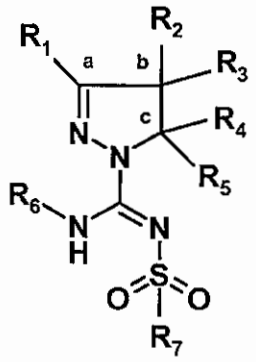
CLAIMS:

1. A process for the preparation of a compound of formula (I):



(I)

or a tautomer, stereoisomer, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms or an hydroxy group,

- R_2 represents hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms, an hydroxy group, a benzyloxymethyl group, an amino group, a monomethyl amino group, a dimethylamino group or a Boc-, Fmoc- or Cbz-protected amino group, which alkyl(C_{1-4}) group may incorporate a keto group, a sulfonyl group or an N, O or S atom,

- R_3 represents hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms, an hydroxy group, a benzyloxymethyl group, an amino group, a monomethyl amino group, a dimethylamino group or a Boc-, Fmoc- or Cbz-protected amino group, which alkyl(C_{1-4}) group may incorporate a keto group, a sulfonyl group or an N, O or S atom, or

R_1 and R_2, together with the carbon atoms marked 'a' and 'b' form a C_{5-8}-cycloalkyl ring, optionally substituted with one to three fluoro atoms, an hydroxy group or an alkyl(C_{1-4}) group, or,

R_2 and R_3, together with the carbon atom marked 'b' form a C_{3-8}-cycloalkyl ring, optionally substituted with one to four fluoro atoms, one or two methyl groups or an hydroxy group, or

R_2 and R_3, together with the carbon atom marked 'b' form a C_{5-8}-heterocycloalkyl ring optionally substituted with one to four fluoro atoms, one or two methyl groups, a benzyl group or an hydroxy group,

- R_4 represents hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms or an hydroxy group, or R_4 represents a monocyclic aryl or heteroaryl group optionally substituted with one to five substituents Q which can be the same or different, chosen from halogen, trifluoromethyl, trifluoromethoxy, cyano, C_{1-3}-alkyl, C_{1-3}-alkoxy, hydroxy, amino, acetyl, acetamido, trifluoroacetamido, $-CONH_2$, $-SO_2NH_2$ or $-CO_2H$, or

  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{3-8}-cycloalkyl ring, optionally substituted with one to four fluoro atoms, one or two methyl groups or an hydroxy group, or
  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{5-8}-heterocycloalkyl ring optionally substituted with one to four fluoro atoms, one or two methyl groups, a benzyl group or an hydroxy group,

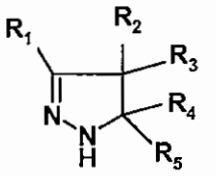
- R_5 represents hydrogen or methyl,

- R_6 is chosen from hydrogen atom, or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms or an hydroxy group,

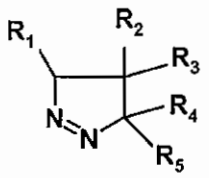
- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one to five substituents Q, as defined above or
  R_7 represents a 2-aryl-ethenyl group or a 2-aryl-ethynyl group, or
  R_7 represents a piperidinyl group unsubstituted or substituted with one to four fluoro atoms or a CF_3 group, or
  R_7 represents a 2,3-dihydroindolyl group or a benzimidazol-2-one group

comprising the steps of:

(i) reacting a substituted 4,5-dihydro-(1H)-pyrazole of formula (II^a) or the isomeric substituted 4,5-dihydro-3H-pyrazole of formula (II^b):

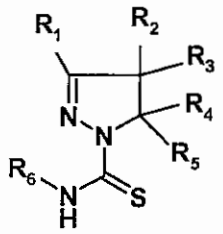


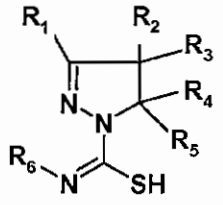
(II^a)



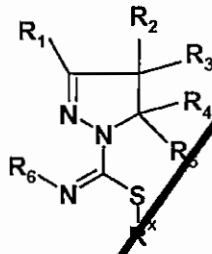
(II^b)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings as given above, with an isothiocyanate of formula R_6-N=C=S, wherein R_6 has the meaning as given above, to give a substituted 4,5-dihydro-(1H)-pyrazole-1-carbothioic acid amide of formula (III^a) or the tautomeric substituted 4,5-dihydro-(1H)-pyrazole-1-carboximidothioic acid of formula (III^b):

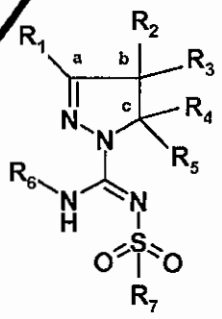

(III^a)


(III^b)

(ii) reacting the obtained compound of formula (III^a) or (III^b), with an alkylating reagent of general formula R^x-L, wherein R^x represents a linear (C_{1-8})-alkyl group and L represents a 'leaving group', to give a compound of formula (IV):


(IV)

(iii) reacting the obtained compound of formula (IV) with a sulfonamide derivative of formula $R_7SO_2NH_2$, wherein R_7 has the meaning given above, to give a compound of formula (I):


(I)

(iv) isolating the compound of formula (I) from the reaction mixture.

2. A process as claimed in claim 1, for the preparation of a compound of formula (I), wherein:

- R_1 is chosen from hydrogen or an alkyl(C_{1-2}) group,

- R_2 represents hydrogen or an alkyl(C_{1-3}) group, optionally substituted with one to three fluoro atoms or an hydroxy group,

- R_3 represents hydrogen or an alkyl(C_{1-3}) group, optionally substituted with one to three fluoro atoms or an hydroxy group, or

  R_1 and R_2, together with the carbon atoms marked 'a' and 'b' form a C_{5-8}-cycloalkyl ring, or,
  R_2 and R_3, together with the carbon atom marked 'b' form a C_{3-8}-cycloalkyl ring, optionally substituted with one to four fluoro atoms or an hydroxy group, or
  R_2 and R_3, together with the carbon atom marked 'b' form a C_{5-8}-heterocycloalkyl ring optionally substituted with a methyl or a benzyl group or an hydroxy group,

- R_4 represents hydrogen or an alkyl(C_{1-2}) group, or R_4 represents a monocyclic aryl or heteroaryl group optionally substituted with one to three substituents Q as defined above, or

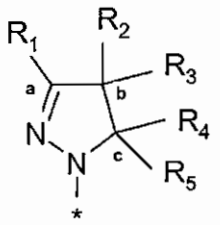
  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{5-8}-cycloalkyl ring, or
  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{5-8}-heterocycloalkyl ring optionally substituted with a methyl or a benzyl group,

- R_5 represents hydrogen,

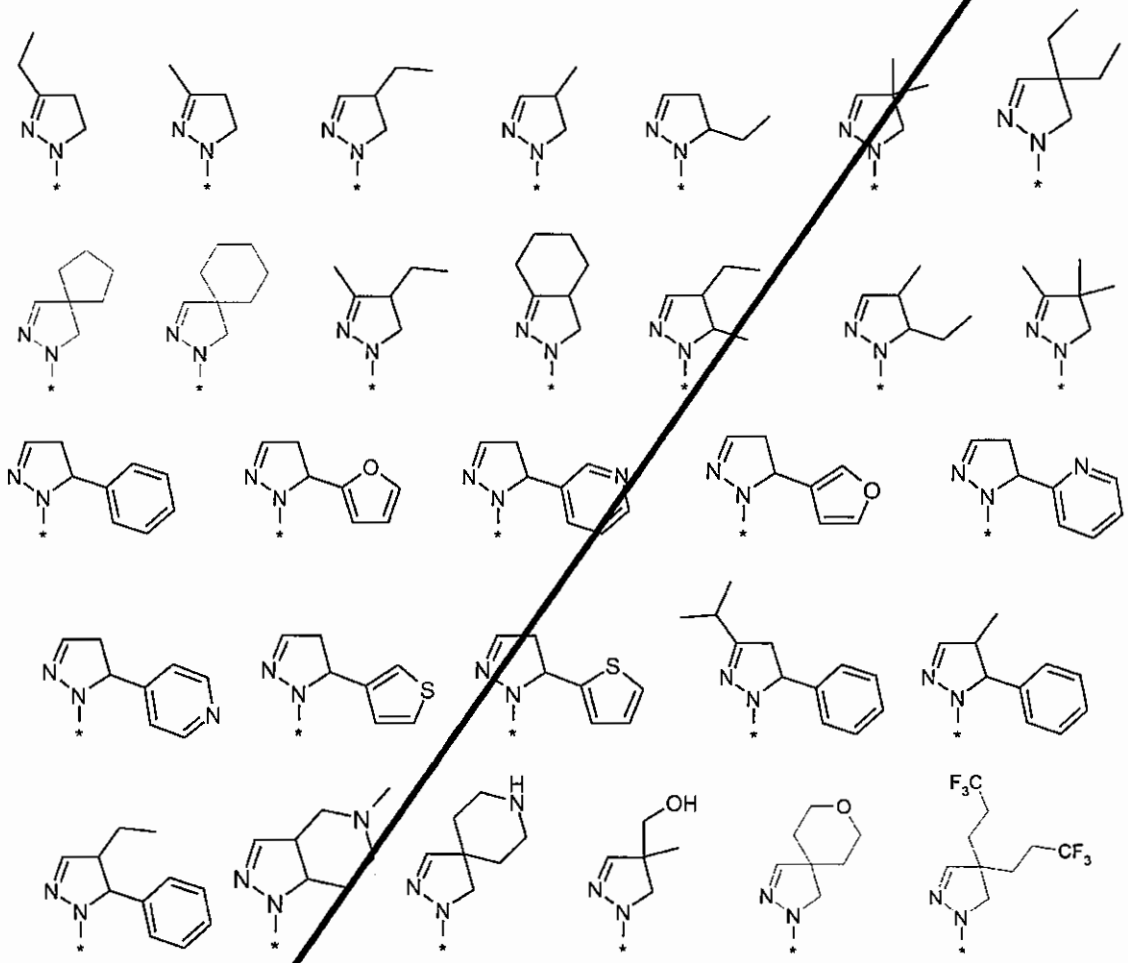
- R_6 is chosen from hydrogen or an alkyl(C_{1-3}) group optionally substituted with one to three fluoro atoms,

- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one to five substituents Q, as defined above or
  R_7 represents a 2-aryl-ethenyl group or a 2-aryl-ethynyl group, or
  R_7 represents a piperidinyl group, or
  R_7 represents a 2,3-dihydroindolyl group or a benzimidazol-2-one group.

3. A process as claimed in claim 1, for the preparation of a compound of formula (I), wherein the moiety:



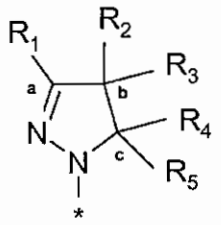
is chosen from:



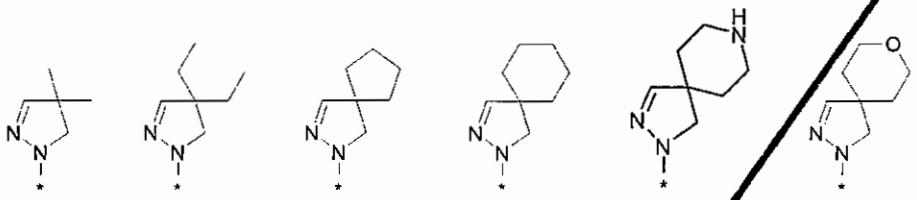
- R_6 is chosen from hydrogen or an alkyl(C_{1-3}) group optionally substituted with one to three fluoro atoms,

- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one to five substituents Q, as defined above, or
  R_7 represents a 2-aryl-ethenyl group or a 2-aryl-ethynyl group, or
  R_7 represents a piperidinyl group, or
  R_7 represents a 2,3-dihydroindolyl group or a benzimidazol-2-one group

4. A process as claimed in claim 1, for the preparation of a compound of formula (I), wherein the moiety:



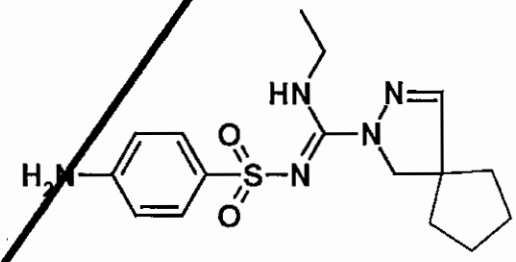
is chosen from:



- R_6 is chosen from hydrogen or an alkyl(C_{1-2}) group optionally substituted with three fluoro atoms,

- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one or two substituents chosen from methyl, methoxy, fluoro, chloro, bromo, cyano, acetamido, trifluoroacetamido, trifluoromethyl, amino or hydroxy

5. A process as claimed in claim 1, for the preparation of a compound of formula

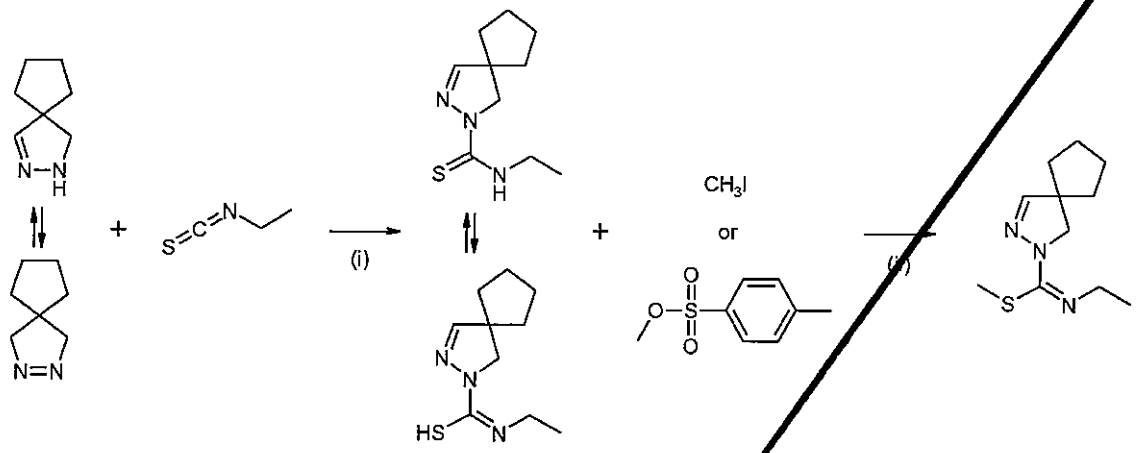


and tautomers and salt forms thereof,

comprising the steps of:

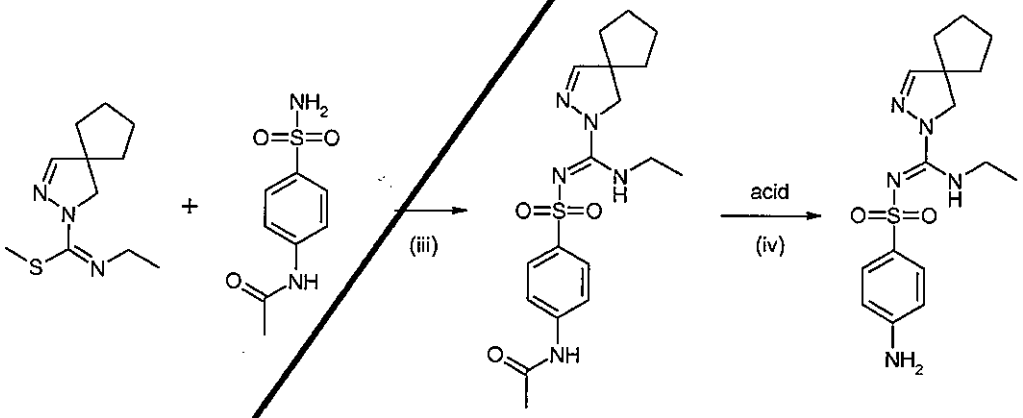
(i) reacting 2,3-diaza-spiro[4.4]non-2-ene or 2,3-diaza-spiro[4.4]non-1-ene, or salts thereof, synthesized as disclosed in WO 2008/034863, with ethyl isothiocyanate, to yield 2,3-diazaspiro[4.4]non-3-ene-2-carbothioic acid ethylamide or its tautomer

(ii) reacting the latter with iodomethane or methyl *p*-toluenesulfonate yielding N-ethyl-2,3-diaza-spiro[4.4]non-3-ene-2-carboximido-thioic acid methyl ester,

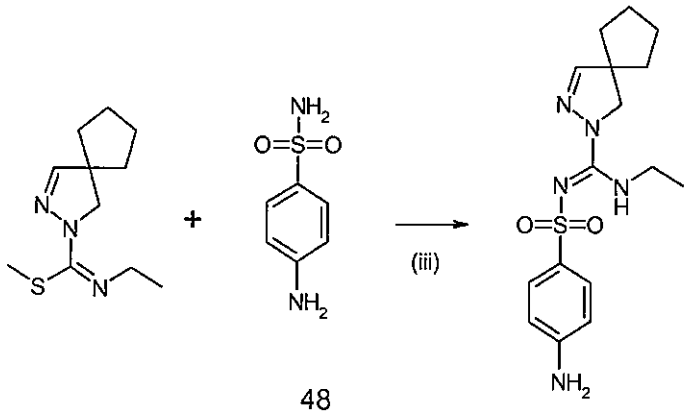


(iii) reacting the latter, as free base or salt thereof, with 4-acetamidobenzenesulfonamide yielding N-(4-{[(2,3-diaza-spiro[4.4]non-3-en-2-yl)-ethylamino-methylene]-sulfamoyl}-phenyl)-acetamide

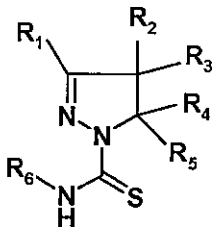
(iv) deprotecting the latter under acidic conditions, yielding 4-amino-N-[(2,3-diaza-spiro[4.4]non-3-en-2-yl)-ethylamino-methylene]-benzenesulfonamide



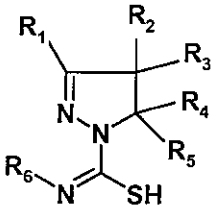
6. A process as claimed in claim 5, wherein step (iii) consists of reacting N-ethyl-2,3-diaza-spiro[4.4]non-3-ene-2-carboximidothioic acid methyl ester with sulfanilamide yielding 4-amino-N-[(2,3-diaza-spiro[4.4]non-3-en-2-yl)-ethylamino-methylene]-benzenesulfonamide:



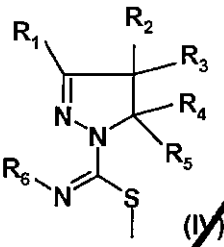
7. A compound of formula (III^a), (III^b) or (IV):



(III^a)



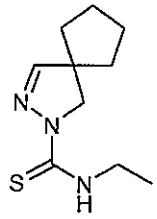
(III^b)

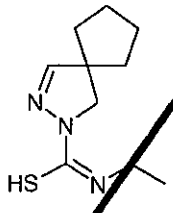


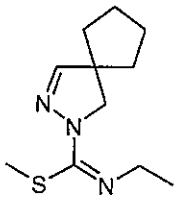
(IV)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings as given in claim 1, as well as tautomers, stereoisomers, and salts of any of the foregoing, such compounds being useful in the synthesis of compounds of formula (I).

8. A compound as claimed in claim 7, selected from those of the formulae:

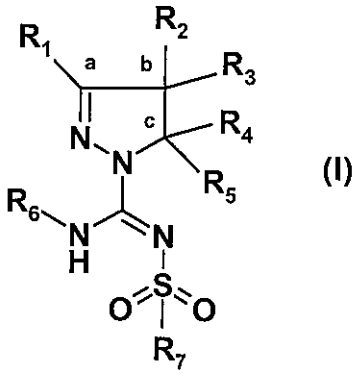






Claims

1. A process for the preparation of a compound of formula (I):



(I)

or a tautomer, stereoisomer, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms or an hydroxy group,

- R_2 represents hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms, an hydroxy group, a benzyloxymethyl group, an amino group, a monomethyl amino group, a dimethylamino group or a Boc-, Fmoc- or Cbz-protected amino group, which alkyl(C_{1-4}) group may incorporate a keto group, a sulfonyl group or an N, O or S atom,

- R_3 represents hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms, an hydroxy group, a benzyloxymethyl group, an amino group, a monomethyl amino group, a dimethylamino group or a Boc-, Fmoc- or Cbz-protected amino group, which alkyl(C_{1-4}) group may incorporate a keto group, a sulfonyl group or an N, O or S atom, or

  R_1 and R_2, together with the carbon atoms marked 'a' and 'b' form a C_{5-8}-cycloalkyl ring, optionally substituted with one to three fluoro atoms, an hydroxy group or an alkyl(C_{1-4}) group, or,

R_2 and R_3, together with the carbon atom marked 'b' form a C_{3-8}-cycloalkyl ring, optionally substituted with one to four fluoro atoms, one or two methyl groups or an hydroxy group, or
R_2 and R_3, together with the carbon atom marked 'b' form a C_{5-8}-heterocycloalkyl ring optionally substituted with one to four fluoro atoms, one or two methyl groups, a benzyl group or an hydroxy group,

- R_4 represents hydrogen or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms or an hydroxy group, or R_4 represents a monocyclic aryl or heteroaryl group optionally substituted with one to five substituents Q which can be the same or different, chosen from halogen, trifluoromethyl, trifluoromethoxy, cyano, C_{1-3}-alkyl, C_{1-3}-alkoxy, hydroxy, amino, acetyl, acetamido, trifluoroacetamido, -$CONH_2$, -SO_2NH_2 or -CO_2H, or

  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{3-8}-cycloalkyl ring, optionally substituted with one to four fluoro atoms, one or two methyl groups or an hydroxy group, or
  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{5-8}-heterocycloalkyl ring optionally substituted with one to four fluoro atoms, one or two methyl groups, a benzyl group or an hydroxy group,

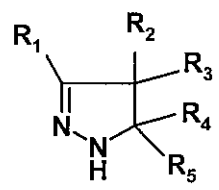
- R_5 represents hydrogen or methyl,

- R_6 is chosen from hydrogen atom, or an alkyl(C_{1-4}) group, optionally substituted with one to three fluoro atoms or an hydroxy group,

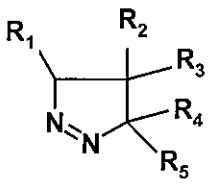
- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one to five substituents Q, as defined above or R_7 represents a 2-aryl-ethenyl group or a 2-aryl-ethynyl group, or R_7 represents a piperidinyl group unsubstituted or substituted with one to four fluoro atoms or a CF_3 group, or
  R_7 represents a 2,3-dihydroindolyl group or a benzimidazol-2-one group

comprising the steps of:

(i) reacting a substituted 4,5-dihydro-(1H)-pyrazole of formula (II^a) or the isomeric substituted 4,5-dihydro-3H-pyrazole of formula (II^b):

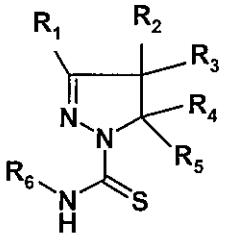


(II^a)

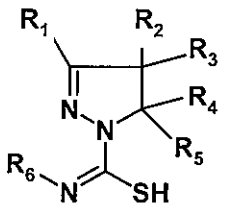


(II^b)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings as given above, with an isothiocyanate of formula R_6-N=C=S, wherein R_6 has the meaning as given above, to give a substituted 4,5-dihydro-(1H)-pyrazole-1-carbothioic acid amide of formula (III^a) or the tautomeric substituted 4,5-dihydro-(1H)-pyrazole-1-carboximidothioic acid of formula (III^b):

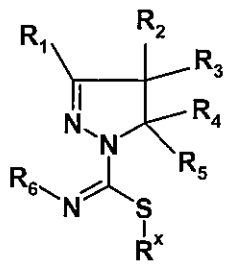


(III^a)



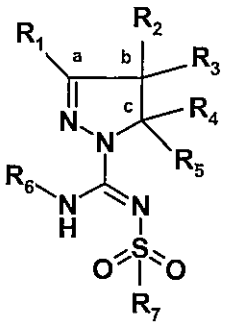
(III^b)

(ii) reacting the obtained compound of formula (III^a) or (III^b), with an alkylating reagent of general formula R^x-L, wherein R^x represents a linear (C_{1-8})-alkyl group and L represents a 'leaving group', to give a compound of formula (IV):



(IV)

(iii) reacting the obtained compound of formula (IV) with a sulfonamide derivative of formula $R_7SO_2NH_2$, wherein R_7 has the meaning given above, to give a compound of formula (I):



(I)

(iv) isolating the compound of formula (I) from the reaction mixture.

2. A process as claimed in claim 1, for the preparation of a compound of formula (I), wherein:

- R_1 is chosen from hydrogen or an alkyl(C_{1-2}) group,

- R_2 represents hydrogen or an alkyl(C_{1-3}) group, optionally substituted with one to three fluoro atoms or an hydroxy group,

- R_3 represents hydrogen or an alkyl(C_{1-3}) group, optionally substituted with one to three fluoro atoms or an hydroxy group, or

  R_1 and R_2, together with the carbon atoms marked 'a' and 'b' form a C_{5-8}-cycloalkyl ring, or,
  R_2 and R_3, together with the carbon atom marked 'b' form a C_{3-8}-cycloalkyl ring, optionally substituted with one to four fluoro atoms or an hydroxy group, or
  R_2 and R_3, together with the carbon atom marked 'b' form a C_{5-8}-heterocycloalkyl ring optionally substituted with a methyl or a benzyl group or an hydroxy group,

- R_4 represents hydrogen or an alkyl(C_{1-2}) group, or R_4 represents a monocyclic aryl or heteroaryl group optionally substituted with one to three substituents Q as defined above, or

  R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{5-8}-cycloalkyl ring, or

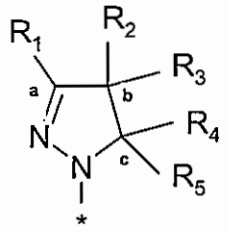
R_3 and R_4, together with the carbon atoms marked 'b' and 'c' form a C_{5-8}-heterocycloalkyl ring optionally substituted with a methyl or a benzyl group,

- R_5 represents hydrogen,

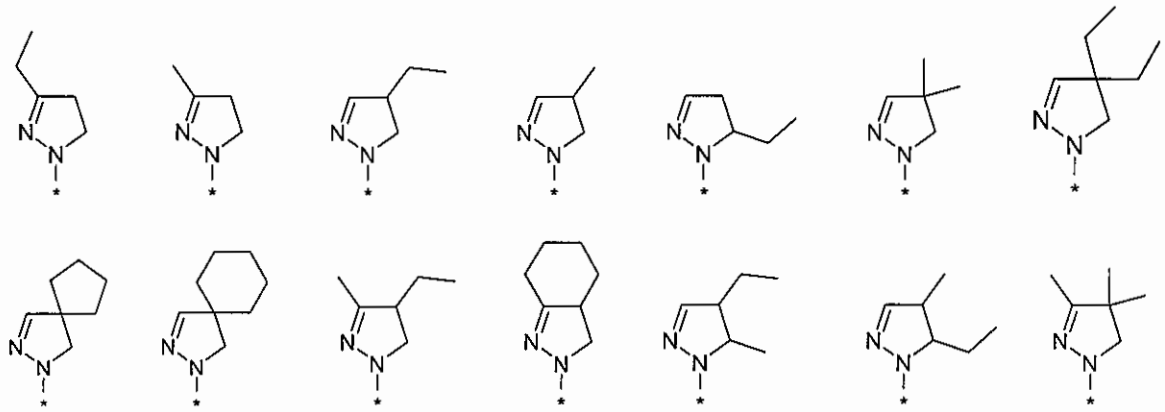
- R_6 is chosen from hydrogen or an alkyl(C_{1-3}) group optionally substituted with one to three fluoro atoms,

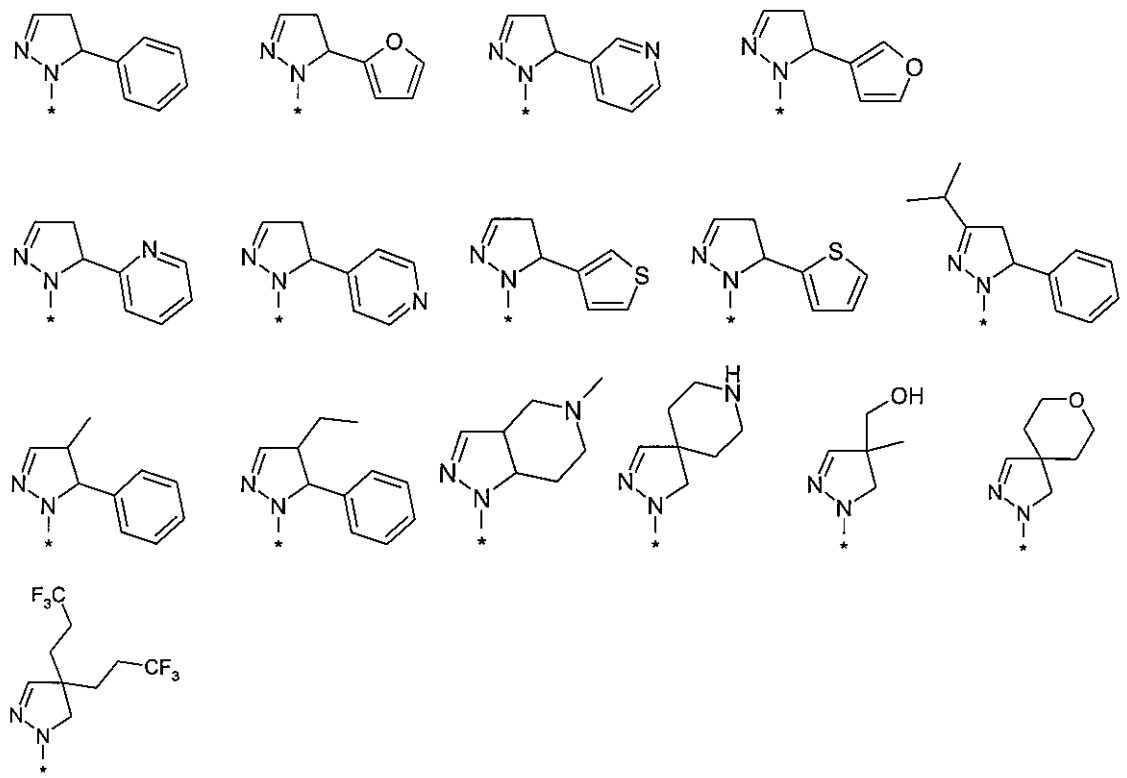
- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one to five substituents Q, as defined above or R_7 represents a 2-aryl-ethenyl group or a 2-aryl-ethynyl group, or R_7 represents a piperidinyl group, or
  R_7 represents à 2,3-dihydroindolyl group or a benzimidazol-2-one group.

3. A process as claimed in claim 1, for the preparation of a compound of formula (I), wherein the moiety:



is chosen from:

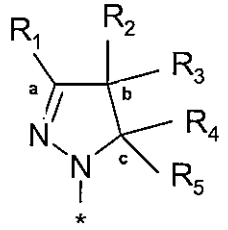




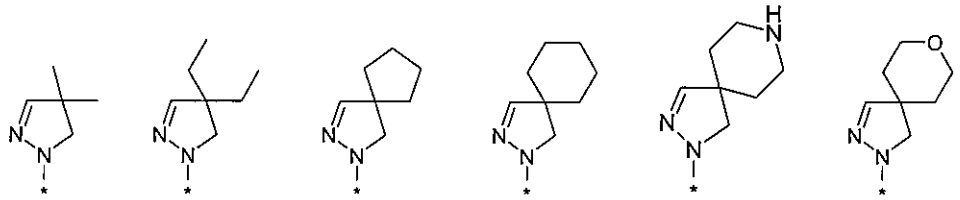
- R_6 is chosen from hydrogen or an alkyl(C_{1-3}) group optionally substituted with one to three fluoro atoms,

- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one to five substituents Q, as defined above, or R_7 represents a 2-aryl-ethenyl group or a 2-aryl-ethynyl group, or R_7 represents a piperidinyl group, or
  R_7 represents a 2,3-dihydroindolyl group or a benzimidazol-2-one group

4. A process as claimed in claim 1, for the preparation of a compound of formula (I), wherein the moiety:



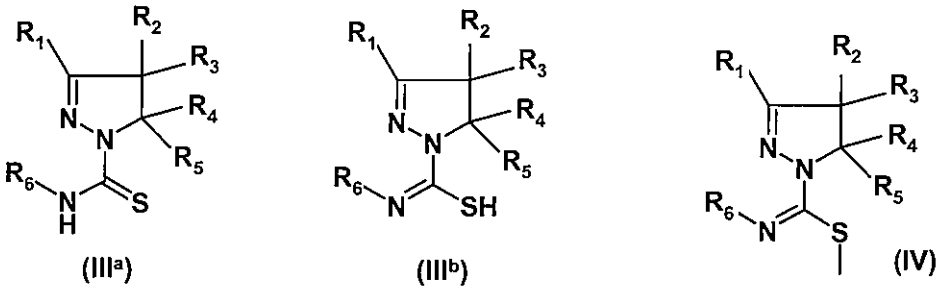
is chosen from:



- R_6 is chosen from hydrogen or an alkyl(C_{1-2}) group optionally substituted with three fluoro atoms,

- R_7 represents a monocyclic, or a fused-bicyclic aromatic or hetero-aromatic group, which groups are unsubstituted or substituted with one or two substituents chosen from methyl, methoxy, fluoro, chloro, bromo, cyano, acetamido, trifluoroacetamido, trifluoromethyl, amino or hydroxy

5. A compound of formula (III^a), (III^b) or (IV):



wherein R_1, R_2, R_3, R_4 and R_5 have the meanings as given in claim 1, as well as tautomers, stereoisomers, and salts of any of the foregoing, such compounds being useful in the synthesis of compounds of formula (I).

6. A compound as claimed in claim 5, selected from those of the formulae:

