



(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
29.12.2004 Bulletin 2004/53

(21) Application number: **99901083.8**

(22) Date of filing: **05.02.1999**

(51) Int Cl.7: **C07D 249/06**, A61K 31/475, A61K 31/495, A61K 31/41, A61K 31/415, A61K 31/425, A61K 31/47, C07D 521/00, C07D 231/14, C07D 401/04, C07D 403/04, C07D 417/04, C07D 405/04, C07D 413/04, C07D 409/04

(86) International application number:
PCT/IB1999/000206

(87) International publication number:
WO 1999/043663 (02.09.1999 Gazette 1999/35)

(54) **N-[(SUBSTITUTED FIVE-MEMBERED DI- OR TRIAZA DIUNSATURATED RING)CARBONYL]GUANIDINE DERIVATIVES FOR THE TREATMENT OF ISCHEMIA**
N-[(SUBSTITUTIERTE FÜNFGLEDRIGE DI- ODER TRIAZA-DOPPELTUNGESÄTTIGTER RING)CARBONYL]GUANIDINDERIVATE ZUR BEHANDLUNG VON ISCHEMIE
DERIVES DE LA N- (A CYCLE DI OU TRIAZA DIINSATURE SUBSTITUE) CARBONYLE]
GUANIDINE UTILISES POUR LE TRAITEMENT DE L'ISCHEMIE

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **27.02.1998 US 76362 P**

(43) Date of publication of application:
06.12.2000 Bulletin 2000/49

(60) Divisional application:
04008203.4 / 1 454 902

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EP-A- 0 676 395 **EP-A- 0 708 091**
EP-A- 0 803 501 **WO-A-94/26709**
WO-A-98/27061 **DE-A- 2 144 568**

EP 1 056 729 B1

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DescriptionBACKGROUND OF INVENTION

5 **[0001]** This invention relates to sodium-hydrogen exchanger type 1 (NHE-1) inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors in the manufacture of a medicament to treat, for example, ischemia particularly, perioperative myocardial ischemic injury in mammals, including humans.

10 **[0002]** Myocardial ischemic injury can occur in out-patient as well as in perioperative settings and can lead to the development of sudden death, myocardial infarction or congestive heart failure. There is an unmet medical need to prevent or minimize myocardial ischemic injury, particularly perioperative myocardial infarction. Such a therapy is anticipated to be life-saving and reduce hospitalizations, enhance quality of life and reduce overall health care costs of high risk patients.

15 **[0003]** Pharmacological cardioprotection would reduce the incidence and progression of myocardial infarction and dysfunction occurring in these surgical settings (perioperatively). In addition to reducing myocardial damage and improving post-ischemic myocardial function in patients with ischemic heart disease, cardioprotection would also decrease the incidence of cardiac morbidity and mortality due to myocardial infarction and dysfunction in patients "at risk" (such as greater than 65 years, exercise intolerant, coronary artery disease, diabetes mellitus, hypertension) that require non-cardiac surgery.

20 **[0004]** The mechanism(s) responsible for the myocardial injury observed after ischemia and reperfusion is not fully understood.

[0005] A variety of publications have disclosed the use of guanidine derivatives as useful for the treatment of, for example arrhythmias.

25 **[0006]** U.S. pat. no. 5,698,581, granted December 16, 1997 (EP 676395 A2 published 1995), discloses certain substituted N-heteroarylguanidines as inhibitors of the (Na⁺/H⁺) exchange transport system useful for the treatment of, for example, arrhythmias.

[0007] EP 803 501 A1, published October 10, 1997, discloses substituted guanidine derivatives useful as (Na⁺/H⁺) exchange inhibitors.

[0008] WO 94/26709 discloses guanidine derivatives as inhibitors of (Na⁺/H⁺) exchange in cells.

30 **[0009]** PCT/JP97/04605 application published on June 25, 1998 (WO-A-98/27061) discloses N-[(substituted five-membered heteroaryl)carbonyl]guanidine compounds which are stated to be useful as inhibitors of Na⁺/H⁺ exchange and consequently effective for the treatment of various diseases such as hypertension, arrhythmia, angina pectoris, myocardial infarct, arteriosclerosis, and complications of diabetes.

[0010] DE-A-2144568 discloses phenylpyrazole derivatives said to have various therapeutic applications, e.g. as anti-inflammatories.

35 **[0011]** EP-A-0708091 discloses indoloylguanidine derivatives which are said to inhibit of Na⁺/H⁺ exchanger activity.

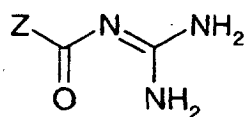
[0012] EP-A-0639573 discloses a group of benzo-fused 5-membered heterocycles which are said to inhibit Na⁺/H⁺ exchangers.

[0013] EP-A-0622356 discloses indoloylguanidine derivatives which are said to inhibit sodium-hydrogen exchange.

40 **[0014]** Thus, there is clearly a need and a continuing search in this field of art for treatments for perioperative myocardial ischemia.

SUMMARY OF THE INVENTION

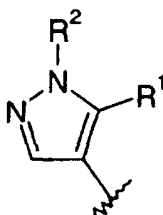
45 **[0015]** This invention is directed to a compound of the Formula I



Formula I

55 or a pharmaceutically acceptable salt of said compound, wherein either Z is

(i)



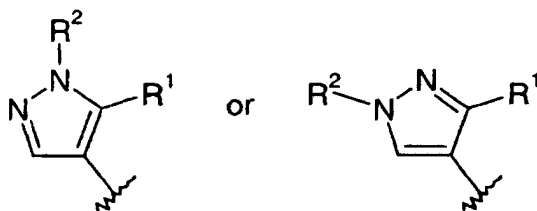
wherein R¹ is (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₃-C₇)cycloalkyl optionally substituted with from one to three fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di- substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; or Z is

(ii)



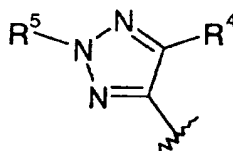
wherein R¹ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R² is phenyl

(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or

Z is

(iii)



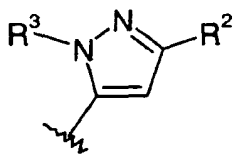
wherein R⁴ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R⁴ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R⁵ is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R⁵ is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R⁵ is phenyl (C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R⁵ substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; or

Z is

(iv)



wherein R² is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di-substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; and

R³ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R³ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or (C₁-C₄)alkyl.

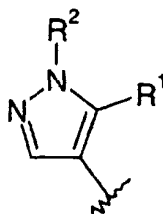
[0016] Especially preferred compounds of Formula I are the compounds [5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine and

the pharmaceutically acceptable salts thereof.

[0017] Especially preferred compounds of Formula I wherein Z is

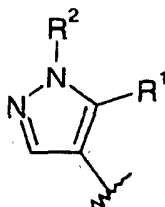


are compounds wherein

- a. R² is 2-trifluoromethylphenyl; and
R¹ is cyclopropyl;
- b. R² is phenyl; and

- R¹ is cyclopropyl; and
 c. R² is 2,6-dichlorophenyl; and
 R¹ is cyclopropyl or the pharmaceutically acceptable salts thereof.

5 **[0018]** A preferred group of compound, designated the C group, contains those compounds of Formula I wherein Z is



R¹ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl; and

R² quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzopyranyl, benzothiophenyl, benzodioxanyl or benzodioxolyl, said R² substituent optionally mono-substituted; or the pharmaceutically acceptable salts thereof.

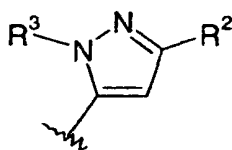
20 **[0019]** Especially preferred compounds of Formula I are the compounds [5-methyl-1-(quinolin-6-yl)-1H-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine and the pharmaceutically acceptable salts thereof.

25 **[0020]** Especially preferred compounds within the C Group of compounds are compounds wherein

- 30 a. R² is 5-quinolinyl; and
 R¹ is cyclopropyl;
 b. R² is 8-quinolinyl; and
 R¹ is cyclopropyl; and
 c. R² is 6-quinolinyl; and
 R¹ is methyl or the pharmaceutically acceptable salts thereof.

35 **[0021]** An especially preferred compound of Formula I is the compound [3-methyl-1-(isoquinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine and the pharmaceutically acceptable salts thereof.

[0022] A preferred group of compounds, designated the J Group, contains those compounds of Formula I wherein Z is



R² is phenyl, optionally mono- or di-substituted; and

R³ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl.

50 **[0023]** Especially preferred compounds of Formula I are the compounds [2-methyl-5-phenyl-2H-pyrazole-3-carbonyl]guanidine;

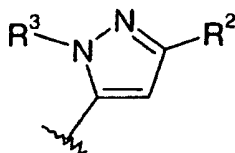
[2-methyl-5-(naphthalen-1-yl)-2H-pyrazole-3-carbonyl]guanidine and the pharmaceutically acceptable salts thereof.

[0024] An especially preferred compound within the J Group of compounds is the compound wherein

R² is phenyl; and

R³ is methyl or the pharmaceutically acceptable salts thereof.

55 **[0025]** A preferred group of compounds, designated the K group, contains those compounds of Formula I wherein Z is



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[0026] R² is naphthalenyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxaliny, quinazoliny, benzopyranyl, benzothiophenyl, benzodioxanyl or benzodioxoly, said R² substituent optionally mono-substituted; and

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[0027] R³ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl or the pharmaceutically acceptable salts thereof.

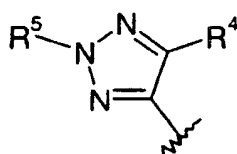
[0028] An especially preferred compound within the K Group of compounds is the compound wherein

R² is 1-naphthalenyl; and

R³ is methyl and the pharmaceutically acceptable salts thereof.

15

[0029] A preferred group of compounds, designated the Q Group, contains those compounds of formula I wherein Z is



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R⁴ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl; and

R⁵ is quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxaliny, quinazoliny, benzopyranyl, benzothiophenyl, benzodioxanyl or benzodioxoly, said R⁵ substituents optionally mono-substituted or the pharmaceutically acceptable salts thereof.

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[0030] Especially preferred compounds of Formula I are the compounds [2-(isoquinolin-5-yl)-5-methyl-2H-1,2,3-triazole-4-carbonyl]guanidine;

[5-methyl-2-(quinolin-5-yl)-2H-1,2,3-triazole-4-carbonyl]guanidine and the pharmaceutically acceptable salts thereof.

[0031] Especially preferred compounds within the Q Group of compounds are compounds wherein

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a. R⁵ is 5-isoquinolinyl; and

R⁴ is methyl; and

b. R⁵ is 5-quinolinyl; and

R⁴ is methyl or the pharmaceutically acceptable salts thereof.

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[0032] Another aspect of this invention is directed to the following compounds:

5-Methyl-2-(5-quinolinyl)-2H-1,2,3-triazole-4-carboxylic acid,

5-Methyl-2-(5-isoquinolinyl)-2H-1,2,3-triazole-4-carboxylic acid,

Ethyl 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylate,

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Ethyl 5-methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate,

Ethyl 5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylate,

Ethyl 5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate,

Methyl 5-ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate,

n-Butyl 1-(isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylate,

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5-Methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid,

5-Cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylic acid,

5-Cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylic acid,

5-Ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid,

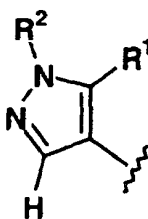
5-Cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid or

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1-(Isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylic acid or a pharmaceutically acceptable salt of said compound.

[0033] A preferred group of compounds designated the R group, contains those compounds having the Formula I

as shown above wherein Z is



R¹ is (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₃-C₇)cycloalkyl optionally substituted with from one to three fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di- substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N, N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines or the pharmaceutically acceptable salts thereof.

[0034] An especially preferred compound of Formula I is the compound [1-(Naphthalen-1-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine or the pharmaceutically acceptable salts thereof.

[0035] A group of compounds which is preferred among the R Group of compounds designated the S Group, contains those compounds wherein

R¹ is cyclopropyl; and

R² is 1-naphthalenyl or the pharmaceutically acceptable salts thereof.

[0036] A group of compounds which is preferred among the R Group of compounds designated the T Group, contains those compounds wherein

R¹ is (C₃-C₇)cycloalkyl; and

R² is a five to six membered monocyclic aromatic ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

said R² ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfo-

nyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines or the pharmaceutically acceptable salts thereof.

[0037] A group of compounds which is preferred among the T Group of compounds designated the U Group, contains those compounds wherein

R¹ is cyclopropyl; and

R² is phenyl, optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines;

or the pharmaceutically acceptable salts thereof.

[0038] Especially preferred compounds of Formula I are the compounds
[5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine;
[5-cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine; or
[5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine
or the pharmaceutically acceptable salts of said compounds.

[0039] Other especially preferred compounds of Formula I are the compounds
[1-(2-Chloro-4-methylsulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Bromophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chloro-5-methoxyphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chloro-4-methylaminosulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2,5-Dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2,3-Dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chloro-5-aminosulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chloro-5-methylsulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Chloro-5-dimethylaminosulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
[1-(2-Trifluoromethyl-4-chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;
or pharmaceutically acceptable salts of said compounds.

[0040] Especially preferred compounds within the U Group are compounds wherein

- a. R² is 2-chloro-4-methylsulfonylphenyl;
- b. R² is 2-chlorophenyl;
- c. R² is 2-trifluoromethyl-4-fluorophenyl;
- d. R² is 2-bromophenyl;
- e. R² is 2-fluorophenyl;
- f. R² is 2-chloro-5-methoxyphenyl;
- g. R² is 2-chloro-4-methylaminosulfonylphenyl;
- h. R² is 2,5-dichlorophenyl;
- i. R² is 2,3-dichlorophenyl;
- j. R² is 2-chloro-5-aminocarbonylphenyl;
- k. R² is 2-chloro-5-aminosulfonylphenyl;
- l. R² is 2-fluoro-6-trifluoromethylphenyl;
- m. R² is 2-chloro-5-methylsulfonylphenyl;
- n. R² is 2-chloro-5-dimethylaminosulfonylphenyl;
- o. R² is 2-trifluoromethyl-4-chlorophenyl; or the pharmaceutically acceptable salts of said compounds.

[0041] A group of compounds which is preferred among the R Group of compounds designated the W Group, contains those compounds wherein

R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄)alkyl, unsubstituted (C₃-C₇)cycloalkyl or phenyl(C₁-C₄)alkyl, wherein said phenyl(C₁-C₄)alkyl is optionally mono-or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines;

or the pharmaceutically acceptable salts thereof.

[0042] A group of compounds which is preferred among the R Group of compounds designated the X Group, contains those compounds wherein

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituent optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono-substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or the pharmaceutically acceptable salts thereof.

[0043] A group of compounds which is preferred among the X Group of compounds designated the Y Group, contains those compounds wherein

R¹ is (C₃-C₇)cycloalkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines or the pharmaceutically acceptable salts thereof.

[0044] A group of compounds which is preferred among the Y Group of compounds designated the Z Group, contains those compounds wherein

R¹ is cyclopropyl; and

R² is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxanyl, quinoxaliny, benzopyranyl, benzothiophenyl, benzodioxoly, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, ben-

zothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines;

or the pharmaceutically acceptable salts thereof.

[0045] A group of compounds which is preferred among the Z Group of compounds designated the AA Group, contains those compounds wherein

R² is a quinolinyl, isoquinolinyl, indazolyl or benzimidazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy or (C₁-C₄)alkyl substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines; or the pharmaceutically acceptable salts thereof.

[0046] Especially preferred compounds of Formula I are the compounds [5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine; or [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine; or the pharmaceutically acceptable salts of said compounds.

[0047] Preferred salts of the immediately preceding compound are the mono- or di-mesylate salts.

[0048] Other especially preferred compounds of Formula I are the compounds

[1-(8-Bromoquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(6-Chloroquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(Indazol-7-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(Benzimidazol-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(1-Isoquinolyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[5-Cyclopropyl-1-(4-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine;

or the pharmaceutically acceptable salts of said compounds.

[0049] Especially preferred compounds within the AA Group are compounds wherein

a. R² is 8-bromoquinolin-5-yl;

b. R² is 6-chloroquinolin-5-yl;

c. R² is indazol-7-yl;

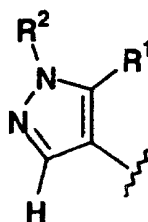
d. R² is benzimidazol-5-yl;

e. R² is 1-isoquinolyl;

f. R² is 4-quinolinyl;

or the pharmaceutically acceptable salts of said compounds.

[0050] A preferred group of compounds, designated the BB Group, contains those compounds having the Formula I as shown above wherein Z is



R¹ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R¹ substituent optionally mono- or di-substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)

alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄) alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R² is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄) alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄) alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono-substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines,

or the pharmaceutically acceptable salts thereof.

[0051] A group of compounds which is preferred among the BB Group of compounds designated the CC Group, contains those compounds wherein

R¹ is (C₁-C₄)alkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines or the pharmaceutically acceptable salts thereof.

[0052] A group of compounds which is preferred among the CC Group of compounds designated the DD Group, contains those compounds wherein

R² is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxany, quinoxaliny, benzopyrany, benzothiopheny, benzodioxoly, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines; or the pharmaceutically acceptable salts thereof.

[0053] Especially preferred compounds of Formula I are the compounds

[1-(Indazol-6-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(Indazol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(Benzimidazol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(1-Methylbenzimidazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine

[1-(5-Quinoliny)-5-*n*-propyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(5-Quinoliny)-5-isopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[5-Ethyl-1-(6-quinoliny)-1*H*-pyrazole-4-carbonyl]guanidine;

5 [1-(2-Methylbenzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(1,4-Benzodioxan-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(Benzotriazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(3-Chloroindazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(5-Quinoliny)-5-butyl-1*H*-pyrazole-4-carbonyl]guanidine;

10 [5-propyl-1-(6-quinoliny)-1*H*-pyrazole-4-carbonyl]guanidine;

[5-Isopropyl-1-(6-quinoliny)-1*H*-pyrazole-4-carbonyl]guanidine;

or pharmaceutically acceptable salts of said compounds.

[0054] Especially preferred compounds within the DD Group are compounds wherein

15 a. R¹ is ethyl; and

R² is indazol-6-yl;

b. R¹ is ethyl; and

R² is indazol-5-yl;

c. R¹ is ethyl; and

20 R² is benzimidazol-5-yl;

d. R¹ is ethyl; and

R² is 1-methylbenzimidazol-6-yl;

e. R¹ is *n*-propyl; and

R² is 5-quinolinyl;

25 f. R¹ is isopropyl; and

R² is 5-quinolinyl;

g. R¹ is ethyl; and

R² is 6-quinolinyl;

h. R¹ is ethyl; and

30 R² is 2-methylbenzimidazol-5-yl;

i. R¹ is ethyl; and

R² is 1,4-benzodioxan-6-yl;

j. R¹ is ethyl; and

R² is benzotriazol-5-yl;

35 k. R¹ is ethyl; and

R² is 3-chloroindazol-5-yl;

l. R¹ is butyl; and

R² is 5-quinolinyl;

m. R¹ is *n*-propyl; and

40 R² is 6-quinolinyl;

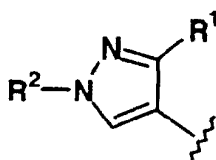
n. R¹ is isopropyl; and

R² is 6-quinolinyl;

or the pharmaceutically acceptable salts of said compounds.

45 **[0055]** A preferred group of compounds, designated the EE Group, contains those compounds having the Formula I as shown above wherein Z is

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R¹ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R² is a five to six membered nonaromatic heterocyclic ring

having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄) alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R² is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄) alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄) alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono-substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or the pharmaceutically acceptable salts thereof.

[0056] A group of compounds which is preferred among the EE Group of compounds designated the FF Group, contains those compounds wherein

R¹ is (C₁-C₄)alkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

or the pharmaceutically acceptable salts thereof.

[0057] A group of compounds which is preferred among the FF Group of compounds designated the GG Group, contains those compounds wherein

R² is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxanyl, quinoxaliny, benzopyranyl, benzothiophenyl, benzodioxolyl, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines;

or the pharmaceutically acceptable salts thereof.

[0058] Especially preferred compounds of Formula I are the compounds [1-(Indazol-7-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2,1,3-Benzothiadiazol-4-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine;

[3-Methyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine;

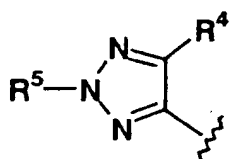
or the pharmaceutically acceptable salts of said compounds.

[0059] Especially preferred compounds within the GG Group of compounds are compounds wherein

- a. R¹ is methyl; and
R² is indazol-7-yl;
5 b. R¹ is methyl; and
R² is 2,1,3-benzothiadiazol-4-yl;
c. R¹ is methyl; and
R² is quinolin-5-yl;

10 or the pharmaceutically acceptable salts of said compounds.

[0060] A preferred group of compounds, designated the HH Group, contains those compounds having the Formula I as shown above wherein Z is



15 R⁴ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R⁴ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R⁵ is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R⁵ is unsubstituted (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl; or R⁵ is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R⁵ substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

25 wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or the pharmaceutically acceptable salts thereof.

30 [0061] A group of compounds which is preferred among the HH Group of compounds designated the II Group, contains those compounds wherein

R⁴ is (C₁-C₄)alkyl; and

R⁵ is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

35 said R⁵ bicyclic ring is optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

40 said R⁵ bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines. or the pharmaceutically acceptable salts thereof.

[0062] A group of compounds which is preferred among the II Group of compounds designated the JJ Group, contains those compounds wherein

R⁵ is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxany, quinoxaliny, benzopyrany, benzothiophenyl, benzodioxoly, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

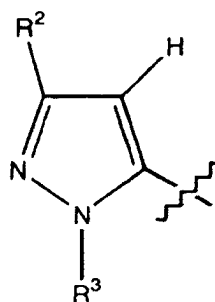
wherein said R⁵ bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines;

or the pharmaceutically acceptable salts thereof.

[0063] A preferred group of compounds, designated the KK Group, contains those compounds having the Formula I as shown above wherein Z is

Z is



R² is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di-substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono-substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N-

or di-N,N-(C₁-C₄)alkylcarbonyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; and

R³ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R³ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or (C₁-C₄)alkyl, or a pharmaceutically acceptable salt thereof.

[0064] A group of compounds which is preferred among the KK Group of compounds designated the LL Group, contains those compounds wherein

R³ is (C₁-C₄)alkyl;

R² is phenyl, said phenyl optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² ring is also optionally mono- or di-substituted independently on carbon with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbonyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbonyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbonyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or the pharmaceutically acceptable salts thereof.

[0065] A group of compounds which is preferred among the KK Group of compounds designated the MM Group, contains those compounds wherein R³ is (C₁-C₄)alkyl;

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently

said R² bicyclic ring is optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbonyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbonyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbonyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or the pharmaceutically acceptable salts thereof.

[0066] A group of compounds which is preferred among the KK Group of compounds designated the NN Group, contains those compounds wherein

R³ is (C₁-C₄)alkyl;

R² is a five to six membered monocyclic aromatic ring having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

said R² ring is optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbonyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbonyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbonyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl,

(C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines or the pharmaceutically acceptable salts thereof.

[0067] A group of compounds which is preferred among the KK Group of compounds designated the OO Group, contains those compounds wherein R³ is (C₁-C₄)alkyl;

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines or the pharmaceutically acceptable salts thereof.

[0068] Another aspect of this invention is directed to the esters of 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1*H*-pyrazole-4-carboxylate,

5-methyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carboxylate,

5-cyclopropyl-1-(quinolin-8-yl)-1*H*-pyrazole-4-carboxylate,

5-cyclopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate,

5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate or

1-(isoquinolin-5-yl)-3-methyl-1*H*-pyrazole-4-carboxylate

wherein said esters are benzyl, (C₁-C₆)alkyl or (C₄-C₈)cycloalkyl, said (C₄-C₈)cycloalkyl optionally mono-substituted with (C₁-C₄)alkyl

or a salt of said esters.

[0069] Yet another aspect of this invention is directed to the following compounds

5-methyl-2-(5-quinolinyl)-2*H*-1,2,3-triazole-4-carboxylic acid,

5-methyl-2-(5-isoquinolinyl)-2*H*-1,2,3-triazole-4-carboxylic acid,

5-methyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carboxylic acid,

5-cyclopropyl-1-(quinolin-8-yl)-1*H*-pyrazole-4-carboxylic acid,

5-cyclopropyl-1-(2-trifluoromethylphenyl)-1*H*-pyrazole-4-carboxylic acid,

5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid,

5-cyclopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid or

1-(isoquinolin-5-yl)-3-methyl-1*H*-pyrazole-4-carboxylic acid or the acid chlorides thereof or a salt of said compounds or of said acid chlorides.

[0070] Another aspect of this invention is the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a mammal (e.g., human) having a disease or condition mediated by NHE-1.

[0071] Another aspect of this invention is the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reducing tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) resulting from ischemia.

[0072] Preferred ischemic tissues taken individually or as a group are wherein the ischemic tissue is cardiac, brain, liver, kidney, lung, gut, skeletal muscle, spleen, pancreas, nerve, spinal cord, retina tissue, the vasculature, or intestinal tissue.

[0073] An especially preferred ischemic tissue is cardiac tissue.

[0074] It is especially preferred that the compounds are administered to prevent perioperative myocardial ischemic injury.

[0075] Preferably, the compounds of this invention are administered prophylactically.

[0076] The ischemic damage may occur during organ transplantation.

[0077] Preferably, the compounds of this invention are administered prior to, during or shortly after, cardiac surgery or non-cardiac surgery.

[0078] In one aspect of this invention a compound of Formula I is administered locally.

[0079] A preferred dosage is about 0.001 to 100 mg/kg/day of the Formula I compound a prodrug thereof. An especially preferred dosage is about 0.01 to 50 mg/kg/day of a compound of Formula I, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug.

5 **[0080]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reducing myocardial tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) during surgery (e.g., coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA) or any percutaneous transluminal coronary intervention (PTCI), organ transplantation, or other non-cardiac surgeries).

10 **[0081]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reducing myocardial tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) in patients presenting with ongoing cardiac (acute coronary syndromes, e.g. myocardial infarction or unstable angina) or cerebral ischemic events (e.g. stroke).

15 **[0082]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reducing myocardial tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) in a patient with diagnosed coronary heart disease (e.g. previous myocardial infarction or unstable angina) or patients who are at high risk for myocardial infarction (age > 65 and two or more risk factors for coronary heart disease).

[0083] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for preventing ischemic damage.

20 **[0084]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cardiovascular diseases.

[0085] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating arteriosclerosis.

25 **[0086]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating hypertension.

[0087] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating arrhythmia.

[0088] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating angina pectoris.

30 **[0089]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cardiac hypertrophy.

[0090] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating renal diseases.

35 **[0091]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating diabetic complications.

[0092] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating restenosis.

[0093] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating diseases of cell proliferation.

40 **[0094]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancerous diseases.

[0095] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating fibrotic diseases.

45 **[0096]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating glomerular nephrosclerosis.

[0097] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating organ hypertrophies or hyperplasias.

[0098] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating pulmonary fibrosis.

50 **[0099]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cerebro ischemic disorders.

[0100] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating myocardial stunning.

55 **[0101]** Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating myocardial dysfunction.

[0102] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cerebrovascular diseases.

[0103] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically

acceptable salt thereof, for the manufacture of a medicament for treating organ hypertrophies or hyperplasias.

[0104] Another aspect of this invention is directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating organ hypertrophies or hyperplasias.

[0105] This invention is also directed to pharmaceutical compositions which comprise a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0106] This invention is also directed to pharmaceutical compositions for the reduction of tissue damage resulting from ischemia which comprise a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0107] Yet another aspect of this invention are combinations of a compound of Formula I, or a pharmaceutically acceptable salt thereof and other compounds as described below.

[0108] Yet another aspect of this invention is directed to pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a cardiovascular agent and for the use of such compositions for the manufacture of a medicament for the reduction of tissue damage resulting from tissue ischemia in mammals (e.g., humans, male or female).

[0109] In the above pharmaceutical compositions and uses, preferred Formula I compounds include the preferred groups of compounds described above.

[0110] Another aspect of this invention is the use of

- a. a first compound, said first compound being a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and
- b. a second compound, said second compound being a cardiovascular agent for the manufacture of a medicament for reducing tissue damage (e.g. substantially preventing tissue damage, inducing tissue production) resulting from or which could result from ischaemia.

[0111] Another aspect of this invention is a kit comprising:

- a. a therapeutically effective amount of a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;
- b. a therapeutically effective amount of a cardiovascular agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and
- c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

[0112] In the above combination compositions, combination uses and kits, preferably the cardiovascular agents are for example, β -blockers (e.g., acebutolol, atenolol, bopindolol, labetalol, mepindolol, nadolol, oxprenol, pindolol, propranolol, sotalol), calcium channel blockers (e.g., amlodipine, nifedipine, nisoldipine, nitrendipine, verapamil), potassium channel openers, adenosine, adenosine agonists, ACE inhibitors (e.g., captopril, enalapril), nitrates (e.g., isosorbide dinitrate, isosorbide 5-mononitrate, glyceryl trinitrate), diuretics (e.g., hydrochlorothiazide, indapamide, piretanide, xipamide), glycosides (e.g., digoxin, metildigoxin), thrombolytics (e.g. tPA), platelet inhibitors (e.g., reopro), aspirin, dipyridamol, potassium chloride, clonidine, prazosin or adenosine A_3 receptor agonists.

[0113] In the above combination compositions, combination uses and kits preferred Formula I compounds include the preferred groups of compounds described above.

[0114] This invention is also directed to a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

- a first compound, said first compound being a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug;
- a second compound, said second compound being a glycogen phosphorylase inhibitor; and/or optionally a pharmaceutical carrier, vehicle or diluent.

[0115] Another aspect of this invention is the use of

- a. a first compound, said first compound being a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and
- b. a second compound, said second compound being a glycogen phosphorylase inhibitor

for the manufacture of a medicament for reducing tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) resulting from or which could result from ischemia.

[0116] Another aspect of this invention is a kit comprising:

- a. a therapeutically effective amount of a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;
- b. a therapeutically effective amount of a glycogen phosphorylase inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and
- c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

[0117] In the above combination compositions, combination uses and kits preferred Formula I compounds include the preferred groups of compounds described above.

[0118] In the above combination compositions, combination methods and kits preferred glycogen phosphorylase inhibitors are

5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amide, 5,6-dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide,

5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide,

5-chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl}-2-phenyl-ethyl)-amide,

5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methyl-pyridin-2-yl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide or

5-chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[methyl-(2-pyridin-2-yl-ethyl)-carbamoyl]-methyl}-2-phenyl-ethyl)-amide.

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-(4-methyl-piperazin-1-yl)-3-oxo-propyl]-amide hydrochloride,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-(3-hydroxy-azetidin-1-yl)-3-oxo-propyl]-amide,

5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide,

5-Chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-(2R)-hydroxy-3-[1,2]oxazinan-2-yl-3-oxo-propyl)-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-3-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide or

5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide.

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid (2-oxo-2-thiazolidin-3-yl-ethyl)-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [2-oxo-2-((1RS)-oxo-1-thiazolidin-3-yl)-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide,

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide,

5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxyimino-azetidin-1-yl)-2-oxo-ethyl]-amide or

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.

[0119] This invention is also directed to a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug;

a second compound, said second compound being an aldose reductase inhibitor; and/or optionally a pharmaceutical carrier, vehicle or diluent.

[0120] Another aspect of this invention is the use

- a. a first compound, said first compound being a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and
- b. a second compound, said second compound being an aldose reductase inhibitor

for the manufacture of a medicament for reducing tissue damage (e.g., substantially preventing tissue damage, inducing tissue protection) resulting from or which could result from ischemia.

[0121] Another aspect of this invention is a kit comprising:

- a. a therapeutically effective amount of a Formula I compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;
- b. a therapeutically effective amount of an aldose reductase inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and
- c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

[0122] In the above combination compositions, combination uses and kits preferred Formula I compounds include the preferred groups of compounds described above.

[0123] In the above combination compositions, combination uses and kits a preferred aldose reductase inhibitor is zopolrestat: 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]-.

[0124] In the uses as applied to the combinations described above the following are preferred administration routes, modes etc.

[0125] Preferred ischemic tissues taken individually or as a group are wherein the ischemic tissue is cardiac, brain, liver, kidney, lung, gut, skeletal muscle, spleen, pancreas, nerve, spinal cord, retina tissue, the vasculature, or intestinal tissue.

[0126] An especially preferred ischemic tissue is cardiac tissue.

[0127] It is especially preferred that the compounds are administered to prevent perioperative myocardial ischemic injury.

[0128] Preferably, the compounds of this invention are administered prophylactically.

[0129] The ischemic damage may occur during organ transplantation.

[0130] Preferably, the compounds of this invention are administered prior to, during or shortly after, cardiac surgery or non-cardiac surgery.

[0131] In one aspect of this invention the compounds are administered locally.

[0132] In one aspect of this invention myocardial tissue damage is reduced during surgery.

[0133] In another aspect of this invention myocardial tissue damage is reduced in patients presenting with ongoing cardiac or cerebral ischemic events.

[0134] In yet another aspect of this invention myocardial tissue damage is reduced by chronic administration of the combination in a patient with diagnosed coronary heart disease.

[0135] The term "reduction" is intended to include partial prevention or prevention which, although greater than that which would result from taking no compound or from taking a placebo, is less than 100% in addition to substantially total prevention.

[0136] The term "damage resulting from ischemia" as employed herein refers to conditions directly associated with reduced blood flow to tissue, for example due to a clot or obstruction of blood vessels which supply blood to the subject tissue and which result, *inter alia*, in lowered oxygen transport to such tissue, impaired tissue performance, tissue dysfunction and/or necrosis. Alternatively, where blood flow or organ perfusion may be quantitatively adequate, the oxygen carrying capacity of the blood or organ perfusion medium may be reduced, e.g., in hypoxic environment, such that oxygen supply to the tissue is lowered, and impaired tissue performance, tissue dysfunction, and/or tissue necrosis ensues.

[0137] The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

[0138] By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

[0139] The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

[0140] Exemplary five to six membered aromatic rings optionally having one or two heteroatoms selected independ-

ently from oxygen, nitrogen and sulfur are phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl and pyrazinyl.

[0141] Exemplary partially saturated, fully saturated or fully unsaturated five to eight membered rings optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five membered rings are furyl, thienyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathioly, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazo, 1,3,4-thiadiazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathioly.

[0142] Further exemplary six membered rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl and 1,4,2-oxadiazinyl.

[0143] Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

[0144] Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

[0145] Exemplary bicyclic rings consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen are indoliziny, indolyl, isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazoliny, quinoxaliny, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

[0146] By alkylene is meant saturated hydrocarbon (straight chain or branched) wherein a hydrogen atom is removed from each of the terminal carbons. Exemplary of such groups (assuming the designated length encompasses the particular example) are methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene).

[0147] By halo is meant chloro, bromo, iodo, or fluoro.

[0148] By alkyl is meant straight chain saturated hydrocarbon or branched saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, neopentyl, tertiary pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl and octyl.

[0149] By alkoxy is meant straight chain saturated alkyl or branched saturated alkyl bonded through an oxygen. Exemplary of such alkoxy groups, (assuming the designated length encompasses the particular example) are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, neopentoxy, tertiary pentoxy, hexoxy, isohexoxy, heptoxy and octoxy .

[0150] As used herein the term mono-N- or di-N,N-(C₁-C_x)alkyl... refers to the (C₁-C_x)alkyl moiety taken independently when it is di-N,N-(C₁-C_x)alkyl...(x refers to integers).

[0151] It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3-, or 4-pyridyl, the term "thienyl" means 2-, or 3-thienyl, and so forth.

[0152] The expression "pharmaceutically-acceptable salt" refers to nontoxic anionic salts containing anions such as (but not limited to) chloride, bromide, iodide, sulfate, bisulfate, phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, methanesulfonate and 4-toluene-sulfonate. Where more than one basic moiety exists the expression includes multiple salts (e.g., di-salt). The expression also refers to nontoxic cationic salts such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-methyl-glucamine), benethamine (N-benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

[0153] As used herein, the expressions "reaction-inert solvent" and "inert solvent" refers to a solvent or mixture of solvents which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

[0154] The chemist of ordinary skill will recognize that certain compounds of this invention will contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixtures thereof are included in this invention. Hydrates of the compounds of this invention are also included.

[0155] DMF means N,N-dimethylformamide. DMSO means dimethyl sulfoxide. THF means tetrahydrofuran.

[0156] The subject invention also includes isotopically-labelled compounds, which are identical to those recited in

Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

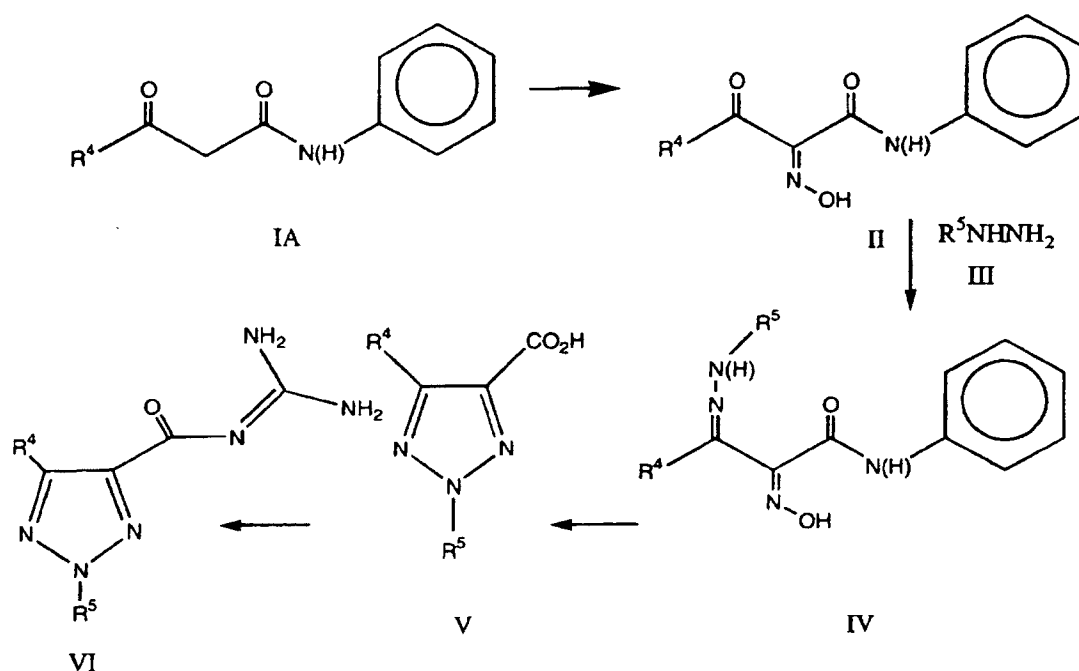
[0157] Other features and advantages will be apparent from the specification and claims which describe the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0158] In general the compounds of this invention can be made by processes which include processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of this invention are provided as further features of the invention and are illustrated by the following reaction schemes. Other processes are described in the experimental section.

[0159] Briefly, in general, a compound of the Formula Z-C(O)OH is coupled with guanidine in the presence of a suitable coupling agent.

SCHEME I



SCHEME II

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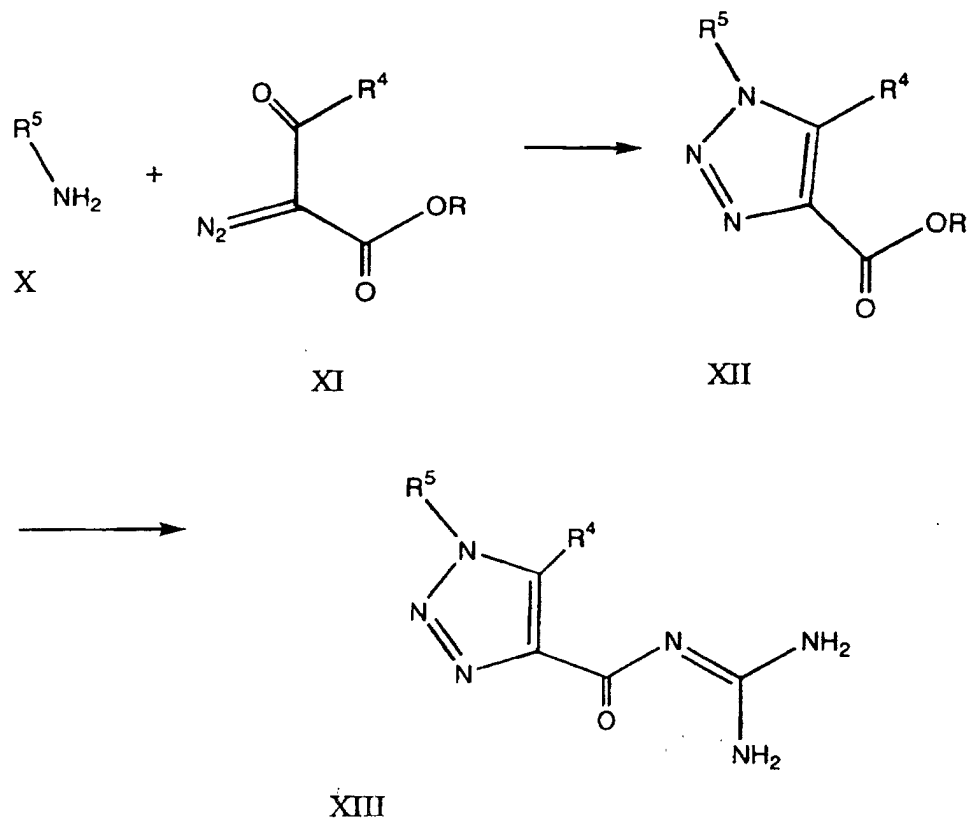
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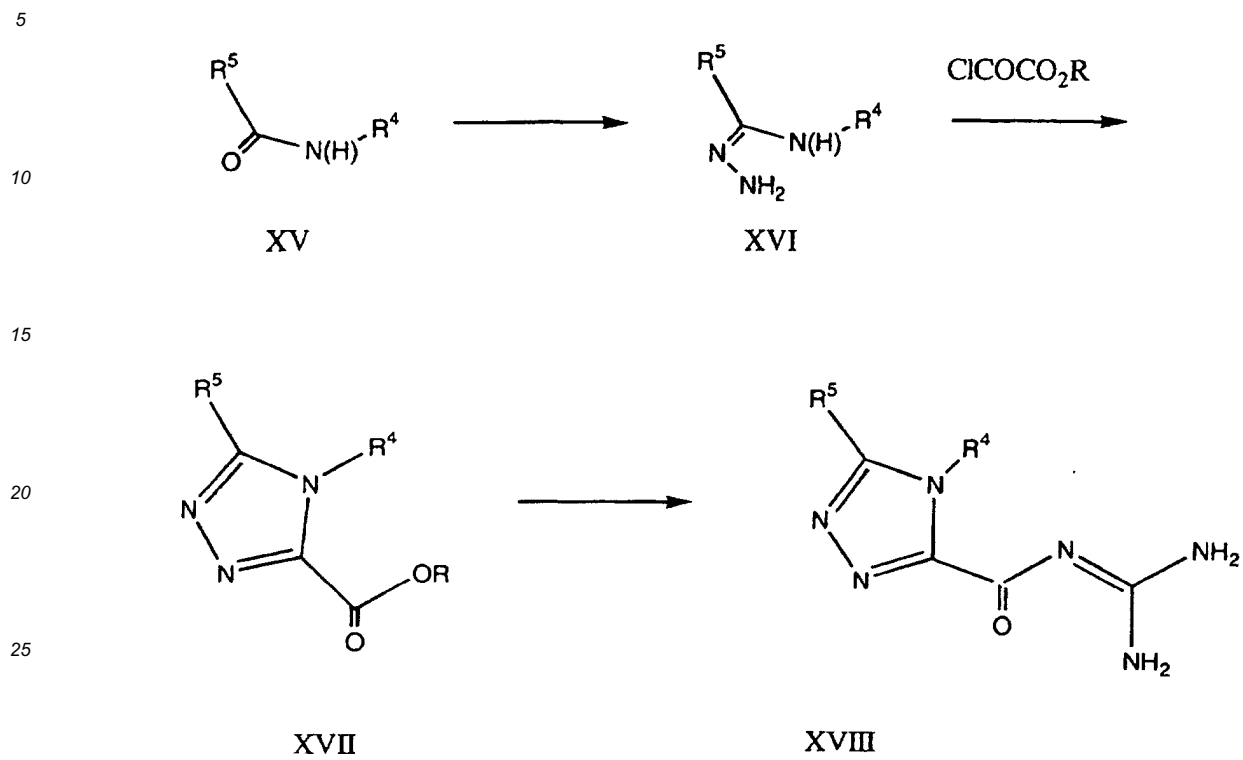
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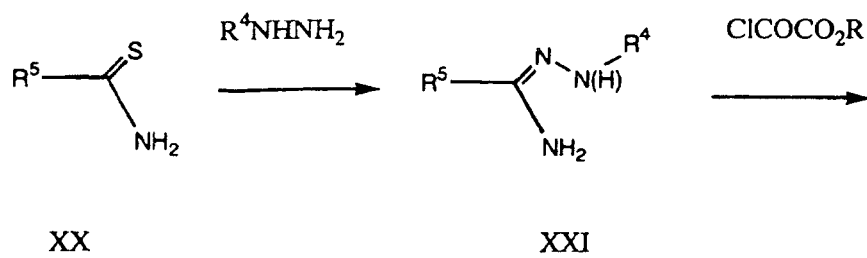
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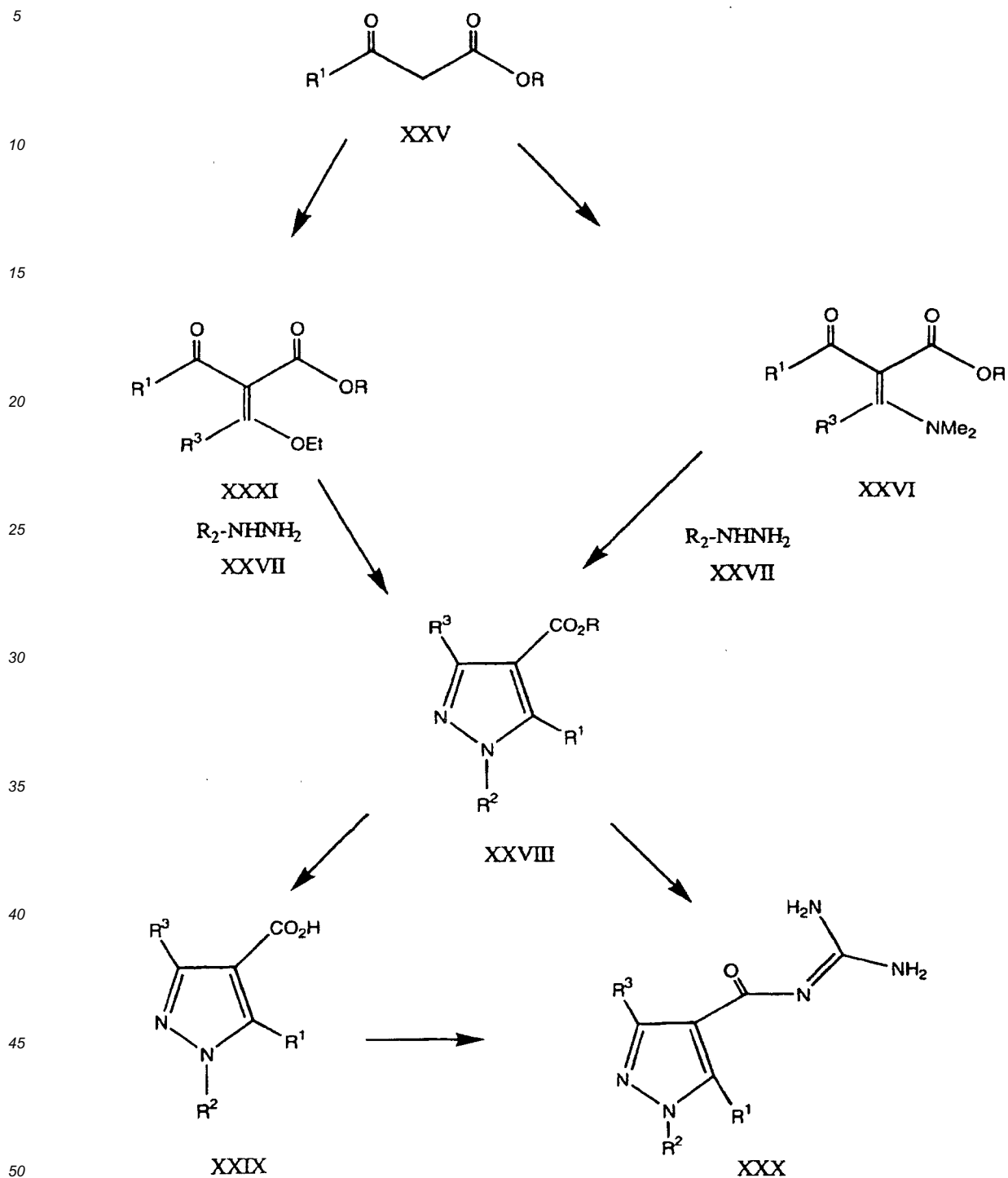
SCHEME III



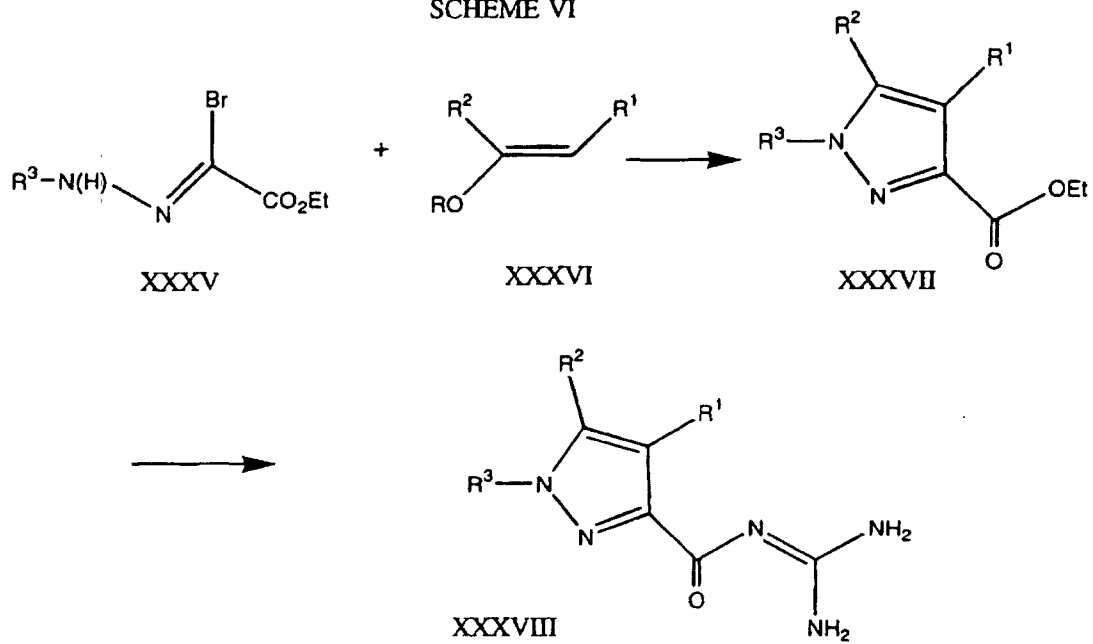
SCHEME IV



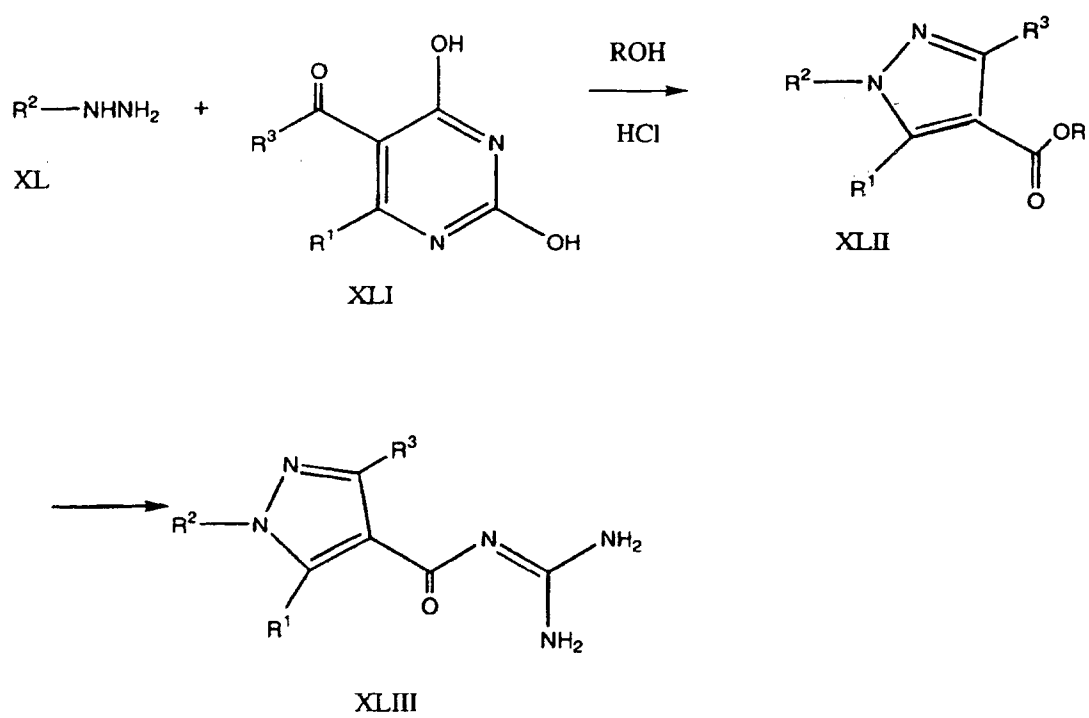
SCHEME V



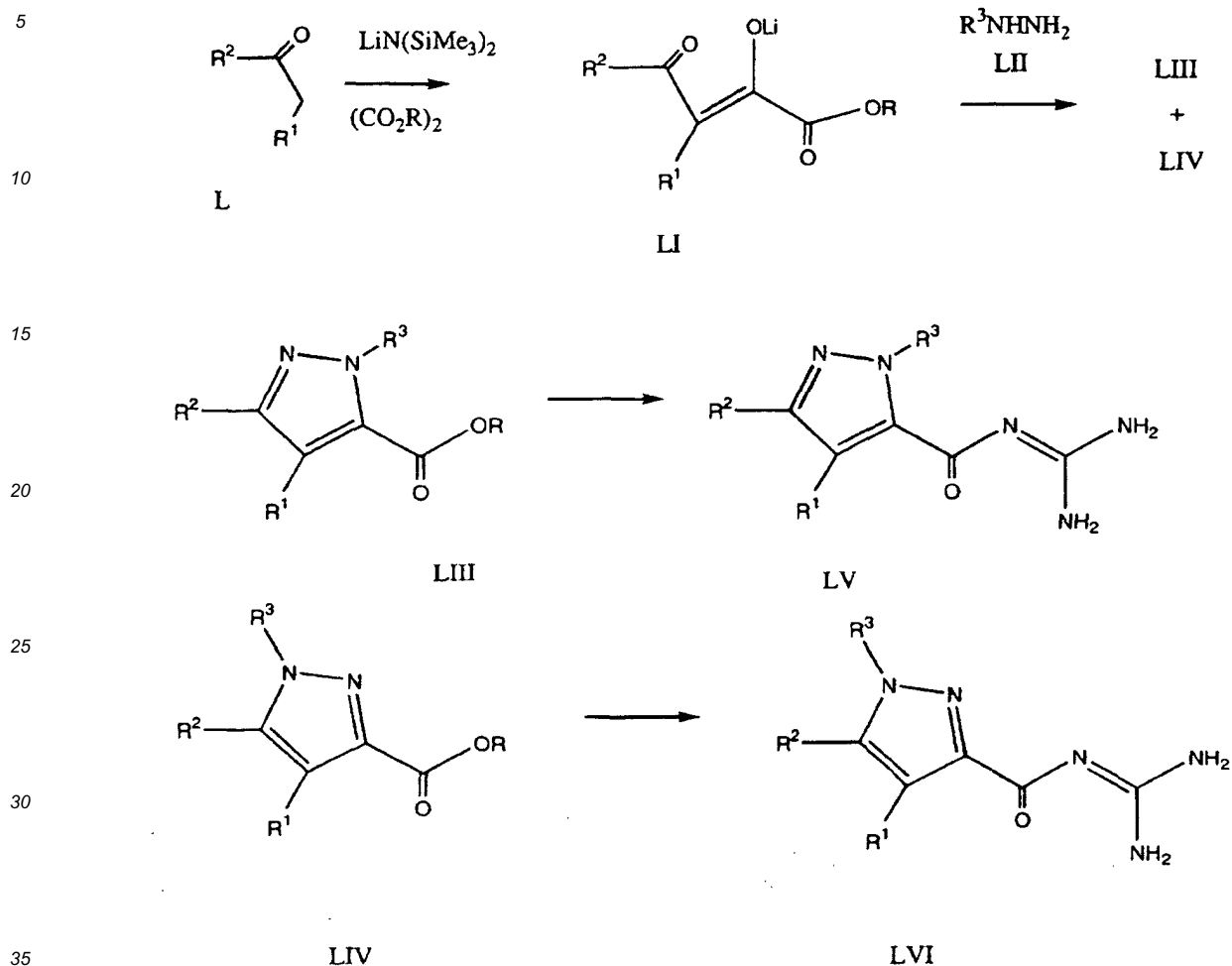
SCHEME VI



SCHEME VII



SCHEME VIII



[0160] According to Scheme I the Formula IA compound, wherein R^4 is as described above, is dissolved or suspended in an aqueous alkali metal hydroxide solution (e.g. 1 N sodium hydroxide) along with sodium nitrite and the mixture is added to an aqueous acidic solution (e.g. 10% v/v sulfuric acid) at a pH of about 0 at a temperature of about 0°C to about 5°C for about 30 min to about 1 hour. The resulting mixture is filtered to yield the Formula II oxime. Alternatively, the Formula IA compound is dissolved in 1:1 acetic acid/propionic acid and solid sodium nitrite is added at about 0°C . The reaction mixture is stirred at about 0°C for about 2 hours, then poured into ice water and the Formula II oxime is obtained by filtration.

[0161] The Formula II compound is reacted with a Formula III compound, wherein R^5 is as described above in a protic solvent such as ethanol at a temperature of about 50°C to about 110°C for about 10 min to about 1 hour to form the Formula IV hydrazone.

[0162] The Formula IV hydrazone is cyclized and hydrolyzed to the Formula V triazole in an alcoholic solvent such as 2-ethoxyethanol under basic conditions (e.g., potassium hydroxide) at a temperature of about 100°C to about 175°C for about 1/2 hour to about 2 hours followed by acidification to yield the Formula V triazole acid.

[0163] The Formula V acid is coupled with guanidine in the presence of a suitable coupling agent. A suitable coupling agent is one which transforms a carboxylic acid into a reactive species which forms an amide linkage on reaction with an amine.

[0164] The coupling agent may be a reagent which effects this condensation in a one pot process when mixed together with the carboxylic acid and guanidine. Exemplary coupling reagents are 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride-hydroxybenzotriazole (EDC/HBT), dicyclohexylcarbodiimide/hydroxybenzotriazole (HBT), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), and diethylphosphorylcyanide. The coupling is performed in an inert solvent, preferably an aprotic solvent at a temperature of about -20°C to about 50°C for about 1 to about 48

hours, in the presence of excess guanidine as base. Exemplary solvents include acetonitrile, dichloromethane, dimethylformamide and chloroform or mixtures thereof.

[0165] The coupling agent may also be that agent which converts the carboxylic acid to an activated intermediate which is isolated and/or formed in a first step and allowed to react with guanidine in a second step. Examples of such coupling agents and activated intermediates are thionyl chloride or oxalyl chloride to form the acid chloride, cyanuric fluoride to form an acid fluoride or an alkyl chloroformate such as isobutyl or isopropenyl chloroformate or propanephosphonic anhydride (propanephosphonic acid anhydride, PPA) (with a tertiary amine base) to form a mixed anhydride of the carboxylic acid, or carbonyldiimidazole to form an acylimidazole. If the coupling agent is oxalyl chloride, it is advantageous to employ a small amount of dimethylformamide as cosolvent with another solvent (such as dichloromethane) to catalyze the formation of the acid chloride. This activated acid derivative may be coupled by mixing with excess guanidine in an appropriate solvent together with an appropriate base. Appropriate solvent/base combinations are for example, dichloromethane, dimethylformamide or acetonitrile or mixtures thereof in the presence of excess guanidine as base. Other appropriate solvent/base combinations include water or a ((C₁-C₅)alcohol) or a mixture thereof together with a cosolvent such as dichloromethane, tetrahydrofuran or dioxane and a base such as sodium, potassium or lithium hydroxide in sufficient quantity to consume the acid liberated in the reaction. Use of these coupling agents and appropriate selection of solvents and temperatures are known to those skilled in the art or can be readily determined from the literature. These and other exemplary conditions useful for coupling carboxylic acids are described in Houben-Weyl, Vol XV, part II, E. Wunsch, Ed., G. Theime Verlag, 1974, Stuttgart; M. Bodansky, Principles of Peptide Synthesis, Springer-Verlag, Berlin 1984; and The Peptides, Analysis, Synthesis and Biology (ed. E. Gross and J. Meienhofer), vols 1-5 (Academic Press, NY 1979-1983).

[0166] According to Scheme II, the Formula X primary amine wherein R⁵ is as described above is reacted with a Formula XI α -diazo- β -keto-ester wherein R⁴ is as described above, and R is lower alkyl, in the presence of titanium tetrachloride analogously to the method described in Eguchi S. *et al. Synthesis 1993*, 793 to form the Formula XII triazole carboxylic acid ester. The Formula XII ester is converted directly to the acylguanidine XIII by reaction with guanidine in an alcoholic solvent at a temperature of about 60 to about 110°C, preferably refluxing methanol, for a period of 8 to 20 hours.

[0167] According to Scheme III, the Formula XV compound wherein R⁴ and R⁵ are as described above is treated with Lawesson's reagent (i.e., 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in an aprotic solvent such as dimethoxyethane at a temperature of about 20°C to about 120°C for about one to eight hours. The resulting thioamide is treated with an alkylating agent such as methyl iodide in a polar, inert solvent such as acetone, conveniently at ambient temperature for about eight hours to about forty-eight hours. The resulting compound is reacted with anhydrous hydrazine in an alcoholic solvent at a temperature of about 0°C to about 25°C for about one to eight hours to provide the Formula XVI compound (analogously as described in Doyle and Kurzer, *Synthesis 1974*, 583).

[0168] The Formula XVI compound is treated with a monoalkyloxalyl chloride in an aprotic solvent at a temperature of about 25°C to about 50°C for about one to eight hours to provide the Formula XVII carboxylic ester compound wherein R is lower alkyl. The Formula XVII ester is directly coupled with guanidine in an alcoholic solvent at a temperature of about 60°C to about 110 °C, preferably refluxing methanol, for a period of eight to twenty hours, to prepare the Formula XVIII triazole carbonyl guanidines.

[0169] According to Scheme IV the Formula XX compound wherein R⁵ is as described above is treated with methyl iodide in an inert solvent, conveniently at ambient temperature for about four to twenty-four hours. The resulting compound is reacted with anhydrous R⁴-hydrazine (wherein R⁴ is as described above) in an alcoholic solvent at a temperature of about 0°C to about 25°C for about one to eight hours to provide the Formula XXI amidrazone compound (analogously as described in Doyle and Kurzer, *Synthesis 1974*, 583).

[0170] The Formula XXI compound is treated with a monoalkyloxalyl chloride in an aprotic solvent at a temperature of about 25°C to about 50°C for about one to eight hours to provide the Formula XXII carboxylic ester compound wherein R is lower alkyl. The Formula XXII ester is directly coupled with guanidine in an alcoholic solvent at a temperature of about 60°C to about 110°C, preferably refluxing methanol, for a period of eight to twenty hours to prepare the Formula XXIII triazole carbonyl guanidines.

[0171] According to Scheme V the Formula XXV compound wherein R¹ is as described above is combined with excess (CH₃O)₂C(R³)N(CH₃)₂ (N,N-dimethyl amide dimethyl acetal) wherein R³ is as described above, optionally in the presence of an acid catalyst such as *p*-toluenesulfonic acid at a temperature of about 90°C to about 110°C for about one to about two hours to prepare the Formula XXVI compound above.

[0172] The Formula XXVI compound is cyclized with a Formula XXVII compound, wherein R² is as described above, in an inert solvent such as ethanol at a temperature of about 20°C to about 30°C for about 5 minutes to about one hour followed by heating to a temperature of about 70°C to about 110°C for about two hours to about four hours to form the Formula XXVIII pyrazole.

[0173] Alternatively, according to Scheme V the Formula XXV compound, wherein R¹ is as described above, is combined with a triethylorthoester (i.e., R³C(OEt)₃ wherein R³ is as described above) and acetic anhydride at a tem-

perature of about 120°C to about 150 °C for about two to about five hours to prepare the Formula XXXI compound.

[0174] The Formula XXXI compound is cyclized with a Formula XXVII compound, wherein R² is as described above, to form the Formula XXVIII pyrazole.

[0175] The Formula XXVIII pyrazole is hydrolyzed with a base such as sodium hydroxide or lithium hydroxide in a solvent such as water and/or methanol and/or THE conveniently at ambient temperature or at elevated temperature (e.g., reflux) for about one hour to about five hours to prepare the Formula XXIX acid.

[0176] The Formula XXIX acid is coupled with guanidine in the presence of a suitable coupling agent as described for the above coupling of the Formula V acid and guanidine. In one embodiment, the Formula XXIX acid is activated with thionyl chloride at a temperature of about 60°C to about 90°C for about fifteen minutes to about two hours. The resulting activated acid chloride is combined with guanidine hydrochloride and an inorganic base (e.g., sodium hydroxide) in anhydrous tetrahydrofuran and optionally methanol and/or water. The solution is heated, conveniently at reflux, for about one hour to about eight hours to prepare the Formula XXX compound.

[0177] Alternatively according to Scheme V the Formula XXVIII compound can be directly converted to the Formula XXX compound by several methods. For example, the Formula XXVIII compound can be heated in the presence of excess guanidine, in a polar protic solvent for example, methanol or isopropanol at a suitable temperature conveniently, at reflux for about one to about seventy-two hours. This transformation may also be performed by repeatedly removing the solvent, for example removing ethanol or toluene about four times, from a mixture of the Formula XXVIII compound and excess guanidine at a pressure of about one to about 100 mmHg and at a temperature of about 25°C to about 95°C. This reaction may also be performed in the absence of solvent by heating the mixture of the Formula XXVIII compound and excess guanidine at a temperature of about 100°C to about 180°C, optionally at about a pressure of about 1 to about 100 mmHg for about five minutes to about eight hours.

[0178] According to Scheme VI, the Formula XXXV compound, wherein R³ is as described above, is reacted with the Formula XXXVI compound, wherein R¹ and R² are as described above, in an aprotic solvent at a temperature of about 0°C to about 25°C for about two hours to about twenty-four hours in the presence of an appropriate amine base, such as triethylamine, to form the Formula XXXVII compound.

[0179] The resulting Formula XXXVII compound is hydrolyzed and coupled with guanidine using one of the methods described in earlier Schemes, such as the method employing carbonyldiimidazole, to form the Formula XXXVIII compound.

[0180] According to Scheme VII, the Formula XL hydrazine, wherein R² is as described above, is reacted with the appropriate Formula XLI compound to form the Formula XLII pyrazole ester wherein R is lower alkyl according to the method of Bajnati, A. and Hubert-Habart, M. *Bull. Soc. Chim. France 1988*, 540. The resulting pyrazole ester is converted to the Formula XLIII acyl guanidine using the hydrolysis and coupling methods described above.

[0181] According to Scheme VIII, the Formula L compound wherein R² and R¹ are as described above is transformed to the Formula LI lithium salt where R is lower alkyl according to the method described in *J. Het. Chem. 1989*, 26, 1389. The Formula LI lithium salt is combined with the Formula LII hydrazine, wherein R³ is as described above, in an inert solvent such as ethanol, in the presence of a mineral acid, at a temperature of about 20°C to about 30°C for about five minutes to about one hour followed by heating to a temperature of about 70°C to about 110°C for two hours to about four hours to form both the Formula LIII and LIV pyrazoles. The Formula LIII and LIV pyrazoles are converted to the Formula LV and LVI acyl guanidines respectively using the hydrolysis and coupling methods described above.

[0182] Some of the methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in Formula I precursors). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

[0183] The starting materials and reagents for the above described compounds, are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, the aromatic hydrazines used in this invention can be prepared from the corresponding aromatic amines by diazotization followed by reduction conveniently using stannous chloride using procedures known to those skilled in the art. For example, many of the compounds used herein are related to, or are derived from compounds found in nature, in which there is a large scientific interest and commercial need, and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature.

[0184] Some of the compounds of this invention have asymmetric carbon atoms and therefore are enantiomers or diastereomers. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known per se., for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyz-

ing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers and mixtures thereof are considered as part of this invention. Also, some of the compounds of this invention are atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

[0185] Those skilled in the art will recognize that the compounds of Formula I can exist in several tautomeric forms. All such tautomeric forms are considered as part of this invention. For example, all of the tautomeric forms of the carbonylguanidine moiety of the compounds of Formula I are included in this invention. Also, for example all enol-keto forms of the compounds of Formula I are included in this invention.

[0186] Some of the compounds of this invention are acidic and they form a salt with a pharmaceutically acceptable cation. All of the compounds of this invention are basic and they form a salt with a pharmaceutically acceptable anion. All such salts, including di-salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, in either an aqueous, non-aqueous or partially aqueous medium. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

[0187] In addition, when the compounds of this invention form metabolites, hydrates or solvates they are also within the scope of the invention.

[0188] Other cardiovascular agents known to those skilled in the art for example β -blockers (e.g., acebutolol, atenolol, bopindolol, labetalol, mepindolol, nadolol, oxprenol, pindolol, propranolol, sotalol), calcium channel blockers (e.g., amlodipine, nifedipine, nisoldipine, nitrendipine, verapamil), potassium channel openers, adenosine, adenosine agonists, ACE inhibitors (e.g., captopril, enalapril), nitrates (e.g., isosorbide dinitrate, isosorbide 5-mononitrate, glyceryl trinitrate), diuretics (e.g., hydrochlorothiazide, indapamide, piretanide, xipamide), glycosides (e.g., digoxin metildigoxin), thrombolytics (e.g. tPA), platelet inhibitors (e.g., reopro), aspirin, dipyridamol, potassium chloride, clonidine, prazosin, aldose reductase inhibitors (e.g., zopolrestat) and adenosine A_3 receptor agonists may be used in conjunction with the compounds of this invention.

[0189] In combination therapy treatment, both the compounds of this invention and the other drug therapies are administered to mammals (e.g., humans, male or female) by conventional methods.

[0190] Any aldose reductase inhibitor may be used as the second compound (active agent) of this invention for combination therapies. The term aldose reductase inhibitor refers to compounds which inhibit the bioconversion of glucose to sorbitol catalyzed by the enzyme aldose reductase. Such inhibition is readily determined by those skilled in the art according to standard assays (J. Malone, *Diabetes*, 29:861-864, 1980. "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are described and referenced below, however, other aldose reductase inhibitors will be known to those skilled in the art. The disclosures of U.S. patents listed below are hereby incorporated by reference. Also, common chemical USAN names or other designation are in parentheses where applicable, together with reference to appropriate patent literature disclosing the compound.

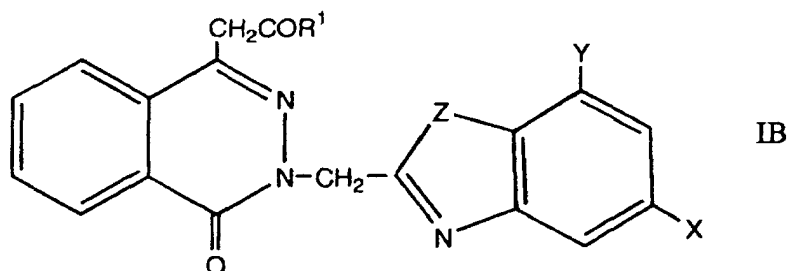
[0191] The activity of an aldose reductase inhibitor in a tissue can be determined by testing the amount of aldose reductase inhibitor that is required to lower tissue sorbitol (i.e., by inhibiting the further production of sorbitol consequent to blocking aldose reductase) or lower tissue fructose (by inhibiting the production of sorbitol consequent to blocking aldose reductase and consequently the production of fructose). While not wishing to be bound by any particular theory or mechanism, it is believed that an aldose reductase inhibitor, by inhibiting aldose reductase, prevents or reduces ischemic damage as described hereinafter.

[0192] Accordingly, examples of aldose reductase inhibitors useful in the compositions and methods of this invention include:

1. 3-(4-bromo-2-fluorobenzyl)-3,4-dihydro-4-oxo-1-phthalazineacetic acid (ponalrestat, US 4,251,528);
2. N[[5-(trifluoromethyl)-6-methoxy-1-naphthalenyl]thioxomethyl]-N-methylglycine (tolrestat, US 4,600,724);
3. 5-[(Z,E)- β -methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolideneacetic acid (epalrestat, US 4,464,382, US 4,791,126, US 4,831,045);
4. 3-(4-bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetic acid (zenarestat, US 4,734,419, and 4,883,800);
5. 2R,4R-6,7-dichloro-4-hydroxy-2-methylchroman-4-acetic acid (US 4,883,410);
6. 2R,4R-6,7-dichloro-6-fluoro-4-hydroxy-2-methylchroman-4-acetic acid (US 4,883,410);
7. 3,4-dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetic acid (US 4,771,050);
8. 3,4-dihydro-3-oxo-4-[(4,5,7-trifluoro-2-benzothiazolyl)methyl]-2H-1,4-benzothiazine-2-acetic acid (SPR-210, U.S. 5,252,572);
9. N-[3,5-dimethyl-4-[(nitromethyl)sulfonyl]phenyl]-2-methyl-benzeneacetamide (ZD5522, U.S. 5,270,342 and U.S. 5,430,060);
10. (S)-6-fluorospiro[chroman-4,4'-imidazolidine]-2,5'-dione (sorbiniil, US 4,130,714);
11. d-2-methyl-6-fluoro-spiro(chroman-4',4'-imidazolidine)-2',5'-dione (US 4,540,704);
12. 2-fluoro-spiro(9H-fluorene-9,4'-imidazolidine)2',5'-dione (US 4,438,272);

13. 2,7-di-fluoro-spiro(9H-fluorene-9,4'imidazolidine)2',5'-dione (US 4,436,745, US 4,438,272);
 14. 2,7-di-fluoro-5-methoxy-spiro(9H-fluorene-9,4' imidazolidine)2',5'-dione (US 4,436,745, US 4,438,272);
 15. 7-fluoro-spiro(5H-indenol[1,2-b]pyridine-5,3'-pyrrolidine)2,5'-dione (US 4,436,745, US 4,438,272);
 16. d-cis-6'-chloro-2',3'-dihydro-2'-methyl-spiro-(imidazolidine-4,4'-4'-H-pyrano(2,3-b)pyridine)-2,5'-dione (US
 4,980,357);
 17. spiro[imidazolidine-4,5'(6H)-quinoline]2,5'-dione-3'-chloro-7',8'-dihydro-7'-methyl-(5'-cis) (US 5,066,659);
 18. (2S,4S)-6-fluoro-2',5'-dioxospiro(chroman-4,4'-imidazolidine)-2-carboxamide (US 5,447,946); and
 19. 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (ARI-
 509, US 5,037,831).

Other aldose reductase inhibitors include compounds having formula IB



or a pharmaceutically acceptable salt thereof, wherein

Z is O or S;

R¹ is hydroxy or a group capable of being removed *in vivo* to produce a compound of formula IB wherein R¹ is OH; and

X and Y are the same or different and are selected from hydrogen, trifluoromethyl, fluoro, and chloro.

A preferred subgroup within the above group of aldose reductase inhibitors includes numbered compounds

1, 2, 3, 4, 5, 6, 9, 10, and 17, and the following compounds of Formula IB:

20. 3,4-dihydro-3-(5-fluorobenzothiazol-2-ylmethyl)-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=F; Y=H];
 21. 3-(5,7-difluorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=Y=F];
 22. 3-(5-chlorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=Cl; Y=H];
 23. 3-(5,7-dichlorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=Y=Cl];
 24. 3,4-dihydro-4-oxo-3-(5-trifluoromethylbenzoxazol-2-ylmethyl)phthalazin-1-ylacetic acid [R¹=hydroxy; X=CF₃; Y=H];
 25. 3,4-dihydro-3-(5-fluorobenzoxazol-2-ylmethyl)-4-oxophthalazin-1-yl-acetic acid [R¹=hydroxy; X=F; Y=H];
 26. 3-(5,7-difluorobenzoxazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=Y=F];
 27. 3-(5-chlorobenzoxazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=Cl; Y=H];
 28. 3-(5,7-dichlorobenzoxazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R¹=hydroxy; X=Y=Cl];
 and
 29. zopolrestat; 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-
 [R¹=hydroxy; X=trifluoromethyl; Y=H].

[0193] In compounds 20-23, and 29 Z is S. In compounds 24-28, Z is O.

[0194] Of the above subgroup, compounds 20-29 are more preferred with 29 especially preferred.

[0195] An especially preferred aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl)-2-benzothiazolyl]methyl]-.

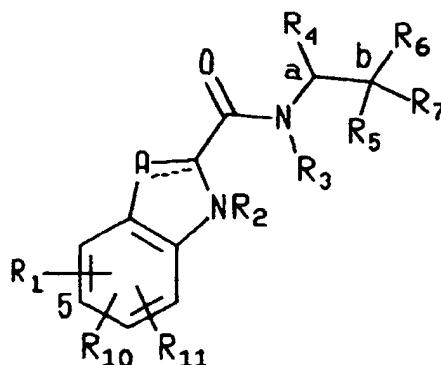
[0196] The aldose reductase inhibitor compounds of this invention are readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis, particularly in view of the pertinent patent specification descriptions.

[0197] An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention may be used. Typically, an effective dosage for the aldose reductase inhibitors of this invention is in the range of about 0.1 mg/kg/day to 100 mg/kg/day in single or divided doses, preferably 0.1 mg/kg/day to 20 mg/kg/day in single or divided doses.

[0198] Any glycogen phosphorylase inhibitor may be used as the second compound of this invention. The term glycogen phosphorylase inhibitor refers to any substance or agent or any combination of substances and/or agents which reduces, retards, or eliminates the enzymatic action of glycogen phosphorylase. The currently known enzymatic

action of glycogen phosphorylase is the degradation of glycogen by catalysis of the reversible reaction of a glycogen macromolecule and inorganic phosphate to glucose-1-phosphate and a glycogen macromolecule which is one glucosyl residue shorter than the original glycogen macromolecule (forward direction of glycogenolysis). Such actions are readily determined by those skilled in the art according to standard assays (e.g., as described hereinafter). A variety of these compounds are included in the following published international patent applications: PCT application publication WO 96/39384 and W096/39385. However, other glycogen phosphorylase inhibitors will be known to those skilled in the art.

[0199] Preferred glycogen phosphorylase inhibitors include compounds having the Formula IC



Formula IC

and the pharmaceutically acceptable salts and prodrugs thereof
wherein

the dotted line (---) is an optional bond;

A is -C(H)=, -C((C₁-C₄)alkyl)= or -C(halo)= when the dotted line (---) is a bond, or A is methylene or -CH((C₁-C₄)alkyl)- when the dotted line (---) is not a bond;

R₁, R₁₀ or R₁₁ are each independently H, halo, 4-, 6- or 7-nitro, cyano, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl;

R₂ is H;

R₃ is H or (C₁-C₅)alkyl;

R₄ is H, methyl, ethyl, n-propyl, hydroxy(C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, phenyl(C₁-C₄)alkyl, phenylhydroxy(C₁-C₄)alkyl, phenyl(C₁-C₄)alkoxy(C₁-C₄)alkyl, thien-2- or -3-yl(C₁-C₄)alkyl or fur-2- or -3-yl(C₁-C₄)alkyl wherein said R₄ rings are mono-, di- or tri-substituted independently on carbon with H, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, trifluoromethyl, hydroxy, amino or cyano; or

R₄ is pyrid-2-, -3- or -4-yl(C₁-C₄)alkyl, thiazol-2-, -4- or -5-yl(C₁-C₄)alkyl, imidazol-1-, -2-, -4- or -5-yl(C₁-C₄)alkyl, pyrrol-2- or -3-yl(C₁-C₄)alkyl, oxazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isoxazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isothiazol-3-, -4- or -5-yl(C₁-C₄)alkyl, pyridazin-3- or -4-yl(C₁-C₄)alkyl, pyrimidin-2-, -4-, -5- or -6-yl(C₁-C₄)alkyl, pyrazin-2- or -3-yl(C₁-C₄)alkyl or 1,3,5-triazin-2-yl(C₁-C₄)alkyl, wherein said preceding R₄ heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, amino or hydroxy and said mono- or di-substituents are bonded to carbon;

R₅ is H, hydroxy, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₆)alkanoyl, amino(C₁-C₄)alkoxy, mono-N- or di-N, N-(C₁-C₄)alkylamino(C₁-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, (C₁-C₅)alkoxy-carbonyl(C₁-C₄)alkoxy, benzyloxycarbonyl(C₁-C₄)alkoxy, or carbonyloxy wherein said carbonyloxy is carbon-carbon linked with phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and wherein said preceding R₅ rings are optionally mono-substituted with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, amino or trifluoromethyl and said mono-substituents are bonded to carbon;

R₇ is H, fluoro or (C₁-C₅)alkyl; or

R₅ and R₇ can be taken together to be oxo;

R₆ is carboxy, (C₁-C₈)alkoxycarbonyl, C(O)NR₈R₉ or C(O)R₁₂,

wherein

R₈ is H, (C₁-C₃)alkyl, hydroxy or (C₁-C₃)alkoxy; and

R₉ is H, (C₁-C₈)alkyl, hydroxy, (C₁-C₈)alkoxy, methylene-perfluorinated(C₁-C₈)alkyl, phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or 1,3,5-triazinyl wherein said preceding R₉ rings

are carbon-nitrogen linked; or

R₉ is mono-, di- or tri-substituted (C₁-C₅)alkyl, wherein said substituents are independently H, hydroxy, amino, mono-N- or di-N,N-(C₁-C₅)alkylamino; or

R₉ is mono- or di-substituted (C₁-C₅)alkyl, wherein said substituents are independently phenyl, pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or 1,3,5-triazinyl

wherein the nonaromatic nitrogen-containing R₉ rings are optionally mono-substituted on nitrogen with (C₁-C₆)alkyl, benzyl, benzoyl or (C₁-C₆)alkoxycarbonyl and wherein the R₉ rings are optionally mono-substituted on carbon with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, amino, or mono-N- and di-N,N (C₁-C₅)alkylamino provided that no quaternized nitrogen is included and there are no nitrogen-oxygen, nitrogen-nitrogen or nitrogen-halo bonds;

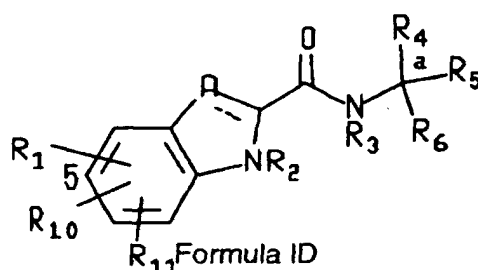
R₁₂ is piperazin-1-yl, 4-(C₁-C₄)alkylpiperazin-1-yl, 4-formylpiperazin-1-yl, morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxo-thiomorpholino, thiazolidin-3-yl, 1-oxo-thiazolidin-3-yl, 1,1-dioxo-thiazolidin-3-yl, 2-(C₁-C₆)alkoxycarbonylpyrrolidin-1-yl, oxazolidin-3-yl or 2(R)-hydroxymethylpyrrolidin-1-yl; or

R₁₂ is 3- and/or 4-mono- or di-substituted oxazetidin-2-yl, 2-, 4-, and/or 5-mono- or di-substituted oxazolidin-3-yl, 2-, 4-, and/or 5-mono- or di-substituted thiazolidin-3-yl, 2-, 4-, and/or 5-mono- or di-substituted 1-oxothiazolidin-3-yl, 2-, 4-, and/or 5-mono- or di-substituted 1,1-dioxothiazolidin-3-yl, 3- and/or 4-, mono- or di-substituted pyrrolidin-1-yl, 3-, 4- and/or 5-, mono-, di- or tri-substituted piperidin-1-yl, 3-, 4-, and/or 5-mono-, di-, or tri-substituted piperazin-1-yl, 3-substituted azetidin-1-yl, 4- and/or 5-, mono- or di-substituted 1,2-oxazinan-2-yl, 3-and/or 4-mono- or di-substituted pyrazolidin-1-yl, 4- and/or 5-, mono- or di-substituted isoxazolidin-2-yl, 4- and/or 5-, mono- and/or di-substituted isothiazolidin-2-yl wherein said R₁₂ substituents are independently H, halo, (C₁-C₅)-alkyl, hydroxy, amino, mono-N- or di-N,N-(C₁-C₅)alkylamino, formyl, oxo, hydroxyimino, (C₁-C₅)alkoxy, carboxy, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkoxyimino, (C₁-C₄)alkoxymethoxy, (C₁-C₆)alkoxycarbonyl, carboxy(C₁-C₅)alkyl or hydroxy (C₁-C₅)alkyl;

with the proviso that if R₄ is H, methyl, ethyl or n-propyl R₅ is OH;

with the proviso that if R₅ and R₇ are H, then R₄ is not H, methyl, ethyl, n-propyl, hydroxy(C₁-C₃)alkyl or (C₁-C₃)alkoxy(C₁-C₃)alkyl and R₆ is C(O)NR₈R₉, C(O)R₁₂ or (C₁-C₄)alkoxycarbonyl.

[0200] Preferred glycogen phosphorylase inhibitors include compounds having the Formula ID



and the pharmaceutically acceptable salts and prodrugs thereof wherein

the dotted line (---) is an optional bond;

A is -C(H)=, -C((C₁-C₄)alkyl)=, -C(halo)= or -N=, when the dotted line (---) is a bond, or A is methylene or -CH((C₁-C₄)alkyl)-, when the dotted line (---) is not a bond;

R₁, R₁₀ or R₁₁ are each independently H, halo, cyano, 4-, 6-, or 7-nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl;

R₂ is H;

R₃ is H or (C₁-C₅)alkyl;

R₄ is H, methyl, ethyl, n-propyl, hydroxy(C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, phenyl(C₁-C₄)alkyl, phenylhydroxy(C₁-C₄)alkyl, (phenyl)((C₁-C₄)-alkoxy)(C₁-C₄)alkyl, thien-2- or -3-yl(C₁-C₄)alkyl or fur-2- or -3-yl(C₁-C₄)alkyl wherein said R₄ rings are mono-, di- or tri-substituted independently on carbon with H, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, trifluoromethyl, hydroxy, amino, cyano or 4,5-dihydro-1H-imidazol-2-yl; or

R₄ is pyrid-2-, -3- or -4-yl(C₁-C₄)alkyl, thiazol-2-, -4- or -5-yl(C₁-C₄)alkyl, imidazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrrol-2- or -3-yl(C₁-C₄)alkyl, oxazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isoxazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isothiazol-3-, -4- or -5-yl(C₁-C₄)alkyl, pyridazin-3- or -4-yl(C₁-C₄)alkyl, pyrimidin-2-, -4-, -5- or -6-yl(C₁-C₄)alkyl, pyrazin-2- or -3-yl(C₁-C₄)alkyl, 1,3,5-triazin-2-yl(C₁-C₄)alkyl or indol-2-(C₁-C₄)alkyl, wherein said preceding R₄ heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, (C₁-C₄)alkyl, (C₁-C₄)

alkoxy, amino, hydroxy or cyano and said substituents are bonded to carbon; or

R_4 is R_{15} -carbonyloxymethyl, wherein said R_{15} is phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and wherein said preceding R_{15} rings are optionally mono- or di-substituted independently with halo, amino, hydroxy, (C₁-C₄)alkyl, (C₁-C₄)alkoxy or trifluoromethyl and said mono- or di-substituents are bonded to carbon;

R_5 is H;

R_6 is carboxy, (C₁-C₈)alkoxycarbonyl, benzyloxycarbonyl, C(O)NR₈R₉ or C(O)R₁₂

wherein

R_8 is H, (C₁-C₆)alkyl, cyclo(C₃-C₆)alkyl, cyclo(C₃-C₆)alkyl(C₁-C₅)alkyl, hydroxy or (C₁-C₈)alkoxy; and

R_9 is H, cyclo(C₃-C₈)alkyl, cyclo(C₃-C₈)alkyl(C₁-C₅)alkyl, cyclo(C₄-C₇)alkenyl, cyclo(C₃-C₇)alkyl(C₁-C₅)alkoxy, cyclo(C₃-C₇)alkoxy, hydroxy, methylene-perfluorinated(C₁-C₈)alkyl, phenyl, or a heterocycle wherein said heterocycle is pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, thiochromanyl or tetrahydrobenzothiazolyl wherein said heterocycle rings are carbon-nitrogen linked; or

R_9 is (C₁-C₆)alkyl or (C₁-C₈)alkoxy wherein said (C₁-C₆)alkyl or (C₁-C₈)alkoxy is optionally monosubstituted with cyclo(C₄-C₇)alken-1-yl, phenyl, thienyl, pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, thiomorpholinyl, 1-oxothiomorpholinyl, 1,1-dioxothiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl or indolyl and wherein said (C₁-C₆)alkyl or (C₁-C₈)alkoxy are optionally additionally independently mono- or di-substituted with halo, hydroxy, (C₁-C₅)alkoxy, amino, mono-N- or di-N,N-(C₁-C₅)alkylamino, cyano, carboxy, or (C₁-C₄)alkoxycarbonyl; and

wherein the R_9 rings are optionally mono- or di-substituted independently on carbon with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, hydroxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino; mono-N- or di-N,N-(C₁-C₄)alkylamino, cyano, carboxy, (C₁-C₅)alkoxycarbonyl, carbamoyl, formyl or trifluoromethyl and said R_9 rings may optionally be additionally mono- or di-substituted independently with (C₁-C₅)alkyl or halo;

with the proviso that no quaternized nitrogen on any R_9 heterocycle is included;

R_{12} is morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, thiazolidin-3-yl, 1-oxothiazolidin-3-yl, 1,1-dioxothiazolidin-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, piperazin-4-yl, azetid-1-yl, 1,2-oxazinan-2-yl, pyrazolidin-1-yl, isoxazolidin-2-yl, isothiazolidin-2-yl, 1,2-oxazetid-2-yl, oxazolidin-3-yl, 3,4-dihydroisoquinolin-2-yl, 1,3-dihydroisoindol-2-yl, 3,4-dihydro-2H-quinol-1-yl, 2,3-dihydro-benzo[1,4]oxazin-4-yl, 2,3-dihydro-benzo[1,4]-thiazine-4-yl, 3,4-dihydro-2H-quinoxalin-1-yl, 3,4-dihydro-benzo[c][1,2]oxazin-1-yl, 1,4-dihydro-benzo[d][1,2]oxazin-3-yl, 3,4-dihydro-benzo[e][1,2]-oxazin-2-yl, 3H-benzo[d]isoxazol-2-yl, 3H-benzo[c]isoxazol-1-yl or azepan-1-yl,

wherein said R_{12} rings are optionally mono-, di- or tri-substituted independently with halo, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, hydroxy, amino, mono-N- or di-N,N-(C₁-C₅)alkylamino, formyl, carboxy, carbamoyl, mono-N- or di-N,N-(C₁-C₅)alkylcarbamoyl, (C₁-C₆)alkoxy(C₁-C₃)alkoxy, (C₁-C₅)alkoxycarbonyl, benzyloxycarbonyl, (C₁-C₅)alkoxycarbonyl(C₁-C₅)alkyl, (C₁-C₄)alkoxycarbonylamino, carboxy(C₁-C₅)alkyl, carbamoyl(C₁-C₅)alkyl, mono-N- or di-N,N-(C₁-C₅)alkylcarbamoyl(C₁-C₅)alkyl, hydroxy(C₁-C₅)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl, oxo, hydroxyimino or (C₁-C₆)alkoxyimino and wherein no more than two substituents are selected from oxo, hydroxyimino or (C₁-C₆)alkoxyimino and oxo, hydroxyimino or (C₁-C₆)alkoxyimino are on non-aromatic carbon; and

wherein said R_{12} rings are optionally additionally mono- or di-substituted independently with (C₁-C₅)alkyl or halo;

with the proviso that when R_6 is (C₁-C₅)alkoxycarbonyl or benzyloxycarbonyl then R_1 is 5-halo, 5-(C₁-C₄)alkyl or 5-cyano and R_4 is (phenyl)(hydroxy)(C₁-C₄)alkyl, (phenyl)((C₁-C₄)alkoxy)(C₁-C₄)alkyl, hydroxymethyl or Ar(C₁-C₂)alkyl, wherein Ar is thien-2- or -3-yl, fur-2- or -3-yl or phenyl wherein said Ar is optionally mono- or di-substituted independently with halo; with the provisos that when R_4 is benzyl and R_5 is methyl, R_{12} is not 4-hydroxy-piperidin-1-yl or when R_4 is benzyl and R_5 is methyl R_6 is not C(O)N(CH₃)₂;

with the proviso that when R_1 and R_{10} and R_{11} are H, R_4 is not imidazol-4-ylmethyl, 2-phenylethyl or 2-hydroxy-2-phenylethyl;

with the proviso that when both R_8 and R_9 are n-pentyl, R_1 is 5-chloro, 5-bromo, 5-cyano, 5(C₁-C₅)alkyl, 5(C₁-C₅)alkoxy or trifluoromethyl;

with the proviso that when R_{12} is 3,4-dihydroisoquinol-2-yl, said 3,4-dihydroisoquinol-2-yl is not substituted with carboxy((C₁-C₄)alkyl);

with the proviso that when R_8 is H and R_9 is (C₁-C₆)alkyl, R_9 is not substituted with carboxy or (C₁-C₄)alkoxycarbonyl on the carbon which is attached to the nitrogen atom N of NHR₉; and

with the proviso that when R_6 is carboxy and R_1 , R_{10} , R_{11} and R_5 are all H, then R_4 is not benzyl, H, (phenyl)(hydroxy)methyl, methyl, ethyl or n-propyl.

[0201] In general an effective dosage for the pharmacological combination compositions of this invention, for example

the ischemic damage reducing activities of combinations containing the glycogen phosphorylase inhibitor compounds of this invention, is in the range of 0.005 to 50 mg/kg/day, preferably 0.01 to 25 mg/kg/day and most preferably 0.1 to 15 mg/kg/day.

[0202] The compounds of the present invention inhibit the sodium/proton (Na⁺/H⁺) exchange transport system and hence are useful as a therapeutic or prophylactic agent for diseases caused or aggravated by the acceleration of the sodium/proton (Na⁺/H⁺) exchange transport system, for example, cardiovascular diseases [e.g., arteriosclerosis, hypertension, arrhythmia (e.g. ischemic arrhythmia, arrhythmia due to myocardial infarction, myocardial stunning, myocardial dysfunction, arrhythmia after PTCA or after thrombolysis, etc.), angina pectoris, cardiac hypertrophy, myocardial infarction, heart failure (e.g. congestive heart failure, acute heart failure, cardiac hypertrophy, etc.), restenosis after PTCA, PTCL, shock (e.g. hemorrhagic shock, endotoxin shock, etc.)], renal diseases (e.g. diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion [(e.g. heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) surgeries, vascular surgeries, organ transplantation, non-cardiac surgeries or percutaneous transluminal coronary angioplasty (PTCA)], cerebrovascular diseases (e.g. ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e.g. disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema. The compounds of this invention can also be used as an agent for myocardial protection during coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA), PTCL, organ transplantation, or non-cardiac surgeries.

[0203] Preferably, the compounds of this invention can be used as agents for myocardial protection before, during, or after coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA), organ transplantation, or non-cardiac surgeries.

[0204] Preferably, the compounds of this invention can be used as agents for myocardial protection in patients presenting with ongoing cardiac (acute coronary syndromes, e.g. myocardial infarction or unstable angina) or cerebral ischemic events (e.g. stroke).

[0205] Preferably, the compounds of this invention can be used as agents for chronic myocardial protection in patients with diagnosed coronary heart disease (e.g. previous myocardial infarction or unstable angina) or patients who are at high risk for myocardial infarction (age greater than 65 and two or more risk factors for coronary heart disease).

[0206] In addition to this, the compounds of this invention are notable for their strong inhibitory effect on the proliferation of cells, for example the proliferation of fibroblast cells and the proliferation of the smooth muscle cells of the blood vessels. For this reason, the compounds of this invention are valuable therapeutic agents for use in diseases in which cell proliferation represents a primary or secondary cause and may, therefore, be used as antiatherosclerotic agents, and as agents against diabetic late complications, cancerous diseases, fibrotic diseases such as pulmonary fibrosis, hepatic fibrosis or renal fibrosis, glomerular nephrosclerosis, organ hypertrophies or hyperplasias, in particular hyperplasia or hypertrophy of the prostate, pulmonary fibrosis, diabetic complications or recurrent stricture after PTCA, or diseases caused by endothelial cell injury.

[0207] The utility of the compounds of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g. humans) for example, myocardial protection during surgery or myocardial protection in patients presenting with ongoing cardiac or cerebral ischemic events or chronic cardioprotection in patients with diagnosed coronary heart disease, or at risk for coronary heart disease, cardiac dysfunction or myocardial stunning is demonstrated by the activity of the compounds of this invention in conventional preclinical cardioprotection assays [see the *in vivo* assay in Klein, H. et al., *Circulation* 92:912-917 (1995); the isolated heart assay in Scholz, W. et al., *Cardiovascular Research* 29:260-268 (1995); the antiarrhythmic assay in Yasutake M. et al., *Am. J. Physiol.*, 36: H2430-H2440 (1994); the NMR assay in Kolke et al., *J. Thorac. Cardiovasc. Surg.* 112: 765-775 (1996)] and the additional *in vitro* and *in vivo* assays described below. Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

Measurement of Human NHE-1 Inhibitory Activity

[0208] Methodologies for measurement of human NHE-1 activity and inhibitor potency are based on those published by Watson et al., *Am. J. Physiol.*, 24:G229-G238, 1991), where NHE-mediated recovery of intracellular pH is measured following intracellular acidification. Thus, fibroblasts stably expressing human NHE-1 (Counillon, L. et al., *Mol. Pharmacol.*, 44:1041-1045 (1993) are plated onto collagen coated 96 well plates (50,000/well) and grown to confluence in growth media (DMEM high glucose, 10% fetal bovine serum, 50 u/ml penicillin and streptomycin). Confluent plates are incubated for 30 min at 37°C with the pH sensitive fluorescent probe BCECF (5 μM; Molecular Probes, Eugene, OR). BCECF loaded cells are incubated for 30 min at 37°C in acid loading media (70 mM choline chloride, 50 mM NH₄Cl, 5 mM KCl, 1 mM MgCl₂, 1.8 mM CaCl₂, 5 mM glucose, 10 mM HEPES, pH 7.5), and then placed in a Fluorescent

Imaging Plate Reader (Molecular Devices, CA). BCECF fluorescence is monitored using excitation and emission wavelengths of 485 nM and 525 nM, respectively. Intracellular acidification is initiated via rapid replacement of acid loading media with recovery media (120 mM NaCl, 5 mM KCl, 1 mM MgCl₂, 1.8 mM CaCl₂, 5 mM glucose, 10 mM HEPES, pH 7.5) ± test compound, and NHE-mediated recovery of intracellular pH is monitored as the subsequent time-dependent increase BCECF fluorescence. The potency of human NHE-1 inhibitors is calculated as the concentration that reduces recovery of intracellular pH by 50% (IC₅₀). Under these conditions reference NHE inhibitors amiloride and HOE-642 had IC₅₀ values for human NHE-1 of 50 μM and 0.5 μM, respectively.

[0209] As background information, it is noted that brief periods of myocardial ischemia followed by coronary artery reperfusion protects the heart from subsequent severe myocardial ischemia (Murry et al., *Circulation* 74:1124-1136, 1986).

[0210] The therapeutic effects of the compounds of this invention in preventing heart tissue damage resulting from an ischemic insult can be demonstrated *in vitro* along lines presented in Liu *et al.* (*Cardiovasc. Res.*, 28:1057-1061, 1994), as described specifically herein. Cardioprotection, as indicated by a reduction in infarcted myocardium, can be induced pharmacologically using adenosine receptor agonists in isolated, retrogradely perfused rabbit hearts as an *in vitro* model of myocardial ischemic preconditioning (Liu *et al.*, *Cardiovasc. Res.*, 28:1057-1061, 1994). The *in vitro* test described below demonstrates that a test compound (*i.e.*, a compound as claimed herein) can also pharmacologically induce cardioprotection, *i.e.*, reduced myocardial infarct size, when administered to a rabbit isolated heart. The effects of the test compound are compared to ischemic preconditioning and the A1/A3 adenosine agonist, APNEA (N⁶-[2-(4-aminophenyl)ethyl]adenosine), that has been shown to pharmacologically induce cardioprotection in the rabbit isolated heart (Liu *et al.*, *Cardiovasc. Res.*, 28:1057-1061, 1994). The exact methodology is described below.

[0211] The protocol used for these experiments closely follows that described by Liu *et al.*, *Cardiovasc. Res.*, 28:1057-1061, 1994. Male New Zealand White rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, *i.v.*). After deep anesthesia is achieved (determined by the absence of an ocular blink reflex) the animal is intubated and ventilated with 100% O₂ using a positive pressure ventilator. A left thoracotomy is performed, the heart exposed, and a snare (2-0 silk) is placed loosely around a prominent branch of the left coronary artery, approximately 2/3 of the distance towards the apex of the heart. The heart is removed from the chest and rapidly (<30 sec) mounted on a Langendorff apparatus. The heart is retrogradely perfused in a non-recirculating manner with a modified Krebs solution (NaCl 118.5 mM, KCl 4.7 mM, Mg SO₄ 1.2 mM, KH₂PO₄ 1.2 mM, NaHCO₃ 24.8 mM, CaCl₂ 2.5 mM, and glucose 10 mM), at a constant pressure of 80 mmHg and a temperature of 37°C. Perfusate pH is maintained at 7.4-7.5 by bubbling with 95% O₂/5% CO₂. Heart temperature is tightly controlled by using heated reservoirs for the physiological solution and water jacketing around both the perfusion tubing and the isolated heart. Heart rate and left ventricular pressures are determined via a latex balloon which is inserted in the left ventricle and connected by stainless steel tubing to a pressure transducer. The intraventricular balloon is inflated to provide a systolic pressure of 80-100 mmHg, and a diastolic pressure ≤ 10 mmHg. Total coronary flow is also continuously monitored using an in-line flow probe and normalized for heart weight.

[0212] The heart is allowed to equilibrate for 30 min, over which time the heart must show stable left ventricular pressures within the parameters outlined above. If the heart rate falls below 180 bpm at any time prior to the 30 min period of regional ischemia, the heart is paced at about 200 bpm for the remainder of the experiment. Ischemic preconditioning is induced by total cessation of cardiac perfusion (global ischemia) for 5 min, followed by reperfusion for 10 min. The regional ischemia is provided by tightening the snare around the coronary artery branch. Following the 30 min regional ischemia, the snare is released and the heart reperfused for an additional 120 min.

[0213] Pharmacological cardioprotection is induced by infusing the test compound at predetermined concentrations, starting 30 min prior to the 30 min regional ischemia, and continuing until the end of the 120 min reperfusion period. Hearts which receive test compounds do not undergo the period of ischemic preconditioning. The reference compound, APNEA (500 nM) is perfused through hearts (which do not receive the test compound) for a 5 min period which ends 10 min before the 30 min regional ischemia.

[0214] At the end of the 120 min reperfusion period, the coronary artery snare is tightened, and a 0.5% suspension of fluorescent zinc cadmium sulfate particles (1-10 μM) Duke Scientific Corp. (Palo Alto, CA) is perfused through the heart; this stains all of the myocardium, except that area-at-risk for infarct development (area-at-risk). The heart is removed from the Langendorff apparatus, blotted dry, wrapped in aluminum foil and stored overnight at -20°C. The next day, the heart is sliced into 2 mm transverse sections from the apex to the top of the ventricles. The slices are stained with 1% triphenyl tetrazolium chloride (TTC) in phosphate-buffered saline for 20 min at 37°C. Since TTC reacts with living tissue (containing NAD-dependent dehydrogenases), this stain differentiates between living (red stained) tissue, and dead tissue (unstained infarcted tissue). The infarcted area (no stain) and the area-at-risk (no fluorescent particles) are calculated for each slice of left ventricle using a precalibrated image analyzer. To normalize the ischemic injury for differences in the area-at-risk between hearts, the data is expressed as the ratio of infarct area vs. area-at-risk (%IA/AAR). All data are expressed as mean ± SE and compared statistically using a Mann-Whitney non-parametric test with a Bonferroni correction for multiple comparisons. Significance is considered as p < 0.05.

[0215] The results from the above *in vitro* test demonstrate that compounds of this invention induce significant cardioprotection relative to the control group.

[0216] The therapeutic effects of the compounds of this invention in preventing heart tissue damage otherwise resulting from an ischemic insult can also be demonstrated *in vivo* along lines presented in Liu et al. (Circulation, Vol. 84:350-356, 1991) as described specifically herein. The *in vivo* assay tests the cardioprotection of the test compound relative to the control group which receives saline vehicle. Cardioprotection, as indicated by a reduction in infarcted myocardium, can be induced pharmacologically using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied as an *in situ* model of myocardial ischemic preconditioning (Liu et al., Circulation 84: 350-356, 1991). The *in vivo* assay tests whether compounds can pharmacologically induce cardioprotection, i.e., reduced myocardial infarct size, when parenterally administered to intact, anesthetized rabbits. The effects of the compounds of this invention can be compared to ischemic preconditioning using the A1 adenosine agonist, N⁶-1-(phenyl-2R-isopropyl) adenosine (PIA) that has been shown to pharmacologically induce cardioprotection in intact anesthetized rabbits studied *in situ* (Liu et al., Circulation 84:350-356, 1991). The methodology is described below.

Surgery: New Zealand White male rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, i.v.). A tracheotomy is performed via a ventral midline cervical incision and the rabbits are ventilated with 100% oxygen using a positive pressure ventilator. Catheters are placed in the left jugular vein for drug administration and in the left carotid artery for blood pressure measurements. The hearts are then exposed through a left thoracotomy and a snare (00 silk) placed around a prominent branch of the left coronary artery. Ischemia is induced by pulling the snare tight and clamping it in place. Releasing the snare allows the affected area to reperfuse. Myocardial ischemia is evidenced by regional cyanosis; reperfusion is evidenced by reactive hyperemia.

Protocol: Once arterial pressure and heart rate have been stable for at least 30 minutes the test is started. Ischemic preconditioning is induced by occluding the coronary artery for 5 min followed by a 10 min reperfusion. Pharmacological preconditioning is induced by infusing test compound over, for example 5 minutes and allowing 10 minutes before further intervention or by infusing the adenosine agonist, PIA (0.25 mg/kg). Following ischemic preconditioning, pharmacological preconditioning or no conditioning (unconditioned, vehicle control) the artery is occluded for 30 minutes and then reperfused for two hours to induce myocardial infarction. The test compound and PIA are dissolved in saline or other suitable vehicle and delivered at 1 to 5 mg/kg, respectively.

Staining (Liu et al., Circulation 84:350-356, 1991): At the end of the 2 hour reperfusion period, the hearts are quickly removed, hung on a Langendorff apparatus, and flushed for 1 minute with normal saline heated to body temperature (38°C). The silk suture used as the snare is then tied tightly to reocclude the artery and a 0.5% suspension of fluorescent zinc cadmium sulphate particles (1-10 µm) Duke Scientific Corp. (Palo Alto, CA) is infused with the perfusate to stain all of the myocardium except the area at risk (nonfluorescent ventricle). The hearts are then quickly frozen and stored overnight at -20°C. On the following day, the hearts are cut into 2 mm slices and stained with 1% triphenyl tetrazolium chloride (TTC). Since TTC reacts with living tissue, this stain differentiates between living (red stained) tissue, and dead tissue (unstained infarcted tissue). The infarcted area (no stain) and the area at risk (no fluorescent particles) are calculated for each slice of left ventricle using a pre-calibrated image analyzer. To normalize the ischemic injury for differences in the area at risk between hearts, the data is expressed as the ratio of infarct area vs. area at risk (%IA/AAR). All data are expressed as Mean±SEM and compared statistically using single factor ANOVA or Mann Whitney non parametric test. Significance is considered as p<0.05.

[0217] The compounds of this invention can be tested for their utility in reducing or preventing ischemic injury in non-cardiac tissues, for example, the brain, or the liver, utilizing procedures reported in the scientific literature. The compounds of this invention in such tests can be administered by the preferred route and vehicle of administration and at the preferred time of administration either prior to the ischemic episode, during the ischemic episode, following the ischemic episode (reperfusion period) or during any of the below-mentioned experimental stages.

[0218] The benefit of the invention to reduce ischemic brain damage can be demonstrated, for example, in mammals using the method of Park, et al (Ann. Neurol. 1988;24:543-551). According to the procedure of Park, et al., adult male Sprague Dawley rats are anesthetized initially with 2% halothane, and thereafter by mechanical ventilation with a nitrous oxide-oxygen mixture (70%:30%) containing 0.5-1% halothane. A tracheostomy is then performed. The stroke volume of the ventilator is adjusted to maintain arterial carbon dioxide tension at approximately 35 mm Hg and adequate arterial oxygenation (PaO₂>90 mm Hg). Body temperature can be monitored by a rectal thermometer, and the animals can be maintained normothermic, if necessary, by external heating. The animals next undergo subtemporal craniectomy to expose the main trunk of the left middle cerebral artery (MCA) under an operating microscope, and the exposed artery is occluded with microbipolar coagulation to generate large ischemic lesions in the cerebral cortex and basal ganglia. After three hours of MCA occlusion, the rats are deeply anesthetized with 2% halothane and a thoracotomy is performed to infuse heparinized saline into the left ventricle. The effluent is collected via an incision of the right atrium. The saline washout is followed by approximately 200 ml of a 40% formaldehyde, glacial acetic acid and absolute methanol solution (FAM; 1:1:8, v/v/v), then the animals are decapitated and the head is stored in fixative for 24 hours. The brain is then removed, dissected, embedded in paraffin wax, and sectioned (approximately 100 sections 0.2mm

per brain). The sections are then stained with hematoxylin-eosin or with a combination of cresyl violet and Luxol fast blue, and examined by light microscopy to identify and quantitate the ischemic damage using a precalibrated image analyzer. The ischemic volumes and areas are expressed in absolute units (mm^3 and mm^2) and as a percentage of the total region examined. The effect of the compositions and methods of this invention to reduce ischemic brain damage induced by MCA occlusion is noted based on a reduction in the area or volume of relative or absolute ischemic damage in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

[0219] Other methods which could alternatively be utilized to demonstrate the benefit of the invention to reduce ischemic brain damage include those described by Nakayama, et al. in *Neurology* 1988,38:1667-1673; Memezawa, et al. in *Stroke* 1992,23:552-559; Folbergrova, et al. in *Proc. Natl. Acad. Sci* 1995,92:5057-5059; and Gotti, et al. in *Brain Res.* 1990,522:290-307.

[0220] The benefit of the compounds, compositions and methods of this invention to reduce ischemic liver damage can be demonstrated, for example, in mammals using the method of Yokoyama, et al. (*Am. J. Physiol.* 1990;258:G564-G570). According to the procedure of Yokoyama, et al., fasted adult male Sprague Dawley rats are anesthetized with sodium pentobarbital (40 mg/kg i.p.), then the animals are tracheotomized and mechanically ventilated with room air. The liver is extirpated and placed in an environmental chamber maintained at constant temperature (37 °C), then perfused through the portal vein at a constant pressure of 15 cm H_2O with a modified, hemoglobin-free Krebs-Henseleit buffer (in mM: 118 NaCl, 4.7 KCl, 27 NaHCO_3 , 2.5 CaCl_2 , 1.2 MgSO_4 , 1.2 KH_2PO_4 , 0.05 EDTA, and 11 mM glucose, plus 300 U heparin). The pH of the perfusate is maintained at 7.4 by gassing the buffer with 95% O_2 - 5% CO_2 . Each liver is perfused at a flow rate of 20 ml/min in a single-pass manner for a 30 min washout and equilibration period (preischemic period), followed by a 2 hour period of global ischemia, and then a 2 hour period of reperfusion under conditions identical to the preischemic period. Aliquots (20 ml) of the perfusate are collected during the preischemic period, immediately after the occlusive ischemic period, and every 30 min of the 2 hour reperfusion period. The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate amino-transferase (AST), alanine amino-transferase (ALT), and lactate dehydrogenase (LDH), which are taken to quantitatively reflect the degree of ischemic liver tissue damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several methods, for example, by the reflectometry method using an automatic Kodak Ektachem 500 analyzer reported by Nakano, et al. (*Hepatology* 1995;22:539-545). The effect of the compounds, compositions and methods of this invention in reducing ischemic liver damage induced by occlusion is noted based on a reduction in the release of hepatocellular enzymes immediately following the occlusive period and/or during the postischemic-reperfusion period in the perfused livers from the rats in the treatment group compared to perfused livers from rats in a placebo-treated control group.

[0221] Other methods and parameters which could alternatively be utilized to demonstrate the benefit of the compositions and methods of this invention in reducing ischemic liver damage include those described by Nakano, et al. (*Hepatology* 1995;22:539-545).

ALDOSE REDUCTASE INHIBITOR ASSAYS

[0222] Male Sprague-Dawley rats are rendered diabetic by injection of streptozocin at 55 mg/kg, i.v., in pH 4.5 citrate buffer. They are fed ad libitum in controlled conditions of housing, temperature and lighting. After five weeks of diabetes, the rats are anesthetized with an overdose of pentobarbital, and tissues are rapidly removed and analyzed for sorbitol and fructose.

[0223] Sorbitol levels are analyzed according to the method of Donald M. Eades et al., "Rapid Analysis of Sorbitol, Galactitol, Mannitol and Myoinositol Mixtures From Biological Sources", *Journal of Chromatography*, 490, 1-8, (1989).

[0224] Fructose in rat tissues is enzymatically measured using a modification of the method of Ameyama (*Methods in Enzymology*, 89:20-29, 1982), in which ferricyanide was replaced by resazurin, a dye that is reduced to the highly fluorescent resorufin. The amount of resorufin fluorescence is stoichiometric with the amount of fructose oxidized by fructose dehydrogenase. The assay contains 0.1 ml neutralized 6% perchloric acid nerve extract in a final volume of 1.5 ml. Following incubation for 60 minutes at room temperature in a closed drawer, sample fluorescence is determined at excitation = 560 nm, emission = 580 nm with slits of 5 mm each in a Perkin-Elmer model 650-40 fluorescence spectrophotometer. Fructose concentrations are calculated by comparison with a series of known fructose standards.

GLYCOGEN PHOSPHORYLASE INHIBITOR ASSAYS

[0225] The three different purified glycogen phosphorylase (GP) isoenzymes, wherein glycogen phosphorylase is in the activated "a" state (referred to as glycogen phosphorylase a, or the abbreviation GP_a), and referred to here as human liver glycogen phosphorylase a (HLGP_a), human muscle glycogen phosphorylase a (HMG_a), and human brain glycogen phosphorylase a (HBGP_a), can be obtained by the following procedures.

Expression and fermentation

[0226] The HLGP and HMGP cDNAs are expressed from plasmid pKK233-2 (Pharmacia Biotech. Inc., Piscataway, New Jersey) in *E. coli* strain XL-1 Blue (Stratagene Cloning Systems, LaJolla, CA). The strain is inoculated into LB medium (consisting of 10 g tryptone, 5 g yeast extract, 5 g NaCl, and 1 ml 1 N NaOH per liter) plus 100 mg/L ampicillin, 100 mg/L pyridoxine and 600 mg/L MnCl₂ and grown at 37°C to a cell density of OD₅₅₀ = 1.0. At this point, the cells are induced with 1 mM isopropyl-1-thio-β-D-galactoside (IPTG). Three hours after induction the cells are harvested by centrifugation and cell pellets are frozen at -70°C until needed for purification.

[0227] The HBGP cDNA can be expressed by several methodologies, for example, by the method described by Crerar, et al. (J. Biol. Chem. 270:13748-13756). The method described by Crerar, et al. (J. Biol. Chem. 270:13748-13756) for the expression of HBGP is as follows: the HBGP cDNA can be expressed from plasmid pTACTAC in *E. Coli* strain 25A6. The strain is inoculated into LB medium (consisting of 10 g tryptone, 5 g yeast extract, 5 g NaCl, and 1 ml 1N NaOH per liter) plus 50 mg/L ampicillin and grown overnight, then resuspended in fresh LB medium plus 50 mg/L ampicillin, and reinoculated into a 40X volume of LB/amp media containing 250 μM isopropyl-1-thio-β-D-galactoside (IPTG), 0.5 mM pyridoxine and 3 mM MgCl₂ and grown at 22°C for 48-50 hours. The cells can then be harvested by centrifugation and cell pellets are frozen at -70°C until needed for purification.

[0228] The HLGP cDNA is expressed from plasmid pBlueBac III (Invitrogen Corp., San Diego, CA) which is cotransfected with BaculoGold Linear Viral DNA (Pharmingen, San Diego, CA) into Sf9 cells. Recombinant virus is subsequently plaque-purified. For production of protein, Sf9 cells grown in serum-free medium are infected at a multiplicity of infection (moi) of 0.5 and at a cell density of 2x10⁶ cells/ml. After growth for 72 hours at 27°C, cells are centrifuged, and the cell pellets frozen at -70°C until needed for purification. Purification of Glycogen Phosphorylase expressed in *E. coli*

[0229] The *E. coli* cells in pellets described above are resuspended in 25 mM β-glycerophosphate (pH 7.0) with 0.2 mM DTT, 1 mM MgCl₂, plus the following protease inhibitors:

0.7 μg/mL	Pepstatin A
0.5 μg/mL	Leupeptin
0.2 mM	phenylmethylsulfonyl fluoride (PMSF), and
0.5 mM	EDTA,

lysed by pretreatment with 200 μg/mL lysozyme and 3 μg/mL DNAase followed by sonication in 250 mL batches for 5 x 1.5 minutes on ice using a Branson Model 450 ultrasonic cell disrupter (Branson Sonic Power Co., Danbury CT). The *E. coli* cell lysates are then cleared by centrifugation at 35,000 X g for one hour followed by filtration through 0.45 micron filters. GP in the soluble fraction of the lysates (estimated to be less than 1% of the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Immobilized Metal Affinity Chromatography (IMAC)

[0230] This step is based on the method of Luong et al (Luong et al. Journal of Chromatography (1992) 584, 77-84.). 500 mL of the filtered soluble fraction of cell lysates (prepared from approximately 160 - 250 g of original cell pellet) are loaded onto a 130 mL column of IMAC Chelating-Sepharose (Pharmacia LKB Biotechnology, Piscataway, New Jersey) which has been charged with 50 mM CuCl₂ and 25 mM β-glycerophosphate, 250 mM NaCl and 1 mM imidazole at pH 7 equilibration buffer. The column is washed with equilibration buffer until the A₂₈₀ returns to baseline. The sample is then eluted from the column with the same buffer containing 100 mM imidazole to remove the bound GP and other bound proteins. Fractions containing the GP activity are pooled (approximately 600 mL), and ethylenediaminetetraacetic acid (EDTA), DL-dithiothreitol (DTT), phenylmethylsulfonyl fluoride (PMSF), leupeptin and pepstatin A are added to obtain 0.3 mM, 0.2 mM, 0.2 mM, 0.5 μg/mL and 0.7 μg/mL concentrations respectively. The pooled GP is desalted over a Sephadex G-25 column (Sigma Chemical Co., St. Louis, Missouri) equilibrated with 25 mM Tris-HCl (pH 7.3), 3 mM DTT buffer (Buffer A) to remove imidazole and is stored on ice until the second chromatographic step.

5'-AMP-Sepharose Chromatography

[0231] The desalted pooled GP sample (approximately 600mL) is next mixed with 70 mL of 5'-AMP Sepharose (Pharmacia LKB Biotechnology, Piscataway, New Jersey) which has been equilibrated with Buffer A (see above). The mixture is gently agitated for one hour at 22°C then packed into a column and washed with Buffer A until the A₂₈₀ returns to baseline. GP and other proteins are eluted from the column with 25 mM Tris-HCl, 0.2 mM DTT and 10 mM

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adenosine 5'-monophosphate (AMP) at pH 7.3 (Buffer B). GP-containing fractions are pooled following identification by determining enzyme activity (described below) and visualizing the M_r approximately 97 kdal GP protein band by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) followed by silver staining (2D-silver Stain II "Daiichi Kit", Daiichi Pure Chemicals Co., LTD., Tokyo, Japan) and then pooled. The pooled GP is dialyzed into 25 mM β -glycerophosphate, 0.2 mM DTT, 0.3 mM EDTA, 200 mM NaCl, pH 7.0 buffer (Buffer C) and stored on ice until use. **[0232]** Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in *E. coli* strain XL-1 Blue (designated GPb) (Stragene Cloning Systems, La Jolla, California), to the active form (designated GPa) by the procedure described in Section (A) Activation of GP below.

Purification of Glycogen Phosphorylase expressed in Sf9 cells

[0233] The Sf9 cells in pellets described above are resuspended in 25 mM β -glycerophosphate (pH 7.0) with 0.2 mM DTT, 1 mM $MgCl_2$, plus the following protease inhibitors:

0.7 μ g/mL	Pepstatin A
0.5 μ g/mL	Leupeptin
0.2 mM	phenylmethylsulfonyl fluoride (PMSF), and
0.5 mM	EDTA,

lysed by pretreatment with 3 μ g/mL DNAase followed by sonication in batches for 3 x 1 minutes on ice using a Branson Model 450 ultrasonic cell disrupter (Branson Sonic Power Co., Danbury CT). The Sf9 cell lysates are then cleared by centrifugation at 35,000 X g for one hour followed by filtration through 0.45 micron filters. GP in the soluble fraction of the lysates (estimated to be 1.5% of the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Immobilized Metal Affinity Chromatography (IMAC)

[0234] Immobilized Metal Affinity Chromatography is performed as described in the section above. The pooled, de-salted GP is then stored on ice until further processed.

Activation of GP

[0235] Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is converted to the active form (designated GPa) by the following procedure described in Section (A) Activation of GP below.

Anion Exchange Chromatography

[0236] Following activation of the IMAC purified GPb to GPa by reaction with the immobilized phosphorylase kinase, the pooled GPa fractions are dialyzed against 25 mM Tris-HCl, pH 7.5, containing 0.5 mM DTT, 0.2 mM EDTA, 1.0 mM phenylmethylsulfonyl fluoride (PMSF), 1.0 μ g/mL leupeptin and 1.0 μ g/mL pepstatin A. The sample is then loaded onto a MonoQ Anion Exchange Chromatography column (Pharmacia Biotech. Inc., Piscataway, New Jersey). The column is washed with equilibration buffer until the A_{280} returns to baseline. The sample is then eluted from the column with a linear gradient of 0-0.25 M NaCl to remove the bound GP and other bound proteins. GP-containing fractions elute between 0.1-0.2 M NaCl range, as detected by monitoring the eluant for peak protein absorbance at A_{280} . The GP protein is then identified by visualizing the M_r approximately 97 kdal GP protein band by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) followed by silver staining (2D-silver Stain II "Daiichi Kit", Daiichi Pure Chemicals Co., LTD., Tokyo, Japan) and then pooled. The pooled GP is dialyzed into 25 mM N,N-bis[2-Hydroxyethyl]-2-aminoethanesulfonic acid, 1.0 mM DTT, 0.5 mM EDTA, 5 mM NaCl, pH 6.8 buffer and stored on ice until use.

Determination of GP Enzyme Activity

A) Activation of GP: Conversion of GPb to GPa

[0237] Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in *E. coli* strain XL-1 Blue (designated GPb) (Stragene Cloning Systems, La Jolla, California), to the active form (designated GPa) by phosphorylation of GP using phosphorylase kinase as follows. The fraction of inactive enzyme as

expressed in Sf9 cells (designated GPb) is also converted to the active form (designated GPa) by the following procedure.

GP reaction with Immobilized Phosphorylase Kinase

[0238] Phosphorylase kinase (Sigma Chemical Company, St. Louis, MO) is immobilized on Affi-Gel 10 (BioRad Corp., Melville, NY) as per the manufacturer's instructions. In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads (1 mL) in 2.5 mL of 100 mM HEPES and 80 mM CaCl₂ at pH 7.4 for 4 hours at 4°C. The Affi-Gel beads are then washed once with the same buffer prior to blocking with 50 mM HEPES and 1 M glycine methyl ester at pH 8.0 for one hour at room temperature. Blocking buffer is removed and replaced with 50 mM HEPES (pH 7.4), 1 mM β-mercaptoethanol and 0.2% NaN₃ for storage. Prior to use to convert GPb to GPa, the Affi-Gel immobilized phosphorylase kinase beads are equilibrated by washing in the buffer used to perform the kinase reaction, consisting of 25 mM β-glycerophosphate, 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).

[0239] The partially purified, inactive GPb obtained from 5'-AMP-Sepharose chromatography above (from *E. coli*) or the mixture of GPa and GPb obtained from IMAC above (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads. NaATP is added to 5 mM and MgCl₂ to 6 mM. The resulting mixture is mixed gently at 25°C for 30 to 60 minutes. The sample is removed from the beads and the percent activation of GPb by conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows:

$$\% \text{ of total HLGPa} = \frac{\text{HLGP activity} - \text{AMP}}{\text{HLGP activity} + \text{AMP}}$$

[0240] Alternately, the conversion of GPb to GPa can be monitored by isoelectric focusing, based on the shift in electrophoretic mobility that is noted following conversion of GPb to GPa. GP samples are analyzed by isoelectric focusing (IEF) utilizing the Pharmacia PfastGel System (Pharmacia Biotech. Inc., Piscataway, New Jersey) using pre-cast gels (pI range 4-6.5) and the manufacturer's recommended method. The resolved GPa and GPb bands are then visualized on the gels by silver staining (2D-silver Stain II "Daiichi Kit", Daiichi Pure Chemicals Co., LTD., Tokyo, Japan). Identification of GPa and GPb is made by comparison to *E. coli* derived GPa and GPb standards that are run in parallel on the same gels as the experimental samples.

B) GPa Activity Assay

[0241] The disease/condition treating/preventing activities described herein of the glycogen phosphorylase inhibitor compounds of this invention can be indirectly determined by assessing the effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase (GPa) by one of two methods; glycogen phosphorylase activity is measured in the forward direction by monitoring the production of glucose-1-phosphate from glycogen or by following the reverse reaction, measuring glycogen synthesis from glucose-1-phosphate by the release of inorganic phosphate. All reactions can be run in triplicate in 96-well microtiter plates and the change in absorbance due to formation of the reaction product is measured at the wavelength specified below in a MCC/340 MKII Elisa Reader (Lab Systems, Finland), connected to a Titertech Microplate Stacker (ICN Biomedical Co, Huntsville, Alabama).

[0242] To measure the GPa enzyme activity in the forward direction, the production of glucose-1-phosphate from glycogen is monitored by the multienzyme coupled general method of Pesce et al. [Pesce, M.A., Bodourian, S.H., Harris, R.C. and Nicholson, J.F. (1977) *Clinical Chemistry* 23, 1711-1717] modified as follows: 1 to 100 μg GPa, 10 units phosphoglucomutase and 15 units glucose-6-phosphate dehydrogenase (Boehringer Mannheim Biochemicals, Indianapolis, IN) are diluted to 1 mL in Buffer A (described hereinafter). Buffer A is at pH 7.2 and contains 50 mM HEPES, 100 mM KCl, 2.5 mM ethyleneglycoltetraacetic acid (EGTA), 2.5 mM MgCl₂, 3.5 mM KH₂PO₄ and 0.5 mM dithiothreitol. 20 μl of this stock is added to 80 μl of Buffer A containing 0.47 mg/mL glycogen, 9.4 mM glucose, 0.63 mM of the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP⁺). The compounds to be tested are added as 5 μL of solution in 14% dimethylsulfoxide (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by adding 5 μL of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 μL of 50 mM of the positive control test substance, caffeine. The reaction is followed at room temperature by measuring the conversion of oxidized NADP⁺ to reduced NADPH at 340 nm.

[0243] To measure the GPa enzyme activity in the reverse direction, the conversion of glucose-1-phosphate into glycogen plus inorganic phosphate is measured by the general method described by Engers et al. [Engers, H.D., Shechosky, S. and Madsen, N.B. (1970) *Can. J. Biochem.* 48, 746-754] modified as follows: 1 to 100 μg GPa is diluted to 1 mL in Buffer B (described hereinafter). Buffer B is at pH 7.2 and contains 50 mM HEPES, 100 mM KCl, 2.5 mM

EGTA, 2.5 mM MgCl₂ and 0.5 mM dithiothreitol. 20 μL of this stock is added to 80 μL of Buffer B with 1.25 mg/mL glycogen, 9.4 mM glucose, and 0.63 mM glucose-1-phosphate. The compounds to be tested are added as 5 μL of solution in 14% DMSO prior to the addition of the enzyme. The basal rate of GPα enzyme activity in the absence of added inhibitors is determined by adding 5 μL of 14% DMSO and a fully-inhibited rate of GPα enzyme activity is obtained by adding 20 μL of 50 mM caffeine. This mixture is incubated at room temperature for 1 hour and the inorganic phosphate released from the glucose-1-phosphate is measured by the general method of Lanzetta et al. [Lanzetta, P.A., Alvarez, L.J., Reinach, P.S. and Candia, O.A. (1979) Anal. Biochem. 100, 95-97] modified as follows: 150 μL of 10 mg/mL ammonium molybdate, 0.38 mg/mL malachite green in 1 N HCl is added to 100 μL of the enzyme mix. After a 20 minute incubation at room temperature, the absorbance is measured at 620 nm.

[0244] The above assays carried out with a range of concentrations of test compound allows the determination of an IC₅₀ value (concentration of test compound required for 50% inhibition) for the *in vitro* inhibition of GPα enzyme activity by that test compound.

[0245] Administration of the compounds of this invention can be via any method which delivers a compound of this invention preferentially to the desired tissue (e.g., liver and/or cardiac tissues). These methods include oral routes, parenteral, intraduodenal routes, etc. Generally, the compounds of the present invention are administered in single (e.g., once daily) or multiple doses or via constant infusion.

[0246] The compounds of this invention are useful, for example, in reducing or minimizing damage effected directly to any tissue that may be susceptible to ischemia/reperfusion injury (e.g., heart, brain, lung, kidney, liver, gut, skeletal muscle, retina) as the result of an ischemic event (e.g., myocardial infarction). The active compound is therefore usefully employed prophylactically to prevent, i.e. (prospectively or prophylactically) to blunt or stem, tissue damage (e.g., myocardial tissue) in patients who are at risk for ischemia (e.g., myocardial ischemia).

[0247] Generally, the compounds of this invention are administered orally, or parenterally (e.g., intravenous, intramuscular, subcutaneous or intramedullary). Topical administration may also be indicated, for example, where the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to the surface of a tissue or organ as determined by the attending physician.

[0248] The amount and timing of compounds administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgement of the prescribing physician. Thus, because of patient to patient variability, the dosages given below are a guideline and the physician may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of factors such as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

[0249] Thus, for example, in one mode of administration the compounds of this invention may be administered just prior to surgery (e.g., within twenty-four hours before surgery for example cardiac surgery) during or subsequent to surgery (e.g., within twenty-four hours after surgery) where there is risk of myocardial ischemia. The compounds of this invention may also be administered in a chronic daily mode.

[0250] An amount of the compounds of this invention is used that is effective for ischemic protection. A preferred dosage is about 0.001 to 100 mg/kg/day of the compound of this invention. An especially preferred dosage is about 0.01 to 50 mg/kg/day of the compound of this invention.

[0251] The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of this invention can be administered individually or together in any conventional oral, parenteral, rectal or transdermal dosage form.

[0252] For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0253] For purposes of parenteral administration, solutions, for example, in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable

by standard techniques well-known to those skilled in the art.

[0254] For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

[0255] Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

[0256] Pharmaceutical compositions according to the invention may contain for example 0.0001%-95% of the compound(s) of this invention. In any event; the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the disease/condition of the subject being treated.

[0257] The two different compounds of this combination of this invention can be co-administered simultaneously or sequentially in any order, or as a single pharmaceutical composition comprising a compound of Formula I and an aldose reductase inhibitor as described above or a glycogen phosphorylase inhibitor as described above or a cardiovascular agent.

[0258] Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula I a prodrug thereof or a salt of such compound or prodrug and a second compound as described above. The kit comprises means for containing the separate compositions such as a container, a divided bottle or a divided foil packet. Typically the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

[0259] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0260] It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of Formula I compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

[0261] In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered microchip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

[0262] The compounds of this invention generally will be administered in a convenient formulation. The following formulation examples are illustrative only and are not intended to limit the scope of the present invention.

[0263] In the formulations which follow, "active ingredient" means a compound(s) of this invention.

Formulation 1: Gelatin Capsules Hard gelatin capsules are prepared using the following:	
Ingredient	Quantity (mg/capsule)
Active ingredient	0.25-100
Starch, NF	0-650
Starch flowable powder	0-50
Silicone fluid 350 centistokes	0-15

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[0264] A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets	
Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Cellulose, microcrystalline	200-650
Silicon dioxide, fumed	10-650
Stearate acid	5-15

[0265] The components are blended and compressed to form tablets.

[0266] Alternatively, tablets each containing 0.25-100 mg of active ingredients are made up as follows:

Formulation 3: Tablets	
Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

[0267] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0268] Suspensions each containing 0.25-100 mg of active ingredient per 5 ml dose are made as follows:

Formulation 4: Suspensions	
Ingredient	Quantity (mg/5 ml)
Active ingredient	0.25-100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to	5 mL

[0269] The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume. An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol	
Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00

[0270] The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to

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30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Suppositories are prepared as follows:

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Formulation 6: Suppositories	
Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

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[0271] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

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[0272] An intravenous formulation is prepared as follows:

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Formulation 7: Intravenous Solution	
Ingredient	Quantity
Active ingredient	25 mg-10,000 mg
Isotonic saline	1,000 mL

[0273] The solution of the above ingredients is intravenously administered to a patient.

[0274] The active ingredient above may also be a combination of agents.

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GENERAL EXPERIMENTAL PROCEDURES

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[0275] NMR spectra were recorded on a Varian XL-300 (Varian Co., Palo Alto, California) a Bruker AM-300 spectrometer (Bruker Co., Billerica, Massachusetts) or a Varian Unity 400 at about 23°C at 300 or 400 MHz for proton. Chemical shifts are expressed in parts per million downfield from trimethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs,=broad singlet. Resonances designated as exchangeable did not appear in a separate NMR experiment where the sample was shaken with several drops of D₂O in the same solvent. Atmospheric pressure chemical ionization mass spectra (APCIMS) were obtained on a Fisons Platform II Spectrometer. Chemical ionization mass spectra (CIMS) were obtained on a Hewlett-Packard 5989 instrument (Hewlett-Packard Co., Palo Alto, California) (ammonia ionization, PBMS). Where the intensity of chlorine or bromine-containing ions are described the expected intensity ratio was observed (approximately 3:1 for ³⁵Cl/³⁷Cl-containing ions and 1:1 for ⁷⁹Br/⁸¹Br-containing ions) and M is based on ³⁵Cl and ⁷⁹Br. In some cases only representative ¹H NMR and APCIMS peaks are given.

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[0276] Column chromatography was performed with either Baker Silica Gel (40 μm) (J.T. Baker, Phillipsburg, N.J.) or Silica Gel 60 (EM Sciences, Gibbstown, N.J.) in glass columns or in Flash 40™ or Flash 12™ (Biotage) (Charlottesville, VA) columns under low nitrogen pressure. Radial Chromatography was performed using a Chromatron, (Harrison Research) (Palo Alto, CA.) Unless otherwise specified, reagents were used as obtained from commercial sources. Dimethylformamide, 2-propanol, tetrahydrofuran, and dichloromethane used as reaction solvents were the anhydrous grade supplied by Aldrich Chemical Company (Milwaukee, Wisconsin). Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. The terms "concentrated" and "coevaporated" refer to removal of solvent at water aspirator pressure on a rotary evaporator with a bath temperature of less than 50°C. Reactions conducted at "0-20°C" or "0-25°C" were conducted with initial cooling of the vessel in an insulated ice bath which was allowed to warm to room temperature over several hours. The abbreviation "min" and "h" stand for "minutes" and "hours" respectively.

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[0277] Reference to the hydrochloride salt in the Example names below includes mono- or di-salts as appropriate in the particular Example.

[0278] The title compounds of Examples 3A-3T were prepared using procedures analogous to that described in Klinsberg, E. *Synthesis* 1972, 475.

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REFERENCE EXAMPLE 3A5-Methyl-2-(4-methoxyphenyl)-2H-1,2,3-triazole-4-carboxylic acid

- 5 **[0279]** Acetoacetanilide (25.0 g, 0.14 mol) and sodium nitrite (12.65 g, 0.18 mol) were dissolved in aqueous sodium hydroxide solution (140 ml, 1 N) and the resulting solution was added dropwise over 20 min to an aqueous solution of sulfuric acid (120 ml conc. H₂SO₄ in 950 ml water) cooled in an ice bath. The reaction mixture was stirred at 0 °C for 30 min, then the precipitate was filtered and washed with water to yield 2-hydroxyiminoacetanilide (22.64g., 78% yield) as a pale yellow solid.
- 10 **[0280]** Sodium methoxide (0.89 g, 0.017 mol) was added to a solution of 4-methoxyphenylhydrazine hydrochloride (2.89 g, 0.016 mol) in 10 ml ethanol and after 5 min the mixture was filtered and the filtrate added to a warm solution of 2-hydroxyiminoacetoacetanilide (3.25 g, 0.0158 mol) in 5 ml ethanol. The resulting solution was briefly heated to reflux, then allowed to cool to room temperature, whereupon a precipitate formed. The precipitate was filtered and washed with 2:1 hexane/ethyl acetate to yield 2-hydroxyimino-3-(4-methoxyphenyl)hydrazonobutanoic acid anilide as
- 15 a yellow solid (3.16 g, 61% yield).
- [0281]** 2-Hydroxyimino-3-(4-methoxyphenyl)hydrazonobutanoic acid anilide (3.16 g, 0.01 mol) was added over a 2 min period to a refluxing solution of potassium hydroxide (3.2 g, 0.05 mol) in 12 ml 2-ethoxyethanol. The reaction mixture was refluxed for 15 min, then cooled to room temperature. The precipitate that formed was filtered and washed with diethyl ether. The solid was dissolved in 15 ml water and the resulting solution was acidified with dilute aqueous hydrochloric acid. The aqueous solution was extracted with 3x20 ml ethyl acetate and the combined ethyl acetate
- 20 extracts were washed with 40 ml water and 40 ml brine, dried (anhydrous sodium sulfate) and concentrated *in vacuo* to yield the title compound (0.84 g) as a reddish solid. By a similar treatment of the solids that formed in the filtrate from the ether wash, a further 0.805 g of the product was obtained (1.65 g total yield, 73% yield).
- [0282]** ¹H NMR (CD₃OD) δ 2.58 (s, 3H); 3.83 (s, 3H); 6.9-7.0 (m, 2H); 7.74 (d, 1H); 7.99 (d, 1H).
- 25 **[0283]** The title compounds of Examples 3B-3T were prepared using procedures analogous to that used for Example 3A.

EXAMPLE 3F30 5-Methyl-2-(5-quinoliny)-2H-1,2,3-triazole-4-carboxylic acid**[0284]** 67% yield.**[0285]** ¹H NMR (DMSO-*d*₆) δ 2.56 (s, 3H); 7.67 (m, 1H); 7.89-7.99 (m, 2H); 8.2 (d, 1H); 8.55 (d, 1H); (9.01, s, 1H).35 EXAMPLE 3G5-Methyl-2-(5-isoquinoliny)-2H-1,2,3-triazole-4-carboxylic acid**[0286]** 31 % yield.40 **[0287]** ¹H NMR (DMSO-*d*₆) δ 2.57 (s, 3H); 7.85 (t, 1H); 8.09 (d, 1H); 8.17 (d, 1H); 8.34 (d, 1H); 8.63 (d, 1H); 9.48 (s, 1H).EXAMPLE 3S45 5-Methyl-2-(8-quinoliny)-2H-1,2,3-triazole-4-carboxylic acid**[0288]** 24% yield**[0289]** ¹H NMR (400 MHz, CD₃OD) δ 2.63 (s, 3H), 7.64 (dd, J=4.4, 8, 1H), 7.76 (t, J=7.8, 1H), 8.00 (dd, J=1.4, 7.4, 1H), 8.18 (dd, J=1.2, 8.4, 1H), 8.50 (dd, J=1.6, 8.4, 1H), 8.88 (dd, J=1.6, 4, 1H).50 **[0290]** APCIMS 253 [M-1]⁻REFERENCE EXAMPLE 6A[5-Methyl-2-(2-methoxyphenyl)-2H-1,2,3-triazole-4-carbonyl]guanidine hydrochloride

- 55
- [0291]**
- Guanidine hydrochloride (5.29 g, 55.3 mmol) was dissolved in 30 ml of anhydrous methanol and then treated with sodium methoxide (3.04 g, 56.2 mmol), added in one portion at room temperature. The reaction mixture was stirred under nitrogen for 1 hour, then filtered under a nitrogen atmosphere. The solids were washed with anhydrous methanol

(3 x 15 ml) and the filtrate concentrated under reduced pressure. Anhydrous benzene (60 ml) was added to the residue, the mixture reconcentrated *in vacuo* and the resulting guanidine free base was dried under high vacuum. The residue was suspended in a mixture of 10 ml anhydrous THF and 10 ml anhydrous DMF and the resulting mixture was used in the subsequent step.

5 **[0292]** A solution of 5-methyl-2-(2-methoxyphenyl)-2*H*-1,2,3-triazole-4-carboxylic acid (2.15 g, 9.2 mmol) and carbonyldiimidazole (1.64 g, 10 mmol) in 30 ml DMF was stirred at room temperature under nitrogen for 2 h. The resulting mixture was added to the mixture of guanidine in THF and DMF previously prepared and the reaction mixture was stirred overnight under nitrogen at room temperature. The reaction mixture was then poured into 200 ml of cold water and the aqueous mixture was extracted with 10x70 ml ethyl acetate. The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to an orangish solid (1.83 g). The crude product was triturated with diethyl ether to yield 0.59 g of the free base corresponding to the title compound. The title compound was prepared by dissolving the free base in 40 ml methanol and bubbling excess hydrogen chloride gas into the solution. After stirring for several hours the resulting precipitate was filtered and washed with diethyl ether to give the title compound as a tan solid (0.5 g, 17% yield).

10 **[0293]** ¹H NMR (DMSO-*d*₆) δ 2.54 (s, 3H); 3.8 (s, 3H); 7.14 (t, 1H); 7.32 (d, 1H); 7.52-7.7 (m, 3H); 8.45 (s, 2H); 8.66 (s, 2H); 11.37 (s, 1H).

15 **[0294]** The title compounds of Examples 6B-6V were prepared according to procedures analogous to those described in Example 6A.

20 EXAMPLE 6F

[5-Methyl-2-(5-quinolinyl)-2*H*-1,2,3-triazole-4-carbonyl]guanidine hydrochloride

[0295] 67% yield.

25 **[0296]** ¹H NMR (DMSO-*d*₆) δ 2.62 (s, 3H); 7.79 (m 1H); 8.02 (m, 1H); 8.17 (d, 1H); 8.32 (d, 1H); 8.69 (bs, 4H); 8.92 (d, 1H); 9.12 (s, 1H); 11.7 (s, 1H).

EXAMPLE 6G

30 [5-Methyl-2-(5-isoquinolinyl)-2*H*-1,2,3-triazole-4-carbonyl]guanidine hydrochloride

[0297] 52% yield.

[0298] ¹H NMR (DMSO-*d*₆) δ 2.63 (s, 3H); 8.01 (t, 1H); 8.46 (d, 1H); 8.52 (d, 1H); 8.7 (m, 6H); 9.74 (s, 1H); 11.7 (s, 1H).

35 EXAMPLE 6T

[2-(8-Quinolinyl)-5-methyl-2*H*-1,2,3-triazole-4-carbonyl]guanidine hydrochloride

[0299] 6% yield

40 **[0300]** ¹H NMR (400 MHz, CD₃OD) δ 2.64 (s, 3H), 7.61 (m, 1H), 7.73 (t, J=7.8, 1H), 7.96 (dd, J=1.4, 7.4, 1H), 8.13 (dd, J=1.4, 4.2, 1H), 8.45 (dd, J=1.8, 8.6, 1H), 8.86 (dd, J=1.6, 4.4, 1H).

[0301] APCIMS 296 [M+1]⁺

[0302] APCIMS 302 [M+1]⁺

45 **[0303]** The title compounds of Examples 9A-9N were prepared using procedures analogous to that described in Bajnati, A.; Kokel, B.; Hubert-Habart, M. *Bull. Soc. Chim. Fr.* 1987, 318.

EXAMPLE 9H

Ethyl 5-methyl-1-(5-quinolinyl)-1*H*-pyrazole-4-carboxylate

50 **[0304]** 6% yield.

[0305] ¹H NMR (DMSO-*d*₆) δ 1.27 (t, 3H); 2.27 (s, 3H); 4.25 (q, 2H); 7.55 (m, 1H); 7.60 (m, 1H); 7.74 (d, 1H); 7.89 (t, 1H); 8.1 (s, 1H); 8.2 (d, 1H); 8.97 (m, 1H).

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EXAMPLE 9KEthyl 5-methyl-1-(1-phthalazinyl)-1H-pyrazole-4-carboxylate5 **[0306]** 43% yield.**[0307]** $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 1.28 (t, 3H); 2.51 (s, 3H); 4.25 (q, 2H); 7.89 (d, 1H); 8.09 (q, 1H); 8.1 (q, 1H); 8.19 (s, 1H); 8.32 (d, 1H); 9.84 (s, 1H).EXAMPLE 9L

10

Ethyl 5-methyl-1-(4-quinolinyl)-1H-pyrazole-4-carboxylate and Ethyl 3-methyl-1-(4-quinolinyl)-1H-pyrazole-4-carboxylate**[0308]** 68% yield.15 **[0309]** $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 1.19, 1.25 (2t, 3H); 2.33 (s, 3H); 4.06, 4.25 (2q, 2H); 7.41, 7.70 (2d, 1H); 7.61, 7.82 (2t, 1H); 8.15 (m, 2H); 9.06 (d, 1H).EXAMPLE 9M20 Ethyl 5-methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate**[0310]** 40% yield.**[0311]** $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 1.26 (t, 3H); 2.57 (s, 3H); 4.22 (q, 2H); 7.61 (m, 1H); 7.89 (d, 1H); 8.04 (s, 1H); 8.16 (d, 1H); 8.19 (s, 1H); 8.43 (d, 1H); 8.96 (d, 1H).

25

EXAMPLE 9NEthyl 1-(2-bromophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate30 **[0312]** 78% yield**[0313]** $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.80 (bs, 4H), 1.36 (t, $J=7.2$, 3H), 1.87 (m, 1H), 4.30 (q, $J=7.2$, 2H), 7.41 (m, 3H), 7.71 (dd, $J=1.4$, 8, 1H), 8.03 (s, 1H).**[0314]** APCIMS 335 $[\text{M}+1]^+$, 337 $[\text{M}+3]^+$ 35 **[0315]** The title compounds of Examples 10A-10K were prepared using procedures analogous to that described in Menozzi, G.; Mosti, L.; Schenone, P. J. *Heterocycl. Chem.*, 1987, 24, 1669.EXAMPLE 10AEthyl 5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carboxylate

40

[0316] 82% yield.**[0317]** APCIMS 325 $[\text{M}+1]^+$ **[0318]** $^1\text{H NMR}$ (CDCl_3) δ 1.77-1.84 (m, 1H), 8.07 (s, 1H).45 EXAMPLE 10CEthyl 5-methyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylate**[0319]** 66% yield.50 **[0320]** APCIMS 282 $[\text{M}+1]^+$ **[0321]** $^1\text{H NMR}$ (CDCl_3) δ 2.33 (s, 3H), 8.13 (s, 1H).EXAMPLE 10D55 Ethyl 5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylate**[0322]** 89% yield.**[0323]** APCIMS 308 $[\text{M}+1]^+$

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[0324] $^1\text{H NMR}$ (CDCl_3) δ 1.81-1.88 (m, 1H) , 8.10 (s, 1H).

EXAMPLE 10E

5 Ethyl 5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate

[0325] 88% yield.

[0326] APCIMS 308 $[\text{M}+1]^+$

10 **[0327]** $^1\text{H NMR}$ (CDCl_3) δ .8.95 (dd, $J=1.8, 4.2$, 1H), 8.24 (d, $J=8.8$, 1H), 8.10 (s, 1H), 7.79 (t, $J=7.8$, 1H), 7.72 (dt, $J=8.4, 0.8$, 1H), 7.58 (d, $J=7.2$, 1H), 7.41 (m, 1H), 4.31 (q, $J=7.2$, 2H), 1.76 (m, 1H), 1.37 (t, $J=7.2$, 3H), 0.67 (m, 4H).

EXAMPLE 10F

15 Ethyl 5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylate

[0328] 82% yield.

[0329] APCIMS 308 $[\text{M}+1]^+$

[0330] NMR (CDCl_3) δ 1.80-1.87 (m, 1H) , 8.09 (s, 1H).

20 EXAMPLE 10G

Methyl 5-ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate

25 **[0331]** 30% yield.

APCIMS 280 $[\text{M}-1]^-$

[0332] $^1\text{H NMR}$ (CDCl_3) δ 0.94-0.97 (t, 3H), 8.10 (s, 1H).

30 EXAMPLE 10H

Ethyl 5-cyclopropyl-1-(isoquinolin-8-yl)-1H-pyrazole-4-carboxylate

35 **[0333]** 24% yield.

[0334] APCIMS 308 $[\text{M}+1]^+$

[0335] $^1\text{H NMR}$ (CDCl_3) δ 3.25-3.31 (m, 1H) , 9.57 (s, 1H).

EXAMPLE 10J

40 Ethyl 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylate

[0336] 88% yield.

[0337] APCIMS 325 $[\text{M}+1]^+$

45 **[0338]** $^1\text{H NMR}$ (CDCl_3) δ 1.70-1.77 (m, 1H) , 8.00 (s, 1H) ;

EXAMPLE 10K

Ethyl 5-cyclopropyl-1-phenyl-1H-pyrazole-4-carboxylate

50 **[0339]** 89% yield.

[0340] APCIMS 257 $[\text{M}+1]^+$

[0341] $^1\text{H NMR}$ (CDCl_3) δ 1.87-2.00 (m, 1H) , 8.00 (s, 1H).

55

EXAMPLE 11

Ethyl 2-methyl-5-phenyl-2H-pyrazole-3-carboxylate (Example 11A) and Ethyl 1-methyl-5-phenyl-1H-pyrazole-3-carboxylate (Reference Example 11B).

[0342] The lithium salt of ethyl 2,4-dioxo-4-phenyl-butyrate (Murray, W. V.; Wachter, M. P. *J. Heterocycl. Chem.* 1989, 26, 1389) (1.0 g, 4.4 mmol) was combined in 4 mL absolute ethanol with methyl hydrazine (0.2 g, 4.4 mmol), and hydrochloric acid (1.2 mL of a 4 N solution in dioxane, 4.8 mmol). After heating the mixture at reflux for 2 h, the solution was concentrated *in vacuo* and the residue purified by silica gel chromatography using 5-20% ethyl acetate in hexanes as eluant to provide earlier eluting Example 11A (0.32 g, 31 %) and later eluting Reference Example 11B (0.38 g, 38%).

EXAMPLE 11A

Ethyl 2-methyl-5-phenyl-2H-pyrazole-3-carboxylate

[0343] ¹H NMR (CD₃OD) δ 1.4 (t, 3H), 4.15 (s, 3H), 4.3 (q, 2H), 7.2 (s, 1H), 7.3 (t, 1H), 7.4 (t, 2H), 7.8 (d, 2H).

[0344] APCIMS 231 [M+1]⁺

[0345] The title compounds of Example 12A-12B were prepared using procedures analogous to that described in Bajnati, A.; Hubert-Habart, M. *Bull. Soc. Chim. Fr.* **1988**, 540.

EXAMPLE 12A

n-Butyl 3-methyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate

[0346] A mixture of 5-acetyluracil (0.231 g, 1.5 mmol), 5-quinolinylhydrazine dihydrochloride (0.418 g, 1.8 mmol) and HCl (conc., 0.75 mL, 9 mmol) in *n*-butanol (15 mL) was heated at reflux for 20 h, cooled to 23 °C, and concentrated *in vacuo*. The residue was dissolved in *n*-butanol (10 mL). The resulting solution was treated with H₂SO₄ (conc., 0.96 mL, 18 mmol), heated at reflux for 20 h, cooled to 23 °C and concentrated *in vacuo*. The residue was partitioned between EtOAc and NaOH (1 M). The aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The brown solid residue was purified by flash chromatography (Flash 40S, hexanes-acetone 8:2) to afford 0.279 g (60%) of the desired product as a white solid.

[0347] ¹H NMR (400 MHz, CDCl₃) δ 0.96 (t, J=7, 3H), 1.45 (sextuplet, J=7.2, 2H), 1.72 (quintet, J=6.8, 2H), 2.60 (s, 3H), 4.28 (quartet, J=6.6, 2H), 7.24 (s, 1H), 7.47 (ddd, J=0.8, 4.4, 8.8, 1H), 7.58 (d, J=7.2, 1H), 7.76 (t, J=8, 1H), 8.21 (m, 1H), 8.30 (d, J=8, 1H), 8.98 (dd, J=1.4, 3, 1H).

[0348] APCIMS 310 [M+1]⁺

[0349] The title compound of Example 12B was prepared using a procedure analogous to that used for Example 12A.

EXAMPLE 12B

n-Butyl 1-(isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylate

[0350] 43% yield

[0351] ¹H NMR (400 MHz, CDCl₃) δ 0.94 (t, J=7.4, 3H), 1.44 (sextuplet, J=7.6, 2H), 1.70 (quintuplet, J=6.8, 2H), 2.58 (s, 3H), 4.26 (t, J=6.6, 2H), 7.66 (t, J=7.7, 1H), 7.75 (m, 2H), 8.05 (d, J=8, 1H), 8.21 (s, 1H), 8.57 (d, J=6, 1H), 9.33 (s, 1H).

[0352] APCIMS 310 [M+1]⁺

REFERENCE EXAMPLE 13A

5-Methyl-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxylic acid

[0353] To a solution of ethyl 5-methyl-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxylate in 15 ml methanol and 17 ml water was added 20 ml of 1 N sodium hydroxide and the resulting mixture was refluxed overnight under nitrogen. The methanol was removed *in vacuo* and the aqueous phase was acidified with dilute aqueous hydrochloric acid solution and extracted with 2x70 ml ethyl acetate. The combined ethyl acetate extracts were washed with 70 ml water and 70 ml brine, dried over sodium sulfate and concentrated *in vacuo* to a white solid (2.14 g, 85% yield).

[0354] ¹H NMR (CDCl₃) δ 2.37 (s, 3H); 3.79 (s, 3H); 7.04 (q, 2H); 7.3 (d, 1H); 7.44 (m, 1H); 8.09 (s, 1H).

[0355] The title compounds of Examples 13B-13Z were prepared using procedures analogous to that used for Ex-

ample 13A.

EXAMPLE 13H

5 5-Methyl-1-(5-quinolinyl)-1H-pyrazole-4-carboxylic acid

[0356] 75% yield.

[0357] ¹H NMR (DMSO-*d*₆) δ 2.27 (s, 3H); 7.56 (m, 1H); 7.62 (m, 1H); 7.77 (d, 1H); 7.91 (t, 1H); 8.07 (s, 1H); 8.21 (d, 1H); 8.99 (m, 1H).

10

EXAMPLE 13K

5-Methyl-1-(1-phthalaziny)-1H-pyrazole-4-carboxylic acid

15 **[0358]** 84% yield.

[0359] ¹H NMR (DMSO-*d*₆) δ 2.57 (s, 3H); 7.88 (d, 1H); 8.07-8.18 (m, 3H); 8.34 (d, 1H); 9.86 (s, 1H).

EXAMPLE 13L

20 5-Methyl-1-(4-quinolinyl)-1H-pyrazole-4-carboxylic acid

[0360] 66% yield.

[0361] ¹H NMR (DMSO-*d*₆) δ 2.31 (s, 3H); 7.42 (d, 1H); 7.62 (dd, 1H); 7.7 (d, 1H); 7.83 (t, 1H); 8.10 (d and s, 2H); 9.06 (d, 1H); 12.5 (bs, 1H).

25

EXAMPLE 13M

5-Methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid

30 **[0362]** 84% yield.

[0363] ¹H NMR (DMSO-*d*₆) δ 2.63 (s, 3H); 7.66 (m, 1H); 7.98 (d, 1H); 8.07 (s, 1H); 8.22 (m, 2H); 8.48 (d, 1H); 9.02 (d, 1H).

EXAMPLE 13N

35

4-Methyl-1-phenyl-1H-pyrazole-3-carboxylic acid

[0364] ¹H NMR (CDCl₃) δ 2.4 (s, 3H), 7.4 (t, 1H), 7.5 (t, 2H), 7.7 (d, 2H), 7.8 (s, 1H).

[0365] APCIMS 203 [M+1]⁺

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EXAMPLE 13P

5-Cyclopropyl-1-phenyl-1H-pyrazole-4-carboxylic acid

45 **[0366]** 94% yield.

[0367] APCIMS 227 [M-1]⁻

[0368] ¹H NMR (DMSO-*d*₆) δ 1.99-2.06 (m, 1H), 7.88 (s, 1H).

EXAMPLE 13Q

50

5-Cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carboxylic acid

[0369] 99% yield.

[0370] APCIMS 295 [M-1]⁻

55 **[0371]** ¹H NMR (DMSO-*d*₆) δ 1.73-1.80 (m, 1H), 7.98 (s, 1H).

EXAMPLE 13R1-(2-Bromophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

- 5 **[0372]** 93% yield
[0373] ^1H NMR (400 MHz, DMSO- d_6) δ 0.66 (bs, 4H), 1.82 (m, 1H), 7.50 (m, 3H), 7.80 (dd, J=1.2, 7.6, 1H), 7.89 (s, 1H), 12.33 (s, 1H).
[0374] APCIMS 307 [M+1]⁺, 309 [M+3]⁺

10 EXAMPLE 13T5-Methyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylic acid

- [0375]** 65% yield.
15 **[0376]** APCIMS 252 [M-1]⁻
[0377] ^1H NMR (DMSO- d_6) δ 2.13 (s, 3H), 8.84-8.85 (d, 1H).

EXAMPLE 13U20 5-Methyl-1-(isoquinolin-5-yl)-1H-pyrazole-4-carboxylic acid

- [0378]** 45% yield.
[0379] APCIMS 252 [M-1]⁻
25 **[0380]** ^1H NMR (DMSO- d_6) δ 2.24 (s, 3H), 8.05 (s, 1H).

EXAMPLE 13V5-Cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylic acid

- 30 **[0381]** 66% yield.
[0382] APCIMS 278 [M-1]⁻
[0383] ^1H NMR (DMSO- d_6) δ 1.69-1.76 (m, 1H), 7.97 (s, 1H).

EXAMPLE 13W35 5-Cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid

- [0384]** 56% yield.
[0385] APCIMS 278 [M-1]⁻
40 **[0386]** ^1H NMR (DMSO- d_6) δ 8.94 (dd, J=1.6, 4.0, 1H), 8.15 (dd, J=0.8, 8.4, 1H), 7.87 (s, 1H), 7.85-7.83 (m, 1H), 7.71 (dd, J=1.2, 7.2, 1H), 7.59-7.51 (m, 2H), 1.79 (m, 1H), 0.69 (m, 2H), 0.51-0.47 (m, 2H).

EXAMPLE 13X45 5-Cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylic acid

- [0387]** 72% yield.
[0388] APCIMS 295 [M-1]⁻
50 **[0389]** ^1H NMR (DMSO- d_6) δ 1:71-1.78 (m, 1H), 7.89 (s, 1H).

EXAMPLE 13Y5-Ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid

- 55 **[0390]** 98% yield.
[0391] APCIMS 266 [M-1]⁻
[0392] ^1H NMR (DMSO- d_6) δ 0.75-0.79 (t, 3H), 8.94-8.94 (d, 1H).

EXAMPLE 14A2-Methyl-5-phenyl-2H-pyrazole-3-carboxylic acid.

5 **[0393]** 2-Methyl-5-phenyl-2H-pyrazole-3-carboxylic acid ethyl ester (0.32 g, 1.39 mmol) was dissolved in 4.5 mL of tetrahydrofuran, 1.5 mL of methanol and 1.5 mL of water, and treated with lithium hydroxide hydrate (0.12 g, 2.78 mmol). After stirring at room temperature overnight, the mixture was acidified (pH = 1) with hydrochloric acid, and extracted with ethyl acetate (3 x 10 mL) and the combined organic phases washed with 10 mL of brine. The organic
10 extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a quantitative yield of the title compound.

[0394] ¹H NMR (CD₃OD) δ 4.2 (s, 3H), 7.2 (s, 1H), 7.3 (t, 1H), 7.4 (t, 2H), 7.8 (d, 2H).

[0395] APCIMS 203 [M+1]⁺

[0396] The title compounds of Examples 14B-14D were prepared using a procedure analogous to that used for Example 14A.

EXAMPLE 14C3-Methyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid

20 **[0397]** 86% yield

[0398] ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.45 (s, 3H), 7.60 (ddd, J=1.2, 4.0, 8.8, 1H), 7.73 (d, J=7.6., 1H), 7.84 (t, J=8, 1H), 8.12 (d, J=8.4, 1H), 8.26 (d, J=8.8, 1H), 8.59 (s, 1H), 8.97 (dd, J=1.2, 2.8, 1H), 8.98 (dd, J=1.4, 3, 1H).

[0399] APCIMS 252 [M-1]⁻

EXAMPLE 14D1-(Isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylic acid

30 **[0400]** 97% yield

[0401] ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.46 (s, 3H), 7.60 (m, 2H), 7.92 (d, J=7.2, 1H), 8.25 (d, J=8, 1H), 8.56 (d, J=6, 1H), 8.64 (s, 1H), 9.44 (s, 1H), 12.50 (bs, 1H).

[0402] APCIMS 252 [M-1]⁻

[0403] The title compounds of Examples 15A-15II were prepared using procedures analogous to that used for Example 6A.

EXAMPLE 15H[5-Methyl-1-(5-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

40 **[0404]** 53% yield.

[0405] ¹H NMR (DMSO-*d*₆) δ 2.31 (s, 3H); 7.59 (m, 1H); 7.68 (d, 1H); 7.79 (d, 1H); 7.93 (t, 1H); 8.27 (d, 1H); 8.55 (bs, 2H); 8.81 (bs, 2H); 8.98 (s, 1H); 9.00 (d, 1H).

EXAMPLE 15K[5-Methyl-1-(1-phthalazinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

45 **[0406]** 18% yield.

[0407] ¹H NMR (DMSO-*d*₆) δ 2.57 (s, 3H); 7.87 (d, 1H); 8.09 (q, 1H); 8.16 (q, 1H); 8.36 (d, 1H); 8.49 (bs, 1H); 8.76 (bs, 2H); 9.90 (s, 1H).

EXAMPLE 15L[5-Methyl-1-(4-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

55 **[0408]** 45% yield.

[0409] ¹H NMR (DMSO-*d*₆) δ 2.39 (s, 3H); 7.5 (d, 1H); 7.70 (t, 1H); 7.86 (d, 1H); 7.92 (t, 1H); 8.23 (d, 1H); 8.5 (bs, 2H); 8.77 (bs, 2H); 9.01 (s, 1H); 9.18 (s, 1H); 12.2 (s, 1H).

EXAMPLE 15M[5-Methyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride5 **[0410]** 92% yield.**[0411]** ¹H NMR (DMSO-*d*₆) δ 2.69 (s, 3H); 7.87 (m, 1H); 8.11 (d, 1H); 8.33 (d, 1H); 8.42 (s, 1H); 8.46 (bs, 2H); 8.73 (bs, 2H); 8.79 (d, 1H); 8.88 (s, 1H); 9.16 (d, 1H); 12.1 (s, 1H).EXAMPLE 15O

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[1-(2-Bromophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride**[0412]** 66% yield15 **[0413]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.59 (bs, 2H), 0.74 (d, J=7.6, 2H), 1.92 (m, 1H), 7.55 (m, 3H), 7.85 (d, J=7.6, 1H), 8.41 (bs, 2H), 8.66 (s, 1H), 8.70 (bs, 2H), 11.83 (s, 1H).**[0414]** APCIMS 348 [M+1]⁺, 350 [M+3]⁺EXAMPLE 15V20 (2-Methyl-5-phenyl-2H-pyrazole-3-carbonyl)guanidine hydrochloride**[0415]** ¹H NMR (DMSO-*d*₆) δ 4.1 (s, 3H), 7.3 (s, 1H), 7.4 (t, 1H), 7.4 (t, 2H), 7.7 (d, 2H), 8.5 (bs, 2H), 8.6 (bs, 2H), 11.4 (bs, 1H).25 **[0416]** APCIMS 244 [M+1]⁺EXAMPLE 15X[2-Methyl-5-(naphthalen-1-yl)-2H-pyrazole-3-carbonyl]guanidine hydrochloride30 **[0417]** ¹H NMR (DMSO-*d*₆) δ 4.2 (s, 3H), 7.6 (m, 3H), 7.67 (d, 1H), 7.9 (s, 1H), 8.0 (m, 2H), 8.5 (m, 3H), 8.6 (bs, 2H).**[0418]** APCIMS 292 [M-1]⁻EXAMPLE 15Y35 [5-(*tert*-Butyl)-2-methyl-2H-pyrazole-3-carbonyl]guanidine hydrochloride**[0419]** ¹H NMR (DMSO-*d*₆) δ 1.2 (s, 9H), 4.0 (s, 3H), 7.4 (s, 1H), 8.4 (bs, 2H), 8.6 (bs, 2H), 11.8 (bs, 1H).**[0420]** APCIMS 224 [M+1]⁺40 EXAMPLE 15CC(2-Methyl-5-phenyl-2H-pyrazole-3-carbonyl)guanidine hydrochloride45 **[0421]** ¹H NMR (DMSO-*d*₆) δ 4.1 (s, 3H), 7.3 (s, 1H), 7.4 (t, 1H), 7.4 (t, 2H), 7.7 (d, 2H), 8.5 (bs, 2H), 8.6 (bs, 2H), 11.4 (bs, 1H).**[0422]** APCIMS 244 [M+1]⁺EXAMPLE 15EE50 [5-(*tert*-Butyl)-2-methyl-2H-pyrazole-3-carbonyl]guanidine hydrochloride**[0423]** ¹H NMR (DMSO-*d*₆) δ 1.2 (s, 9H), 4.0 (s, 3H), 7.4 (s, 1H), 8.4 (bs, 2H), 8.6 (bs, 2H), 11.8 (bs, 1H).**[0424]** APCIMS 224 [M+1]⁺

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EXAMPLE 15HH[3-Methyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride5 **[0425]** 23% yield**[0426]** ¹H NMR (400 MHz, CD₃OD) δ 2.62 (s, 3H), 8.07 (m, 2H), 8.22 (t, J=7.8, 1H), 8.36 (d, J=7.6, 1H), 9.12 (s, 1H), 9.20 (d, J=8.8, 1H), 9.27 (d, J=5.2, 1H).**[0427]** APCIMS 296 [M+1]⁺10 EXAMPLE 15II[1-(Isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride15 **[0428]** 93% yield**[0429]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.49 (s, 3H), 7.03 (s, 1H), 8.02 (m, 1H), 8.18 (m, 2H), 8.58 (m, 6H), 9.50 (s, 1H), 9.82 (s, 1H), 12.38 (s, 1H).**[0430]** APCIMS 295 [M+1]⁺20 EXAMPLE 16A[5-Cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

[0431] A mixture of 5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid (4.08 g, 14.6 mmol) and 25 ml SOCl₂ was heated to reflux for 1 hour. The excess SOCl₂ was removed *in vacuo* via codistillation with toluene. The solid residue was added portionwise over 45 minutes to a vigorously stirred 40 °C solution of guanidine hydrochloride (5.02 g, 52.6 mmol) in 59 ml of 2 N NaOH and 29 ml THF. The resulting mixture was heated at reflux for 1 hour and then cooled to 23 °C. The organic solvent and 40 ml of the H₂O were removed *in vacuo*. The tan solid that precipitated was filtered and washed with 2X5 ml portions of cold H₂O. This solid was air-dried for 1 hour and then dried for 24 h under high vacuum at 40 °C to afford 3.5 g of the free base of the title compound. This solid was dissolved in 25 ml of hot methanol and treated with 1.85 ml of conc. HCl. This pale yellow solution was stirred for 15 min at room temperature and concentrated *in vacuo* to a light amber gum. The residual H₂O was removed *in vacuo* via codistillation with 3X25 ml portions of anhydrous ethanol. The resulting pale yellow solid was recrystallized from hot ethanol to afford 3.58 g of the title compound (62% yield).

30 **[0432]** APCIMS 319 [M-1]⁻35 **[0433]** ¹H NMR (DMSO-*d*₆) δ 9.16 (m, 1H), 8.86 (s, 1H), 8.85 (bs, 2H), 8.50 (bs, 2H), 8.37 (d, J=8.4, 1H), 8.08-7.97 (m, 3H), 7.78 (dd, J=4.4, 8.4, 1H), 1.99-1.93 (m, 1H), 0.64-0.62 (m, 2H), 0.42 (m, 2H).**[0434]** The title compounds of Examples 16B-16AA were prepared using procedures analogous to that used for Example 16A.40 EXAMPLE 16C(1-Benzyl-5-methyl-1H-pyrazole-4-carbonyl)guanidine hydrochloride45 **[0435]** 24% yield.**[0436]** APCIMS 256 [M-1]⁻**[0437]** ¹H NMR (DMSO-*d*₆) δ 2.48 (s, 3H), 8.84 (s, 1H)EXAMPLE 16F50 (1,5-Diphenyl-1H-pyrazole-4-carbonyl)guanidine hydrochloride55 **[0438]** 17% yield.**[0439]** APCIMS 304 [M-1]⁻**[0440]** ¹H NMR (DMSO-*d*₆) δ 7.17-7.35 (m, 10H), 8.81 (s, 1H)

EXAMPLE 16Q(1-Cyclohexyl-5-methyl-1H-pyrazole-4-carbonyl)guanidine hydrochloride

- 5 [0441] 59 % yield.
[0442] APCIMS 248 [M -1]⁻
[0443] ¹H NMR (DMSO-*d*₆) δ 2.50 (s, 3H), 8.41 (s, 1H)

EXAMPLE 16R[5-Methyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 10 [0444] 60% yield.
[0445] APCIMS 293 [M -1]⁻
15 [0446] ¹H NMR (DMSO-*d*₆) δ 2.22 (s, 3H), 8.75 (s, 1H)

EXAMPLE 16T[5-Cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 20 [0447] 70% yield.
[0448] APCIMS 336 [M -1]⁻
[0449] ¹H NMR (DMSO-*d*₆) δ 1.83-1.90 (m, 1H), 8.57 (s, 1H)

EXAMPLE 16U[1-(Isoquinolin-5-yl)-5-methyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 25 [0450] 51% yield.
30 [0451] APCIMS 293 [M -1]⁻
[0452] ¹H NMR (DMSO-*d*₆) δ 2.33 (s, 3H), 8.98 (s, 1H)

EXAMPLE 16W[5-Cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 35 [0453] 22% yield.
[0454] APCIMS 268 [M -1]⁻
[0455] ¹H NMR (DMSO-*d*₆) δ 2.11-2.17 (m, 1H), 8.56 (s, 1H)

EXAMPLE 16Y[5-Cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 40 [0456] 61 % yield.
45 [0457] APCIMS 337 [M-1]⁻
[0458] ¹H NMR (DMSO-*d*₆) δ 1.82-1.89 (m, 1H), 8.65 (s, 1H)

EXAMPLE 16Z[5-Cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 50 [0459] APCIMS 319 [M-1]⁻
[0460] ¹H NMR DMSO-*d*₆) δ 1.77-1.84 (m, 1H), 8.87(s, 1H).
55 [0461] Yield of HCl salt 3.5%

EXAMPLE 16AA[5-Ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 [0462] 14% yield.
 [0463] APCIMS 307 [M-1]⁻
 [0464] ¹H NMR (DMSO-*d*₆) δ 0.86-0.89 (t, 3H), 8.93 (s, 1H).
 [0465] The title compounds of Examples 19A-19000 were prepared using procedures analogous to that described in Menozzi, G.; Mosti, L.; Schenone, P. *J. Heterocycl. Chem.*, **1987**, 24, 1669.

EXAMPLE 19AEthyl 5-cyclopropyl-1-(2,3-dimethoxyphenyl)-1H-pyrazole-4-carboxylate

- 15 [0466] 89% yield.
 [0467] APCIMS 317 [M+1]⁺
 [0468] ¹H NMR (400 MHz, CDCl₃) δ 0.66-0.88 (m, 4H), 1.36 (t, J=7.2, 3H), 1.93 (m, 1H), 3.60 (s, 3H), 3.92 (s, 3H), 4.30 (q, J=7.2, 2H), 6.93 (d, J=8, 1H), 7.02 (d, J=8.4, 1H), 7.13 (t, J=8, 1H), 8.01 (s, 1H).

EXAMPLE 19BEthyl 5-cyclopropyl-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylate

- 25 [0469] 72% yield.
 [0470] APCIMS 307 [M+1]⁺
 [0471] ¹H NMR (400 MHz, CDCl₃) δ 0.6-0.8 (m, 4H), 1.39 (t, J=7.2, 3H), 1.80 (m, 1H), 4.33 (q, J=7.2, 2H), 7.30 (d, J=7.6, 1H), 7.52 (m, 4H), 7.92 (d, J=8, 1H), 7.98 (d, J=7.6, 1H), 8.12 (s, 1H).

EXAMPLE 19CEthyl 5-cyclopropyl-1-(naphthalen-2-yl)-1H-pyrazole-4-carboxylate

- 30 [0472] 96% yield.
 [0473] APCIMS 307 [M+1]⁺
 35 [0474] ¹H NMR (400 MHz, CDCl₃) δ 0.64 (m, 2H), 0.91 (m, 2H), 1.39 (m, 3H), 2.07 (m, 1H), 4.33 (m, 2H), 7.25 (m, 1H), 7.56 (m, 2H), 7.66 (m, 1H), 8.06 (m, 4H).

EXAMPLE 19DEthyl 5-cyclopropyl-1-(o-biphenyl)-1H-pyrazole-4-carboxylate

- 40 [0475] 57% yield.
 [0476] APCIMS 333 [M+1]⁺
 45 [0477] ¹H NMR (400 MHz, CDCl₃) δ 0.46 (m, 4H), 0.99 (m, 1H), 1.28 (m, 3H), 4.19 (m, 2H), 7.03 (m, 2H), 7.22 (m, 3H), 7.41-7.53 (m, 4H), 7.97 (s, 1H).

EXAMPLE 19EEthyl 5-cyclopropyl-1-(2-nitrophenyl)-1H-pyrazole-4-carboxylate

- 50 [0478] 51% yield.
 [0479] APCIMS 302 [M+1]⁺
 55 [0480] ¹H NMR (400 MHz, CDCl₃) δ 0.68 (m, 2H), 0.86 (m, 2H), 1.36 (m, 3H), 1.82 (m, 1H), 4.32 (m, 2H), 7.55-7.76 (m, 3H), 8.03 (m, 3H).

EXAMPLE 19FEthyl 5-cyclopropyl-1-(2-ethylphenyl)-1H-pyrazole-4-carboxylate

- 5 **[0481]** 53% yield.
[0482] APCIMS 285 [M+1]⁺
[0483] ¹H NMR (400 MHz, CDCl₃) δ 0.75 (m, 2H), 0.85 (m, 2H), 1.07 (m, 3H), 1.35 (m, 3H), 1.78 (m, 1H), 2.36 (q, J=7.4, 2H), 4.27 (m, 2H), 7.23 (m, 2H), 7.29-7.42 (m, 2H), 7.98 (s, 1H).

10 EXAMPLE 19GEthyl 5-cyclopropyl-1-(2-methylphenyl)-1H-pyrazole-4-carboxylate

- [0484]** 73% yield.
15 **[0485]** APCIMS 291 [M+1]⁺
[0486] ¹H NMR (400 MHz, CDCl₃) δ 0.75-0.81 (m, 4H), 1.34 (dt, J=7, 0.8, 3H), 1.83 (m, 1H), 2.05 (s, 3H), 4.28 (dq, J=7.2, 0.4, 2H), 7.30-7.38 (m, 4H), 7.99 (s, 1H).

20 EXAMPLE 19HEthyl 5-cyclopropyl-1-(2-chlorophenyl)-1H-pyrazole-4-carboxylate

- [0487]** 75% yield.
[0488] APCIMS 291 [M+1]⁺
25 **[0489]** ¹H NMR (400 MHz, CDCl₃) δ 0.6-0.9 (bs, 4H), 1.34 (dt, J=7.2, 3.6, 3H), 1.85 (m, 1H), 4.28 (q, J=7.2, 2H), 7.37-7.44 (m, 3H), 7.52 (m, 1H), 8.03 (s, 1H).

30 EXAMPLE 19IEthyl 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylate

- [0490]** 69% yield.
[0491] APCIMS 341 [M+1]⁺
35 **[0492]** ¹H NMR (400 MHz, CDCl₃) δ 0.62 (d, J=8.8, 2H), 0.78-0.85 (m, 2H), 1.35 (t, J=7.2, 3H), 1.85 (m, 1H), 4.20 (dq, J=14.4, 7.2, 2H), 7.35-7.6 (m, 4H), 8.03 (s, 1H).

40 EXAMPLE 19JEthyl 5-cyclopropyl-1-(2-fluorophenyl)-1H-pyrazole-4-carboxylate

- [0493]** 81 % yield.
[0494] APCIMS 275 [M+1]⁺
45 **[0495]** ¹H NMR (400 MHz, CDCl₃) δ 0.63 (m, 2H), 0.83 (m, 2H), 1.36 (t, J=7.2, 3H), 1.92 (m, 1H), 4.20 (q, J=7.2, 2H), 7.21-7.29 (m, 2H), 7.43-7.48 (m, 2H), 8.04 (s, 1H).

50 EXAMPLE 19KEthyl 5-cyclopropyl-1-(indazol-7-yl)-1H-pyrazole-4-carboxylate

- [0496]** 59% yield.
[0497] APCIMS 297 [M+1]⁺
55 **[0498]** ¹H NMR (400 MHz, CDCl₃) δ 0.56-0.60 (m, 2H), 1.00-1.23 (m, 2H), 1.37 (m, 3H), 2.07 (m, 1H), 4.33 (dq, J=6.8, 1.6, 2H), 7.22 (m, 1H), 7.60 (d, J=6.8, 1H), 7.75 (d, J=7.6, 1H), 8.12 (s, 1H), 10.97 (bs, 1H).

EXAMPLE 19LMethyl 5-ethyl-1-(benzothiazol-2-yl)-1H-pyrazole-4-carboxylate

- 5 **[0499]** 69% yield.
[0500] APCIMS 288 [M+1]⁺
[0501] ¹H NMR (400 MHz, CDCl₃) δ 1.34 (t, J=6.8, 3H), 3.69 (q, J=6.8, 2H), 3.85 (s, 3H), 7.36 (t, J=7.6, 1H), 7.46 (t, J=7.2, 1H), 7.83 (d, J=8.0, 1H), 7.91 (d, J=8.0, 1H), 8.01 (s, 1H).

10 EXAMPLE 19MEthyl 5-cyclopropyl-1-(2,4-dichloro-6-trifluoromethylphenyl)-1H-pyrazole-4-carboxylate

- [0502]** 43% yield.
15 **[0503]** APCIMS 393 [M+1]⁺
[0504] ¹H NMR (400 MHz, CDCl₃) δ 0.78-0.85 (m, 2H), 0.85-0.91 (m, 2H), 1.37 (t, J=7.2, 3H), 1.70 (m, 1H), 4.30 (q, J=6.8, 2H), 7.3-7.7 (m, 2H), 8.08 (s, 1H).

20 EXAMPLE 19NEthyl 5-cyclopropyl-1-(2-chloro-4-{methylsulfonyl}phenyl)-1H-pyrazole-4-carboxylate

- [0505]** 70% yield.
[0506] APCIMS 369 [M+1]⁺
25 **[0507]** ¹H NMR (400 MHz, CDCl₃) δ 0.68 (d, J=4.8, 2H), 0.82 (d, J=7.6, 2H), 1.37 (t, J=7.2, 3H), 1.84 (m, 1H), 4.30 (q, J=7.2, 2H), 7.61 (d, J=8.4, 1H), 7.96 (m, 1H), 8.04 (s, 1H), 8.12 (s, 1H).

30 EXAMPLE 19OEthyl 5-cyclopropyl-1-(2-chloro-4-{methylsulfonylmethylenesulfonyl}phenyl)-1H-pyrazole-4-carboxylate

- [0508]** 61% yield.
[0509] APCIMS 447 [M+1]⁺
35 **[0510]** ¹H NMR (400 MHz, CDCl₃) δ 0.65 (s, 2H), 0.84 (d, J=7.2, 2H), 1.35 (t, J=7.6, 3H), 1.84 (m, 1H), 3.29 (s, 3H), 4.30 (q, J=6.8, 2H), 4.62 (s, 2H), 7.64 (d, J=7.6, 1H), 8.01 (dd, J=8.4, 2.0, 1H), 8.06 (s, 1H), 8.16 (s, 1H).

40 EXAMPLE 19PEthyl 5-cyclopropyl-1-(2,5-dichlorophenyl)-1H-pyrazole-4-carboxylate

- [0511]** 72% yield.
[0512] APCIMS 325 [M+1]⁺
45 **[0513]** ¹H NMR (400 MHz, CDCl₃) δ 0.73 (s, 2H), 0.84 (d, J=6.8, 2H), 1.34 (t, J=7.2, 3H), 1.85 (m, 1H), 4.32 (q, J=7.2, 2H), 7.39-7.47 (m, 3H), 8.02 (s, 1H).

50 EXAMPLE 19QEthyl 5-cyclopropyl-1-(2,4-dichlorophenyl)-1H-pyrazole-4-carboxylate

- [0514]** 72% yield.
[0515] APCIMS 325 [M+1]⁺
55 **[0516]** ¹H NMR (400 MHz, CDCl₃) δ 0.73 (s, 2H), 0.84 (d, J=6.8, 2H), 1.34 (t, J=7.2, 3H), 1.85 (m, 1H), 4.32 (q, J=7.2, 2H), 7.39-7.47 (m, 3H), 8.02 (s, 1H).

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EXAMPLE 19R

Ethyl 5-cyclopropyl-1-(2,3-dichlorophenyl)-1H-pyrazole-4-carboxylate

- 5 [0517] 74% yield.
[0518] APCIMS 325 [M+1]⁺
[0519] ¹H NMR (400 MHz, CDCl₃) δ 0.67 (s, 2H), 0.78 (s, 2H), 1.34 (t, J=7.2, 3H), 1.83 (m, 1H), 4.32 (m, 2H), 7.30-7.35 (m, 2H), 7.59 (m, 1H), 8.02 (s, 1H).

10 EXAMPLE 19S

Ethyl 5-cyclopropyl-1-(2-chloro-5-methylsulfonylphenyl)-1H-pyrazole-4-carboxylate

- [0520] 38% yield.
15 [0521] APCIMS 369 [M+1]⁺
[0522] ¹H NMR (400 MHz, CDCl₃) δ 0.70 (s, 2H), 0.82 (d, J=7.2, 2H), 1.35 (t, J=7.2, 3H), 1.83 (m, 1H), 3.08 (s, 3H), 4.33 (q, J=7.2, 2H), 7.75 (dd, J=6.4, 2.4, 1H), 7.98-8.04 (m, 2H), 8.05 (s, 1H).

20 EXAMPLE 19T

Methyl 5-ethyl-1-(benzimidazol-5-yl)-1H-pyrazole-4-carboxylate

- [0523] 56% yield.
[0524] APCIMS 271 [M+1]⁺
25 [0525] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.98-1.16 (m, 3H), 2.81-3.07 (m, 2H), 3.76 (s, 3H), 7.23 (d, J=8.4, 1H), 7.68 (bs, 2H), 7.96 (s, 1H), 8.38 (bs, 1H), 12.75 (bs, 1H).

EXAMPLE 19U

30 Ethyl 5-cyclopropyl-1-(benzimidazol-5-yl)-1H-pyrazole-4-carboxylate

- [0526] 75% yield.
[0527] APCIMS 297 [M+1]⁺
35 [0528] ¹H NMR (400 MHz, CDCl₃) δ 0.61 (dd, J=5.4, 1.4, 2H), 0.85-0.87 (m, 2H), 1.37 (m, 3H), 1.98 (m, 1H), 4.31 (q, J=7.2, 2H), 7.44 (m, 1H), 7.76 (d, J=8.8, 1H), 7.85 (s, 1H), 8.01 (s, 1H), 8.37 (bs, 1H), 11.82 (bs, 1H).

EXAMPLE 19V

40 Methyl 5-ethyl-1-(3-chloroindazol-5-yl)-1H-pyrazole-4-carboxylate

- [0529] 63% yield.
[0530] APCIMS 305 [M+1]⁺
[0531] ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, J=7.6, 3H), 2.96 (q, J=7.6, 2H), 3.88 (s, 3H), 7.43-7.46 (m, 1H), 7.53 (d, J=8.8, 1H), 7.74 (s, 1H), 8.06 (s, 1H).

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EXAMPLE 19W

Methyl 5-ethyl-1-(2-methylbenzimidazol-5-yl)-1H-pyrazole-4-carboxylate

- 50 [0532] 65% yield.
[0533] APCIMS 284 [M+1]⁺
[0534] ¹H NMR (400 MHz, CDCl₃) δ 1.11 (t, J=7.6, 3H), 2.62 (s, 3H), 2.93 (q, J=7.6, 2H), 7.18 (dd, J=8.4, 2.0, 1H), 7.54-7.56 (m, 2H), 8.01 (s, 1H).

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EXAMPLE 19XEthyl 5-cyclopropyl-1-(2-chloro-5-hydroxysulfonylphenyl)-1H-pyrazole-4-carboxylate

- 5 **[0535]** 82% yield.
[0536] APCIMS 369 [M-1]⁻
[0537] ¹H NMR (CDCl₃) δ 0.89-1.11 (m, 4H), 1.39 (t, J=7.2, 3H), 1.83 (q, J=7.0, 1H), 4.35 (q, J=7.0, 2H), 6.92 (bs, 1H), 7.58 (d, J=8.4, 1H), 7.91-7.95 (m, 2H), 8.44 (s, 1H).

10 EXAMPLE 19YEthyl 5-cyclopropyl-1-(2-chloro-4-hydroxysulfonylphenyl)-1H-pyrazole-4-carboxylate

- [0538]** 96% yield.
15 **[0539]** APCIMS 369 [M-1]⁻
[0540] ¹H NMR (CDCl₃) δ 0.85-0.91 (m, 4H), 1.37 (dt, J=7.0, 5.2, 3H), 1.75-1.87 (m, 1H), 4.33 (q, J=7.0, 2H), 7.42 (d, J=8.0, 1H), 7.80 (d, J=8.0, 1H), 8.02 (s, 1H), 8.16 (s, 1H).

20 EXAMPLE 19ZEthyl 5-isopropyl-1-(5-quinolinyl)-1H-pyrazole-4-carboxylate

- [0541]** 88% yield.
[0542] APCIMS 310 [M+1]⁺
25 **[0543]** ¹H NMR (400, MHz, CDCl₃) δ 8.95 (dd, J= 4, 1.6, 1H), 8.26 (d, J=8, 1H), 8.12 (s, 1H), 7.79 (t, J=8, 1H), 7.53 (m, 2H), 7.39 (dd, J=9, 4, 1H), 4.32 (q, J=7, 2H), 3.01 (m, 1H), 1.38 (t, J=7, 3H), 1.21 (m, 6H).

30 EXAMPLE 19AAEthyl 5-*n*-propyl-1-(5-quinolinyl)-1H-pyrazole-4-carboxylate

- [0544]** 97% yield.
[0545] APCIMS 310 [M+1]⁺
35 **[0546]** ¹H NMR (400 MHz, CDCl₃) δ 8.95 (d, J=4, 1H), 8.25 (d, J=9, 1H), 8.12 (s, 1H), 7.79 (t, J=8, 1H), 7.56 (m, 2H), 7.38 (dd, J=8, 4, 1H), 4.32 (q, J=7, 2H), 2.71 (bs, 2H), 1.36 (m, 5H), 0.70 (t, J=7, 3H).

40 EXAMPLE 19BBEthyl 5-cyclopropyl-1-(2,1,3-benzothiazol-4-yl)-1H-pyrazole-4-carboxylate

- [0547]** 67% yield.
[0548] APCIMS 315 [M+1]⁺
[0549] ¹H NMR (400 MHz, CDCl₃) δ 8.11 (m, 2H), 7.70 (m, 2H), 4.31 (q, J=7, 2H), 1.97 (m, 1H), 1.36 (t, J=7, 3H), 0.53-0.85 (m, 4H).

45 EXAMPLE 19CCEthyl 5-cyclopropyl-1-(2-aminosulfonylphenyl)-1H-pyrazole-4-carboxylate

- 50 **[0550]** 72% yield.
[0551] APCIMS 336 [M+1]⁺
[0552] ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, J=7, 1H), 8.04 (s, 1H), 7.69 (t, J=7, 1H), 7.63 (t, J=7, 1H), 7.42 (d, J=7, 1H), 5.81 (s, 2H), 4.29 (q, J=7, 2H), 1.80 (m, 1H), 1.34 (t, J=7, 3H), 0.4-1.0 (bs, 4H).

55

EXAMPLE 19DDEthyl 5-cyclopropyl-1-(2-methylthiophenyl)-1H-pyrazole-4-carboxylate

- 5 **[0553]** 76% yield.
[0554] APCIMS 303 [M+1]⁺
[0555] ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.43 (m, 1H), 7.30 (d, J=8, 1H), 7.23 (m, 2H), 4.27 (q, J=7, 2H), 2.36 (s, 3H), 1.86 (m, 1H), 1.34 (t, J=7, 3H), 0.75 (m, 4H).

10 EXAMPLE 19EEMethyl 5-methoxymethyl-1-(5-quinolinyl)-1H-pyrazole-4-carboxylate

- [0556]** 90% yield.
15 **[0557]** APCIMS 298 [M+1]⁺
[0558] ¹H NMR (300 MHz, CDCl₃) δ 8.99 (d, J=4, 1H), 8.30 (d, J=9, 1H), 8.20 (s, 1H), 7.83 (t, J=8, 1H), 7.71 (m, 2H), 7.43 (dd, J=9,5, 1H), 4.56 (s, 2H), 3.93 (s, 3H), 3.21 (s, 3H).

20 EXAMPLE 19FFEthyl 5-cyclopropyl-1-(isoquinolin-5-yl)-1H-pyrazole-4-carboxylate

- [0559]** 69% yield.
25 **[0560]** APCIMS 308 [M+1]⁺
[0561] ¹H NMR (CDCl₃) δ 1.68-1.75 (m, 1H), 8.07 (s, 1H).

EXAMPLE 19GGEthyl 5-benzyloxymethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate

- 30 **[0562]** 93.5% yield.
[0563] APCIMS 388 [M+1]⁺
[0564] ¹H NMR (CDCl₃) δ 1.32-1.36 (s, 3H), 8.15 (s, 1H).

35 EXAMPLE 19HHMethyl 5-ethyl-1-(benzotriazol-5-yl)-1H-pyrazole-4-carboxylate

- [0565]** 95% yield
40 **[0566]** APCIMS 272 [M+1]⁺
[0567] ¹H NMR (CDCl₃) δ 1.12-1.16 (t, 3H), 8.07 (s, 1H).

EXAMPLE 19II45 Methyl 5-ethyl-1-(indazol-6-yl)-1H-pyrazole-4-carboxylate

- [0568]** 87% yield
[0569] APCIMS 270 [M+1]⁺
50 **[0570]** ¹H NMR (CDCl₃) δ 1.06-1.10 (t, 3H) ; 8.07 (s, 1H)

EXAMPLE 19JJMethyl 5-ethyl-1-(benzothiazol-6-yl)-1H-pyrazole-4-carboxylate

- 55 **[0571]** 74% yield
[0572] APCIMS 288 [M+1]⁺
[0573] ¹H NMR (CDCl₃) δ 1.11-1.15 (t, 3H), 8.20 (s, 1H)

EXAMPLE 19LLEthyl 5-cyclobutyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate

- 5 [0574] 93% yield
[0575] APCIMS 322 [M+1]⁺
[0576] ¹H NMR (CDCl₃) δ 3.44-3.53 (m, 1H), 8.08 (s, 1H)

EXAMPLE 19MMEthyl 5-cyclopropyl-1-(6-chloroquinolin-5-yl)-1H-pyrazole-4-carboxylate

- 10 [0577] 23% yield
[0578] APCIMS 342 [M+1]⁺
15 [0579] ¹H NMR (CDCl₃) δ 1.70-1.80 (m, 1H), 8.04 (s, 1H)

EXAMPLE 19NNMethyl 5-ethyl-1-(indazol-5-yl)-1H-pyrazole-4-carboxylate

- 20 [0580] 71.5% yield
[0581] APCIMS 271 [M+1]⁺
[0582] ¹H NMR (CDCl₃) δ 1.06-1.10 (t, 3H), 8.02 (s, 1H)

EXAMPLE 19OOMethyl 5-ethyl-1-(1,4-benzodioxan-6-yl)-1H-pyrazole-4-carboxylate

- 25 [0583] 85% yield
30 [0584] APCIMS 289 [M+1]⁺
[0585] ¹H NMR (CDCl₃) δ 1.12-1.16 (t, 3H), 7.96 (s, 1H)

EXAMPLE 19PPEthyl 5-isobutyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate

- 35 [0586] 98% yield
[0587] APCIMS 324 [M+1]⁺
[0588] ¹H NMR (CDCl₃) δ 2.68-2.70 (m, 1H), 8.14 (s, 1H)

40

EXAMPLE 19QQMethyl 5-ethyl-1-(1,3-benzodioxol-5-yl)-1H-pyrazole-4-carboxylate

- 45 [0589] 76.6% yield
[0590] APCIMS 275 [M+1]⁺
[0591] ¹H NMR (CDCl₃) δ 1.10-1.14 (t, 3H), 7.94 (s, 1H)

EXAMPLE 19RR

50

Ethyl 5-cyclopropyl-1-(8-Bromoquinolin-5-yl)-1H-pyrazole-4-carboxylate

- [0592] 49% yield
[0593] APCIMS 388 [M+2]⁺
55 [0594] ¹H NMR (CDCl₃) δ 1.64-1.72 (m, 1H), 8.04 (s, 1H)

EXAMPLE 19SSEthyl 5-Cyclopropyl-1-(6-trifluoromethylquinolin-7-yl)-1H-pyrazole-4-carboxylate

- 5 [0595] 65% yield
 [0596] APCIMS 376 [M+1]⁺
 [0597] ¹H NMR (CDCl₃) δ 1.81-1.88 (m, 1H), 8.12 (s, 1H)

EXAMPLE 19TTEthyl 5-methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate

- 10 [0598] 40% yield.
 [0599] ¹H NMR (DMSO-*d*₆) δ 1.26 (t, 3H); 2.57 (s, 3H); 4.22 (q, 2H); 7.6 (dd, 1H); 7.89 (dd, 1H); 8.04 (s, 1H); 8.12-8.19 (m, 2H); 8.43 (d, 1H); 8.95 (dd, 1H).
 15

EXAMPLE 19UUEthyl 5-cyclopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate

- 20 [0600] 73.2 % yield.
 [0601] ¹H NMR (DMSO-*d*₆) δ 0.43 (dd, 2H); 0.83 (m, 2H); 1.29 (t, 3H); 2.18 (m, 1H); 4.24 (q, 2H); 7.61 (dd, 1H); 7.98-8.04 (dd +s, 2H); 8.12 (d, 1H); 8.26 (s, 1H); 8.46 (d, 1H); 8.96 (t, 1H);
 25

EXAMPLE 19VVEthyl 5-methyl-1-(6-methoxy-5-quinolinyl)-1H-pyrazole-4-carboxylate

- 30 [0602] 25% yield.
 [0603] ¹H NMR (DMSO-*d*₆) δ 1.27 (t, 3H); 2.16 (s, 3H); 3.9 (s, 3H); 4.23 (q, 2H); 7.34 (dd, 1H); 7.46 (m, 1H); 7.87 (d, 1H); 8.07 (s, 1H); 8.24 (d, 1H); 8.8 (dd, 1H).
 35

EXAMPLE 19WWEthyl 5-cyclopropyl-1-(6-methyl-5-quinolinyl)-1H-pyrazole-4-carboxylate

- 40 [0604] 55.2% yield.
 [0605] ¹H NMR (DMSO-*d*₆) δ 0.48-0.78 (m, 4H); 1.27 (t, 3H); 1.66 (m, 1H); 2.13, (s, 3H); 4.21 (q, 2H); 7.35 (dd, 1H); 7.5 (m, 1H); 7.8 (d, 1H); 8.11 (m, 2H); 8.89 (t, 1H).
 45

EXAMPLE 19XXEthyl 5-ethyl-1-(2-methyl-6-quinolinyl)-1H-pyrazole-4-carboxylate

- 50 [0606] 36.1% yield.
 [0607] ¹H NMR (DMSO-*d*₆) δ 1.05 (t, 3H); 1.3 (t, 3H); 2.64 (s, 3H); 2.9 (q, 2H); 4.2 (2q, 2H); 7.45 (d, 1H); 7.56 (d, 1H); 7.82 (m, 3H); 8.6 (d, 1H).
 55

EXAMPLE 19YYEthyl 5-ethyl-1-(6-methyl-5-quinolinyl)-1H-pyrazole-4-carboxylate

- [0608] 70.8 % yield.
 [0609] ¹H NMR (DMSO-*d*₆) δ 0.83 (t, 3H); 1.33 (t, 3H); 2.15 (s, 3H); 2.50 (2q, 2H); 4.31 (q, 2H); 7.33 (d, 1H); 7.53 (q, 1H); 7.87 (d, 1H); 8.19 (d+s, 2H); 8.95 (d, 1H).
 55

EXAMPLE 19ZZEthyl 5-ethyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate

5 [0610] 99.1% yield.

[0611] ¹H NMR (DMSO-*d*₆) δ 1.04 (t, 3H); 1.26 (t, 3H); 2.94 (q, 2H); 4.23 (q, 2H); 7.61 (q, 1H); 7.82 (dd, 1H); 8.03 (s, 1H); 8.15 (d, 2H); 8.47 (d, 1H); 8.97 (d, 1H).EXAMPLE 19AAA

10

Methyl 1-(2-quinoxaliny)-5-ethyl-1H-pyrazole-4-carboxylate

[0612] 77% yield

15 [0613] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.41 (s, 1H), 8.17 (s, 1H), 8.13 (dd, J=1.2, 8, 1H), 8.01 (dd, J=1, 8, 1H), 7.87 (m, 2H), 3.78 (s, 3H), 3.40 (q, J=7, 2H), 1.30 (t, J=7, 3H).[0614] APCIMS 283 [M+1]⁺EXAMPLE 19BBB20 Methyl 1-(2-benzimidazolyl)-5-ethyl-1H-pyrazole-4-carboxylate

[0615] 61% yield.

[0616] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.14 (s, 1H), 8.19 (s, 1H), 7.63 (d, J=8, 1H), 7.45 (d, J=8, 1H), 7.2 (m, 2H) 3.77 (s, 1H), 3.52 (q, J=7, 2H), 1.22 (t, J=7, 3H).25 [0617] APCIMS 271 [M+1]⁺EXAMPLE 19CCC

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Ethyl 1-(2-trifluoromethyl-4-Chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0618] 54% yield.

[0619] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (d, J=2.4, 1H), 7.96 (d, J=3, 1H), 7.93 (d, J=2, 1H), 7.76 (d, J=8, 1H), 4.19 (q, J=7, 2H), 1.76 (m, 1s), 1.24 (t, J=7, 3H), 0.73 (d, J=8, 2H), 0.62 (d, J=4, 2H).[0620] APCIMS 359 [M+1]⁺

35

EXAMPLE 19DDDEthyl 1-(2-fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

40 [0621] 70% yield.

[0622] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.08 (s, 1H), 7.97-7.87 (m, 3H), 4.24 (q, J=7, 2H), 1.74 (m, 1H), 1.30 (t, J=7, 3H), 0.86-0.68 (m, 4H).[0623] APCIMS 343 [M+1]⁺45 EXAMPLE 19EEEEthyl 1-(2-trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0624] 72% yield.

50 [0625] ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 (s, 1H), 7.93 (dd, J=8, 3, 1H), 7.84-7.73 (m, 2H), 4.21 (q, J=7, 2H), 1.77 (m, 1H), 1.26 (t, J=7, 3H), 0.75-0.65 (m, 4H).[0626] APCIMS 343 [M+1]⁺55 EXAMPLE 19FFFMethyl 1-(2-quinolinyl)-5-ethyl-1H-pyrazole-4-carboxylate

[0627] 82% yield

EP 1 056 729 B1

[0628] ^1H NMR (300 MHz, DMSO- d_6) δ 8.63 (d, J=9, 1H), 8.15 (s, 1H), 8.11-8.00 (m, 3H), 7.86 (m, 1H), 7.69 (t, J=9, 1H), 3.82 (s, 3H), 3.50 (q, J=7, 2H), 1.33 (t, J=7, 3H).

[0629] APCIMS 282 [M+1]⁺

5 EXAMPLE 19GGG

Ethyl 1-(2-chloro-5-hydroxycarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0630] 89% yield

10 **[0631]** ^1H NMR (300 MHz, DMSO- d_6) δ 8.11 (dd, J=2.1, 8, 1H), 8.06 (d, J=1.8, 1H), 8.040 (s, 1H), 7.88 (d, J=8, 1H), 4.25 (q, J=7, 2H), 1.87 (m, 1H), 1.30 (t, J=7, 3H), 0.800-0.74 (m, 2H), 0.70-0.64 (m, 2H).

[0632] APCIMS 335 [M+1]⁺

15 EXAMPLE 19HHH

Ethyl 1-(4-benzimidazolyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0633] 60% yield

20 **[0634]** ^1H NMR (300 MHz, DMSO- d_6) δ 8.28 (s, 1H), 8.01 (bs, 1H), 7.72 (bs, 1H), 7.38-7.33 (m, 2H), 4.26 (q, J=7, 2H), 2.02 (m, 1H), 1.31 (t, J=7, 3H), 0.56-0.48 (m, 4H).

[0635] APCIMS 297 [M+1]⁺

25 EXAMPLE 19III

Ethyl 1-(2-chloro-5-iodophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0636] 79% yield

30 **[0637]** ^1H NMR (300 MHz, CDCl₃) δ 8.06 (s, 1H), 7.93 (d, J=1.5, 1H), 7.76 (dd, J=1.5, 8, 1H), 7.15 (d, J=8, 1H), 4.33 (q, J=7.2, 2H), 1.88 (m, 1H), 1.39 (t, J=7.5, 3H), 0.91-0.76 (m, 4H).

[0638] APCMIS 417 [M+1]⁺

35 EXAMPLE 19KKK

Ethyl 1-(2-chloro-5-methoxyphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0639] 70% yield

[0640] APCIMS 321 [M+1]⁺

40 **[0641]** ^1H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 7.44 (d, J=9, 1H), 7.01 (m, 1H), 6.69 (d, J=3, 1H), 4.34 (q, J=7, 2H), 1.94 (m, 1H), 1.40 (t, J=7, 3H), 0.82 (bs, 4H).

45 EXAMPLE 19LLL

Ethyl 1-(1-isoquinolyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

[0642] 15 % yield

[0643] APCIMS 308 [M+1]⁺

50 **[0644]** ^1H NMR (400 MHz, DMSO- d_6) δ 8.51 (d, J=6, 1H), 8.13 (d, J=8, 1H), 8.08 (d, 6, 1H), 8.07 (s, 1H), 7.85 (t, J=9, 1H), 7.67 (t, J=8, 1H), 7.44 (d, J=8, 1H), 4.23 (q, J=7, 2H), 1.96 (m, 1H), 1.27 (t, J=7, 3H), 0.62-0.56 (m, 2H), 0.47-0.41 (m, 2H).

55 EXAMPLE 19MMM

Methyl 5-butyl-1-(5-quinolinyl)-1H-pyrazole-4-carboxylate

[0645] 93% yield.

[0646] APCIMS 310 [M+1]⁺

[0647] ^1H NMR (300 MHz, CDCl₃) δ 9.01 (m, 1H), 8.31 (d, J=8, 1H), 8.16 (s, 1H), 7.85 (t, J=8, 1H), 7.61 (m, 2H), 7.44 (dd, J=9, 4, 1H), 3.91 (s, 3H), 2.79 (bs, 2H), 1.37 (quintet, J=8, 2H), 1.15 (quintet, 2H), 0.69 (t, J=7, 3H).

EXAMPLE 19NNNEthyl 5-isopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate

5 [0648] 81.1 % yield.

[0649] ¹H NMR (DMSO-*d*₆) δ 1.27 (d+t, 9H); 3.17 (m, 1H); 4.23 (q, 2H); 7.63 (q, 1H); 7.75 (dd, 1H); 8.01 (s, 1H); 8.11 (d, 1H); 8.15 (d, 1H); 8.48 (dd, 1H); 8.98 (q, 1H).

EXAMPLE 19OOO

10

Ethyl 5-propyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate

[0650] 91.5% yield.

15 [0651] ¹H NMR (DMSO-*d*₆) δ 0.69 (t, 3H); 1.26 (t, 3H); 1.42 (q, 2H); 2.93 (t, 2H); 4.22 (q, 2H); 7.61 (q, 1H); 7.82 (dd, 1H); 8.04 (s, 1H); 8.16 (d+s, 2H); 8.47 (d, 1H); 8.98 (q, 1H).

[0652] The title compounds of Examples 20A-20G were prepared using procedures analogous to that described in Bajnati, A.; Hubert-Habart, M. *Bull. Soc. Chim. Fr.* **1988**, 540, and Example 12A.

EXAMPLE 20E

20

n-Butyl 1-(2,1,3-benzothiadiazol-4-yl)-3-methyl-1H-pyrazole-4-carboxylate

[0653] 25% yield

25 [0654] ¹H NMR (400 MHz, CDCl₃) δ 0.97 (t, J=7.2, 3H), 1.46 (m, 2H), 1.74 (m, 2H), 2.58 (s, 3H), 4.28 (t, J=6.8, 2H), 7.68 (t, J=8.6, 1H), 7.92 (d, J=8.8, 1H), 8.21 (d, J=7.2, 1H), 9.53 (s, 1H).

[0655] APCIMS 217[M+1]⁺

EXAMPLE 20F

30

n-Butyl 1-(indazol-7-yl)-3-methyl-1H-pyrazole-4-carboxylate

[0656] 35% yield

35 [0657] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.90 (t, J=7.4, 3H), 1.40 (m, 2H), 1.64 (m, 2H), 2.83 (s, 3H), 4.19 (t, J=6.4, 2H), 7.17 (t, J=7.6, 1H), 7.72 (d, J=7.6, 1H), 8.18 (s, 1H), 9.03 (s, 1H), 13.13 (bs, 1H).

[0658] APCIMS 299 [M+1]⁺

EXAMPLE 20G

40

n-Butyl 1-benzyl-3-methyl-1H-pyrazole-4-carboxylate

[0659] 68% yield

[0660] ¹H NMR (400 MHz, CDCl₃) δ 0.93 (t, J=7.2, 3H), 1.40 (m, 2H), 1.66 (m, 2H), 2.45 (s, 3H), 4.19 (t, J=6.6, 2H), 5.2 (s, 2H), 7.20-7.24 (m, 2H), 7.32-7.36 (m, 3H), 7.77 (s, 1H).

45 [0661] APCIMS 273 [M+1]⁺

EXAMPLE 21Ethyl 5-cyclopropyl-1-(2-pyrrol-1-ylphenyl)-1H-pyrazole-4-carboxylate

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[0662] A mixture of ethyl 5-cyclopropyl-1-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (2.5 g, 8.3 mmol) and Pd/C (10%, 0.550 g, 20% w/w) in ethyl acetate (60 mL) was shaken under a H₂ atmosphere (50 psig) for 3 h. The resulting mixture was filtered through Celite® and concentrated *in vacuo* to afford 2.52 g of a reddish oil.

55 [0663] A portion of the residue (458.5 mg, 1.69 mmol) and 2,5-dimethoxytetrahydrofuran (0.328 mL, 2.53 mmol) in glacial acetic acid (6 mL) was heated to 110 °C under a N₂ atmosphere for 1 h. The reaction mixture was cooled to 23 °C and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed twice with NaHCO₃ (sat aq sol) and brine, dried over MgSO₄, and filtered. The filtrate was passed over a short column of silica gel. The eluate was concentrated *in vacuo* to yield 0.4965 g (91%) of the title compound as a dark oil.

[0664] APCIMS 322 [M+1]⁺

EP 1 056 729 B1

[0665] ^1H NMR (400 MHz, CDCl_3) δ 0.35-0.80 (m, 4H), 1.01 (m, 1H), 1.36 (t, $J=9.4$, 3H), 4.30 (q, $J=8.8$, 2H), 7.42-7.61 (m, 4H), 8.08 (s, 1H).

EXAMPLE 22A

Ethyl 5-cyclopropyl-1-(2-chloro-5-{dimethylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylate

[0666] A mixture of ethyl 5-cyclopropyl-1-(2-chloro-5-{hydroxysulfonyl}phenyl)-1H-pyrazole-4-carboxylate (1.48 g, 4.0 mmol) and PCl_5 (1.79 g, 8.6 mmol) in POCl_3 (6 mL) under a nitrogen atmosphere was heated at 95 °C for 30 min, cooled to 23 °C and poured slowly over ice. The resulting mixture was extracted with EtOAc. The organic layer was washed three times with cold water, brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to afford 1.48 g (95% yield) of ethyl 5-cyclopropyl-1-(2-chloro-5-{chlorosulfonyl}phenyl)-1H-pyrazole-4-carboxylate as a yellow oil.

[0667] A solution of ethyl 5-cyclopropyl-1-(2-chloro-5-{chlorosulfonyl}phenyl)-1H-pyrazole-4-carboxylate (0.315 g, 0.812 mmol) in CH_2Cl_2 (3 mL) was treated at 23 °C with dimethylamine (2 M in THF, 3 mL, 6 mmol). The resulting mixture was stirred for 15 min and concentrated *in vacuo*. The residue was partitioned between EtOAc and HCl (0.1 M aq). The organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by Flash 40S™ chromatography (65:35 hexanes-EtOAc) to afford 0.276 g (86% yield) of desired product as a colorless oil.

[0668] APCIMS 397 $[\text{M}+1]^+$

[0669] ^1H NMR (400 MHz, CDCl_3) δ 0.68 (d, $J=5.6$, 2H), 0.81 (d, $J=8.4$, 2H), 1.35 (t, $J=7.2$, 3H), 1.83 (m, 1H), 2.74 (s, 6H), 4.30 (q, $J=7.2$, 2H), 7.70-7.25 (m, 1H), 7.80-7.83 (m, 2H), 8.04 (s, 1H).

[0670] The title compounds of Examples 22B-22E were prepared using procedures analogous to that used for Example 22A.

EXAMPLE 22B

Ethyl 5-cyclopropyl-1-(2-chloro-5-{aminosulfonyl}phenyl)-1H-pyrazole-4-carboxylate

[0671] 58% yield.

[0672] APCIMS 368 $[\text{M}-1]^-$

[0673] ^1H NMR (400 MHz, CDCl_3) δ 0.73 (s, 2H), 0.84 (d, $J=5.6$, 2H), 1.37 (t, $J=7.2$, 3H), 1.85 (m, 1H), 4.31 (q, $J=7.2$, 2H), 7.69 (d, $J=7.2$, 1H), 7.96 (m, 2H), 8.06 (s, 1H).

EXAMPLE 22C

Ethyl 5-cyclopropyl-1-(2-chloro-5-{methylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylate

[0674] 97% yield.

[0675] APCIMS 368 $[\text{M}+1]^+$

[0676] ^1H NMR (400 MHz, CDCl_3) δ 0.72 (s, 2H), 0.86 (d, $J=8$, 2H), 1.37 (t, $J=7.2$, 3H), 1.85 (m, 1H), 2.70 (s, 3H), 4.32 (q, $J=7.2$, 2H), 7.71 (d, $J=9.2$, 1H), 7.90-7.93 (m, 2H), 8.06 (s, 1H).

EXAMPLE 22D

Ethyl 5-cyclopropyl-1-(2-chloro-4-{dimethylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylate

[0677] 100% yield.

[0678] APCIMS 397 $[\text{M}+1]^+$

[0679] ^1H NMR (400 MHz, CDCl_3) δ 0.67 (bs, 2H), 0.82 (d, $J=6.4$, 2H), 1.35 (t, $J=7.2$, 3H), 1.85 (m, 1H), 2.76 (s, 6H), 4.32 (q, $J=7.2$, 2H), 7.57 (d, $J=8.4$, 1H), 7.78 (dd, $J=8.4$, 2.0, 1H), 7.94 (s, 1H), 8.05 (s, 1H).

EXAMPLE 22E

Ethyl 5-cyclopropyl-1-(2-chloro-4-{methylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylate

[0680] 93% yield.

[0681] APCIMS 384 $[\text{M}+1]^+$

[0682] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.58-0.61 (m, 2H), 0.73-0.78 (m, 2H), 1.35 (t, $J=6.8$, 3H), 1.85 (m, 1H), 2.47,

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(s, 6H), 4.21 (q, J=7.2, 2H), 7.77 (dd, J=9.6, 4.8, 1H), 7.88 (s, 1H), 8.03 (d, J=3.5, 1H).

[0683] The title compounds of Examples 23A-23B were prepared using procedures analogous to that described in Kikugawa, Y. *Synthesis*, **1981**, 124.

5 EXAMPLE 23A

Methyl 1-(1-methylbenzimidaz-2-yl)-5-ethyl-1H-pyrazole-4-carboxylate

[0684] 61% yield

10 **[0685]** ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 7.78-7.69 (m, 2H), 7.45-7.32 (m, 2H), 8.83 (s, 3H), 3.72 (s, 3H), 3.04 (q, J=7, 2H), 1.14 (t, J=7, 3H).

[0686] APCIMS 285 [M+1]⁺

15 EXAMPLE 23B

Methyl 5-ethyl-1-(1-methylbenzimidazol-6-yl)-1H-pyrazole-4-carboxylate

[0687] 35% yield.

[0688] APCIMS 284 [M+1]⁺

20 **[0689]** ¹H NMR (300 MHz, CDCl₃) δ 1.03 (t, J=7.35, 3H), 2.87 (q, J=7.35, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 7.26-7.30 (m, 1H), 7.78-7.81 (m, 2H), 8.02 (s, 1H), 8.36 (s, 1H).

25 EXAMPLE 24

Ethyl 5-cyclopropyl-1-(2-methylsulfonylphenyl)-1H-pyrazole-4-carboxylate

[0690] A solution of ethyl 5-cyclopropyl-1-(2-methylthiophenyl)-1H-pyrazole-4-carboxylate (0.456 g, 1.51 mmol) in methanol (6 mL) at 0 °C was treated with a solution of oxone (1.40 g, 2.27 mmol) in water (6 mL). The resulting slurry was stirred at 23 °C for 8 h. The mixture was treated with additional oxone (0.46 g, 0.76 mmol), stirred for 14 h and partitioned between CH₂Cl₂ and water. The organic layer was washed with water, dried over MgSO₄ and concentrated *in vacuo* to afford 0.504 g (100%) of the title compound.

[0691] APCIMS 335 [M+1]⁺

30 **[0692]** ¹H NMR (400 MHz, CDCl₃) δ 8.23 (dd, J=8, 2, 1H), 8.03 (s, 1H), 7.77 (t, J=8, 1H), 7.71 (t, J=8, 1H), 4.43 (d, J=7, 1H), 4.30 (q, J=7, 2H), 3.27 (s, 3H), 1.81 (m, 1H), 1.36 (t, J=7, 3H), 0.4-1.0 (bs, 4H).

35 EXAMPLE 25

Ethyl 5-cyclopropyl-1-(2-methylaminosulfonylphenyl)-1H-pyrazole-4-carboxylate and (Example 25A) Ethyl 5-cyclopropyl-1-(2-dimethylaminosulfonylphenyl)-1H-pyrazole-4-carboxylate (Example 25B)

40 **[0693]** A solution of ethyl 5-cyclopropyl-1-(2-aminosulfonylphenyl)-1H-pyrazole-4-carboxylate (0.503 g, 1.50 mmol) in dry DMSO (5 mL) at 23 °C was treated with NaH (60% in mineral oil, 0.090 g, 2.25 mmol) and stirred for 1.5 h. The resulting mixture was treated with dimethylsulfate (0.213 mL, 2.25 mmol), stirred for 20 h and partitioned between EtOAc and water. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by Flash 40M™ chromatography (hexanes-EtOAc 60:40 to 50:50) to provide 0.141 g (27%) of Example 25A and 0.231 g (42%) of Example 25B.

45 EXAMPLE 25A

50 Ethyl 5-cyclopropyl-1-(2-methylaminosulfonylphenyl)-1H-pyrazole-4-carboxylate

[0694] APCIMS 350 [M+1]⁺

55 **[0695]** ¹H NMR (400 MHz, CDCl₃) δ 8.13 (dd, J=8, 1.4, 1H), 8.04 (s, 1H), 7.71 (t, J=8, 1.6, 1H), 7.65 (t, J=8, 1.6, 1H), 7.44 (dd, 8, 1.2, 1H), 5.93 (q, J=5, 1H), 4.31 (q, J=7, 2H), 2.65 (d, J=5, 3H), 1.82 (m, 1H), 1.36 (t, J=7, 3H), 0.4-1.1 (m, 4H).

EXAMPLE 25BEthyl 5-cyclopropyl-1-(2-dimethylaminosulfonylphenyl)-1H-pyrazole-4-carboxylate

- 5 **[0696]** APCIMS 364 [M+1]⁺
[0697] ¹H NMR (400 MHz, CDCl₃) δ 8.07 (dd, J=7, 2, 1H), 8.00 (s, 1H), 7.68 (m, 2H), 7.35 (dd, J=7, 2, 1H), 4.29 (q, J=7, 2H), 2.67 (s, 6H), 1.88 (m, 1H), 1.36 (t, J=7, 3H), 0.64-0.93 (m, 4H).

EXAMPLE 26AEthyl 1-(2-chloro-5-methylaminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

- 15 **[0698]** A solution of ethyl 1-(2-chloro-5-hydroxycarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate (1.32 g, 3.73 mmol) in thionyl chloride (7.5 mL) was heated at reflux for 2 h under a nitrogen atmosphere. The resulting solution was concentrated *in vacuo*. A solution of the residue in anhydrous CH₂Cl₂ (10 mL) under a nitrogen atmosphere was treated with methylamine (2 M solution in THF, 9.33 mL, 18.7 mmol) followed by a catalytic amount of 4-dimethylaminopyridine. The resulting mixture was stirred for 6 h and partitioned between ethyl acetate and HCl (1 M aq). The organic layer was washed with brine, NaHCO₃ (sat aq sol), and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash 40M™ chromatography (75:25 ethyl acetate/hexanes) to afford 1.00 g (77% yield) of the title compound.

- 20 **[0699]** ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1H), 7.88 (dd, J=2, 8, 1H), 7.81 (d, J=2, 1H), 7.63 (d, J=9, 1H), 6.40 (bs, 1H), 4.33 (q, J=7, 2H), 3.02 (d, J=4, 3H), 1.89 (m, 1H), 1.40 (t, J=7, 3H), 0.92-0.75 (m, 4H).

[0700] APCIMS 348 [M+1]⁺

- 25 **[0701]** The title compounds of Examples 26B-26C were prepared using procedures analogous to that used for Example 26A.

EXAMPLE 26BEthyl 1-(2-chloro-5-dimethylaminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

- 30 **[0702]** 45% yield
[0703] ¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 7.59 (d, J=6, 1H), 7.52 (dd, J=2, 6, 1H), 7.48 (d, J=2, 1H), 4.33 (q, J=7, 2H), 3.12 (bs, 3H), 3.05 (bs, 3H), 1.88 (m, 1H), 1.39 (t, J=7, 3H), 0.94-0.80 (m, 4H).
[0704] APCIMS 362 [M+1]⁺

EXAMPLE 26CEthyl 1-(2-chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylate

- 40 **[0705]** 27% yield
[0706] ¹H NMR (300 MHz, CDCl₃) δ 8.17 (s, 1H), 8.10-8.07 (m, 2H), 8.05 (s, 1H), 7.85 (d, J=9, 1H), 7.67 (s, 1H), 4.25 (q, J=7, 2H), 1.88 (m, 1H), 1.30 (t, J=7, 3H), 0.81-0.74 (m, 2H), 0.70-0.63 (m, 2H).
[0707] APCIMS 334 [M+1]⁺
[0708] The title compound of Example 27 was prepared using a procedure analogous to that used for Example 13A.

EXAMPLE 275-Ethyl-1-(benzothiazol-6-yl)-1H-pyrazole-4-carboxylic acid

- 50 **[0709]** 78% yield.
[0710] APCIMS 272 [M-1]⁻
[0711] ¹H NMR (DMSO-*d*₆) δ 0.96-1.02 (t, 3H); 7.81 (s, 1H)
[0712] The title compounds of Examples 28A-28RRR were prepared using a procedure analogous to that used for Example 14A.

55

EXAMPLE 28A5-Cyclopropyl-1-(2,3-dimethoxyphenyl)-1H-pyrazole-4-carboxylic acid

- 5 **[0713]** 83% yield
[0714] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.68 (d, J=8.4, 4H), 1.83 (m, 1H), 3.54 (s, 3H), 3.85 (s, 3H), 6.94 (d, J=7.6, 1H), 7.19 (m, 2H), 7.87 (s, 1H), 12.26 (s, 1H).
[0715] APCIMS 287 [M-1]⁻

10 EXAMPLE 28C5-Cyclopropyl-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylic acid

- [0716]** 87% yield
15 **[0717]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.56 (d, J=7.2, 4H), 1.82 (m, 1H), 7.12 (d, J=7.6, 1H), 7.58 (m, 4H), 8.10 (m, 3H), 12.38 (s, 1H).
[0718] APCIMS 279 [M+1]⁺

20 EXAMPLE 28D5-Cyclopropyl-1-(naphthalen-2-yl)-1H-pyrazole-4-carboxylic acid

- [0719]** 91% yield
25 **[0720]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.48 (m, 2H), 0.80 (m, 2H), 2.15 (m, 1H), 7.58 (m, 2H), 7.71 (m, 1H), 8.01 (m, 4H), 8.16 (s, 1H), 12.35 (s, 1H).
[0721] APCIMS 277 [M-1]⁻

30 EXAMPLE 28G5-Cyclopropyl-1-(o-biphenyl)-1H-pyrazole-4-carboxylic acid

- [0722]** 75% yield
35 **[0723]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.44 (m, 4H), 1.04 (m, 1H), 6.98 (m, 2H), 7.25 (m, 3H), 7.44-7.62 (m, 4H), 7.85 (s, 1H), 12.14 (s, 1H).
[0724] APCIMS 303 [M-1]⁻

EXAMPLE 28I5-Cyclopropyl-1-(2-nitrophenyl)-1H-pyrazole-4-carboxylic acid

- 40 **[0725]** 89% yield
[0726] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.58 (m, 2H), 0.77 (m, 2H), 1.94 (m, 1H), 7.79 (m, 1H), 7.91 (m, 2H), 8.13 (d, J=7.6, 1H), 12.48 (s, 1H).
45 **[0727]** APCIMS 273[M-1]⁻

EXAMPLE 28J5-Cyclopropyl-1-(2-pyrrol-1-ylphenyl)-1H-pyrazole-4-carboxylic acid

- 50 **[0728]** 95% yield
[0729] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.41-0.62 (m, 4H), 1.04 (m, 1H), 6.13 (m, 2H), 6.52 (m, 2H), 7.50-7.71 (m, 4H), 7.98 (s, 1H).
55 **[0730]** APCIMS 292[M-1]⁻

EXAMPLE 28K5-Cyclopropyl-1-(2-ethylphenyl)-1H-pyrazole-4-carboxylic acid

- 5 **[0731]** 73% yield
[0732] ^1H NMR (400 MHz, CDCl_3) δ 0.78 (dd, $J=8.4, 1.6$, 2H), 0.88 (m, 2H), 1.09 (dt, $J=7.6, 1.2$, 3H), 1.84 (m, 1H), 2.37 (q, $J=7.6$, 2H), 7.24 (m, 2H), 7.40 (m, 2H), 8.07 (s, 1H).
[0733] APCIMS 255 $[\text{M}-1]^-$

10 EXAMPLE 28L5-Cyclopropyl-1-(2-methylphenyl)-1H-pyrazole-4-carboxylic acid

- 15 **[0734]** ^1H NMR (400 MHz, CDCl_3) δ 0.8-0.89 (m, 4H), 1.87 (m, 1H), 2.09 (s, 3H), 7.2-7.5 (m, 4H), 8.10 (s, 1H).
[0735] APCIMS 241 $[\text{M}-1]^-$

EXAMPLE 28M5-Cyclopropyl-1-(2-chlorophenyl)-1H-pyrazole-4-carboxylic acid

- 20 **[0736]** 55% yield.
[0737] APCIMS 261 $[\text{M}+1]^+$
[0738] ^1H NMR (400 MHz, CDCl_3) δ 0.84 (bs, 4H), 1.95 (m, 1H), 7.41-7.52 (m, 3H), 7.58 (dd, $J=9.4, 2.2$, 1H), 8.15 (s, 1H).
25

EXAMPLE 28N5-Cyclopropyl-1-(2-trifluoromethoxyphenyl)-1H-pyrazole-4-carboxylic acid

- 30 **[0739]** 100% yield.
[0740] APCIMS 311 $[\text{M}-1]^-$
[0741] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.56 (d, $J=5.6$, 2H), 0.71 (dd, $J=8.4, 4.4$, 2H), 1.78 (m, 1H), 7.5-7.7 (m, 4H), 7.93 (s, 1H), 12.38 (s, 1H).
35

EXAMPLE 28O5-Cyclopropyl-1-(2-fluorophenyl)-1H-pyrazole-4-carboxylic acid

- 40 **[0742]** 84% yield.
[0743] APCIMS 245 $[\text{M}-1]^-$
[0744] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.56 (m, 2H), 0.72 (m, 2H), 1.85 (m, 1H), 7.35 (m, 1H), 7.45 (m, 1H), 7.58 (m, 2H), 7.92 (s, 1H).
45

EXAMPLE 28P3-Methyl-1-(2,1,3-benzothiadiazol-4-yl)-1H-pyrazole-4-carboxylic acid

- [0745]** 79% yield.
[0746] APCIMS 259 $[\text{M}-1]^-$
50 **[0747]** ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.47 (s, 3H), 7.82 (m, 1H), 8.05 (dd, $J=8.4, 2.8$, 1H), 8.15 (dd, $J=7.6, 2.8$, 1H), 9.41 (s, 1H), 12.63 (s, 1H).
45

EXAMPLE 28Q5-Cyclopropyl-1-(indazol-7-yl)-1H-pyrazole-4-carboxylic acid

- 55 **[0748]** 78% yield.
[0749] APCIMS 267 $[\text{M}-1]^-$

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[0750] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.47-0.51 (m, 2H), 0.61-0.66 (m, 2H), 1.96 (m, 1H), 7.20 (t, J=7.6, 1H), 7.45 (d, J=7.6, 1H), 7.87 (d, J=8.0, 1H), 7.99 (s, 1H), 8.19 (s, 1H).

EXAMPLE 28R

5

3-Methyl-1-(indazol-7-yl)-1H-pyrazole-4-carboxylic acid

[0751] 79% yield.

[0752] APCIMS 241 [M-1]⁻

10 [0753] ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.51 (s, 3H), 7.17 (t, J=8.0, 1H), 7.73 (d, J=8.0, 1H), 7.81 (d, J=7.6, 1H), 8.22 (s, 1H), 9.03 (bs, 1H).

EXAMPLE 28S

5-Ethyl-1-(benzothiazol-2-yl)-1H-pyrazole-4-carboxylic acid

[0754] 84% yield.

[0755] APCIMS 272 [M-1]⁻

20 [0756] ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.25 (t, J=6.8, 3H), 3.61 (q, J=6.8, 2H), 7.41-7.53 (m, 2H), 7.92 (d, J=8.4, 1H), 8.08 (s, 1H).

EXAMPLE 28T

5-Cyclopropyl-1-(2-chloro-4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carboxylic acid

25

[0757] 98% yield.

[0758] APCIMS 339 [M-1]⁻

30 [0759] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.68-0.70 (m, 2H), 0.76-0.79 (m, 2H), 1.87 (m, 1H), 3.34 (s, 3H), 7.95-8.10 (m, 3H), 8.29 (s, 1H).

EXAMPLE 28U

5-Cyclopropyl-1-(2-chloro-4-(methylsulfonylmethylsulfonyl)phenyl)-1H-pyrazole-4-carboxylic acid

35 [0760] 78% yield.

[0761] APCIMS 417 [M-1]⁻

[0762] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.63 (m, 2H), 0.73-0.79 (m, 2H), 1.88 (m, 1H), 3.27(s, 3H), 7.99-8.16 (m, 3H), 8.30 (s, 1H).

EXAMPLE 28V

5-Cyclopropyl-1-(2-chloro-5-(dimethylaminosulfonyl)phenyl)-1H-pyrazole-4-carboxylic acid

45 [0763] 82% yield.

[0764] APCIMS 368 [M-1]⁻

[0765] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.61 (d, J=2.0, 2H), 0.72 (d, J=7.6, 2H), 1.86 (m, 1H), 2.63 (s, 6H), 7.92-8.01 (m, 3H), 12.44 (s, 1H).

EXAMPLE 28W

50

5-Cyclopropyl-1-(2-chloro-5-(aminosulfonyl)phenyl)-1H-pyrazole-4-carboxylic acid

[0766] 82% yield.

[0767] APCIMS 368 [M-1]⁻

55 [0768] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.65 (s, 2H), 0.75 (d, J=8.0, 2H), 1.84 (m, 1H), 7.61 (s, 1H), 7.92-7.98 (m, 2H), 12.47 (s, 1H).

EXAMPLE 28X5-Cyclopropyl-1-(2-chloro-5-{methylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylic acid

- 5 **[0769]** 75% yield.
[0770] APCIMS 354 [M-1]⁻
[0771] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.62 (s, 2H), 0.73 (d, J=8.0, 2H), 1.86 (m, 1H), 2.43 (d, J=2.8, 3H), 7.67 (d, J=4.8, 1H), 7.92-7.98 (m, 3H), 12.47 (s, 1H).

10 EXAMPLE 28Y5-Cyclopropyl-1-(2,5-dichlorophenyl)-1H-pyrazole-4-carboxylic acid

- [0772]** 97% yield.
15 **[0773]** APCIMS 295 [M-1]⁻
[0774] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.62-0.64 (m, 2H), 0.70-0.74 (m, 2H), 1.82 (m, 1H), 7.65 (dd, J=8.8, 2.4, 1H), 7.72 (d, J=8.4, 1H), 7.85 (d, J=2.4, 1H), 7.93 (s, 1H).

20 EXAMPLE 28Z5-Cyclopropyl-1-(2,4-dichlorophenyl)-1H-pyrazole-4-carboxylic acid

- [0775]** 94% yield.
[0776] APCIMS 295 [M-1]⁻
25 **[0777]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.64-0.65 (m, 2H), 0.71-0.74 (m, 2H), 1.83 (m, 1H), 7.60-7.68 (m, 3H), 7.92 (s, 1H), 12.41 (s, 1H).

30 EXAMPLE 28AA5-Cyclopropyl-1-(2,3-dichlorophenyl)-1H-pyrazole-4-carboxylic acid

- [0778]** 91% yield.
[0779] APCIMS 295 [M-1]⁻
35 **[0780]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.65 (s, 2H), 0.73 (s, 2H), 1.83 (m, 1H), 7.53 (t, J=8.0, 1H), 7.63 (dd, J=8.0, 1.6, 1H), 7.86 (dd, J=8.0, 1.2, 1H), 7.96 (s, 1H), 12.41 (s, 1H).

40 EXAMPLE 28BB5-Cyclopropyl-1-(2-chloro-5-methylsulfonylphenyl)-1H-pyrazole-4-carboxylic acid

- [0781]** 77% yield.
[0782] APCIMS 339 [M-1]⁻
[0783] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.61-0.63 (m, 2H), 0.71 (d, J=6.8, 2H), 1.83 (m, 1H), 3.29 (s, 3H), 7.97-8.09 (m, 3H), 8.18 (s, 1H), 12.44 (s, 1H).

45 EXAMPLE 28CC5-Ethyl-1-(benzimidazol-5-yl)-1H-pyrazole-4-carboxylic acid

- [0784]** 82% yield.
50 **[0785]** APCIMS 255 [M-1]⁻
[0786] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.97 (t, J=7.2, 3H), 2.84 (q, J=7.2, 2H), 7.21 (d, J=8.4, 1H), 7.65-7.69 (m, 2H), 7.88 (s, 1H), 8.33 (s, 1H).

55

EXAMPLE 28DD5-Cyclopropyl-1-(2-chloro-4-{dimethylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylic acid

- 5 [0787] 92% yield.
 [0788] APCIMS 368 [M-1]
 [0789] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.60-0.63 (m, 2H), 0.80-0.82 (m, 2H), 1.80 (m, 1H), 2.68(s, 6H), 7.70 (s, 1H), 7.78-7.97 (m, 2H), 7.97 (s, 1H).

10 EXAMPLE 28EE5-Cyclopropyl-1-(2-chloro-4-{methylaminosulfonyl}phenyl)-1H-pyrazole-4-carboxylic acid

- [0790] 84% yield.
 15 [0791] APCIMS 354 [M-1]
 [0792] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.63 (d, J=4.8, 2H), 0.73 (d, J=8.4, 2H), 1.84 (m, 1H), 2.47(s, 3H), 7.76 (t, J=4.6, 1H), 7.88 (s, 1H), 8.00 (d, J=15.2, 1H), 12.42 (s, 1H).

20 EXAMPLE 28FF5-Cyclopropyl-1-(benzimidazol-5-yl)-1H-pyrazole-4-carboxylic acid

- [0793] 59% yield.
 [0794] APCIMS 267 [M-1]
 25 [0795] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.50-0.54 (m, 2H), 0.71-0.76 (m, 2H), 2.05 (m, 1H), 7.33 (dd, J=9.4, 1.8, 1H), 7.66 (d, J=8.4, 1H), 7.73 (s, 1H), 7.89 (s, 1H), 8.32 (s, 1H), 12.25 (s, 1H) 12.69 (bs, 1H).

30 EXAMPLE 28GG3-Methyl-1-benzyl-1H-pyrazole-4-carboxylic acid

- [0796] 96% yield.
 [0797] APCIMS 215 [M-1]
 35 [0798] ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.29 (s, 3H), 5.26 (s, 2H), 7.25-7.38 (m, 5H), 8.27 (s, 1H), 12.18 (bs, 1H).

EXAMPLE 28HH5-Ethyl-1-(3-chloroindazol-5-yl)-1H-pyrazole-4-carboxylic acid

- 40 [0799] 85% yield.
 [0800] APCIMS 289 [M-1]
 [0801] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.97 (t, J=7.2, 3H), 2.83 (q, J=7.2, 2H), 7.48 (dd, J=8.8, 1.6, 1H), 7.69-7.75 (m, 2H), 7.92 (s, 1H), 12.41 (s, 1H), 13.60 (s, 1H).

45 EXAMPLE 28II5-Ethyl-1-(1-methyl benzimidazol-6-yl)-1H-pyrazole-4-carboxylic acid

- [0802] 76% yield.
 50 [0803] APCIMS 269 [M-1]
 [0804] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.97 (t, J=7.6, 3H), 2.86 (q, J=7.2, 2H), 3.90 (s, 3H), 7.38 (dd, J=8.6, 2.2, 1H), 7.81-7.93 (m, 3H), 8.75 (s, 1H).

55 EXAMPLE 28JJ5-Ethyl-1-(2-methyl benzimidazol-5-yl)-1H-pyrazole-4-carboxylic acid

- [0805] 72% yield.

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[0806] APCIMS 269 [M-1]⁻

[0807] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.97 (t, J=7.4, 3H), 2.49 (s, 3H), 2.81 (q, J=7.4, 2H), 7.38 (d, J=8.8, 1H), 7.50-7.55 (m, 2H), 7.88 (s, 1H), 12.36 (s, 1H), 12.61 (bs, 1H).

5 EXAMPLE 28KK

5-Isopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid

[0808] 90% yield

10 [0809] ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.51 (s, 1H), 8.99 (t, J=1.6, 1H), 8.24 (d, J=8, 1H), 8.06 (s, 1H), 7.91 (t, J=8, 1H), 7.76 (d, J=7, 1H), 7.58 (dd, J= 8, 4, 1H), 7.47 (d, J=8, 1H), 2.93 (quintet, J=7, 1H), 1.15 (m, 6H).

[0810] APCIMS 282 [M+1]⁺

EXAMPLE 28LL

15

1-(Quinolin-5-yl)-5-*n*-propyl-1H-pyrazole-4-carboxylic acid

[0811] 91% yield

20 [0812] ¹H NMR (400 MHz, CDCl₃) δ 9.03 (d, J=4, 1H), 8.35 (d, J=8, 1H), 8.25 (s, 1H), 7.86 (t, J=8, 1H), 7.66 (d, J=8, 1H), 7.61 (d, J=7, 1H), 7.47 (dd, J=8, 4, 1H), 2.81 (bs, 2H), 1.45 (s sextuplet, J=8, 2H), 0.75 (t, J=8, 3H).

[0813] APCIMS 282 [M+1]⁺

EXAMPLE 28MM

25

5-Cyclopropyl-1-(2-dimethylaminosulfonylphenyl)-1H-pyrazole-4-carboxylic acid

[0814] 88% yield

30 [0815] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.01 (m, 1H), 7.91 (s, 1H), 7.84 (m, 2H), 7.60 (m, 1H), 2.64 (s, 6H), 1.81 (m, 1H), 0.59-0.77 (m, 4H).

[0816] APCIMS 336 [M+1]⁺

EXAMPLE 28NN

35

5-Cyclopropyl-1-(2-methylsulfonylphenyl)-1H-pyrazole-4-carboxylic acid

[0817] 79% yield

[0818] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.15 (m, 1H), 7.83-7.99 (m, 3H), 7.75 (m, 1H), 3.34 (s, 3H), 1.86 (m, 1H), 0.5-0.9 (m, 4H).

[0819] APCIMS 307 [M+1]⁺

40

EXAMPLE 28OO

5-Cyclopropyl-1-(2-methylaminosulfonylphenyl)-1H-pyrazole-4-carboxylic acid

45

[0820] 70% yield

[0821] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.02 (m, 1H), 7.94 (s, 1H), 7.73-7.86 (m, 2H), 7.69 (m, 1H), 6.88 (q, J=5, 1H), 2.50 (s, 3H), 1.89 (m, 1H), 0.5-0.9 (m, 4H).

[0822] APCIMS 322 [M+1]⁺

50

EXAMPLE 28PP

5-Cyclopropyl-1-(2,1,3-benzothiadiazol-4-yl)-1H-pyrazole-4-carboxylic acid

[0823] 91 % yield

55 [0824] ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 8.14 (dd, J=7, 3, 1H), 7.73 (m, 2H), 2.01 (m, 1H), 0.68 (m, 2H), 0.61 (m, 2H).

[0825] APCIMS 287 [M+1]⁺

EXAMPLE 28RR5-Cyclopropyl-1-(2-aminosulfonylphenyl)-1H-pyrazole-4-carboxylic acid

- 5 **[0826]** 93% yield
[0827] ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.34 (s, 1H), 8.03 (m, 1H), 7.93 (s, 1H), 7.73 (m, 2H), 7.63 (m, 1H), 7.18 (s, 2H), 1.85 (m, 1H), 0.3-0.9 (m, 4H).
[0828] APCIMS 308 [M+1]⁺

10 EXAMPLE 28SS5-Cyclopropyl-1-(2-methylthiophenyl)-1H-pyrazole-4-carboxylic acid

- [0829]** 97% yield
15 **[0830]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.27 (s, 1H), 7.87 (s, 1H), 7.51 (t, J=8, 1H), 7.41 (d, J=8, 1H), 7.34 (d, J=8, 1H), 7.27 (t, J=7, 1H), 2.36 (s, 3H), 1.83 (m, 1H), 0.65 (m, 4H).
[0831] APCIMS 275 [M+1]⁺

20 EXAMPLE 28TT5-Methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid

- [0832]** 84.4% yield.
25 **[0833]** ¹H NMR (DMSO-*d*₆) δ 2.62 (s, 3H); 7.66 (dd, 1H); 7.95 (dd, 1H); 8.06 (s, 1H); 8.18-8.24 (m, 2H); 8.51 (d, 1H); 9.01 (t, 1H).

EXAMPLE 28UU5-Cyclopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid

- 30 **[0834]** 75.5% yield.
[0835] ¹H NMR (DMSO-*d*₆) δ 0.49 (m, 2H); 0.86 (m, 2H); 2.2 (m, 1H); 7.64 (dd, 1H); 8.01 (m, 1H); 8.03 (s, 1H); 8.16 (dd, 1H); 8.28 (d, 1H); 8.49 (d, 1H); 9.0 (dd, 1H).

35 EXAMPLE 28VV5-Cyclopropyl-1-(4-quinolinyl)-1H-pyrazole-4-carboxylic acid

- [0836]** 78.2% yield.
40 **[0837]** ¹H NMR (DMSO-*d*₆) δ 0.56 (m, 2H); 0.64 (m, 2H); 1.91 (m, 1H); 7.49 (dd, 1H); 7.68 (m, 1H); 7.8 (d, 1H); 7.88 (m, 1H); 8.13 (s, 1H); 8.19 (d, 1H); 9.11 (d, 1H).

EXAMPLE 28WW5-Methyl-1-(6-methoxy-5-quinolinyl)-1H-pyrazole-4-carboxylic acid

- [0838]** 80.1 % yield.
50 **[0839]** ¹H NMR (DMSO-*d*₆) δ 2.2 (s, 3H); 3.96 (s, 3H); 7.38 (dd, 1H); 7.52 (m, 1H); 7.92 (d, 1H); 8.08 (s, 1H); 8.3 (d, 1H); 8.86 (dd, 1H).

EXAMPLE 28XX5-Cyclopropyl-1-(6-methoxy-5-quinolinyl)-1H-pyrazole-4-carboxylic acid

- 55 **[0840]** 41.6% yield.
[0841] ¹H NMR (DMSO-*d*₆) δ 0.45 (m, 2H); 0.65 (m, 2H); 1.72 (m, 1H); 3.91 (s, 3H); 7.33 (d, 1H); 7.47 (m, 1H); 7.85 (d, 1H); 7.99 (s, 1H); 8.23 (d, 1H); 8.8 (dd, 1H); 12.3 (s, 1H).

EXAMPLE 28YY5-Cyclopropyl-1-(6-methyl-5-quinolinyl)-1H-pyrazole-4-carboxylic acid5 **[0842]** 82.5% yield**[0843]** ¹H NMR (DMSO-*d*₆) δ 0.52-0.77 (m, 4H); 1.7 (m, 1H); 2.19 (s, 3H); 7.4 (dd, 1H); 7.57 (m, 1H); 7.85 (d, 1H); 8.15 (m, 2H); 8.93 (t, 1H).EXAMPLE 28ZZ

10

5-Ethyl-1-[2-methyl-6-quinolinyl]-1H-pyrazole-4-carboxylic acid**[0844]** 30 % yield.15 **[0845]** ¹H NMR (DMSO-*d*₆) δ 1.06 (t, 3H); 2.71 (s, 3H); 2.95 (q, 2H); 7.55 (d, 1H); 7.82 (d, 1H); 8.02-8.13 (m, 3H); 8.38 (d, 1H).EXAMPLE 28AAA

20

5-Ethyl-1-(6-methyl-5-quinolinyl)-1H-pyrazole-4-carboxylic acid**[0846]** 81.5 % yield.**[0847]** ¹H NMR (DMSO-*d*₆) δ 0.83 (t, 3H); 2.5-2.6 (2q, 2H); 2.15 (s, 3H); 7.33 (q, 1H); 7.54 (q, 1H); 7.86 (dd, 1H); 8.14 (s, 1H); 8.19 (d, 1H); 8.94 (d, 1H).25 EXAMPLE 28BBB5-Ethyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid**[0848]** 71.9% yield.30 **[0849]** ¹H NMR (DMSO-*d*₆) δ 1.04 (t, 3H); 2.96 (q, 2H); 7.63 (q, 1H); 7.85 (dd, 1H); 8.01 (s, 1H); 8.17 (s+d, 2H); 8.49 (d, 1H); 8.99 (q, 1H).EXAMPLE 28CCC35 1-(2-Quinoxaliny)-5-ethyl-1H-pyrazole-4-carboxylic acid**[0850]** 82% yield**[0851]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (s, 1H), 8.14-8.11 (m, 2H), 8.00 (d, J=8 1H), 7.91-7.83 (m, 2H), 3.44 (q, J=7, 2H), 1.29 (t, J=7, 3H).40 **[0852]** APCIMS 267 [M-1]⁻EXAMPLE 28DDD

45

1-(2-Benzimidazolyl)-5-ethyl-1H-pyrazole-4-carboxylic acid**[0853]** 66% yield**[0854]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.1 (s, 1H), 12.74 (bs, 1H), 8.12 (s, 1H), 7.63 (d, J=6, 1H), 7.44 (d, J=6, 1H), 7.20 (bs, 2H), 3.52 (q, J=7, 2H), 1.21 (t, J=7, 3H).50 **[0855]** APCIMS 257 [M+1]⁺EXAMPLE 28EEE1-(2-Fluoromethyl-4-chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid55 **[0856]** 92% yield**[0857]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.43 (bs, 1H), 8.07 (s, 1H), 7.96-7.93 (m, 2H), 7.76 (d, J=8, 1H), 1.76 (m, 1H), 0.68-0.74 (m, 4H).**[0858]** APCIMS 331 [M+1]⁺

EXAMPLE 28FFF1-(2-Fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

- 5 **[0859]** 55% yield
[0860] ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.50 (s, 1H), 7.98 (s, 1H), 7.92-7.82 (m, 3H), 1.68 (m, 1H), 0.79-0.67 (m, 4H).
[0861] APCIMS 315 [M+1]⁺

EXAMPLE 28GGG1-(2-Trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

- 10 **[0862]** 86% yield
[0863] ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.97-7.93 (m, 2H), 7.91-7.74 (m, 2H), 1.79 (m, 1H), 0.75 (d, J=9, 4H).
15 **[0864]** APCIMS 315 [M+1]⁺

EXAMPLE 28HHH1-(1-Methylbenzimidaz-2-yl)-5-ethyl-1H-pyrazole-4-carboxylic acid

- 20 **[0865]** 39% yield
[0866] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 7.77-7.70 (m, 2H), 7.47-7.32 (m, 2H), 3.72 (s, 3H), 3.04 (q, J=7, 2H), 1.13 (t, J=7, 3H).
25 **[0867]** APCIMS 269 [M-1]⁻

EXAMPLE 28III1-(2-Quinolonyl)-5-ethyl-1H-pyrazole-4-carboxylic acid

- 30 **[0868]** 93% yield
[0869] ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.62 (s, 1H), 8.57 (d, J=7, 1H), 8.05 (s, 1H), 8.02-7.94 (m, 3H), 7.81 (t, J=5, 1H), 7.64 (t, J=5, 1H), 3.47 (q, J=5, 2H), 1.30-1.27 (m, 3H).
[0870] APCIMS 268 [M+1]⁺

EXAMPLE 28JJJ1-(2-Chloro-5-methylaminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

- 35 **[0871]** 87% yield
40 **[0872]** ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.67 (m, 1H), 8.06 (d, J=2, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.85 (d, J=9, 1H), 2.79 (d, J=5, 3H), 1.88 (m, 1H), 0.75-0.66 (m, 4H).
[0873] APCIMS 320 [M+1]⁺

EXAMPLE 28KKK1-(4-Benzimidazolyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

- 45 **[0874]** 83% yield
[0875] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24-8.20 (m, 1H), 7.98-7.89 (m, 1H), 7.77-7.64 (m, 1H), 7.33-7.21 (m, 2H),
50 1.96 (m, 1H), 0.64-0.47 (m, 4H).

EXAMPLE 28LLL1-(2-chloro-5-iodophenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

- 55 **[0876]** 86% yield
[0877] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.15 (s, 1H), 7.96-7.89 (m, 2H), 7.42 (dd, J=1.2, 8, 1H), 1.85 (m, 1H), 0.77-0.67 (m, 4H).

[0878] APCIMS 389 [M+1]⁺

EXAMPLE 28MMM

5 1-(2-Chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

[0879] 31% yield

[0880] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 8.09-8.07 (m, 2H), 8.00 (s, 1H), 7.84 (d, J=9, 1H), 7.66 (s, 1H), 1.85 (m, 1H), 0.76 (d, J=8, 2H), 0.68 (d, J=5, 2H).

10 **[0881]** APCIMS 306 [M+1]⁺

EXAMPLE 28NNN

15 1-(2-Chloro-5-dimethylaminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

[0882] 45% yield

[0883] ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.98 (s, 1H), 7.79 (d, J=9, 1H), 7.72 (d, J=2, 1H), 7.63 (dd, J=2, 8, 1H), 2.99 (s, 3H), 2.93 (s, 3H), 1.89 (m, 1H), 0.77-0.73 (m, 2H), 0.67-0.65 (m, 2H).

20 **[0884]** APCIMS 334 [M+1]⁺

EXAMPLE 28PPP

25 1-(1-Isoquinolyl-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

[0885] 75 % yield

[0886] ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.45 (s, 1H), 8.49 (d, J=6, 1H), 8.11 (d, J=8, 1H), 8.38 (d, J=6, 1H), 8.01 (s, 1H), 7.84 (t, J=8, 1H), 7.66 (t, J=8, 1H), 7.42 (d, J=9, 1H), 1.98 (m, 1H), 0.57 (d, J=6, 2H), 0.428 (d, J=3.6, 2H).

EXAMPLE 28QQQ

30 5-Isopropyl-1-(6-quinoliny)-1H-pyrazole-4-carboxylic acid

[0887] 89.8% yield.

[0888] ¹H NMR (DMSO-*d*₆) δ 1.29 (d, 6H); 3.2 (m, 1H); 7.64 (q, 1H); 7.77 (dd, 1H); 7.99 (s, 1H); 8.12 (s, 1H); 8.16 (dd, 1H); 8.5 (d, 1H); 8.99 (d, 1H); 12.4 (bs, 1H).

EXAMPLE 28RRR

40 5-propyl-1-(6-quinoliny)-1H-pyrazole-4-carboxylic acid

[0889] 86.4 % yield.

[0890] ¹H NMR (DMSO-*d*₆) δ 0.68 (t, 3H); 1.42 (q, 2H); 2.97 (t, 2H); 7.62 (q, 1H); 7.84 (t, 1H); 8.01 (s, 1H); 8.16 (d, 2H); 8.48 (d, 1H); 8.98 (d, 1H); 12.45 (bs, 1H).

[0891] The title compounds of Examples 29A-29D were prepared using procedures analogous to that used for Example 8A.

EXAMPLE 29A

50 [5-Cyclopropyl-1-(2,4-dichloro-6-[trifluoromethyl]phenyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0892] 14% yield.

[0893] APCIMS 406 [M+]⁺

[0894] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.83-0.86 (m, 4H); 1.79 (m, 1H); 8.21 (s, 1H); 8.44 (bs, 3H); 8.71 (bs, 2H); 11.76 (s, 1H).

55

EXAMPLE 29B[5-Methoxymethyl-1-(5-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 5 **[0895]** 13% yield
[0896] APCIMS 325 [M+1]⁺
[0897] ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.12 (bs, 1H), 9.03 (m, 1H), 8.81 (bs, 2H), 8.55 (bs, 2H), 8.36 (m, 1H), 7.06-8.06 (m, 4H), 4.61 (s, 2H), 3.01 (s, 3H).

10 EXAMPLE 29C[1-(5-Methoxy-2-chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [0898]** 17% yield
15 **[0899]** APCIMS 334 [M+1]⁺
[0900] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.72 (bs, 2H), 8.67 (s, 1H), 8.43 (bs, 2H), 7.63 (d, J=9, 1H), 7.29 (d, J=3, 1H), 7.21 (dd, J=3, 9, 1H), 3.82 (s, 3H), 1.99 (m, 1H), 0.79 (d, J=9, 2H), 0.63 (d, J=4, 2H).

20 EXAMPLE 29D[1-(5-quinolinyl)-5-butyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- [0901]** 38% yield.
[0902] APCIMS 337 [M+1]⁺
25 **[0903]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.53 (ts, J=7.0, 3H), 1.01 (t, J=6.8, 2H), 1.26 (s, 2H), 2.75 (s, 2H), 7.72-7.79 (m, 2H), 7.92 (d, J=7.2, 1H), 8.03 (t, J=7.8, 1H), 8.36 (d, J=8.4, 1H), 8.48 (bs, 2H), 8.81 (bs, 2H), 9.00 (s, 1H), 9.12 (s, 1H), 12.169 (s, 1H).

30 EXAMPLE 30A[1-(Quinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- [0904]** A solution of guanidine hydrochloride (3.11 g, 32.6 mmol) in warm anhydrous ethanol (8 mL) under a nitrogen atmosphere was treated in one portion with sodium methoxide (1.76 g, 32.6 mmol). The resulting slurry was concentrated *in vacuo*. The residue was treated with anhydrous toluene (10 mL) and concentrated to dryness *in vacuo* (twice). Each time the vacuum was released to a nitrogen atmosphere. The residue was treated in one portion with ethyl 1-(quinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate (1.00 g, 3.26 mmol) in anhydrous ethanol (8 mL). The resulting mixture was concentrated *in vacuo* (rotatory evaporator, 80 °C water bath). The residue was treated with anhydrous toluene (10 mL) and the resulting mixture was concentrated *in vacuo* (three times). The resulting solid was triturated with water (85 mL) and filtered. The solid was air-dried to provide 0.880 g (76% yield) of [1-(quinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrate.

- [0905]** APCIMS 321 [M+1]
[0906] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.51-0.53 (m, 4H), 1.88-1.95 (m, 1H), 7.52-7.60 (m, 2H), 7.73 (d, J=8, 1H), 7.86 (t, J=9, 1H), 7.94 (s, 1H), 8.16 (d, J=9, 1H), 8.95 (t, J=1.8, 1H).
45 **[0907]** A suspension of [1-(quinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrate (1.28 g, 3.59 mmol) in tetrahydrofuran (38.4 mL) with vigorous stirring was treated with concentrated hydrochloric acid (0.30 mL, 3.6 mmol). The mixture became homogeneous within one minute and then a solid began to precipitate. The resulting mixture was stirred vigorously for 1 h and filtered. The solid was air-dried to provide 1.11 g (82% yield) of the title compound.

- 50 **[0908]** APCIMS 321 [M+1]⁺
[0909] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.42 (m, 2H), 0.59-0.61 (m, 2H), 1.88-1.95 (m, 1H), 7.57 (dd, J=9, 4, 1H), 7.67 (d, J=4, 1H), 7.82 (d, J=7, 1H), 7.90 (t, J=8, 1H), 8.22 (d, J=8, 1H), 8.38 (bs, 2H), 8.69 (bs, 2H), 8.72 (s, 1H), 8.98 (dd, J=4, 1.4, 1H).

- 55 **[0910]** The title compounds of Examples 30B-30M were prepared using procedures analogous to that used for Example 30A.

EXAMPLE 30B[1-(Isoquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 [0911] 14% yield
[0912] APCIMS 321 [M+1]⁺
[0913] ¹H NMR (CDCl₃) δ 1.9-2.0 (s, 1H), 8.80 (s, 1H)

EXAMPLE 30C[1-(Quinolin-5-yl)-5-benzyloxymethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 10 [0914] 41% yield
[0915] APCIMS 401 [M+1]⁺
15 [0916] ¹H NMR (CDCl₃) δ 4.16 (s, 2H), 8.87 (s, 1H)

EXAMPLE 30D[1-(Benzotriazole-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 20 [0917] 49% yield
[0918] APCIMS 299 [M+1]⁺
[0919] ¹H NMR (CDCl₃) δ 0.99-1.03 (t, 3H), 8.61 (s, 1H)

EXAMPLE 30E[1-(Indazol-6-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 25 [0920] 27% yield
30 [0921] APCIMS 298 [M+1]⁺
[0922] ¹H NMR (CDCl₃) δ 1.01-1.05 (t, 3H), 8.64 (s, 1H)

EXAMPLE 30F[1-(Quinolin-5-yl)-5-cyclobutyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 35 [0923] 24% yield
[0924] APCIMS 335 [M+1]⁺
[0925] ¹H NMR (CDCl₃) δ 3.61-3.70 (m, 1H), 8.75 (s, 1H)

EXAMPLE 30G[1-(6-Chloroquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 40 [0926] 8% yield
45 [0927] APCIMS 354 [M+1]⁺
[0928] ¹H NMR (CDCl₃) δ 1.78-1.83 (m, 1H), 8.79 (s, 1H)

EXAMPLE 30H[1-(Indazol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 50 [0929] 39.3% yield
[0930] APCIMS 298 [M+1]⁺
55 [0931] ¹H NMR (CDCl₃) δ 0.99-1.05 (t, 3H), 8.70 (s, 1H)

EXAMPLE 30I[1-(1,4-Benzodioxan-6-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 5 [0932] 27% yield
 [0933] APCIMS 316 [M+1]⁺
 [0934] ¹H NMR (CDCl₃) δ 1.01-1.08 (t, 3H), 8.64 (s, 1H)

EXAMPLE 30J[1-(Quinolin-5-yl)-5-isobutyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 10 [0935] 13.7%
 [0936] APCIMS 337 [M+1]⁺
 15 [0937] ¹H NMR (CDCl₃) δ 1.53-1.60 (m, 1H), 8.97 (s, 1H)

EXAMPLE 30K[1-(1,3-Benzodioxol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 20 [0938] 9.4% yield
 [0939] APCIMS 302 [M+1]⁺
 [0940] ¹H NMR (CDCl₃) δ 0.99-1.02 (t, 3H), 8.63 (s, 1H)

EXAMPLE 30L[1-(8-Bromoquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 25 [0941] 23% yield
 30 [0942] APCIMS 401 [M+2]⁺
 [0943] ¹H NMR (CDCl₃) δ 1.88-1.95 (m, 1H), 8.71 (s, 1H)

EXAMPLE 30M[1-(6-Trifluoromethylquinolin-8-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 35 [0944] 18% yield
 [0945] APCIMS 389 [M+1]⁺
 [0946] ¹H NMR (CDCl₃) δ 1.80-1.87 (m, 1H), 8.80 (s, 1H)
 40 [0947] The title compounds of Examples 31A-31O were prepared using procedures analogous to that used for Example 6A.

EXAMPLE 31B[5-Cyclopropyl-1-(2,1,3-benzothiadiazol-4-yl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 45 [0948] 66% yield.
 [0949] APCIMS 328 [M+1]⁺
 [0950] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.42 (m, 2H); 0.58 (m, 2H); 1.99 (m, 1H); 7.81 (m, 2H); 8.30 (d, J=8.4, 1H);
 50 8.40 (bs, 2H); 8.69 (s, 1H), 8.70 (bs, 2H), 11.83 (s, 1H).

EXAMPLE 31D[5-Cyclopropyl-1-(2-aminosulfonylphenyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 55 [0951] 25% yield.
 [0952] APCIMS 349 [M+1]⁺
 [0953] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.49-0.81 (m, 4H); 1.97 (m, 1H); 7.29 (bs, 2H); 7.66 (d, J=7.2, 1H); 7.77 (m,

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2H), 8.07 (d, J=8, 1H); 8.43 (bs, 2H), 8.68 (s, 1H), 8.71 (bs, 2H), 11.81 (s, 1H).

EXAMPLE 31E

5 [5-Cyclopropyl-1-(2-methylthiophenyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0954] 35% yield.

[0955] APCIMS 316 [M+1]⁺

10 **[0956]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.60 (m, 2H); 0.74 (m, 2H); 1.96 (m, 1H); 7.31-7.98 (m, 4H); 8.40 (bs, 2H), 8.62 (s, 1H); 8.68 (bs, 2H).

EXAMPLE 31F

15 [1-(2-Pyrrol-1-ylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0957] 12% yield.

[0958] APCIMS 335 [M+1]⁺

20 **[0959]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.32-0.53 (m, 4H), 1.04 (m, 1H), 6.09 (s, 2H), 6.49 (s, 2H), 7.49-7.69 (m, 4H), 9.05 (bs, 5H), 10.80 (s, 1H).

EXAMPLE 31G

[5-Methyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

25 **[0960]** 92.4% yield.

[0961] ¹H NMR (DMSO-*d*₆) δ 2.64 (s, 3H); 7.86 (m, 1H); 8.11 (d, 1H); 8.33 (d, 1H); 8.41 (bs+s, 3H); 8.74 (bs, 2H); 8.79 (d, 1H); 8.88 (s, 1H); 9.16 (d, 1H).

EXAMPLE 31H

30 [5-Cyclopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0962] 98.8% yield.

35 **[0963]** ¹H-NMR (DMSO-*d*₆) δ 0.36 (m, 2H); 0.84 (m, 2H); 2.3 (m, 1H); 7.63 (s, 1H); 7.95 (q, 1H); 8.28 (dd, 1H); 8.43 (d, 1H); 8.56 (bs, 2H); 8.79 (bs, 2H); 8.97 (d, 1H); 9.08 (s, 1H); 9.21 (d, 1H).

EXAMPLE 31I

40 [5-Cyclopropyl-1-(4-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0964] 72.4% yield.

[0965] ¹H NMR (DMSO-*d*₆) δ 0.41 (m, 2H); 0.65 (m, 2H); 1.99 (m, 1H); 7.52 (d, 1H); 7.69 (m, 1H); 7.89 (m, 2H); 8.21 (d, 1H); 8.46 (bs, 2H); 8.76 (bs, 2H); 8.85 (d, 1H); 9.13 (t, 1H); 12.1 (s, 1H).

45 EXAMPLE 31J

[5-Methyl-1-(6-methoxy-5-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0966] 55.9% yield.

50 **[0967]** ¹H NMR (DMSO-*d*₆) δ 2.24 (s, 3H); 3.96 (s, 3H); 7.57-7.67 (m, 2H); 8.0 (dd, 1H); 8.37 (d, 1H); 8.43 (bs, 2H); 8.73 (bs, 2H); 8.88 (s, 1H); 8.94 (d, 1H); 12.0 (s, 1H).

EXAMPLE 31K

55 [5-Cyclopropyl-1-(6-methoxy-5-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0968] 24.1% yield.

[0969] ¹H NMR (DMSO-*d*₆) δ 0.34 (m, 1H); 0.52 (m, 1H); 0.62 (m, 2H); 1.79 (m, 1H); 3.94 (s, 3H); 7.51 (d, 1H); 7.6

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(m, 1H); 7.95 (d, 1H); 8.32 (d, 1H); 8.37 (bs, 2H); 8.68 (bs, 2H); 8.71 (s, 1H); 8.89 (d, 1H).

EXAMPLE 31L

5 [5-Cyclopropyl-1-(6-methyl-5-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0970] 70.7% yield.

[0971] ¹H NMR (DMSO-*d*₆) δ 0.49-0.72 (m, 4H); 1.81 (m, 1H); 2.51 (s, 3H); 7.75 (m, 2H); 7.99 (dd, 1H); 8.33 (d, 1H); 8.51 (bs, 2H); 8.81 (bs, 2H); 8.92 (s, 1H); 9.1 (t, 1H).

10

EXAMPLE 31M

[5-Ethyl-1-(2-methyl-6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

15 **[0972]** 47.6% yield.

[0973] ¹H NMR (DMSO-*d*₆) δ 1.11 (t, 3H); 2.89 (s, 3H); 3.0 (q, 2H); 7.86 (d, 1H); 8.06 (d, 1H); 8.34-8.43 (m, 4H); 8.74-8.88 (m, 4H).

EXAMPLE 31N

20

[5-Ethyl-1-(6-methyl-5-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[0974] 53.9% yield.

[0975] ¹H NMR (DMSO-*d*₆) δ 0.84 (t, 3H); 2.16 (s, 3H); 2.59 (2q, 2H); 7.61 (d, 1H); 7.72 (q, 1H); 7.99 (d, 1H); 8.32 (d, 1H); 8.5 (bs, 2H); 8.81 (bs, 2H); 9.07 (s+d, 2H).

25

EXAMPLE 31O

[5-Ethyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride

30

[0976] 63.7% yield.

[0977] ¹H NMR (DMSO-*d*₆) δ 1.11 (t, 3H); 3.04 (q, 2H); 7.91 (q, 1H); 8.08 (dd, 1H); 8.38 (s, 1H); 8.42 (d, 1H); 8.5 (bs, 2H); 8.8 (bs, 2H); 8.86 (d, 1H); 8.93 (s, 1H); 9.21 (d, 1H).

EXAMPLE 32A

[5-Cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

40

[0978] A mixture of 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylic acid (1.00 g, 3.37 mmol) and thionyl chloride (0.739 mL, 10.1 mmol) was heated at reflux for 1 h under a nitrogen atmosphere, and concentrated *in vacuo*. The residue was treated with anhydrous toluene and the mixture was concentrated *in vacuo* (twice). A solution of the resulting thick oil in anhydrous tetrahydrofuran (2.5 mL) was added dropwise to a vigorously stirred mixture of guanidine hydrochloride (1.16 g, 12.0 mmol), sodium hydroxide (2 N aqueous, 12 mL, 24 mmol) and tetrahydrofuran (6 mL) at 23 °C. The resulting mixture was heated at reflux for a 1 h, allowed to cool to room temperature and extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 1.1 g of a pale pink solid. A suspension of the solid in water (3.2 mL) was treated with concentrated hydrochloric acid (0.273 mL, 3.28 mmol) and stirred at room temperature for 1 h. The resulting suspension was filtered. The solid was air-dried and recrystallized from water. The resulting crystalline solid was air-dried to afford 0.98 g (74% yield) of the title compound.

45

[0979] APCIMS 338 [M+1]⁺

[0980] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.57 (bs, 2H), 0.72-0.74 (m, 2H), 1.82-1.89 (m, 1H), 7.71 (d, J=8, 1H), 7.80 (t, J=8, 1H), 7.86 (t, J=7, 1H), 7.97 (d, J=7, 1H), 8.36 (bs, 2H), 8.60 (s, 1H), 8.62 (bs, 2H).

[0981] The title compounds of Examples 32B-32CCC were prepared using procedures analogous to that used for Example 16A and Example 32A.

55

EXAMPLE 32C[1-(Naphthalen-1-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 **[0982]** 84% yield
[0983] APCIMS 320 [M+1]⁺
[0984] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.40-0.70 (m, 4H), 1.90 (m, 1H), 7.13 (d, J=8, 1H), 7.60 (m, 3H), 8.06 (d, J=8, 1H), 8.13 (d, J=8, 1H), 8.39 (bs, 2H), 8.72 (m, 3H).

10 EXAMPLE 32D[1-(Naphthalen-2-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 15 **[0985]** 83% yield
[0986] APCIMS 320 [M+1]⁺
[0987] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.38 (d, J=4.8, 2H), 0.80 (d, J=8, 2H), 2.24 (m, 1H), 7.57 (m, 2H), 7.72 (d, J=8.4, 1H), 8.03 (m, 3H), 8.18 (s, 1H), 8.38 (bs, 2H), 8.64 (s, 1H), 8.70 (bs, 2H), 11.80 (s, 1H).

20 EXAMPLE 32F[1-(*o*-Biphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 25 **[0988]** 72% yield.
[0989] APCIMS 346 [M+1]⁺
[0990] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.25-0.70 (m, 4H), 1.12 (m, 1H), 7.00 (m, 2H), 7.27 (m, 3H), 7.49-7.87 (m, 4H), 8.30 (bs, 2H), 8.56 (bs, 2H), 8.59 (s, 1H), 11.58 (s, 1H).

30 EXAMPLE 32G[1-(5-Quinoliny)-5-isopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 35 **[0991]** 74% yield.
[0992] APCIMS 323 [M+1]⁺
[0993] ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.15 (d, J=6.8, 6H), 3.00 (m, 1H), 7.73 (s, 2H), 7.91 (d, J=7.2, 1H), 8.04 (t, J=8, 1H), 8.38 (d, J=8.4, 1H), 8.51 (bs, 2H), 8.84 (bs, 2H), 8.96 (s, 1H), 9.12 (m, 1H), 12.01 (s, 1H).

40 EXAMPLE 32H[1-(5-Quinoliny)-5-*n*-propyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 45 **[0994]** 78% yield.
[0995] APCIMS 323 [M+1]⁺
[0996] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.61 (t, J=7.4, 6H), 1.33 (m, 2H), 2.73 (m, 2H), 7.69-7.78 (m, 3H), 7.91 (d, J=7.6, 1H), 8.03 (t, J=7.2, 1H), 8.35 (d, J=8, 1H), 8.47 (bs, 2H), 8.81 (bs, 2H), 9.00 (s, 1H), 9.11 (m, 1H), 12.15 (s, 1H).

50 EXAMPLE 32J[1-(2-Nitrophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 55 **[0997]** 76% yield.
[0998] APCIMS 315 [M+1]⁺
[0999] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.52 (bs, 2H), 0.80 (d, J=8.4, 2H), 2.04 (m, 1H), 7.81 (d, J=7.6, 1H), 7.91 (bs, 2H), 8.16 (d, J=8, 1H), 8.47 (bs, 2H), 8.67 (s, 1H), 8.72 (bs, 2H), 11.91 (s, 1H).

EXAMPLE 32K[1-(2-[Dimethylaminosulfonyl]phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 **[1000]** 72% yield.
[1001] APCIMS 377 [M+1]⁺
[1002] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.49 (bs, 2H), 0.67 (d, J=6, 2H), 1.87 (m, 1H), 2.62 (s, 6H), 7.61 (d, J=2, 1H), 7.83 (m, 2H), 7.98 (m, 1H), 8.40 (bs, 2H), 8.64 (s, 1H), 8.68 (bs, 2H), 11.81 (bs, 1H).

10 EXAMPLE 32L[1-(2-[Methanesulfonyl]phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1003]** 68% yield.
15 **[1004]** APCIMS 348 [M+1]⁺
[1005] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.40-0.60 (m, 4H), 1.89 (m, 1H), 3.30 (s, 3H), 7.73 (d, J=6.4, 1H), 7.88 (m, 2H), 8.11 (dd, J=8, 1.6, 1H), 8.36 (bs, 2H), 8.64 (bs, 3H), 11.72 (s, 1H).

EXAMPLE 32M

- 20 [1-(2-[Methylaminosulfonyl]phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride
- [1006]** 44% yield.
[1007] APCIMS 363 [M+1]⁺
25 **[1008]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.48-0.76 (m, 4H), 1.93 (m, 1H), 2.4 (s, 3H), 7.01 (s, 1H), 7.65 (m, 1H), 7.79 (m, 2H), 7.98 (m, 1H), 8.31 (bs, 2H), 8.53 (s, 1H), 8.57 (bs, 2H), 11.58 (s, 1H).

EXAMPLE 32N

- 30 [1-(2-Ethylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride
- [1009]** 48% yield.
[1010] APCIMS 298 [M+1]⁺
35 **[1011]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.61 (d, J=8.8, 2H), 0.71 (d, J=8.4, 2H), 0.98 (t, J=7.4, 3H), 2.26 (d, J=7.2, 2H), 7.33 (m, 2H), 7.46 (m, 2H), 8.35 (bs, 2H), 8.59 (s, 1H), 8.64 (bs, 2H), 11.70 (s, 1H).

EXAMPLE 32O

- 40 [1-(2-Methylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride
- [1012]** 14% yield.
[1013] APCIMS 284 [M+1]⁺
[1014] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.57 (bs, 2H), 0.70 (d, J=5.6, 2H), 1.96 (s, 4H), 7.20-7.60 (m, 4H), 8.40 (bs, 2H), 8.65 (s, 1H), 8.71 (bs, 2H), 11.81 (s, 1H).

EXAMPLE 32P

- 45 [1-(2-Chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride
- [1015]** 74% yield.
50 **[1016]** APCIMS 304 [M+1]⁺
[1017] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.55 (d, J=3.6, 2H), 0.72 (d, J=7.2, 2H), 1.90 (m, 1H), 7.4-7.8 (m, 4H), 8.36 (bs, 2H), 8.61 (s, 1H), 8.63 (bs, 2H), 11.74 (s, 1H).

55

EXAMPLE 32Q[1-(2-Trifluoromethoxyphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 **[1018]** 87% yield.
[1019] APCIMS 354 [M+1]⁺
[1020] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.48 (m, 2H), 0.74 (m, 2H), 1.89 (m, 1H), 7.4-7.8 (m, 4H), 8.36 (bs, 2H), 8.62 (bs, 3H), 11.72 (s, 1H).

10 EXAMPLE 32R[1-(2-Fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1021]** 79% yield.
15 **[1022]** APCIMS 287 [M+1]⁺
[1023] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.49 (d, J=4, 2H), 0.75 (d, J=6.8, 2H), 1.94 (bs, 1H), 7.4-7.6 (m, 4H), 8.34 (bs, 2H), 8.58 (s, 1H), 8.61 (bs, 2H), 11.71 (s, 1H).

20 EXAMPLE 32S[1-(2,1,3-Benzothiadiazol-4-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine

- [1024]** 73% yield.
[1025] APCIMS 302 [M+1]⁺
25 **[1026]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.49 (s, 3H), 7.7-7.81 (m, 1H), 7.98 (dd, J=8.4, 0.8, 1H), 8.13 (dd, J=7.6, 0.6, 1H), 9.36 (s, 1H).

EXAMPLE 32T30 [1-(Indazol-7-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1027]** 62% yield.
[1028] APCIMS 310 [M+1]⁺
35 **[1029]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.44 (dd, J=7.6, 5.2, 2H), 0.67-0.73 (m, 2H), 2.11 (m, 1H), 7.26 (t, J=10, 1H), 7.53 (d, J=8.8, 1H), 7.94 (d, J=9.6, 1H), 8.25 (s, 1H), 8.44 (bs, 2H), 8.79 (bs, 3H), 11.88 (s, 1H).

EXAMPLE 32U40 [1-(Indazol-7-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1030]** 63% yield.
[1031] APCIMS 284 [M+1]⁺
45 **[1032]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.53 (s, 3H), 7.23 (t, J=7.8, 1H), 7.57 (d, J=7.6, 1H), 7.78 (d, J=8.0, 1H), 8.23 (s, 1H), 8.40 (bs, 2H), 8.51 (bs, 3H), 9.76 (s, 1H), 12.15 (bs, 1H).

EXAMPLE 32V50 [1-(Benzothiazol-2-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1033]** 85% yield.
[1034] APCIMS 315 [M+1]⁺
55 **[1035]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.29 (t, J=7.2, 3H), 3.61 (q, J=7.6, 2H), 7.44-7.56 (m, 2H), 7.96 (d, J=8.4, 1H), 8.12 (d, J=8.0, 1H), 8.43 (bs, 2H), 8.62 (bs, 2H), 8.84 (s, 1H), 12.01 (s, 1H).

EXAMPLE 32W[1-(2-Chloro-4-methylsulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride5 **[1036]** 89% yield.**[1037]** APCIMS 382 [M+1]⁺**[1038]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.572 (dd, J=5.6, 2.0, 2H), 0.76 (dd, J=8.8, 2.0, 2H), 1.91 (m, 1H), 3.36 (s, 3H), 7.94 (d, J=8.4, 1H), 8.05 (dd, J=8.4, 2.0 1H), 8.26 (s, 1H), 8.36 (bs, 2H), 8.63 (bs, 2H), 8.67 (s, 1H), 11.80 (s, 1H).10 EXAMPLE 32X[1-(2-Chloro-4-(methylsulfonylmethylenesulfonyl)phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride15 **[1039]** 72% yield.**[1040]** APCIMS 460 [M+1]⁺**[1041]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.53 (m, 2H), 0.77 (m, 2H), 1.94 (m, 1H), 3.23 (s, 3H), 5.91 (s, 2H), 7.96-8.00 (m, 1H), 8.01-8.12 (m, 1H), 8.30 (bs, 2H), 8.65 (bs, 2H), 8.66 (s, 1H), 11.11.73 (d, J=6.4, 1H).20 EXAMPLE 32Y[1-(2-Chloro-5-(dimethylaminosulfonyl)phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride25 **[1042]** 85% yield.**[1043]** APCIMS 411 [M+1]⁺**[1044]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.52 (s, 2H), 0.74 (m, 2H), 1.93 (m, 1H), 2.45 (s, 6H), 7.92-8.08 (m, 3H), 8.35 (bs, 2H), 8.64 (bs, 3H), 11.73 (s, 1H).30 EXAMPLE 32Z[1-(2-Chloro-5-(aminosulfonyl)phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride35 **[1045]** 9% yield.**[1046]** APCIMS 383 [M+1]⁺**[1047]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.57 (d, J=8.6, 2H), 0.78 (d, J=8.0, 2H), 1.94 (m, 1H), 7.14 (t, J=51.0, 2H), 7.63 (s, 2H), 7.97 (m, 2H), 8.36 (bs, 2H), 8.62 (bs, 3H), 8.64 (s, 1H), 11.73 (s, 1H).EXAMPLE 32AA40 [1-(2-Chloro-5-(methylaminosulfonyl)phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride45 **[1048]** 61% yield.**[1049]** APCIMS 397 [M+1]⁺**[1050]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.53 (m, 2H), 0.72-0.76 (m, 2H), 1.92 (m, 1H), 2.43 (d, J=5.2, 3H), 7.70 (d, J=5.2, 1H), 7.93-7.99 (m, 3H), 8.35 (bs, 2H), 8.60 (bs, 2H), 8.61 (s, 1H), 11.70 (s, 1H).EXAMPLE 32BB50 [1-(2,5-Dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride55 **[1051]** 84% yield.**[1052]** APCIMS 338 [M+1]⁺**[1053]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.58 (s, 2H), 0.77 (d, J=7.2, 2H), 1.92 (m, 1H), 7.70-7.77 (m, 2H), 7.90 (d, J=2.4, 1H), 8.37 (bs, 2H), 8.62 (bs, 3H), 11.74 (s, 1H).

EXAMPLE 32CC[1-(2,4-Dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 **[1054]** 62% yield.
[1055] APCIMS 338 [M+1]⁺
[1056] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.54-0.56 (m, 2H), 0.73-0.78 (m, 2H), 1.90 (m, 1H), 7.61-7.70 (m, 2H), 7.93 (s, 1H), 8.35 (bs, 2H), 8.60 (bs, 3H), 11.72 (s, 1H).

10 EXAMPLE 32DD[1-(2,3-Dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1057]** 44% yield.
15 **[1058]** APCIMS 339 [M+1]⁺
[1059] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.56-0.58 (m, 2H), 0.76 (s, 2H), 1.93 (m, 1H), 7.57 (dt, J=7.6, 2.0, 1H), 7.67 (td, J=8.0, 1.6, 1H), 7.89 (td, J=8.0, 1.6, 1H), 8.42 (bs, 2H), 8.68 (bs, 3H), 11.86 (s, 1H).

20 EXAMPLE 32EE[1-(2-Chloro-5-methylsulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1060]** 86% yield.
[1061] APCIMS 382 [M+1]⁺
25 **[1062]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.57 (s, 2H), 0.77 (d, J=7.2, 2H), 1.94 (m, 1H), 3.36 (s, 3H), 8.04 (d, J=8.4, 1H), 8.12 (d, J=8.4, 1H), 8.23 (s, 1H), 8.36 (bs, 2H), 8.61 (bs, 2H), 8.64 (s, 1H), 11.86 (s, 1H).

30 EXAMPLE 32FF[1-(Benzimidazol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- [1063]** 24% yield.
[1064] APCIMS 298 [M+1]⁺
35 **[1065]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.04 (t, J=7.2, 3H), 2.88 (q, J=7.2, 2H), 7.63 (d, J=8.8, 1H), 8.01 (bs, 2H), 8.47 (bs, 2H), 8.78 (bs, 2H), 8.86 (s, 1H), 9.55 (bs, 1H), 12.09 (s, 1H).

40 EXAMPLE 32GG[1-(2-Chloro-4-{dimethylaminosulfonyl}phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1066]** 68% yield.
[1067] APCIMS 411 [M+1]⁺
45 **[1068]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.52 (d, J=4.4, 2H), 0.75 (d, J=8.4, 2H), 1.93 (bs, 1H), 2.67 (s, 6H), 7.84-8.00 (m, 2H), 8.04 (s, 1H), 8.37 (bs, 2H), 8.68 (bs, 3H), 11.82 (s, 1H).

50 EXAMPLE 32HH[1-(2-Chloro-4-{methylaminosulfonyl}phenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1069]** 26% yield.
[1070] APCIMS 397 [M+1]⁺
55 **[1071]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.55-0.58 (m, 2H), 0.75-0.80 (m, 2H), 1.93 (m, 1H), 3.47 (s, 3H), 7.82 (t, J=4.8, 1H), 7.88-8.01 (m, 2H), 8.05 (s, 1H), 8.34 (bs, 2H), 8.57 (bs, 2H), 8.06 (s, 1H), 11.66 (s, 1H).

EXAMPLE 32II[1-(Benzimidazol-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 5 **[1072]** 16% yield.
[1073] APCIMS 310 [M+1]⁺
[1074] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.37-0.41 (m, 2H), 0.75-0.82 (m, 2H), 2.19 (m, 1H), 7.75 (d, J=8.8, 1H), 7.91-7.98 (m, 2H), 8.05 (s, 1H), 8.45 (bs, 2H), 8.70 (s, 1H), 8.76 (bs, 2H), 9.51 (s, 1H), 11.95 (s, 1H).

10 EXAMPLE 32JJ[1-Benzyl-3-methyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1075]** 67% yield.
15 **[1076]** APCIMS 258 [M+1]⁺
[1077] ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.31 (s, 3H), 5.29 (s, 2H), 7.23-7.35 (m, 5H), 8.47 (bs, 2H), 8.53 (bs, 2H), 8.55 (s, 1H), 11.73 (s, 1H).

EXAMPLE 32KK

- 20 [1-(3-Chloroindazol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride
[1078] 66% yield.
[1079] APCIMS 332 [M+1]⁺
25 **[1080]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.03 (d, J=10.4, 3H), 2.84 (d, J=7.6, 2H), 7.49 (d, J=8.4, 1H), 7.72 (d, J=8.8, 1H), 7.79 (s, 1H), 8.41 (bs, 2H), 8.73 (bs, 2H), 8.76 (s, 1H), 11.95 (s, 1H), 13.69 (s, 1H).

EXAMPLE 32LL

- 30 [1-(1-Methylbenzimidazol-6-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride
[1081] 53% yield.
[1082] APCIMS 312 [M+1]⁺
35 **[1083]** ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.02 (m, 3H), 2.84 (d, J=7.6, 2H), 4.03 (s, 3H), 7.64 (d, J=8.8, 1H), 8.00 (d, J=8.4, 1H), 8.20 (s, 1H), 8.47 (bs, 2H), 8.78 (bs, 2H), 8.87 (s, 1H), 9.50 (bs, 1H), 12.12 (s, 1H).

EXAMPLE 32MM

- 40 [1-(2-Methylbenzimidazol-5-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride
[1084] 38% yield.
[1085] APCIMS 312 [M+1]⁺
[1086] ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.05 (bs, 3H), 2.79 (s, 3H), 2.88 (q, J=7.6, 2H), 7.60 (dd, J=8.8, 1.6, 1H), 7.93 (m, 2H), 8.46 (bs, 2H), 8.77 (bs, 2H), 8.85 (s, 1H), 12.09 (s, 1H).

45 EXAMPLE 32NN[1-(Benzothiazol-6-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride monohydrate

- 50 **[1087]** 9.5% yield
[1088] APCIMS 315 [M+1]⁺
[1089] ¹H NMR (CDCl₃) δ 1.01-1.14 (t, 3H), 8.74 (s, 1H)

55 EXAMPLE 32OO[1-(2-Quinoxaliny)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- [1090]** 44% yield.

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[1091] APCIMS 310 [M+1]⁺

[1092] ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.93 (s, 1H), 9.44 (s, 1H), 8.86 (s, 1H), 8.64 (bs, 2H), 8.40 (bs, 2H), 8.16 (d, J=8, 1H), 8.043 (dd, J=2.4, 8, 1H), 7.94-7.87 (m, 2H), 3.43 (q, J=6, 2H), 1.338 (t, J=7, 3H).

5 EXAMPLE 32PP

[1-(2-Benzimidazolyl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

[1093] 44% yield.

10 [1094] APCIMS 298 [M+1]⁺

[1095] ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.15 (s, 1H), 8.97 (s, 1H), 8.73 (bs, 2H), 8.47 (bs, 2H), 7.56 (dd, J=3, 6, 2H), 7.22 (dd, J=3.2, 6, 2H), 3.53 (q, J=7, 2H), 1.24 (t, J=7, 3H).

EXAMPLE 32QQ

15

[1-(2-Trifluoromethyl-4-chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[1096] 60% yield.

[1097] APCIMS 372 [M+1]⁺

20 [1098] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (bs, 3H), 8.43 (bs, 2H), 8.14 (s, 1H), 8.02 (d, J=8, 1H), 7.84 (d, J=9, 1H), 1.90 (m, 1H), 0.80 (d, J=8, 2H), 0.693 (d, J=4, 2H).

EXAMPLE 32RR

25

[1-(2-Fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

[1099] 71% yield

[1100] APCIMS 356 [M+1]⁺

30 [1101] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.71-8.44 (m, 5H), 8.00-7.90 (m, 3H), 1.82 (m, 1H), 0.89-0.70 (m, 4H).

EXAMPLE 32SS

[1-(2-Trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

35 [1102] 58% yield

[1103] APCIMS 356 [M+1]⁺

[1104] ¹H NMR (300MHz, DMSO-*d*₆) δ 8.67 (bs, 3H), 8.43 (bs, 2H), 7.99 (d, J=8, 1H), 7.90-7.78 (m, 2H), 1.89 (m, 1H), 0.81-0.63 (m, 4H).

40 EXAMPLE 32TT

[1-(1-Methylbenzimidazol-2-yl)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

[1105] 86% yield

45 [1106] APCIMS 312 [M+1]⁺

[1107] ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 8.96 (s, 1H), 8.71 (bs, 2H), 8.44 (bs, 2H), 7.69 (dd, J=8,16, 2H) 7.40-7.29 (m, 2H), 3.68 (s, 3H), 3.03 (q, J=7, 2H), 1.12 (t, J=7, 3H).

EXAMPLE 32UU

50

[1-(2-Quinoliny)-5-ethyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

[1108] 65% yield

[1109] APCIMS 309 [M+1]⁺

55 [1110] ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.86 (s, 1H), 8.79 (s, 1H), 8.65 (bs, 2H), 8.61 (d, J=9, 1H), 8.38 (bs, 2H), 8.07 (d, J=8, 1H), 8.01-7.96 (m, 2H), 7.83 (m, 1H), 7.66 (t, J=7, 1H), 3.44 (q, J=7, 2H), 1.31 (t, J=7, 3H).

EXAMPLE 32VV[1-(2-Chloro-5-methylaminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 [1111] 57% yield
 [1112] APCIMS 359 [M-1]
 [1113] ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.71 (s, 1H), 8.67 (m, 1H), 8.61 (bs, 3H), 8.36 (bs, 2H), 8.04 (d, J=7, 1H), 8.03 (s, 1H), 7.84 (d, J=8, 1H), 2.60 (d, J=4, 3H), 1.94 (m, 1H), 0.75 (d, J=7, 2H), 0.57 (m, 2H).

10 EXAMPLE 32WW[1-(4-Bezimidazolyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 15 [1114] 22% yield
 [1115] APCIMS 310 [M+1]⁺
 [1116] ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.19 (bs, 2H), 8.84 (d, J=2, 1H), 8.80 (s, 1H), 8.45 (bs, 2H), 7.92 (m, 1H), 7.69-7.58 (m, 2H), 2.16 (m, 1H), 0.72 (d, J=9, 2H), 0.44 (d, J=5, 2H).

20 EXAMPLE 32XX[1-(2-Chloro-5-iodophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1117] 81 % yield
 [1118] APCIMS 430 [M+1]⁺
 25 [1119] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.66 (bs, 2H), 8.64 (s, 1H), 8.40 (bs, 2H), 8.18 (d, J=2, 1H), 7.94 (dd, J=2, 8, 1H), 7.45 (d, J=8, 1H), 1.94 (m, 1H), 0.84-0.72 (m, 2H), 0.68-0.58 (m, 2H).

30 EXAMPLE 32YY[1-(2-Chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1120] 45% yield
 [1121] APCIMS 347 [M+1]⁺
 35 [1122] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.65 (bs, 2H), 8.62 (s, 1H), 8.37 (bs, 2H), 8.20 (s, 1H), 8.10 (s, 1H), 8.02 (d, J=8, 1H), 7.87 (d, J=9, 1H), 7.68 (s, 1H), 1.96 (m, 1H), 0.80 (d, J=8, 2H), 0.61 (d, J=3, 2H).

40 EXAMPLE 32ZZ[1-(2-Chloro-5-dimethylaminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- [1123] 49% yield
 [1124] APCIMS 375 [M+1]⁺
 45 [1125] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.60 (bs, 3H), 8.38 (bs, 2H), 7.82 (d, J=8, 1H), 7.76 (d, J=2, 1H), 7.66 (m, 1H), 2.99 (s, 3H), 2.93 (s, 3H), 1.96 (m, 1H), 0.79 (d, J=9, 2H), 0.60 (d, J=4, 2H).

50 EXAMPLE 32BBB[1-(1-Isoquinolyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine dihydrochloride

- 55 [1126] 69 % yield
 [1127] APCIMS 321 [M+1]⁺
 [1128] ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.99 (s, 1H), 8.79 (s, 1H), 8.77 (bs, 2H), 8.51 (d, J=6, 1H), 8.49 (bs, 2H), 8.13 (d, J=8, 1H), 8.10 (d, J=6, 1H), 7.85 (dd, J=7, 8, 1H), 7.9-7.6 (bs, 1H), 7.69 (dd, J=7, 8, 1H), 7.46 (d, J=8, 1H), 2.05 (m, 1H), 0.61-0.57 (m, 2H), 0.37-0.33 (m, 2H).

EXAMPLE 32CCC[1-(2,3-Dimethoxyphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine hydrochloride

- 5 **[1129]** 38% yield.
[1130] APCIMS 330 [M+1]⁺
[1131] ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.57 (d, J=4.8, 2H), 0.72 (d, J=8.4, 2H), 1.91 (m, 1H), 3.57 (s, 3H), 3.86 (s, 3H), 6.97 (d, J=8, 1H), 7.22 (m, 2H), 8.34 (bs, 2H), 8.56 (s, 1H), 8.65 (bs, 2H), 11.67 (s, 1H).

10 EXAMPLE 33AN-tert-Butoxycarbonyl-N'-[5-isopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine

- 15 **[1132]** To a solution of 5-isopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid (336.7 mg, 1.2 mmol) in 5 ml dimethylformamide was added N,N-diisopropylethylamine (0.42 ml, 2.39 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (582 mg, 1.32 mmol) and *tert*-butoxycarbonylguanidine (210 mg, 1.32 mmol). The resulting solution was stirred at room temperature for 2 h, then heated to 60 °C for 2 h. The reaction mixture was then cooled to room temperature and concentrated to dryness *in vacuo*. The solid residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (sodium sulfate) and concentrated to dryness *in vacuo*. The solid residue was triturated with methanol (1.5 ml), filtered, washed with diethyl ether and dried to yield the title compound as a white solid (114.3 mg, 22.5% yield).
20 **[1133]** ¹H NMR (DMSO-*d*₆) δ 1.27 (d, 6H); 1.42 (s, 9H); 3.28 (m, 1H); 7.62 (q, 1H); 7.74 (q, 1H); 8.08-8.15 (m, 4H); 8.47 (d, 1H); 8.98 (d, 1H); 9.21 (bs, 1H); 10.9 (bs, 1H).
[1134] The title compound of Example 33B was obtained using a procedure analogous to that used for Example 33A.

25 EXAMPLE 33BN-tert-butoxycarbonyl-N'-[5-propyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine

- 30 **[1135]** 58.9% yield.
[1136] ¹H NMR (DMSO-*d*₆) δ 0.73 (t, 3H); 1.24 (d, 2H); 1.47 (s, 9H); 3.08 (t, 2H); 7.66 (q, 1H); 7.86 (q, 1H); 8.18 (m, 3H); 8.51 (s+d, 2H); 9.01 (t, 1H); 9.39 (bs, 1H); 11.0 (bs, 1H).

35 EXAMPLE 34A[5-Isopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine trifluoroacetate

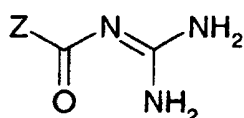
- 40 **[1137]** A solution of N-*tert*-butoxycarbonyl-N'-[5-isopropyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine (114.3 mg, 0.27 mmol) in 2 ml of dichloromethane containing 20% trifluoroacetic acid was stirred at room temperature overnight and treated with ether. The resulting precipitate was filtered, yielding the title compound as a white solid (104.3 mg, 70% yield).
[1138] ¹H NMR (DMSO-*d*₆) δ 1.29 (d, 6H); 3.23 (m, 1H); 7.68 (q, 1H); 7.8 (dd, 1H); 8.18-8.55 (m, 7H); 9.04 (t, 1H); 11.1 (s, 1H).
[1139] The title compound of Example 34B was obtained using a procedure analogous to that used for Example 34A.

45 EXAMPLE 34B[5-propyl-1-(6-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine trifluoroacetate

- 50 **[1140]** 81.2% yield.
[1141] ¹NMR (DMSO-*d*₆) δ 0.72 (t, 3H); 1.47 (d, 2H); 2.97 (t, 2H); 7.67 (t, 1H); 7.87 (d, 1H); 8.19-8.37 (m, 7H); 8.53 (d, 1H); 9.03 (s, 1H); 11.1 (s, 1H).

55 **Claims**

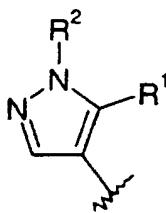
1. A compound having the Formula I



Formula I

or a pharmaceutically acceptable salt of said compound, wherein either Z is

(i)



wherein R¹ is (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₃-C₇)cycloalkyl optionally substituted with from one to three fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di- substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

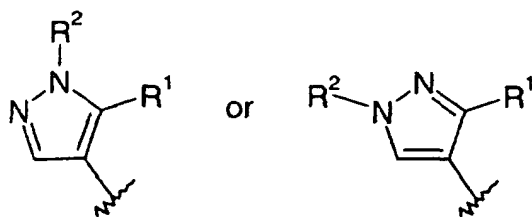
wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; or

Z is

(ii)



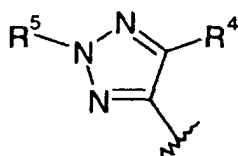
wherein R¹ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R² is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines, or

Z is

(iii)



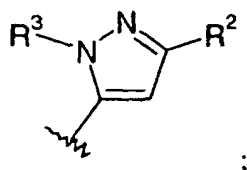
wherein R⁴ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R⁴ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R⁵ is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R⁵ is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R⁵ is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R⁵ substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl,

formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; or
Z is

(iv)



wherein R² is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di- substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

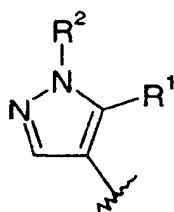
said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; and

R³ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R³ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or (C₁-C₄)alkyl.

2. A compound as recited in claim 1 wherein the compound is
[5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine;
[5-cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine; or
[5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine;
or a pharmaceutically acceptable salt thereof.

3. A compound as recited in claim 1 wherein Z is



R¹ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl; and

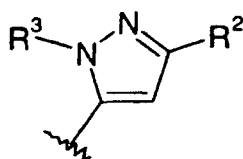
R² is quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxaliny, quinazoliny, benzopyranyl, benzothiophenyl, benzodioxanyl or benzodioxoly, said R² substituent optionally mono-substituted.

15

4. A compound as recited in claim 1 wherein the compound is
 [5-methyl-1-(quinolin-6-yl)-1H-pyrazole-4-carbonyl]guanidine;
 [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine; or
 [5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine;
 or a pharmaceutically acceptable salt thereof.
- 20

5. A compound as recited in claim 3 wherein R¹ is cyclopropyl and R² is quinolin-5-yl.

6. A compound as recited in claim 1 wherein Z is
- 25

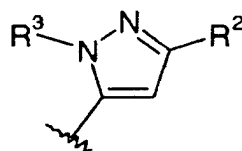


R² is phenyl, optionally mono- or di-substituted; and
 R³ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl.

35

7. A compound as recited in claim 1 wherein the compound is
 [2-methyl-5-phenyl-2H-pyrazole-3-carbonyl]guanidine; or
 [2-methyl-5-(naphthalen-1-yl)-2H-pyrazole-3-carbonyl]guanidine;
 or a pharmaceutically acceptable salt thereof.
- 40

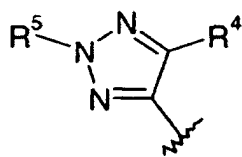
8. A compound as recited in claim 1 wherein Z is
- 45



R² is naphthalenyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxaliny, quinazoliny, benzopyranyl, benzothiophenyl, benzodioxanyl or benzodioxoly, said R² substituent optionally mono-substituted; and
 R³ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl.

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9. A compound as recited in claim 1 wherein Z is

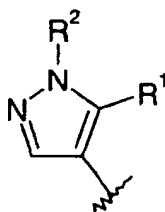


- 5
- 10 R⁴ is (C₁-C₄)alkyl or (C₃-C₇)cycloalkyl; and
 R⁵ is quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxaliny, quinazoliny, benzopyranyl, benzothi-
 ophenyl, benzodioxanyl or benzodioxoly, said R⁵ substituent optionally mono-substituted.

10. A compound as recited in claim 1 wherein the compound is
 15 [2-(isoquinolin-5-yl)-5-methyl-2H-1,2,3-triazole-4-carbonyl]guanidine; or
 [5-methyl-2-(quinolin-5-yl)-2H-1,2,3-triazole-4-carbonyl]guanidine; or a
 pharmaceutically acceptable salt thereof.

11. A compound as recited in claim 1 wherein the compound is
 20 [1-(naphthalen-1-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine
 or a pharmaceutically acceptable salt thereof.

12. A compound as recited in claim 1 wherein Z is



25
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 35 wherein R¹ is (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₃-C₇)cycloalkyl optionally substituted
 with from one to three fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)
 alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and R² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, M
 or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said
 (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di- substituted independently with hydroxy, (C₁-C₄)alkoxy,
 (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl
 40 or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven
 fluorines;

45 wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally
 having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring con-
 sisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken
 independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

50 said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is
 bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein
 one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered
 ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally
 substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)
 alkoxy-carbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, car-
 bamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)
 alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

55 wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)
 alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with
 hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy,
 (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylami-

no, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

5 **13.** A compound as recited in claim 12 wherein

R¹ is (C₃-C₇)cycloalkyl; and

R² is a five to six membered monocyclic aromatic ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

10 said R² ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

15 said R² ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

20 wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

25 **14.** A compound as recited in claim 13 wherein

R¹ is cyclopropyl; and

R² is phenyl, optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

30 wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono- substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

35 **15.** A compound as recited in claim 1 wherein the compound is

[5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine;

40 or a pharmaceutically acceptable salt thereof.

45 **16.** A compound as recited in claim 1 wherein the compound is

[1-(2-chloro-4-methylsulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

50 [1-(2-bromophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-fluorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-methoxyphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-4-methylaminosulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2,5-dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

55 [1-(2,3-dichlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-aminosulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-methylsulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-dimethylaminosulfonylphenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine; or

[1-(2-trifluoromethyl-4-chlorophenyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

or a pharmaceutically acceptable salt thereof.

17. A compound as recited in claim 12 wherein

R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄)alkyl, unsubstituted (C₃-C₇)cycloalkyl or phenyl(C₁-C₄)alkyl, wherein said phenyl(C₁-C₄)alkyl is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono- substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

18. A compound as recited in claim 12 wherein

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituent optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

19. A compound as recited in claim 18 wherein

R¹ is (C₃-C₇)cycloalkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

20. A compound as recited in claim 19 wherein

R¹ is cyclopropyl; and

R² is a quinazolinyl, phthalazinyl, quinolinyl, isoquinolinyl, cinnolinyl, benzodioxanyl, quinoxalinyl, benzopyranyl, benzothiophenyl, benzodioxolyl, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently on carbon or nitrogen with

hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono- substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

21. A compound as recited in claim 20 wherein

R² is a quinolinyl, isoquinolinyl, indazolyl or benzimidazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy or (C₁-C₄)alkyl substituents are optionally mono-substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

22. A compound as recited in claim 1 wherein the compound is

[5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine;
or a pharmaceutically acceptable salt thereof.

23. A compound as recited in claim 1 wherein the compound is

[1-(8-bromoquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(6-chloroquinolin-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(indazol-7-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

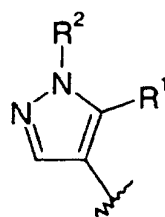
[1-(benzimidazol-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine;

[1-(1-isoquinolyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine; or

[5-cyclopropyl-1-(4-quinolinyl)-1H-pyrazole-4-carbonyl]guanidine;

or a pharmaceutically acceptable salt thereof.

24. A compound as recited in claim 1 wherein Z is



R¹ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R² is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido,

(C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

25. A compound as recited in claim 24 wherein wherein

R¹ is (C₁-C₄)alkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

26. A compound as recited in claim 25 wherein

R² is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxany, quinoxaliny, benzopyrany, benzothiopheny, benzodioxoly, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

wherein said R² bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

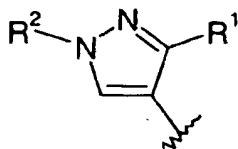
wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono- substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

27. A compound as recited in claim 1 wherein the compound is

[1-(indazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(indazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(benzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(1-methylbenzimidazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine
 [1-(5-quinoliny)-5-*n*-propyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(5-quinoliny)-5-isopropyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [5-ethyl-1-(6-quinoliny)-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(2-methylbenzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(1,4-benzodioxan-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(benzotriazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(3-chloroindazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [1-(5-quinoliny)-5-butyl-1*H*-pyrazole-4-carbonyl]guanidine;
 [5-propyl-1-(6-quinoliny)-1*H*-pyrazole-4-carbonyl]guanidine; or

[5-isopropyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine;
or a pharmaceutically acceptable salt thereof.

28. A compound as recited in claim 1 wherein Z is



R¹ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R¹ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R² is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R² is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R² is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R² substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

29. A compound as recited in claim 28 wherein wherein

R¹ is (C₁-C₄)alkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

30. A compound as recited in claim 29 wherein

R² is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxanyl, quinoxaliny, benzopyranyl, benzothiophenyl, benzodioxoly, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

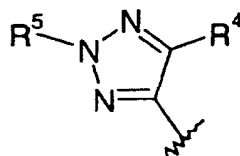
wherein said R² bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄) alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino substituents are optionally mono- substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

31. A compound as recited in claim 1 wherein the compound is

[1-(indazol-7-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine; [1-(2,1,3-benzothiadiazol-4-yl)-3-methyl-1H-pyrazole-4-carbonyl]guanidine; or [3-methyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine; or a pharmaceutically acceptable salt thereof.

32. A compound as recited in claim 1 wherein Z is



R⁴ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R⁴ substituent optionally mono- or di- substituted independently with (C₁-C₄) alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl; and

R⁵ is a five to six membered nonaromatic heterocyclic ring having one to two heteroatoms selected independently from nitrogen, sulfur and oxygen or R⁵ is unsubstituted (C₁-C₄)alkyl or unsubstituted (C₃-C₇)cycloalkyl; or R⁵ is phenyl(C₁-C₄)alkyl, or a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said R⁵ substituents optionally substituted on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

33. A compound as recited in claim 32 wherein

R⁴ is (C₁-C₄)alkyl; and

R⁵ is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen,

sulfur and oxygen,

said R⁵ bicyclic ring is optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R⁵ bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N, N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

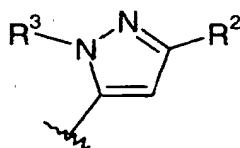
34. A compound as recited in claim 33 wherein

R⁵ is a quinazoliny, phthalaziny, quinoliny, isoquinoliny, cinnoliny, benzodioxany, quinoxaliny, benzopyrany, benzothiopheny, benzodioxoly, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl or benzothiadiazolyl ring,

wherein said R⁵ bicyclic ring is optionally mono- or di-substituted independently with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylamino substituents are optionally mono- substituted with hydroxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to five fluorines.

35. A compound as recited in claim 1 wherein Z is



R² is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, M or M(C₁-C₄)alkyl, any of said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono- or di-substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N, N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N, N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N, N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines; and

R³ is (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, phenyl or phenyl(C₁-C₄)alkyl, said (C₁-C₄)alkyl optionally substituted with from one to nine fluorines, said R³ substituent optionally mono- or di- substituted independently with (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or (C₁-C₄)alkyl.

36. A compound as recited in claim 35 wherein

R³ is (C₁-C₄)alkyl; and

R² is phenyl, said phenyl optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² ring is also optionally mono- or di-substituted independently on carbon with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

37. A compound as recited in claim 35 wherein

R³ is (C₁-C₄)alkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently

said R² bicyclic ring is optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

38. A compound as recited in claim 35 wherein

R³ is (C₁-C₄)alkyl; and

R² is a five to six membered monocyclic aromatic ring having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

said R² ring is optionally mono-substituted on carbon with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

39. A compound as recited in claim 35 wherein

R³ is (C₁-C₄)alkyl; and

R² is a bicyclic ring consisting of two fused five and/or six membered partially saturated, fully saturated or fully unsaturated rings taken independently having one to three heteroatoms selected independently from nitrogen, sulfur and oxygen,

said R² bicyclic ring is optionally mono-substituted on carbon or nitrogen with a fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono-substituted with (C₁-C₄)alkyl

said R² bicyclic ring is also optionally mono- or di-substituted independently on carbon or nitrogen with hydroxy, halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino are optionally mono-substituted with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

40. A pharmaceutical composition comprising a compound of the formula I, or a pharmaceutically acceptable salt of said compound, as claimed in any one of claims 1 to 39, and a pharmaceutically acceptable carrier.

41. A compound of the formula I, or a pharmaceutically acceptable salt of said compound, as claimed in any one of claims 1 to 39, for use as a medicament.

42. The use of a compound of the formula I, or a pharmaceutically acceptable salt of said compound, as claimed in any one of claims 1 to 39, for the manufacture of a medicament for the prevention of myocardial ischemic damage.

43. The use of a compound of the formula I, or a pharmaceutically acceptable salt of said compound, as claimed in any one of claims 1 to 39, for the manufacture of a medicament for reducing tissue damage resulting from ischemia.

44. The use of claim 43 wherein the tissue is cardiac, brain, liver, kidney, lung, gut, skeletal muscle, spleen, pancreas, nerve, spinal cord, retina tissue, the vasculature, or intestinal tissue.

45. The use of claim 44 wherein the amount of the Formula I compound is about 0.01 mg/kg/day to about 50 mg/kg/day.

46. The use of claim 43 wherein the compound is to be administered prophylactically.

47. The use of claim 43 wherein the compound is to be administered prior to surgery.

48. The use of claim 43 wherein the compound is to be administered prior to cardiac surgery.

49. The use of claim 43 wherein the compound is to be administered during surgery.

50. The use of claim 43 wherein the compound is to be administered during cardiac surgery.

51. The use of claim 43 wherein the compound is to be administered within twenty-four hours after surgery.

52. The use of claim 43 wherein the compound is to be administered within twenty four hours after cardiac surgery.

53. The use of claim 43 wherein the compound is to be administered prior to, during and after surgery.
54. The use of claim 43 wherein the compound is to be administered prior to, during and after cardiac surgery.
- 5 55. The use of claim 43 wherein the tissue damage resulting from ischemia is ischemic damage and is incurred during organ transplantation.
56. The use of claim 43 wherein the compound is to be administered to prevent perioperative myocardial ischemic injury.
10 of said compound or of said prodrug and a pharmaceutically acceptable carrier.
57. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising
15 a first compound, said first compound being a compound of the formula I as defined in claim 1, or a pharmaceutically acceptable salt of said compound;
a second compound, said second compound being an aldose reductase inhibitor; and
a pharmaceutical carrier, vehicle or diluent.
58. A pharmaceutical composition as recited in claim 57 wherein the aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]- or a pharmaceutically acceptable salt thereof.
20
59. A pharmaceutical composition as claimed in claim 57 wherein Z is as defined under (i) in claim 1.
- 25 60. The use of a pharmaceutical composition as defined in any one of claims 57 to 59 for the manufacture of a medicament for reducing tissue damage resulting from ischemia.
61. A kit comprising:
30 a. a first compound, said first compound being a compound of claim 1, or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;
b. a second compound, said second compound being an aldose reductase inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and
c. means for containing said first and second dosage forms
35
- wherein the amounts of first and second compounds result in a therapeutic effect.
62. A kit as recited in claim 61 wherein the aldose reductase inhibitor is 1-phthalazineacetic acid 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]- or a pharmaceutically acceptable salt thereof.
40
63. A kit as claimed in claim 61 wherein Z is as defined under (i) in claim 1.
64. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising
45 a first compound, said first compound being a compound of claim 1, or a pharmaceutically acceptable salt of said compound;
a second compound, said second compound being a glycogen phosphorylase inhibitor; and
a pharmaceutical carrier, vehicle or diluent.
- 50 65. A pharmaceutical composition as recited in claim 64 wherein the glycogen phosphorylase inhibitor is 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidin-1-yl)-3-oxopropyl]-amide;
5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((3S,4S)-dihydroxypyrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-amide;
5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amide;
55 5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-methoxy-methylcarbamoyl)-methyl)-2-phenyl-ethyl]-amide;
5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((cis)-dihydroxypyrrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-
 amide;
 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-oxo-2-((1RS)-oxo-thiazolidin-3-yl)-ethyl]-amide; or
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide;
 or a pharmaceutically acceptable salt thereof.

66. A pharmaceutical composition as defined in claim 64 wherein Z is of the formula (i) as defined in claim 1.

67. The use of a pharmaceutical composition as defined in any one of claims 64 to 66 for the manufacture of a medication for reducing tissue damage resulting from ischemia.

68. A kit comprising:

- a. a first compound, said first compound being a compound of claim 1, or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;
- b. a second compound, said second compound being an glycogen phosphorylase inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and
- c. means for containing said first and second dosage forms

wherein the amounts of first and second compounds result in a therapeutic effect.

69. A kit as recited in claim 68 wherein the glycogen phosphorylase inhibitor is 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrrolidin-1-yl)-3-oxopropyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid, [(1S)-benzyl -3-((3S,4S)-dihydroxypyrrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-methoxy-methyl-carbamoyl)-methyl)-2-phenyl-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl)-2-phenyl-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((cis)-dihydroxypyrrrolidin-1-yl)-(2R)-hydroxy- 3-oxopropyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)- dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;
 5-chloro-1H-indole-2-carboxylic acid [2-oxo-2-((1RS)-oxo-thiazolidin-3-yl)-ethyl]-amide; or
 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide;
 or a pharmaceutically acceptable salt thereof.

70. A kit as claimed in claim 68 wherein Z is as defined under (i) in claim 1.

71. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

- a first compound, said first compound being a compound of claim 1, or a pharmaceutically acceptable salt of said compound;
- a second compound, said second compound being a cardiovascular agent; and
- a pharmaceutical carrier, vehicle or diluent.

72. A pharmaceutical composition as recited in claim 71 wherein the cardiovascular agent is a β -blocker, a calcium channel blocker, a potassium channel opener, adenosine, adenosine agonists, an ACE inhibitor, a nitrate, a diuretic, a glycoside, a thrombolytic, a platelet inhibitor, aspirin, dipyridamol, potassium chloride, clonidine, prazosin or an adenosine A₃ receptor agonist.

73. A pharmaceutical composition as claimed in claim 71 wherein Z is as defined under (i) in claim 1.

74. The use of a pharmaceutical composition as claimed in any one of claims 71 to 73 for the manufacture of a medicament for reducing tissue damage resulting from ischemia.

75. A kit comprising:

- a. a first compound, said first compound being a compound of claim 1, or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;
- b. a second compound, said second compound being a cardiovascular agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and
- c. means for containing said first and second dosage forms

wherein the amounts of the first and second compounds result in a therapeutic effect.

76. A kit as recited in claim 75 wherein the cardiovascular agent is a β -blocker, a calcium channel blocker, an ACE inhibitor, a nitrate, a diuretic, a glycoside, a thrombolytic, a platelet inhibitor, aspirin, dipyridamol, potassium chloride, clonidine, prazosin or an adenosine A₃ receptor agonist.

77. A kit as claimed in claim 75 wherein Z is as defined under (i) in claim 1.

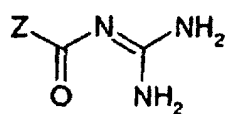
78. A compound, wherein said compound is ethyl 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylate, ethyl 5-methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate, ethyl 5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylate, ethyl 5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate, methyl 5-ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate, *n*-butyl 1-(isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylate, or a pharmaceutically acceptable salt of said compound.

79. A compound selected from the esters of 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylate, 5-methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylate, 5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylate, 5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate, 5-ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylate and 1-(isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylate wherein said esters are benzyl, (C₁-C₆)alkyl or (C₄-C₈)cycloalkyl, said (C₄-C₈)cycloalkyl optionally mono-substituted with (C₁-C₄)alkyl or a pharmaceutically acceptable salt of said compound.

80. A compound selected from 5-methyl-2-(5-quinolinyl)-2H-1,2,3-triazole-4-carboxylic acid, 5-methyl-2-(5-isoquinolinyl)-2H-1,2,3-triazole-4-carboxylic acid, 5-methyl-1-(6-quinolinyl)-1H-pyrazole-4-carboxylic acid, 5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carboxylic acid, 5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxylic acid, 5-ethyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid, 5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carboxylic acid and 1-(isoquinolin-5-yl)-3-methyl-1H-pyrazole-4-carboxylic acid or the acid chlorides thereof or a pharmaceutically acceptable salt of said compounds or of said acid chlorides.

Patentansprüche

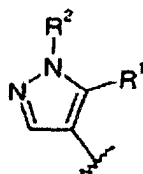
1. Verbindung mit der Formel I :



Formel I

oder ein pharmazeutisch akzeptables Salz dieser Verbindung, wobei entweder Z

(i)



ist,

wobei R¹ (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₃-C₇)Cycloalkyl optional substituiert ist mit ein bis drei Fluoratomen, der R¹ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄) Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und R² (C₁-C₄)Alkyl, (C₃-C₄)Cycloalkyl, M oder M(C₁-C₄)Alkyl ist, wobei irgendeiner der vorigen (C₁-C₄)Alkyl-Reste optional ein bis neun Fluoratome besitzt; wobei (C₁-C₄)Alkyl oder (C₃-C₄)Cycloalkyl optional unabhängig mono- oder di-substituiert ist mit Hydroxy, (C₁-C₄) Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄) Alkylcarbamoyl oder mono-N- oder di-N,N-(C₁-C₄)Alkylaminosulfonyl und (C₃-C₄)Cycloalkyl optional ein bis sieben Fluoratome besitzt,

wobei M ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter fünf- bis achtgliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten dreibis sechsgliedrigen Ringen besteht, die unabhängig genommen optional ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei M optional substituiert ist, an einem Ring, wenn der Rest monocyclisch ist, oder an einem oder beiden Ringen, wenn der Rest bicyclisch ist, am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter dreibis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄) Alkylamino oder (C₃-C₇)Cycloalkyl, R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)

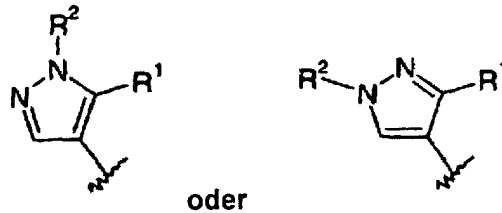
Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl sind oder optional substituiert sind mit ein bis neun Fluoratomen oder
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(ii)

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oder

ist,

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wobei R¹(C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional substituiert ist mit ein bis neun Fluoratomen, der R¹ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und R² ein fünf- bis sechsgliedriger nichtaromatischer heterocyclischer Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, oder R² ein unsubstituiertes (C₁-C₄)Alkyl oder unsubstituiertes (C₃-C₇) Cycloalkyl ist oder R² Phenyl(C₁-C₄)Alkyl oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, wobei die R² Substituenten optional substituiert sind am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter drei- bis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄) Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkynyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

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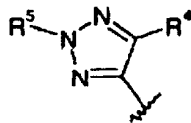
wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄) Alkylamino oder (C₃-C₇)Cycloalkyl, R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄) Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, sind oder optional substituiert sind mit ein bis neun Fluoratomen oder
Z

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(iii)

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ist,

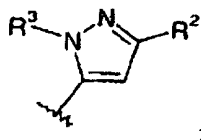
wobei R⁴ (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional sub-

stituiert ist mit ein bis neun Fluoratomen, der R⁴ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und R⁵ ein fünf- bis sechsgliedriger nichtaromatischer heterocyclischer Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, oder R⁵ ein unsubstituiertes (C₁-C₄)Alkyl oder unsubstituiertes (C₃-C₇) Cycloalkyl ist oder R⁵ Phenyl(C₁-C₄)Alkyl oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, wobei die R⁵ Substituenten optional substituiert sind am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter drei- bis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino oder (C₃-C₇)Cycloalkyl, R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen oder

Z

(iv)



ist,

wobei R² (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, M oder M(C₁-C₄)Alkyl ist, irgendeiner der vorstehenden (C₁-C₄) Alkyl-Reste optional ein bis neun Fluoratome besitzt, wobei (C₁-C₄)Alkyl oder (C₃-C₄)Cycloalkyl optional unabhängig mono- oder di-substituiert ist mit Hydroxy, (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl oder mono-N- oder di-N,N-(C₁-C₄)Alkylaminosulfonyl und das (C₃-C₄)Cycloalkyl optional ein bis sieben Fluoratome besitzt,

wobei M ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter fünf- bis achtgliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten dreibis sechsgliedrigen Ringen besteht, die unabhängig genommen optional ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei M optional substituiert ist; an einem Ring, wenn der Rest monocyclisch ist, oder an einem oder beiden Ringen, wenn der Rest bicyclisch ist, am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter dreibis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄) Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxycarbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxycarbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄) Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen und

wobei R³ (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional substituiert ist mit ein bis neun Fluoratomen, der R³ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder (C₁-C₄)Alkyl.

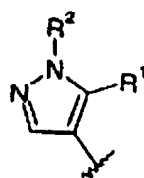
2. Verbindung nach Anspruch 1, wobei die Verbindung

[5-Cyclopropyl-1-(2-trifluormethylphenyl)-1H-pyrazol-4-carbonyl]guanidin,

[5-Cyclopropyl-1-phenyl-1H-pyrazol-4-carbonyl]guanidin oder

[5-Cyclopropyl-1-(2,6-dichlorphenyl)-1H-pyrazol-4-carbonyl]guanidin oder ein pharmazeutisch akzeptables Salz davon ist.

3. Verbindung nach Anspruch 1, wobei Z



ist,

R¹ (C₁-C₄)Alkyl oder (C₃-C₇)Cycloalkyl ist und

R² Chinoliny, Isochinoliny, Cinnoliny, Phthalaziny, Chinoxaliny, Chinazoliny, Benzopyrany, Benzothio-phenyl, Benzodioxany oder Benzodioxoly, wobei der R² Substituent optional mono-substituiert ist.

4. Verbindung nach Anspruch 1, wobei die Verbindung

[5-Methyl-1-(chinolin-6-yl)-1H-pyrazol-4-carbonyl]guanidin,

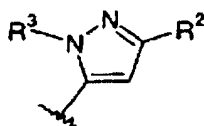
[5-Cyclopropyl-1-(chinolin-5-yl)-1H-pyrazol-4-carbonyl]guanidin oder

[5-Cyclopropyl-1-(chinolin-8-yl)-1H-pyrazol-4-carbonyl]guanidin

oder ein pharmazeutisch akzeptables Salz davon ist.

5. Verbindung nach Anspruch 3, wobei R¹ Cyclopropyl und R² Chinolin-5-yl ist.

6. Verbindung nach Anspruch 1, wobei Z



ist,

R² Phenyl, optional mono- oder di-substituiert und

R³ (C₁-C₄)Alkyl oder (C₃-C₇)Cycloalkyl ist.

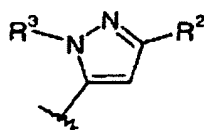
7. Verbindung nach Anspruch 1, wobei die Verbindung

[2-Methyl-5-phenyl-2H-pyrazol-3-carbonyl]guanidin oder,

[2-Methyl-5-(naphthalin-1-yl)-2H-pyrazol-3-carbonyl]guanidin

oder ein pharmazeutisch akzeptables Salz davon ist.

8. Verbindung nach Anspruch 1, wobei Z

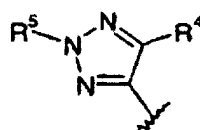


ist,

R² Naphthalinyl, Chinolinyl, Isochinolinyl, Cinnolinyl, Phthalazinyl, Chinoxaliny, Chinazoliny, Benzopyranyl, Benzothiophenyl, Benzodioxanyl oder Benzodioxolyl ist, wobei der R² Substituent optional mono-substituiert ist und

R³ (C₁-C₄)Alkyl oder (C₃-C₇)Cycloalkyl ist.

9. Verbindung nach Anspruch 1, wobei Z



ist,

R⁴ (C₁-C₄)Alkyl oder (C₃-C₇)Cycloalkyl ist und

R⁵ Chinolinyl, Isochinolinyl, Cinnolinyl, Phthalazinyl, Chinoxaliny, Chinazoliny, Benzopyranyl, Benzothiophenyl, Benzodioxanyl oder Benzodioxolyl ist, wobei der R⁵ Substituent optional mono-substituiert ist.

10. Verbindung nach Anspruch 1, wobei die Verbindung

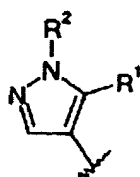
[2-(Isochinolin-5-yl)-5-methyl-2H-1,2,3-triazol-4-carbonyl]guanidin oder,

[5-Methyl-2-(chinolin-5-yl)-2H-1,2,3-triazol-4-carbonyl]guanidin oder ein pharmazeutisch akzeptables Salz davon ist.

11. Verbindung nach Anspruch 1, wobei die Verbindung

[1-(Naphthalin-1-yl)-5-cyclopropyl-1H-pyrazol-4-carbonyl]guanidin oder ein pharmazeutisch akzeptables Salz davon ist.

12. Verbindung nach Anspruch 1, wobei Z



ist,

wobei R¹ (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₃-C₇)Cycloalkyl optional substituiert ist mit ein bis drei Fluoratomen, der R¹ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄) Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und R² (C₁-C₄)Alkyl, (C₃-C₄)Cycloalkyl, M oder M(C₁-C₄)Alkyl ist und irgendeiner der vorstehenden (C₁-C₄)Alkyl-Reste optional ein bis neun Fluoratome besitzt, wobei (C₁-C₄)Alkyl oder (C₃-C₄)Cycloalkyl optional unabhängig mono- oder di-substituiert ist mit Hydroxy, (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, (C₁-C₄)Alkyl, mono-N- oder di-N, N-(C₁-C₄)Alkylcarbamoyl oder mono-N- oder di-N,N-(C₁-C₄)Alkylaminosulfonyl und das (C₃-C₄)Cycloalkyl optional ein bis sieben Fluoratome besitzt,

wobei M ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter fünf- bis achtgliedriger

Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten dreibis sechsgliedrigen Ringen besteht, die unabhängig genommen optional ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei M optional substituiert ist, an einem Ring, wenn der Rest monocyclisch ist, oder an einem oder beiden Ringen, wenn der Rest bicyclisch ist, am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter dreibis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

13. Verbindung nach Anspruch 12, wobei

R¹ (C₃-C₇)Cycloalkyl ist und

R² ein fünf- bis sechsgliedriger monocyclischer aromatischer Ring ist, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind,

dieser R² Ring optional am Kohlenstoff oder Stickstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser R² Ring auch optional am Kohlenstoff oder Stickstoff unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

14. Verbindung nach Anspruch 13, wobei

R¹ Cyclopropyl ist und

R² Phenyl, optional unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylamino Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

15. Verbindung nach Anspruch 1, wobei die Verbindung

[5-Cyclopropyl-1-(2-trifluormethylphenyl)-1H-pyrazol-4-carbonyl]guanidin;

[5-Cyclopropyl-1-phenyl-1H-pyrazol-4-carbonyl]guanidin;

[5-Cyclopropyl-1-(2,6-dichlorphenyl)-1H-pyrazol-4-carbonyl]guanidin oder ein pharmazeutisch akzeptables Salz davon ist.

16. Verbindung nach Anspruch 1, wobei die Verbindung

[1-(2-Chlor-4-methylsulfonylphenyl)-5-cyclopropyl-1*H*-Pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlorphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Trifluormethyl-4-fluorphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Bromphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Fluorphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlor-5-methoxyphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlor-4-methylaminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2,5-Dichlorphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2,3-Dichlorphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlor-5-aminocarbonylphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlor-5-aminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Fluor-6-trifluormethylphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlor-5-methylsulfonylphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin,
 [1-(2-Chlor-5-dimethylaminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin, oder
 [1-(2-Trifluormethyl-4-chlorphenyl)-5-cyclopropyl-1*H*-pyrazol-4-carbonyl]guanidin, oder
 ein pharmazeutisch akzeptables Salz davon ist.

17. Verbindung nach Anspruch 12, wobei

R² ein fünf- bis sechsgliedriger nichtaromatischer heterocyclischer Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, oder R² nicht substituiertes (C₁-C₄)Alkyl, nicht substituiertes (C₃-C₇)Cycloalkyl oder Phenyl(C₁-C₄)Alkyl ist, wobei das Phenyl(C₁-C₄)Alkyl optional unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylamino Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

18. Verbindung nach Anspruch 12, wobei

R² ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, wobei dieser R² Substituent optional substituiert ist am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig ausgewählt sind aus R⁶, R⁷ und R⁸, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter dreibis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

19. Verbindung nach Anspruch 18, wobei

R¹ (C₃-C₇)Cycloalkyl ist und

R² ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis drei Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei dieser bicyclische R² Ring optional am Kohlenstoff oder Stickstoff mono-substituiert ist mit einen voll-

ständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser bicyclische R² Ring auch optional am Kohlenstoff oder Stickstoff unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

20. Verbindung nach Anspruch 19, wobei

R¹ Cyclopropyl ist und

R² ein Chinazoliny, Phthalaziny, Chinoliny, Isochinoliny, Cinnoliny, Benzodioxany, Chinoxaliny, Benzopyrany, Benzothiophenyl, Benzodioxoly, Benzimidazolyl, Indazolyl, Indolyl, Benzotriazolyl, Benzoxazolyl, Benzisoxazolyl, Benzothiazolyl, Benzisothiazolyl, Benzoxadiazolyl oder Benzothiadiazolyl Ring ist,

wobei der bicyclische R² Ring optional unabhängig am Kohlenstoff oder Stickstoff mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylamino Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

21. Verbindung nach Anspruch 20, wobei

R² ein Chinoliny, Isochinoliny, Indazolyl, Benzimidazolyl Ring ist,

wobei der bicyclische R² Ring optional unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy oder (C₁-C₄)Alkyl Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

22. Verbindung nach Anspruch 1, wobei die Verbindung

[5-Cyclopropyl-1-(chinolin-5-yl)-1H-pyrazol-4-carbonyl]guanidin oder ein pharmazeutisch akzeptables Salz davon ist.

23. Verbindung nach Anspruch 1, wobei die Verbindung

[1-(8-Bromchinolin-5-yl)-5-cyclopropyl-1H-Pyrazol-4-carbonyl]guanidin,

[1-(6-Chlorchinolin-5-yl)-5-cyclopropyl-1H-pyrazol-4-carbonyl]guanidin,

[1-(Indazol-7-yl)-5-cyclopropyl-1H-pyrazol-4-carbonyl]guanidin,

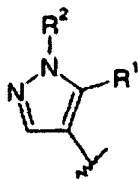
[1-(Benzimidazol-5-yl)-5-cyclopropyl-1H-pyrazol-4-carbonyl]guanidin,

[1-(1-Isochinolyl)-5-cyclopropyl-1H-pyrazol-4-carbonyl]guanidin, oder

[1-(5-Cyclopropyl-1-(4-chinoliny)-1H-pyrazol-4-carbonyl]guanidin,

oder ein pharmazeutisch akzeptables Salz davon ist.

24. Verbindung nach Anspruch 1, wobei Z



5

10 ist,

wobei R¹ (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional substituiert ist mit ein bis neun Fluoratomen, der R¹ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und

15 R² ein fünf- bis sechsgliedriger nichtaromatischer heterocyclischer Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, oder R² nicht substituiertes (C₁-C₄)Alkyl oder nicht substituiertes (C₃-C₇)Cycloalkyl oder R² Phenyl(C₁-C₄)Alkyl oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, wobei diese R² Substituenten optional substituiert sind am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig ausgewählt sind aus R⁶, R⁷ und R⁸, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter dreibis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

25 wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

35

25. Verbindung nach Anspruch 24, wobei

R¹ (C₁-C₄)Alkyl ist und

R² ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis drei Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

40

wobei dieser bicyclische R² Ring optional am Kohlenstoff oder Stickstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

45

dieser bicyclische R² Ring auch optional am Kohlenstoff oder Stickstoff unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

50

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

55

26. Verbindung nach Anspruch 25, wobei

R² ein Chinazoliny, Phthalaziny, Chinoliny, Isochinoliny, Cinnoliny, Benzodioxany, Chinoxaliny, Benzopyrany, Benzothiopheny, Benzodioxoly, Benzimidazol, Indazol, Indoly, Benzotriazol, Benzoxazol, Benzisoxazol, Benzothiazol, Benzisothiazol, Benzoxadiazol oder Benzothiadiazol Ring ist,

wobei der bicyclische R² Ring optional unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄) Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylamino Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

27. Verbindung nach Anspruch 1, wobei die Verbindung

[1-(Indazol-6-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(Indazol-5-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(Benzimidazol-5-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(1-Methylbenzimidazol-6-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(5-Chinoliny)-5-*n*-propyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(5-Chinoliny)-5-isopropyl-1*H*-pyrazol-4-carbonyl]guanidin,

[5-Ethyl-1-(6-chinoliny)-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(2-Methylbenzimidazol-5-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(1,4-Benzodioxan-6-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(Benzotriazol-5-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

[1-(3-Chlorindazol-5-yl)-5-ethyl-1*H*-pyrazol-4-carbonyl]guanidin,

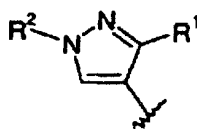
[1-(5-Chinoliny)-5-butyl-1*H*-pyrazol-4-carbonyl]guanidin,

[5-Propyl-1-(6-chinoliny)-1*H*-pyrazol-4-carbonyl]guanidin, oder

[5-Isopropyl-1-(6-chinoliny)-1*H*-pyrazol-4-carbonyl]guanidin,

oder ein pharmazeutisch akzeptables Salz davon ist.

28. Verbindung nach Anspruch 1, wobei Z



ist,

wobei R¹ (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional substituiert ist mit ein bis neun Fluoratomen, der R¹ Substituent optional unabhängig mono - oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und

R² ein fünf- bis sechsgliedriger nichtaromatischer heterocyclischer Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, oder R² nicht substituiertes (C₁-C₄)Alkyl, nichts substituiertes (C₃-C₇)Cycloalkyl ist oder R² Phenyl(C₁-C₄)Alkyl oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, wobei diese R² Substituenten optional substituiert sind am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter drei- bis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)

Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxycarbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxycarbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

29. Verbindung nach Anspruch 28, wobei

R¹ (C₁-C₄)Alkyl ist und

R² ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis drei Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei dieser bicyclische R² Ring optional am Kohlenstoff oder Stickstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser bicyclische R² Ring auch optional unabhängig am Kohlenstoff oder Stickstoff mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxycarbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxycarbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxycarbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxycarbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

30. Verbindung nach Anspruch 29, wobei

R² ein Chinazoliny, Phthalaziny, Chinoliny, Isochinoliny, Cinnoliny, Benzodioxany, Chinoxaliny, Benzopyrany, Benzothiopheny, Benzodioxoly, Benzimidazolyl, Indazolyl, Indolyl, Benzotriazolyl, Benzoxazolyl, Benzisoxazolyl, Benzothiazolyl, Benzisothiazolyl, Benzoxadiazolyl oder Benzothiadiazolyl Ring ist,

wobei der bicyclische R² Ring optional unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxycarbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxycarbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylamino Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

31. Verbindung nach Anspruch 1, wobei die Verbindung

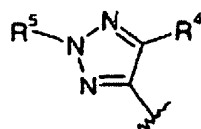
[1-(Indazol-7-yl)-3-methyl-1H-pyrazol-4-carbonyl]guanidin,

[1-(2,1,3-Benzothiadiazol-4-yl)-3-methyl-1H-pyrazol-4-carbonyl]guanidin, oder

[3-Methyl-1-(chinolin-5-yl)-1H-pyrazol-4-carbonyl]guanidin,

oder ein pharmazeutisch akzeptables Salz davon ist.

32. Verbindung nach Anspruch 1, wobei Z



ist,

wobei R⁴ (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional substituiert ist mit ein bis neun Fluoratomen, der R⁴ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl oder (C₁-C₄)Alkylsulfonyl, und

R⁵ ein fünf- bis sechsgliedriger nichtaromatischer heterocyclischer Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, oder R⁵ nicht substituiertes (C₁-C₄)Alkyl oder nicht substituiertes (C₃-C₇)Cycloalkyl ist oder R⁵ Phenyl(C₁-C₄)Alkyl oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind, wobei diese R⁵ Substituenten optional substituiert sind am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter drei- bis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

33. Verbindung nach Anspruch 32, wobei

R⁴ (C₁-C₄)Alkyl ist und

R⁵ ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis drei Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei dieser bicyclische R⁵ Ring optional am Kohlenstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser bicyclische R⁵ Ring auch optional am Kohlenstoff oder Stickstoff unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

34. Verbindung nach Anspruch 33, wobei

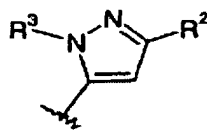
R⁵ ein Chinazoliny, Phthalaziny, Chinoliny, Isochinoliny, Cinnoliny, Benzodioxany, Chinoxaliny, Benzopyrany, Benzothiopheny, Benzodioxoly, Benzimidazolyl, Indazolyl, Indolyl, Benzotriazolyl, Benzoxazolyl, Benzisoxazolyl, Benzothiazolyl, Benzisothiazolyl, Benzoxadiazolyl oder Benzothiadiazolyl Ring ist,

wobei der bicyclische R⁵ Ring optional unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylamino Substituenten optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-

N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis fünf Fluoratomen.

35. Verbindung nach Anspruch 1, wobei Z



ist,

wobei R² (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, M oder M(C₁-C₄)Alkyl ist, irgendeiner der vorstehenden (C₁-C₄) Alkyl-Reste optional ein bis neun Fluoratome besitzt, wobei (C₁-C₄)Alkyl oder (C₃-C₄)Cycloalkyl optional unabhängig mono- oder di-substituiert ist mit Hydroxy, (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄) Alkylsulfonyl, (C₁-C₄)Alkyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl oder mono-N- oder di-N,N-(C₁-C₄)Alkylaminosulfonyl und das (C₃-C₄)Cycloalkyl optional ein bis sieben Fluoratome besitzt,

wobei M ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter fünf- bis achtgliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, oder ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten dreibis sechsgliedrigen Ringen besteht, die unabhängig genommen optional ein bis vier Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei M optional substituiert ist, an einem Ring, wenn der Rest monocyclisch ist, oder an einem oder beiden Ringen, wenn der Rest bicyclisch ist, am Kohlenstoff oder Stickstoff mit bis zu drei Substituenten, die unabhängig aus R⁶, R⁷ und R⁸ ausgewählt sind, wobei einer von R⁶, R⁷ und R⁸ optional ein teilweise gesättigter, vollständig gesättigter oder vollständig ungesättigter dreibis siebengliedriger Ring ist, der optional ein bis drei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, die optional substituiert sind mit (C₁-C₄)Alkyl und zusätzlich R⁶, R⁷ und R⁸ optional Hydroxy, Nitro, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, Formyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl, mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl, (C₂-C₄)Alkenyl, (C₂-C₄)Alkynyl oder (C₅-C₇)Cycloalkenyl sind,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄) Alkylamino oder (C₃-C₇)Cycloalkyl R⁶, R⁷ und R⁸ Substituenten optional unabhängig mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₃-C₇)Cycloalkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, Thiol, Nitro, (C₁-C₄)Alkylthio, (C₁-C₄) Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen und

wobei R³ (C₁-C₄)Alkyl, (C₃-C₇)Cycloalkyl, Phenyl oder Phenyl(C₁-C₄)Alkyl ist, das (C₁-C₄)Alkyl optional substituiert ist mit ein bis neun Fluoratomen, dieser R³ Substituent optional unabhängig mono- oder di-substituiert ist mit (C₁-C₄)Alkoxy, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder (C₁-C₄)Alkyl.

36. Verbindung nach Anspruch 35, wobei

R³ (C₁-C₄)Alkyl ist und

R² Phenyl ist, das optional am Kohlenstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

wobei dieser R² Ring auch optional am Kohlenstoff unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N, N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄) Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄) Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio,

(C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

37. Verbindung nach Anspruch 35, wobei

R³ (C₁-C₄)Alkyl ist und

R² ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen werden, wobei dieser bicyclische R² Ring optional am Kohlenstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser bicyclische R² Ring auch optional am Kohlenstoff unabhängig mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N, N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

38. Verbindung nach Anspruch 35, wobei

R³ (C₁-C₄)Alkyl ist und

R² ein monocyclischer aromatischer fünf- bis sechsgliedriger Ring ist, der ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind,

wobei dieser R² Ring optional am Kohlenstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser R² Ring auch optional unabhängig am Kohlenstoff oder Stickstoff mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N, N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

39. Verbindung nach Anspruch 35, wobei

R³ (C₁-C₄)Alkyl ist und

R² ein bicyclischer Ring ist, der aus zwei kondensierten, teilweise gesättigten, vollständig gesättigten oder vollständig ungesättigten fünf- und/oder sechsgliedrigen Ringen besteht, die unabhängig genommen ein bis drei Heteroatome besitzen, die unabhängig aus Stickstoff, Schwefel und Sauerstoff ausgewählt sind,

wobei dieser bicyclische R² Ring optional am Kohlenstoff oder Stickstoff mono-substituiert ist mit einem vollständig gesättigten oder vollständig ungesättigten fünf- bis sechsgliedrigen Ring, der optional ein bis zwei Heteroatome besitzt, die unabhängig aus Sauerstoff, Schwefel und Stickstoff ausgewählt sind, wobei dieser Ring optional mono-substituiert ist mit (C₁-C₄)Alkyl,

dieser bicyclische R² Ring auch optional unabhängig am Kohlenstoff oder Stickstoff mono- oder di-substituiert ist mit Hydroxy, Halo, (C₁-C₄)Alkoxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkanoylamino, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, Zyano, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfanyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl,

wobei diese (C₁-C₄)Alkoxy, (C₁-C₄)Alkyl, (C₁-C₇)Alkanoyl, (C₁-C₄)Alkylthio, mono-N- oder di-N,N-(C₁-C₄)

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Alkylamino optional mono-substituiert sind mit Hydroxy, (C₁-C₄)Alkoxy-carbonyl, (C₁-C₄)Alkanoyl, (C₁-C₄)Alkanoyl-amino, (C₁-C₄)Alkanoyloxy, (C₁-C₄)Alkoxy-carbonylamino, Sulfonamido, (C₁-C₄)Alkylsulfonamido, Amino, mono-N- oder di-N,N-(C₁-C₄)Alkylamino, Carbamoyl, mono-N- oder di-N,N-(C₁-C₄)Alkylcarbamoyl, (C₁-C₄)Alkylthio, (C₁-C₄)Alkylsulfinyl, (C₁-C₄)Alkylsulfonyl oder mono-N oder di-N,N-(C₁-C₄)Alkylaminosulfonyl oder optional substituiert sind mit ein bis neun Fluoratomen.

- 5
40. Eine pharmazeutische Zusammensetzung, die eine Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz dieser Verbindung, wie in irgendeinem der Ansprüche von 1 bis 39 geltend gemacht, und einen pharmazeutisch akzeptablem Träger umfasst.
- 10
41. Eine Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz dieser Verbindung, wie in irgendeinem der Ansprüche von 1 bis 39 geltend gemacht, zur Verwendung als Medikament.
- 15
42. Verwendung einer Verbindung der Formel I oder eines pharmazeutisch akzeptablen Salzes dieser Verbindung, wie in irgendeinem der Ansprüche von 1 bis 39 geltend gemacht, zur Herstellung eines Medikamentes zur Verhinderung einer ischämischen Myokardschädigung.
- 20
43. Verwendung einer Verbindung der Formel I oder eines pharmazeutisch akzeptablen Salzes dieser Verbindung, wie in irgendeinem der Ansprüche von 1 bis 39 geltend gemacht, zur Herstellung eines Medikamentes zur Reduzierung einer durch Ischämie verursachten Gewebeschädigung.
- 25
44. Verwendung nach Anspruch 43, wobei das Gewebe Herz-, Hirn-, Leber-, Nieren-, Lungen-, Bauch-, Skelettmuskel-, Milz-, Bauchspeicheldrüsen-, Nerven-, Rückenmarks-, Netzhautgewebe, das Gefäßsystem oder Darmgewebe ist.
- 30
45. Verwendung nach Anspruch 44, wobei die Menge der Verbindung der Formel I etwa 0,01 mg/kg/Tag bis etwa 50 mg/kg/Tag beträgt.
- 35
46. Verwendung nach Anspruch 43, wobei die Verbindung prophylaktisch zu verabreichen ist.
47. Verwendung nach Anspruch 43, wobei die Verbindung vor einer Operation zu verabreichen ist.
48. Verwendung nach Anspruch 43, wobei die Verbindung vor einer Herzoperation zu verabreichen ist.
- 40
49. Verwendung nach Anspruch 43, wobei die Verbindung während einer Operation zu verabreichen ist.
- 50
50. Verwendung nach Anspruch 43, wobei die Verbindung während einer Herzoperation zu verabreichen ist.
51. Verwendung nach Anspruch 43, wobei die Verbindung innerhalb von vierundzwanzig Stunden nach einer Operation zu verabreichen ist.
- 45
52. Verwendung nach Anspruch 43, wobei die Verbindung innerhalb von vierundzwanzig Stunden nach einer Herzoperation zu verabreichen ist.
53. Verwendung nach Anspruch 43, wobei die Verbindung vor, während und nach einer Operation zu verabreichen ist.
54. Verwendung nach Anspruch 43, wobei die Verbindung vor, während und nach einer Herzoperation zu verabreichen ist.
- 50
55. Verwendung nach Anspruch 43, wobei die durch Ischämie verursachte Gewebeschädigung eine ischämische Schädigung ist und während einer Organtransplantation aufgetreten ist.
- 55
56. Verwendung nach Anspruch 43, wobei die Verbindung zu verabreichen ist, um eine perioperativ auftretende ischämische Myokardschädigung zu verhindern.
57. Pharmazeutische Kombinationszusammensetzung, umfassend eine therapeutisch wirksame Menge einer Zusammensetzung, die umfasst
eine erste Verbindung, wobei diese erste Verbindung eine Verbindung der in Anspruch 1 definierten Formel

I ist, oder ein pharmazeutisch akzeptables Salz dieser Verbindung,
eine zweite Verbindung, die ein Aldosereduktaseinhibitor ist, und
einen pharmazeutischen Träger, Vehikel oder Verdünner.

5 **58.** Pharmazeutische Zusammensetzung nach Anspruch 57, wobei der Aldosereduktaseinhibitor 1-Phthalazinessigsäure, 3,4-Dihydro-4-Oxo-3-[[5-Trifluormethyl]-2-Benzothiazolyl]Methyl]- oder ein pharmazeutisch akzeptables Salz davon ist.

10 **59.** Pharmazeutische Zusammensetzung nach Anspruch 57, wobei Z wie unter (i) in Anspruch 1 definiert ist.

60. Verwendung einer pharmazeutischen Zusammensetzung nach irgendeinem der Ansprüche 57 bis 59 zur Herstellung eines Medikamentes zur Reduzierung einer durch Ischämie verursachten Gewebeschädigung.

15 **61.** Ein Satz (kit), der umfasst

a. eine erste Verbindung, wobei diese erste Verbindung eine Verbindung nach Anspruch 1 ist, oder ein pharmazeutisch akzeptables Salz dieser Verbindung und einen pharmazeutisch akzeptablen Träger, Vehikel oder Verdünner in einer ersten Darreichungsform,

20 b. eine zweite Verbindung, wobei diese zweite Verbindung ein Aldosereduktaseinhibitor ist, und einen pharmazeutisch akzeptablen Träger, Vehikel oder Verdünner in einer zweiten Darreichungsform und

c. Mittel zur Aufnahme der ersten und zweiten Darreichungsform,

wobei die Mengen der ersten und zweiten Verbindung therapeutisch wirksam sind.

25 **62.** Satz (kit) nach Anspruch 61, wobei der Aldosereduktaseinhibitor 1-Phthalazinessigsäure, 3,4-Dihydro-4-Oxo-3-[[5-Trifluormethyl]-2-Benzothiazolyl]Methyl]- oder ein pharmazeutisch akzeptables Salz davon ist.

30 **63.** Satz (kit) nach Anspruch 61, wobei Z wie unter (i) in Anspruch 1 definiert ist.

64. Pharmazeutische Kombinationszusammensetzung, umfassend eine therapeutisch wirksame Menge einer Zusammensetzung die umfasst

eine erste Verbindung, wobei diese erste Verbindung eine Verbindung nach Anspruch 1 ist, oder ein pharmazeutisch akzeptables Salz dieser Verbindung,

35 eine zweite Verbindung, die ein Glykogenphosphorylaseinhibitor ist, und einen pharmazeutischen Träger, Vehikel oder Verdünner.

65. Pharmazeutische Zusammensetzung nach Anspruch 64, wobei der Glykogenphosphorylaseinhibitor:

40 5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidin-1-yl)-3-oxopropyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-3-((3S,4S)-dihydroxypyrrolidin-1-yl)- (2R)-hydroxy-3-oxopropyl]-Amid,

45 5-Chlor-1H-indol-2-carbonsäure [(1S)-((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-((R)-hydroxy-methoxy-methylcarbamoyl)-methyl)-2-phenyl-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-((R)-hydroxy-[(2-hydroxy-ethyl)-methylcarbamoyl]-methyl)-2-phenyl-ethyl]-amid,

50 5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-3-((cis-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl)-amid,

5-Chlor-1H-indol-2-carbonsäure [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)- 2-oxoethyl]-amid,

55 5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-(4-fluor-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [2-oxo-2-((1RS)-oxo-thiazolidin-3-yl)-ethyl]-amid oder

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxoethyl]-amid

oder ein pharmazeutisch akzeptables Salz davon ist.

5 **66.** Pharmazeutische Zusammensetzung nach Anspruch 64, wobei Z die unter (i) in Anspruch 1 definierte Formel hat.

67. Verwendung einer pharmazeutischen Zusammensetzung nach irgendeinem der Ansprüche 64 bis 66 zur Herstellung eines Medikamentes zur Reduzierung einer durch Ischämie verursachten Gewebeschädigung.

10 **68.** Satz (kit), der umfasst

a. eine erste Verbindung, wobei diese erste Verbindung eine Verbindung nach Anspruch 1 ist, oder ein pharmazeutisch akzeptables Salz dieser Verbindung und einen pharmazeutisch akzeptablen Träger, Vehikel oder Verdünner in einer ersten Darreichungsform,

15 b. eine zweite Verbindung, wobei diese zweite Verbindung ein Glykogenphosphorylaseinhibitor ist, und einen pharmazeutisch akzeptablen Träger, Vehikel oder Verdünner in einer zweiten Darreichungsform, und

c. Mittel zur Aufnahme der ersten und zweiten Darreichungsform,

wobei die Mengen der ersten und zweiten Verbindung therapeutisch wirksam sind.

20

69. Satz (kit) nach Anspruch 68, wobei der Glykogenphosphorylaseinhibitor:

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidin-1-yl)-3-oxopropyl]-amid,

25 5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-3-((3S,4S)-dihydroxypyrrolidin-1-yl)- (2R)-hydroxy-3-oxopropyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-((R)-hydroxy-methoxy-methylcarbamoyl)-methyl)-2-phenyl-ethyl]-amid,

30 5-Chlor-1H-indol-2-carbonsäure [(1S)-((R)-hydroxy-[(2-hydroxy-ethyl)-methylcarbamoyl]-methyl)-2-phenyl-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-3-((cis-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl)-amid,

35

5-Chlor-1H-indol-2-carbonsäure [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [(1S)-(4-fluor-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amid,

40

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amid,

5-Chlor-1H-indol-2-carbonsäure [2-oxo-2-((1RS)-oxo-thiazolidin-3-yl)-ethyl]-amid oder

5-Chlor-1H-indol-2-carbonsäure [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxoethyl]-amid

oder ein pharmazeutisch akzeptables Salz davon ist.

45

70. Satz (kit) nach Anspruch 68, wobei Z wie unter (i) in Anspruch 1 definiert ist.

71. Pharmazeutische Kombinationszusammensetzung, umfassend eine therapeutisch wirksame Menge einer Zusammensetzung, die umfasst

50 eine erste Verbindung, wobei diese erste Verbindung eine Verbindung nach Anspruch 1 ist, oder ein pharmazeutisch akzeptables Salz dieser Verbindung,

eine zweite Verbindung, die ein kardiovaskulärer Wirkstoff ist, und

einen pharmazeutischen Träger, Vehikel oder Verdünner.

55 **72.** Pharmazeutische Zusammensetzung nach Anspruch 71, wobei der kardiovaskuläre Wirkstoff ein β -Blocker, ein Calciumkanalblocker, ein Kaliumkanalöffner, Adenosin, Adenosinagonisten, ein ACE-Inhibitor, Nitrat, Diuretikum, Glykosid, ein Thrombolytikum, ein Thrombozytenaggregationsinhibitor (platelet inhibitor), Aspirin, Dipyridamol, Kaliumchlorid, Clonidin, Prazosin oder ein Adenosin A₃ Rezeptoragonist ist.

73. Pharmazeutische Zusammensetzung nach Anspruch 71, wobei Z wie unter (i) in Anspruch 1 definiert ist.

74. Verwendung einer pharmazeutischen Zusammensetzung nach irgendeinem der Ansprüche 71 bis 73 zur Herstellung eines Medikamentes zur Reduzierung einer durch Ischämie verursachten Gewebeschädigung.

75. Satz (kit), der umfasst

- a. eine erste Verbindung, wobei diese erste Verbindung eine Verbindung nach Anspruch 1 ist, oder ein pharmazeutisch akzeptables Salz dieser Verbindung und einen pharmazeutisch akzeptablen Träger, Vehikel oder Verdünner in einer ersten Darreichungsform,
- b. eine zweite Verbindung, wobei diese zweite Verbindung ein kardiovaskulärer Wirkstoff ist, und einen pharmazeutisch akzeptablen Träger, Vehikel oder Verdünner in einer zweiten Darreichungsform,
- c. Mittel zur Aufnahme der ersten und zweiten Darreichungsform,

wobei die Mengen der ersten und zweiten Verbindung therapeutisch wirksam sind.

76. Satz (kit) nach Anspruch 75, wobei der kardiovaskuläre Wirkstoff ein β -Blocker, ein Calciumkanalblocker, ACE-Inhibitor, Nitrat, Diuretikum, Glykosid, Thrombolytikum, Thrombozytenaggregationsinhibitor, Aspirin, Dipyridamol, Kaliumchlorid, Clonidin, Prazosin oder ein Adenosin A₃ Rezeptoragonist ist.

77. Satz (kit) nach Anspruch 75, wobei Z wie unter (i) in Anspruch 1 definiert ist.

78. Verbindung, die:

- Ethyl 5-cyclopropyl-1-(2-trifluormethylphenyl)-1H-pyrazol-4-carboxylate,
- Ethyl 5-methyl-1-(6-chinolinyl)-1H-pyrazol-4-carboxylate,
- Ethyl 5-cyclopropyl-1-(chinolin-8-yl)-1H-pyrazol-4-carboxylate,
- Ethyl 5-cyclopropyl-1-(chinolin-5-yl)-1H-pyrazol-4-carboxylate,
- Methyl 5-ethyl-1-(chinolin-5-yl)-1H-pyrazol-4-carboxylate,
- n-Butyl 1-(isochinolin-5-yl)-3-methyl-1H-pyrazol-4-carboxylate,

oder ein pharmazeutisch akzeptables Salz davon ist.

79. Verbindung, die aus folgenden Estern ausgewählt ist:

- 5-Cyclopropyl-1-(2-trifluormethylphenyl)-1H-pyrazol-4-carboxylate,
- 5-Methyl-1-(6-chinolinyl)-1H-pyrazol-4-carboxylate,
- 5-Cyclopropyl-1-(chinolin-8-yl)-1H-pyrazol-4-carboxylate,
- 5-Cyclopropyl-1-(chinolin-5-yl)-1H-pyrazol-4-carboxylate,
- 5-Ethyl-1-(chinolin-5-yl)-1H-pyrazol-4-carboxylate, und
- 1-(Isochinolin-5-yl)-3-methyl-1H-pyrazol-4-carboxylate,

wobei diese Ester Benzyl, (C₁-C₆)Alkyl oder (C₄-C₈)Cycloalkyl sind, das (C₄-C₈)Cycloalkyl optional mono-substituiert ist mit (C₁-C₄)Alkyl,

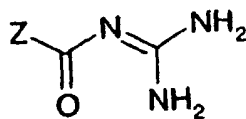
oder ein pharmazeutisch akzeptables Salz davon.

80. Verbindung, die aus Folgendem ausgewählt ist:

- 5-Methyl-2-(5-chinolinyl)-2H-1,2,3-triazol-4-carbonsäure,
- 5-Methyl-2-(5-isochinolinyl)-2H-1,2,3-triazol-4-carbonsäure,
- 5-Methyl-1-(6-chinolinyl)-1H-pyrazol-4-carbonsäure,
- 5-Cyclopropyl-1-(chinolin-8-yl)-1H-pyrazol-4-carbonsäure,
- 5-Cyclopropyl-1-(2-trifluormethylphenyl)-1H-pyrazol-4-carbonsäure,
- 5-Ethyl-1-(chinolin-5-yl)-1H-pyrazol-4-carbonsäure,
- 5-Cyclopropyl-1-(chinolin-5-yl)-1H-pyrazol-4-carbonsäure, und
- 1-(Isochinolin-5-yl)-3-methyl-1H-pyrazol-4-carbonsäure oder deren Säurechloriden oder aus einem pharmazeutisch akzeptablen Salz dieser Verbindungen oder dieser Säurechloride.

Revendications

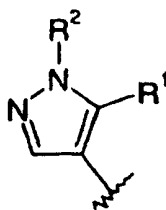
1. Composé répondant à la formule I



Formule I

ou un sel pharmaceutiquement acceptable dudit composé, formule dans laquelle soit Z représente un groupe

(i)



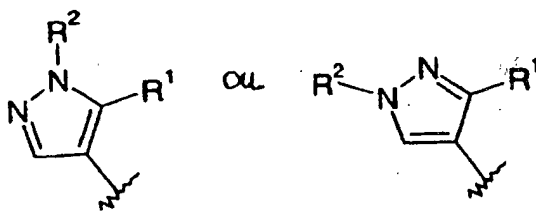
dans lequel R¹ représente un groupe cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe cycloalkyle en C₃ à C₇ étant facultativement substitué avec un à trois atomes de fluor, ledit substituant R¹ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄ ou alkylsulfonyle en C₁ à C₄; et R² représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ ou C₄, M ou M(alkyle en C₁ à C₄), n'importe lequel desdits groupements alkyle en C₁ à C₄ précédents ayant facultativement un à neuf atomes de fluor; ledit groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ ou C₄ étant facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, alkyle en C₁ à C₄, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbonyle ou mono-N- ou di-N, N-(alkyle en C₁ à C₄)aminosulfonyle; et ledit groupe cycloalkyle en C₃ ou C₄ ayant facultativement un à sept atomes de fluor;

dans lequel m représente un noyau penta- à octogonal partiellement saturé, totalement saturé ou totalement insaturé ayant un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ou un noyau bicyclique consistant en deux noyaux tri- à hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant facultativement un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène,

ledit groupe M est facultativement substitué, sur un noyau si le groupement est monocyclique, ou sur l'un ou les deux noyaux si le groupement est bicyclique, sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre des substituants R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, facultativement substitué avec un substituant alkyle en C₁ à C₄ et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, formyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N, N-(alkyle en C₁ à C₄)amino, carbamoyloxy, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbamoyloxy, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N, N-(alkyle en C₁ à C₄)aminosulfonyle, alcényloxy en C₂ à C₄, alcényloxy en C₂ à C₄ ou cycloalcényloxy en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyloxy, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbamoyloxy, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor ; soit
Z représente un groupe

(ii)

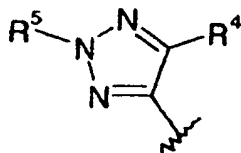


dans lequel R¹ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R¹ étant facultativement substitué mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄ ou alkylsulfonyloxy en C₁ à C₄ ; et

R² représente un noyau hétérocyclique non aromatique penta- ou hexagonal ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ou bien R² représente un groupe alkyle en C₁ à C₄ non substitué ou cycloalkyle en C₃ à C₇ non substitué ; ou bien R² représente un groupe phényl (alkyle en C₁ à C₄), ou un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, lesdits substituants R² étant facultativement substitués sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre des substituants R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé comprenant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitué avec un substituant alkyle en C₁ à C₄, et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à C₄, formyle, alcanoyloxy en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyloxy, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbamoyloxy, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy, alcényloxy en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloalcényloxy en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyloxy, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbamoyloxy, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor, soit
Z représente un groupe

(iii)

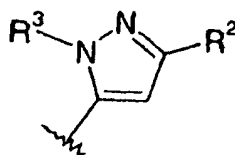


dans lequel R⁴ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R⁴ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄ ou alkylsulfonyle en C₁ à C₄; et

R¹ représente un noyau hétérocyclique penta- ou hexagonal non aromatique ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène ou bien R⁵ représente un groupe alkyle en C₁ à C₄ non substitué ou cycloalkyle en C₃ à C₇ non substitué; ou bien R⁵ représente un groupe phényle, (alkyle en C₁ à C₄), ou un noyau bicyclique consistant en des noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ledit substituant R⁵ étant facultativement substitué sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre des substituants R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitué avec un substituant alkyle en C₁ à C₄ et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à C₄, formyle, alcanoyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄) carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle, alcényle en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloalcényle en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyle en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄) carbonyle, cycloalkyle en C₃ à C₇, alcanoyle en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor; soit

(iv)



dans lequel R² représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, M ou M(alkyle en C₁ à C₄),

n'importe lequel desdits groupements alkyle en C₁ à C₄ précédents ayant facultativement un à neuf atomes de fluor ; ledit groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ ou C₄ étant facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄, alkyle en C₁ à C₄, mono-N ou di-N,N-(alkyle en C₁ à C₄)carbamoyne ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne ; et ledit groupe cycloalkyle en C₃ ou C₄ ayant facultativement un à sept atomes de fluor ;

dans lequel M représente un noyau penta- à octogonal partiellement saturé, totalement saturé ou totalement insaturé, ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ou un noyau bicyclique consistant en deux noyaux tri- à hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant facultativement un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène ;

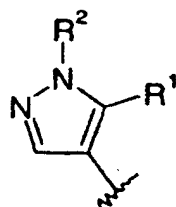
ledit groupe M étant facultativement substitué, sur un noyau si le groupement est monocyclique, ou sur l'un ou les deux noyaux si le groupement est bicyclique, sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé, ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitués avec un substituant alkyle en C₁ à C₄ et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyne, alkyle en C₁ à C₄, formyle, alcanoyne en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyne, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyne, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne, alcényne en C₂ à C₄, alcynoyne en C₂ à C₄ ou cycloalcényne en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyne en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyne, cycloalkyle en C₃ à C₇, alcanoyne en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyne, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyne, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne ou étant facultativement substitués avec un à neuf atomes de fluor ;

R³ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R³ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄ ou alkyle en C₁ à C₄.

2. Composé suivant la revendication 1, ledit composé étant
 la [5-cyclopropyl-1-(2-trifluorométhylphényl)-1H-pyrazole-4-carbonyl]guanidine ;
 la [5-cyclopropyl-1-phényl-1H-pyrazole-4-carbonyl] guanidine ; ou
 la [5-cyclopropyl-1-(2,6-dichlorophényl)-1H-pyrazole-4-carbonyl]guanidine ;
 ou un de ses sels pharmaceutiquement acceptables.

3. Composé suivant la revendication 1, dans lequel Z représente un groupe

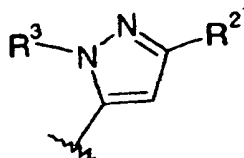


R¹ représente un groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ à C₇ ;
 R² représente un groupe quinoléinyle, isoquinoléinyle, cinnolinyle, phtalazinyle, quinoxalinyle, quinazolinyle, benzopyrannyle, benzothiophényle, benzodioxannyle ou benzodioxolyle, ledit substituant R² étant facultativement monosubstitué.

4. Composé suivant la revendication 1, ledit composé étant
la [5-méthyl-1-(quinoléine-6-yl)-1H-pyrazole-4-carbonyl]guanidine ;
la [5-cyclopropyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carbonyl]-guanidine ; ou
la [5-cyclopropyl-1-(quinoléine-8-yl)-1H-pyrazole-4-carbonyl]-guanidine ;
ou un de ses sels pharmaceutiquement acceptables.

5. Composé suivant la revendication 3, dans lequel R¹ représente un groupe cyclopropyle et R² représente un groupe quinoléine-5-yle.

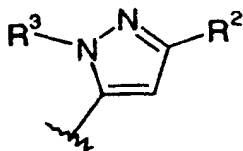
6. Composé suivant la revendication 1, dans lequel Z représente un groupe



R² représente un groupe phényle, facultativement mono- ou disubstitué ; et
R³ représente un groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ à C₇.

7. Composé suivant la revendication 1, ledit composé étant
la [2-méthyl-5-phényl-2H-pyrazole-3-carbonyl]guanidine ; ou
la [2-méthyl-5-(naphthalène-1-yl)-2H-pyrazole-3-carbonyl]-guanidine ;
ou un de ses sels pharmaceutiquement acceptables.

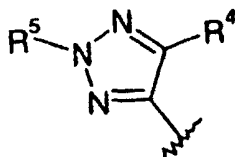
8. Composé suivant la revendication 1, dans lequel Z représente un groupe



R² représente un groupe naphthalényle, quinoléinyle, isoquinoléinyle, cinnolinyle, phtalazinyle, quinoxalinyle, quinazolinyle, benzopyrannyle, benzothiophényle, benzodioxannyle ou benzodioxolyle, ledit substituant R² étant facultativement monosubstitué ; et

R³ représente un groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ à C₇.

9. Composé suivant la revendication 1, dans lequel Z représente un groupe



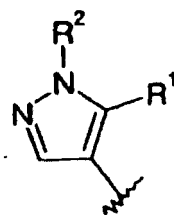
R⁴ représente un groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ à C₇ ;

R⁵ représente un groupe quinoléinyle, isoquinoléinyle, cinnolinyle, phtalazinyle, quinoxalinyle, quinazolinyle, benzopyrannyle, benzothiophényle, benzodioxannyle ou benzodioxolyle, ledit substituant R⁵ étant facultativement monosubstitué.

10. Composé suivant la revendication 1, ledit composé étant
la [2-(isoquinoléine-5-yl)-5-méthyl-2H-1,2,3-triazole-4-carbonyl]guanidine ; ou
la [5-méthyl-2-(quinoléine-5-yl)-2H-1,2,3-triazole-4-carbonyl]guanidine ; ou un de ses sels pharmaceutiquement
acceptables.

11. Composé suivant la revendication 1, ledit composé étant
la [1-(naphtalène-1-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine
ou un de ses sels pharmaceutiquement acceptables.

12. Composé suivant la revendication 1, dans lequel Z représente un groupe



dans lequel R¹ représente un groupe cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit
groupe cycloalkyle en C₃ à C₇ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R¹
étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en
C₁ à C₄, alkylsulfinyle en C₁ à C₄ ou alkylsulfonyle en C₁ à C₄ ; et R² représente un groupe alkyle en C₁ à C₄,
cycloalkyle en C₃ ou C₄, M ou M(alkyle en C₁ à C₄) , n'importe lequel desdits groupements alkyle en C₁ à C₄
précédents ayant facultativement un à neuf atomes de fluor ; ledit groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃
ou C₄ étant facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, alkoxy en C₁ à
C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, alkyle en C₁ à C₄, mono-N- ou di-N,
N-(alkyle en C₁ à C₄) carbamoyle ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ; et ledit groupe cy-
cloalkyle en C₃ ou C₄ ayant facultativement un à sept atomes de fluor ;

dans lequel M représente un noyau penta- à octogonal partiellement saturé, totalement saturé ou totalement
insaturé, ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de
soufre et d'azote, ou un noyau bicyclique consistant en deux noyaux tri- à hexagonaux condensés partiellement
saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant facultativement un à quatre
hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène ;

ledit groupe M étant facultativement substitué, sur un noyau si le groupement est monocyclique, ou sur l'un
ou les deux noyaux si le groupement est bicyclique, sur le carbone ou l'azote avec jusqu'à trois substituants choisis
indépendamment entre R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement
un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé, ayant facultativement
un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement
substitué avec un substituant alkyle en C₁ à C₄ et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes
hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, formyle, alcanoyle
en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido,
alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,
N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁
à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄) aminosulfonyle, alcényle en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloal-
cényle en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyle en C₁ à C₇, alkylthio en C₁
à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués
indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyle
en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido,
alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄) amino, carbamoyle, mono-N- ou di-N,
N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle
en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un
à neuf atomes de fluor.

13. Composé suivant la revendication 12, dans lequel

R¹ représente un groupe cycloalkyle en C₃ à C₇ ; et

R² représente un noyau aromatique monocyclique, penta- ou hexagonal ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote

ledit noyau R² étant facultativement monosubstitué sur le carbone ou l'azote avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement substitué un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄,

ledit noyau R² est également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄, ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ;

ledit groupe alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitué avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitué avec un à neuf atomes de fluor.

14. Composé suivant la revendication 13, dans lequel

R¹ représente un groupe cyclopropyle ; et

R² représente un groupe phényle, facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy,

lesdits substituants alkoxy en C₁ à C₄, alkyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, alcanoylamino en C₁ à C₄, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor.

15. Composé suivant la revendication 1, ledit composé étant

la [5-cyclopropyl-1-(2-trifluorométhylphényl)-1H-pyrazole-4-carbonyl]guanidine ;

la [5-cyclopropyl-1-phényl-1H-pyrazole-4-carbonyl]guanidine ;

la [5-cyclopropyl-1-(2,6-dichlorophényl)-1H-pyrazole-4-carbonyl]guanidine ;

ou un de ses sels pharmaceutiquement acceptables.

16. Composé suivant la revendication 1, ledit composé étant

la [1-(2-chloro-4-méthylsulfonylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chlorophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-trifluorométhyl-4-fluorophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-bromophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-fluorophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chloro-5-méthoxyphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chloro-4-méthylaminosulfonylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2,5-dichlorophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2,3-dichlorophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chloro-5-aminocarbonylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chloro-5-aminosulfonylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-fluoro-6-trifluorométhylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chloro-5-méthylsulfonylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2-chloro-5-diméthylaminosulfonylphényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ; ou

la [1-(2-trifluorométhyl-4-chlorophényl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

ou un de ses sels pharmaceutiquement acceptables.

17. Composé suivant la revendication 12, dans lequel

R² représente un noyau hétérocyclique non aromatique penta- ou hexagonal ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ou bien R² représente un groupe alkyle en C₁ à C₄ non substitué, cycloalkyle en C₃ à C₇ non substitué ou phényl (alkyle en C₁ à C₄), ledit groupe phényl (alkyle en C₁ à C₄) étant facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, halogène, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyl en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyl,

lesdits substituants alkoxy en C₁ à C₄, alkyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, alcanoylamino en C₁ à C₄, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyl en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyl ou étant facultativement substitués avec un à neuf atomes de fluor.

18. Composé suivant la revendication 12, dans lequel

R² représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ledit substituant R² étant facultativement substitué sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre les substituants R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé comprenant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitué avec un substituant alkyle en C₁ à C₄ et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, formyle, alcanoyl en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyl en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyl, alcényl en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloalcényl en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyl en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyl en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyl en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyl ou étant facultativement substitués avec un à neuf atomes de fluor.

19. Composé suivant la revendication 18, dans lequel

R¹ représente un groupe cycloalkyle en C₃ à C₇; et

R² représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à trois hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène,

ledit noyau bicyclique R² étant facultativement monosubstitué sur le carbone ou l'azote avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄,

ledit noyau bicyclique R² étant également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoyl en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyl en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyl,

ledit groupe alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyl en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitué avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyl en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino,

carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitué avec un à neuf atomes de fluor.

5 **20.** Composé suivant la revendication 19, dans lequel

R¹ représente un groupe cyclopropyle ; et

R² représente un noyau quinazolinyne, phtalazinyle, quinoléinyne, isoquinoléinyne, cinnolinyne, benzodioxan-
nyne, quinoxalinyne, benzopyrannyne, benzothiophényne, benzodioxolyne, benzimidazolyle, indazolyle, indolyle,
10 benzotriazolyle, benzoxazolyle, benzisoxazolyle, benzothiazolyle, benzisothiazolyle, benzoxadiazolyle ou benzo-
thiadiazolyle,

ledit noyau bicyclique R² étant facultativement mono- ou disubstitué indépendamment sur le carbone ou
l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à
C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄) carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄,
15 mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N- (alkyle en C₁ à C₄)carbamoyle,
alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle,

lesdits substituants alkoxy en C₁ à C₄, alkyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant
facultativement monosubstitués avec un substituant hydroxy, alcanoylamino en C₁ à C₄, alkylsulfonamido en C₁
à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, mono-N-ou di-N,N-(alkyle en C₁ à C₄)carbamoyle,
20 alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement subs-
titués avec un à neuf atomes de fluor.

21. Composé suivant la revendication 20, dans lequel

R² représente un groupe quinoléinyne, isoquinoléinyne, indazolyle ou benzimidazolyle,

ledit noyau bicyclique R² étant facultativement mono- ou disubstitué indépendamment avec un substituant
25 hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoylamino en C₁ à
C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, mono-N- ou di-N,N-(alkyle en
C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou
mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle,

lesdits substituants alkoxy en C₁ à C₄ ou alkyle en C₁ à C₄ étant facultativement monosubstitués avec un
30 substituant hydroxy, alcanoyle en C₁ à C₄, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁
à C₄)amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,
N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor.

22. Composé suivant la revendication 1, ledit composé étant

35 la [5-cyclopropyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carbonyl]guanidine ;
ou un de ses sels pharmaceutiquement acceptables.

23. Composé suivant la revendication 1, ledit composé étant

40 la [1-(8-bromoquinoléine-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(6-chloroquinoléine-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(indazole-7-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

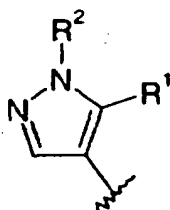
la [1-(benzimidazole-5-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(1-isoquinolyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]guanidine ;

45 la [5-cyclopropyl-1-(4-quinolinyne)-1H-pyrazole-4-carbonyl]guanidine ;

ou un de ses sels pharmaceutiquement acceptables.

24. Composé suivant la revendication 1, dans lequel Z représente un groupe



R¹ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R¹ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄ ou alkylsulfonyne en C₁ à C₄; et

R² représente un noyau hétérocyclique penta- ou hexagonal non aromatique ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ou bien R² représente un groupe phényl (alkyle en C₁ à C₄), ou un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, lesdits substituants R² étant facultativement substitués sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre des substituants R⁶, R⁷ et R⁸, un des substituants R⁶, R⁷ et R⁸ représentant facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitué avec un substituant alkyle en C₁ à C₄, et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à C₄, formyle, alcanoyne en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄) carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne, alcényne en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloalcényne en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyne en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄) amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyne en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne ou étant facultativement substitués avec un à neuf atomes de fluor.

25. Composé suivant la revendication 24, dans lequel

R¹ représente un groupe alkyle en C₁ à C₄; et

R² représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à trois hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène,

ledit noyau bicyclique R² étant facultativement monosubstitué sur le carbone ou l'azote avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄,

ledit noyau bicyclique R² étant également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à C₄, alcanoyne en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne,

lesdits groupes alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyne en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyne en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyne en C₁ à C₄, alkylsulfonyne en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyne ou étant facultativement substitués avec un à neuf atomes de fluor.

26. Composé suivant la revendication 25, dans lequel

R² représente un noyau quinazolinyne, phtalazinyne, quinoléinyne, isoquinolinyle, cinnolinyle, benzodioxanyle, quinoxalinyne, benzopyranyne, benzothiophényne, benzodioxolyne, benzimidazolyle, indazolyle, indolyne, benzotriazolyle, benzoxazolyle, benzisoxazolyle, benzothiazolyle, benzisothiazolyle, benzoxadiazolyle ou benzothiadiazolyle,

ledit noyau bicyclique R² étant facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄) carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou

5 lesdits substituants alkoxy en C₁ à C₄, alkyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄) amino étant facultativement monosubstitués avec un substituant hydroxy, alcanoylamino en C₁ à C₄, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, mono-N-ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor.

27. Composé suivant la revendication 1, ledit composé étant

la [1-(indazole-6-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(indazole-5yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

15 la [1-(benzimidazole-5-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-méthylbenzimidazole-6-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(5-quinoléinyl)-5-*n*-propyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(5-quinoléinyl)-5-isopropyl-1H-pyrazole-4-carbonyl]guanidine ;

la [5-éthyl-1-(6-quinoléinyl)-1H-pyrazole-4-carbonyl]guanidine ;

20 la [1-(2-méthylbenzimidazol-5-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(1,4-benzodioxanne-6-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(bentriazole-5-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ; la [1-(3-chloroindazole-5-yl)-5-éthyl-1H-pyrazole-4-carbonyl]guanidine ;

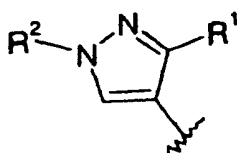
la [1-(5-quinoléinyl)-5-butyl-1H-pyrazole-4-carbonyl]guanidine ;

25 la [5-propyl-1-(6-quinoléinyl)-1H-pyrazole-4-carbonyl]guanidine ; ou

la [5-isopropyl-1-(6-quinoléinyl)-1H-pyrazole-4-carbonyl]guanidine ;

ou un de ses sels pharmaceutiquement acceptables.

28. Composé suivant la revendication 1, dans lequel Z représente un groupe



40 R¹ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R¹ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄ ou alkylsulfonyle en C₁ à C₄ ;

45 R² représente un noyau hétérocyclique penta- ou hexagonal non aromatique ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ou bien R² représente un groupe alkyle en C₁ à C₄ non substitué ou cycloalkyle en C₃ à C₇ non substitué ; ou bien R² représente un groupe phényl (alkyle en C₁ à C₄), ou un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, lesdits substituants R² étant facultativement substitués sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre des substituants R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitué avec un substituant alkyle en C₁ à C₄, et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, formyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄,

mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle, alcényle en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloalcényle en C₅ à C₇,

lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyle en C¹ à C⁷, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyle en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor.

29. Composé suivant la revendication 28, dans lequel

R¹ représente un groupe alkyle en C₁ à C₄ ; et

R² représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à trois hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène,

ledit noyau bicyclique R² étant facultativement monosubstitué sur le carbone ou l'azote avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄,

ledit noyau bicyclique R² étant également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄) carbonyle, alkyle en C₁ à C₄, alcanoyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle,

lesdits groupes alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyle en C₁ à C₇, alkylthio en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyle en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor.

30. Composé suivant la revendication 29, dans lequel

R² représente un noyau quinazolinyne, phtalazinyne, quinoléinyne, isoquinolinyne, cinnolinyne, benzodioxanyle, quinoxalinyne, benzopyrannyle, benzothiophényne, benzodioxolyne, benzimidazolyle, indazolyle, indolyne, benzotriazolyle, benzoxazolyle, benzisoxazolyle, benzothiazolyle, benzisothiazolyle, benzoxadiazolyle ou benzothiadiazolyle,

ledit noyau bicyclique R² étant facultativement mono- ou disubstitué indépendamment avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle,

lesdits substituants alkoxy en C₁ à C₄, alkyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, alcanoylamino en C₁ à C₄, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à cinq atomes de fluor.

31. Composé suivant la revendication 1, ledit composé étant

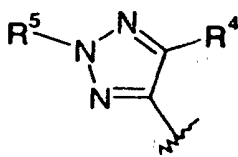
la [1-(indazole-7-yl)-3-méthyl-1H-pyrazole-4-carbonyl]guanidine ;

la [1-(2,1,3-benzothiadiazole-4-yl)-3-méthyl-1H-pyrazole-4-carbonyl]guanidine ; ou

la [3-méthyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carbonyl]guanidine ;

ou un de ses sels pharmaceutiquement acceptables.

32. Composé suivant la revendication 1, dans lequel Z représente un groupe



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10 R⁴ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R⁴ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄ ou alkylsulfonyle en C₁ à C₄ ; et

15 R⁵ représente un noyau hétérocyclique penta- ou hexagonal non aromatique ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, ou bien R⁵ représente un groupe alkyle en C₁ à C₄ non substitué ou cycloalkyle en C₃ à C₇ non substitué ; ou bien R⁵ représente un groupe phényl (alkyle en C₁ à C₄), ou un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à quatre hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène, lesdits substituants R⁵ étant facultativement substitués sur le carbone ou l'azote avec jusqu'à trois substituants choisis indépendamment entre des substituants R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement substitué avec un substituant alkyle en C₁ à C₄, et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, formyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄) amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle, alcényle en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloalcényle en C₅ à C₇,

25 lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor.

40 **33.** Composé suivant la revendication 32, dans lequel

R⁴ représente un groupe alkyle en C₁ à C₄ ; et

R⁵ représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à trois hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène,

45 ledit noyau bicyclique R⁵ étant facultativement monosubstitué sur le carbone avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué, avec un substituant alkyle en C₁ à C₄,

50 ledit noyau bicyclique R⁵ étant également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle,

55 lesdits groupes alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitué avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino,

carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués avec un à neuf atomes de fluor.

5 **34.** Composé suivant la revendication 33, dans lequel

R⁵ représente un noyau quinazolinyne, phtalazinyne, quinoléinyne, isoquinolinyne, cinnolinyne, benzodioxan-
nyne, quinoxalinyne, benzopyrannyne, benzothiophényne, benzodioxolyne, benzimidazolyle, indazolyle, indolyle,
benzotriazolyle, benzoxazolyle, benzisoxazolyle, benzothiazolyle, benzisothiazolyle, benzoxadiazolyle ou benzo-
thiadiazolyle,

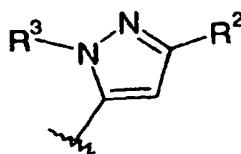
10 ledit noyau bicyclique R⁵ étant facultativement mono- ou disubstitué indépendamment avec un substituant
hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoylamino en C₁ à
C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, mono-N- ou di-N,N- (alkyle en
C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylsulfonyle en C₁ à C₄ ou
mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle,

15 lesdits substituants alkoxy en C₁ à C₄, alkyle en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant
facultativement monosubstitués avec un substituant hydroxy, (alkyle en C₁ à C₄)amino, alkylsulfonamido en C₁ à
C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, mono-N-ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alk-
ylsulfonyle en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle ou étant facultativement substitués
avec un à neuf atomes de fluor.

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35. Composé suivant la revendication 1, dans lequel Z représente un groupe

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R² représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, M ou M(alkyle en C₁ à C₄), n'importe
lequel desdits groupements alkyle en C₁ à C₄ précédents ayant facultativement un à neuf atomes de fluor ; ledit
groupe alkyle en C₁ à C₄ ou cycloalkyle en C₃ ou C₄ étant facultativement mono- ou disubstitué indépendamment
avec un substituant hydroxy, alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en
C₁ à C₄, alkyle en C₁ à C₄, mono-N- ou di-N, N- (alkyle en C₁ à C₄) carbonyle ou mono-N- ou di-N,N-(alkyle en
C₁ à C₄)aminosulfonyle ; et ledit groupe cycloalkyle en C₃ ou C₄ ayant facultativement un à sept atomes de fluor ;

35

dans lequel M représente un noyau penta- à octogonal partiellement saturé, totalement saturé ou totalement
insaturé, ayant facultativement un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de
soufre et d'azote, ou un noyau bicyclique consistant en deux noyaux tri- à hexagonaux condensés partiellement
saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant facultativement un à quatre
hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène ;

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ledit groupe M étant facultativement substitué, sur un noyau si le groupement est monocyclique, ou sur l'un
ou les deux noyaux si le groupement est bicyclique, sur le carbone ou l'azote avec jusqu'à trois substituants choisis
indépendamment entre R⁶, R⁷ et R⁸, dans lesquels un des substituants R⁶, R⁷ et R⁸ représente facultativement
un noyau tri- à heptagonal partiellement saturé, totalement saturé ou totalement insaturé, ayant facultativement
un à trois hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote facultativement
substitué avec un substituant alkyle en C₁ à C₄ et, en outre, R⁶, R⁷ et R⁸ représentent facultativement des groupes
hydroxy, nitro, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, formyle, alcanoyle
en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido,
alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,
N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, alkylthio en C₁ à C₄, alkylsulfinyle en C₁ à C₄, alkylsulfonyle en C₁
à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyle, alcényne en C₂ à C₄, alcynyle en C₂ à C₄ ou cycloal-
cényne en C₅ à C₇,

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lesdits substituants R⁶, R⁷ et R⁸ alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyle en C₁ à C₇, alkylthio en C₁
à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino ou cycloalkyle en C₃ à C₇ étant facultativement monosubstitués
indépendamment avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, cycloalkyle en C₃ à C₇, alcanoyle
en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido,

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alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbamoyle, cyano, thiol, nitro, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor.

5 R³ représente un groupe alkyle en C₁ à C₄, cycloalkyle en C₃ à C₇, phényle ou phényl(alkyle en C₁ à C₄), ledit groupe alkyle en C₁ à C₄ étant facultativement substitué avec un à neuf atomes de fluor, ledit substituant R³ étant facultativement mono- ou disubstitué indépendamment avec un substituant alkoxy en C₁ à C₄, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou alkyle en C₁ à C₄.

10 **36.** Composé suivant la revendication 35, dans lequel

R³ représente un groupe alkyle en C₁ à C₄ ; et

R² représente un groupe phényl, ledit groupe phényl étant facultativement monosubstitué sur le carbone avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄,

15 ledit noyau R² étant également facultativement mono ou disubstitué indépendamment sur le carbone avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyloxy, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoyloxyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N, N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy,

20 lesdits groupe alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄ et mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyloxy, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor.

30 **37.** Composé suivant la revendication 35, dans lequel

R³ représente un groupe alkyle en C₁ à C₄ ; et

R² représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment

35 ledit noyau bicyclique R² étant facultativement monosubstitué sur le carbone avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄

40 ledit noyau bicyclique R² étant également facultativement mono- ou disubstitué indépendamment sur le carbone avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyloxy, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoyloxyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄) amino, carbamoyle, mono-N- ou di-N, N-(alkyle en C₁ à C₄) carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy,

45 lesdits groupes alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, (alkoxy en C₁ à C₄) carbonyloxy, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄) amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄) carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor.

38. Composé suivant la revendication 35, dans lequel

R³ représente un groupe alkyle en C₁ à C₄ ; et

55 R² représente un noyau aromatique monocyclique penta- ou hexagonal ayant un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote ;

ledit noyau R² étant facultativement monosubstitué sur le carbone avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un subs-

tituant alkyle en C₁ à C₄ ;

ledit noyau R² est également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy,

lesdits groupes alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄ et mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor.

39. Composé suivant la revendication 35, dans lequel

R³ représente un groupe alkyle en C₁ à C₄ ; et

R² représente un noyau bicyclique consistant en deux noyaux penta- et/ou hexagonaux condensés partiellement saturés, totalement saturés ou totalement insaturés, pris indépendamment, ayant un à trois hétéroatomes choisis indépendamment entre des atomes d'azote, de soufre et d'oxygène ;

ledit noyau bicyclique R² étant facultativement monosubstitué sur le carbone ou l'azote avec un noyau penta- ou hexagonal totalement saturé ou totalement insaturé ayant facultativement un ou deux hétéroatomes choisis indépendamment entre des atomes d'oxygène, de soufre et d'azote, ledit noyau étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄ ;

ledit noyau bicyclique R² étant également facultativement mono- ou disubstitué indépendamment sur le carbone ou l'azote avec un substituant hydroxy, halogéno, alkoxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonyle, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, cyano, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy,

lesdits groupes alkoxy en C₁ à C₄, alkyle en C₁ à C₄, alcanoyloxy en C₁ à C₇, alkylthio en C₁ à C₄ et mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino étant facultativement monosubstitués avec un substituant hydroxy, (alkoxy en C₁ à C₄)carbonyle, alcanoyloxy en C₁ à C₄, alcanoylamino en C₁ à C₄, alcanoyloxy en C₁ à C₄, (alkoxy en C₁ à C₄)carbonylamino, sulfonamido, alkylsulfonamido en C₁ à C₄, amino, mono-N- ou di-N,N-(alkyle en C₁ à C₄)amino, carbamoyle, mono-N- ou di-N,N-(alkyle en C₁ à C₄)carbamoyle, alkylthio en C₁ à C₄, alkylsulfinyloxy en C₁ à C₄, alkylsulfonyloxy en C₁ à C₄ ou mono-N- ou di-N,N-(alkyle en C₁ à C₄)aminosulfonyloxy ou étant facultativement substitués avec un à neuf atomes de fluor.

40. Composition pharmaceutique comprenant un composé de formule I, ou un sel pharmaceutiquement acceptable dudit composé, suivant l'une quelconque des revendications 1 à 39, et un support pharmaceutiquement acceptable.

41. Composé de formule I, ou un sel pharmaceutiquement acceptable dudit composé, suivant l'une quelconque des revendications 1 à 39, destiné à être utilisé comme médicament.

42. Utilisation d'un composé de formule I, ou d'un sel pharmaceutiquement acceptable dudit composé, suivant l'une quelconque des revendications 1 à 39, pour la production d'un médicament destiné à la prévention d'une altération ischémique du myocarde.

43. Utilisation d'un composé de formule I, ou d'un sel pharmaceutiquement acceptable dudit composé, suivant l'une quelconque des revendications 1 à 39, pour la production d'un médicament destiné à réduire l'altération tissulaire résultant d'une ischémie.

44. Utilisation suivant la revendication 43, dans laquelle le tissu est le tissu du coeur, du cerveau, du foie, des reins, des poumons, du tube digestif, des muscles squelettiques, de la rate, du pancréas, des nerfs, de la moelle épinière, de la rétine, du système vasculaire ou de l'intestin.

45. Utilisation suivant la revendication 44, dans laquelle la quantité du composé de formule I est comprise dans l'in-

tervalle d'environ 0,01 mg/kg/jour à environ 50 mg/kg/jour.

46. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré à titre prophylactique.
- 5 47. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré avant une intervention chirurgicale.
- 10 48. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré avant une intervention de chirurgie cardiaque.
- 15 49. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré au cours d'une intervention chirurgicale.
- 20 50. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré au cours d'une intervention de chirurgie cardiaque.
- 25 51. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré dans les vingt-quatre heures suivant une intervention chirurgicale.
- 30 52. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré dans les vingt-quatre heures suivant une intervention de chirurgie cardiaque.
- 35 53. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré avant, pendant et après une intervention chirurgicale.
- 40 54. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré avant, pendant et après une intervention de chirurgie cardiaque.
- 45 55. Utilisation suivant la revendication 43, dans laquelle l'altération tissulaire résultant d'une ischémie est une altération ischémique et est subie au cours d'une transplantation d'organes.
- 50 56. Utilisation suivant la revendication 43, dans laquelle le composé est destiné à être administré pour la prévention d'une lésion ischémique périopératoire du myocarde.
- 55 57. Composition en association pharmaceutique, comprenant une quantité thérapeutiquement efficace d'une composition comprenant :
- un premier composé, ledit premier composé étant un composé de formule I tel que défini dans la revendication 1, ou un sel pharmaceutiquement acceptable dudit composé ;
 - un second composé, ledit second composé étant un inhibiteur d'aldose-réductase ; et
 - un support, véhicule ou diluant pharmaceutique.
58. Composition pharmaceutique suivant la revendication 57, dans laquelle l'inhibiteur d'aldose-réductase est le 1-phthalazineacetic acid 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]- ou un de ses sels pharmaceutiquement acceptables.
59. Composition pharmaceutique suivant la revendication 57, dans laquelle Z est tel que défini en (i) dans la revendication 1.
60. Utilisation d'une composition pharmaceutique telle que définie dans l'une quelconque des revendications 57 à 59 pour la production d'un médicament destiné à réduire l'altération tissulaire résultant d'une ischémie.
61. Kit comprenant :
- a. un premier composé, ledit premier composé étant un composé suivant la revendication 1, ou un sel pharmaceutiquement acceptable dudit composé, et un support, véhicule ou diluant pharmaceutiquement acceptable dans une première forme posologique unitaire ;
 - b. un second composé, ledit second composé étant un inhibiteur d'aldose-réductase, et un support, véhicule

ou diluant pharmaceutiquement acceptable dans une seconde forme posologique unitaire ;
 c. un moyen pour contenir lesdites première et seconde formes posologiques,

dans lequel les quantités des premiers composés ont pour résultat un effet thérapeutique.

- 5
62. Kit suivant la revendication 61, dans lequel l'inhibiteur d'aldose-réductase est le 1-phtalazineacetic acid 3,4-dihydro-4-oxo-3-[[5-trifluorométhyl]-2-benzothiazolyl]-méthyl]- ou un de ses sels pharmaceutiquement acceptables.
- 10
63. Kit suivant la revendication 61, dans lequel Z est tel que défini en (i) dans la revendication 1.
- 15
64. Composition en association pharmaceutique, comprenant : une quantité thérapeutiquement efficace d'une composition comprenant :
- un premier composé, ledit premier composé étant un composé suivant la revendication 1, ou un sel pharmaceutiquement acceptable dudit composé ;
 un second composé, ledit second composé étant un inhibiteur de glycogène-phosphorylase ;
 un support, véhicule ou diluant pharmaceutique.
- 20
65. Composition pharmaceutique suivant la revendication 64, dans laquelle l'inhibiteur de glycogène-phosphorylase est le
- 25
- [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidine-1-yl)-3-oxopropyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-benzyl-3-((3S, 4S)-dihydroxypyrrolidine-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-((R)-hydroxy-diméthylcarbamoyl-méthyl)-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-((R)-hydroxy-méthoxy-méthyl-carbamoyl)-méthyl]-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-((R)-hydroxy-[(2-hydroxy-éthyl)-méthylcarbamoyl]-méthyl)-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-((R)-hydroxy-[(2-hydroxyéthyl)-méthyl-carbamoyl]-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(2-(cis-3,4-dihydroxy-pyrrolidine-1-yl)2-oxo-éthyl)-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-benzyl-3-((cis)-dihydroxypyrrolidine-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [2-((3S,4S)-dihydroxypyrrolidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-benzyl-2-((cis-3,4)-dihydroxypyrrolidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [2-(1,1-dioxo-thiazolidine-3-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-(4-fluorobenzyl)-2-(4-hydroxy-pipéridine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-benzyl-2-((3RS)-hydroxy-pipéridine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [2-oxo-2-((1RS)-oxo-thiazolidine-3-yl)-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ; ou
 [(1S)-benzyl-2-(3-hydroxy-azétidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 ou un de ses sels pharmaceutiquement acceptables.
- 30
- 35
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66. Composition pharmaceutique telle que définie dans la revendication 64, dans laquelle Z répond à la formule (i) telle que définie dans la revendication 1.
- 50
67. Utilisation d'une composition pharmaceutique telle que définie dans l'une quelconque des revendications 64 à 66 pour la production d'un médicament destiné à réduire l'altération tissulaire résultant d'une ischémie.
- 55
68. Kit comprenant :
- a. un premier composé, ledit premier composé étant un composé suivant la revendication 1, ou un sel pharmaceutiquement acceptable dudit composé, et un support, véhicule ou diluant pharmaceutiquement acceptable dans une première forme posologique unitaire ;
 b. un second composé, ledit composé étant un inhibiteur de glycogène-phosphorylase, et un support, véhicule

ou diluant pharmaceutiquement acceptable, dans une seconde forme posologique unitaire ;
c. un moyen pour contenir lesdites première et seconde formes posologiques,

dans lequel les quantités des premier et second composés ont pour résultat un effet thérapeutique.

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69. Kit suivant la revendication 68, dans lequel l'inhibiteur de glycogène-phosphorylase est le
 [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidine-1-yl)-3-oxopropyl]-amide d'acide 5-chloro-1H-indole-
 2-carboxylique ;
 [(1S)-benzyl-3-((3S,4S)-dihydroxypyrrolidine-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide d'acide 5-chloro-1H-indole-
 10 2-carboxylique ;
 [(1S)-((R)-hydroxy-diméthylcarbamoyl-méthyl)-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-((R)-hydroxy-méthoxy-méthyl-carbamoyl)-méthyl]-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-
 2-carboxylique ;
 [(1S)-((R)-hydroxy-[(2-hydroxy-éthyl)-méthylcarbamoyl]-méthyl)-2-phényléthyl]-amide d'acide 5-chloro-1H-
 15 le-2-carboxylique ;
 [(1S)-((R)-hydroxy-[(2-hydroxyéthyl)-méthyl-carbamoyl]-2-phényléthyl]-amide d'acide 5-chloro-1H-indole-
 2-carboxylique ;
 [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(2-(cis-3,4-dihydroxy-pyrrolidine-1-yl)2-oxo-éthyl)-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 20 [(1S)-benzyl-3-((cis)-dihydroxypyrrolidine-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide d'acide 5-chloro-1H-indole-
 2-carboxylique ;
 [2-((3S,4S)-dihydroxypyrrolidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-benzyl-2-((cis-3,4-)-dihydroxypyrrolidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-
 2-carboxylique ;
 25 [2-(1,1-dioxo-thiazolidine-3-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [(1S)-(4-fluorobenzyl)-2-(4-hydroxy-pipéridine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-
 2-carboxylique ;
 [(1S)-benzyl-2-((3RS)-hydroxy-pipéridine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 [2-oxo-2-((1RS)-oxo-thiazolidine-3-yl)-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ; ou
 30 [(1S)-benzyl-2-(3-hydroxy-azétidine-1-yl)-2-oxo-éthyl]-amide d'acide 5-chloro-1H-indole-2-carboxylique ;
 ou un de ses sels pharmaceutiquement acceptables.
70. Kit suivant la revendication 68, dans lequel Z est tel que défini en (i) dans la revendication 1.
- 35 71. Composition en association pharmaceutique comprenant : une quantité thérapeutiquement efficace d'une com-
 position comprenant
 un premier composé, ledit premier composé étant un composé suivant la revendication 1, ou un sel phar-
 maceutiquement acceptable dudit composé ;
 un second composé, ledit second composé étant un agent cardiovasculaire ;
 40 un support, véhicule ou diluant pharmaceutique.
72. Composition pharmaceutique suivant la revendication 71, dans laquelle l'agent cardiovasculaire est un bêta-blo-
 quant, un agent de blocage du canal calcium, un agent d'ouverture du canal potassium, l'adénosine, des agonistes
 d'adénosine, un inhibiteur de ACE, un nitrate, un diurétique, un glycoside, un agent thrombolytique, un inhibiteur
 45 plaquettaire, l'aspirine, le dipyridamol, le chlorure de potassium, la clonidine, la prazosine ou un agoniste du ré-
 cepteur d'adénosine A₃.
73. Composition pharmaceutique suivant la revendication 71, dans laquelle Z est tel que défini en (i) dans la reven-
 dication 1.
- 50 74. Utilisation d'une composition pharmaceutique suivant l'une quelconque des revendications 71 à 73 pour la pro-
 duction d'un médicament destiné à réduire l'altération tissulaire résultant d'une ischémie.
75. Kit comprenant :
- 55 a. un premier composé, ledit premier composé étant un composé suivant la revendication 1, ou un sel phar-
 maceutiquement acceptable dudit composé, et un support, véhicule ou diluant pharmaceutiquement accep-
 table dans une première forme posologique unitaire ;

- b. un second composé, ledit second composé étant un agent cardiovasculaire, et un support, véhicule ou diluant pharmaceutiquement acceptable dans une seconde forme posologique unitaire ;
 c. un moyen pour contenir lesdites première et seconde formes posologiques,

5 dans lequel les quantités des premier et second composés ont pour résultat un effet thérapeutique.

76. Kit suivant la revendication 75, dans lequel l'agent cardiovasculaire est un bêta-bloquant, un agent de blocage du canal calcium, un inhibiteur de ACE, un nitrate, un diurétique, un glycoside, un agent thrombolytique, un inhibiteur plaquettaire, l'aspirine, le dipyridamol, le chlorure de potassium, la clonidine, la prazosine ou un agoniste du récepteur d'adénosine A₃.

77. Kit suivant la revendication 75, dans lequel Z est tel que défini en (i) dans la revendication 1.

78. Composé, ledit composé étant
 15 le 5-cyclopropyl-1-(2-trifluorométhylphényl)-1H-pyrazole-4-carboxylate d'éthyle,
 le 5-méthyl-1-(6-quinoléinyl)-1H-pyrazole-4-carboxylate d'éthyle,
 le 5-cyclopropyl-1-(quinoléine-8-yl)-1H-pyrazole-4-carboxylate d'éthyle,
 le 5-cyclopropyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carboxylate d'éthyle,
 le 5-éthyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carboxylate de méthyle,
 20 le 1-(isoquinoléine-5-yl)-3-méthyl-1H-pyrazole-4-carboxylate de n-butyle, ou
 un sel pharmaceutiquement acceptable dudit composé.

79. Composé choisi entre les esters de
 25 5-cyclopropyl-1-(2-trifluorométhylphényl)-1H-pyrazole-4-carboxylate,
 5-méthyl-1-(6-quinoléinyl)-1H-pyrazole-4-carboxylate,
 5-cyclopropyl-1-(quinoléine-8-yl)-1H-pyrazole-4-carboxylate,
 5-cyclopropyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carboxylate,
 5-éthyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carboxylate, et
 1-(isoquinoléine-5-yl)-3-méthyl-1H-pyrazole-4-carboxylate,
 30 lesdits esters étant des esters de benzyle, d'alkyle en C₁ à C₆ ou de cycloalkyle en C₄ à C₈, ledit groupe
 cycloalkyle en C₄ à C₈ étant facultativement monosubstitué avec un substituant alkyle en C₁ à C₄,
 ou un sel pharmaceutiquement acceptable dudit composé.

80. Composé choisi entre
 35 l'acide 5-méthyl-2-(5-quinoléinyl)-2H-1,2,3-triazole-4-carboxylique,
 l'acide 5-méthyl-2-(5-isoquinoléinyl)-2H-1,2,3-triazole-4-carboxylique,
 l'acide 5-méthyl-1-(6-quinoléinyl)-1H-pyrazole-4-carboxylique,
 l'acide 5-cyclopropyl-1-(quinoléine-8-yl)-1H-pyrazole-4-carboxylique,
 l'acide 5-cyclopropyl-1-(2-trifluorométhylphényl)-1H-pyrazole-4-carboxylique,
 40 l'acide 5-éthyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carboxylique,
 l'acide 5-cyclopropyl-1-(quinoléine-5-yl)-1H-pyrazole-4-carboxylique,
 l'acide 1-(isoquinoléine-5-yl)-3-méthyl-1H-pyrazole-4-carboxylique
 ou leurs chlorures d'acides ou un sel pharmaceutiquement acceptable desdits composés ou desdits chlorures
 d'acides.

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