	375.38
36				7.61	429.18
37				6.92	386.32
38				7.27	375.30
39				7.13	436.32

40				7.64	437.33
41				7.41	411.33
42				7.45	389.37
43				7.04	424.30
44				7.48	491.29
45				7.73	435.35
46				3.87	341.25
47				3.95	371.28
48				4.02	386.18
49				3.98	386.18

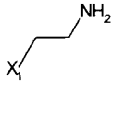
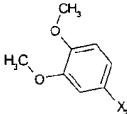
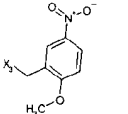

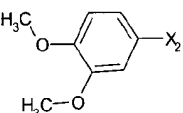
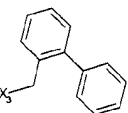
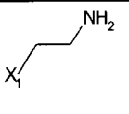
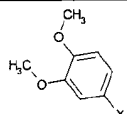
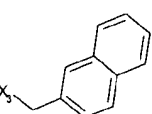
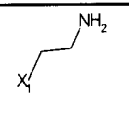
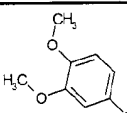
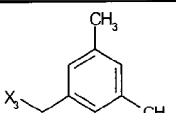
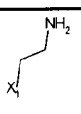
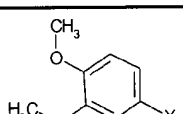
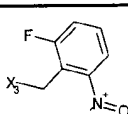
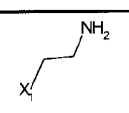
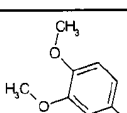
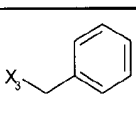
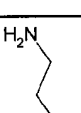
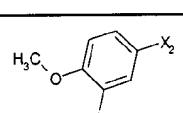
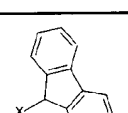
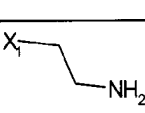
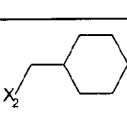
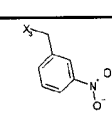
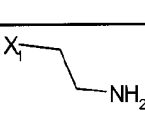
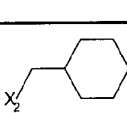
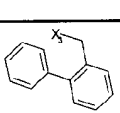
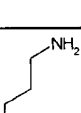
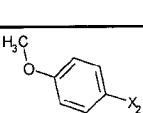
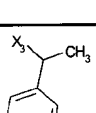
50				3.96	399.20
51				3.96	399.20
52				3.98	359.21
53				4.02	355.24
54				4.20	375.18
55				3.90	359.20
56				4.83	397.26
57				4.49	409.17
58				3.54	419.23
59				4.14	355.24

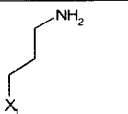
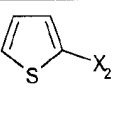
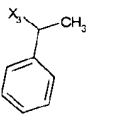
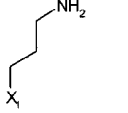
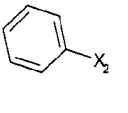
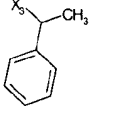
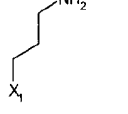
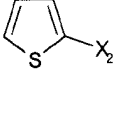
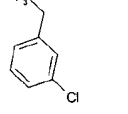
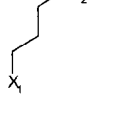
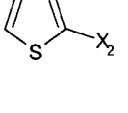
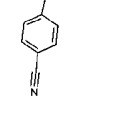
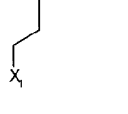
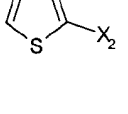
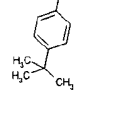
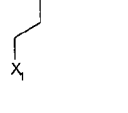
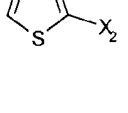
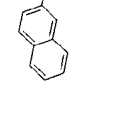
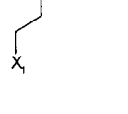

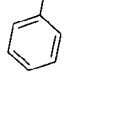
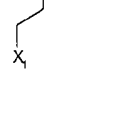
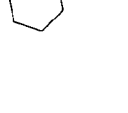
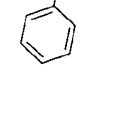
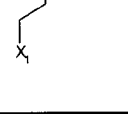
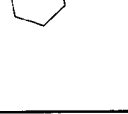
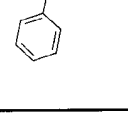
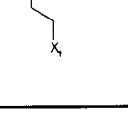
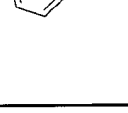
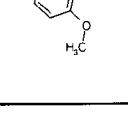
60				7.57	385.23
61				4.09	345.08
62				4.16	375.05
63				4.31	359.06
64				4.23	390.03
65				4.19	390.04
66				4.20	403.19
67				4.17	403.02
68				4.02	370.06
69				4.43	379.16

70				4.62	413.00
71				4.03	370.06
72				4.25	420.05
73				4.68	413.00
74				4.83	421.07
75				4.59	395.04
76				4.26	359.06
77				4.55	373.07
78				4.40	377.10
79				4.12	390.04

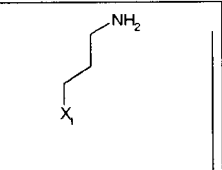
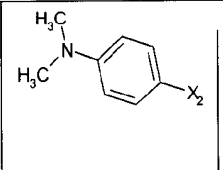
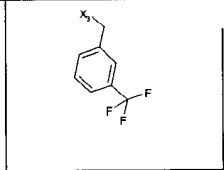
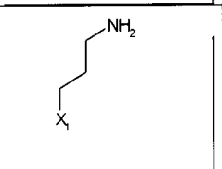
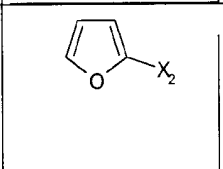
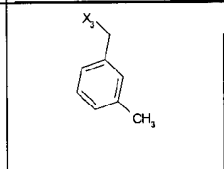
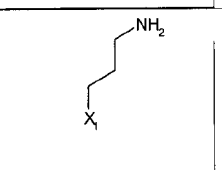
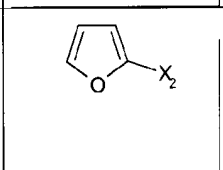
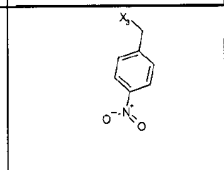
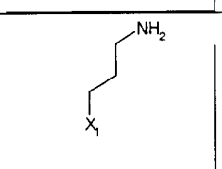
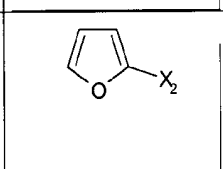
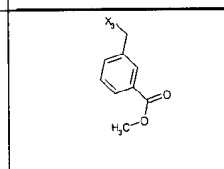
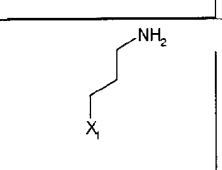
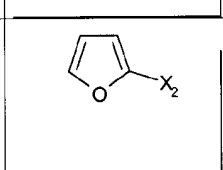
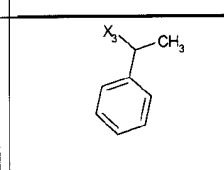
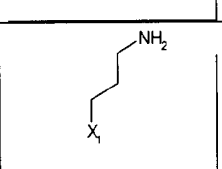
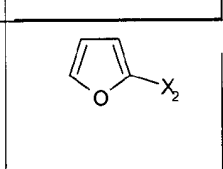
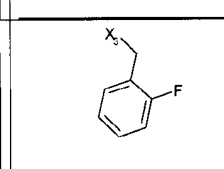
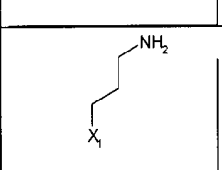
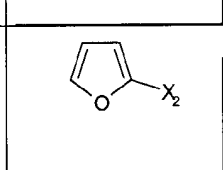
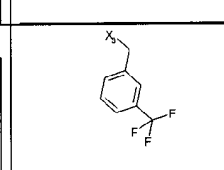
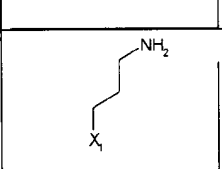
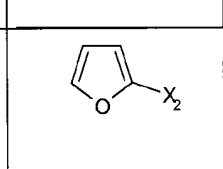
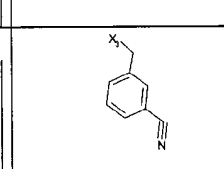
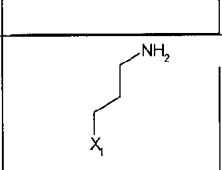
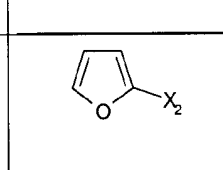
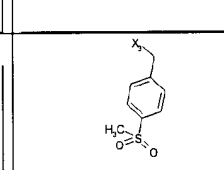
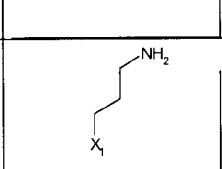
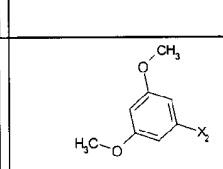
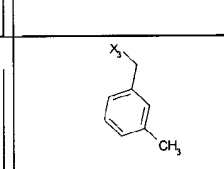


80				4.08	407.99
81				4.54	413.17
82				7.74	389.16
83				6.55	401.32
84				6.62	416.31
85				6.70	389.20
86				6.64	385.37
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88				6.47	396.30
89				6.79	385.29

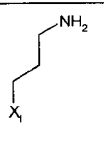
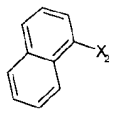
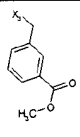
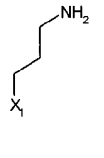
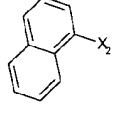
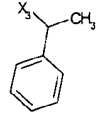
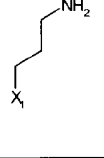
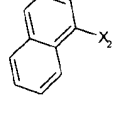
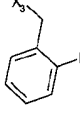
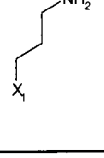
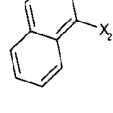
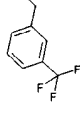
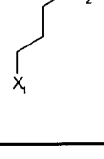
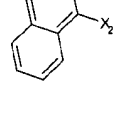
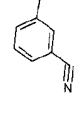
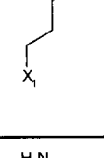
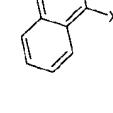
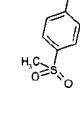
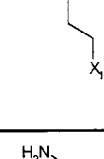
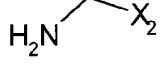
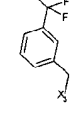
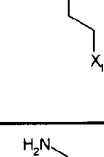
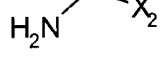
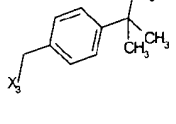
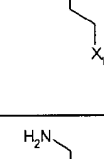
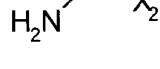
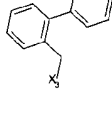
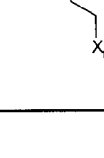

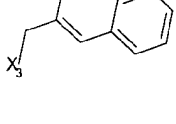
90				6.68	446.32
91				7.21	447.33
92				6.96	421.32
93				6.97	399.37
94				6.57	434.30
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98				7.65	407.36
99				4.18	369.31

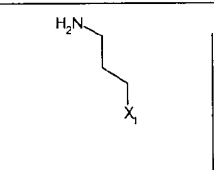
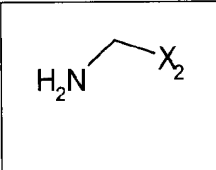
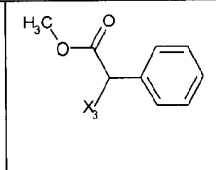
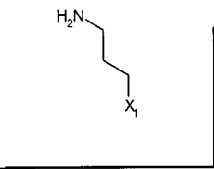
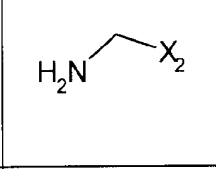
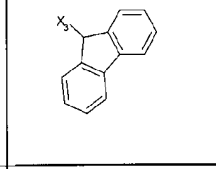
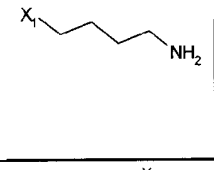
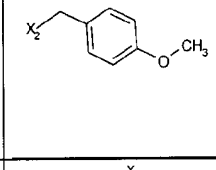
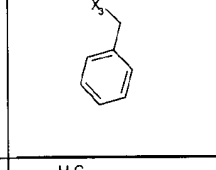
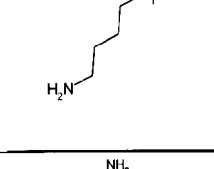
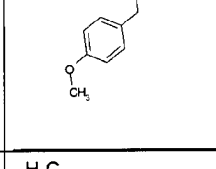
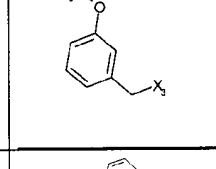
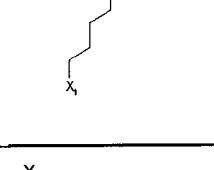
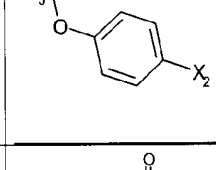
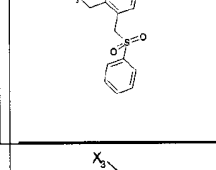
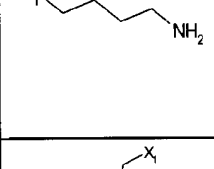
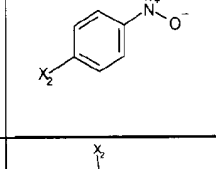
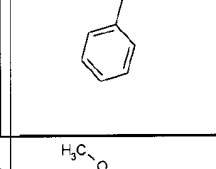
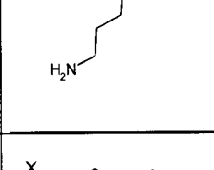
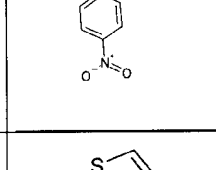
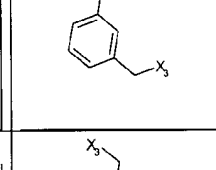
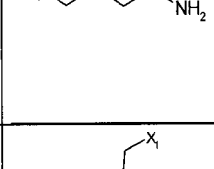
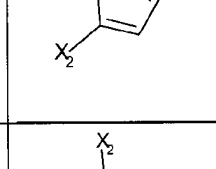
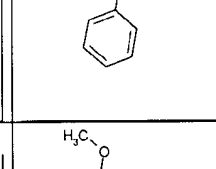
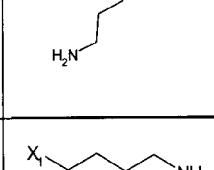
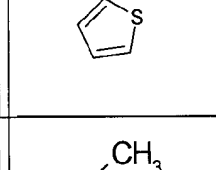
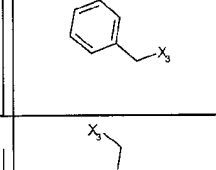
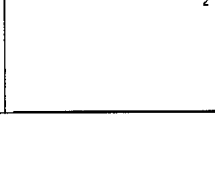
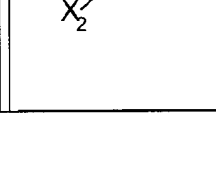
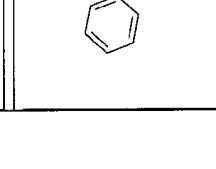
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101				4.08	339.31
102				4.21	365.21
103				3.82	356.23
104				4.87	387.26
105				4.45	381.23
106				4.61	347.36
107				4.55	359.34
108				5.01	421.33
109				3.54	383.19

110				4.23	353.31
111				4.65	389.27
112				4.51	420.24
113				4.47	433.25
114				4.53	393.24
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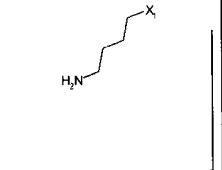
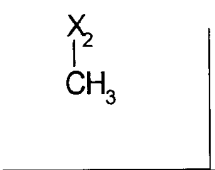
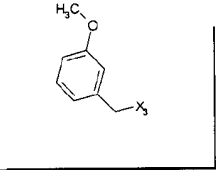
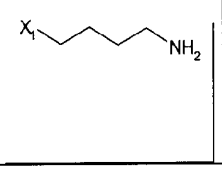
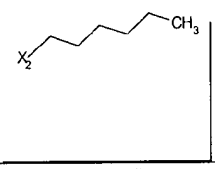
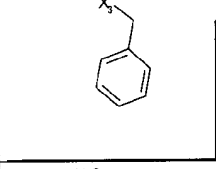
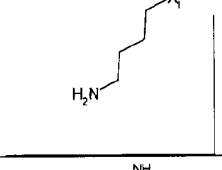
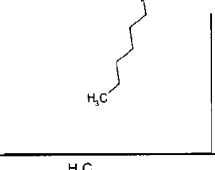
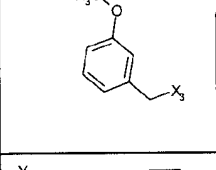
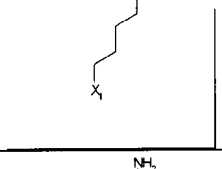
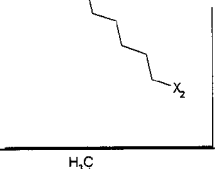
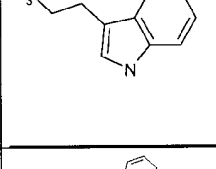
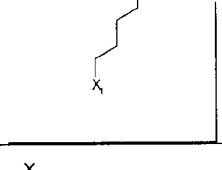
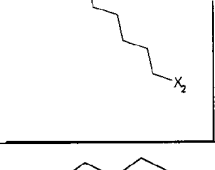
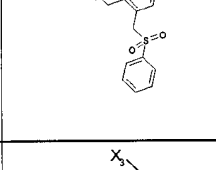
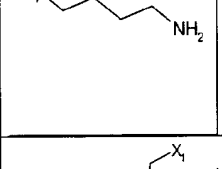
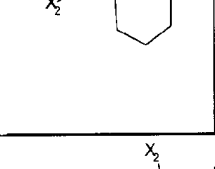
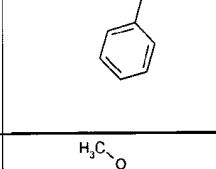
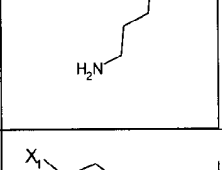
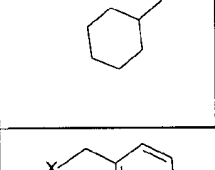
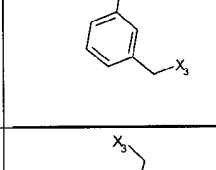
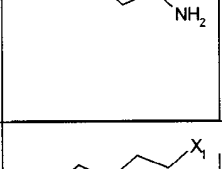
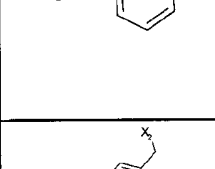
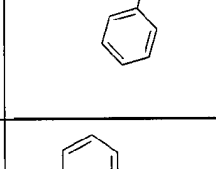
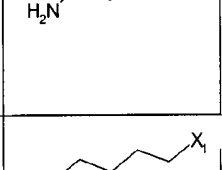
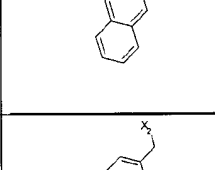
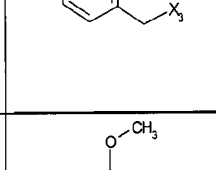
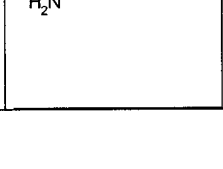
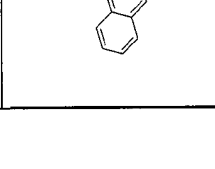
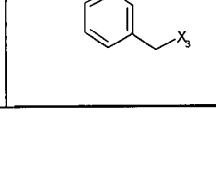
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121				4.13	329.29
122				3.96	360.27
123				3.94	373.26
124				4.04	329.29
125				3.91	333.27
126				4.47	383.24
127				3.78	340.29
128				3.47	393.23
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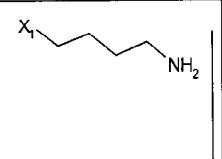
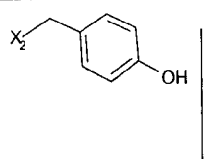
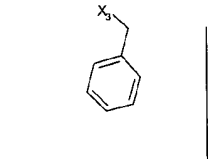
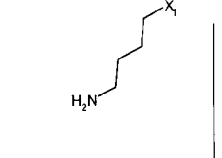
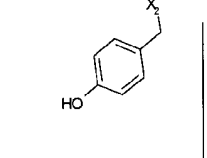
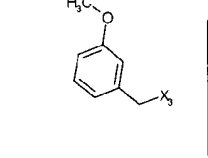
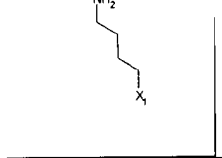
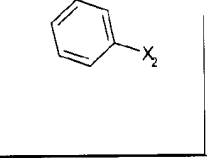
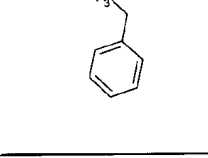
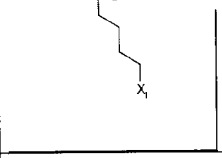
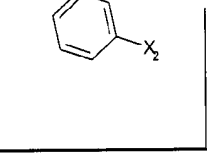
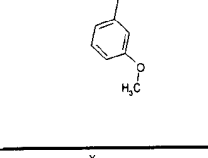
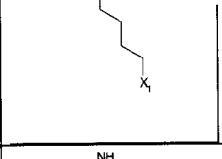
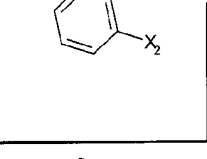
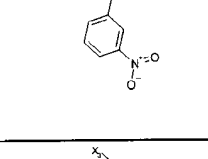
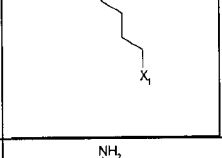
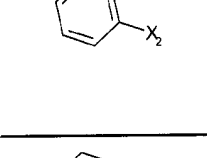
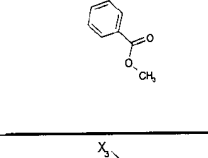
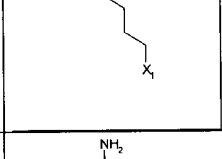
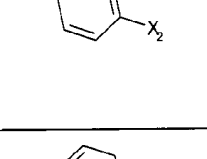
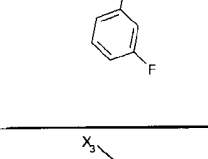
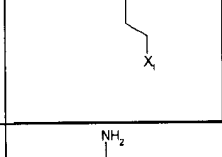
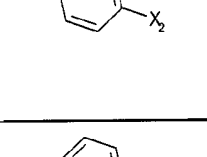
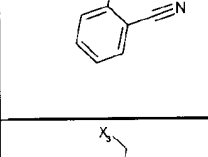
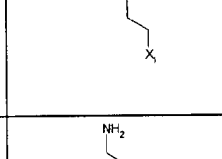
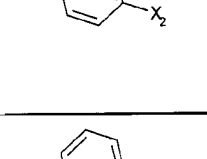
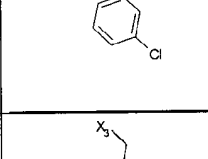
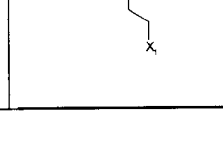
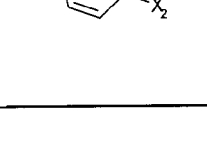
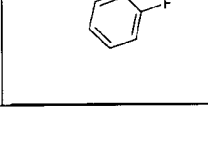
130				4.35	430.30
131				4.29	443.32
132				4.37	399.31
133				4.26	403.27
134				4.76	453.29
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136				3.90	463.28
137				4.48	399.31
138				4.57	389.31
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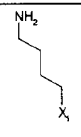
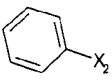
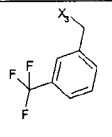
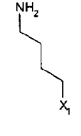
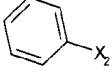
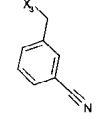
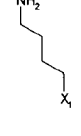
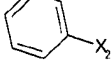
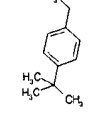
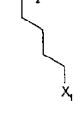
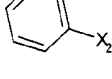
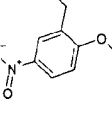
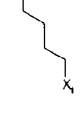
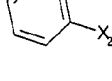
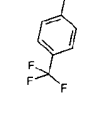
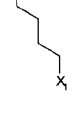
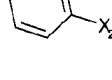
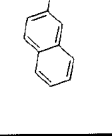
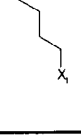
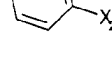
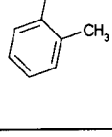
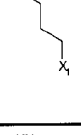
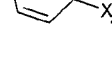
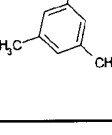
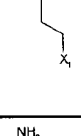
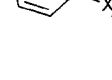
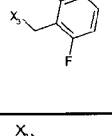
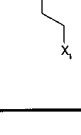

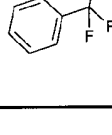
140				4.40	433.29
141				4.51	389.31
142				4.39	393.28
143				4.87	443.30
144				4.28	400.28
145				4.01	453.26
146				6.11	346.28
147				6.50	334.35
148				6.37	354.30
149				6.17	328.30

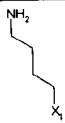
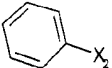
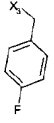
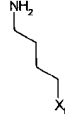
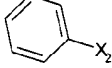
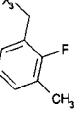
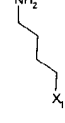
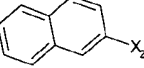
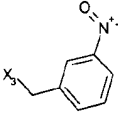
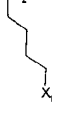
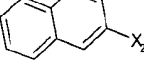
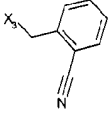
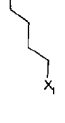
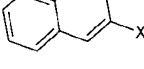
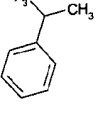
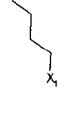
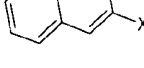
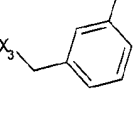
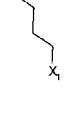
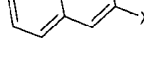
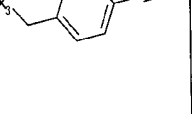
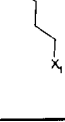
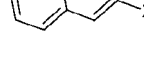
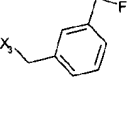
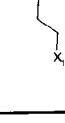
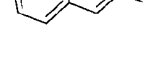
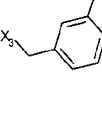
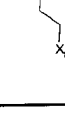
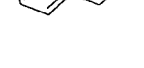
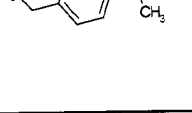
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152				3.52	383.19
153				3.58	413.18
154				7.99	523.30
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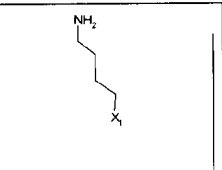
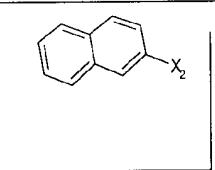
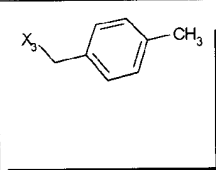
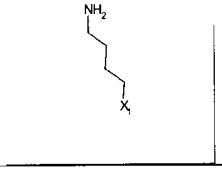
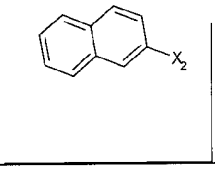
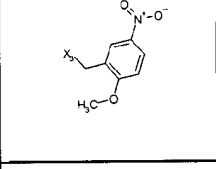
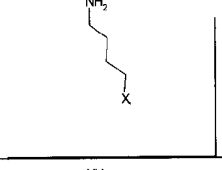
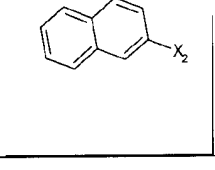
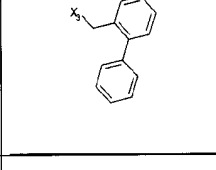
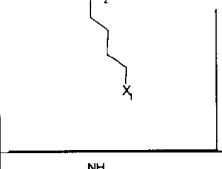
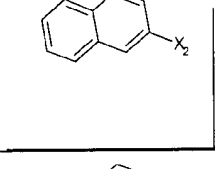
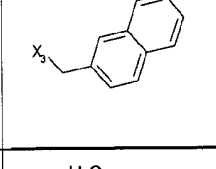
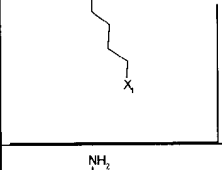
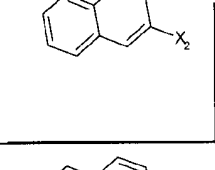
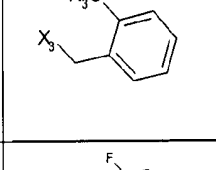
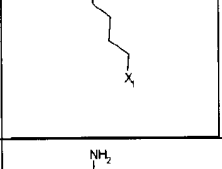
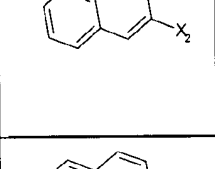
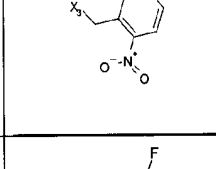
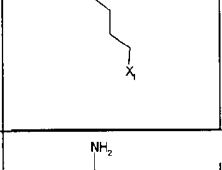
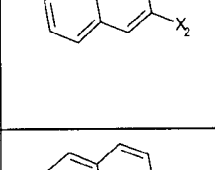
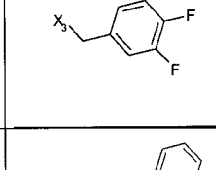
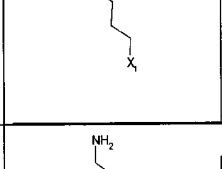
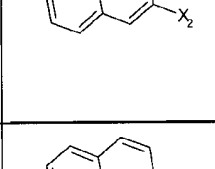
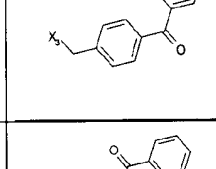
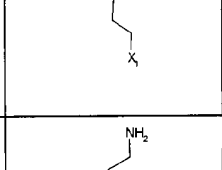
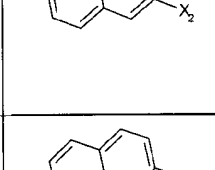
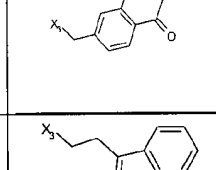
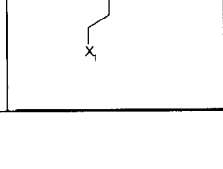
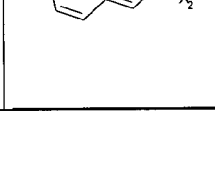
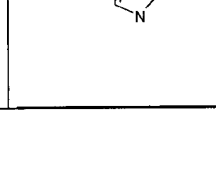


160				2.84	307.18
161				3.93	347.26
162				3.94	377.25
163				8.04	400.37
164				8.25	501.33
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166				3.87	389.25
167				3.50	353.21
168				3.94	403.18
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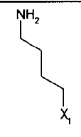
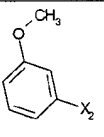
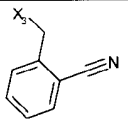
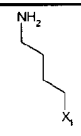
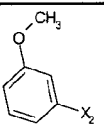
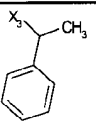
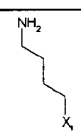
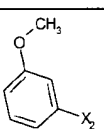
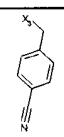
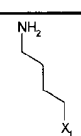
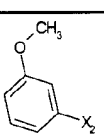
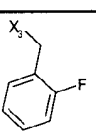
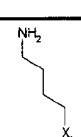
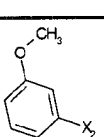
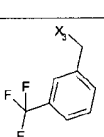
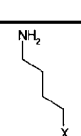
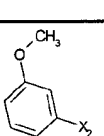
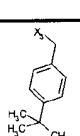
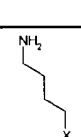
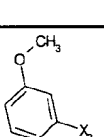
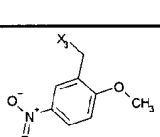
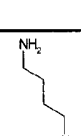
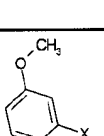
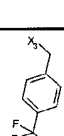
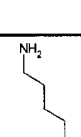
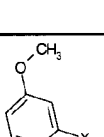
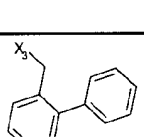
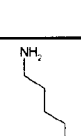
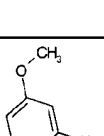
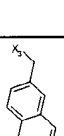
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171				3.12	399.18
172				3.90	339.20
173				4.07	369.16
174				4.08	384.10
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176				4.12	357.14
177				3.90	364.13
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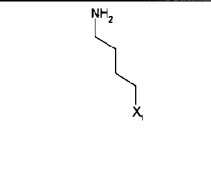
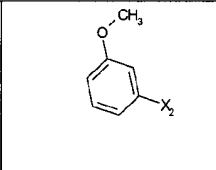
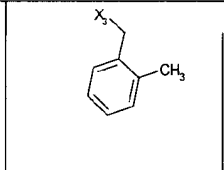
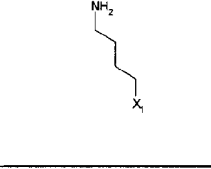
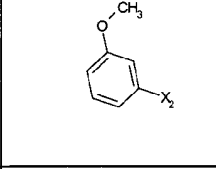
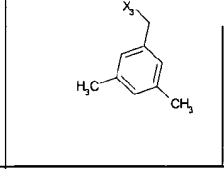
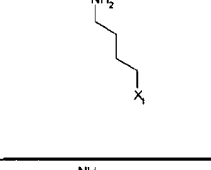
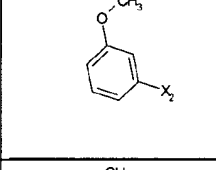
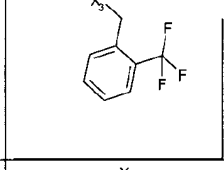
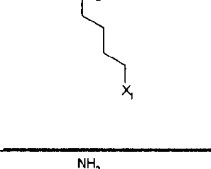
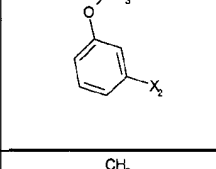
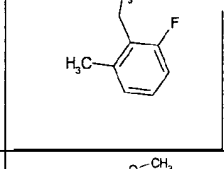
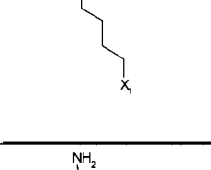
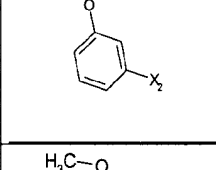
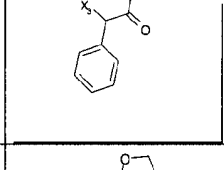
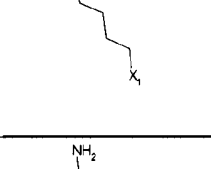
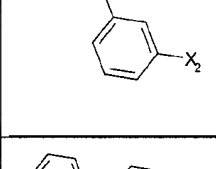
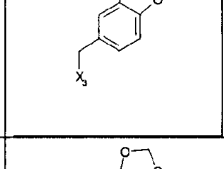
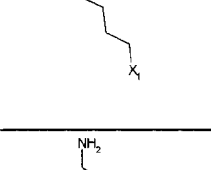
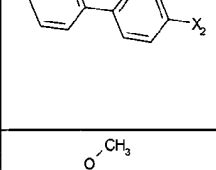
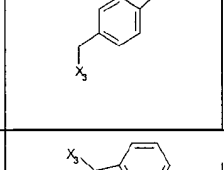
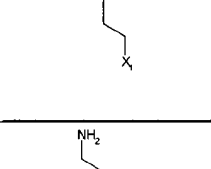
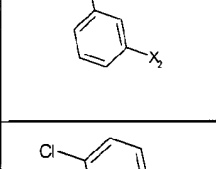
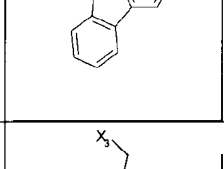
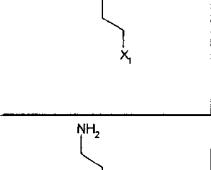
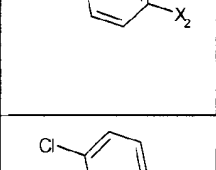
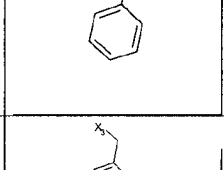
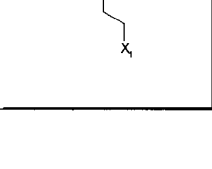
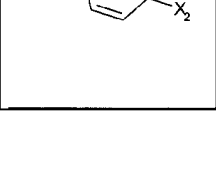
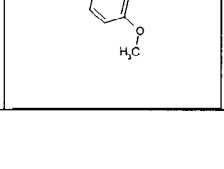
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184				4.58	407.08
185				4.51	389.12
186				4.22	353.17
187				4.51	367.17
188				4.00	402.06
189				4.47	407.25

190				4.14	357.29
191				4.31	371.14
192				7.96	433.90
193				7.80	413.93
194				8.01	402.95
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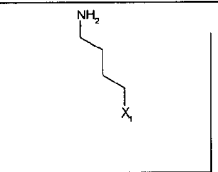
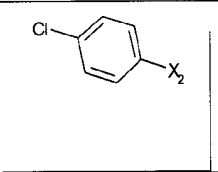
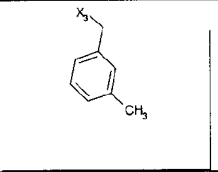
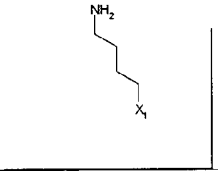
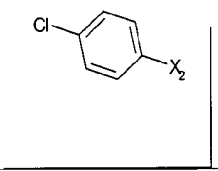
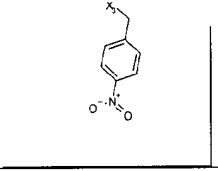
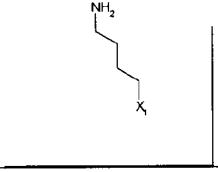
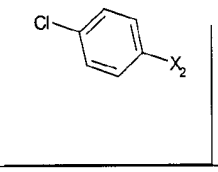
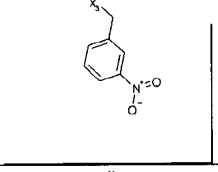
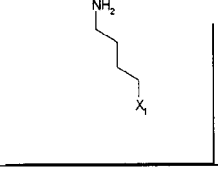
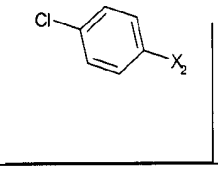
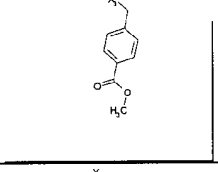
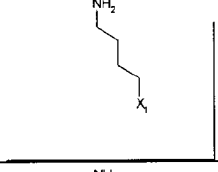
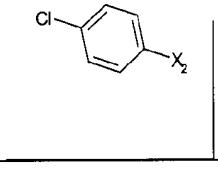
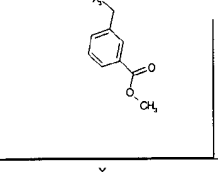
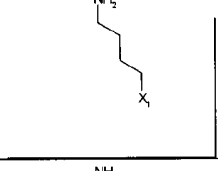
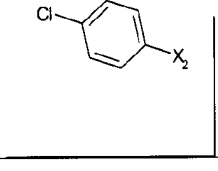
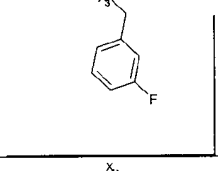
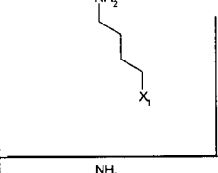
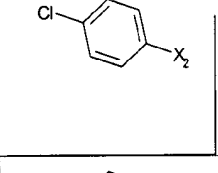
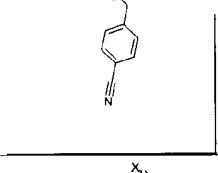
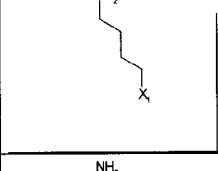
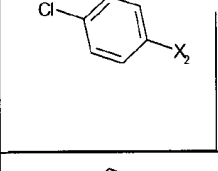
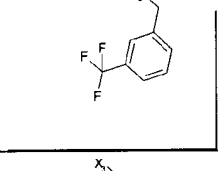
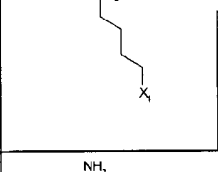
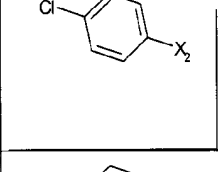
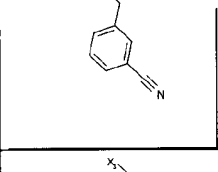
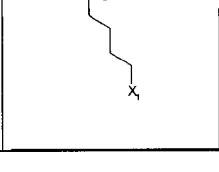
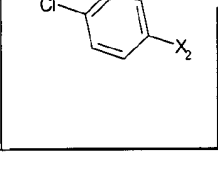
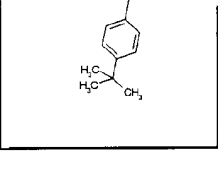
200				8.03	403.02
201				7.99	463.90
202				8.51	464.93
203				8.25	438.94
204				8.04	402.96
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206				8.13	442.95
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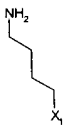
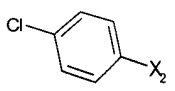
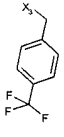
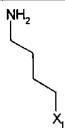
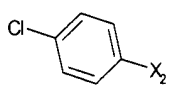
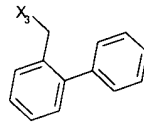

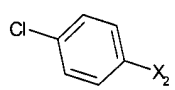
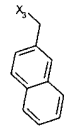
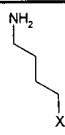
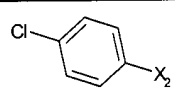
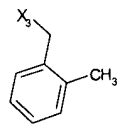
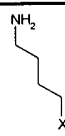
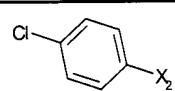
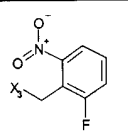
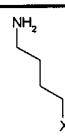
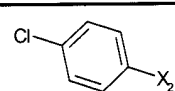
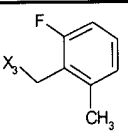
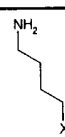
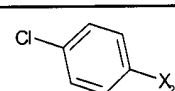
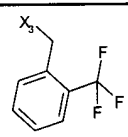

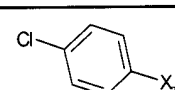
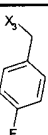
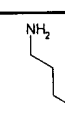
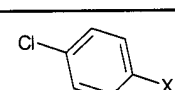
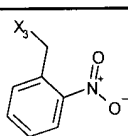
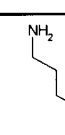
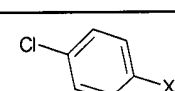
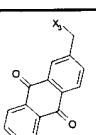
210				8.03	433.25
211				4.22	415.18
212				4.16	369.24
213				4.24	445.21
214				8.19	444.94
215				4.21	399.23
216				4.38	383.23
217				4.25	414.20
218				4.20	414.19
219				4.24	387.20

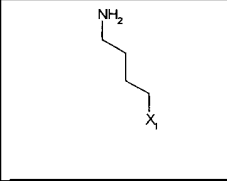
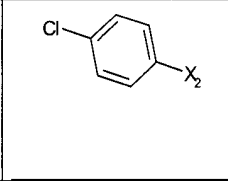
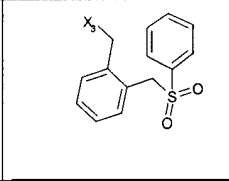
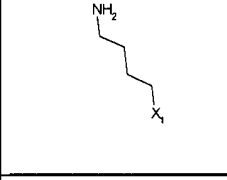
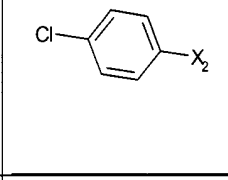
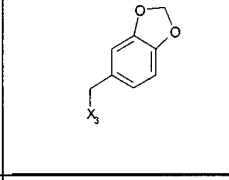
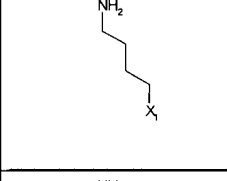
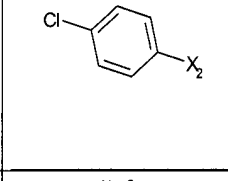
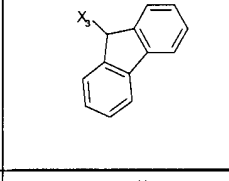
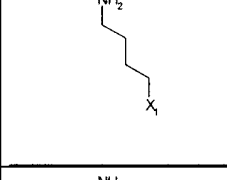
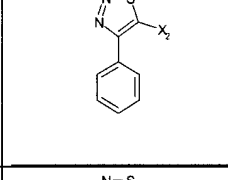
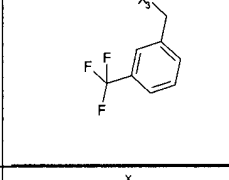
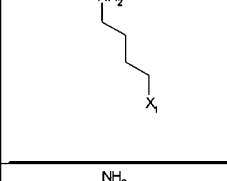
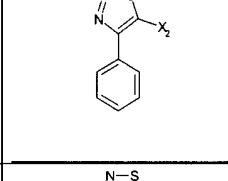
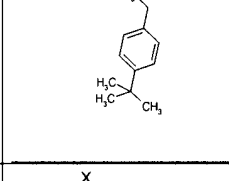
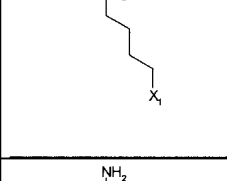
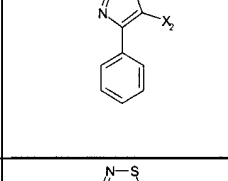
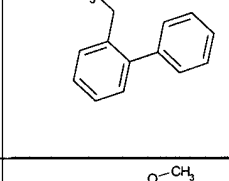
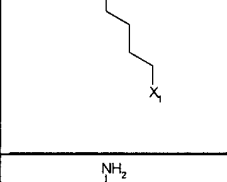
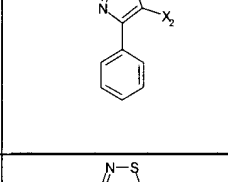
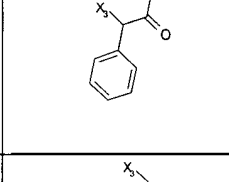
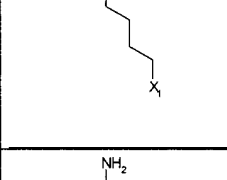
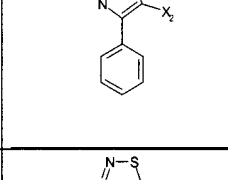
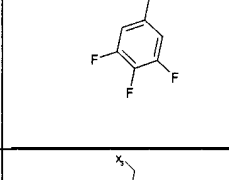
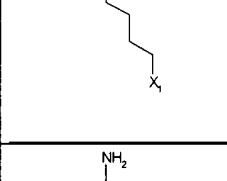
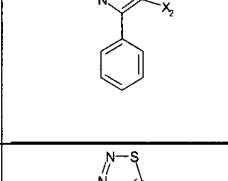
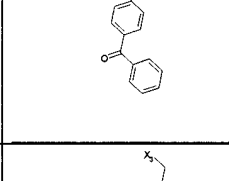
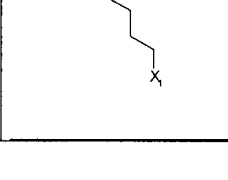
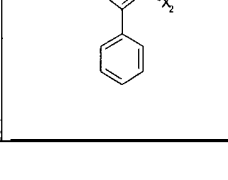
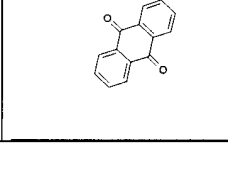
220				4.05	394.22
221				4.31	383.23
222				4.06	394.22
223				4.19	387.20
224				4.62	437.21
225				5.01	425.28
226				4.28	444.24
227				4.68	437.21
228				4.84	445.27
229				4.60	419.25


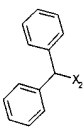
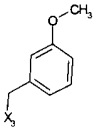

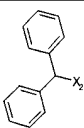
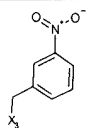

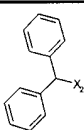
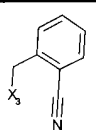

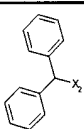
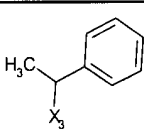

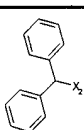
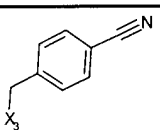

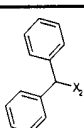
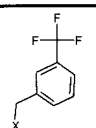

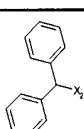
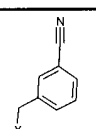

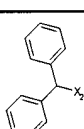
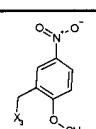
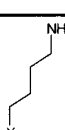
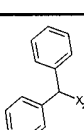
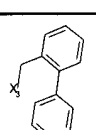
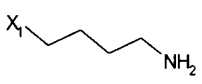
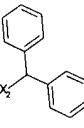
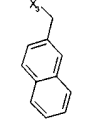
230				4.32	383.23
231				4.60	397.24
232				4.56	437.21
233				4.42	401.21
234				4.28	427.22
235				7.73	413.24
236				8.26	459.27
237				4.84	443.26
238				4.34	373.18
239				4.39	403.16


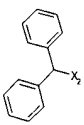
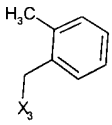

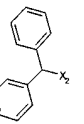
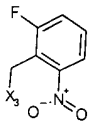

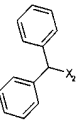
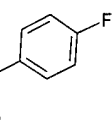

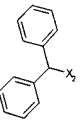
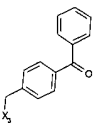

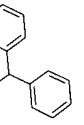
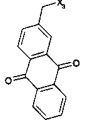

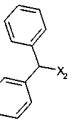
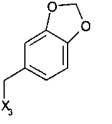
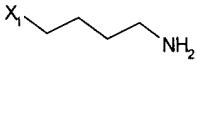
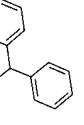
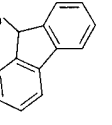

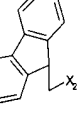
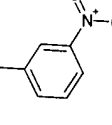

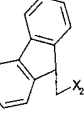
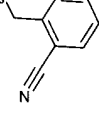

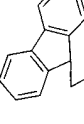
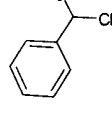



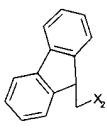
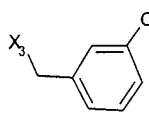

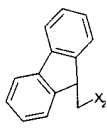
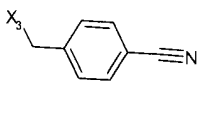

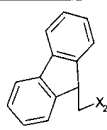
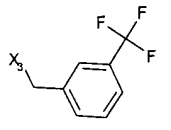

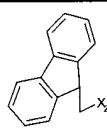
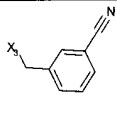

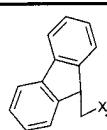
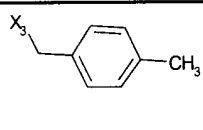

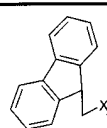
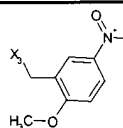

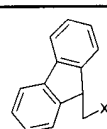
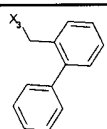

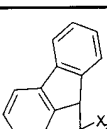
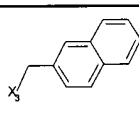

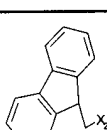
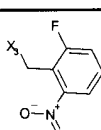

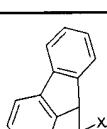
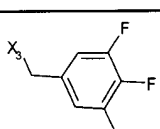
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241				4.44	418.14
242				4.40	418.14
243				4.37	431.17
244				4.38	431.18
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248				4.26	398.14
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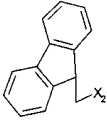
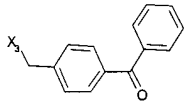
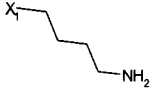
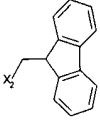
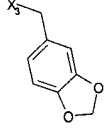

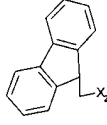
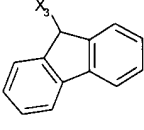

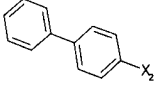
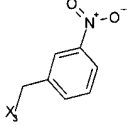

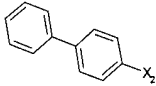
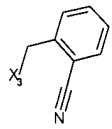

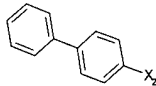
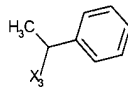
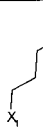
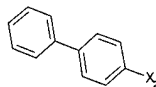
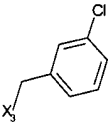

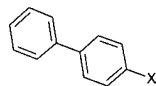
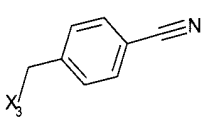
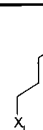
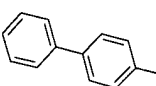
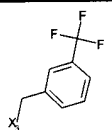

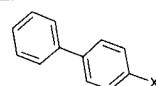
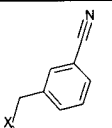
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252				4.77	423.18
253				4.50	387.18
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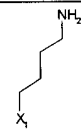
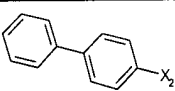
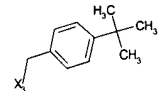
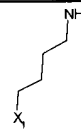
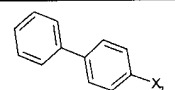
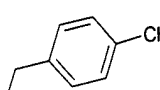
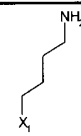
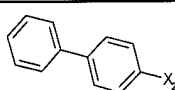
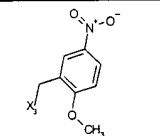
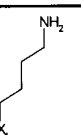
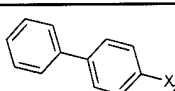
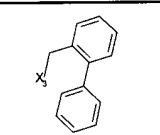
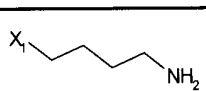
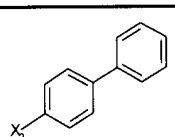
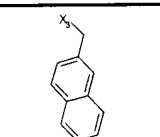
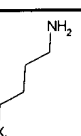
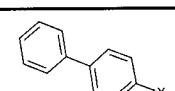
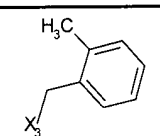
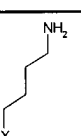
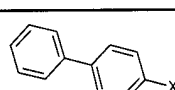
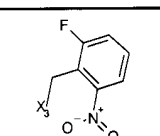
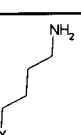
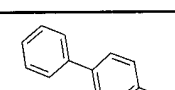
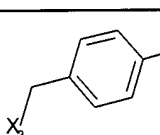
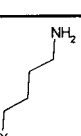
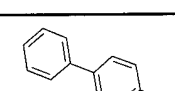
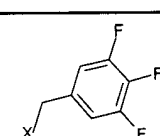
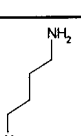
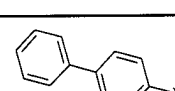
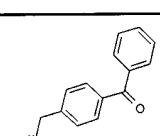
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262				5.00	447.19
263				4.93	491.19
264				5.29	479.27
265				5.13	499.24
266				4.62	481.21
267				4.83	477.18
268				4.93	527.24
269				4.97	553.19

270				8.10	458.96
271				8.13	473.89
272				7.98	453.96
273				8.19	442.97
274				7.97	453.95
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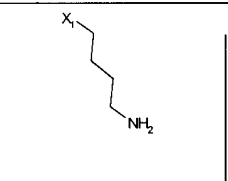
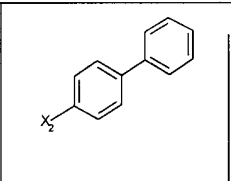
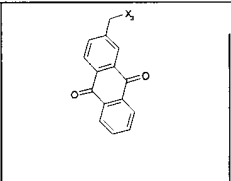
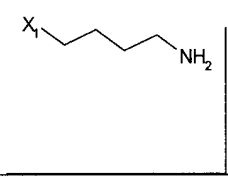
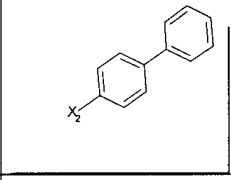
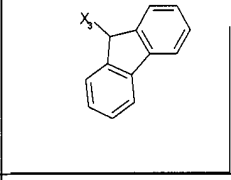
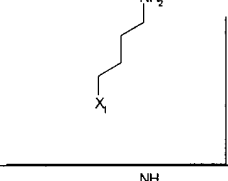
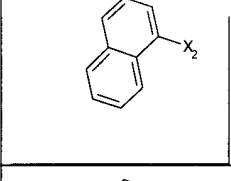
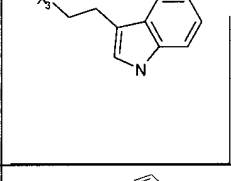
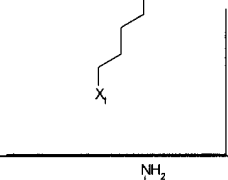
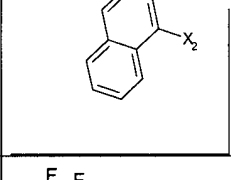
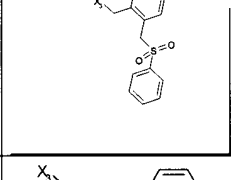
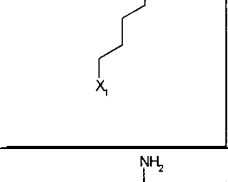
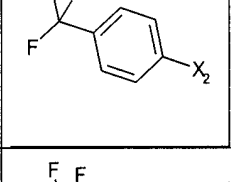
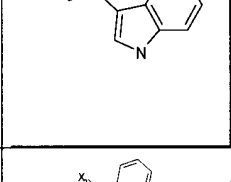
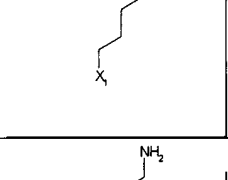
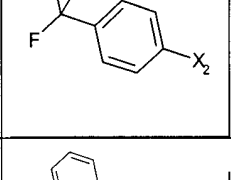
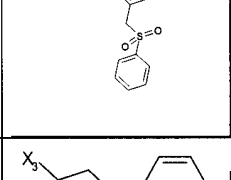
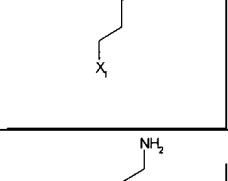
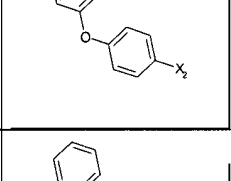
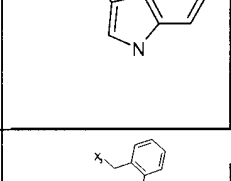
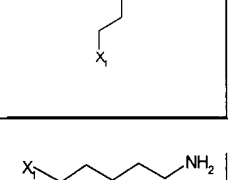
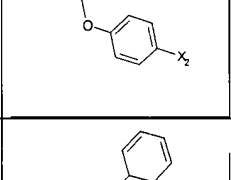
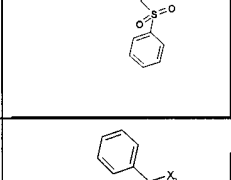
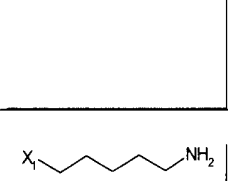
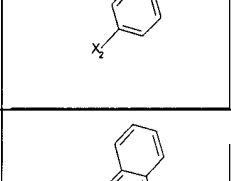
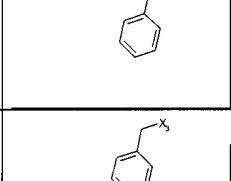
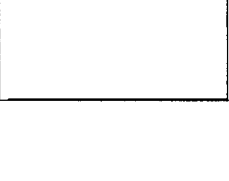
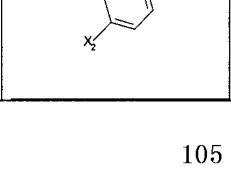
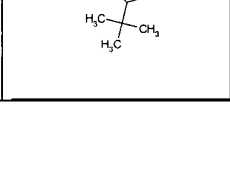
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281				8.07	491.89
282				8.14	446.92
283				8.46	532.87
284				8.51	558.83
285				8.17	473.28
286				8.71	502.91
287				8.33	485.89
288				8.21	465.93
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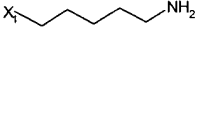
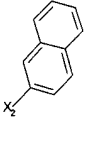
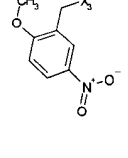
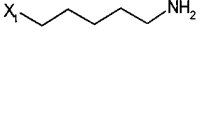
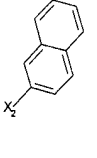
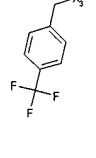
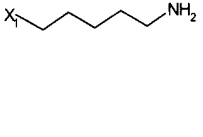
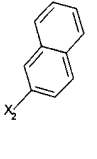
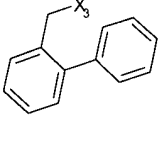
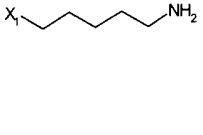
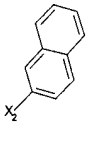
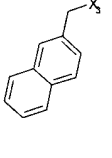
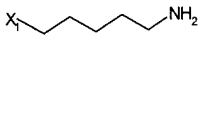
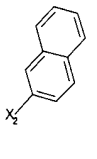
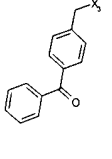
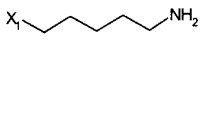
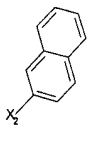
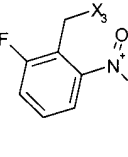
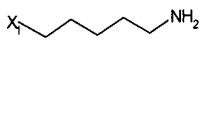
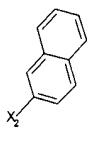
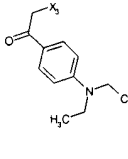
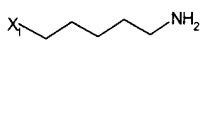
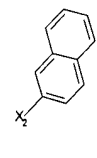
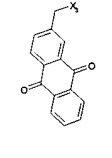
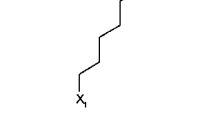
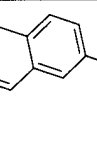
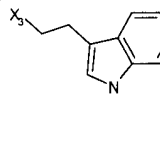
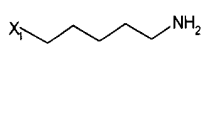
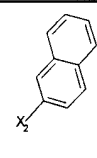
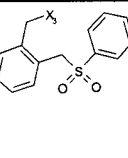
290				8.55	474.88
291				8.17	465.93
292				8.69	511.31
293				8.19	465.93
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296				8.92	516.91
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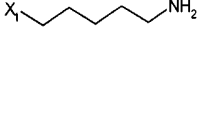
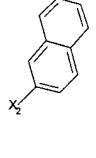
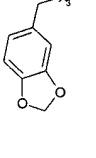
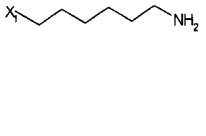
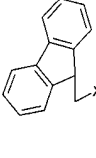
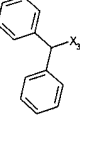
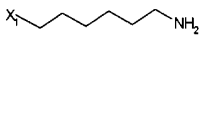
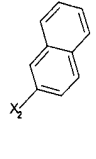
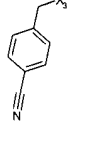
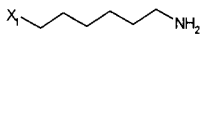
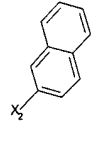
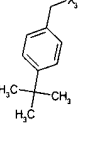
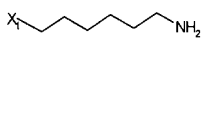
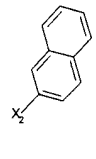
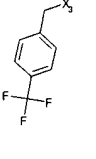
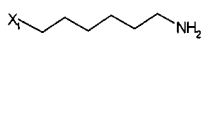
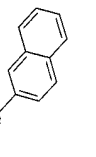
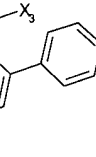
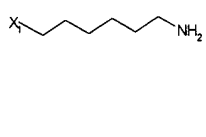
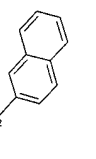
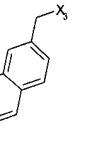
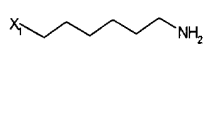
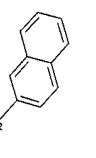
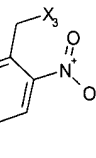
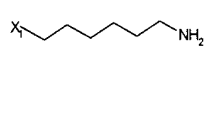
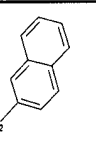
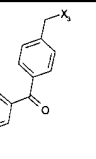
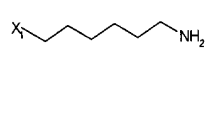
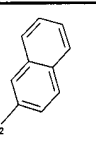
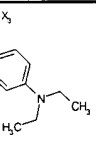
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306				8.41	448.90
307				8.08	439.94
308				8.54	482.90
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310				8.94	470.96
311				8.36	428.97
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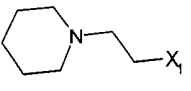
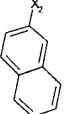
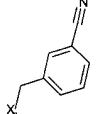
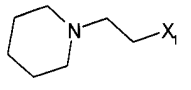
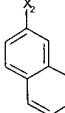
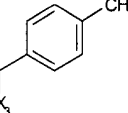
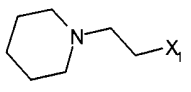
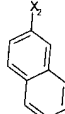
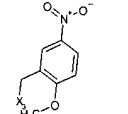
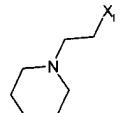
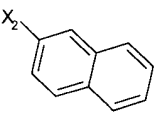
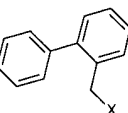
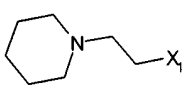
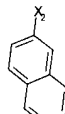
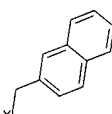
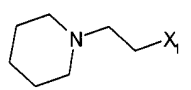
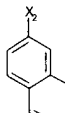
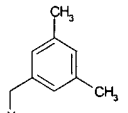
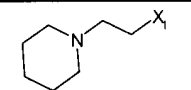
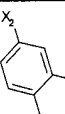
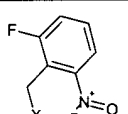
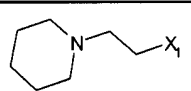
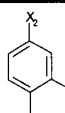
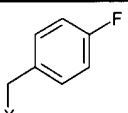
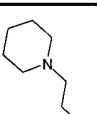
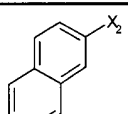
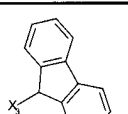
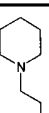
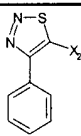
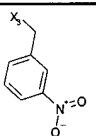


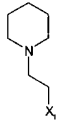
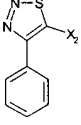
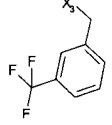
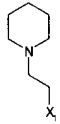
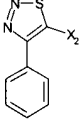
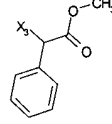
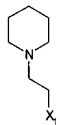
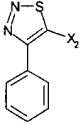
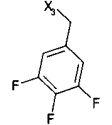
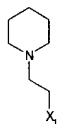
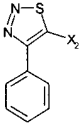
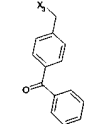
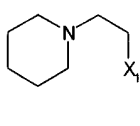
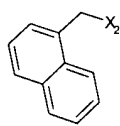
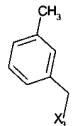
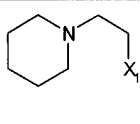
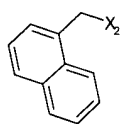
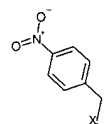
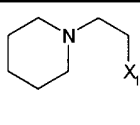
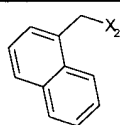
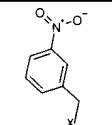
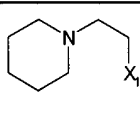
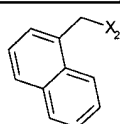
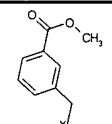
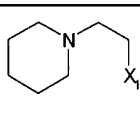
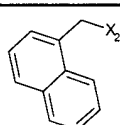
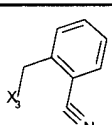
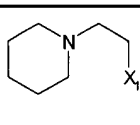
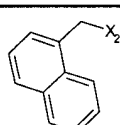
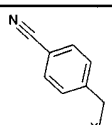
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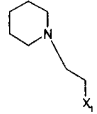
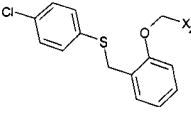
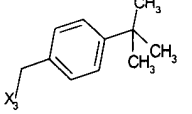
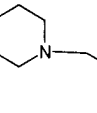
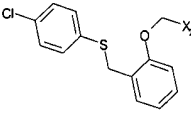
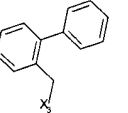
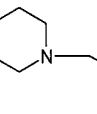
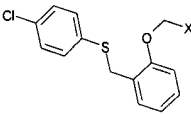
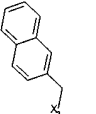
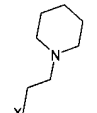
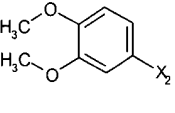
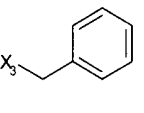
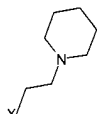
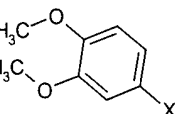
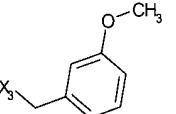
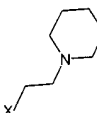
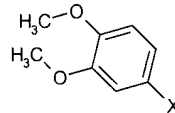
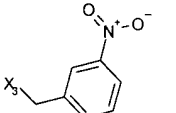
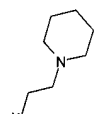
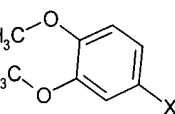
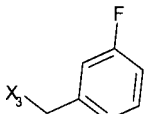
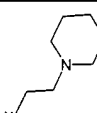
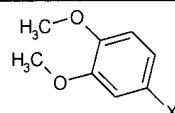
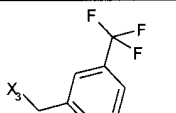
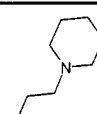
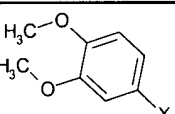
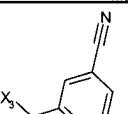
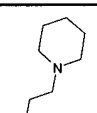
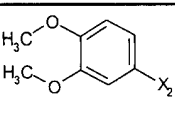
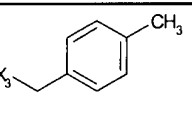
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341				8.78	493.36
342				8.14	442.29
343				8.94	473.36
344				8.61	485.31
345				8.79	493.36
346				8.55	467.32
347				8.24	480.30
348				8.61	521.35
349				8.60	516.40

350				8.61	547.30
351				8.40	470.30
352				8.48	571.30
353				8.23	461.28
354				7.56	429.26
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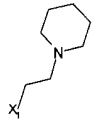
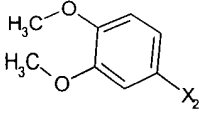
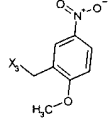
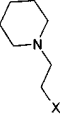
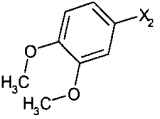
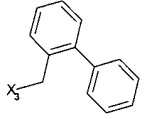
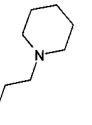
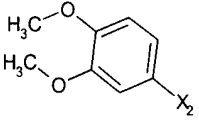
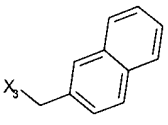
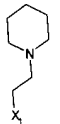
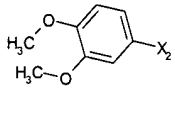
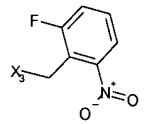
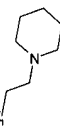
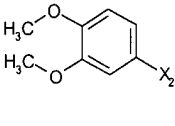
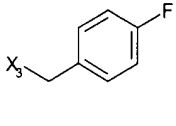
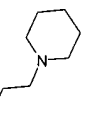
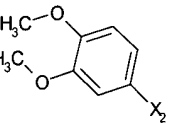
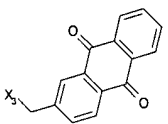
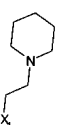
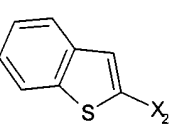
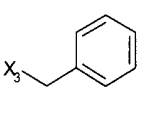
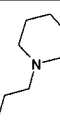
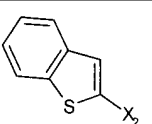
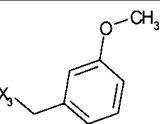
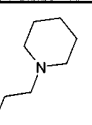
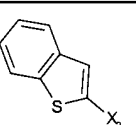
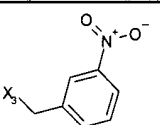
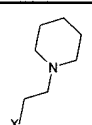
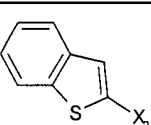
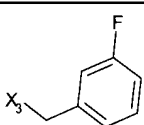
360				7.29	454.40
361				7.59	443.38
362				7.50	504.41
363				8.07	505.42
364				7.78	479.43
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366				7.45	492.38
367				7.55	447.39
368				8.18	503.46
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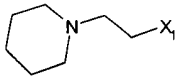
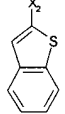
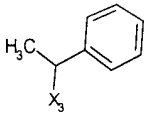
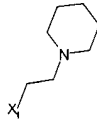
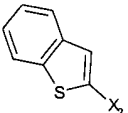
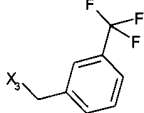
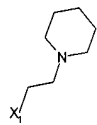
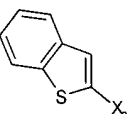
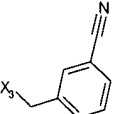

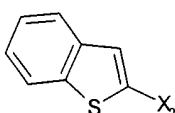
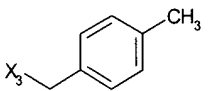
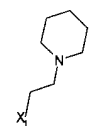
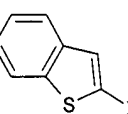
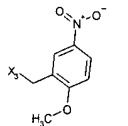
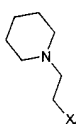
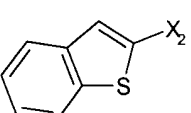
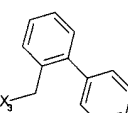
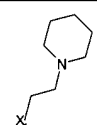
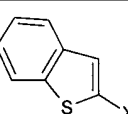
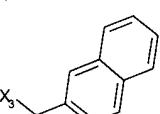
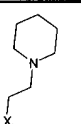
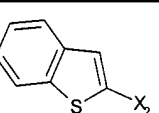
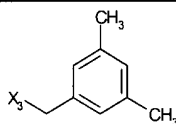
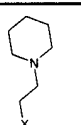
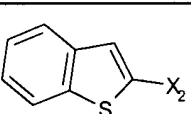
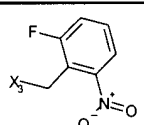
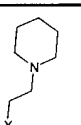
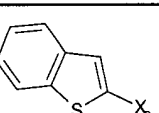
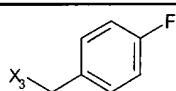
370				5.18	531.21
371				4.85	521.22
372				5.07	517.21
373				5.17	567.23
374				7.56	457.26
375				10.90	488.31
376				7.48	488.21
377				7.38	501.23
378				12.40	465.28
379				7.25	468.24

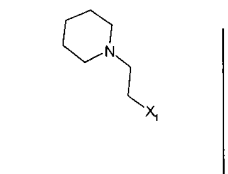
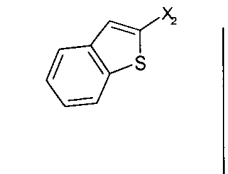
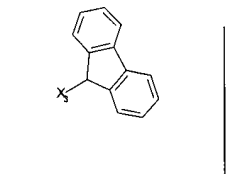
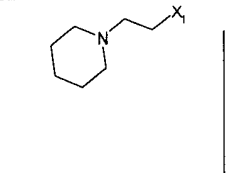
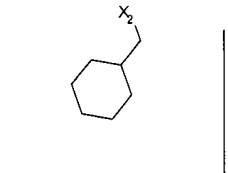
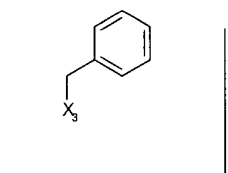
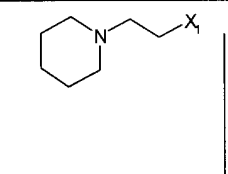
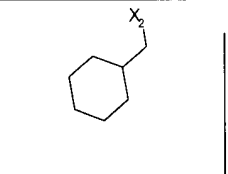
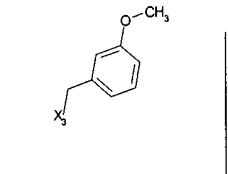
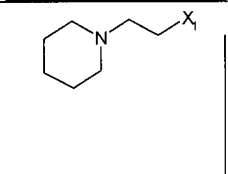
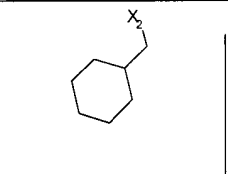
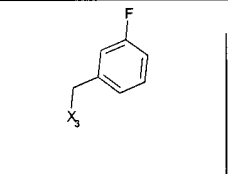
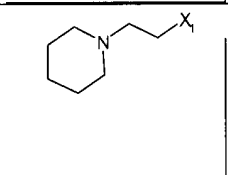
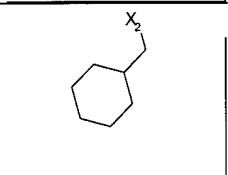
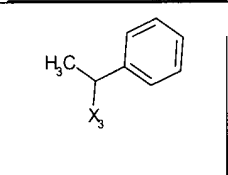
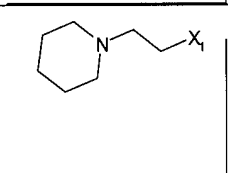
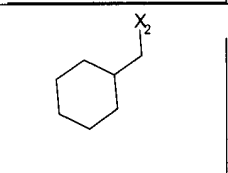
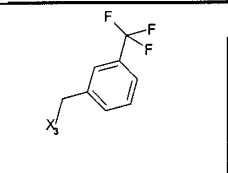
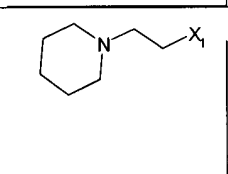
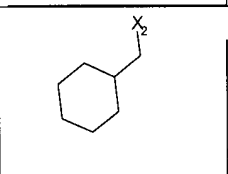
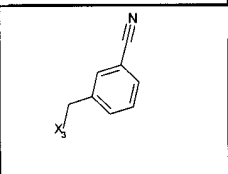
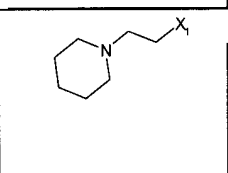
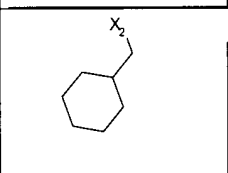
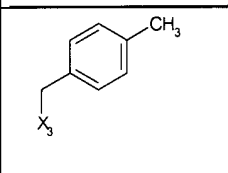
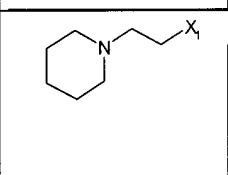
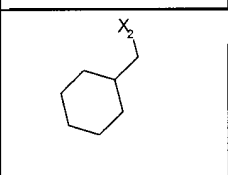
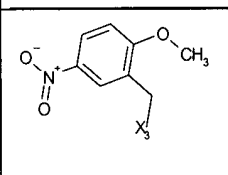
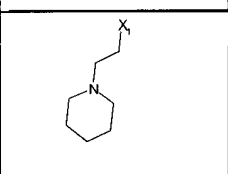
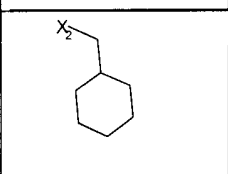
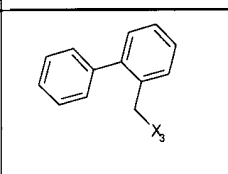
380				7.30	468.24
381				8.12	519.26
382				7.84	493.34
383				7.48	457.26
384				7.40	506.23
385				11.16	511.31
386				7.42	488.23
387				7.89	573.20
388				8.98	623.35
389				9.29	633.34

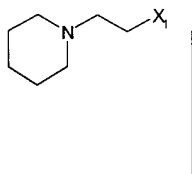
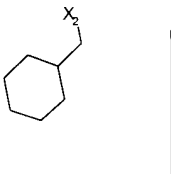
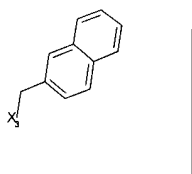
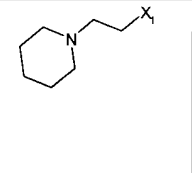
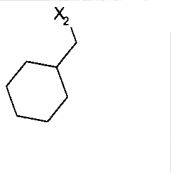
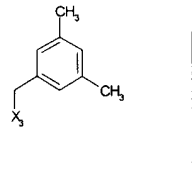
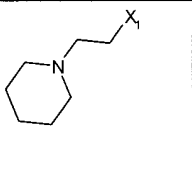
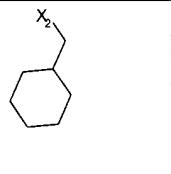
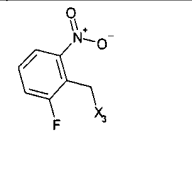
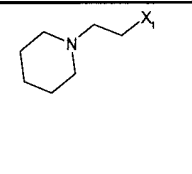
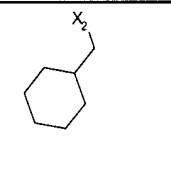
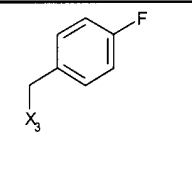
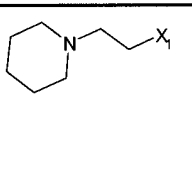
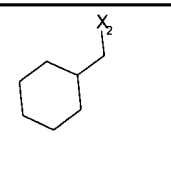
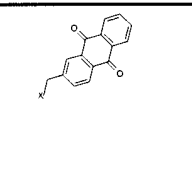
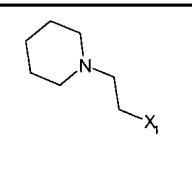
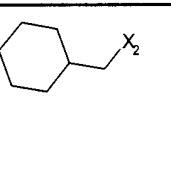
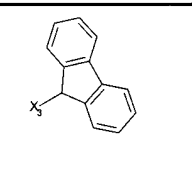
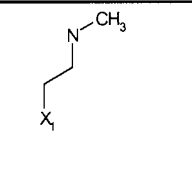
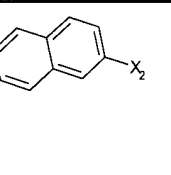
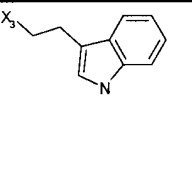
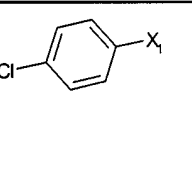
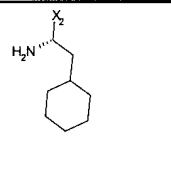
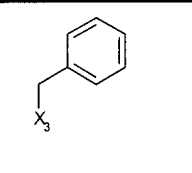
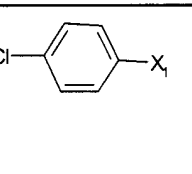
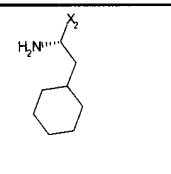
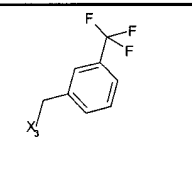
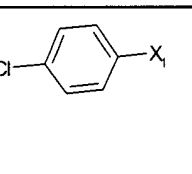
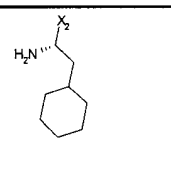
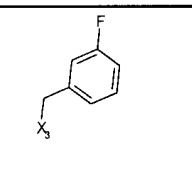
390				9.77	621.41
391				9.52	641.39
392				9.28	615.35
393				6.95	439.28
394				6.86	469.39
395				6.91	484.42
396				7.01	457.29
397				7.45	507.26
398				6.76	464.41
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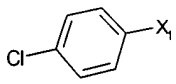
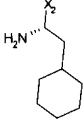
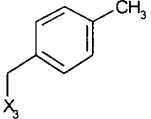
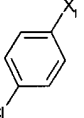
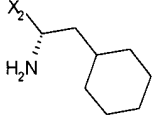
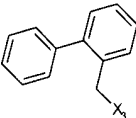
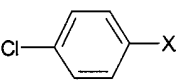
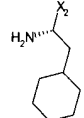
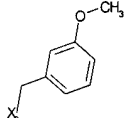
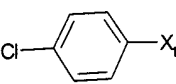
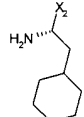
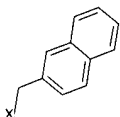
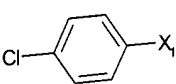
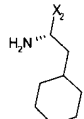
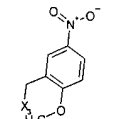
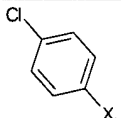
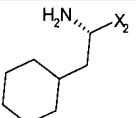
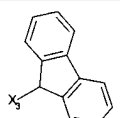
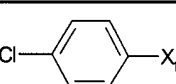
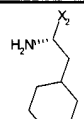
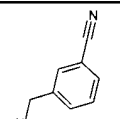
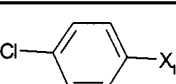
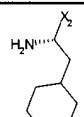
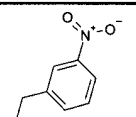
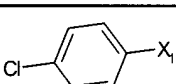
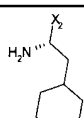
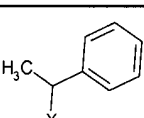
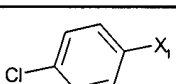
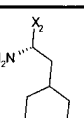
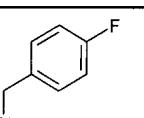


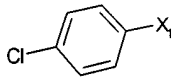
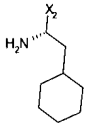
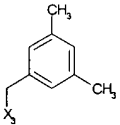
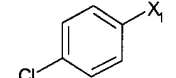
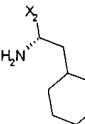
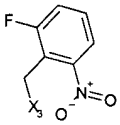
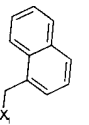
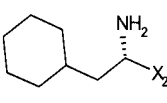
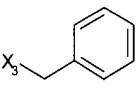
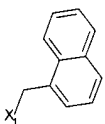
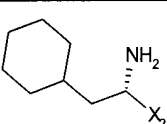
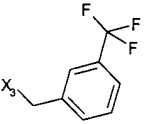
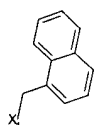
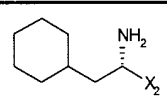
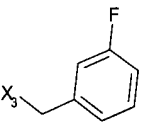
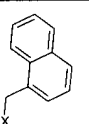
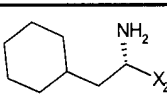
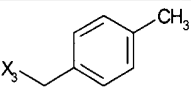
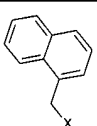
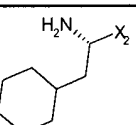
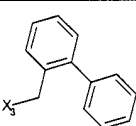
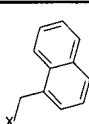
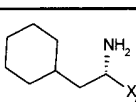
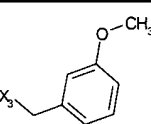
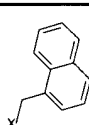
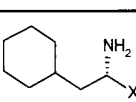
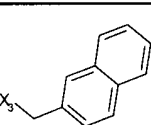
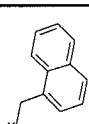
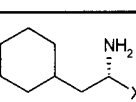
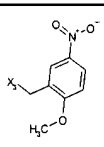
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406				7.67	435.22
407				7.49	465.36
408				7.58	480.37
409				7.70	453.27

410				7.69	449.38
411				8.16	503.23
412				7.40	460.35
413				7.71	449.33
414				7.60	510.35
415				8.16	511.37
416				7.94	485.38
417				7.99	463.40
418				7.59	498.34
419				7.68	453.36

420				8.38	509.41
421				7.43	399.31
422				7.30	429.44
423				7.46	417.33
424				7.49	413.45
425				7.92	467.31
426				7.19	424.45
427				7.48	413.40
428				7.39	474.44
429				8.01	475.47

430				7.70	449.45
431				7.79	427.46
432				7.37	462.42
433				7.45	417.43
434				7.79	529.46
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436				8.10	428.20
437				8.97	427.28
438				9.02	495.23
439				8.62	445.21

440				8.68	441.31
441				9.07	503.39
442				8.34	457.36
443				8.84	477.40
444				8.35	502.38
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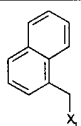
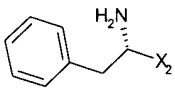
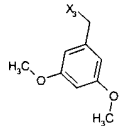
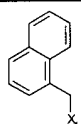
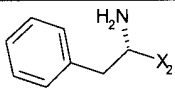
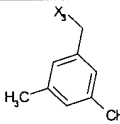
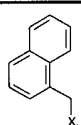
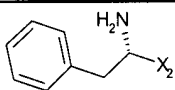
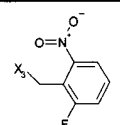
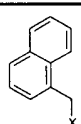
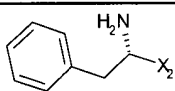
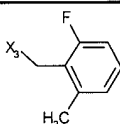
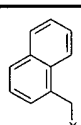
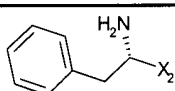
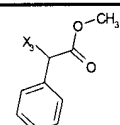
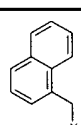
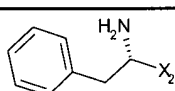
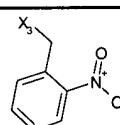
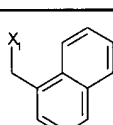
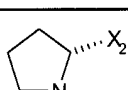
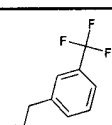
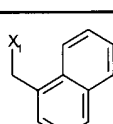
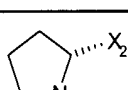
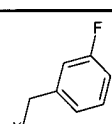
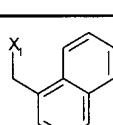
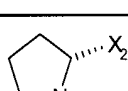
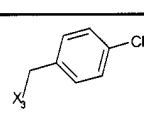
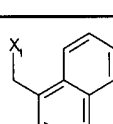
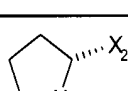
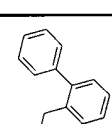
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456				9.33	533.42
457				8.55	487.42
458				9.01	507.45
459				8.53	532.43

460				8.88	587.37
461				9.53	531.47
462				8.34	482.43
463				8.48	502.46
464				8.91	471.44
465				9.24	485.47
466				8.58	520.40
467				5.49	451.23
468				5.81	519.22
469				5.52	469.23

470				5.67	465.25
471				6.05	527.28
472				5.46	481.25
473				5.83	501.27
474				5.43	526.25
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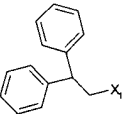
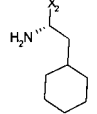
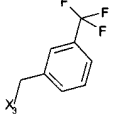
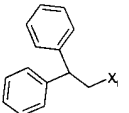
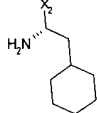
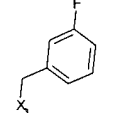
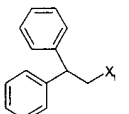
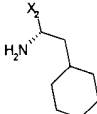
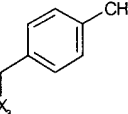
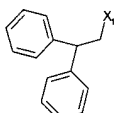
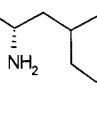
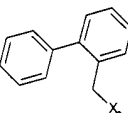
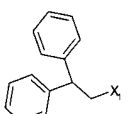
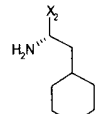
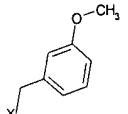
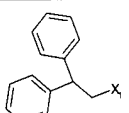
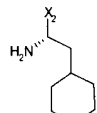
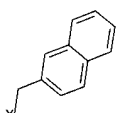
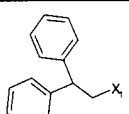
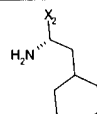
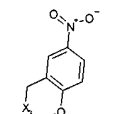
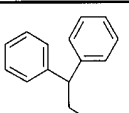
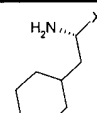
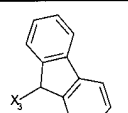
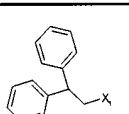
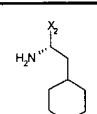
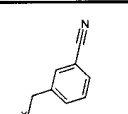
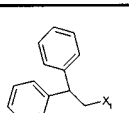
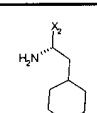
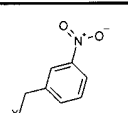


480				5.26	476.24
481				5.79	519.23
482				5.68	465.25
483				5.25	476.25
484				5.25	476.25
485				5.39	496.23
486				5.71	485.21
487				5.66	465.25
488				5.51	469.24
489				5.65	465.24

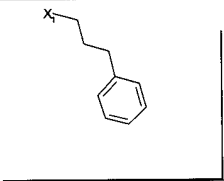
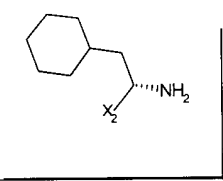
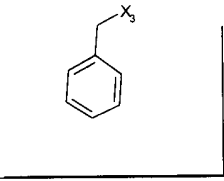
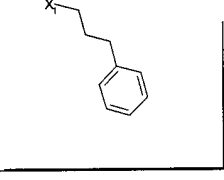
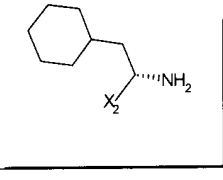
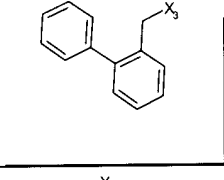
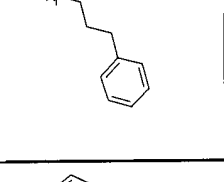
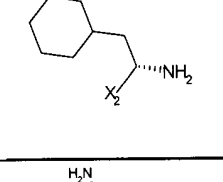
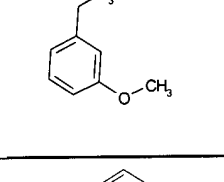
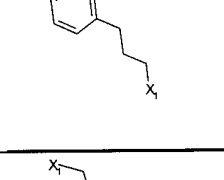
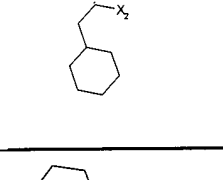
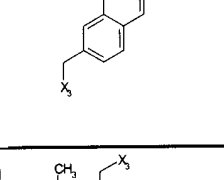
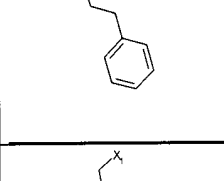
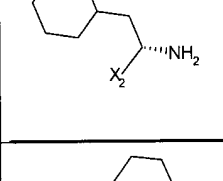
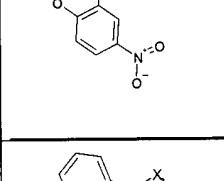
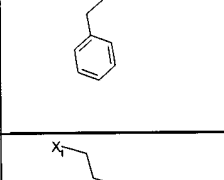
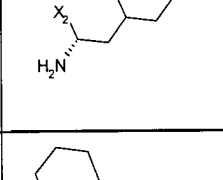
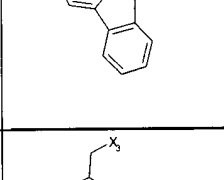
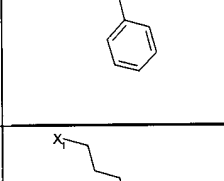
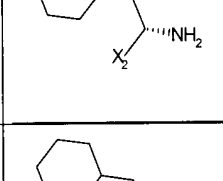
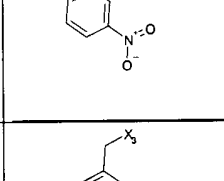
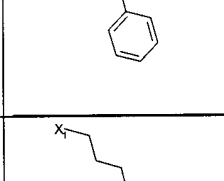
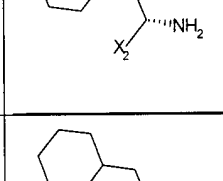
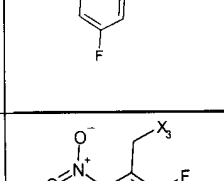
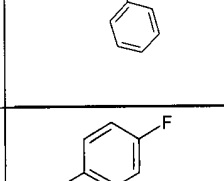
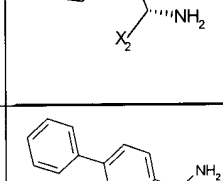
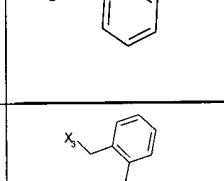
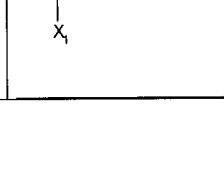
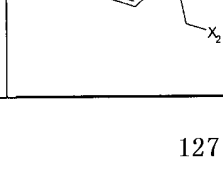
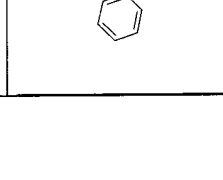
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491				5.91	479.28
492				5.38	514.23
493				5.70	483.28
494				5.53	509.26
495				5.39	496.24
496				9.20	469.12
497				8.87	419.10
498				9.09	415.14
499				9.55	477.18

500				8.82	431.14
501				9.25	451.15
502				8.85	476.15
503				8.81	446.11
504				8.75	459.14
505				9.18	531.14
506				8.61	426.13
507				9.21	469.11
508				8.64	426.13
509				8.64	426.13

510				8.77	446.11
511				9.01	415.14
512				8.74	464.11
513				9.11	433.14
514				9.77	457.21
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516				8.77	446.11
517				9.09	455.09
518				9.25	505.17
519				9.56	497.37

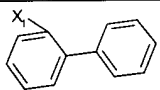
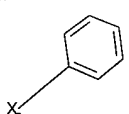
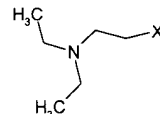
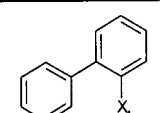
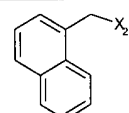
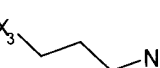
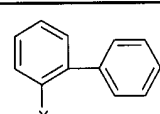
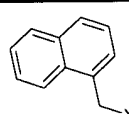
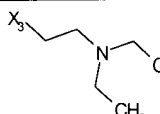
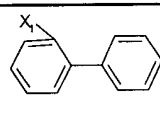
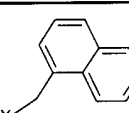
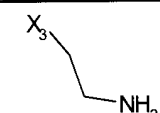
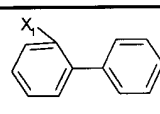
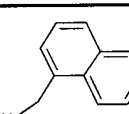
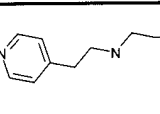
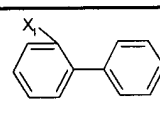
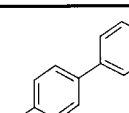
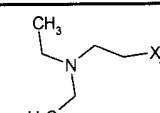
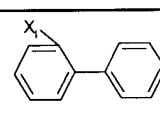
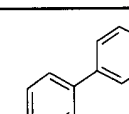

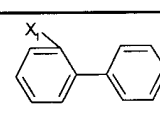
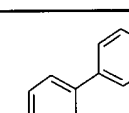
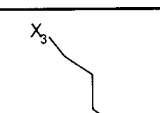
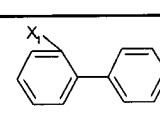
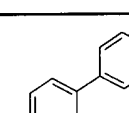
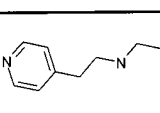
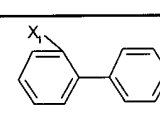
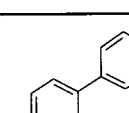
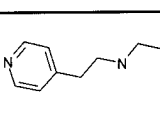
520				9.51	565.28
521				9.11	515.32
522				9.15	511.44
523				9.58	573.42
524				8.83	527.44
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526				8.83	572.42
527				9.78	571.48
528				8.61	522.47
529				8.80	542.45

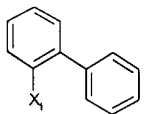
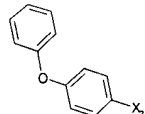
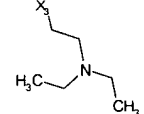
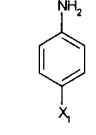
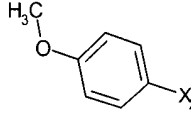
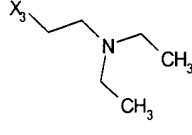
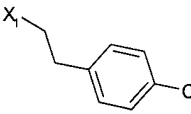
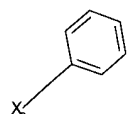
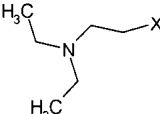
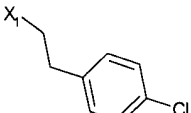
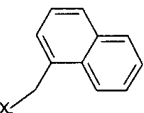
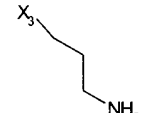
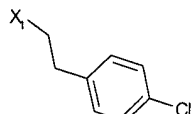
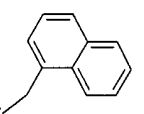
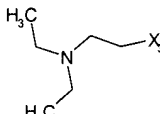
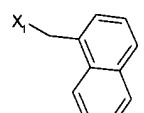
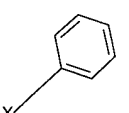
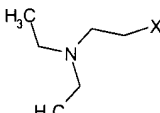
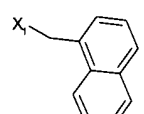
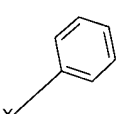
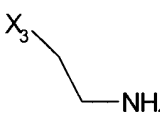
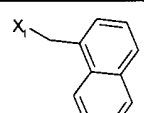
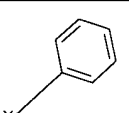
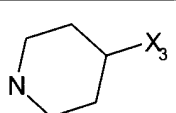
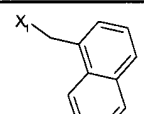
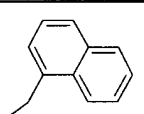
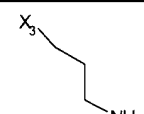
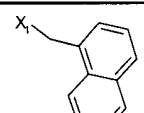
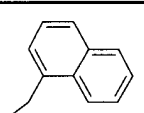
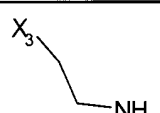
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534				4.74	401.2
535				4.67	387.2
536				5.43	455.18
537				5.46	437.21
538				8.40	461.29
539				7.63	432.24

540				8.62	435.39
541				9.46	511.45
542				8.63	465.43
543				9.08	485.44
544				8.59	510.40
545				9.40	509.43
546				8.54	480.41
547				8.62	453.41
548				8.52	498.39
549				9.51	570.89

550				9.21	544.90
551				9.51	568.87
552				3.70	325.20
553				8.09	520.34
554				8.50	479.30
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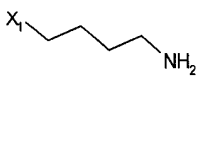
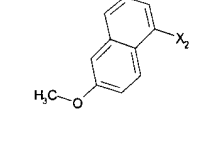
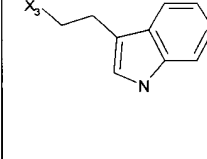
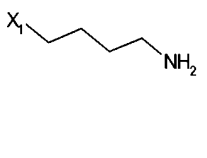
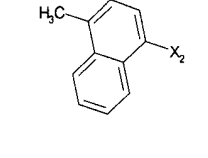
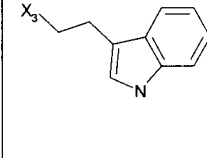
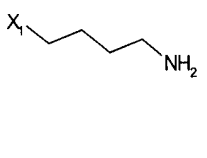
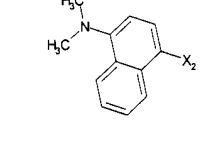
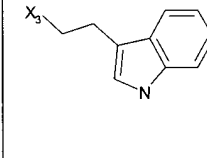
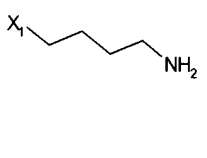
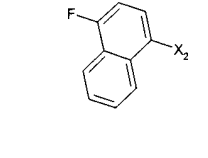
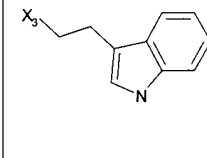
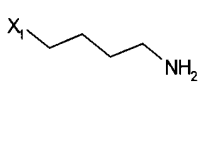
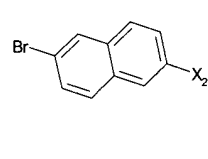
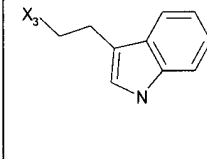
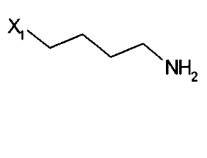
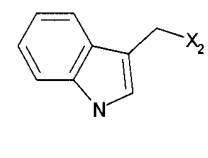
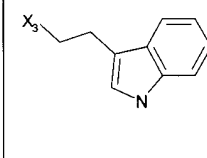
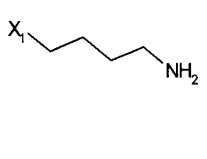
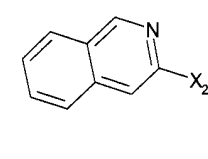
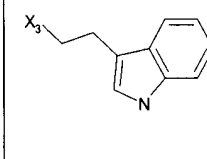
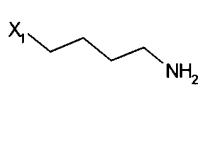
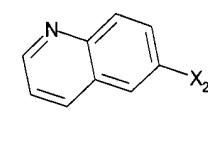
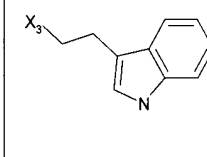
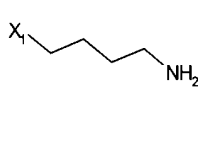
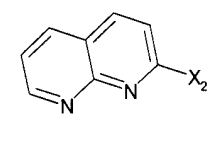
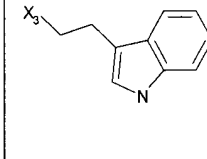
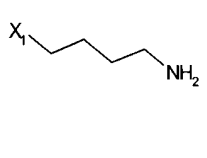
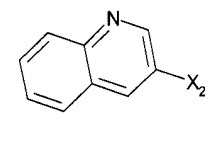
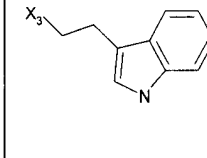
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562				8.70	493.30
563				8.80	437.29
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565				9.50	505.20
566				8.74	462.93
567				9.10	463.30
568				8.40	554.20
569				8.38	554.33

570				9.40	521.20
571				6.90	398.20
572				8.68	429.30
573				8.72	437.26
574				9.05	479.34
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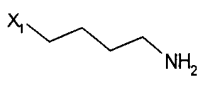
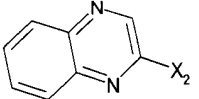
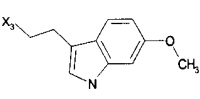
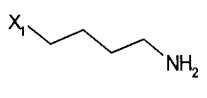
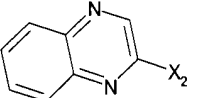
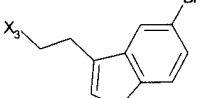
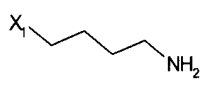
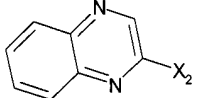
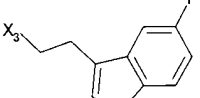
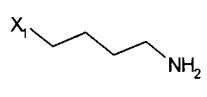
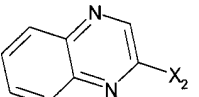
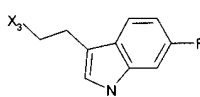
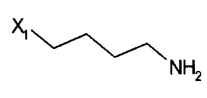
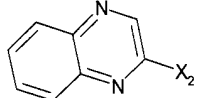
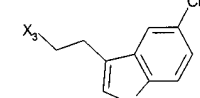
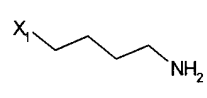
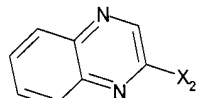
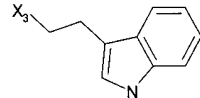
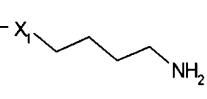
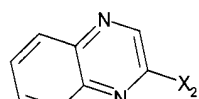
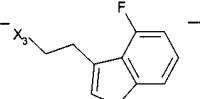
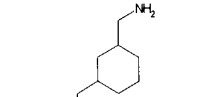
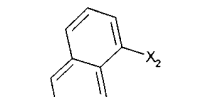
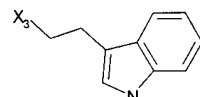
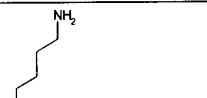
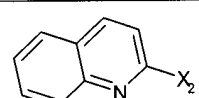
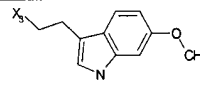
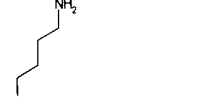
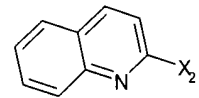
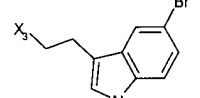
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585				7.90	482.20
586				8.35	448.21
587				8.22	460.08
588				8.22	448.13
589				7.81	435.19

590				8.90	597.10
591				8.30	496.20
592				8.30	460.00
593				8.30	486.20
594				7.98	437.15
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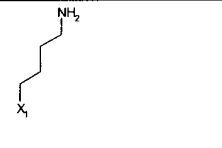
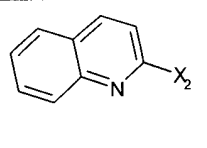
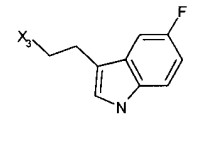
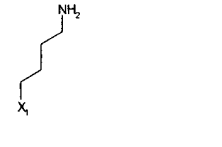
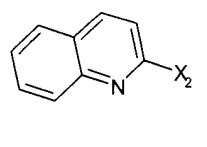
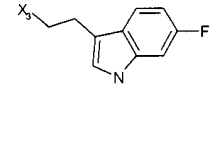
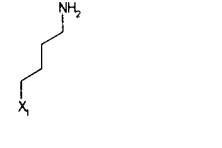
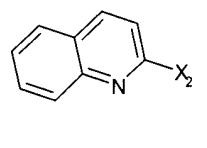
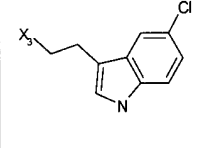
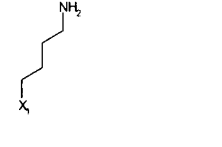
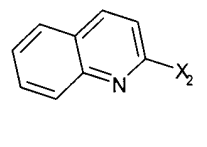
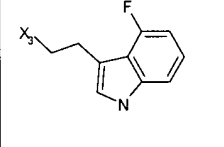
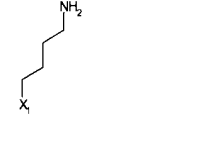
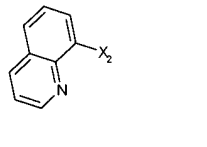
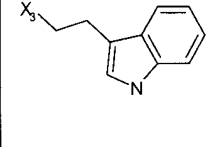
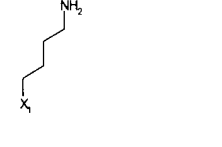
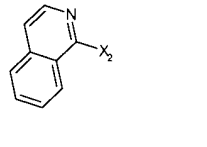
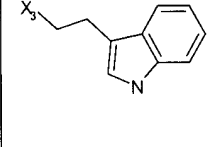
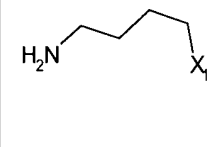
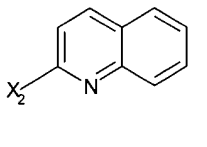
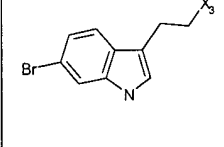
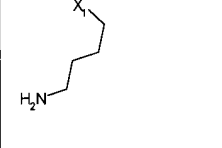
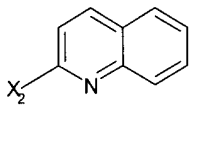
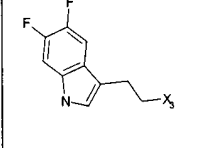
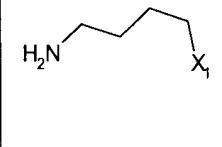
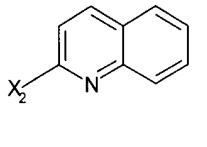
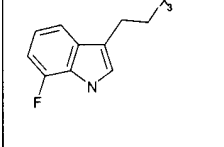
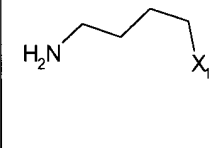
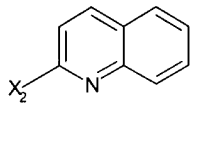
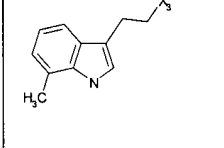
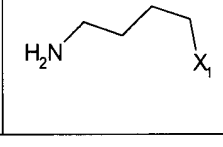
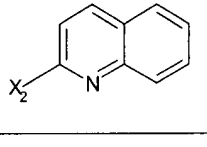
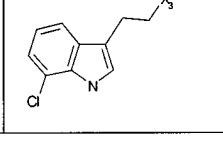
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603				7.88	410.16
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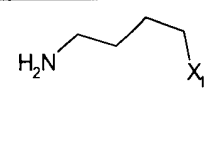
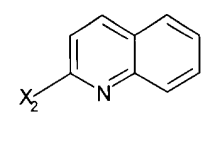
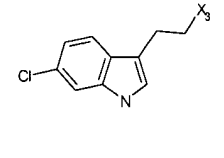
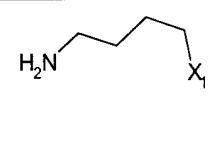
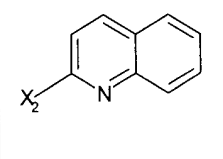
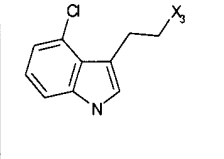
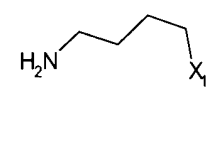
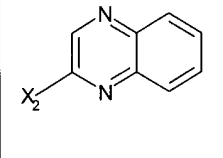
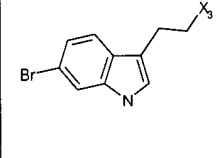
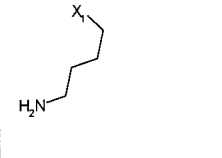
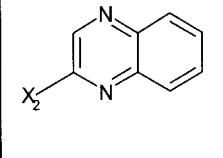
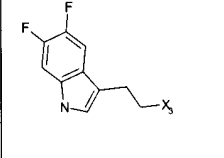
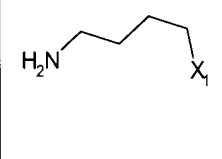
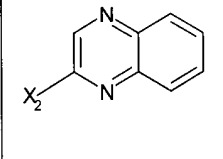
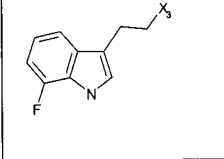
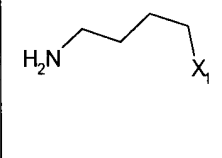
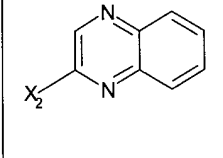
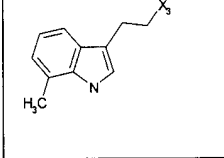
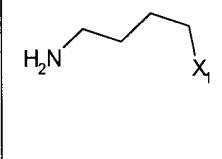
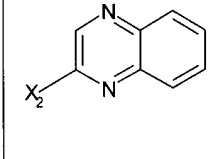
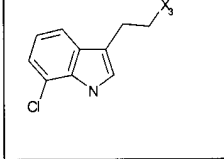
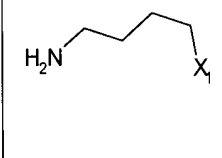
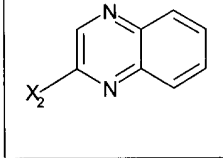
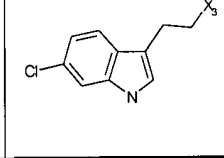
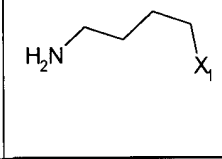
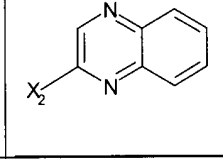
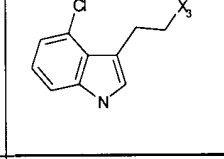
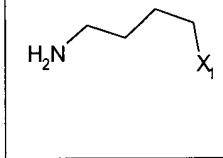
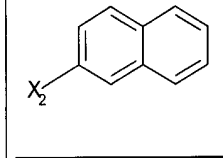
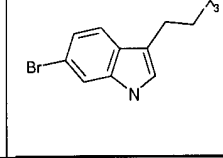
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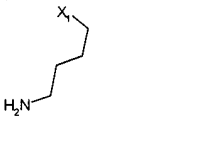
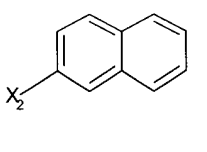
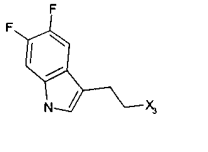
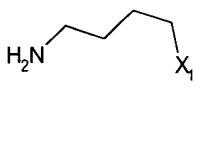
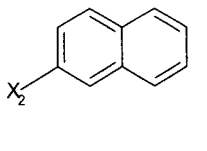
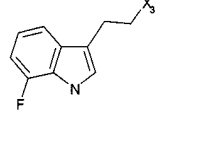
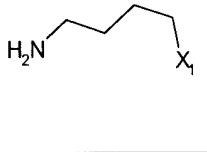
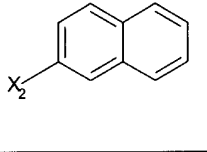
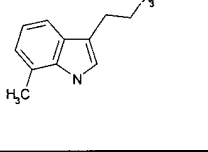
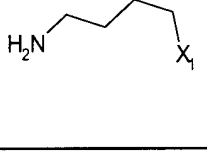
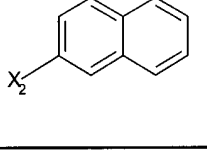
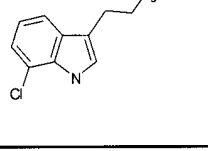
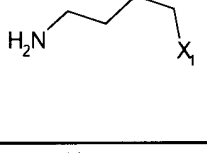
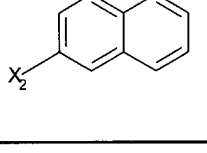
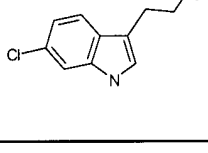
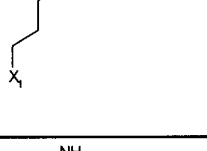
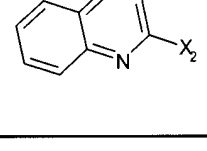
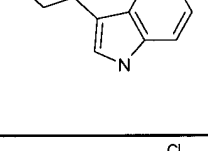
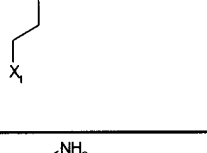
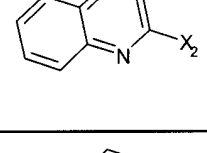
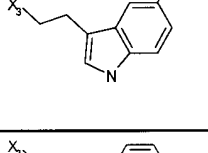
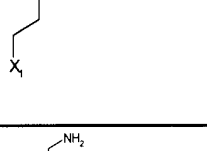
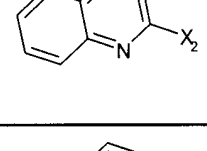
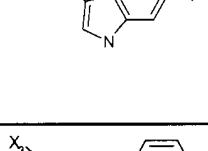
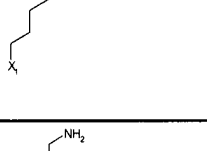
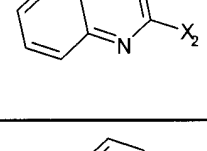
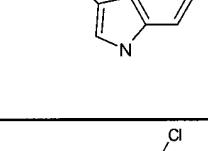
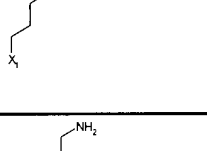
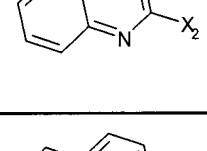
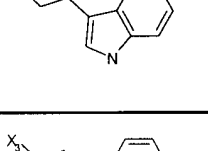
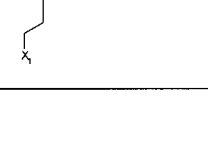
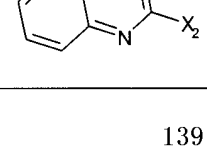
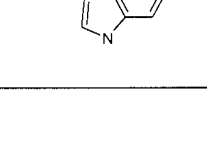
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621				8.60	410.10
622				8.10	431.10
623				8.50	479.10
624				8.40	520.10
625				8.10	472.20
626				8.10	472.10
627				8.50	476.20
628				8.30	460.10
629				8.43	460.19
630				8.20	460.10

631				8.19	474.11
632				8.60	522.07
633				8.38	462.16
634				8.38	462.18
635				8.40	478.10
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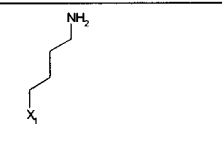
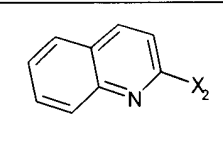
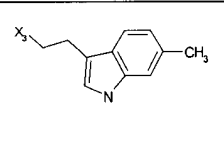
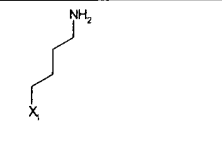
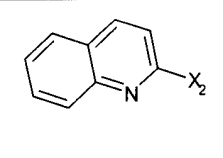
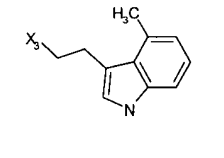
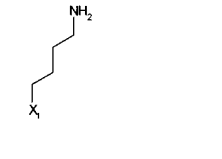
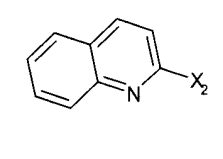
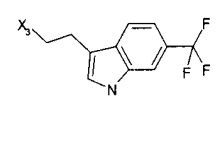
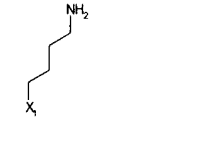
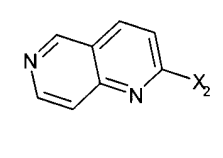
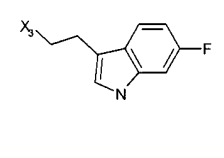
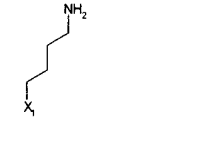
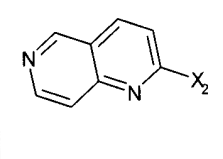
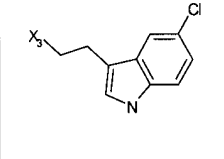
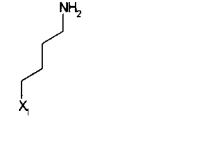
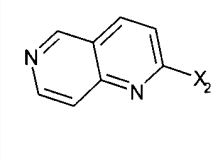
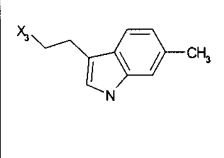
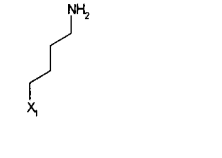
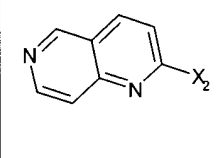
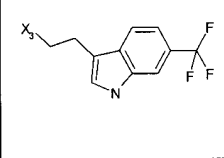
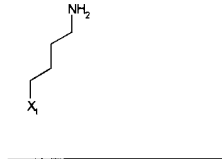
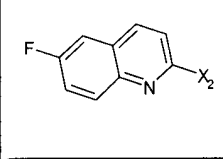
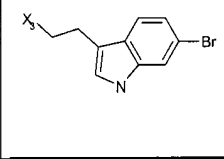
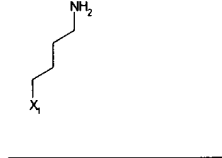
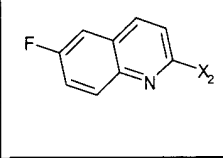
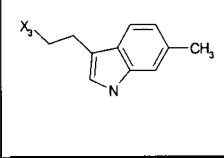
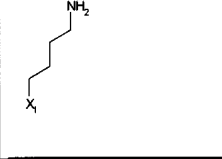
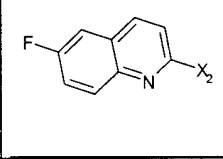
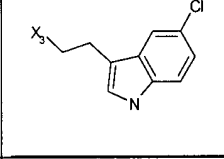
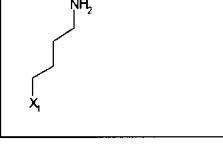
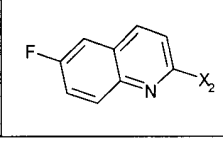
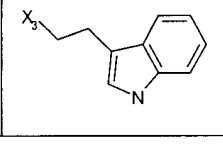


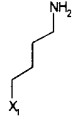
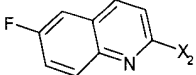
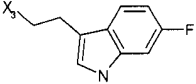
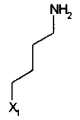
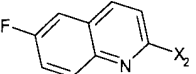
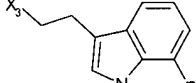
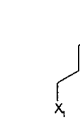
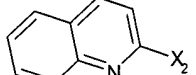
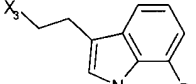
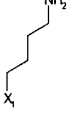
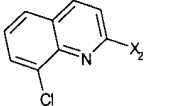
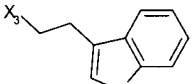
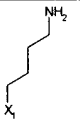
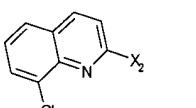
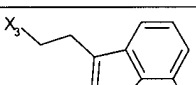
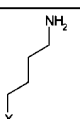
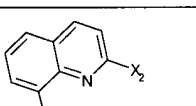
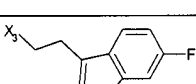
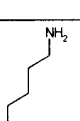
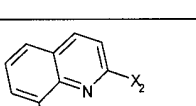
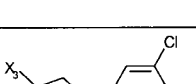
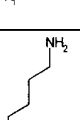
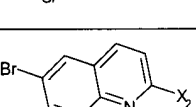
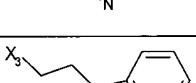
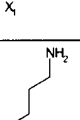
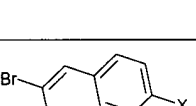
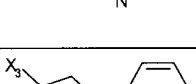
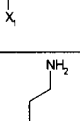
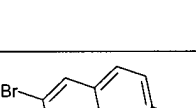
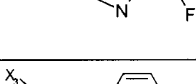
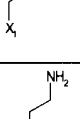
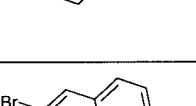
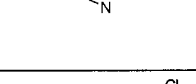
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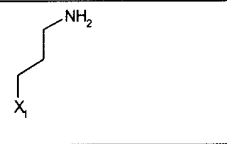
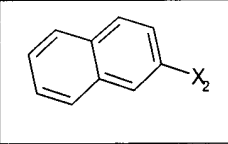
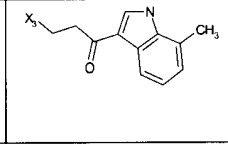
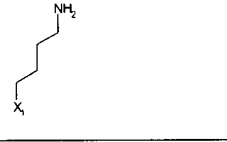
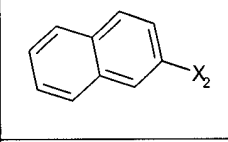
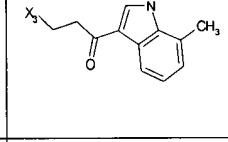
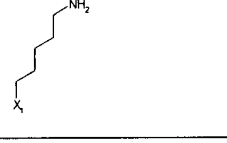
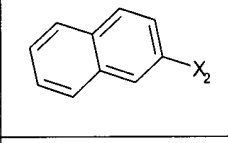
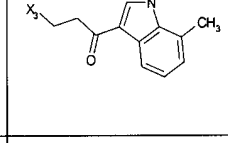
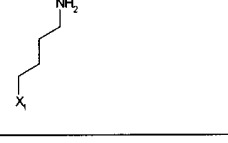
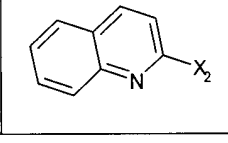
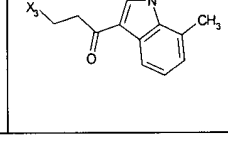
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683				8.5	457.20
684				8.5	457.20
685				8.77	511.08
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704				9.03	555.01

705				8.62	470.16
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### 药理学研究

根据下面描述的步骤，试验了有关本发明化合物对生长激素的不同受体亚型的亲合性。

对人生长激素的受体亚型亲合性研究：

5 通过测定抑制转染 CHO-K1 细胞与 $[^{125}\text{I-Tyr}^{11}]$ SRIF-14 的结合，可以测定本发明化合物对生长激素的第 2 受体亚型的亲合性。试验了这些化合物，显示出对其它亚型的亲合性，并且任选地进行了有关它们抑制细胞内 cAMP 产生的功能试验。

10 以染色体组片段形式克隆了人的生长激素  $\text{sst}_1$  受体基因。通过附加衔接物 Bg1II，修饰含有 100 bp 非转录 5' 区的 1.5 Kb 片段 *PstI-XmnI*、1.17 Kb 的整个编码区和 230 bp 的非转录 3' 区。得到的 DNA 片段在 pCMV-81 的 *BamHI* 位点进行亚克隆，以便得到在哺乳动物中表达的质粒(由 Dr. Graeme Bell, Univ. Chicago 提供)。稳定地表达  $\text{sst}_1$  受体的克隆细胞系是采用磷酸钙共沉淀法在 CHO-K1 细胞(ATCC)中转染得到的。作为选择标记物包括质粒 pRSV-neo(ATCC)。在含有 0.5mg/ml G418(Gibco)的 RPMI 15 1640 培养基中选择了克隆细胞系，接着循环克隆和培养扩增。

Dr. G. Bell (Univ. of Chicago)提供了人的生长激素的  $\text{sst}_2$  受体基因，它是以 1.7 Kb *BamHI-HindIII* 的 DNA 染色体组片段形式分离的，并且在质粒载体 pGEM3Z(Promega)中进行亚克隆。通过 1.7 Kb *BamHI-HindIII* 片段插入与质粒 pCMV5 相容的核酸内切酶限制位点中，构建了哺乳动物细胞的表达载体。采用磷酸钙共沉淀法，通过在 CHO-K1 细胞中转染可以得到克隆细胞系。作为选择标记物包括了质粒 pRSV-neo。 20

作为染色体组片段分离了受体  $\text{sst}_3$ ，并且在 2.4 Kb 的 *BamHI/HindIII* 片段中含有完全编码的顺序。在终止子修饰与附加衔接物 *EcoR1* 后，通过将 2.0 Kb 的 *NcoI-HindIII* 片段插入载体 pCMV 的位点 *EcoR 1* 中，可构建哺乳动物中表达的质粒，pCMV-h3。采用磷酸钙共沉淀法，通过在 CHO-K1 细胞(ATCC)中转染可以得到稳定表达  $\text{sst}_3$  受体的克隆细胞系。作为选择标记物包括了质粒 pRSV-neo(ATCC)。在含有 0.5 mg/ml G418(Gibco)的 RPMI 1640 介质中选择了克隆细胞系，接着循环克隆与培 25 养扩增。 30



Dr. Graeme Bell (Univ. Chicago)提供了人 *sst*<sub>4</sub> 受体的表达质粒, pCMV-HX。这种载体含有 1.4 Kb *NheI-NheI* 的人 *sst*<sub>4</sub> 受体、456 bp 的非转录 5'区和 200bp 非转录 3'区的编码染色体组片段, 该片段在 pCMV-HX 的 *XbaI/EcoR1* 位点已克隆。采用磷酸钙共沉淀法, 通过在 CHO-K1 细胞 (ATCC) 中转染可以得到稳定表达 *sst*<sub>4</sub> 受体的克隆细胞系。作为选择标记物包括了质粒 pRSV-neo(ATCC)。在含有 0.5 mg/ml 的 G418 (Gibco) 的 RPMI 1640 介质中选择了克隆细胞系, 接着循环克隆与培养扩增。

Dr. Graeme Bell (Univ. Chicago)提供了相应于人 *sst*<sub>5</sub> 受体的基因, 这种基因是采用 PCR 方法使用染色体组克隆  $\lambda$  作为探针得到的。得到的 1.2 Kb 的 PCR 片段含有 21 个非转录 5'区的碱基对, 整个编码区和 55bp 的非转录 3'区。在质粒 pBSSK(+) 的 *EcoR1* 位点插入该克隆。该插入子以 1.2 Kb 的 *HindIII-XbaI* 片段形式回收, 以便在哺乳动物中进行表达载体(pCVM5) 的亚克隆。采用磷酸钙共沉淀法, 通过在 CHO-K1 细胞(ATCC) 中转染可以得到稳定表达 *sst*<sub>5</sub> 受体的克隆细胞系。作为选择标记物包括了质粒 pRSV-neo(ATCC)。在含有 0.5 mg/ml of G418(Gibco) 的 RPMI 1640 介质中选择了克隆细胞系, 接着循环克隆与培养扩增。

在含有 10% 胎牛血清和 0.4mg/ml 遗传霉素的 RPMI 1640 培养基中, 培养了稳定表达其中一种人 *sst* 受体的 CHO-K1 细胞。这些细胞用 0.5 mM EDTA 收集, 并且在约 4°C 于 500 g 离心近 5 分钟。该离心液再悬浮于 pH 7.4 的 50 mM Tris 缓冲液中, 再在约 4°C 于 500 g 离心近 5 分钟, 离心两次。这些细胞采用超声处理进行细胞溶解, 然后在 4°C 于 39000g 离心近 10 分钟。该离心液再悬浮于同样缓冲液中, 在约 4°C 于 50000g 离心 10 分钟, 由离心液中得到的膜储存在 -80°C 下。

使用 96 孔聚丙烯培养板中以一式两份进行 [<sup>125</sup>I-Tyr<sup>11</sup>]SRIF-14 竞争性结合的抑制试验。在含有 0.2 % BSA、5 mM MgCl<sub>2</sub>、200 KIU/ml 的 Trasylol、0.02 mg/ml 杆菌肽和 0.02 mg/ml 苯甲基磺酰基氟的 50 mM HEPES 缓冲液 (pH 7.4) 中, 在约 37°C 下将这些细胞膜与 [<sup>125</sup>I-Tyr<sup>11</sup>]SRIF-14 一起培养约 60min。

采用立刻通过 GF/C 玻璃纤维过滤板(Unifilter, Packard)过滤的方法, 使用 Filtermate 196(Packard) 将结合的 [<sup>125</sup>I-Tyr<sup>11</sup>]SRIF-14 与游离的

[<sup>125</sup>I-Tyr<sup>11</sup>]SRIF-14 分离,该玻璃纤维已用 0.1%聚乙烯亚胺(P.E.I.)预浸渍。这些过滤器用 50mM HEPES 缓冲液在约 0-4°C 洗涤约 4 秒,再使用计数器(Packard Top Count)测定它们的放射性。

从总结合中减去非特异性结合(在 0.1 μM SRIF-14 存在下测定)可以得到特异性结合。分析相对于该键的数据,可计算出一定浓度的抑制百分数,或根据该实验确定抑制常数值(K<sub>i</sub>)。

借助下述试验可以确定本发明化合物的激动剂或拮抗剂特性。

功能测定: 抑制细胞内 cAMP 的产生:

在 24 孔板中,在含有 10% 胎牛血清和 0.4mg/ml 遗传霉素的 RPMI 1640 培养基中培养表达人生长激素的这些受体亚型(SRIF-14)的 CHO-K1 细胞。在试验的当天更换培养基。

这些细胞(比率为 10<sup>5</sup> 细胞/孔)用 0.5ml 新 RPMI 培养基洗涤两次,该培养基含有 0.2 % BSA,用 0.5mM 3-异丁基-1-甲基黄嘌呤(IBMX)补足,并且将这些细胞在约 37°C 培育近 5 分钟。

- 在 37°C,通过添加 1μM 毛喉素(FSK)刺激产生环 AMP 达 15-30 分钟;

- 同时添加 FSK(1 μM)和待试验化合物(10<sup>-10</sup> M-10<sup>-5</sup> M),测定促效药化合物的生长激素的抑制作用;

- 同时添加 FSK(1 μM)、SRIF-14(1 nM)和待试验化合物(10<sup>-10</sup>M-10<sup>-5</sup> M),测定了化合物的拮抗作用。

除去反应介质,添加 200μl 0.1N HCl。通过放射免疫测定试验(FlashPlate SMP001A kit, New England Nuclear)测定了 cAMP 的量。

结果:

根据前面描述试验方法可以表明,在本申请中定义的通式(I)化合物,对生长激素的至少一个受体亚型具有良好的亲合性,某些示例化合物的抑制常数 K<sub>i</sub> 低于微摩尔。