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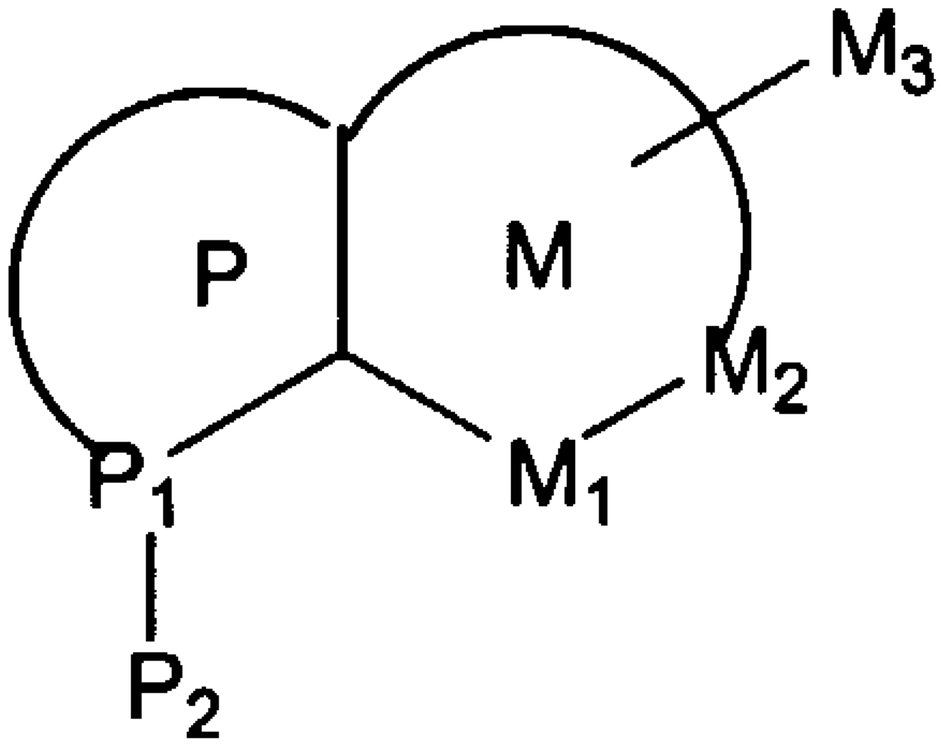
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(54) Titre : INHIBITEURS BICYCLIQUES DU FACTEUR XA
(54) Title: BICYCLIC INHIBITORS OF FACTOR XA



(I)

(57) Abrégé/Abstract:
This invention relates generally to a novel class of bicyclic heterocyclic compounds of the Formula (I), or pharmaceutically acceptable salt forms thereof, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

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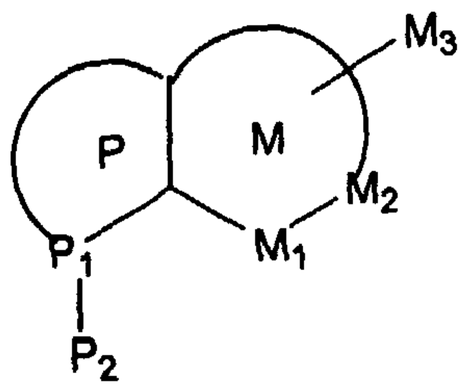
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(54) Title: BICYCLIC INHIBITORS OF FACTOR XA



(I)

(57) Abstract: This invention relates generally to a novel class of bicyclic heterocyclic compounds of the Formula (I), or pharmaceutically acceptable salt forms thereof, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

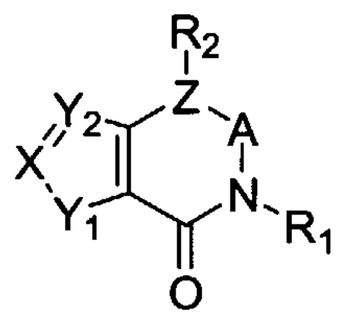
Bicyclic Inhibitors of Factor Xa

FIELD OF THE INVENTION

This invention relates generally to a novel class of bicyclic heterocycles, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

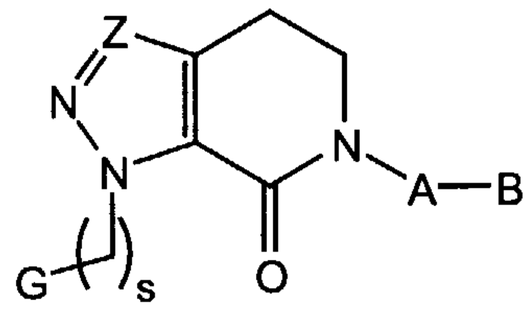
BACKGROUND OF THE INVENTION

WO98/52948 details inhibitors of ceramide-mediated signal transduction. One of the types of inhibitors described is of the following formula:



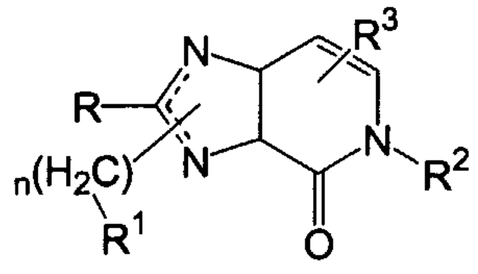
wherein Y_1 can be N-R_6, R_6 can be unsubstituted aryl-alkyl or unsubstituted heterocyclic-alkyl and R_1 can be a substituted aryl group. WO98/52948 does not mention factor Xa inhibition or show compounds like those of the present invention.

WO99/39131 describes heterobicyclic Factor Xa inhibitors of which the following is an example formula:



wherein Z is C or N, G is a mono- or bicyclic group, A is a cyclic moiety and B is a basic group or a cyclic moiety. Compounds with this substitution pattern are not considered to be part of the present invention.

WO00/40583 and WO00/20416 describes factor Xa inhibitors of the following formula:



wherein R is alkyl or cycloalkyl, R^1 and R^2 are optionally substituted phenyl, naphthyl, or biphenyl.

WO01/19798 describes factor Xa inhibitors of the following formula:

A-Q-D-E-G-J-X

wherein A, D, G, and X can be phenyl or heterocycle. However, none of the presently claimed compounds are exemplified or suggested in WO01/19798.

None of the above references teaches or suggests the compounds of the present invention that are described in detail below.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S, Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* **1979**, *15*, 617-629), inhibition of factor Xa may be more efficient than

inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel bicyclic heterocycles that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

The present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

The present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

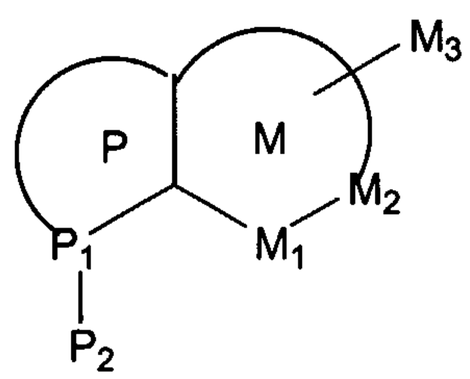
The present invention to provide novel bicyclic compounds for use in therapy.

The present invention provides the use of novel bicyclic compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other features of the invention, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that the presently claimed fused heterocyclic compounds, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] In an embodiment, the present invention provides a novel compound of Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

ring M, including M_1 and M_2, is a 5, 6, or 7 membered carbocycle or heterocycle, consisting of: carbon atoms, 0-3 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NZ^2; and ring M is substituted with 0-2 R^3;

M_1 is C(O), CH, CH_2, O, N, SO or SO_2;

M_2 is C, CH, or N;

ring P, including P_1, is a 5, 6, or 7 membered non-aromatic carbocycle or heterocycle, consisting of: carbon atoms, 0-2 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NH; and ring P is substituted with 0-2 R^{1a};

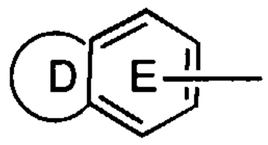
P_1 is C or N;

one of P_2 and M_3 is -Z-A-B and the other $-G_1-G$;

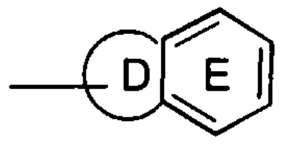
G_1 is absent or is selected from $(CR^3R^{3a})_{1-5}$, $(CR^3R^{3a})_{0-2}CR^3=CR^3(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_{0-2}C\equiv C(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(S)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}S(O)_2NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3e}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}S(O)_2(CR^3R^{3a})_w$, and

$(CR^3R^{3a})_uS(O)_2NR^{3b}C(O)NR^{3b}CR^3R^{3a})_w$, wherein (u + w) or (u + u +w) is 0, 1, 2, 3, or 4, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of ring E to which it is attached, is a 5-6 membered non-aromatic ring consisting of carbon atoms, 0-1 double bonds, and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and ring D is substituted with 0-2 R^1, provided that ring D has other than a O-O, O-$S(O)_p$, $S(O)_p$-O, and $S(O)_p$-$S(O)_p$, bond;

alternatively, ring D, including the two atoms of ring E to which it is attached, is a 5-6 membered aromatic group consisting of carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and ring D is substituted with 0-2 R^1;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 0-1 R^1;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, thienyl and trizaolyl, and ring E is substituted with 0-2 R^a;

R^a is selected from F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $C(O)NR^7R^8$, $(CR^8R^9)_tNR^7R^8$, SH, SCH_3, SCH_2CH_3, $SCH(CH_3)_2$, $SCH_2CH_2CH_3$, $S(O)R^{3b}$, $S(O)_2R^{3a}$, $S(O)_2NR^2R^{2a}$, and OCF_3;

alternatively, two R^as combine to form methylenedioxy or ethylenedioxy;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, and thienyl, and ring E is substituted with 1 R and with a 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 carbonyl groups and 0-2 R^1;

alternatively, ring D is absent and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with R^e;

R^e is selected from CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

A is selected from:

C_{3-10} carbocycle substituted with 0-2 R^4, and

5-12 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^4;

B is selected from: Y, X-Y, $(CH_2)_{0-2}C(O)NR^2R^{2a}$, $(CH_2)_{0-2}NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, and $NR^2C(=NR^2)NR^2R^{2a}$, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^2R^{2a})-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$, $-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

$-(CH_2)_rNR^2R^{2a}$;

C_{3-10} carbocycle substituted with 0-2 R^{4a}; and

5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{4a};

provided that X-Y do not form a N-N, O-N, or S-N bond;

Z is selected from a bond, $-(CR^3R^{3a})_{1-4}-$, $(CR^3R^{3a})_qO(CR^3R^{3a})_m$, $(CR^3R^{3a})_qNR^{3b}(CR^3R^{3a})_m$, $(CR^3R^{3a})_qC(O)(CR^3R^{3a})_m$, $(CR^3R^{3a})_qC(O)O(CR^3R^{3a})_m$, $(CR^3R^{3a})_qOC(O)(CR^3R^{3a})_m$, $(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_m$, $(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_m$, $(CR^3R^{3a})_qOC(O)O(CR^3R^{3a})_m$,

$(CR^3R^{3a})_qOC(O)NR^{3b}(CR^2R^{2a})_m$, $(CR^3R^{3a})_qNR^{3b}C(O)O(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qC(O)(CR^3R^{3a})_qC(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_m$,
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$(CR^3R^{3a})_qS(CR^3R^{3a})_m$, $(CR^3R^{3a})_qS(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qS(O)_2(CR^3R^{3a})_m$, $(CR^3R^{3a})_qSO_2NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}SO_2(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qS(O)NR^{3b}C(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qC(O)NR^{3b}S(O)_2(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}SO_2NR^{3b}(CR^3R^{3a})_m$, wherein (q + m) or (q + q + m) is 0, 1, 2, 3, or 4, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z^2 is selected from H; $S(O)_2NHR^3$; $C(O)R^3$; $C(O)NHR^3$; $C(O)OR^{3f}$; $S(O)R^{3f}$; $S(O)_2R^{3f}$; C_{1-6} alkyl substituted with 0-2 R^{1a}; C_{2-6} alkenyl substituted with 0-2 R^{1a}; C_{2-6} alkynyl substituted with 0-2 R^{1a}; -(C_{0-4} alkyl)-C_{3-10}-carbocycle substituted with 0-3 R^{1a}; -(C_{0-4} alkyl)-5-12 membered-heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl),

$N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tC(O)H$, $(CR^8R^9)_tC(O)R^{2c}$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, $(CR^8R^9)_tNR^7C(O)R^7$, $(CR^8R^9)_tOR^3$, $(CR^8R^9)_tS(O)_pNR^7R^8$, $(CR^8R^9)_tNR^7S(O)_pR^7$, $(CR^8R^9)_tSR^3$, $(CR^8R^9)_tS(O)R^3$, $(CR^8R^9)_tS(O)_2R^3$, and OCF_3;

R^1 is selected from F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl$)_2$;

R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-(CH_2)_r-O-(CH_2)_r-R^{1b}$, $-CH=CH-R^{1b}$, NCH_2R^{1c}, NR^2R^{2a}, OCH_2R^{1c}, SCH_2R^{1c}, $NH(CH_2)_2(CH_2)_tR^{1b}$, $C(O)NR^2(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and $NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

alternatively, when two R^{1a}s are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)^P$, this ring being substituted with 0-2 R^{4b}, and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN,

-CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, substituted with 0-2 R^{4a}, provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond with the group to which it is attached;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-6} carbocycle substituted with 0-2 R^{4a} and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^2 and R^{2a}, at each occurrence, are independently selected from H; CF_3; C_{1-6} alkyl; benzyl; $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}; and $-(CH_2)_r$-5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and consisting of: carbon

atoms and 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl substituted with 0-2 R^{4b}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^3 and R^{3a}, at each occurrence, is independently selected from H, C_{1-4} alkyl, benzyl and phenyl;

R^{3b}, at each occurrence, is selected from H, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and $-(C_{0-4}$ alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, benzyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

R^{3e}, is selected from H, $S(O)_2NHR^3$, $C(O)R^3$, $C(O)NHR^3$, $C(O)OR^{3f}$, $S(O)R^{3f}$, $S(O)_2R^{3f}$, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, -(C_{0-4} alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and -(C_{0-4} alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3f}, at each occurrence, is selected from: C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, -(C_{0-4} alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and -(C_{0-4} alkyl)-5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $(CH_2)_rNR^2C(O)R^{2b}$, $(CH_2)_rC(O)NR^2R^{2a}$, $(CH_2)_rNR^2C(O)NR^2R^{2a}$, $(CH_2)_rC(=NR^2)NR^2R^{2a}$, $(CH_2)_rC(=NS(O)_2R^5)NR^2R^{2a}$, $(CH_2)_rNHC(=NR^2)NR^2R^{2a}$, $(CH_2)_rC(O)NHC(=NR^2)NR^2R^{2a}$, $(CH_2)_rSO_2NR^2R^{2a}$, $(CH_2)_rNR^2SO_2NR^2R^{2a}$, $(CH_2)_rNR^2SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^2SO_2R^5$, $(CH_2)_rS(O)_pR^{5a}$, $(CF_2)_rCF_3$, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$,

$O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, $(CR^3R^{3a})_rF$, $(CR^3R^{3a})_rBr$, $(CR^3R^{3a})_rCl$, C_{1-4} alkyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rN=CHOR^3$, $(CR^3R^{3a})_rC(O)NH(CH_2)_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rNHC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $(CR^3R^{3a})_rC(O)NHSO_2$-C_{1-4} alkyl, $(CR^3R^{3a})NR^2SO_2R^5$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CR^3R^{3a})_r(CF_2)_rCF_3$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_r$-$C(=NR^3)NR^3R^{3a}$, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$, $(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$,

$(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, and $(CH_2)_r(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^{5a}, at each occurrence, is selected from C_{1-6} alkyl, $(CH_2)_rOR^3$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6, provided that R^{5a} does not form a S-N or $S(O)_p$-C(O) bond;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, $(CH_2)_n$-phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4}

alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $-(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5 or 6 membered saturated ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $-(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5 and 6;

t, at each occurrence, is selected from 0, 1, 2, and 3; and

provided that:

(a) when M_1 is a carbonyl and G is substituted with an amidino, guanidino, amino-ethylene, or amino-propylene group, any of which may be substituted or cyclized, then G_1 is present or Z is other than alkylene; or

(b) when M_1 is a carbonyl and G_1 is absent, then Z is other than alkylene;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) G_1 is $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$, or $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$; u+w is 1, 2, 3, or 4;

then Z is other than $(CH_2)NR^{3b}$, $NR^{3b}(CH_2)$, $(CH_2)NR^{3b}(CH_2)$, $(CH_2)(CH_2)NR^{3b}$, $NR^{3b}(CH_2)(CH_2)$, $(CH_2)_qC(O)NR^{3b}(CH_2)_m$, $(CH_2)_qNR^{3b}C(O)(CH_2)_m$, $(CH_2)_qSO_2NR^{3b}(CH_2)_m$, or $(CH_2)_qNR^{3b}SO_2(CH_2)_m$;

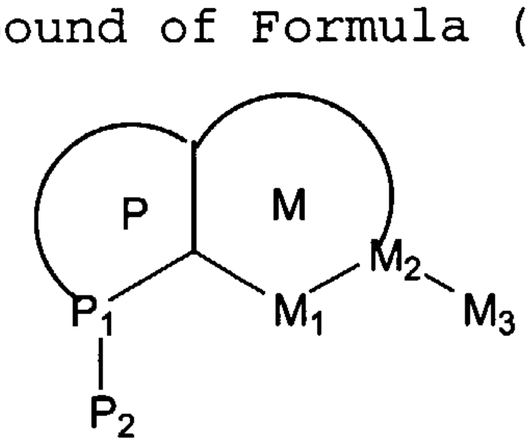
alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) Z is $((CH_2)NR^{3b}$, $NR^{3b}(CH_2)$, $(CH_2)NR^{3b}(CH_2)$, $(CH_2)(CH_2)NR^{3b}$, $NR^{3b}(CH_2)(CH_2)$, $(CH_2)_qC(O)NR^{3b}(CH_2)_m$, $(CH_2)_qNR^{3b}C(O)(CH_2)_m$, $(CH_2)_qSO_2NR^{3b}(CH_2)_m$, or $(CH_2)_qNR^{3b}SO_2(CH_2)_m$;

then G_1 is other than $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$, or $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$; u+w is 1, 2, 3, or 4.

[2] In another embodiment, the present invention provides a novel compound of Formula (Ia):



(Ia)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

ring M, including M_1 and M_2, is a 5, 6, or 7 membered carbocycle or heterocycle, consisting of: carbon atoms, 0-3 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NZ^2; and ring M is substituted with 0-1 R^3;

M_1 is C(O), CH, CH_2, O, N, SO or SO_2;

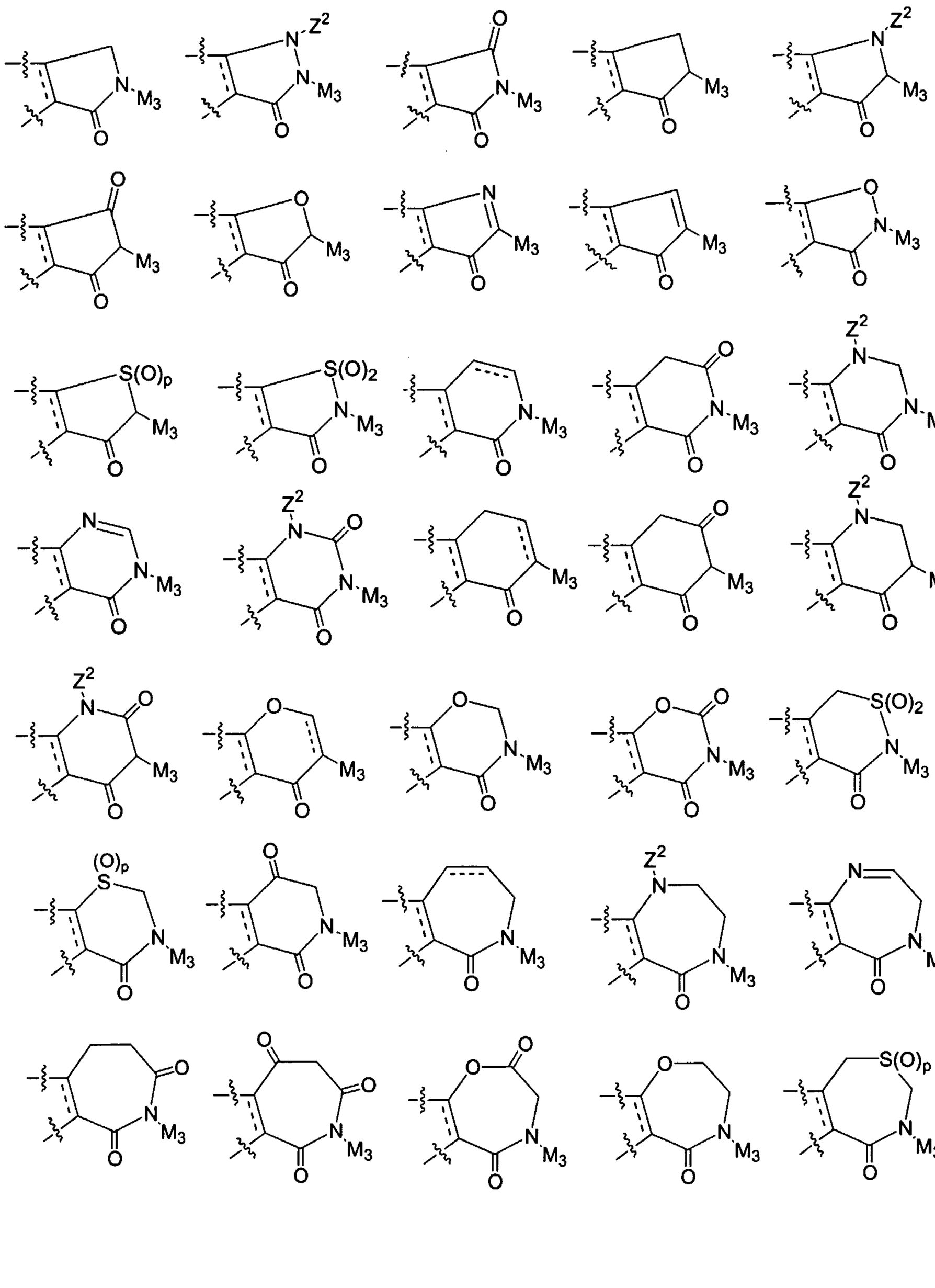
M_2 is C, CH, or N;

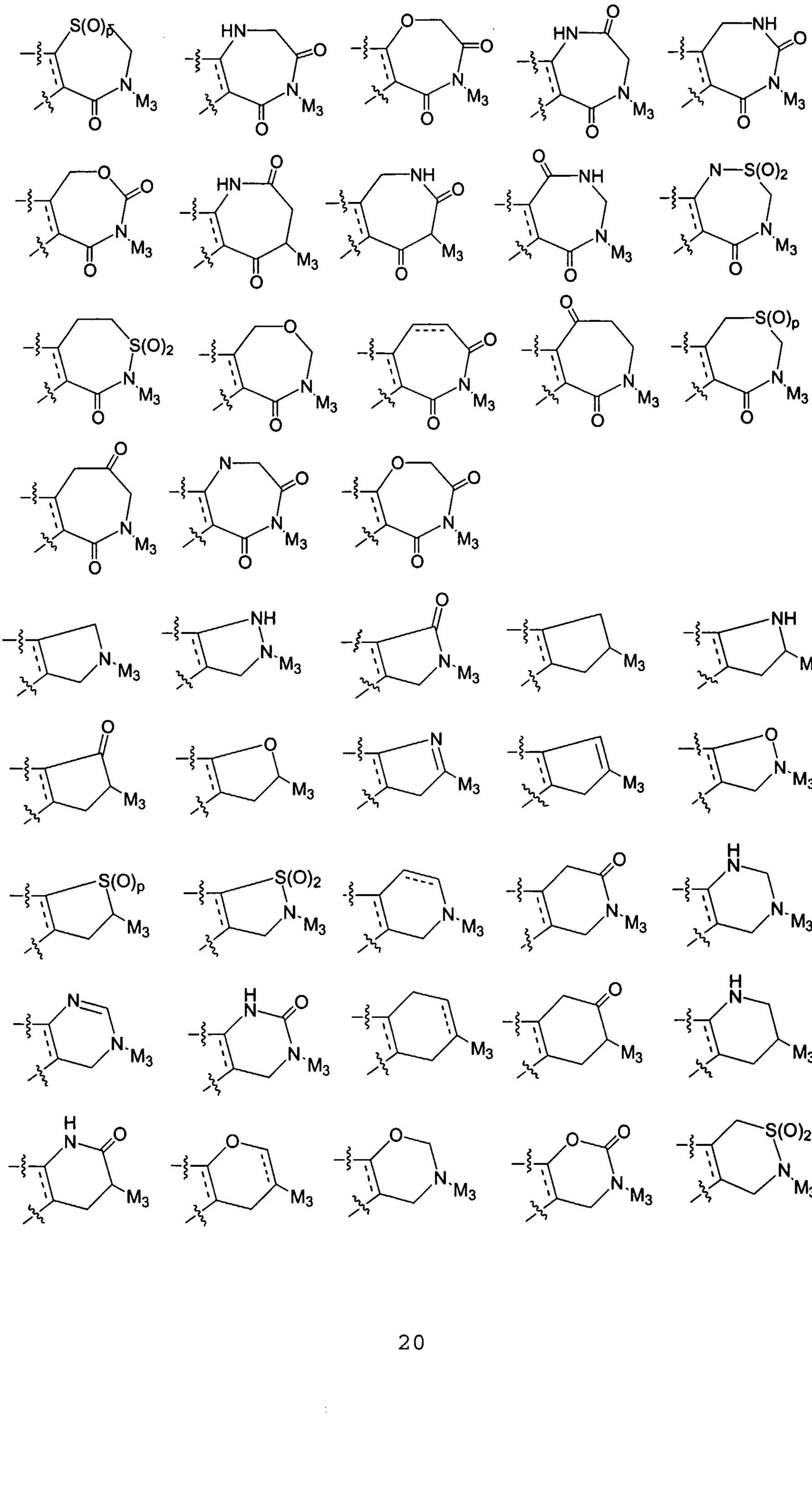
ring P, including P_1, is a 5, 6, or 7 membered non-aromatic carbocycle or heterocycle, consisting of: carbon atoms, 0-2 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NH and ring P is substituted with 0-2 R^{1a}; and,

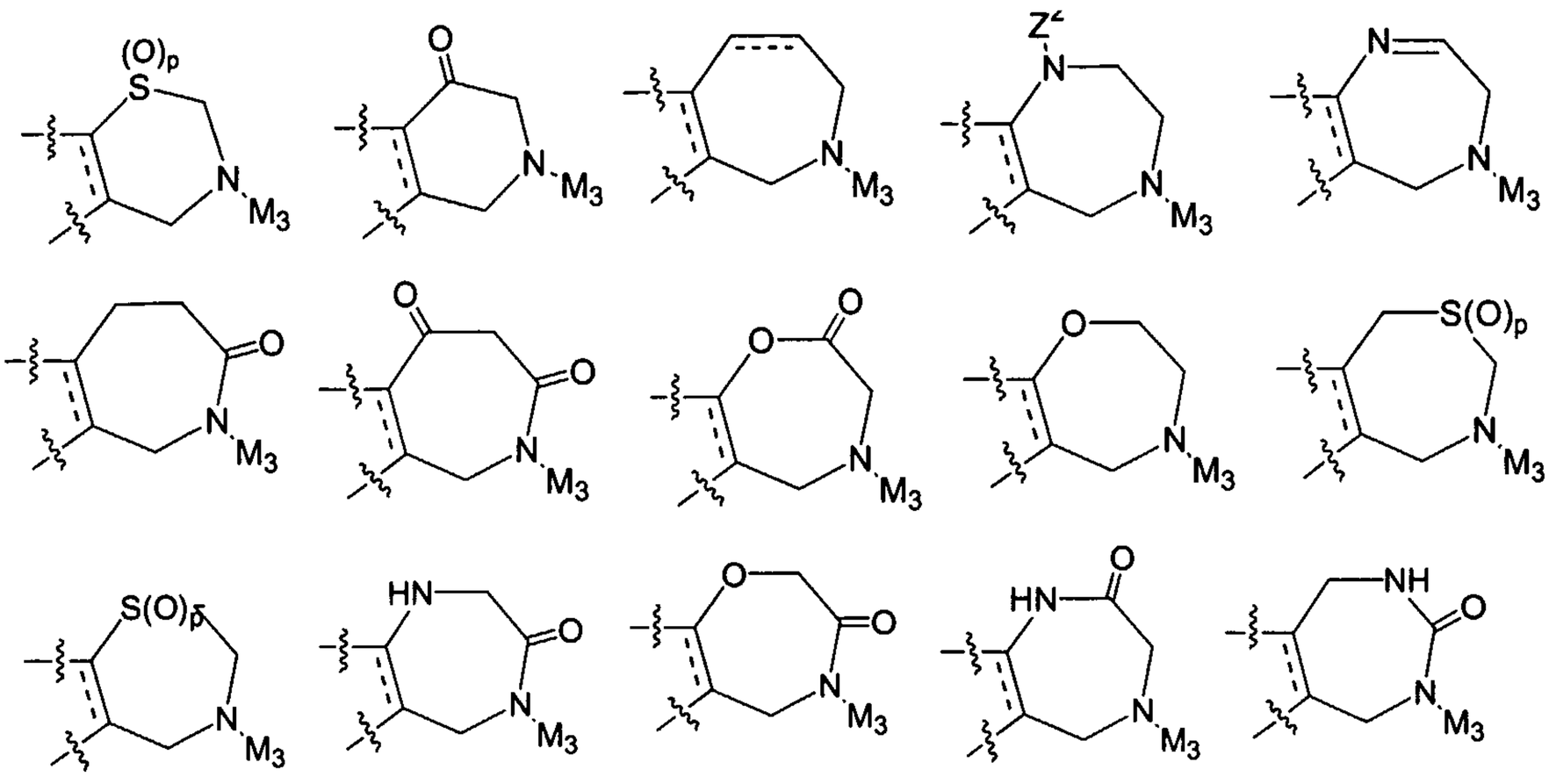
P_1 is C or N.

[3] In another embodiment, the present invention provides a novel compound, wherein:

ring M is substituted with 0-1 R^3 and is selected from the group:

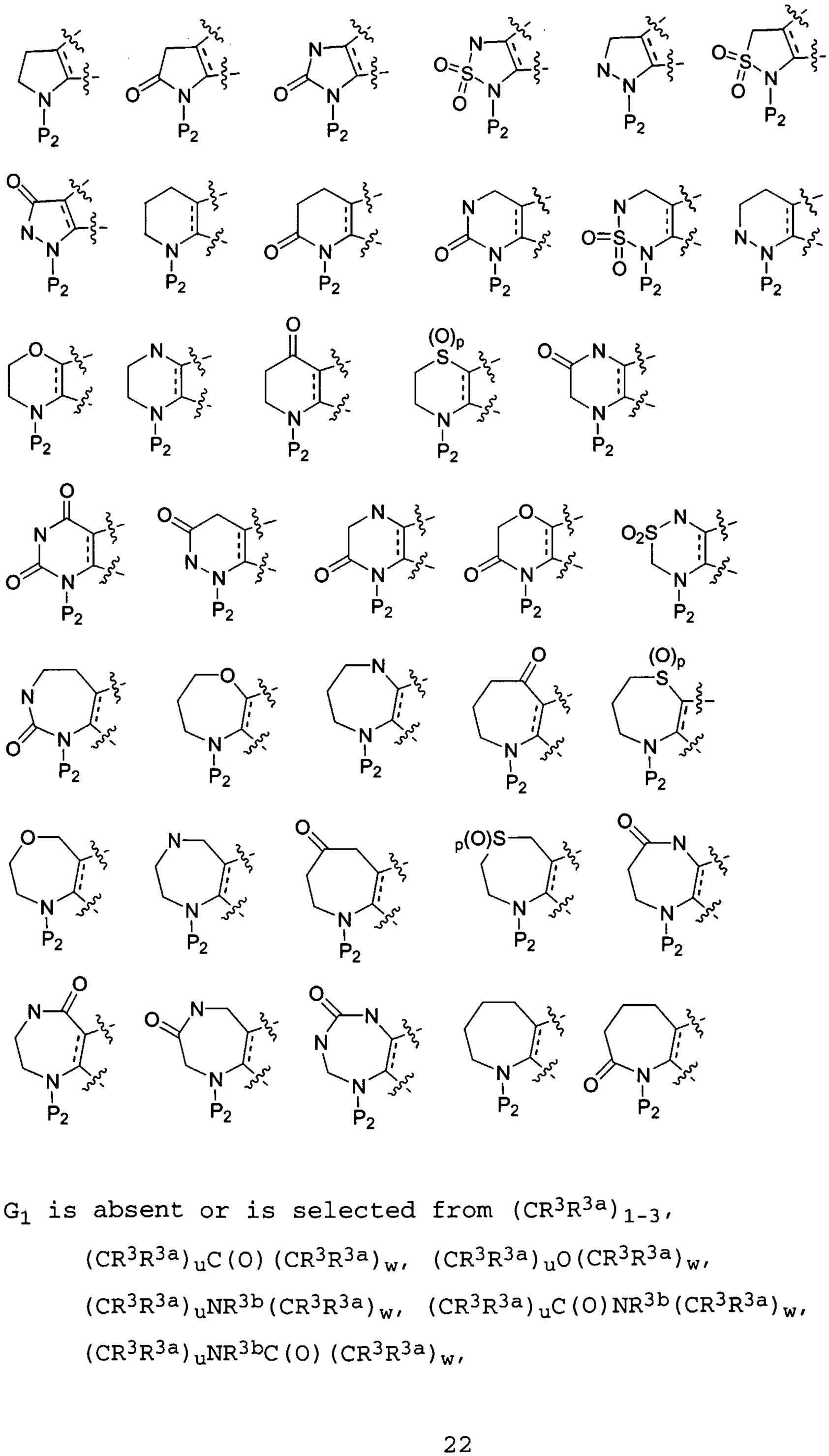






Z^2 is selected from H, C_{1-4} alkyl, phenyl, benzyl, $S(O)_2NHR^3$, $C(O)NHR^3$, $C(O)OR^{3f}$, $S(O)R^{3f}$, and $S(O)_2R^{3f}$;

ring P is substituted with 0-1 R^{1a} and is selected from the group:



5

G_1 is absent or is selected from $(CR^3R^{3a})_{1-3}$,

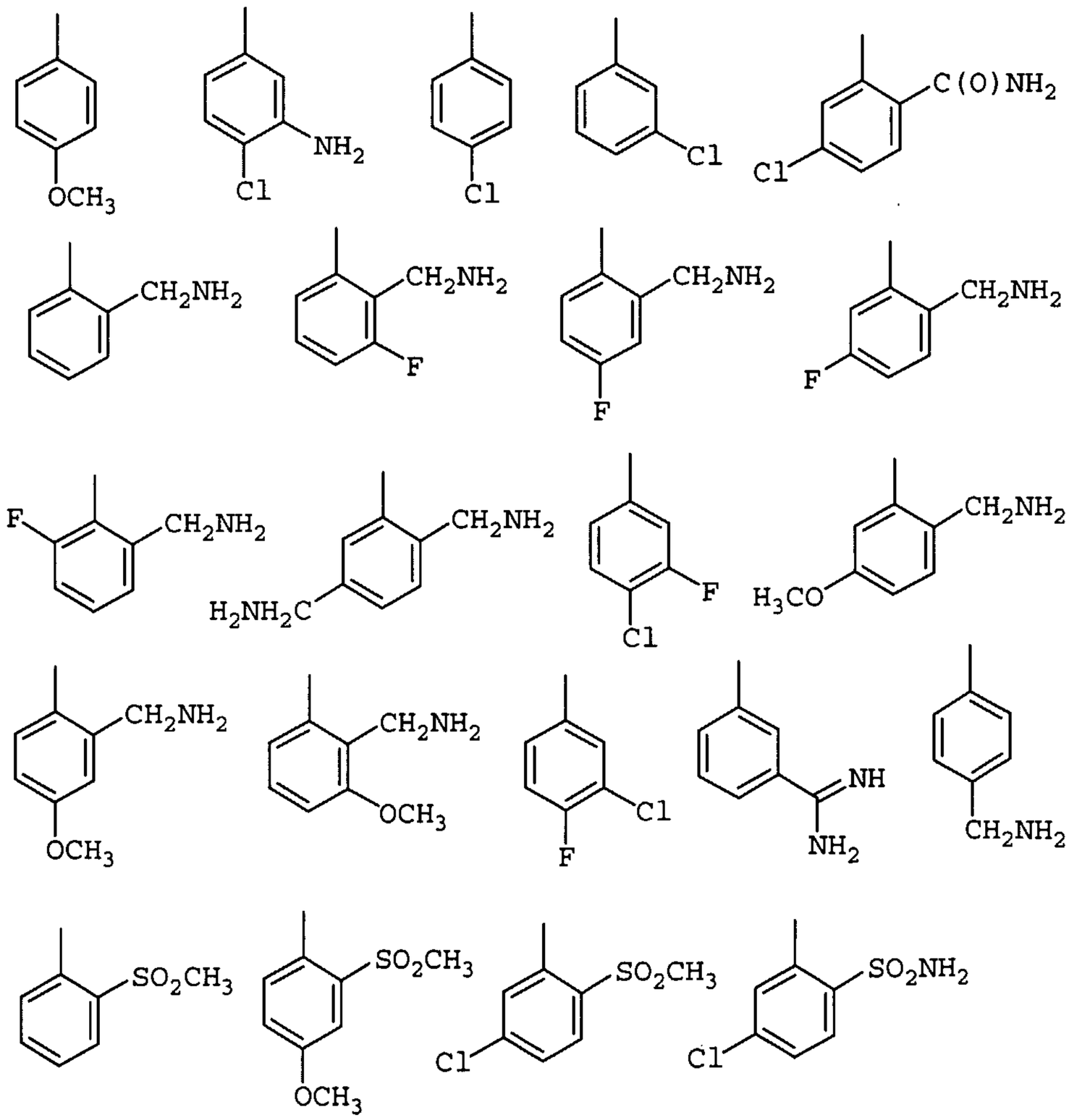
$(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$,

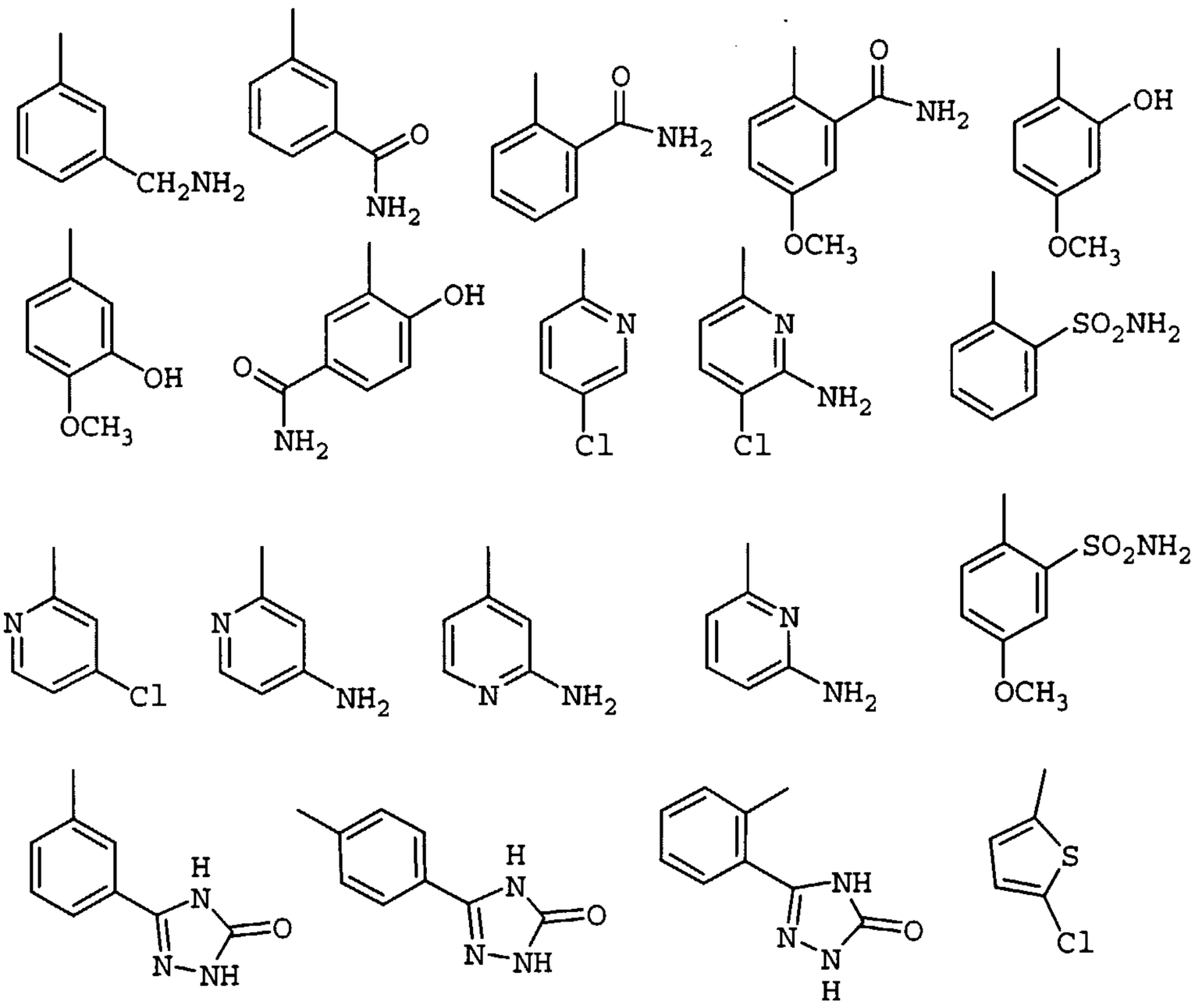
$(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$,

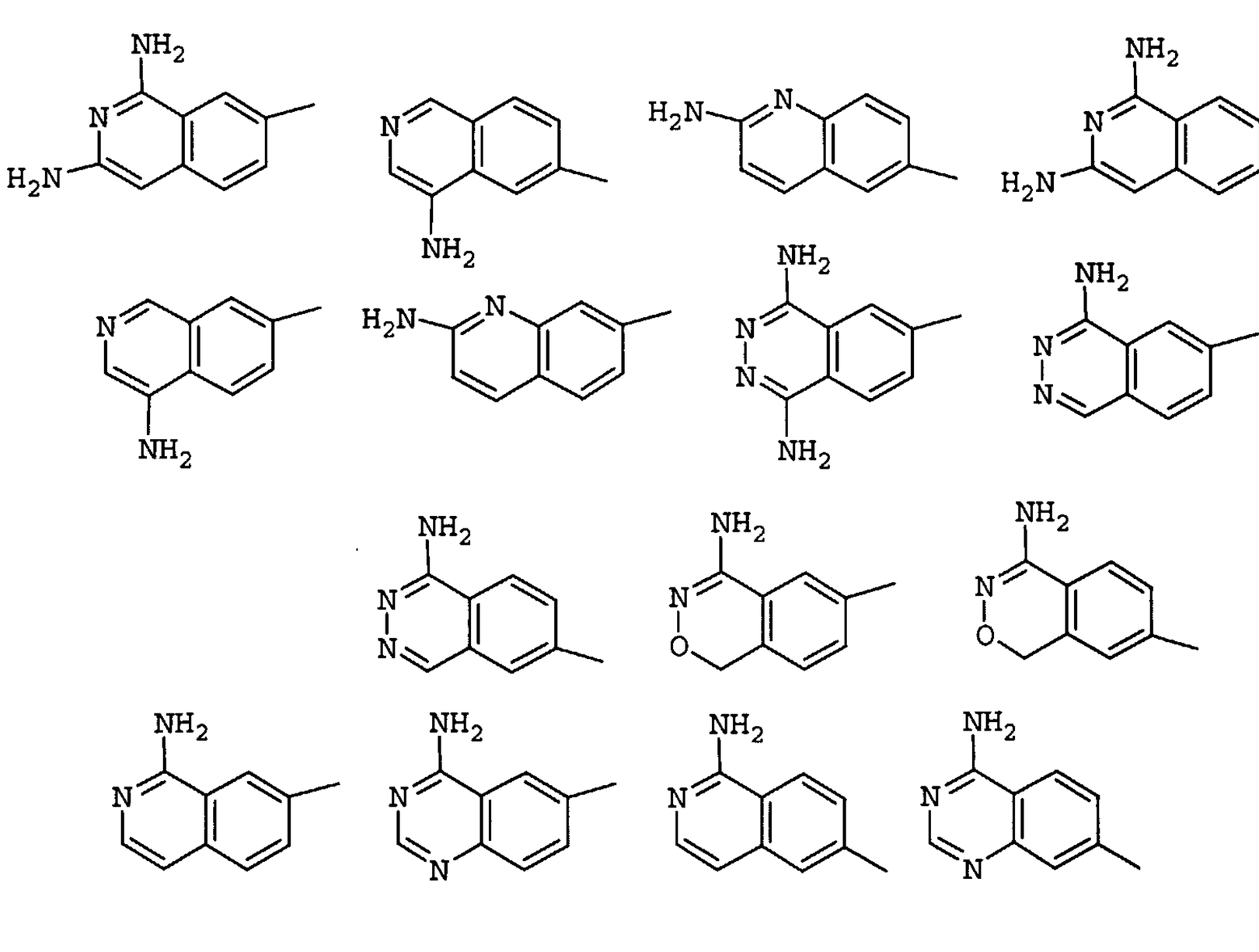
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$,

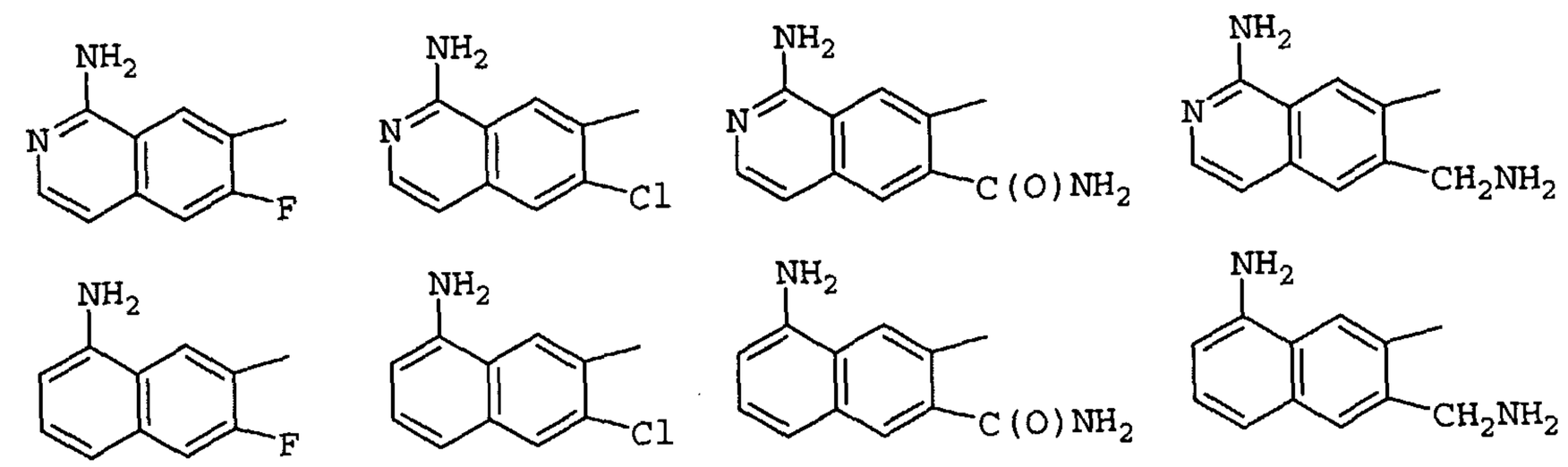
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$, wherein (u + w) or (u + u + w) is 0, 1, or 2, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

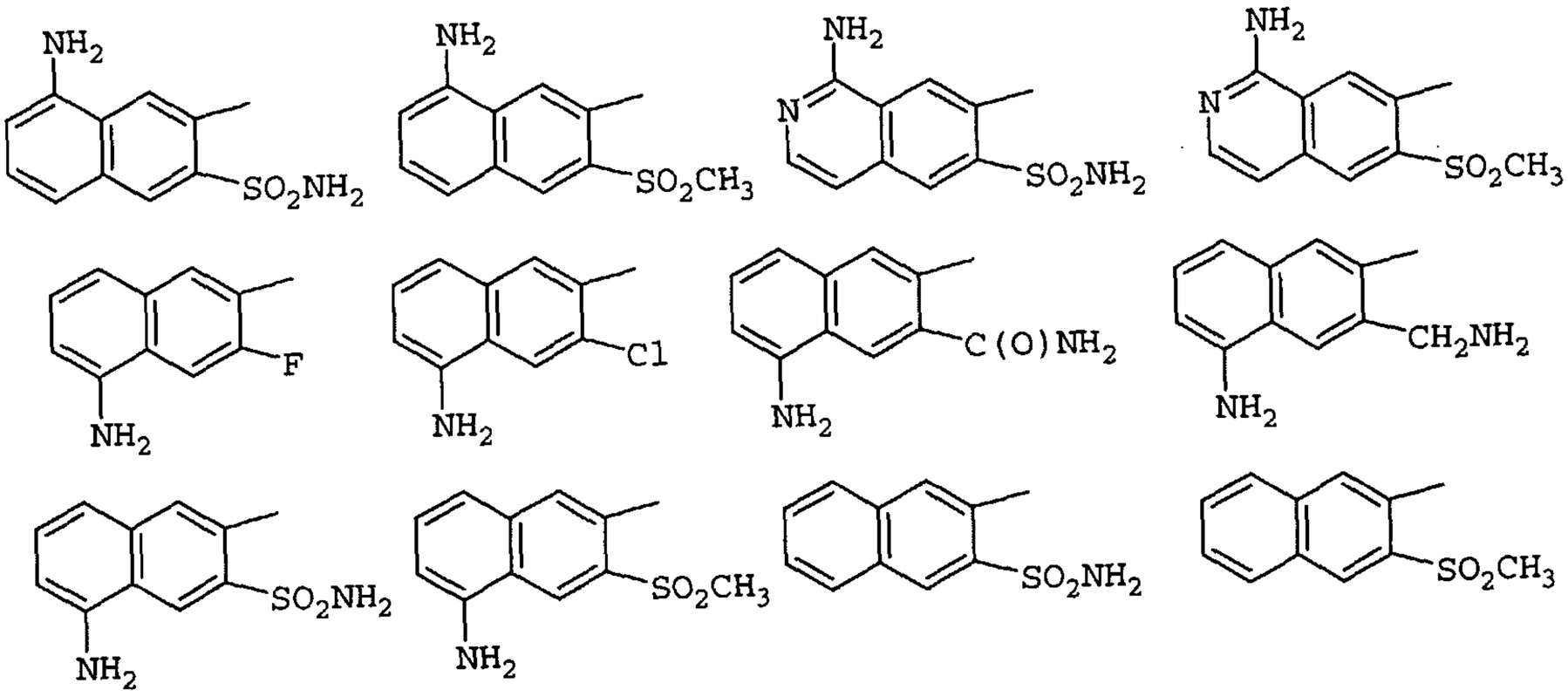
ring G is selected from:

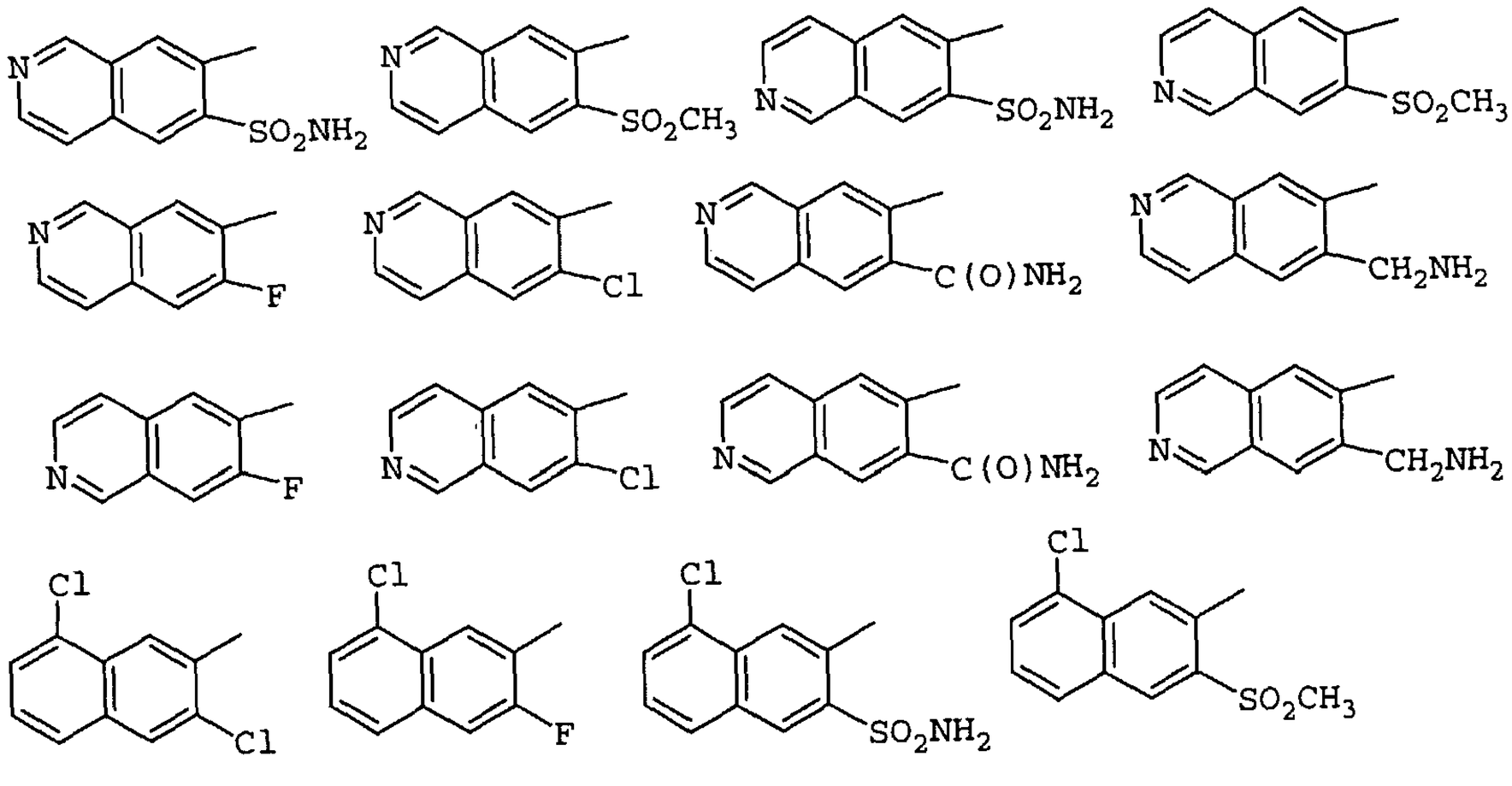


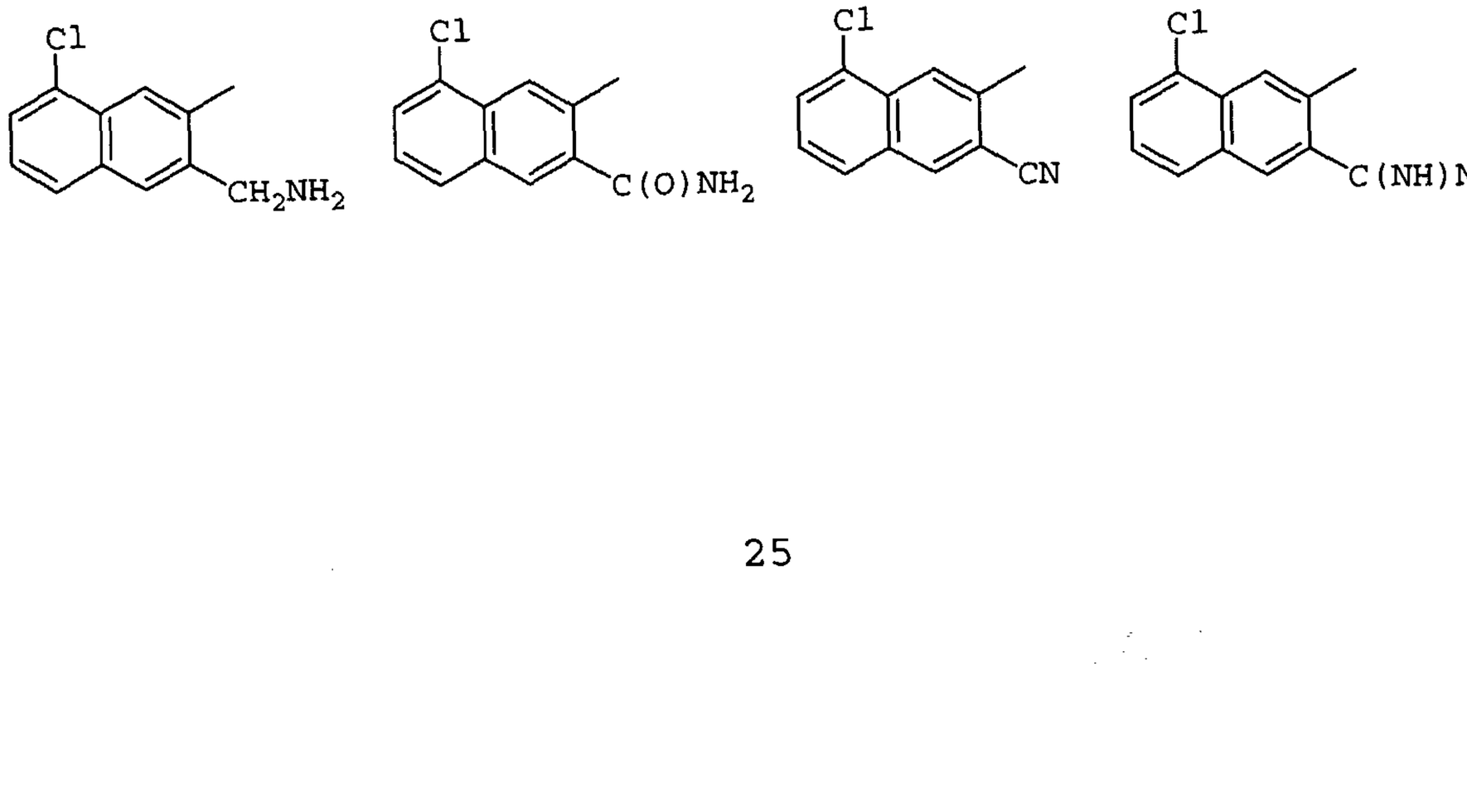


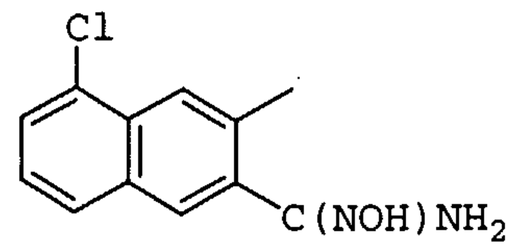
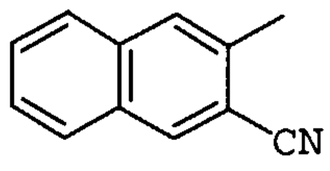
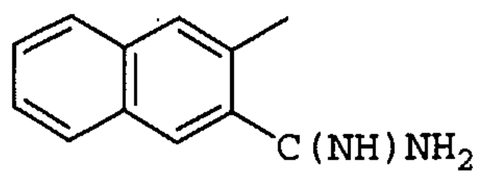
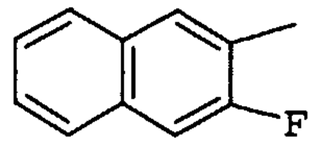
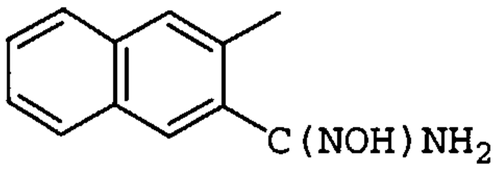
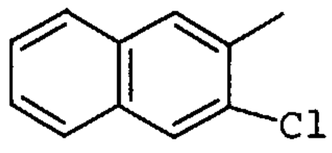
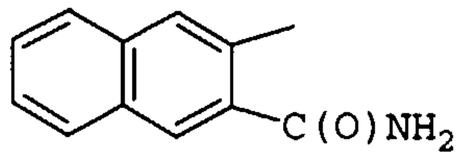
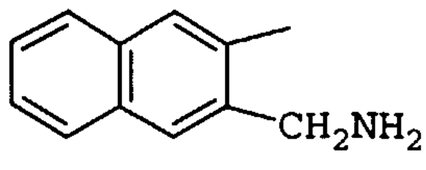
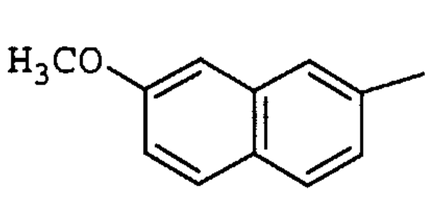
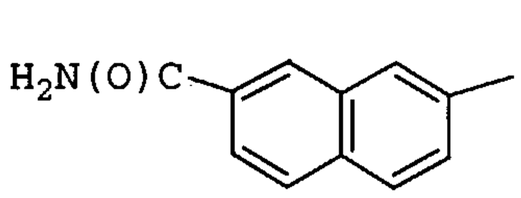
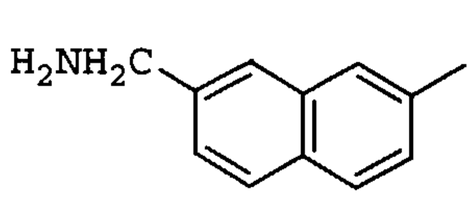
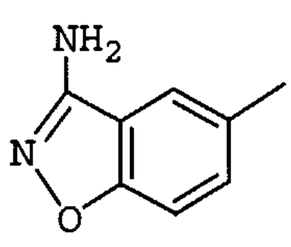
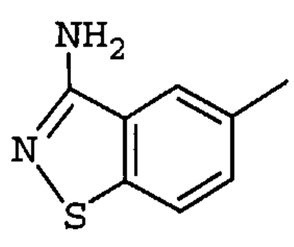
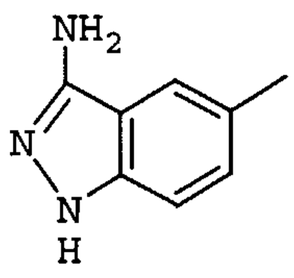
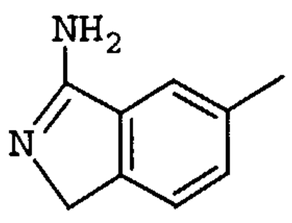
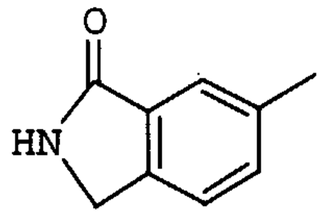
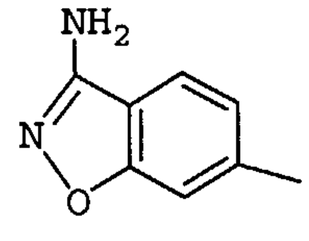
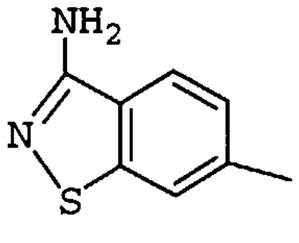
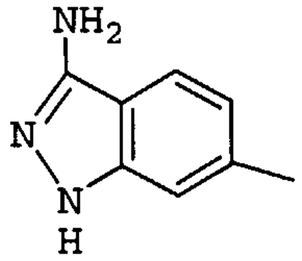
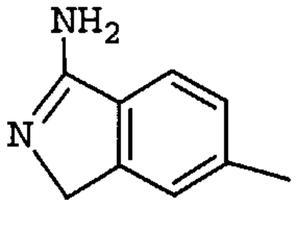
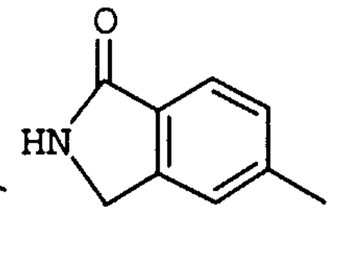
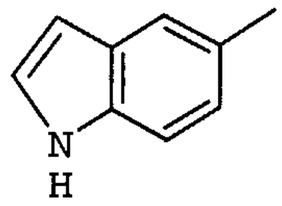
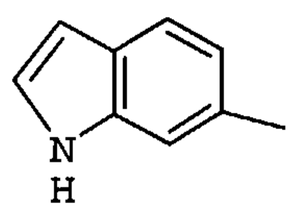
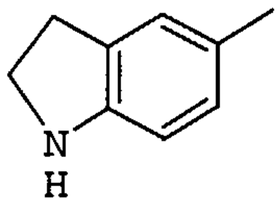
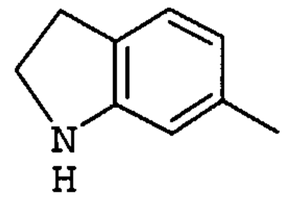
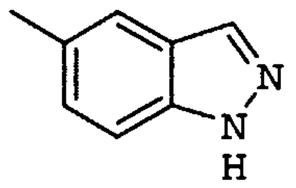
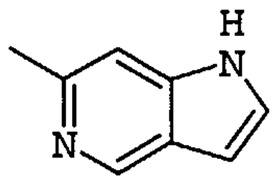
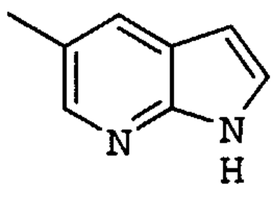
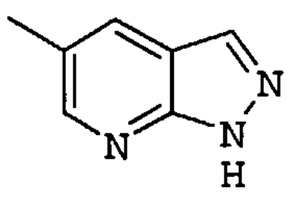
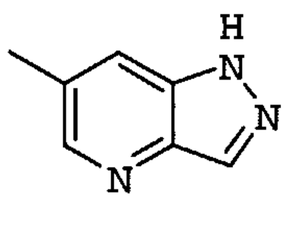
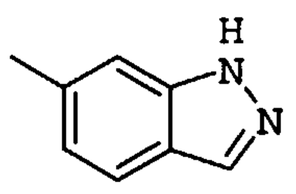
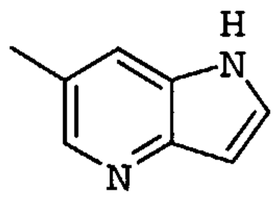
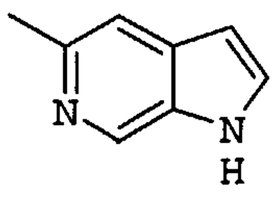
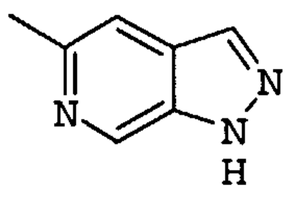
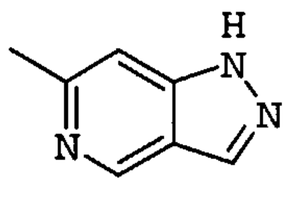
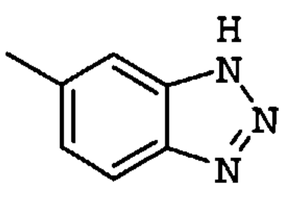


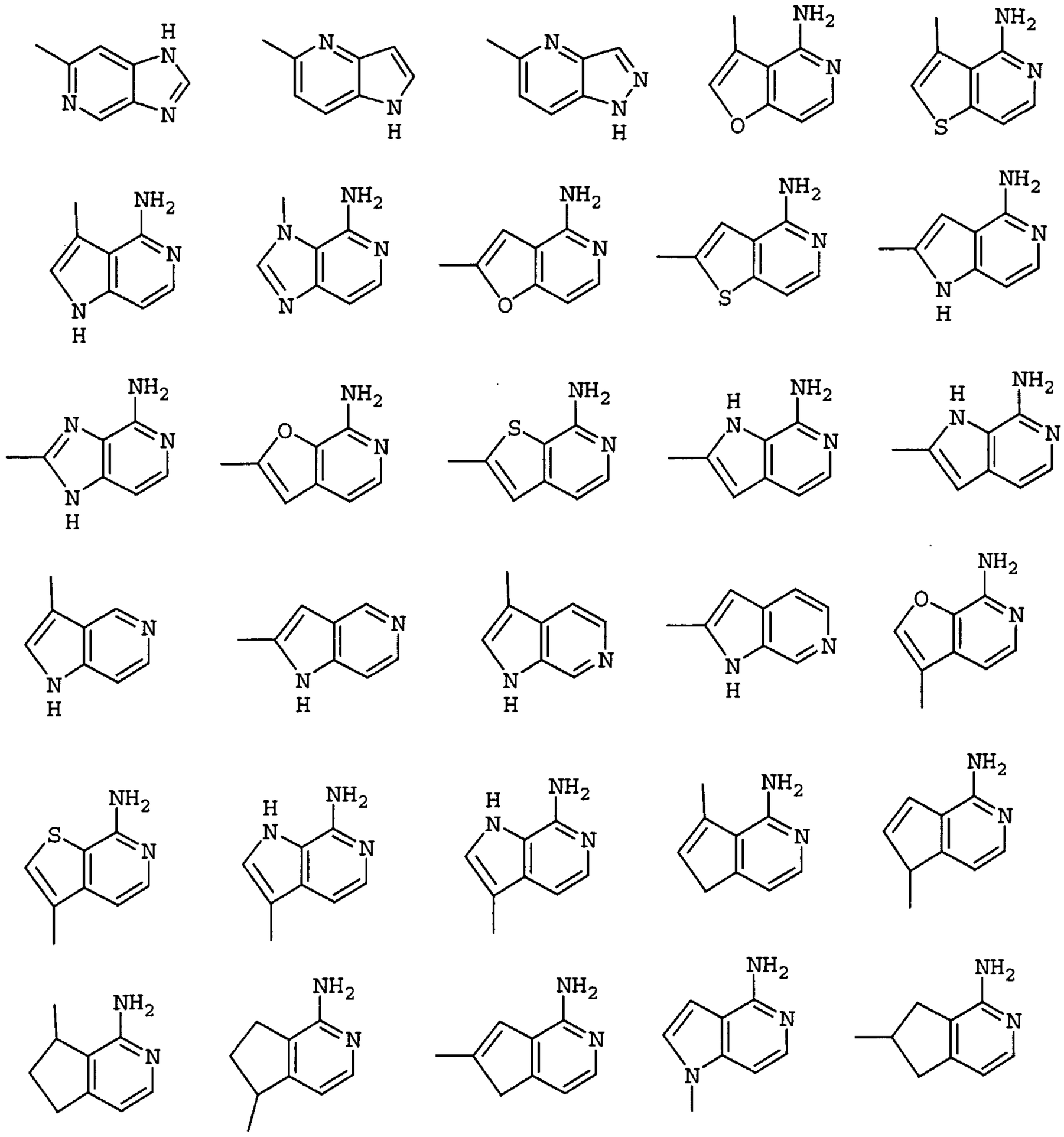










A is selected from one of the following carbocycles and heterocycles which are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,

1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolinyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is selected from Y, X-Y, $CH_2NR^2R^{2a}$, and $CH_2CH_2NR^2R^{2a}$;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^2R^{2a})-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

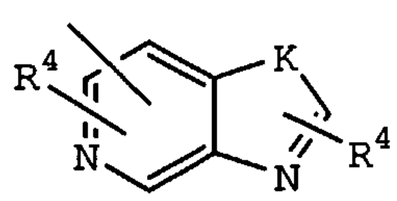
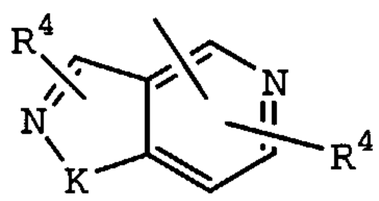
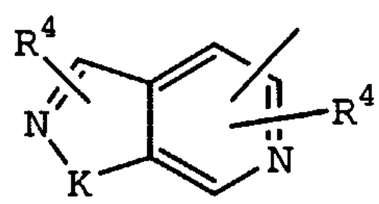
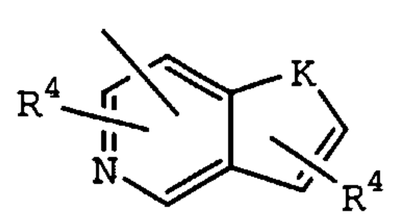
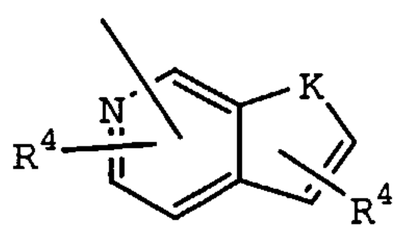
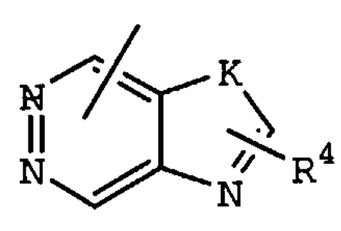
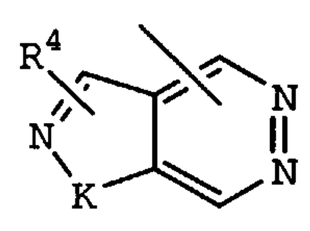
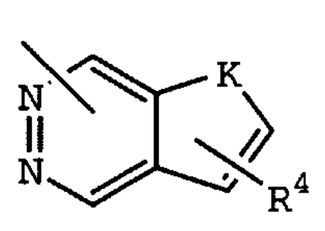
Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocycles and heterocycles which are substituted with 0-2 R^{4a};

cylcopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolinyl, indolyl, benzimidazolyl, benzoxazolyl,

benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:








and


K is selected from O, S, NH, and N;

Z is selected from CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) G_1 is $(CH_2)_uNR^{3b}(CH_2)_w$, $(CH_2)_uC(O)NR^{3b}(CH_2)_w$, $(CH_2)_uNR^{3b}C(O)(CH_2)_w$, $(CH_2)_uS(O)NR^{3b}(CH_2)_w$, $(CH_2)_uS(O)_2NR^{3b}(CH_2)_w$, or $(CH_2)_uNR^{3b}S(O)_2(CH_2)_w$; and

(u + w) is 1 or 2;

then Z is other than CH_2NH, $NHCH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

alternatively, when

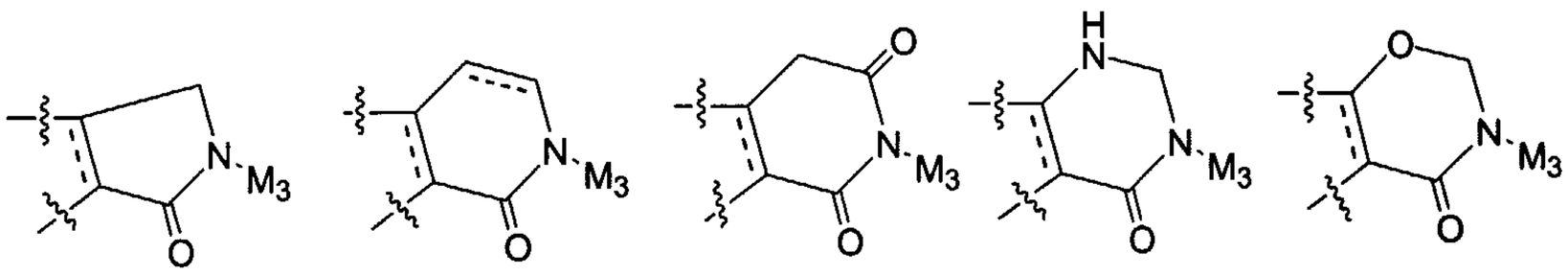
(a) B is other than an optionally substituted carbocycle; and,

(b) Z is CH_2NH, $NHCH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

then G_1 is other than $(CH_2)_uNR^{3b}(CH_2)_w$, $(CH_2)_uC(O)NR^{3b}(CH_2)_w$, $(CH_2)_uNR^{3b}C(O)(CH_2)_w$, $(CH_2)_uS(O)NR^{3b}(CH_2)_w$, $(CH_2)_uS(O)_2NR^{3b}(CH_2)_w$, or $(CH_2)_uNR^{3b}S(O)_2(CH_2)_w$; and (u + w) is 1 or 2.

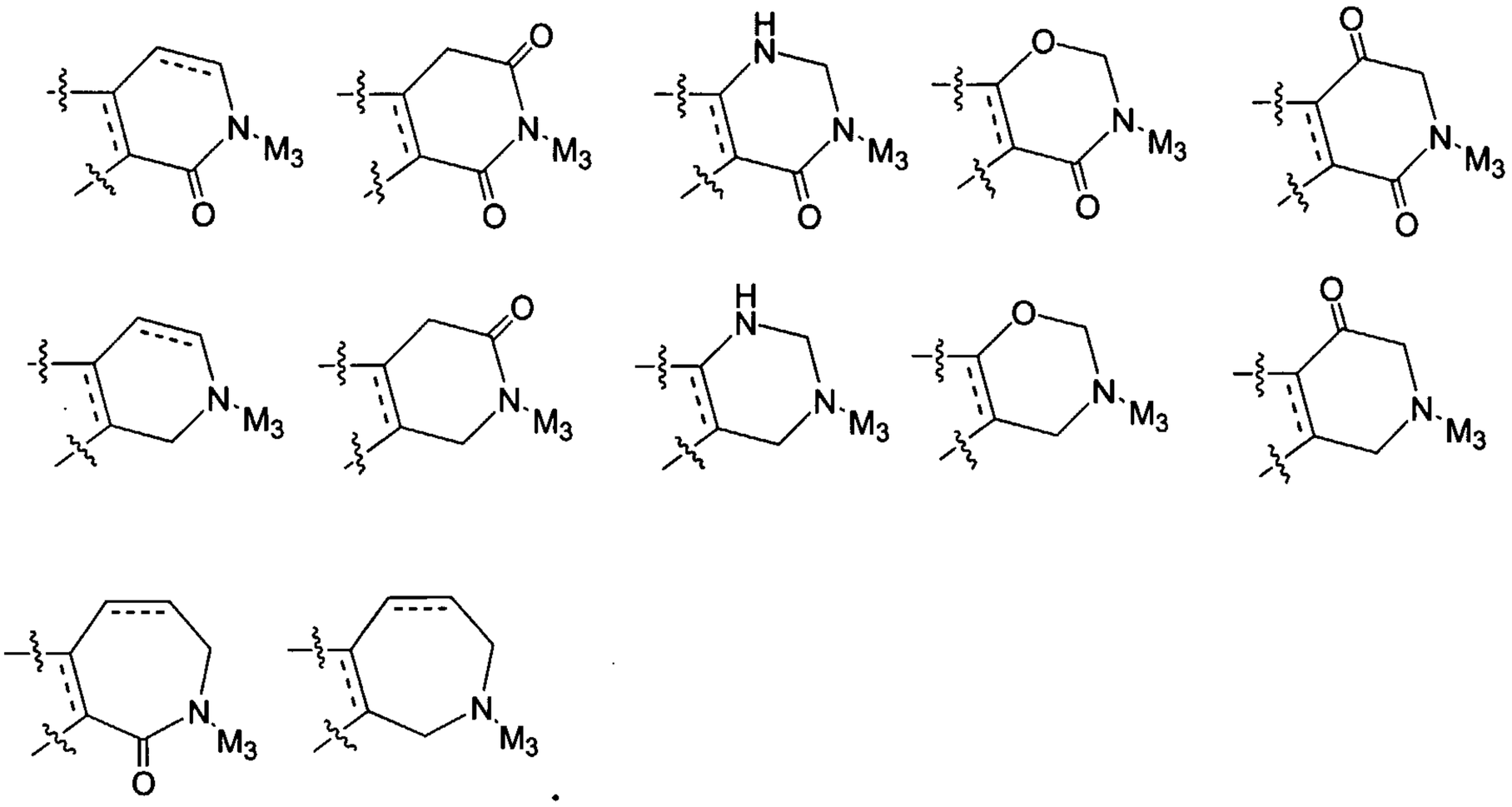
In another embodiment, the present invention provides a novel compound, wherein:

ring M is substituted with 0-1 R^3 and is selected from the group:



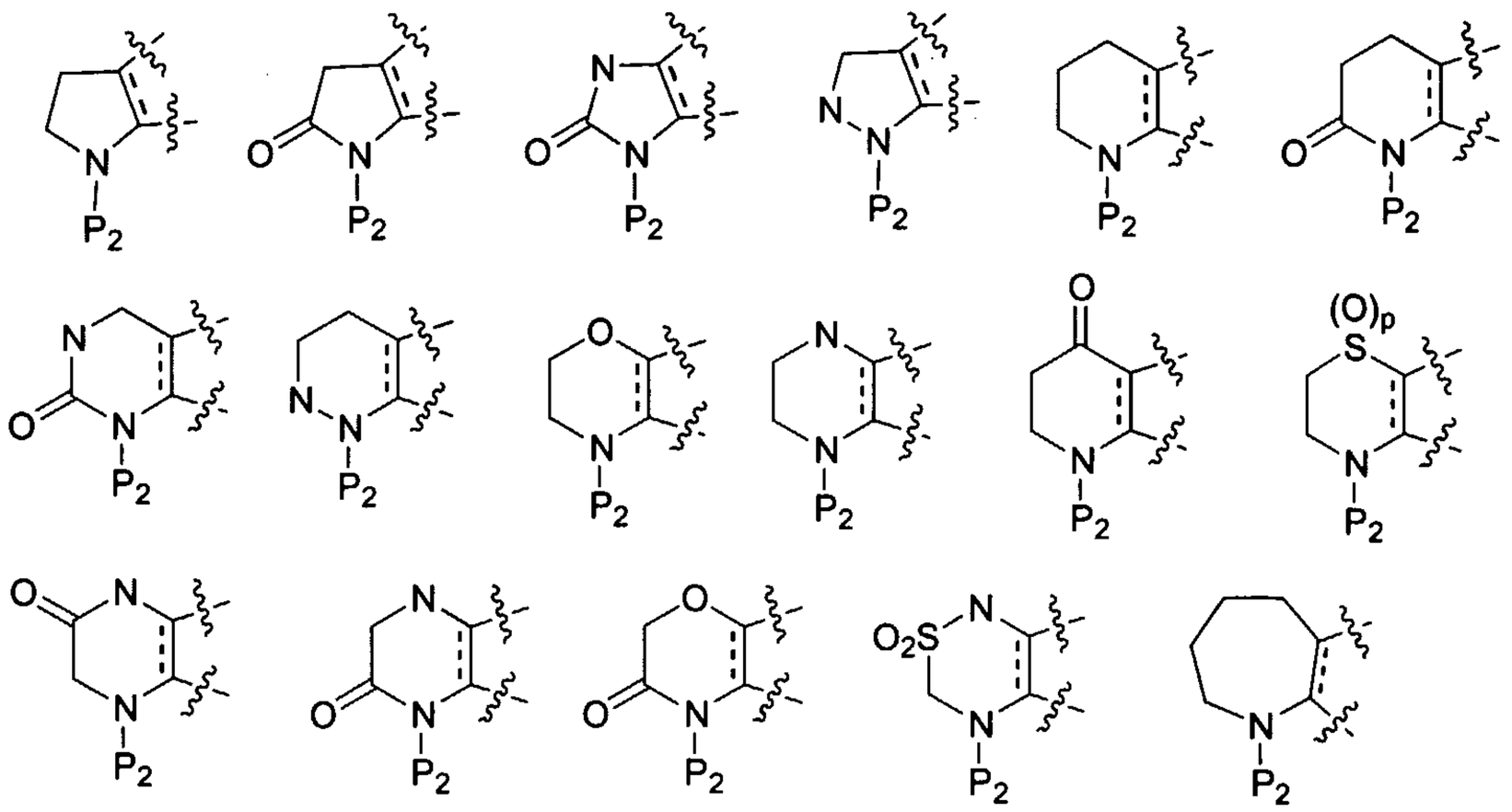
In another embodiment, the present invention provides a novel compound, wherein:

ring M is substituted with 0-2 R^3 and is selected from the group:



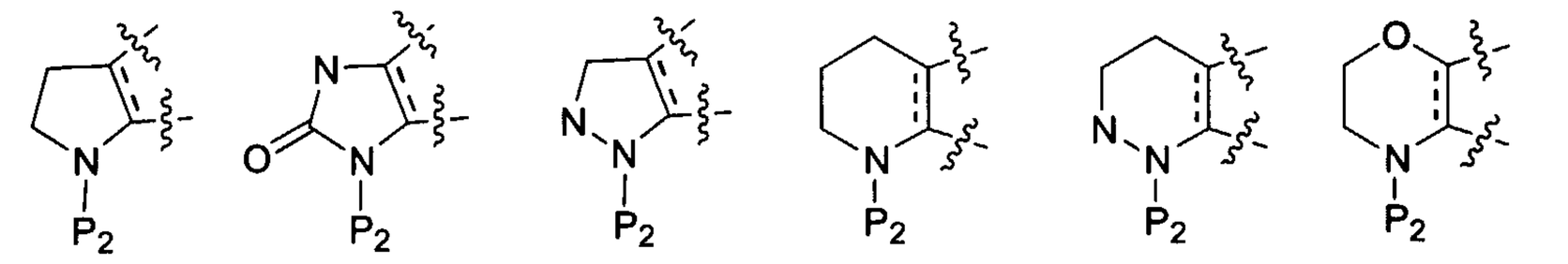
In another embodiment, the present invention provides a novel compound, wherein:

ring P is substituted with 0-1 R^{1a} and is selected from the group:



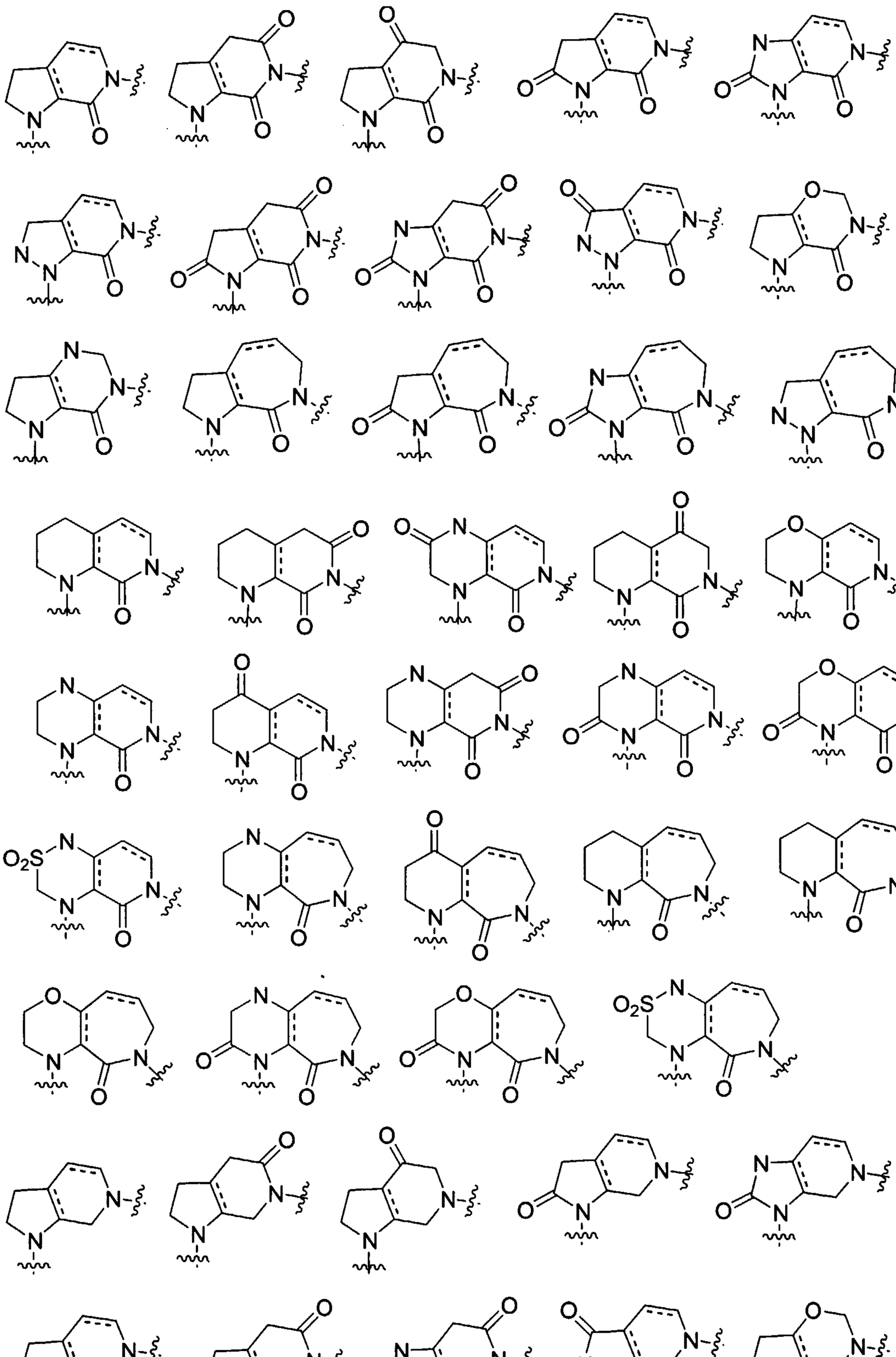
In another embodiment, the present invention provides a novel compound, wherein:

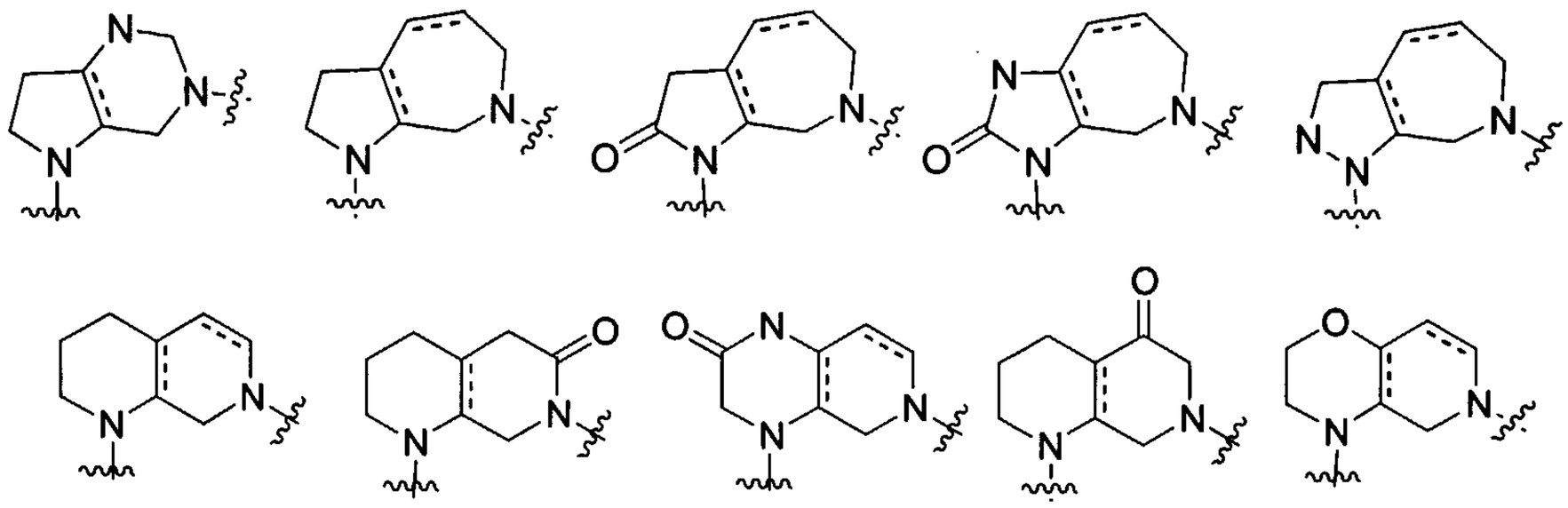
ring P is substituted with 0-1 R^{1a} and is selected from the group:

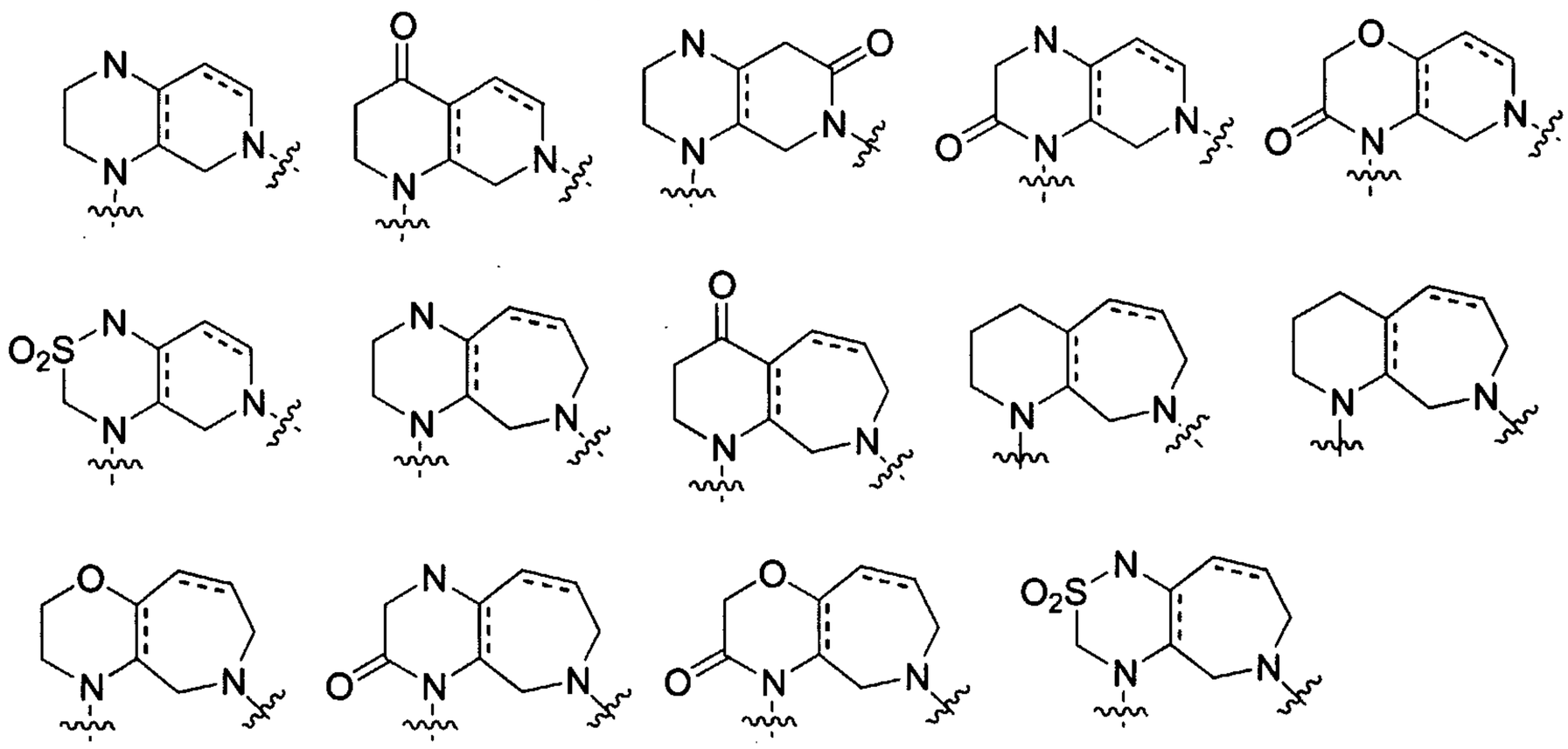


[4] In another embodiment, the present invention provides a novel compound, wherein:

rings P-M are substituted with 0-1 R^{1a} and are selected from the group:

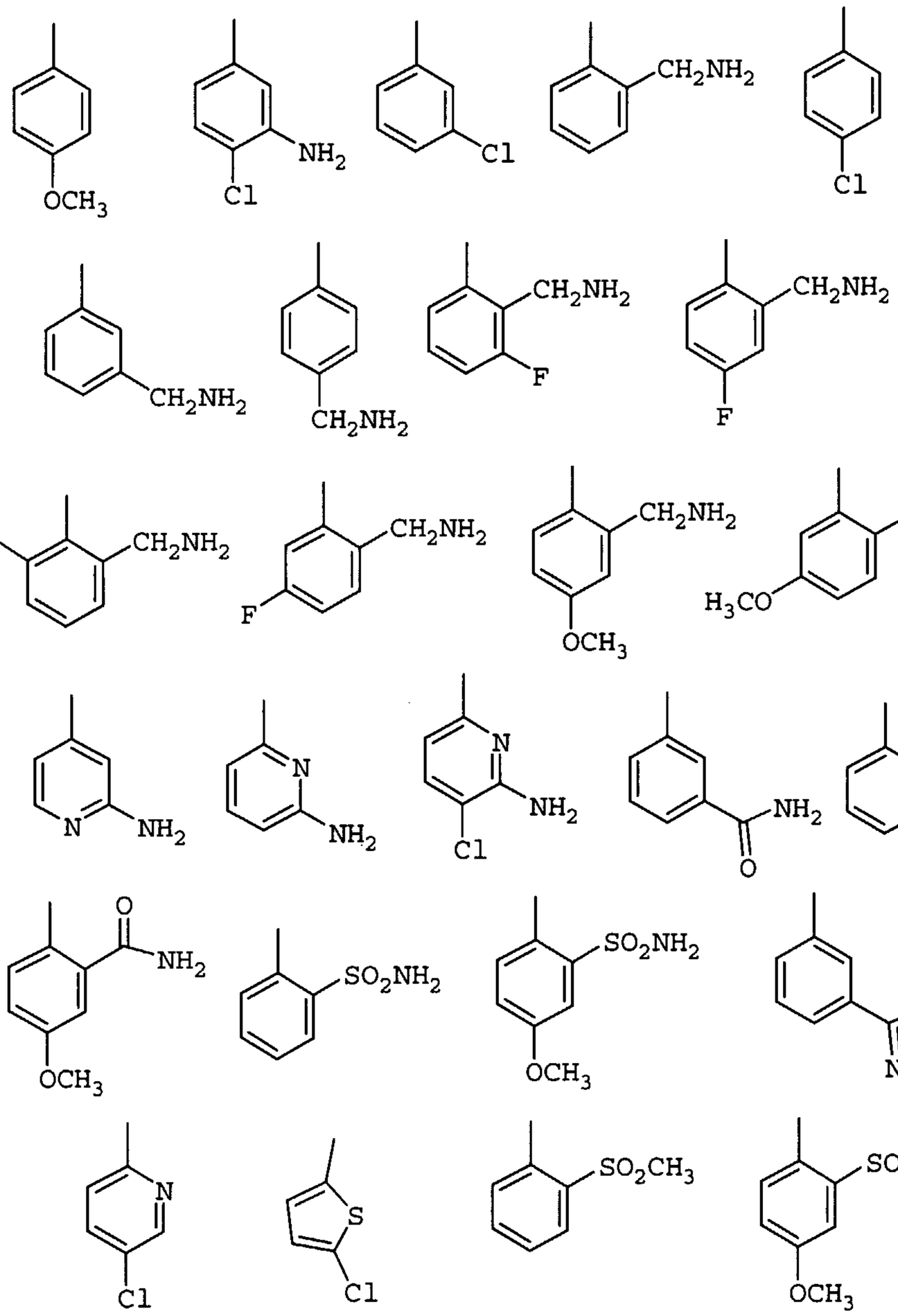


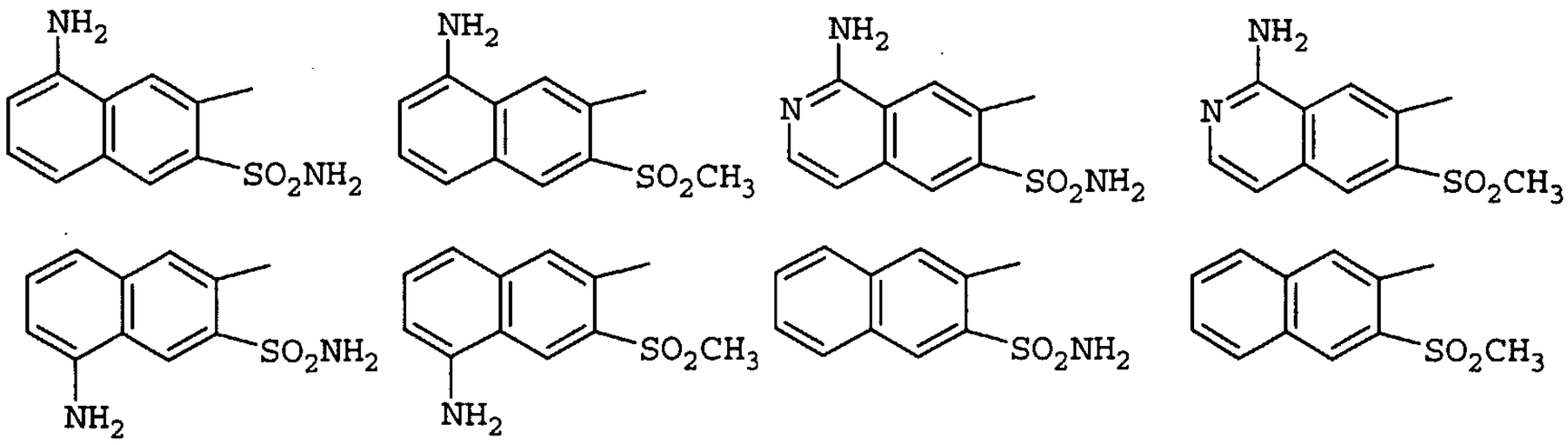
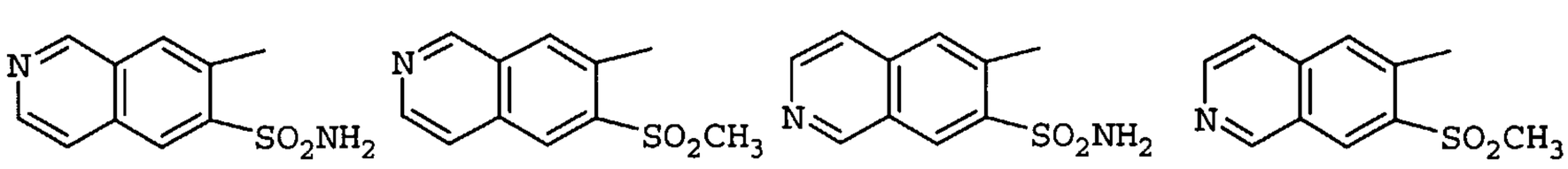
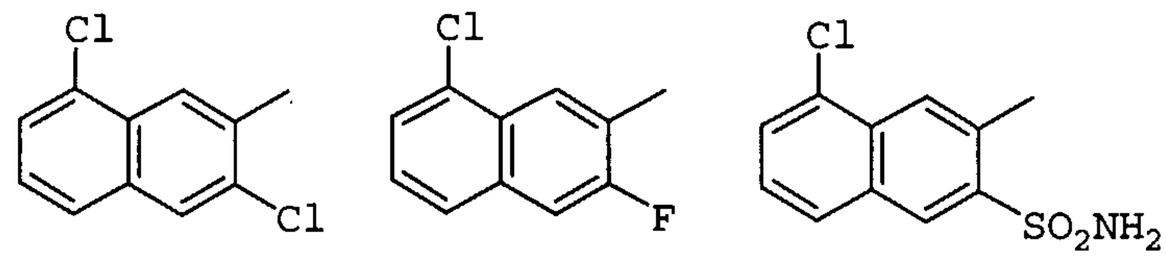
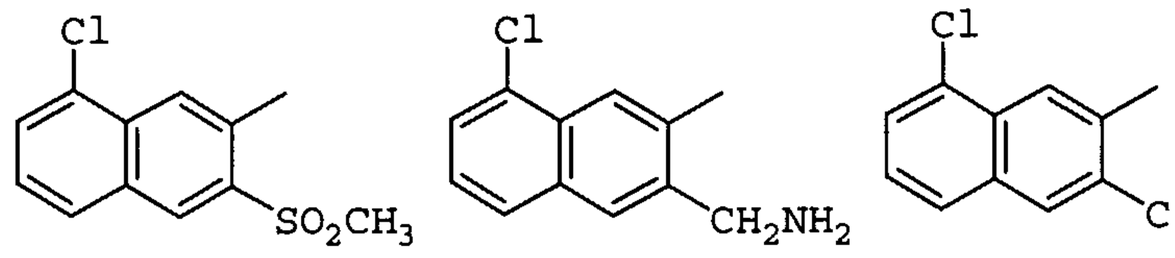
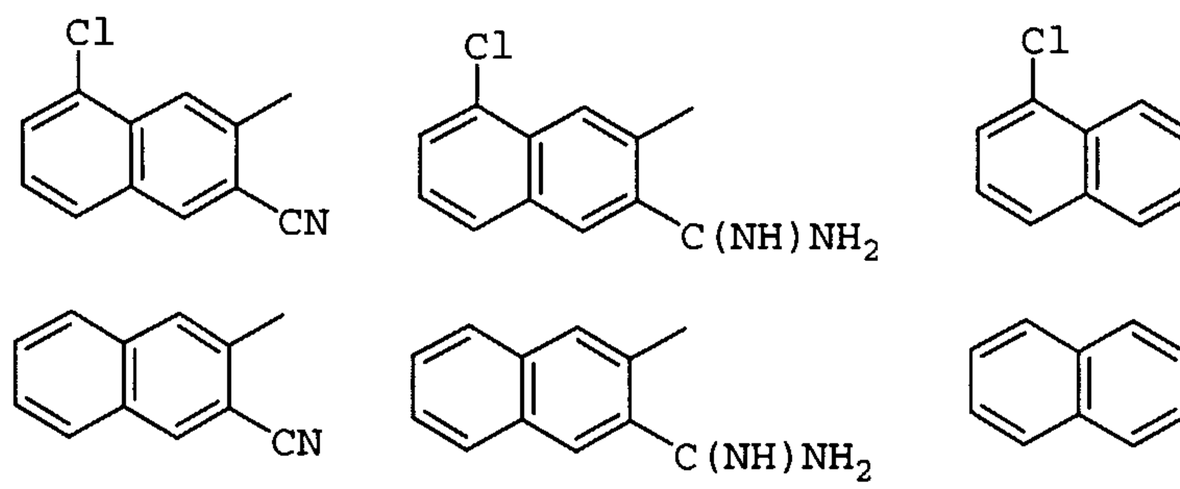
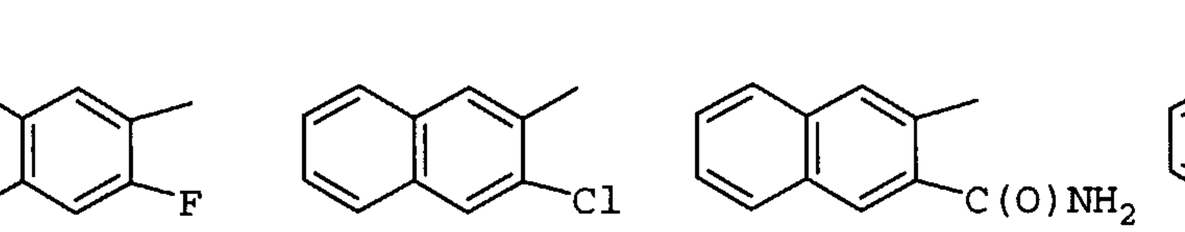
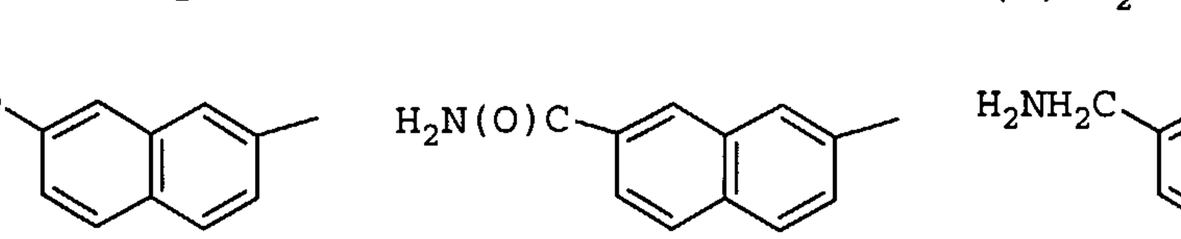




G_1 is absent or is selected from CH_2, CH_2CH_2, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

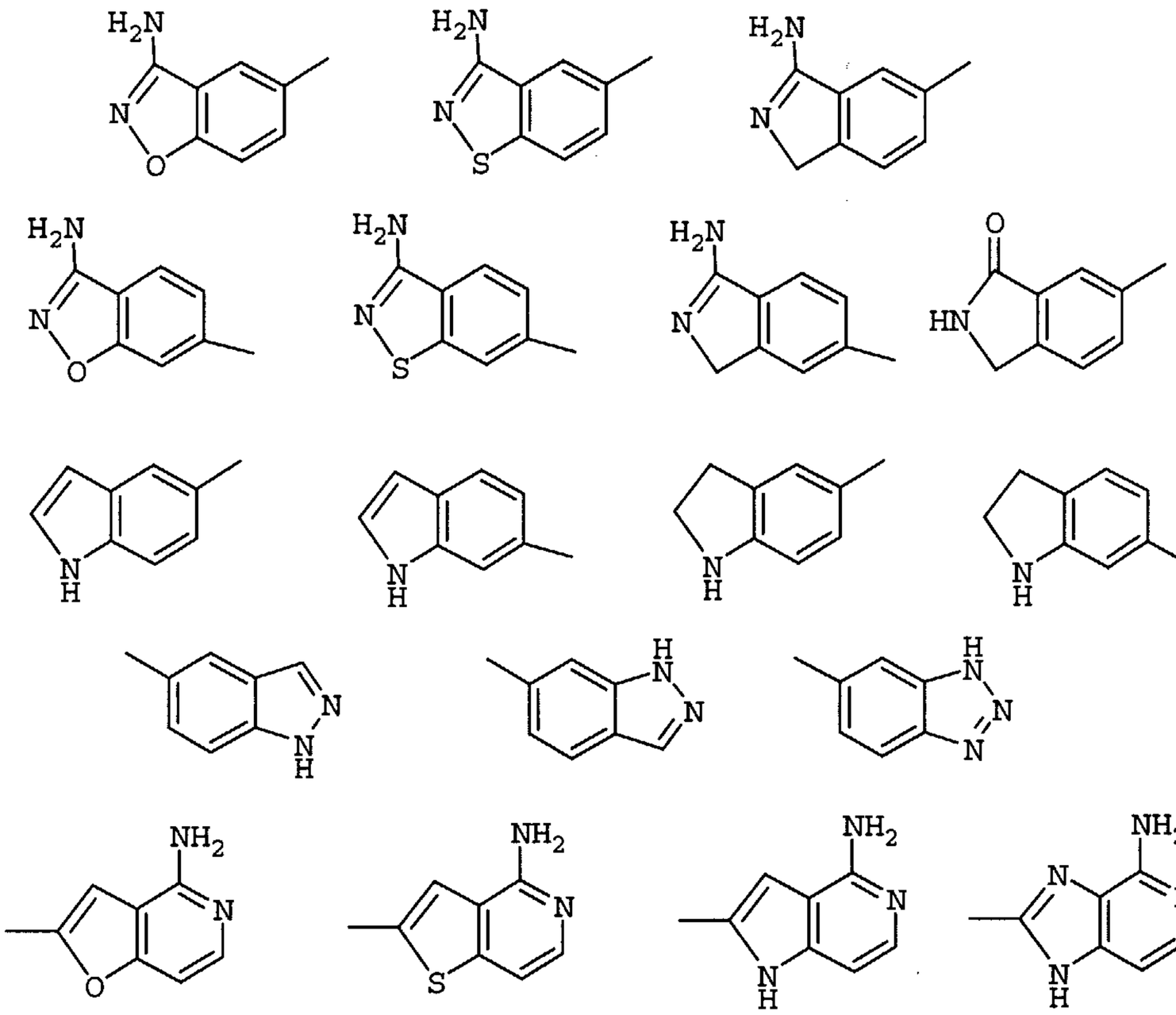
ring G is selected from:

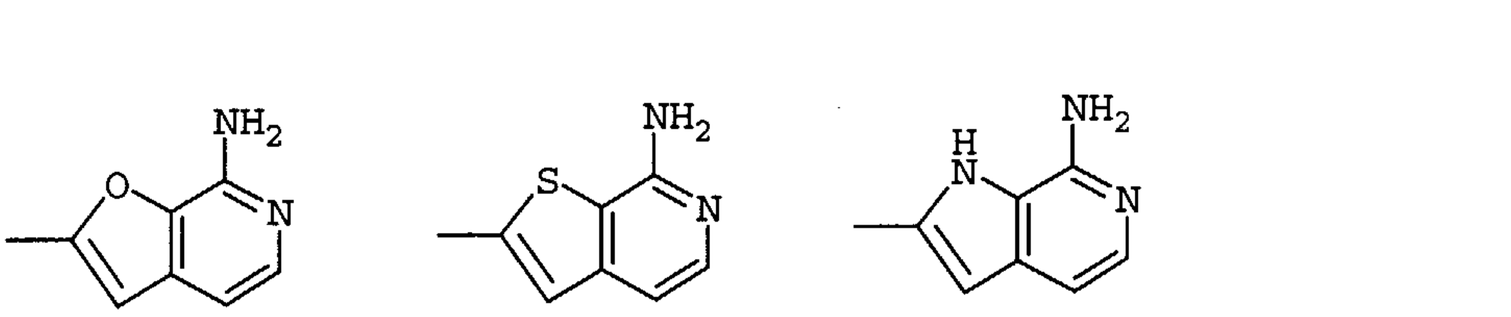




5





alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) G_1 is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

then Z is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

alternatively, when

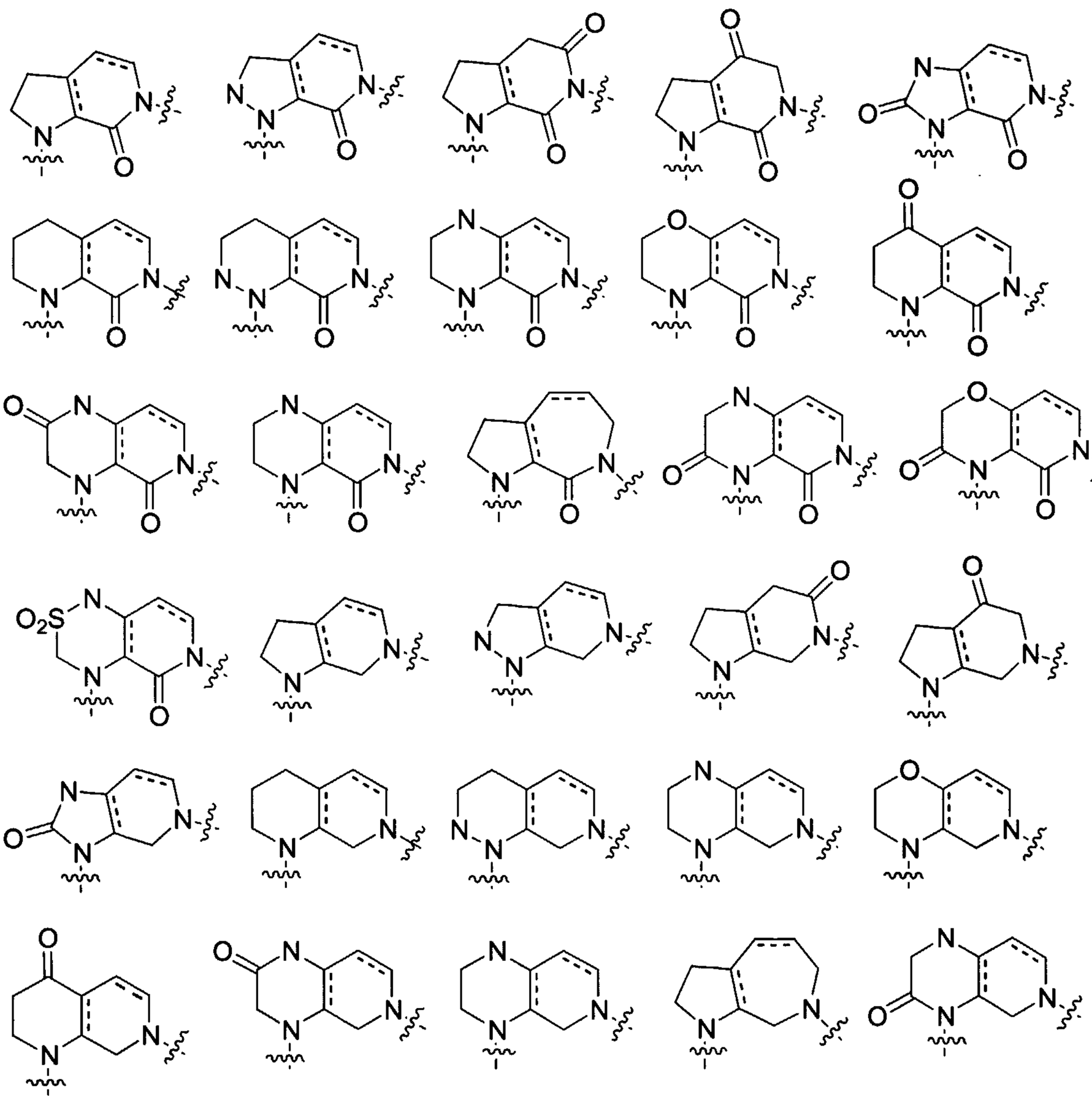
(a) B is other than an optionally substituted carbocycle; and,

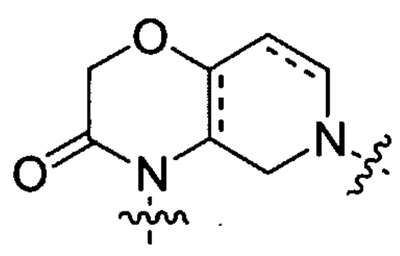
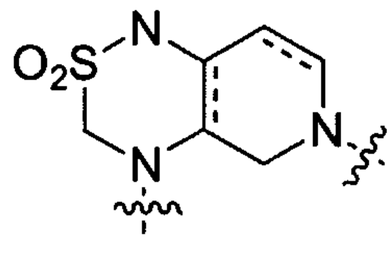
(b) Z is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

then G_1 is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$.

[5] In another embodiment, the present invention provides a novel compound, wherein:

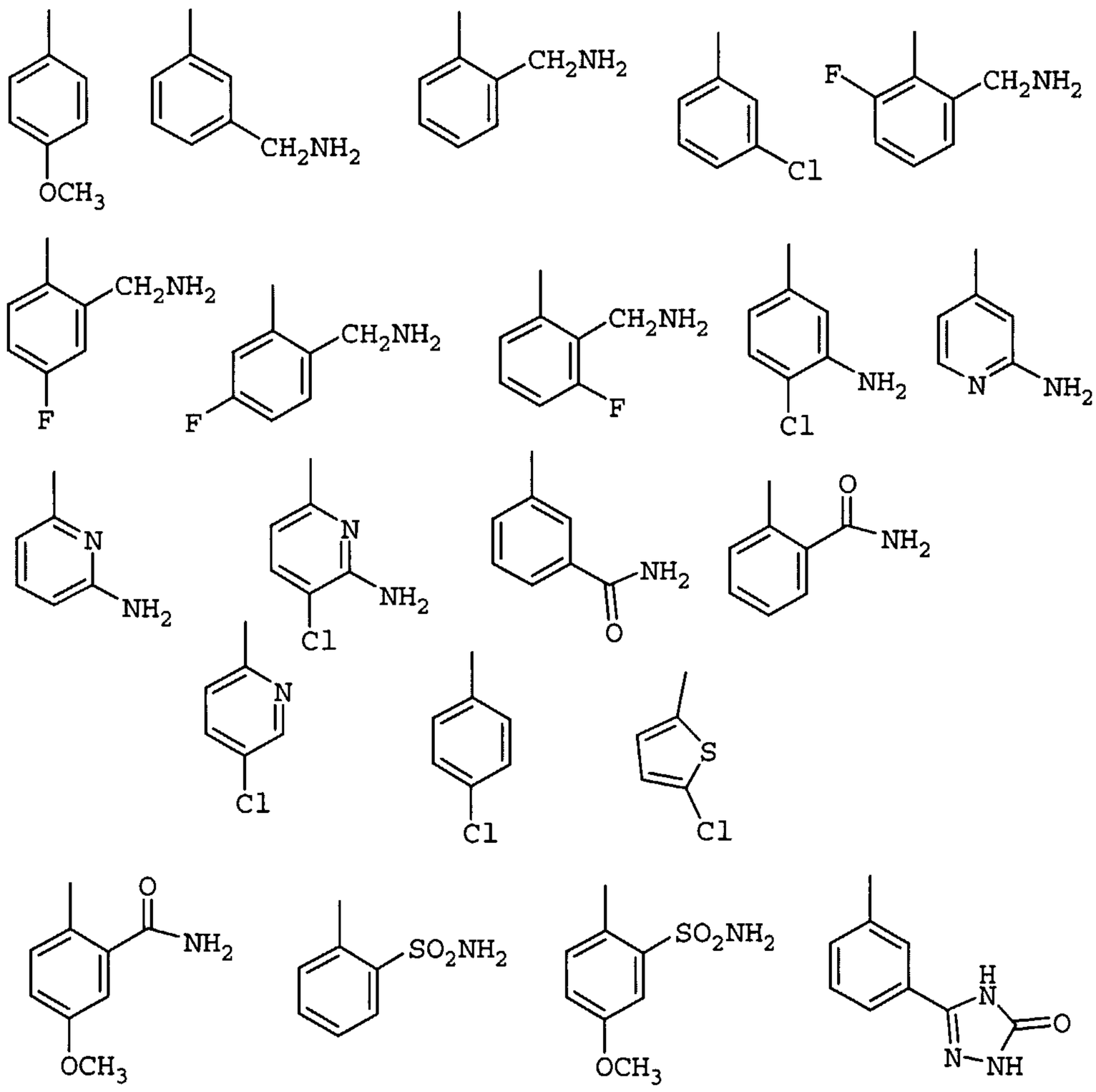
rings P-M are substituted with 0-1 R^{1a} and are selected from the group:





;

G_1 is absent; and

ring G is selected from:



Cl
Cl
Cl
F
Cl
SO2NH2
Cl
SO2CH3
Cl
CH2NH2
Cl
C(O)NH2
Cl
CN
Cl
C(NH)NH2
Cl
C(NOH)NH2
Cl
F
SO2NH2
SO2CH3
CH2NH2
C(O)NH2
CN
C(NH)NH2
C(NOH)NH2
H2N
N
N
H2N
N
N
H2N
N
H2N
N
N
H2N
N
H
H2N
N
H
H2N
N
O
H2N
N
HN
O
NH2
N
F
NH2
N
Cl
NH2
N
C(O)NH2
NH2
N
CH2NH2

5

[6] In another embodiment, the present invention provides a novel compound, wherein:

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl and is substituted with 0-1 R^{4a};

X is CH_2 or C(O);

Y is selected from pyrrolidino and morpholino;

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R^{2a}, at each occurrence, is H or CH_3;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, $(CH_2)_rOR^2$, $(CH_2)_rNR^2R^{2a}$, $S(O)_pR^{5a}$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^{4b}, at each occurrence, is selected from H, CH_3, and OH;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and

r, at each occurrence, is selected from 0, 1, and 2.

[7] In another embodiment, the present invention provides a novel compound, wherein:

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N,N-diethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(N,N-dimethylaminomethyl)-1-imidazolyl, 2-(N-methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl, and 2-(N-(2-hydroxyethyl)methylamino)-methyl)phenyl.

[8] In another embodiment, the present invention provides a novel compound or a pharmaceutically acceptable salt thereof, selected from:

4-(4-methoxyphenyl)-1-methyl-6-{2'-[(methylamino)methyl]-1,1'-biphenyl-4-yl}-1,2,4,6-tetrahydropyrido[3,4-*b*]pyrazine-3,5-dione;

4-(4-methoxyphenyl)-1-methyl-6-[2'-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl}-1,2,4,6-tetrahydropyrido[3,4-*b*]pyrazine-3,5-dione;

6-[2'-(methylsulfonyl)-1-1'-biphenyl-4-yl]- 4-(4-methoxyphenyl)-2,3,4,6-tetrahydropyrido[3,4-b]pyrazin-5(1*H*)-one;

3-{5-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-2,4-dioxo-1,2,4,5-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-3-yl}benzenecarboximidamide;

3-[7-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-8-oxo-3,4,7,8-tetrahydro-1,7-naphthyridin-1(2-*H*)-yl]}benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-5-oxo-2,3,5,6-tetrahydropyrido[3,4-*b*]-pyrazin-4(*1H*)-yl]benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-5-oxo-2,3,5,6-tetrahydropyrido-4*H*-pyrido[4,3-*b*][1,4]-oxazin-4-yl}benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-2,5-dioxo-2,3,5,6-tetrahydropyrido[3,4-b]pyrazin-4(1*H*)-yl]benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-3,5-dioxo-2,3,5,6-tetrahydropyrido-4*H*-pyrido[4,3-*b*][1,4]-oxazin-4-yl}benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-3,5-dioxo-2,3,5,6-tetrahydropyrido[3,4-b]pyrazin-4(1*H*)-yl]benzenecarboximidamide; and

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-2,2-dioxido-5-oxo-5,6-dihydro-1*H*-pyrido[4,3-*c*][1,2,5]thiadiazin-4(3*H*)-yl]benzenecarboximidamide.

In another embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof.

In another embodiment, the thromboembolic disorder is selected from the group consisting of arterial

cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, and venous cerebrovascular thromboembolic disorders.

In another embodiment, the thromboembolic disorder is selected unstable angina, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, and (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

In another embodiment, the present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

In another embodiment, the present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

In another embodiment, the present invention provides novel compounds as described above for use in therapy.

In another embodiment, the present invention provides the use of novel compounds as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

This invention also encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional even more preferred embodiments of the present invention. It is also understood that each and every element of any embodiment is intended to be a separate specific embodiment. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable

isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. Tautomers of compounds shown or described herein are considered to be part of the present invention.

Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, 800, 850, and 900 grams per mole. More preferably, the molecular weight is less than about 850 grams per mole. Even more preferably, the molecular weight is less than about 750 grams per mole. Still more preferably, the molecular weight is less than about 700 grams per mole.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e, =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e. g, R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are amines on the compounds of this invention, these can be converted to amine N-oxides by treatment with MCPBA and or hydrogen peroxides to afford other compounds of this invention. Thus, all shown amines are considered to cover both the shown amine and its N-oxide (N→O) derivative.

As used herein, "alkyl" or "alkylene" is intended to include both C_{1-10} branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-10} alkyl, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n- and s-pentyl, n- and s- heptyl, and, n- and s-octyl. "Haloalkyl"

is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-10} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-10} alkenyl is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkenyl groups. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-10} Alkynyl is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10, 11, or 12-membered bicyclic or tricyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than

1. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]-tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl,

tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containin g, for example, the above heterocycles.

The term "independently selected from", "independently, at each occurrence" or similar language, means that the labeled R substitution group may appear more than once and that each appearance may be a different atom or molecule found in the definition of that labeled R substitution group. Thus if the labeled R^6 substitution group appear four times in a given permutation of Formula (I), then each of those labeled R^6 substitution groups may be a different group falling in the definition of R^6.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the

conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed, Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e. g, solubility, bioavailability, manufacturin g, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in*

vivo when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e, =O) group, then 2 hydrogens on the atom are replaced.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the

disease-state, i.e., causing regression of the disease state.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

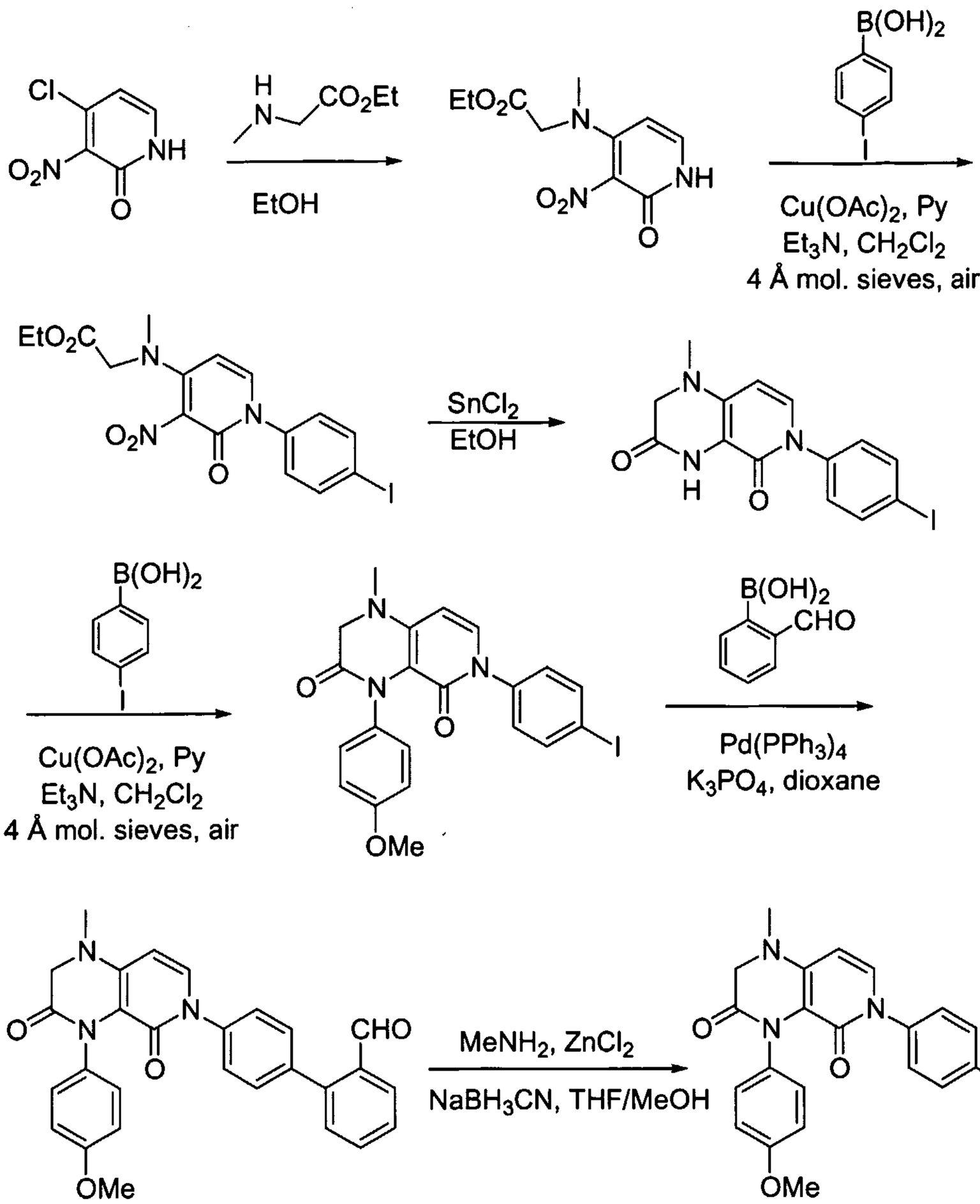
SYNTHESIS

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic

steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, **1991**). All references cited herein are hereby incorporated in their entirety herein by reference.

A general procedure for making the compounds of the present invention is illustrated in Scheme 1. Detailed description of the procedure is demonstrated by Example 1.

Scheme 1

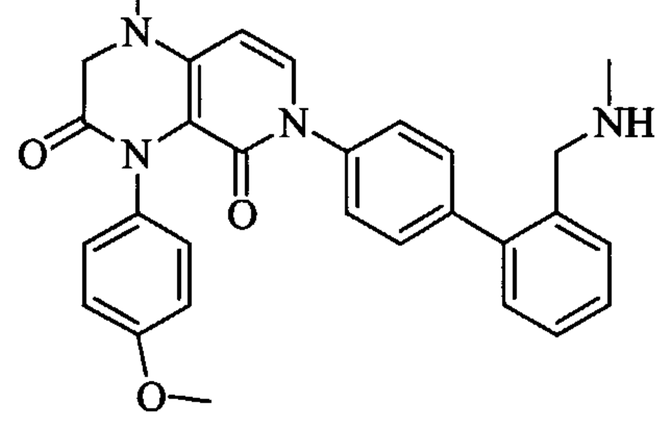


Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1

4-(4-methoxyphenyl)-1-methyl-6-{2'-[(methylamino)methyl]-1,1'-biphenyl-4-yl}-1,2,4,6-tetrahydropyrido[3,4-*b*]pyrazine-3,5-dione



Part A. To a stirred suspension of the 4-chloro-3-nitro-1*H*-pyridin-2-one (5.0 g, 28.6 mmol) in ethanol (100 mL) was added sacosine ethyl ester HCl salt (4.8 g, 31.25 mmol) and TEA (12.0 mL, 85.94 mmol). The reaction mixture was heated at reflux for 2 hr. The resultant dark green solution was cooled to rt. The crystal material was filtered off, washed with EtOAc and dried to provide the corresponding lactam (4.23 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, d, J=7.7 Hz), 5.88 (1H, d, J=7.7 Hz), 4.27 (2H, q, J=6.9 Hz), 4.04 (2H, s), 3.05 (3H, s), 1.31 (3H, t, J=6.9 Hz) ppm.

Part B. Dry air was bubbled through a mixture of the pyridinone (2.0 g, 9.57 mmol) made above. 4-iodophenyl boronic acid (3.54 g, 14.3 mmol), Et_3N (2.67 mL, 19.14 mmol) and pyridine (1.51 mL, 19.14 mmol) in CH_2Cl_2 (50 mL) were added for 15 min. Molecular sieves (4 Å) were added. Dry air was bubbled through the mixture for an additional 10 min. Then, $Cu(OAc)_2$ (3.47 g, 19.14 mmol) was added and the reaction mixture was stirred at 25 °C for 36 hr. The resultant green suspension was filtered through celite,

concentrated, and purified by column chromatography (eluting with 1:1 acetone/hexanes) to give the corresponding pyridinone as a yellow solid (2.4 g, 55%): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, d, J=8.4 Hz), 7.20 (1H, d, J=8.1 Hz), 7.11 (2H, d, J=8.4 Hz), 5.78 (1H, d, J=8.1 Hz), 4.28 (2H, q, J=7.3 Hz), 4.05 (2, s), 3.07 (3H, s), 1.33 (3H, t, J=7.3 Hz) ppm.

Part C. A mixture of the nitro pyridinone made above (2.73 g, 5.97 mmol) and tin (II) chloride dihydrate (5.39 g, 23.88 mmol) in 100 mL of methanol was refluxed overnight. The reaction mixture was quenched with 1N NaOH, filtered through a plug of Celite. The filtration was seperated and the water layer was extracted with methylene chloride. The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide the crude amide (1.8 g, 79%).

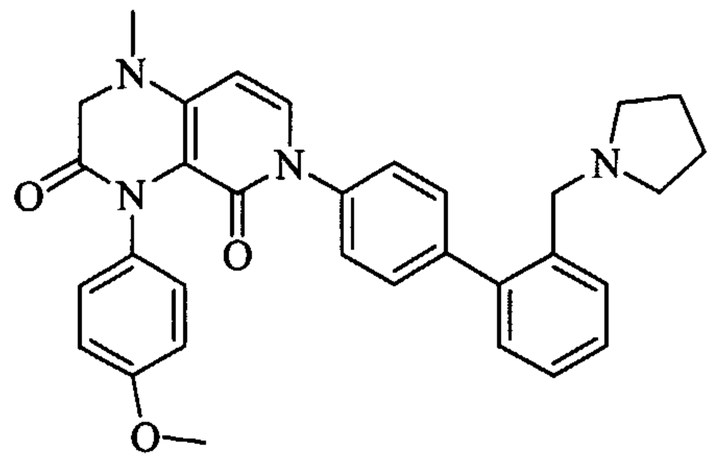
Part D. A mixture of 4-methoxyphenyl boronic acid (398 mg, 2.62 mmol) and molecular sieves (4 Å, 300 mg) in CH_2Cl_2 (20 mL) was stirred at 25 °C for 20 min. To this suspension pyridine (0.21 mL), Et_3N (0.37 mL), $Cu(OAc)_2$ (0.48 g) , and the amide (0.50g, 1.31 mmol) made above were added consecutively. The suspension was stirred at room temperature for 2 hr. The reaction mixture was absorbed onto silica and purified by column chromatography (eluting first with 1:1 acetone/hexane) to provide the desired compound as a yellow solid (550 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ7.70 (2H, d, J=8.4 Hz), 7.15 (2H, d, J=8.4 Hz), 7.14 (1H, d, J=7.7 Hz), 7.15 (2H, d, J=8.8 Hz), 3.85 (2H, d, J=8.8 Hz), 6.10 (1H, d, J=7.7 Hz), 3.91 (2H, s), 3.76 (3H, s), 3.03 (3H, s) ppm.

Part E. To a mixture of the phenyl iodide (0.50 g, 1.026 mmol) made above, 2-formyl-phenyl boronic acid (0.308 g, 2.05 mmol), K_3PO_4 (300 mg) and dioxane (25 mL), $Pd(PPh_3)_4$ (167 mg) were added under an argon atmosphere. The reaction mixture was stirred at reflux for 20 hr then diluted with EtOAc, washed with saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (eluting with 2:1 hexanes/acetone) to provide the biphenyl sulfonamide as a yellow solid.

Part F. A mixture of the crude aldehyde (220 mg, 0.473 mmol) and methylamine (0.47 mL of 2M solution in THF, 0.945 mmol) in 10 mL of THF-MeOH (1:1) solution was treated with $ZnCl_2$ (0.47 mL, 1M solution in ether, 0.47 mmol), at rt, for 30 min. $NaBH_3CN$ (59 mg, 0.945 mmol) was added to the mixture. The resultant mixture was stirred overnight and then concentrated to dry. The residue was quenched with 1N NaOH and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by RP-HPLC to provide the desired amine as a solid (32 mg, 37% in 2 steps): ^1H NMR (300 MHz, CD_3OD) δ 7.57~7.48 (4H, m), 7.42~7.33 (5H, m), 7.10 (2H, d, J=9.2 Hz), 6.85 (2H, d, J=9.2 Hz), 6.46 (1H, d, J=7.7 Hz), 4.17 (2H, s), 3.97 (2H, s), 3.74 (3H, s), 3.09 (3H, s), 2.50 (3H, s) ppm; ESI MS *m/z* 481 $[M+H]^+$.

Example 2

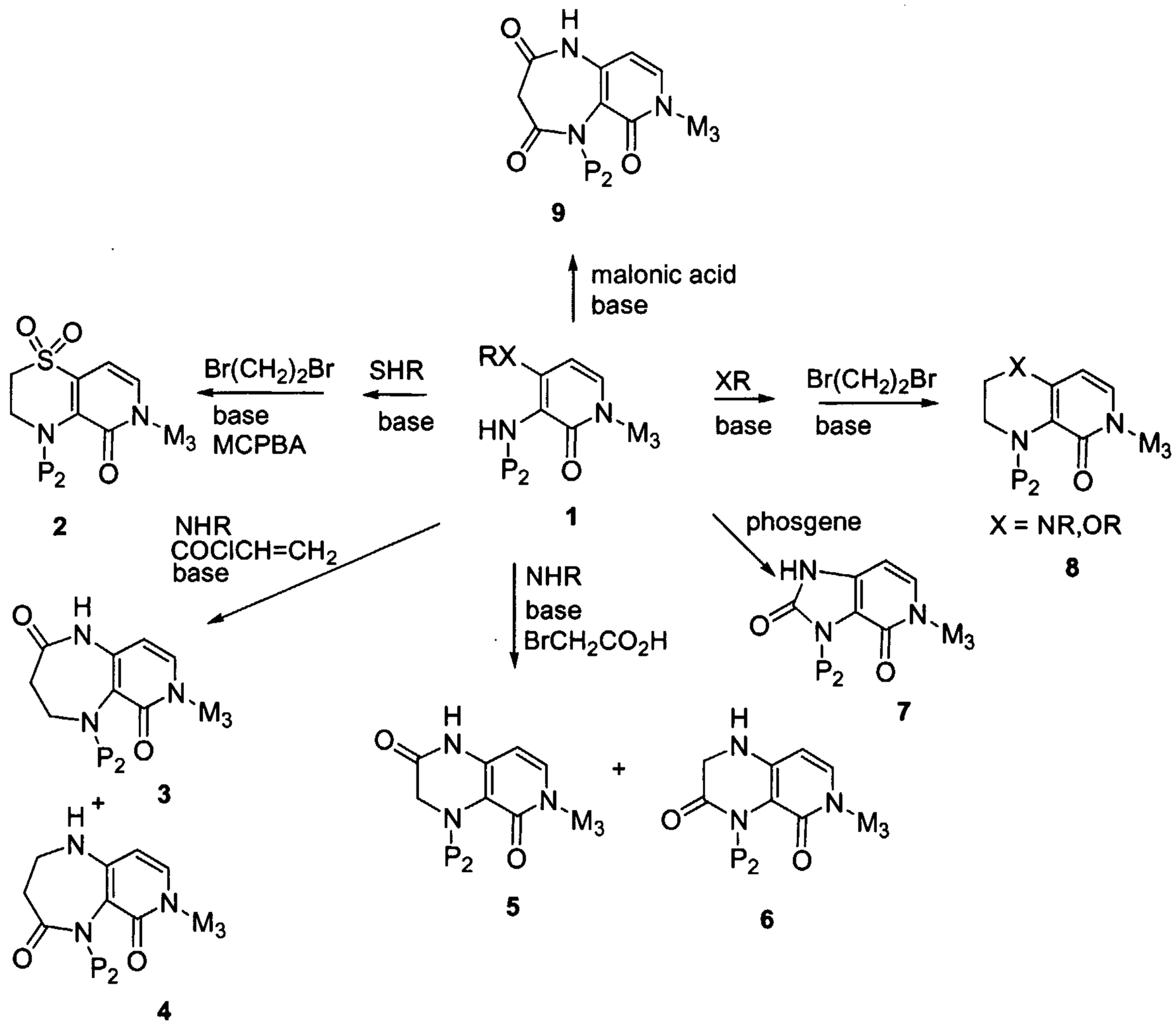
4-(4-methoxyphenyl)-1-methyl-6-[2'-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl}-1,2,4,6-tetrahydropyrido[3,4-*b*]pyrazine-3,5-dione



The title compound was prepared according to the procedures described for Example 1: ^{1}H NMR (300 MHz, CD_3OD) δ 7.64~7.61 (1H, m), 7.54~7.48 (3H, m), 7.42~7.34 (5H, m), 7.10 (2H, d, J=9.1 Hz), 6.87 (2H, d, J=9.1 Hz), 6.46 (1H, d, J=7.7 Hz), 4.38 (2H, s), 3.97 (2H, s), 3.75 (3H, s), 3.33 (2H, m), 3.09 (3H, s), 2.78 (2H, m), 1.92~1.83 (4, m) ppm; ESI MS *m/z* 521 $[M+H]^+$.

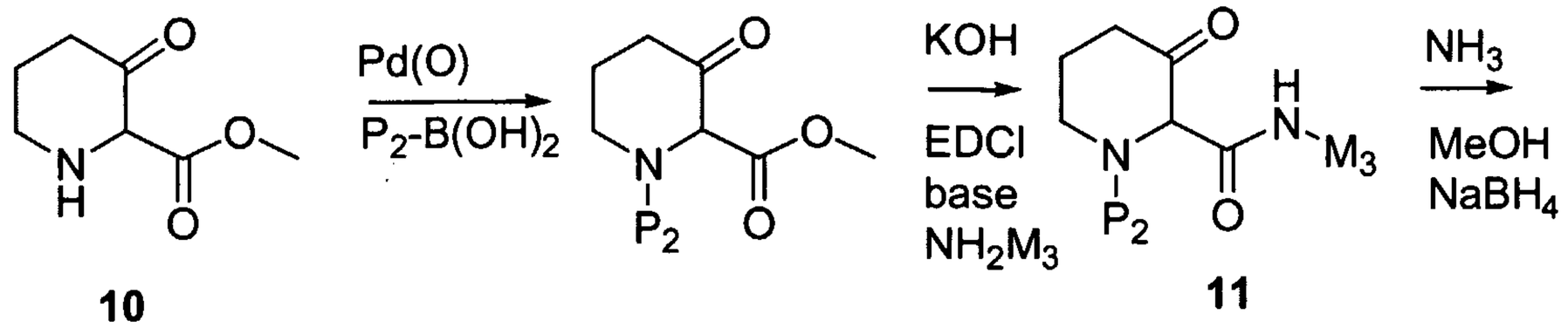
Compounds of this invention can also be prepared as outlined in Schemes 2-4. In Scheme 2, reaction of **1** with an appropriately substituted thiol leads to the intermediate, that is treated with dibromoethane under basic conditions, followed by MCPBA oxidation to afford **2**. Reaction of **1** with an appropriately substituted amine leads to the intermediate that is treated with acrylate chloride under basic conditions to afford **3** and **4** as a mixture of regioisomers. Similarly, reaction of **1** with an appropriately substituted alcohol or amine leads to the intermediate, that is treated with dibromoethane under basic conditions to afford **8**. Reaction of the same amine intermidate with phosgene leads to compound **7** and reaction with malonic acid under standard amide bond coupling conditions affords **9**.

Scheme 2



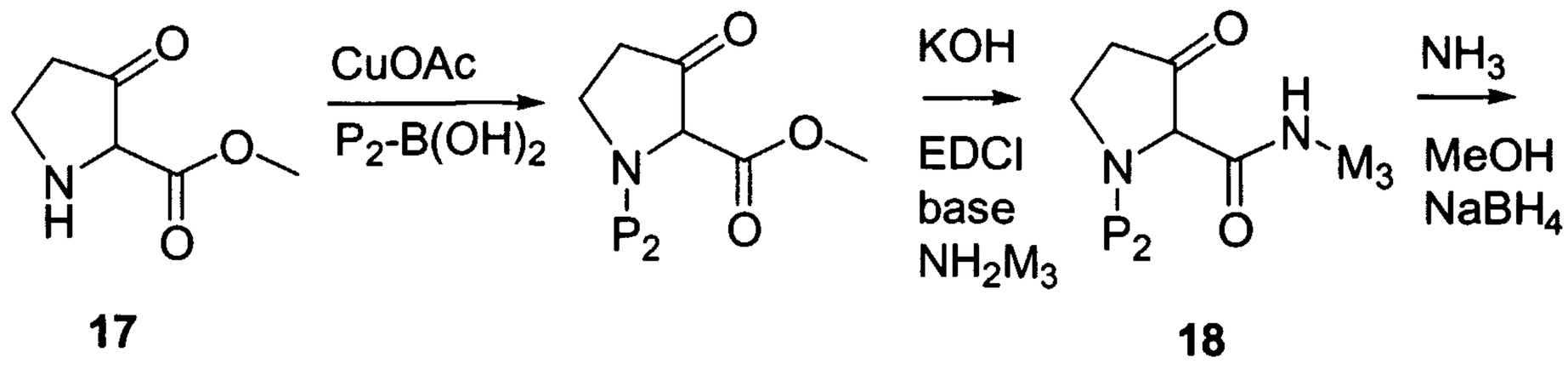
Preparation of the compounds in this scheme commences by the Suzuki reaction of appropriately substituted boronic acid of P_2 with **10**(synthesis described by Knight, D., et. al. Tetrahedron Asymmetry, 1993, p.625). Mild base hydrolysis, followed by the amide bond formation under standard conditions leads to compound **11**. Reductive amination generates the intermediate **12**, which upon treatment with bromo acetyl chloride in a presence of a base affords **15** and **16** as a mixture of regioisomers. Reaction of **12** with SO_2Cl_2 provides **14** and reaction with phosgene affords **13**.

Scheme 3



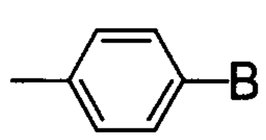
Preparation of the compounds in this scheme is done according to the methodology described in Scheme 3 using **17** (synthesis described by Cooper, J. et. al. J. Chem. Soc., Chem. Comm. 1988, p.509) as a starting material and led to the compounds **20-23** of this invention.

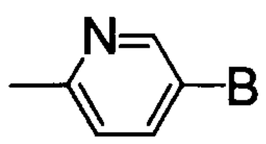
Scheme 4

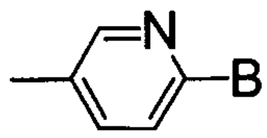


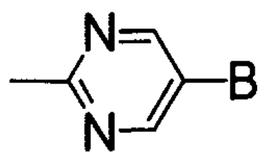
The A-B moieties can be prepared by methods known to those of skill in the art. The following publications, the contents of which are incorporated herein by reference, describe and exemplify means of preparing A-B moieties: WO97/23212, WO97/30971, WO97/38984, WO98/06694, WO98/01428, WO98/28269, WO98/28282, WO99/12903, WO98/57934, WO98/57937, WO98/57951, WO99/32454, WO99/50255, WO00/38683, WO00/39102, WO00/39108, WO00/39131, and WO01/05784.

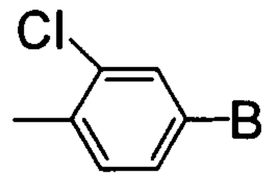
The following nomenclature is intended for group A in the following tables.


phenyl


2-pyridyl


3-pyridyl


2-pyrimidyl


2-Cl-phenyl

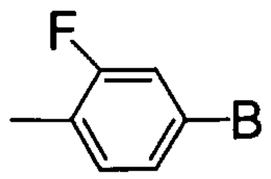
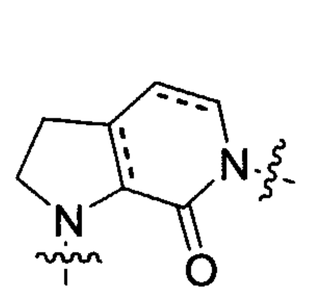
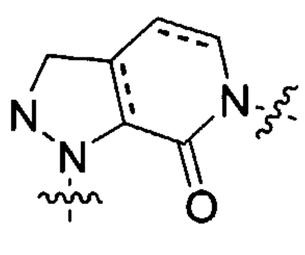
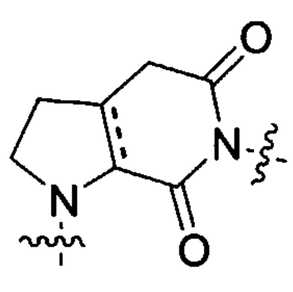
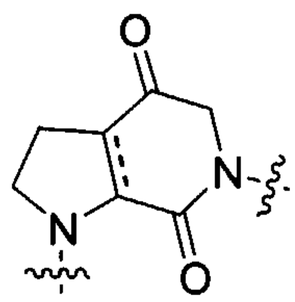
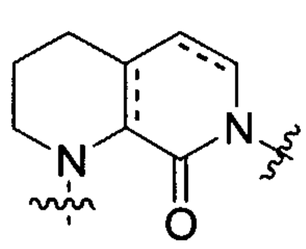
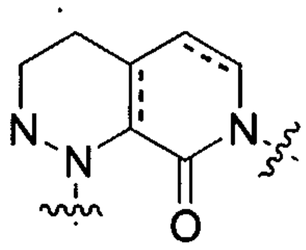
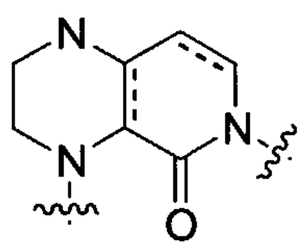
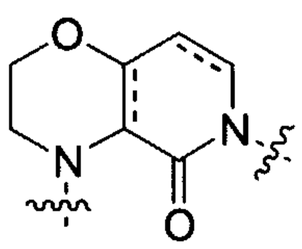
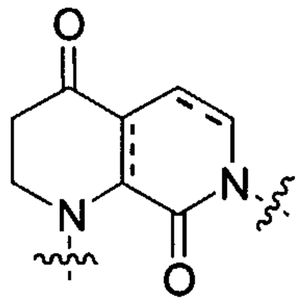
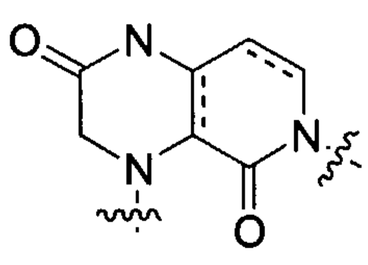
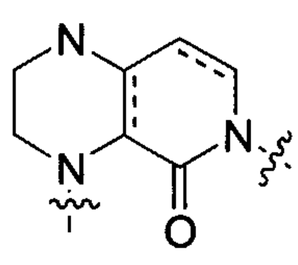
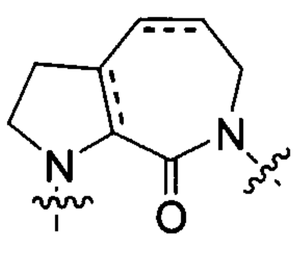
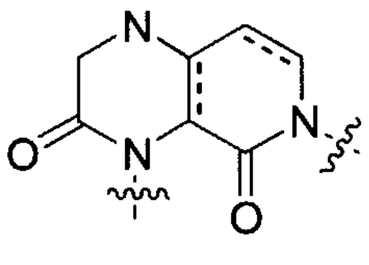
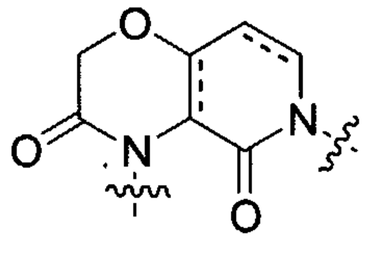
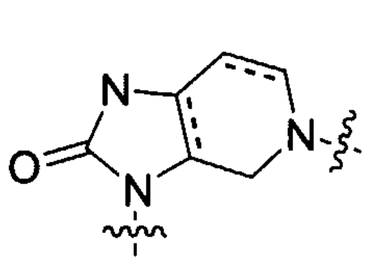
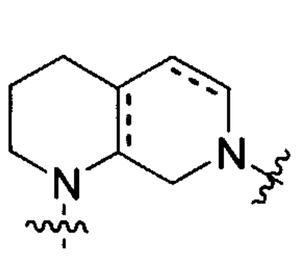
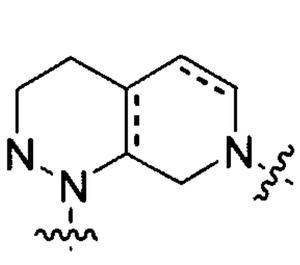
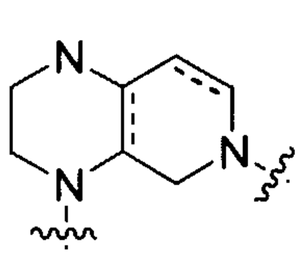
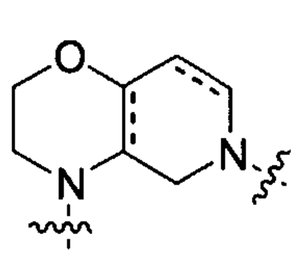

2-F-phenyl

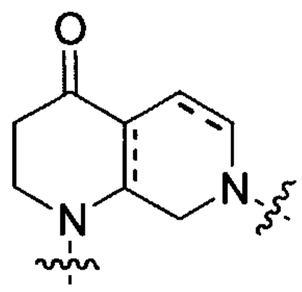
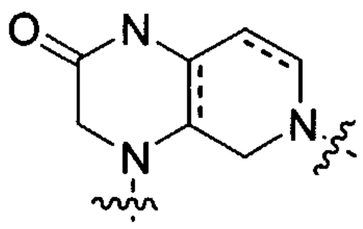
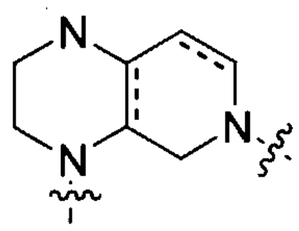
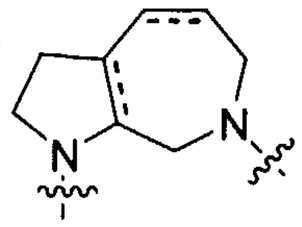
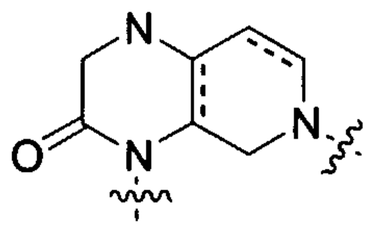
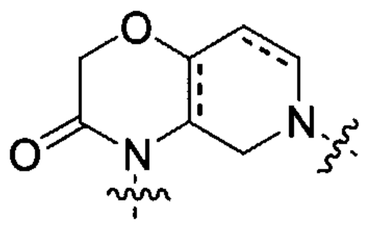
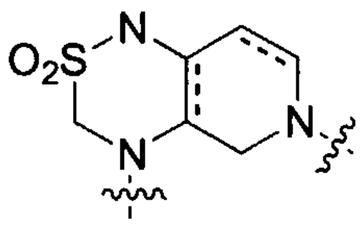
Table 1 demonstrates representative examples in Formula (I).

Table 1

P_2 is Z-A-B, wherein Z is a bond;

M_3 is $-G_1-G$, wherein G_1 is a bond;

G is 4-(methoxy)phenyl;

Ex#	A	B
1	phenyl	2-(NH_2SO_2)phenyl
2	phenyl	2-(CH_3SO_2)phenyl
3	phenyl	3-NH_2SO_2-4-pyridyl
4	phenyl	3-CH_3SO_2-4-pyridyl
5	phenyl	2-(CH_3NH)phenyl
6	phenyl	2-((CH_3)$_2$$NCH_2$)phenyl
7	phenyl	3-((CH_3)$_2$$NCH_2$)-4-pyridyl
8	phenyl	2-((CH_3SO_2)N(CH_3)CH_2)phenyl
9	phenyl	2-(($CH_3C(O)$)N(CH_3)CH_2)phenyl
10	phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
11	phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
12	phenyl	2-($CH_3NHC(O)N(CH_3)CH_2$)phenyl
13	phenyl	1-CH_3-2-imidazolyl
14	2-pyridyl	2-(NH_2SO_2)phenyl
15	2-pyridyl	2-(CH_3SO_2)phenyl
16	2-pyridyl	3-NH_2SO_2-4-pyridyl

	17	2-pyridyl	3-CH_3SO_2-4-pyridyl
	18	2-pyridyl	2-(CH_3NH)phenyl
	19	2-pyridyl	2-((CH_3)$_2$$NCH_2$)phenyl
	20	2-pyridyl	3-((CH_3)$_2$$NCH_2$)-4-pyridyl
5	21	2-pyridyl	2-((CH_3SO_2)N(CH_3)CH_2)phenyl
	22	2-pyridyl	2-((CH_3C(O))N(CH_3)CH_2)phenyl
	23	2-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
	24	2-pyridyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
	25	2-pyridyl	2-(CH_3NHC(O)N(CH_3)CH_2)phenyl
10	26	2-pyridyl	1-CH_3-2-imidazolyl
	27	3-pyridyl	2-(NH_2SO_2)phenyl
	28	3-pyridyl	2-(CH_3SO_2)phenyl
	29	3-pyridyl	3-NH_2SO_2-4-pyridyl
	30	3-pyridyl	3-CH_3SO_2-4-pyridyl
15	31	3-pyridyl	2-(CH_3NH)phenyl
	32	3-pyridyl	2-((CH_3)$_2$$NCH_2$)phenyl
	33	3-pyridyl	3-((CH_3)$_2$$NCH_2$)-4-pyridyl
	34	3-pyridyl	2-((CH_3SO_2)N(CH_3)CH_2)phenyl
	35	3-pyridyl	2-((CH_3C(O))N(CH_3)CH_2)phenyl
20	36	3-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
	37	3-pyridyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
	38	3-pyridyl	2-(CH_3NHC(O)N(CH_3)CH_2)phenyl
	39	3-pyridyl	1-CH_3-2-imidazolyl
	40	2-pyrimidyl	2-(NH_2SO_2)phenyl
25	41	2-pyrimidyl	2-(CH_3SO_2)phenyl
	42	2-pyrimidyl	3-NH_2SO_2-4-pyridyl
	43	2-pyrimidyl	3-CH_3SO_2-4-pyridyl
	44	2-pyrimidyl	2-(CH_3NH)phenyl
	45	2-pyrimidyl	2-((CH_3)$_2$$NCH_2$)phenyl
30	46	2-pyrimidyl	3-((CH_3)$_2$$NCH_2$)-4-pyridyl

	47	2-pyrimidyl	2-((CH_3SO_2)N(CH_3)CH_2)phenyl
	48	2-pyrimidyl	2-(($CH_3C(O)$)N(CH_3)CH_2)phenyl
	49	2-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
	50	2-pyrimidyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
	51	2-pyrimidyl	2-($CH_3NHC(O)N(CH_3)CH_2$)phenyl
	52	2-pyrimidyl	1-CH_3-2-imidazolyl
	53	5-pyrimidyl	2-(NH_2SO_2)phenyl
	54	5-pyrimidyl	2-(CH_3SO_2)phenyl
	55	5-pyrimidyl	3-NH_2SO_2-4-pyridyl
	56	5-pyrimidyl	3-CH_3SO_2-4-pyridyl
	57	5-pyrimidyl	2-(CH_3NH)phenyl
	58	5-pyrimidyl	2-((CH_3)$_2$NCH_2)phenyl
	59	5-pyrimidyl	3-((CH_3)$_2$NCH_2)-4-pyridyl
	60	5-pyrimidyl	2-((CH_3SO_2)N(CH_3)CH_2)phenyl
	61	5-pyrimidyl	2-(($CH_3C(O)$)N(CH_3)CH_2)phenyl
	62	5-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
	63	5-pyrimidyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
	64	5-pyrimidyl	2-($CH_3NHC(O)N(CH_3)CH_2$)phenyl
	65	5-pyrimidyl	1-CH_3-2-imidazolyl
	66	2-Cl-phenyl	2-(NH_2SO_2)phenyl
	67	2-Cl-phenyl	2-(CH_3SO_2)phenyl
	68	2-Cl-phenyl	3-NH_2SO_2-4-pyridyl
	69	2-Cl-phenyl	3-CH_3SO_2-4-pyridyl
	70	2-Cl-phenyl	2-(CH_3NH)phenyl
	71	2-Cl-phenyl	2-((CH_3)$_2$NCH_2)phenyl
	72	2-Cl-phenyl	3-((CH_3)$_2$NCH_2)-4-pyridyl
	73	2-Cl-phenyl	2-((CH_3SO_2)N(CH_3)CH_2)phenyl
	74	2-Cl-phenyl	2-(($CH_3C(O)$)N(CH_3)CH_2)phenyl
	75	2-Cl-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
	76	2-Cl-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl

77	2-Cl-phenyl	2-($CH_3NHC(O)N(CH_3)CH_2$)phenyl
78	2-Cl-phenyl	1-CH_3-2-imidazolyl
79	2-F-phenyl	2-(NH_2SO_2)phenyl
80	2-F-phenyl	2-(CH_3SO_2)phenyl
81	2-F-phenyl	3-NH_2SO_2-4-pyridyl
82	2-F-phenyl	3-CH_3SO_2-4-pyridyl
83	2-F-phenyl	2-(CH_3NH)phenyl
84	2-F-phenyl	2-($(CH_3)_2NCH_2$)phenyl
85	2-F-phenyl	3-($(CH_3)_2NCH_2$)-4-pyridyl
86	2-F-phenyl	2-($(CH_3SO_2)N(CH_3)CH_2$)phenyl
87	2-F-phenyl	2-($(CH_3C(O))N(CH_3)CH_2$)phenyl
88	2-F-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
89	2-F-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
90	2-F-phenyl	2-($CH_3NHC(O)N(CH_3)CH_2$)phenyl
91	2-F-phenyl	1-CH_3-2-imidazolyl
92	2,6-diF-phenyl	2-(NH_2SO_2)phenyl
93	2,6-diF-phenyl	2-(CH_3SO_2)phenyl
94	2,6-diF-phenyl	3-NH_2SO_2-4-pyridyl
95	2,6-diF-phenyl	3-CH_3SO_2-4-pyridyl
96	2,6-diF-phenyl	2-(CH_3NH)phenyl
97	2,6-diF-phenyl	2-($(CH_3)_2NCH_2$)phenyl
98	2,6-diF-phenyl	3-($(CH_3)_2NCH_2$)-4-pyridyl
99	2,6-diF-phenyl	2-($(CH_3SO_2)N(CH_3)CH_2$)phenyl
100	2,6-diF-phenyl	2-($(CH_3C(O))N(CH_3)CH_2$)phenyl
101	2,6-diF-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
102	2,6-diF-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
103	2,6-diF-phenyl	2-($CH_3NHC(O)N(CH_3)CH_2$)phenyl
104	2,6-diF-phenyl	1-CH_3-2-imidazolyl

Examples 105-1864 use the corresponding A and B groups from Examples 1-104 and the recited G group.

Examples 105-208, G is 2-(aminomethyl)phenyl;

Examples 209-312, G is 3-(aminomethyl)phenyl;

Examples 313-416, G is 4-(aminomethyl)phenyl;

Examples 417-520, G is 2-(aminomethyl)-3-F-phenyl;

Examples 521-624, G is 2-(aminomethyl)-4-F-phenyl;

Examples 625-728, G is 2-(aminomethyl)-5-F-phenyl;

Examples 729-832, G is 2-(aminomethyl)-6-F-phenyl;

Examples 833-936, G is 3-CN-phenyl;

Examples 937-1040, G is 4-CN-phenyl;

Examples 1041-1144, G is 3-amino-4-Cl-phenyl;

Examples 1145-1248, G is 3-amidino-phenyl;

Examples 1249-1352, G is 4-amidino-phenyl;

Examples 1353-1456, G is 1-aminoisoquinolin-6-yl;

Examples 1457-1560, G is 1-aminoisoquinolin-7-yl;

Examples 1561-1664, G is 4-aminoquinazol-6-yl;

Examples 1665-1768, G is 4-aminoquinazol-7-yl;

Examples 1769-1872, G is 3-aminobenzisoxazol-5-yl;

Examples 1873-1986, G is 3-aminobenzisoxazol-6-yl;

Examples 1987-2090, G is 3-aminoisobenzazol-5-yl; and,

Examples 2091-2194, G is 3-aminoisobenzazol-6-yl.

UTILITY

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving platelet activation and/or platelet aggregation). The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, and venous cerebrovascular

thromboembolic disorders. The term "thromboembolic disorders" as used herein includes specific disorders selected from, but not limited to, unstable angina, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis. It is noted that thrombosis includes occlusion (e.g. after a bypass) and reocclusion (e.g., during or after percutaneous translumianl coronary angioplasty). The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Diapharma/Chromogenix, West Chester, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5%

PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o-v_s)/v_s=I/(K_i\ (1+\ S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq$10 μM. Preferred compounds of the present invention have K_i's of $\leq$1 μM. More preferred compounds of the present invention have K_i's of $\leq$0.1 μM. Even more preferred compounds of the present invention have K_i's of $\leq$0.01 μM. Still more preferred compounds of the present invention have K_i's of $\leq$0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit a Ki of $\leq$10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, Factor VIIa, Factor IXa, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule

substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **1990**, *265*, 18289-18297, herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm that arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μm, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination

with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine and clopidogrel, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine and clopidogrel are also preferred compounds since they are known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists,

thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator and modified forms thereof, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in EP 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of the present invention in combination with such additional therapeutic

agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which

includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like.

Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a dru g, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous

release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P, and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10

milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric

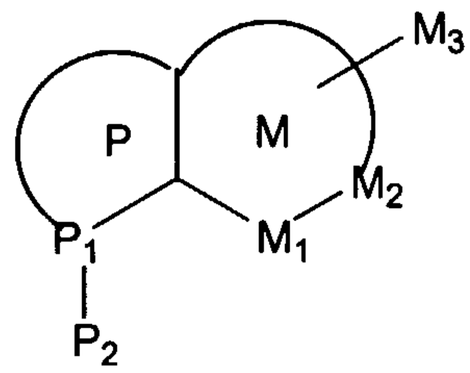
coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

ring M, including M_1 and M_2, is a 5, 6, or 7 membered carbocycle or heterocycle, consisting of: carbon atoms, 0-3 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NZ^2; and ring M is substituted with 0-2 R^3;

M_1 is C(O), CH, CH_2, O, N, SO or SO_2;

M_2 is C, CH, or N;

ring P, including P_1, is a 5, 6, or 7 membered non-aromatic carbocycle or heterocycle, consisting of: carbon atoms, 0-2 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NH; and ring P is substituted with 0-2 R^{1a};

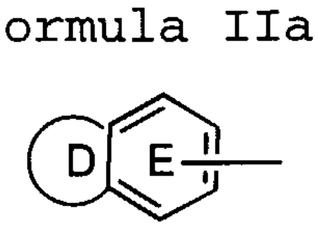
P_1 is C or N;

one of P_2 and M_3 is -Z-A-B and the other $-G_1$-G;

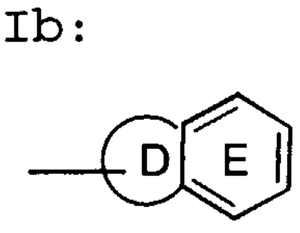
G_1 is absent or is selected from $(CR^3R^{3a})_{1-5}$,

$(CR^3R^{3a})_{0-2}CR^3=CR^3(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_{0-2}C\equiv C(CR^3R^{3a})_{0-2}$,
$(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uOC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}C(O)O(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}C(S)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}S(O)_2NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3e}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uS(O)NR^{3b}C(O)(CR^3R^{3a})_w$,
$(CR^3R^{3a})_uC(O)NR^{3b}S(O)_2(CR^3R^{3a})_w$, and
$(CR^3R^{3a})_uS(O)_2NR^{3b}C(O)NR^{3b}CR^3R^{3a})_w$, wherein (u + w) or (u + u +w) is 0, 1, 2, 3, or 4, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of ring E to which it is attached, is a 5-6 membered non-aromatic ring consisting of carbon atoms, 0-1 double bonds, and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and ring D is substituted with 0-2 R^1, provided that ring D has other than a O-O, $O-S(O)_p$, $S(O)_p-O$, and $S(O)_p-S(O)_p$, bond;

alternatively, ring D, including the two atoms of ring E to which it is attached, is a 5-6 membered aromatic group consisting of carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and ring D is substituted with 0-2 R^1;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 0-1 R^1;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, thienyl and trizaolyl, and ring E is substituted with 0-2 R^a;

R^a is selected from F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $C(O)NR^7R^8$, $(CR^8R^9)_tNR^7R^8$, SH, SCH_3, SCH_2CH_3, $SCH(CH_3)_2$, $SCH_2CH_2CH_3$, $S(O)R^{3b}$, $S(O)_2R^{3a}$, $S(O)_2NR^2R^{2a}$, and OCF_3;

alternatively, two R^as combine to form methylenedioxy or ethylenedioxy;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, and thienyl, and ring E is substituted with 1 R and with a 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 carbonyl groups and 0-2 R^1;

alternatively, ring D is absent and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with R^e;

R^e is selected from CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

A is selected from:

C_{3-10} carbocycle substituted with 0-2 R^4, and

5-12 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^4;

B is selected from: Y, X-Y, $(CH_2)_{0-2}C(O)NR^2R^{2a}$, $(CH_2)_{0-2}NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, and $NR^2C(=NR^2)NR^2R^{2a}$, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^2R^{2a})-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$, $-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$,

$-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$,
$-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$,
$-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$,
$-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$,
$-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

$-(CH_2)_rNR^2R^{2a}$;

C_{3-10} carbocycle substituted with 0-2 R^{4a}; and

5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{4a};

provided that X-Y do not form a N-N, O-N, or S-N bond;

Z is selected from a bond, $-(CR^3R^{3a})_{1-4}-$,
$(CR^3R^{3a})_qO(CR^3R^{3a})_m$, $(CR^3R^{3a})_qNR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qC(O)(CR^3R^{3a})_m$, $(CR^3R^{3a})_qC(O)O(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qOC(O)(CR^3R^{3a})_m$, $(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_m$, $(CR^3R^{3a})_qOC(O)O(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qOC(O)NR^{3b}(CR^2R^{2a})_m$, $(CR^3R^{3a})_qNR^{3b}C(O)O(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qC(O)(CR^3R^{3a})_qC(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_qC(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qC(O)(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qS(CR^3R^{3a})_m$, $(CR^3R^{3a})_qS(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qS(O)_2(CR^3R^{3a})_m$, $(CR^3R^{3a})_qSO_2NR^{3b}(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}SO_2(CR^3R^{3a})_m$,

$(CR^3R^{3a})_qS(O)NR^{3b}C(O)(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qC(O)NR^{3b}S(O)_2(CR^3R^{3a})_m$,
$(CR^3R^{3a})_qNR^{3b}SO_2NR^{3b}(CR^3R^{3a})_m$, wherein (q + m) or (q + q + m) is 0, 1, 2, 3, or 4, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z^2 is selected from H; $S(O)_2NHR^3$; $C(O)R^3$; $C(O)NHR^3$; $C(O)OR^{3f}$; $S(O)R^{3f}$; $S(O)_2R^{3f}$; C_{1-6} alkyl substituted with 0-2 R^{1a}; C_{2-6} alkenyl substituted with 0-2 R^{1a}; C_{2-6} alkynyl substituted with 0-2 R^{1a}; -(C_{0-4} alkyl)-C_{3-10}-carbocycle substituted with 0-3 R^{1a}; -(C_{0-4} alkyl)-5-12 membered-heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tC(O)H$, $(CR^8R^9)_tC(O)R^{2c}$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, $(CR^8R^9)_tNR^7C(O)R^7$, $(CR^8R^9)_tOR^3$, $(CR^8R^9)_tS(O)_pNR^7R^8$, $(CR^8R^9)_tNR^7S(O)_pR^7$, $(CR^8R^9)_tSR^3$, $(CR^8R^9)_tS(O)R^3$, $(CR^8R^9)_tS(O)_2R^3$, and OCF_3;

R^1 is selected from F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$

alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl)$_2$;

R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-(CH_2)_r-O-(CH_2)_r-R^{1b}$, $-CH=CH-R^{1b}$, NCH_2R^{1c}, NR^2R^{2a}, OCH_2R^{1c}, SCH_2R^{1c}, $NH(CH_2)_2(CH_2)_tR^{1b}$, $C(O)NR^2(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and $NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

alternatively, when two R^{1a}s are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)^p$, this ring being substituted with 0-2 R^{4b}, and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, substituted with 0-2 R^{4a}, provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond with the group to which it is attached;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-6} carbocycle substituted with 0-2 R^{4a} and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^2 and R^{2a}, at each occurrence, are independently selected from H; CF_3; C_{1-6} alkyl; benzyl; $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}; and $-(CH_2)_r$-5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and consisting of: carbon atoms and 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl substituted with 0-2 R^{4b}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^3 and R^{3a}, at each occurrence, is independently selected from H, C_{1-4} alkyl, benzyl and phenyl;

R^{3b}, at each occurrence, is selected from H, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and $-(C_{0-4}$ alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, benzyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

R^{3e}, is selected from H, $S(O)_2NHR^3$, $C(O)R^3$, $C(O)NHR^3$, $C(O)OR^{3f}$, $S(O)R^{3f}$, $S(O)_2R^{3f}$, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and

-(C_{0-4} alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3f}, at each occurrence, is selected from: C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, -(C_{0-4} alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and -(C_{0-4} alkyl)-5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $(CH_2)_rNR^2C(O)R^{2b}$, $(CH_2)_rC(O)NR^2R^{2a}$, $(CH_2)_rNR^2C(O)NR^2R^{2a}$, $(CH_2)_rC(=NR^2)NR^2R^{2a}$, $(CH_2)_rC(=NS(O)_2R^5)NR^2R^{2a}$, $(CH_2)_rNHC(=NR^2)NR^2R^{2a}$, $(CH_2)_rC(O)NHC(=NR^2)NR^2R^{2a}$, $(CH_2)_rSO_2NR^2R^{2a}$, $(CH_2)_rNR^2SO_2NR^2R^{2a}$, $(CH_2)_rNR^2SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^2SO_2R^5$, $(CH_2)_rS(O)_pR^{5a}$, $(CF_2)_rCF_3$, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, $(CR^3R^{3a})_rF$, $(CR^3R^{3a})_rBr$, $(CR^3R^{3a})_rCl$, C_{1-4} alkyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rN=CHOR^3$, $(CR^3R^{3a})_rC(O)NH(CH_2)_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rNHC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $(CR^3R^{3a})_rC(O)NHSO_2$-C_{1-4} alkyl, $(CR^3R^{3a})NR^2SO_2R^5$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CR^3R^{3a})_r(CF_2)_rCF_3$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_r$-$C(=NR^3)NR^3R^{3a}$, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$, $(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$, $(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, and $(CH_2)_r(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$,

$NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^{5a}, at each occurrence, is selected from C_{1-6} alkyl, $(CH_2)_rOR^3$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6, provided that R^{5a} does not form a S-N or $S(O)_p$-C(O) bond;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, $(CH_2)_n$-phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $-(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5 or 6 membered saturated

ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $-(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5 and 6;

t, at each occurrence, is selected from 0, 1, 2, and 3; and

provided that:

(a) when M_1 is a carbonyl and G is substituted with an amidino, guanidino, amino-ethylene, or amino-propylene group, any of which may be substituted or cyclized, then G_1 is present or Z is other than alkylene; or

(b) when M_1 is a carbonyl and G_1 is absent, then Z is other than alkylene;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) G_1 is $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$, or $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$; u+w is 1, 2, 3, or 4;

then Z is other than $(CH_2)NR^{3b}$, $NR^{3b}(CH_2)$, $(CH_2)NR^{3b}(CH_2)$, $(CH_2)(CH_2)NR^{3b}$, $NR^{3b}(CH_2)(CH_2)$, $(CH_2)_qC(O)NR^{3b}(CH_2)_m$, $(CH_2)_qNR^{3b}C(O)(CH_2)_m$, $(CH_2)_qSO_2NR^{3b}(CH_2)_m$, or $(CH_2)_qNR^{3b}SO_2(CH_2)_m$;

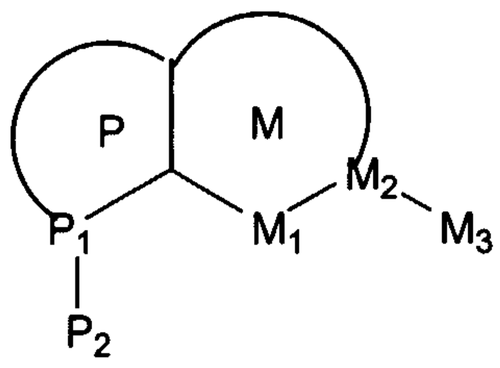
alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) Z is $((CH_2)NR^{3b}$, $NR^{3b}(CH_2)$, $(CH_2)NR^{3b}(CH_2)$, $(CH_2)(CH_2)NR^{3b}$, $NR^{3b}(CH_2)(CH_2)$, $(CH_2)_qC(O)NR^{3b}(CH_2)_m$, $(CH_2)_qNR^{3b}C(O)(CH_2)_m$, $(CH_2)_qSO_2NR^{3b}(CH_2)_m$, or $(CH_2)_qNR^{3b}SO_2(CH_2)_m$;

then G_1 is other than $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$, or $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$; u+w is 1, 2, 3, or 4.

2. A compound according to Claim 1, the compound is of Formula (Ia):



(Ia)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

ring M, including M_1 and M_2, is a 5, 6, or 7 membered carbocycle or heterocycle, consisting of: carbon atoms, 0-3 double bonds, 0-2 carbonyl groups, and 0-3

heteroatoms selected from O, $S(O)_p$, N, and NZ^2; and ring M is substituted with 0-1 R^3;

M_1 is C(O), CH, CH_2, O, N, SO or SO_2;

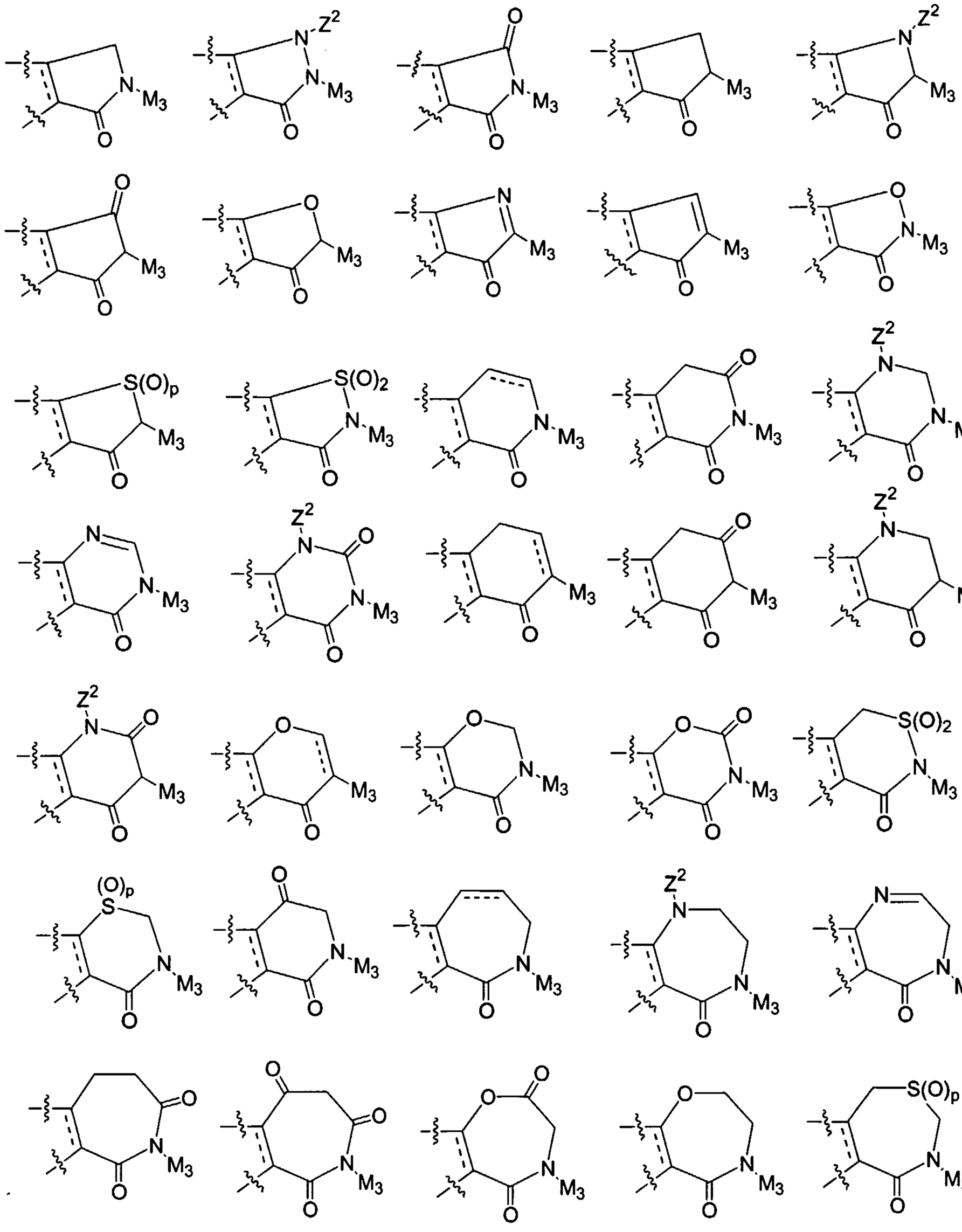
M_2 is C, CH, or N;

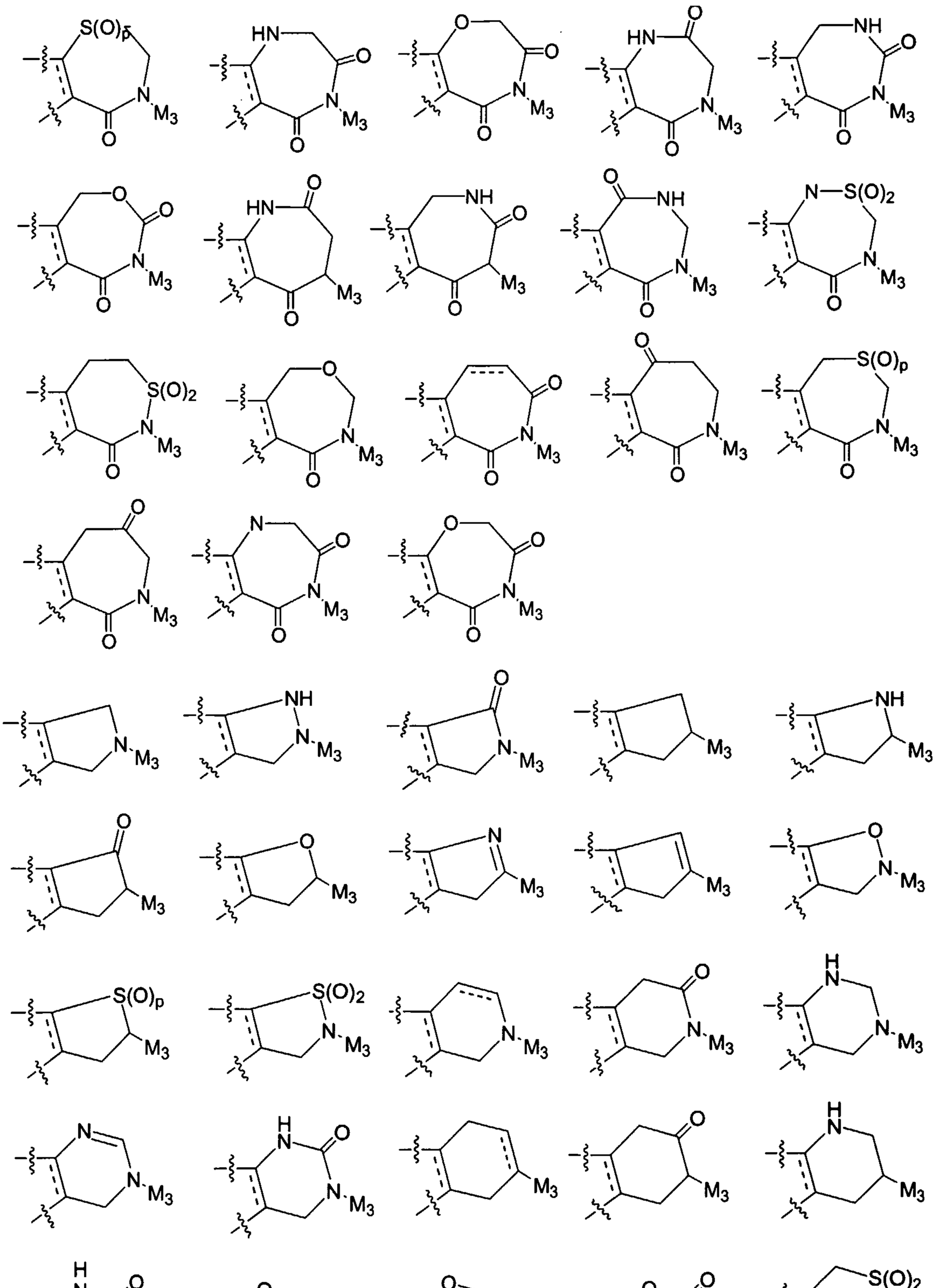
ring P, including P_1, is a 5, 6, or 7 membered non-aromatic carbocycle or heterocycle, consisting of: carbon atoms, 0-2 double bonds, 0-2 carbonyl groups, and 0-3 heteroatoms selected from O, $S(O)_p$, N, and NH and ring P is substituted with 0-2 R^{1a}; and,

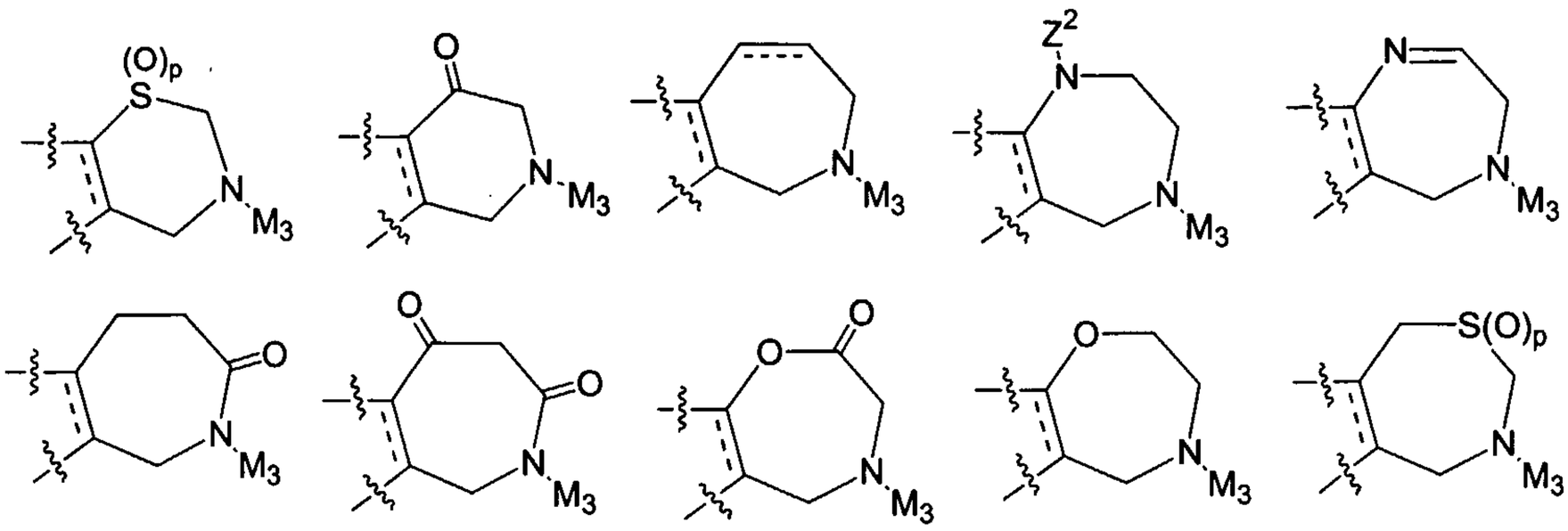
P_1 is C or N.

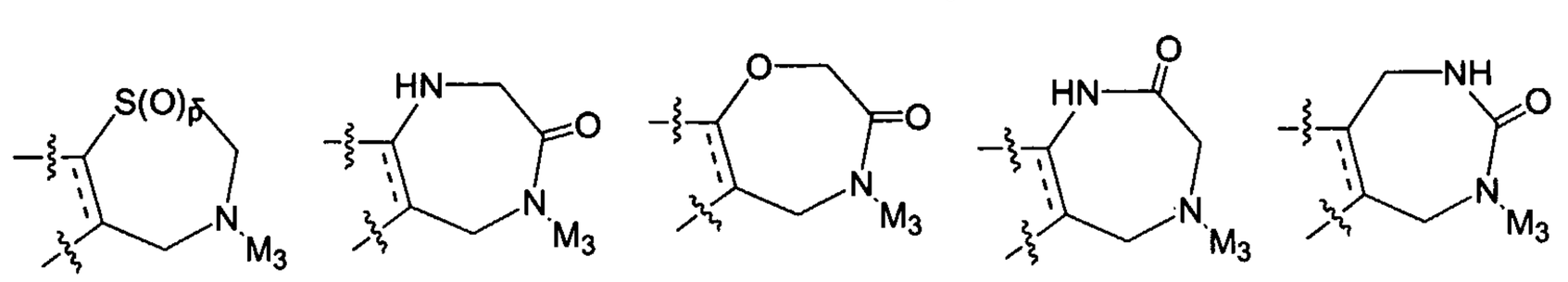
3. A compound of Claim 2, wherein:

ring M is substituted with 0-1 R^3 and is selected from the group:



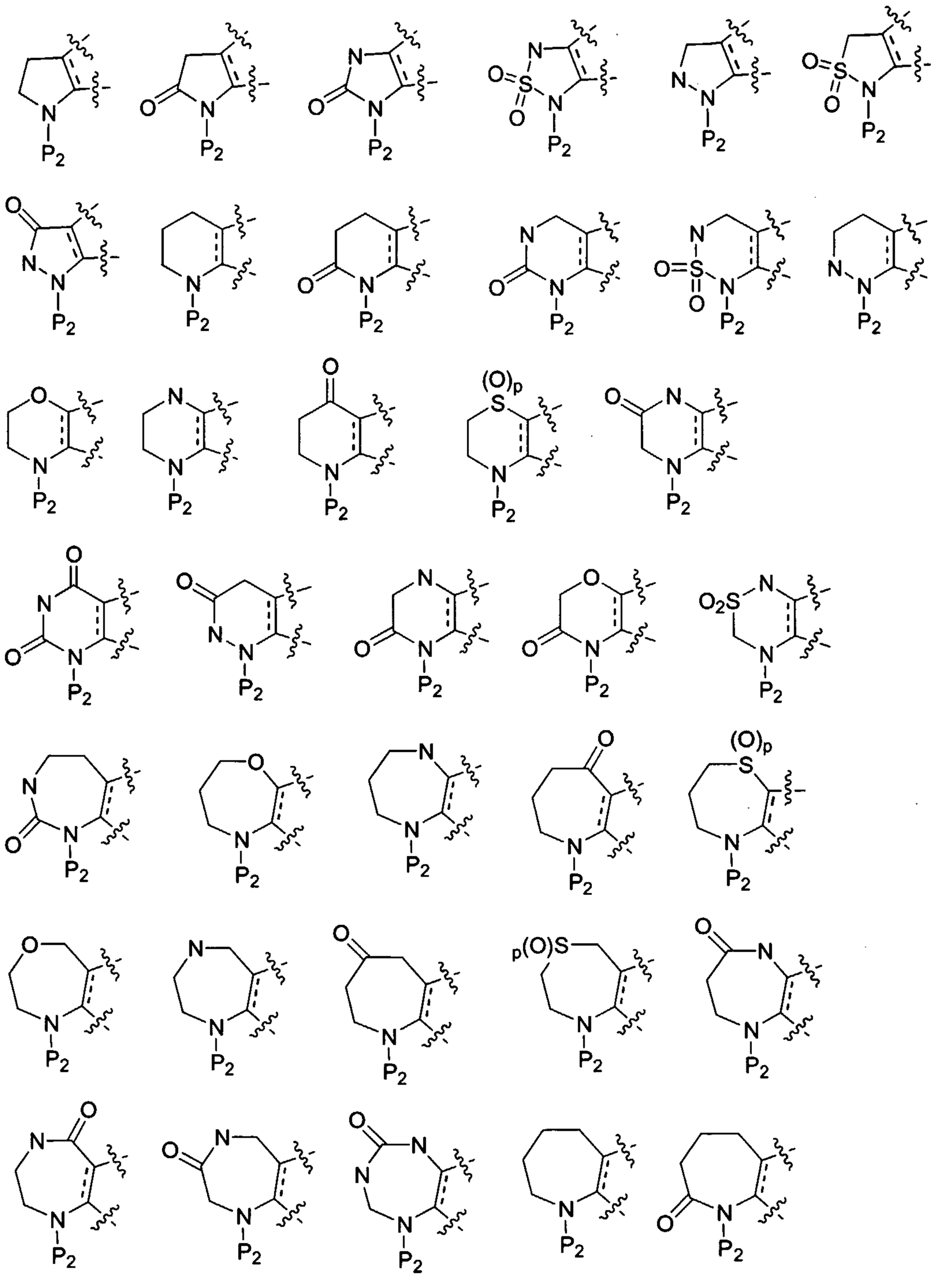






Z^2 is selected from H, C_{1-4} alkyl, phenyl, benzyl, $S(O)_2NHR^3$, $C(O)NHR^3$, $C(O)OR^{3f}$, $S(O)R^{3f}$, and $S(O)_2R^{3f}$;

ring P is substituted with 0-1 R^{1a} and is selected from the group:



G_1 is absent or is selected from $(CR^3R^{3a})_{1-3}$,

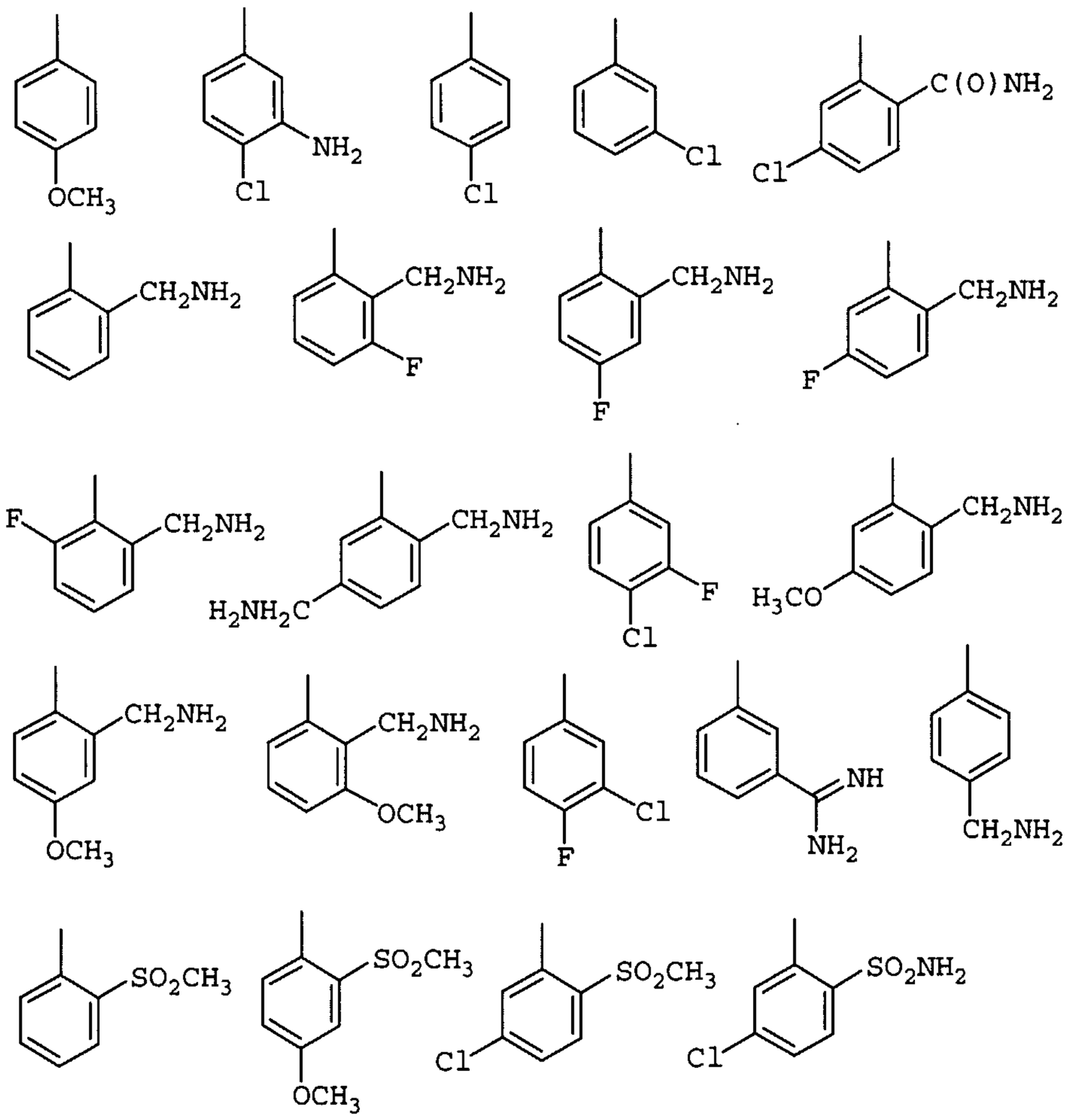
$(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$,

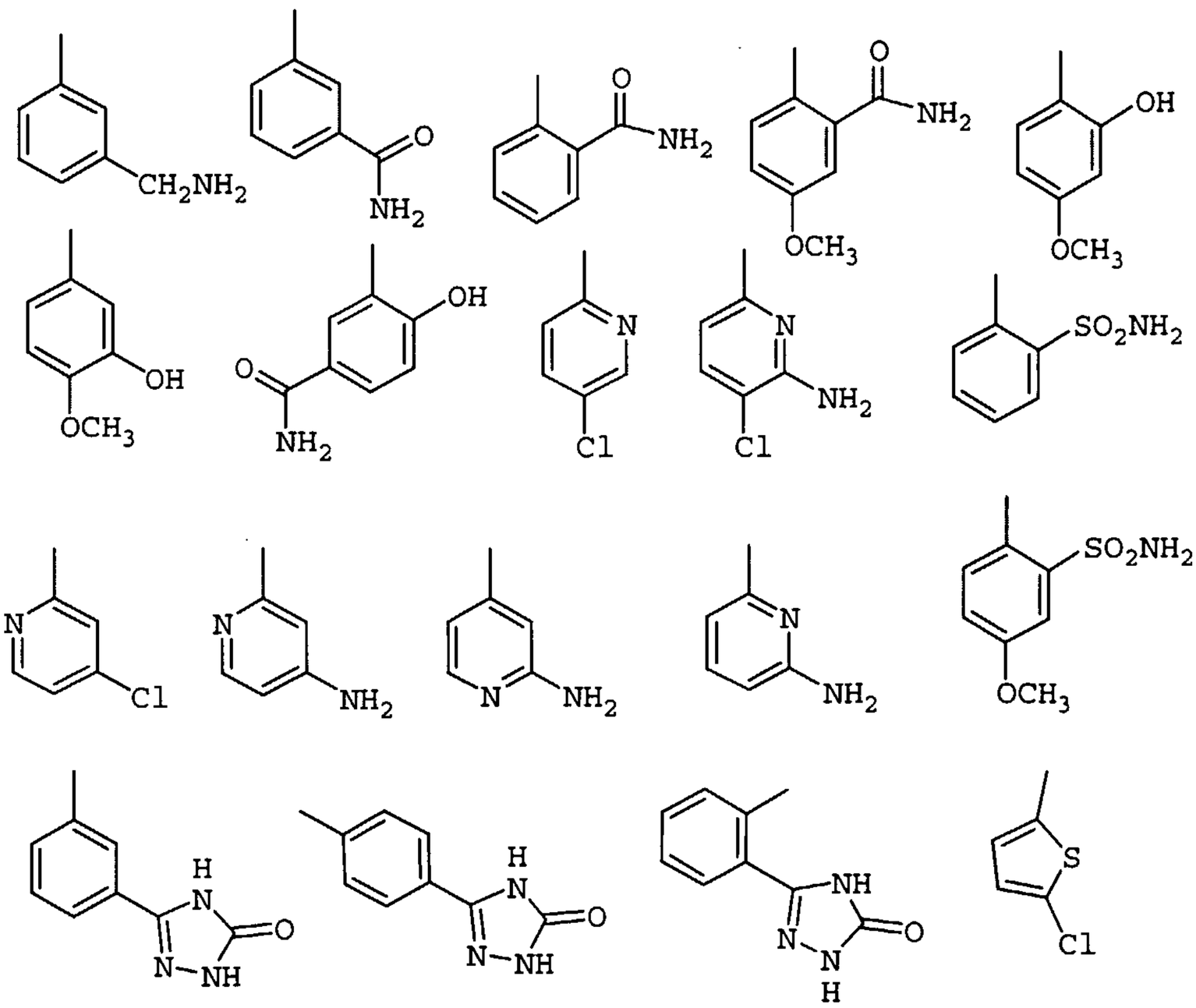
$(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$,

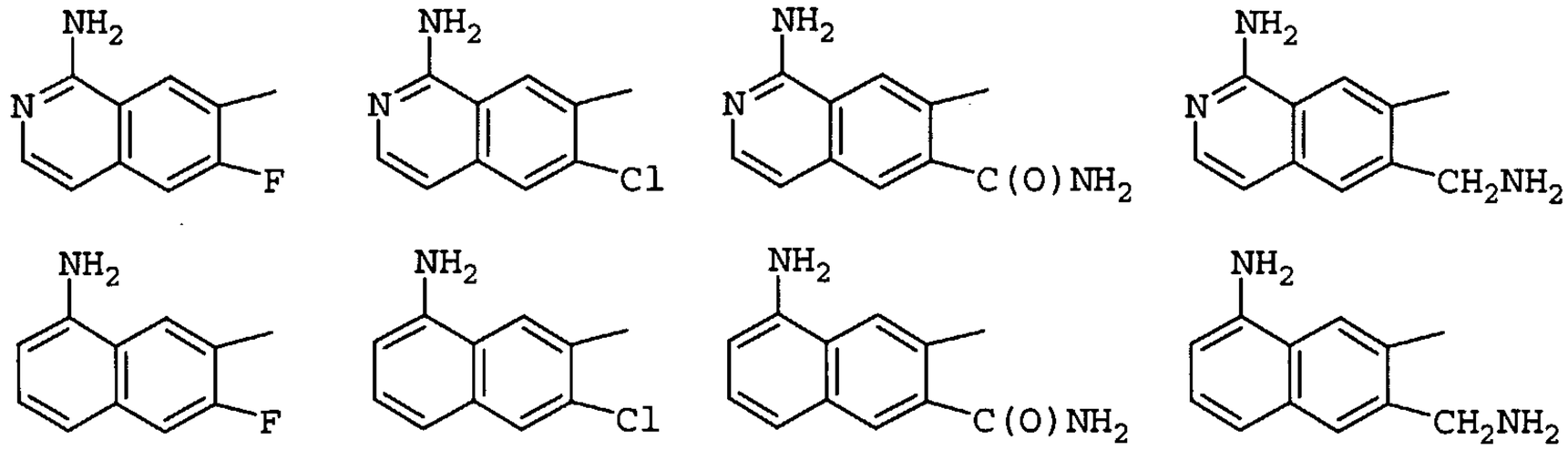
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$,

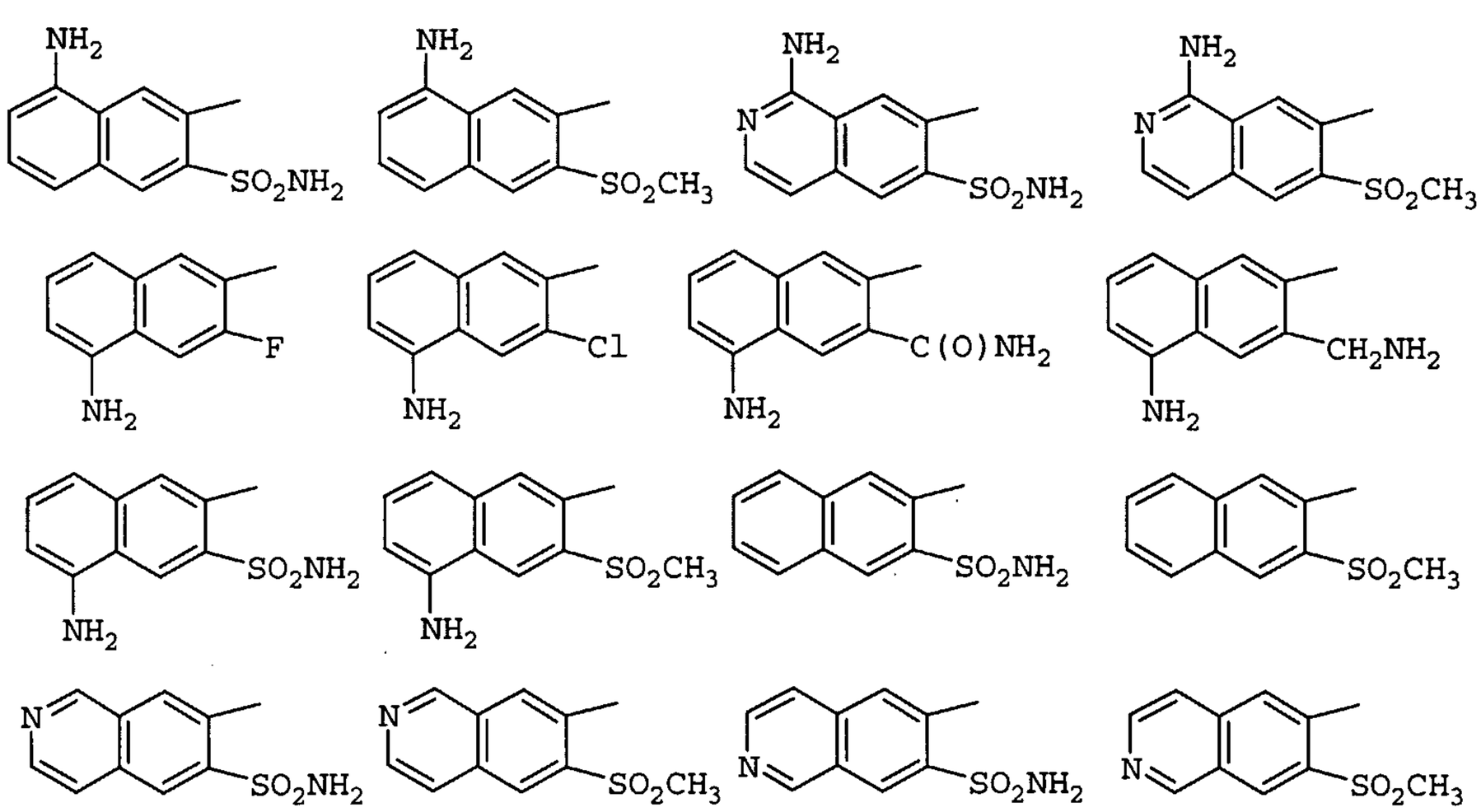
$(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$, wherein (u + w) or (u + u + w) is 0, 1, or 2, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

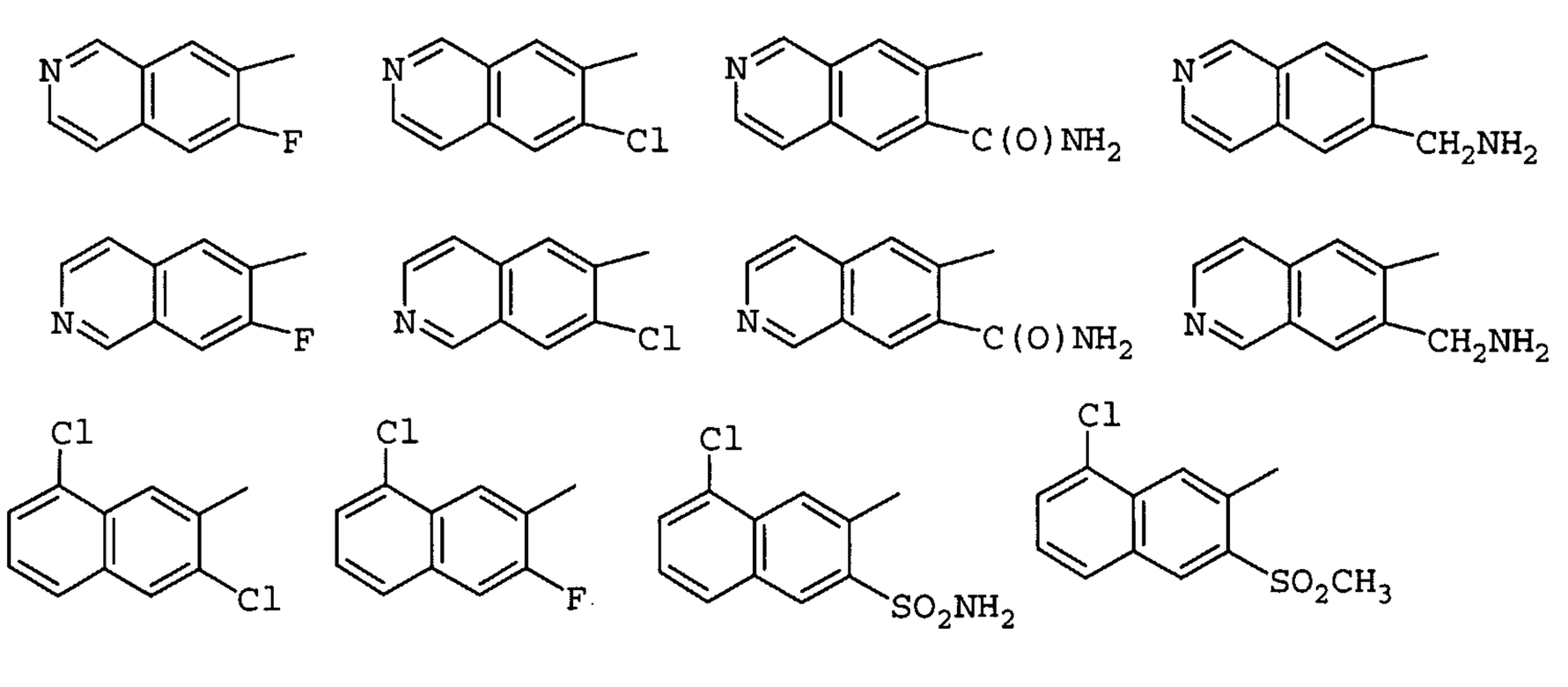
ring G is selected from:

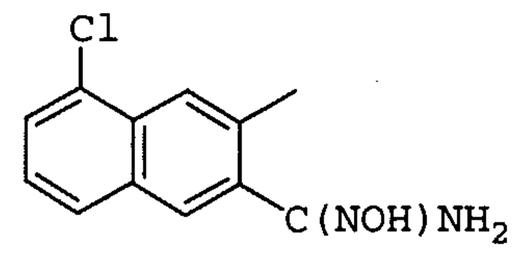
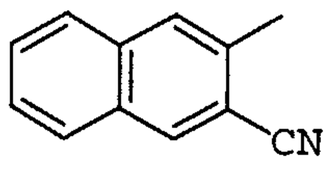
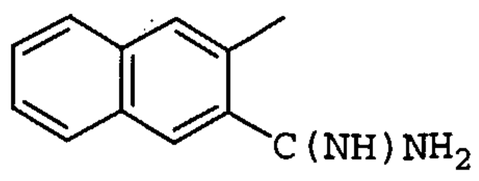
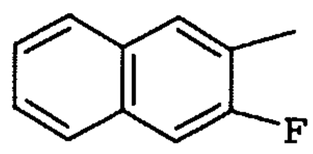
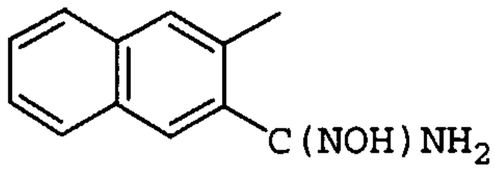
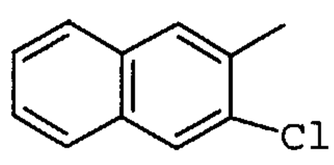
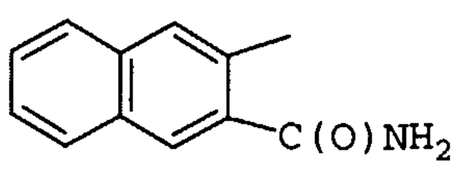
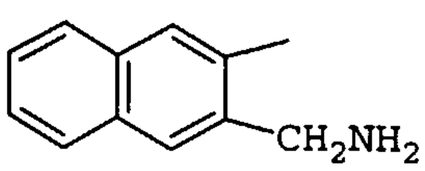
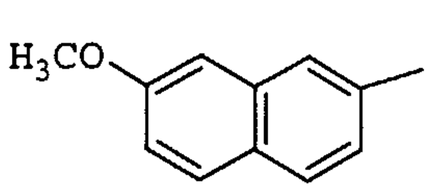
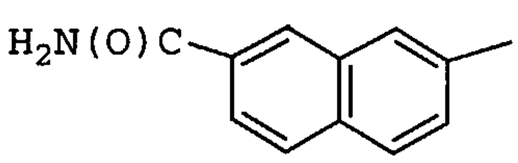
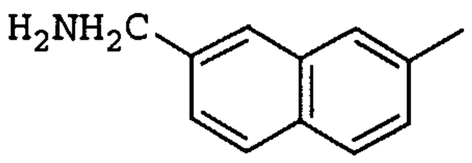
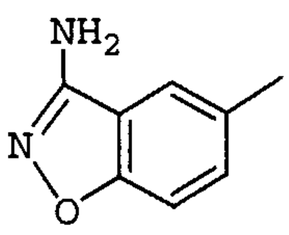
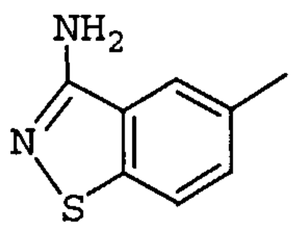
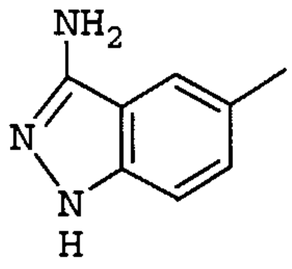
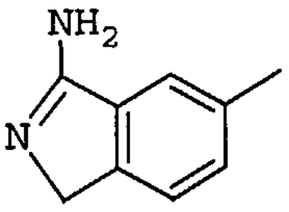
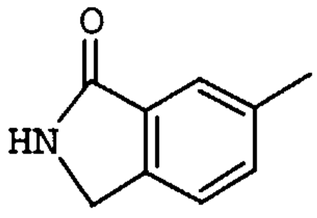
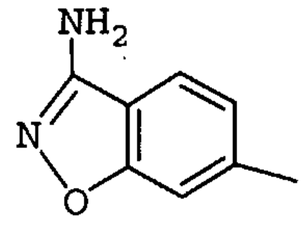
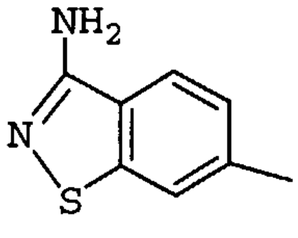
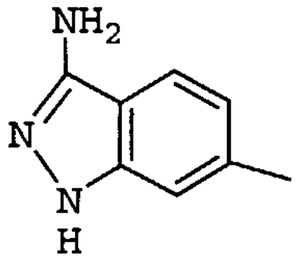
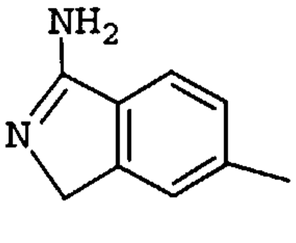
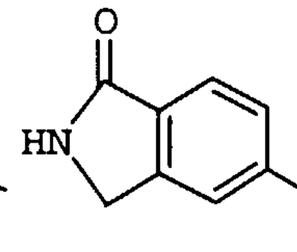
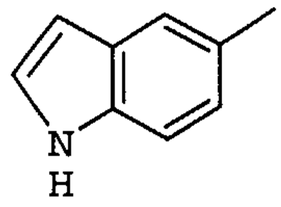
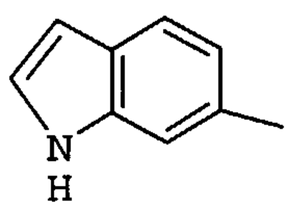
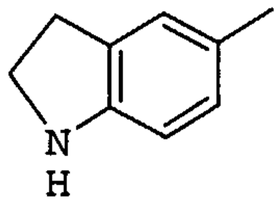
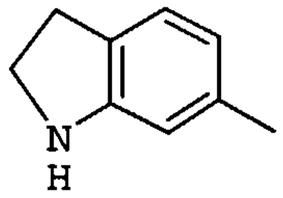
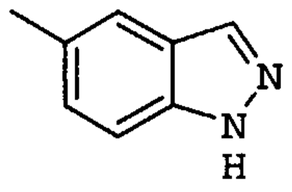
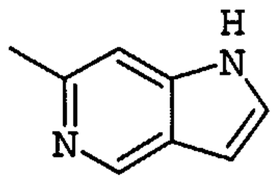
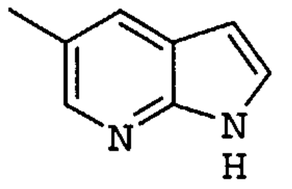
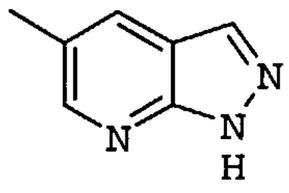
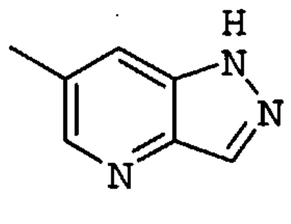
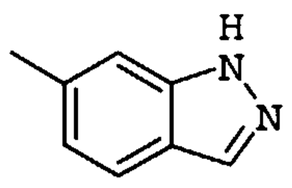
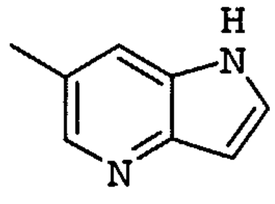
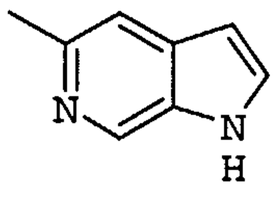
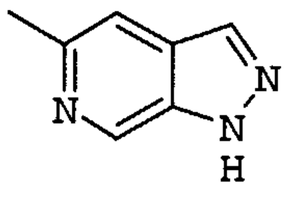
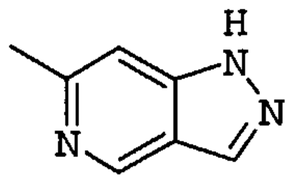
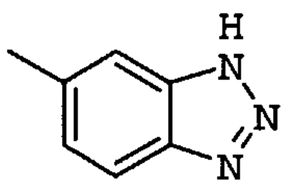


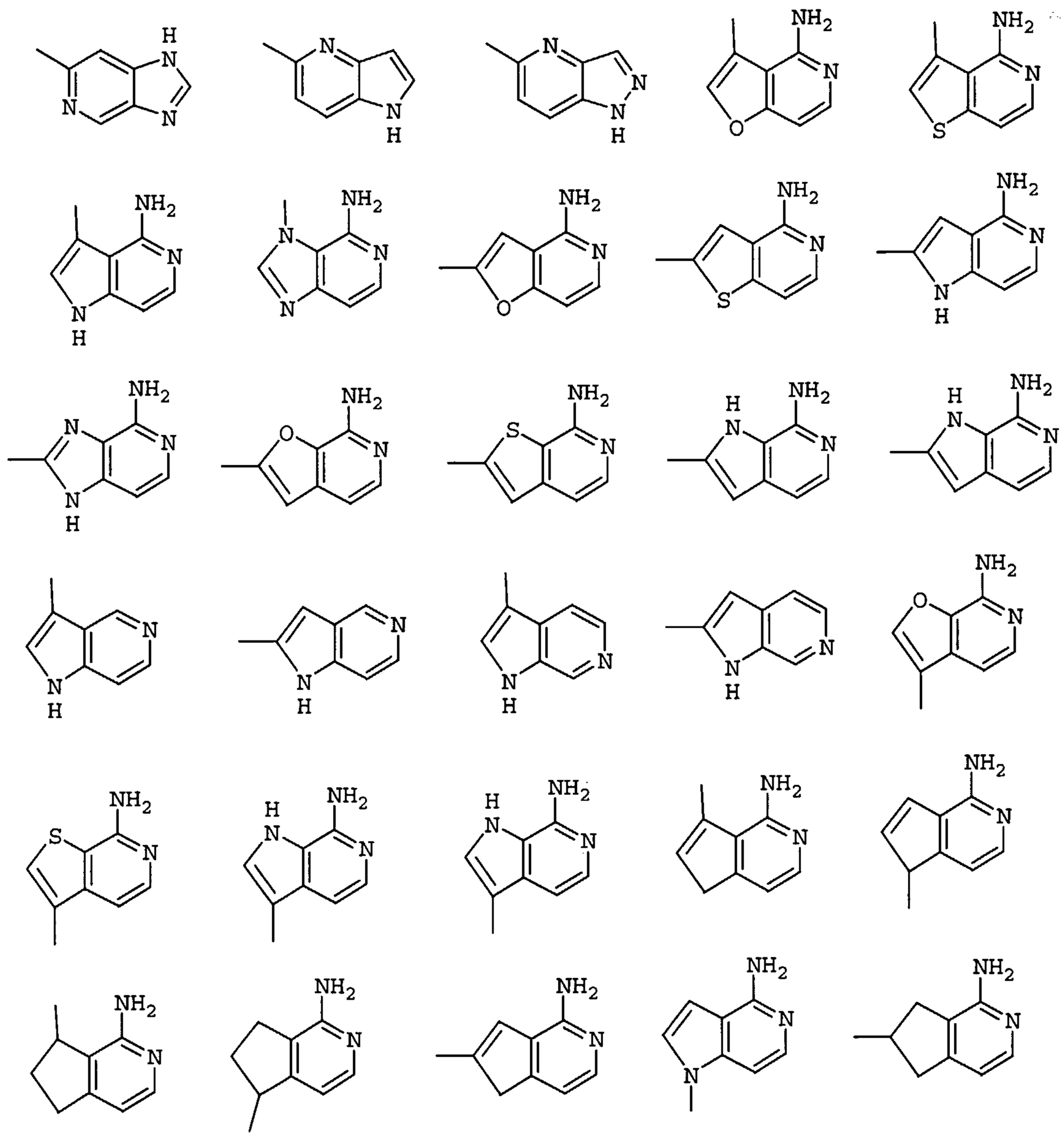










A is selected from one of the following carbocycles and heterocycles which are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,

1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolinyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is selected from Y, X-Y, $CH_2NR^2R^{2a}$, and $CH_2CH_2NR^2R^{2a}$;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^2R^{2a})-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

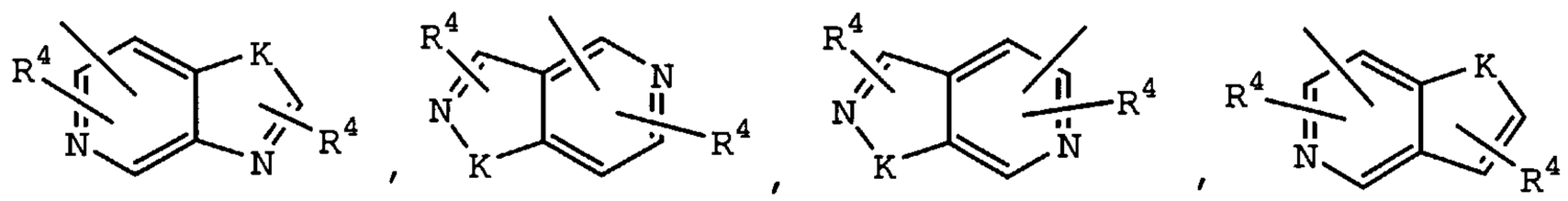
Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

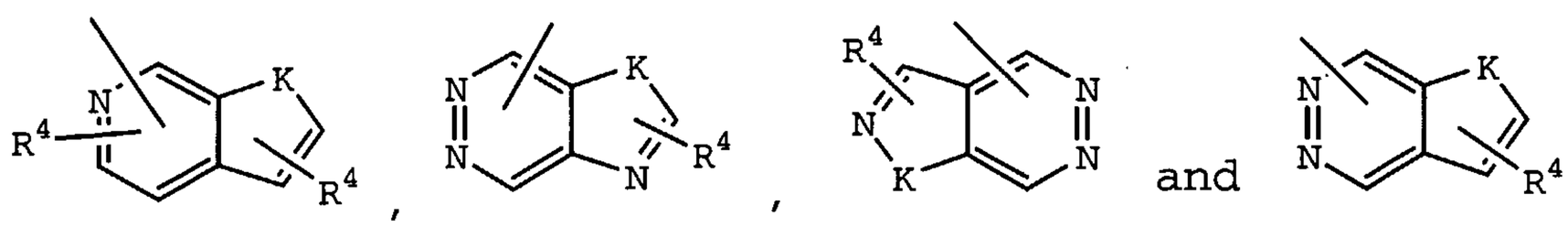
alternatively, Y is selected from one of the following carbocycles and heterocycles which are substituted with 0-2 R^{4a};

cylcopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolinyl, indolyl, benzimidazolyl, benzoxazolyl,

benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:





and

K is selected from O, S, NH, and N;

Z is selected from CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) G_1 is $(CH_2)_uNR^{3b}(CH_2)_w$, $(CH_2)_uC(O)NR^{3b}(CH_2)_w$, $(CH_2)_uNR^{3b}C(O)(CH_2)_w$, $(CH_2)_uS(O)NR^{3b}(CH_2)_w$, $(CH_2)_uS(O)_2NR^{3b}(CH_2)_w$, or $(CH_2)_uNR^{3b}S(O)_2(CH_2)_w$; and

(u + w) is 1 or 2;

then Z is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

alternatively, when

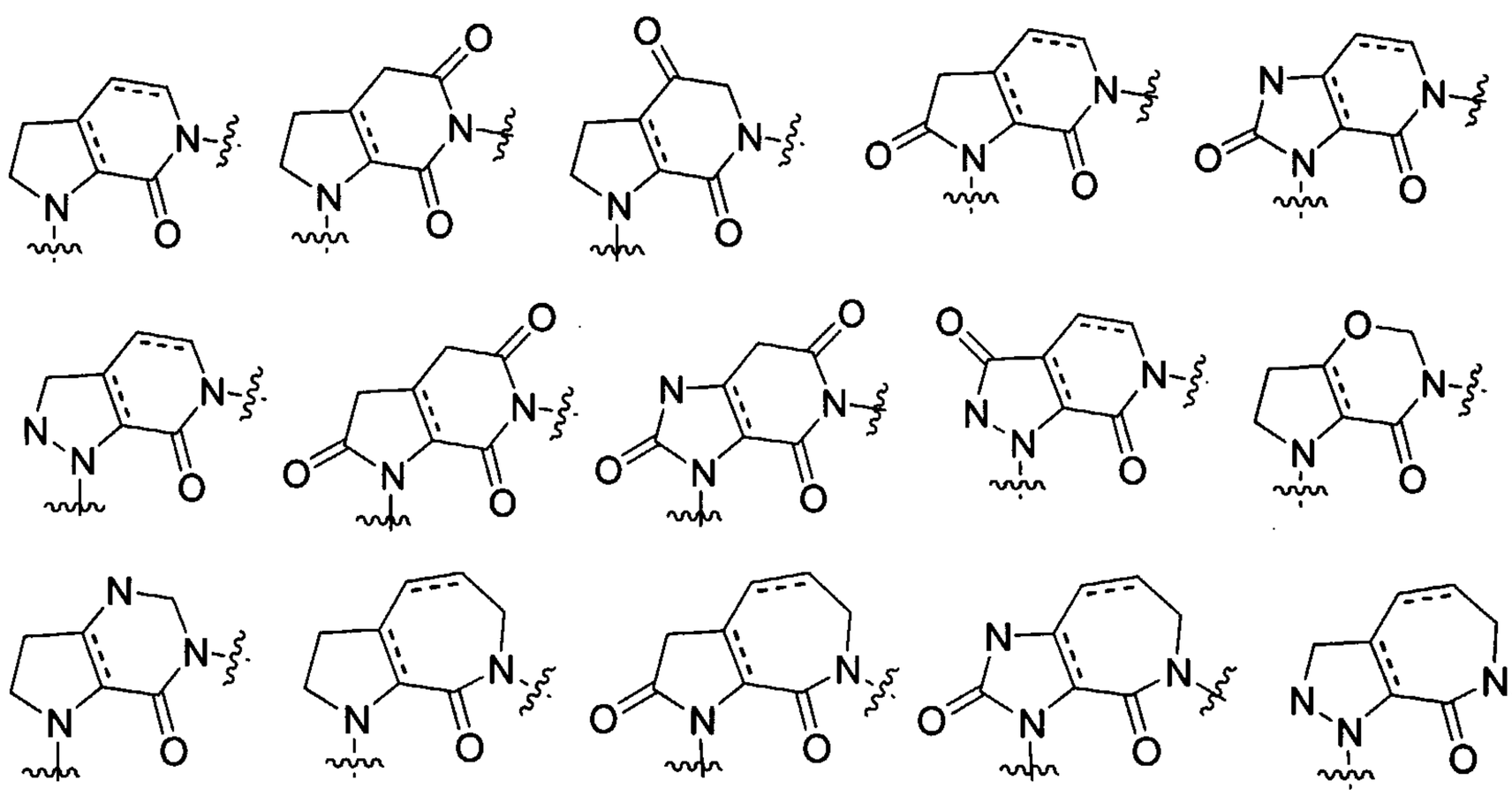
(a) B is other than an optionally substituted carbocycle; and,

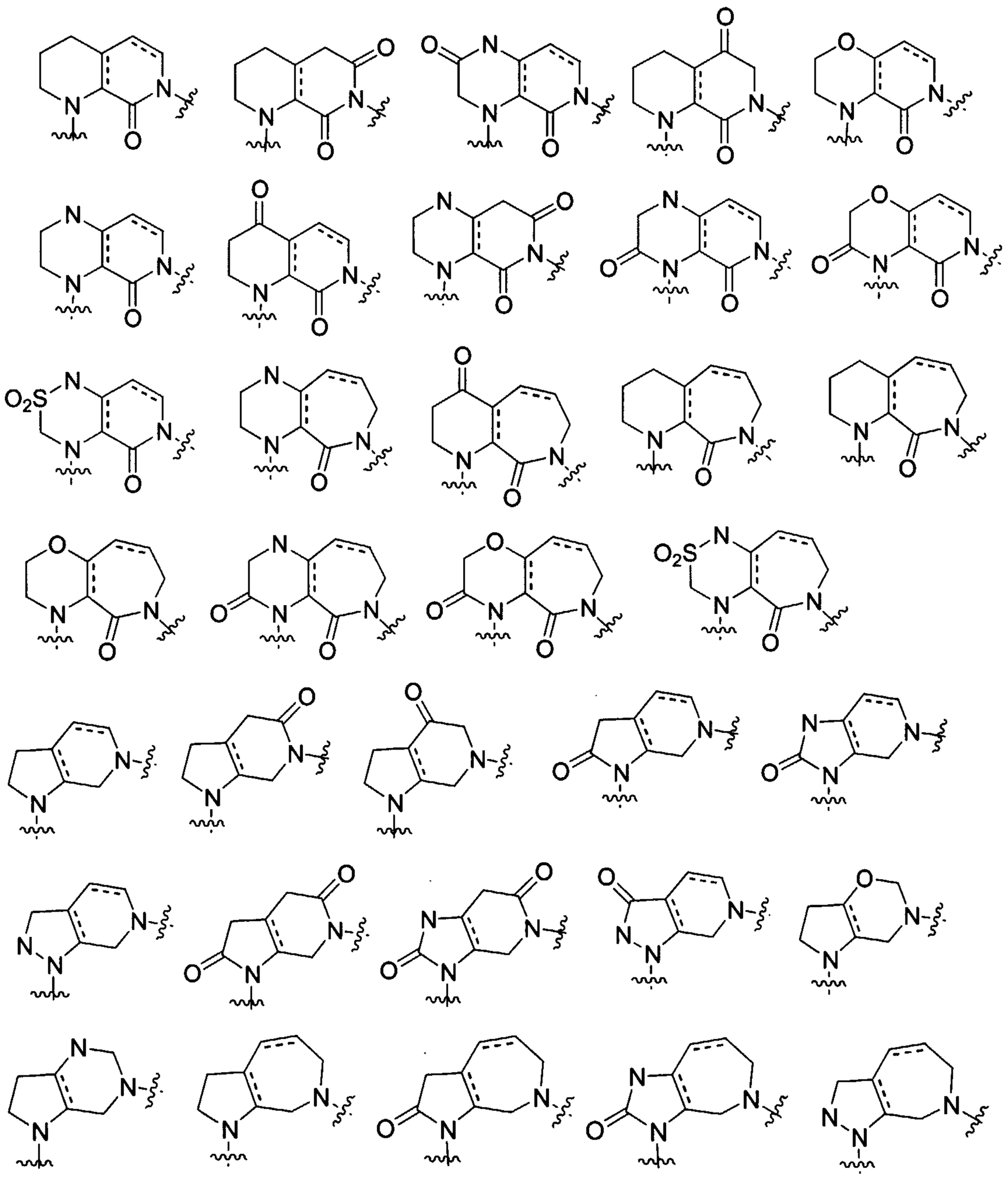
(b) Z is CH_2NH, $NHCH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

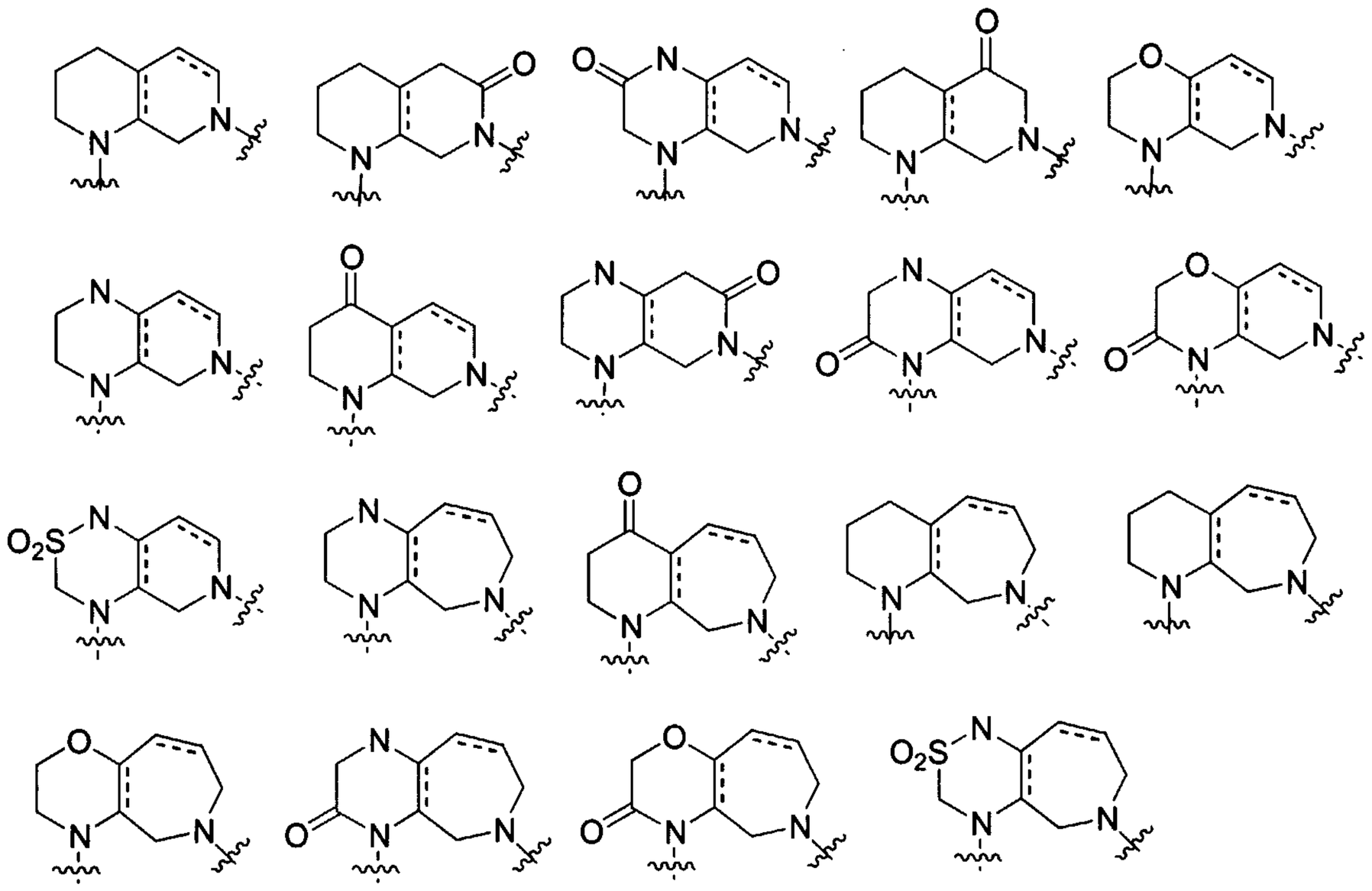
then G_1 is other than $(CH_2)_uNR^{3b}(CH_2)_w$, $(CH_2)_uC(O)NR^{3b}(CH_2)_w$, $(CH_2)_uNR^{3b}C(O)(CH_2)_w$, $(CH_2)_uS(O)NR^{3b}(CH_2)_w$, $(CH_2)_uS(O)_2NR^{3b}(CH_2)_w$, or $(CH_2)_uNR^{3b}S(O)_2(CH_2)_w$; and (u + w) is 1 or 2.

4. A compound according to Claim 3, wherein:

rings P-M are substituted with 0-1 R^{1a} and are selected from the group:

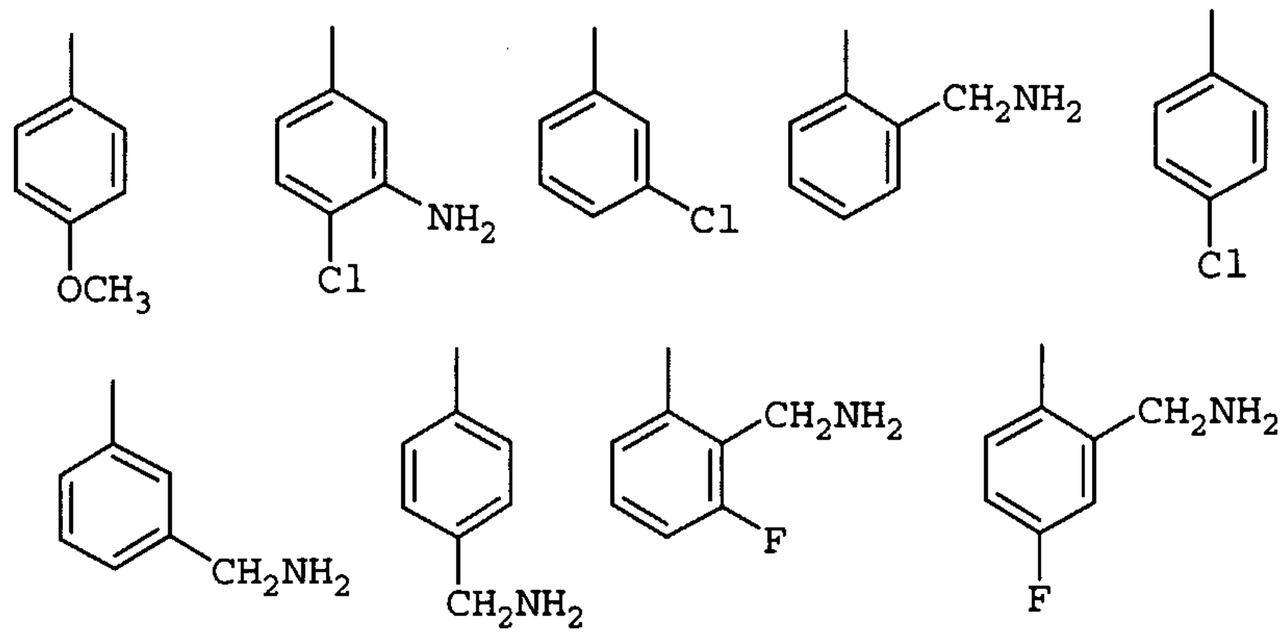


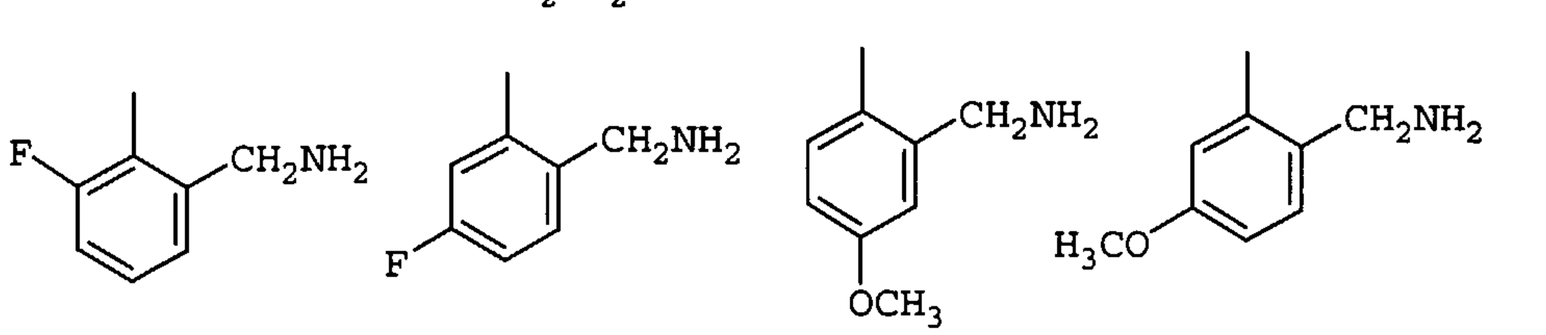


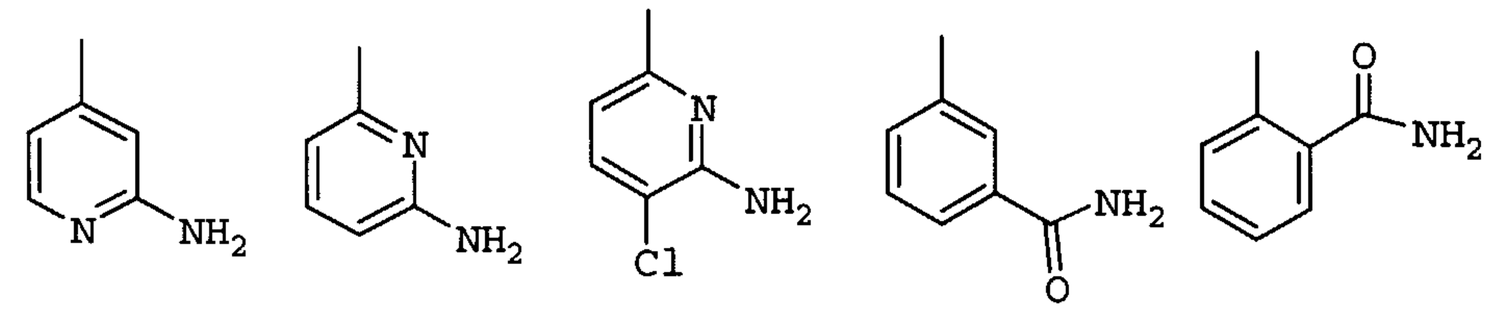


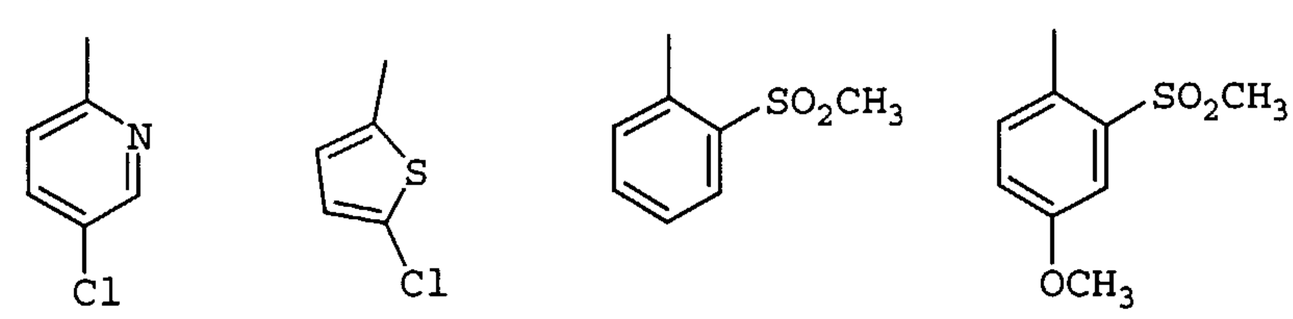
G_1 is absent or is selected from CH_2, CH_2CH_2, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

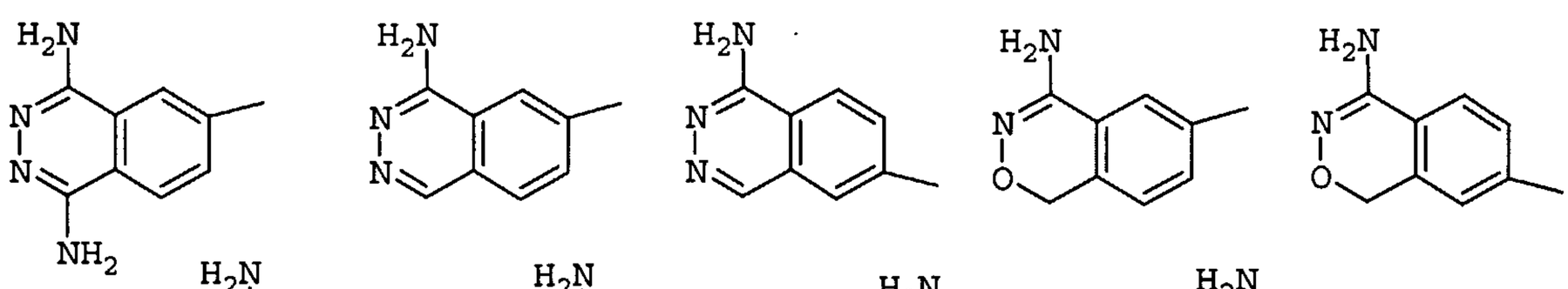
ring G is selected from:

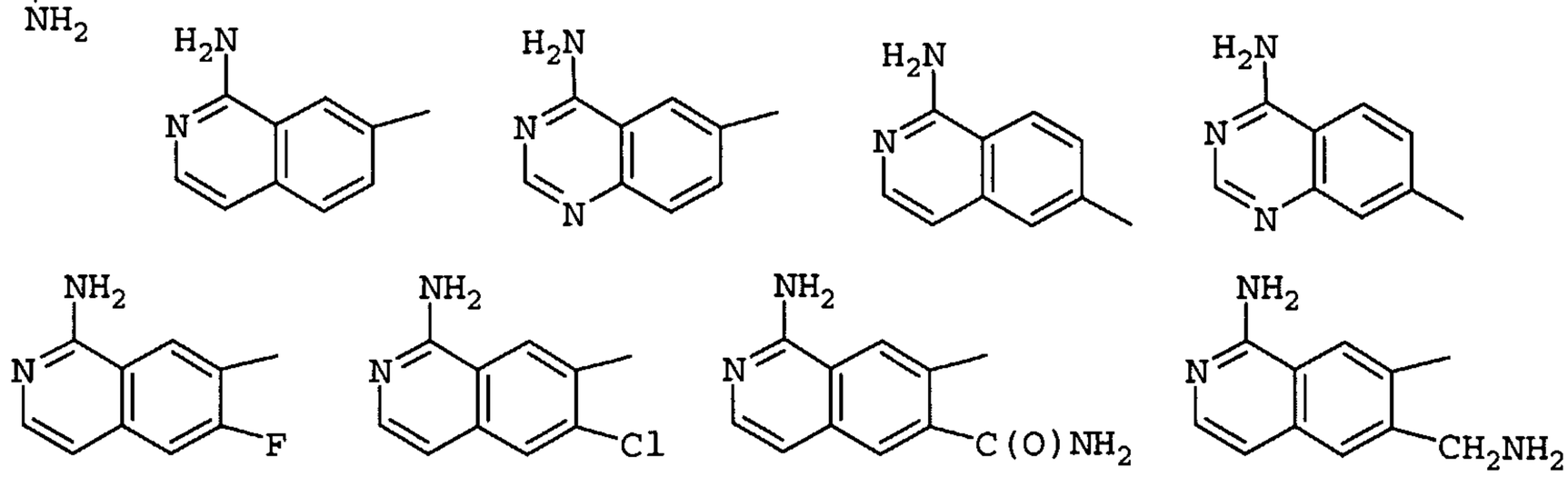


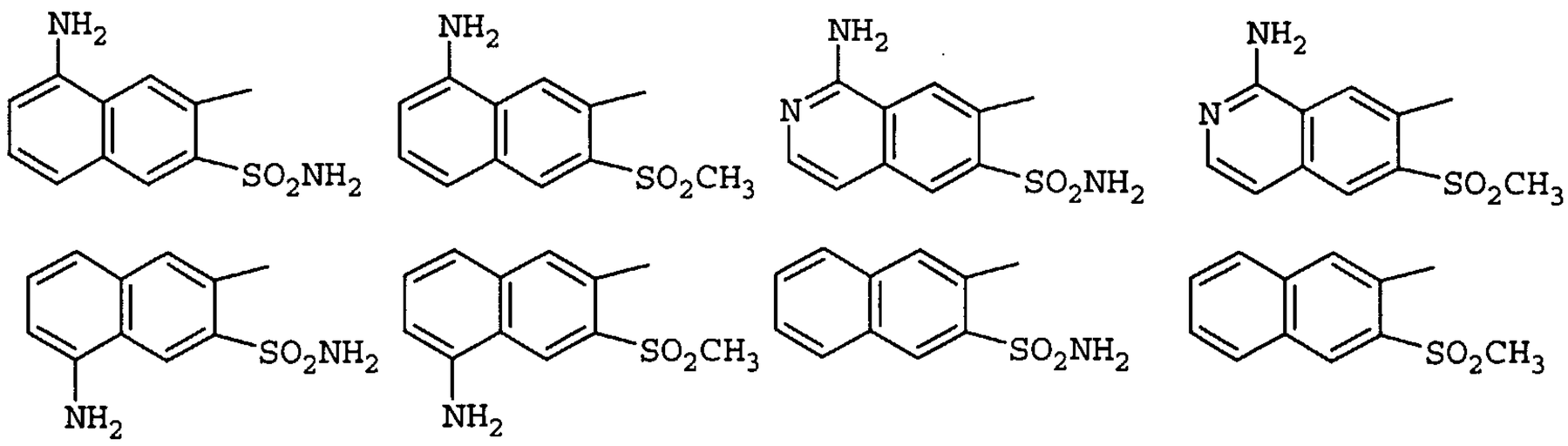


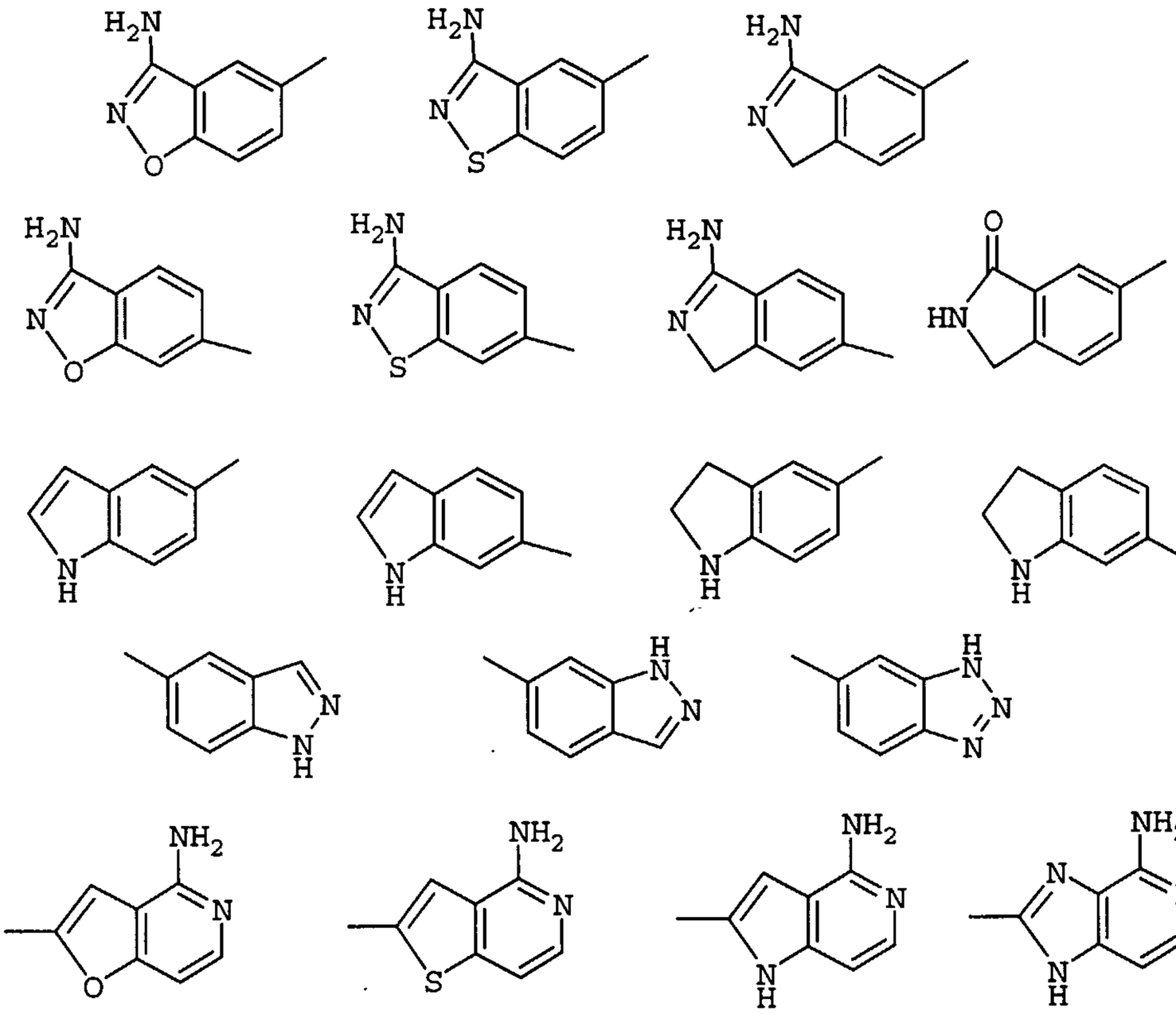


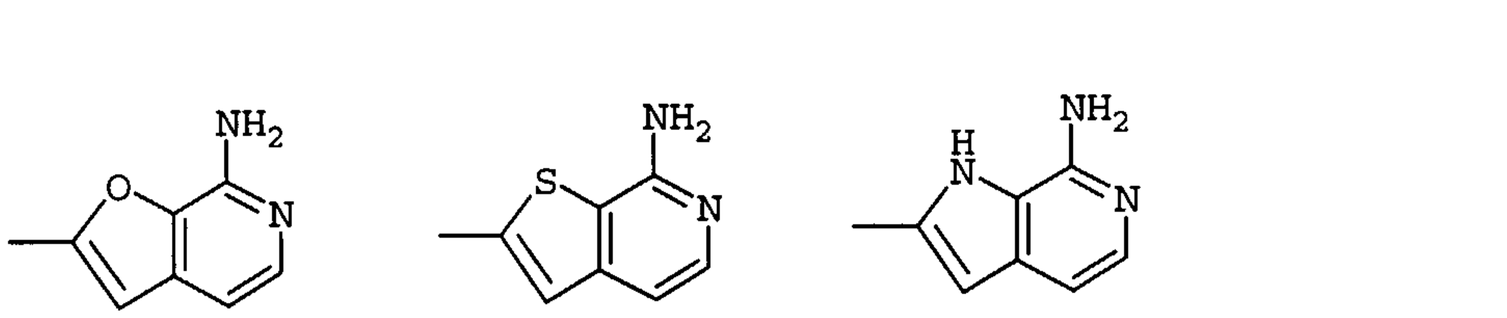







NH2
SO2NH2
NH2
SO2CH3
NH2
N
SO2NH2
NH2
N
SO2CH3
SO2NH2
NH2
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NH2
SO2NH2
N
SO2NH2
N
SO2CH3
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Cl
F
Cl
SO2NH2
Cl
SO2CH3
Cl
CH2NH2
Cl
C(O)NH2
Cl
CN
Cl
C(NH)NH2
Cl
C(NOH)NH2
CN
C(NH)NH2
C(NOH)NH2
F
Cl
C(O)NH2
CH2NH2
H3CO
H2N(O)C
H2NH2C





alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) G_1 is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

then Z is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

alternatively, when

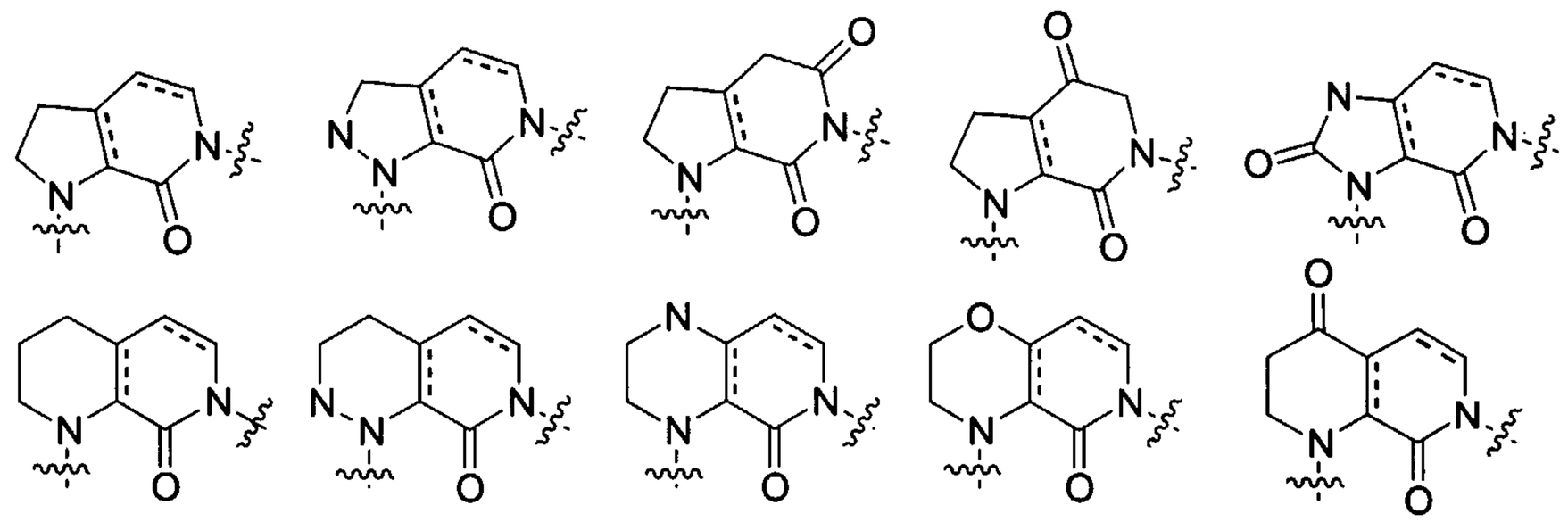
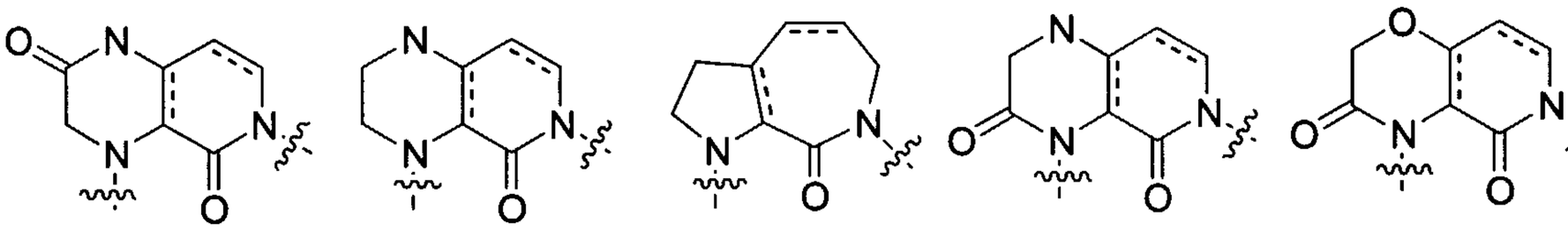
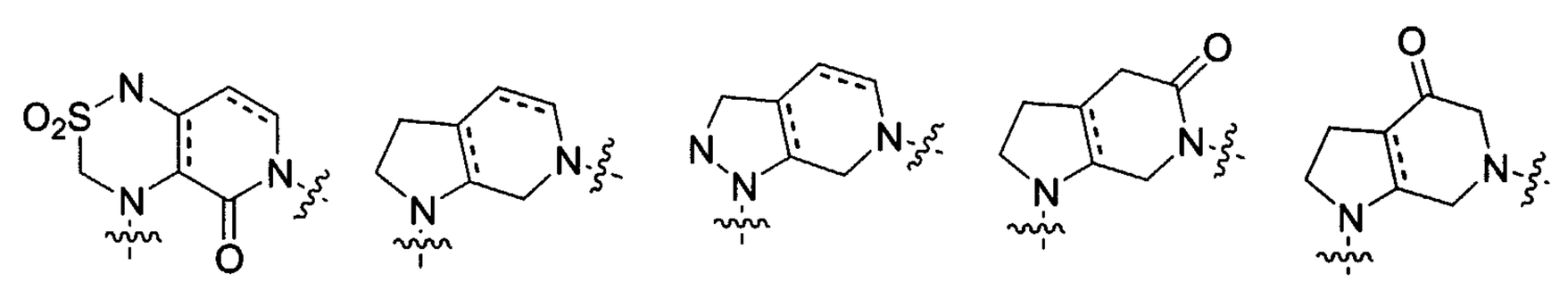
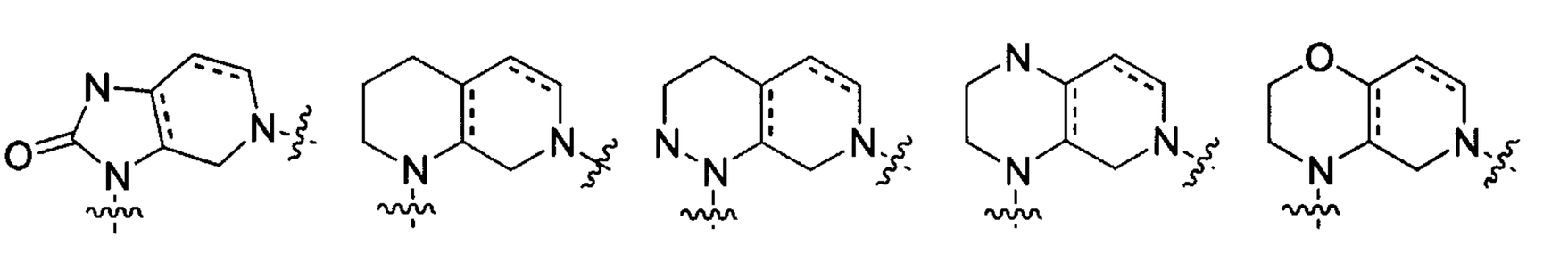
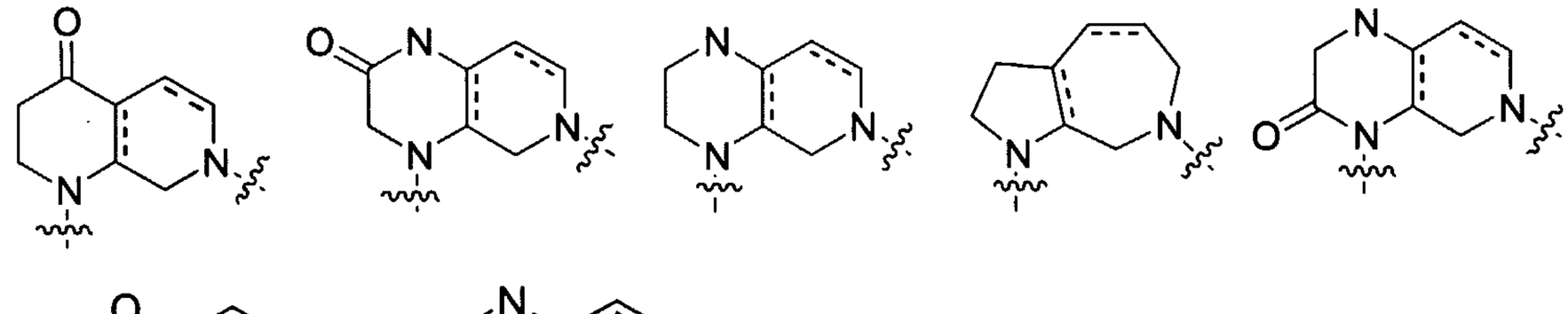
(a) B is other than an optionally substituted carbocycle; and,

(b) Z is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

then G_1 is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$.

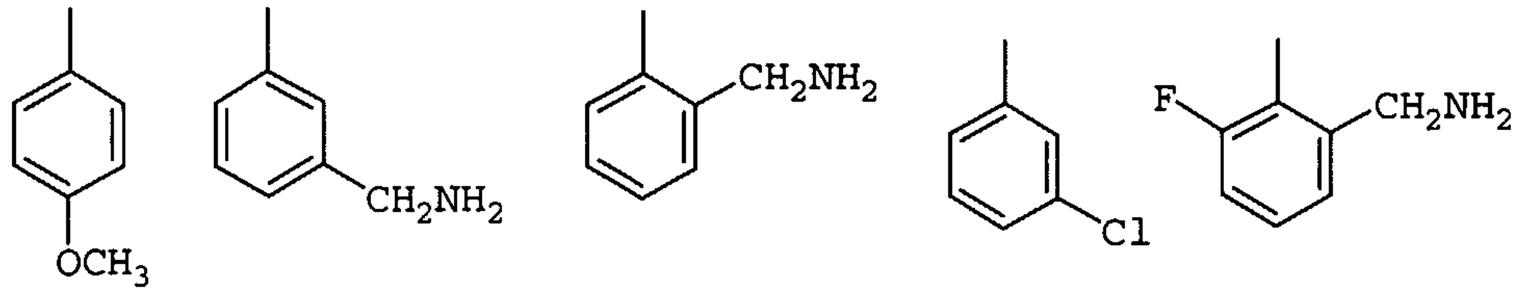
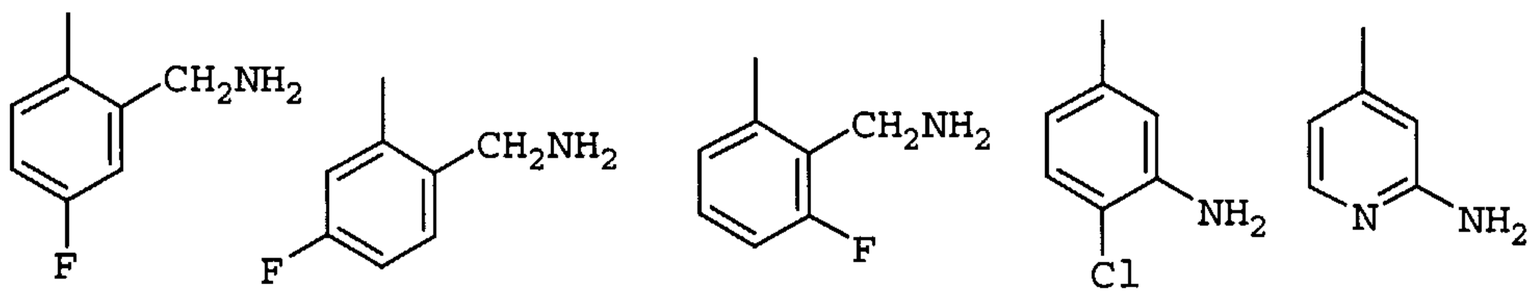
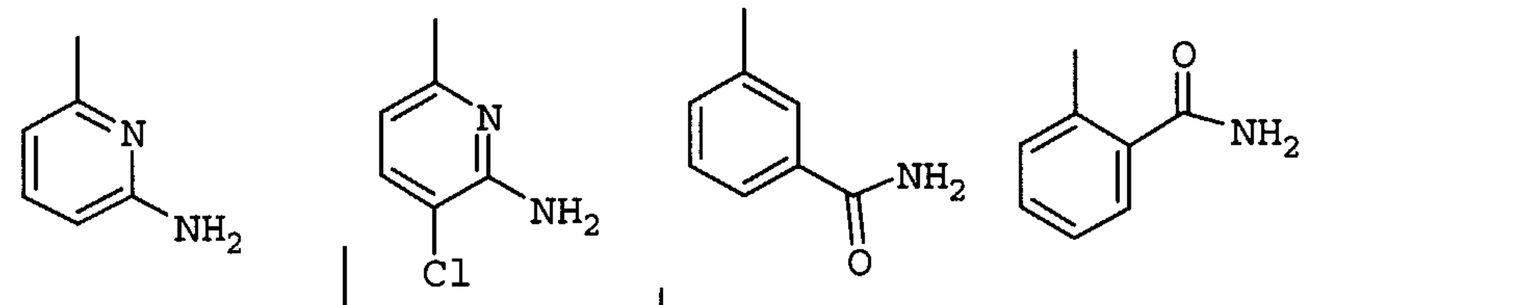
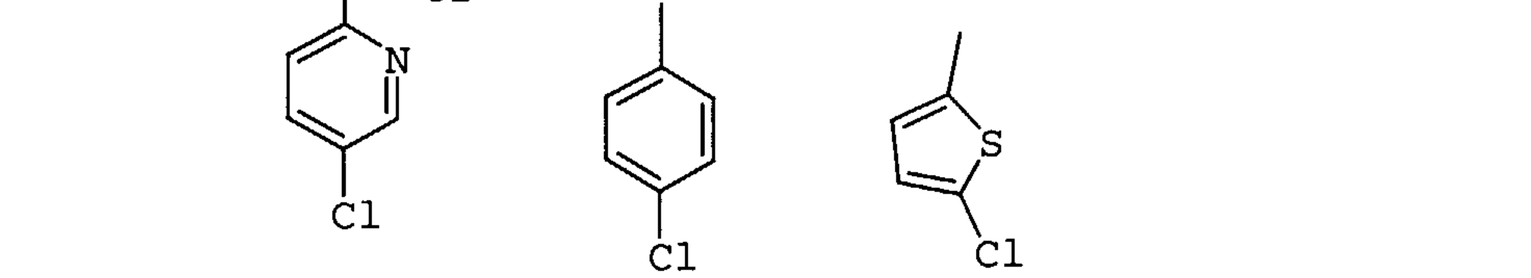
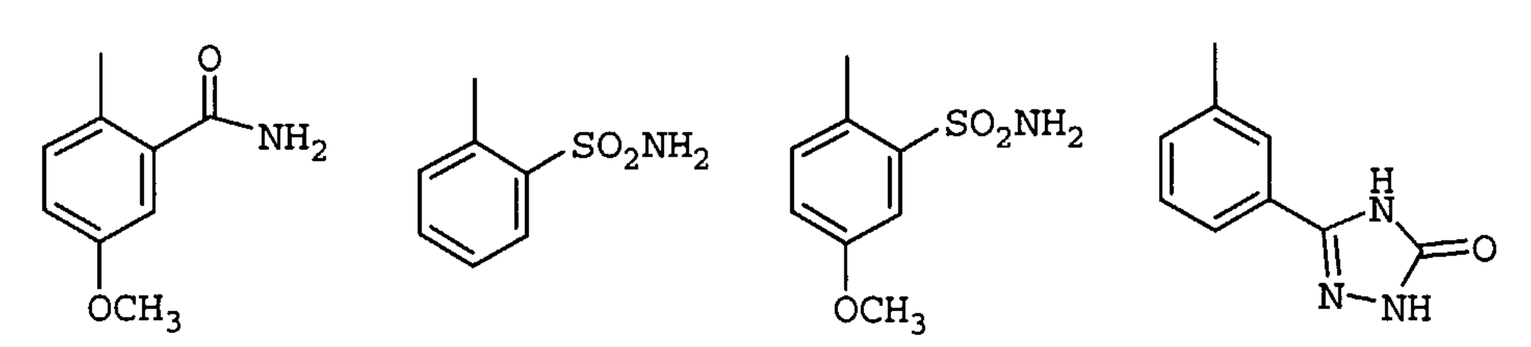
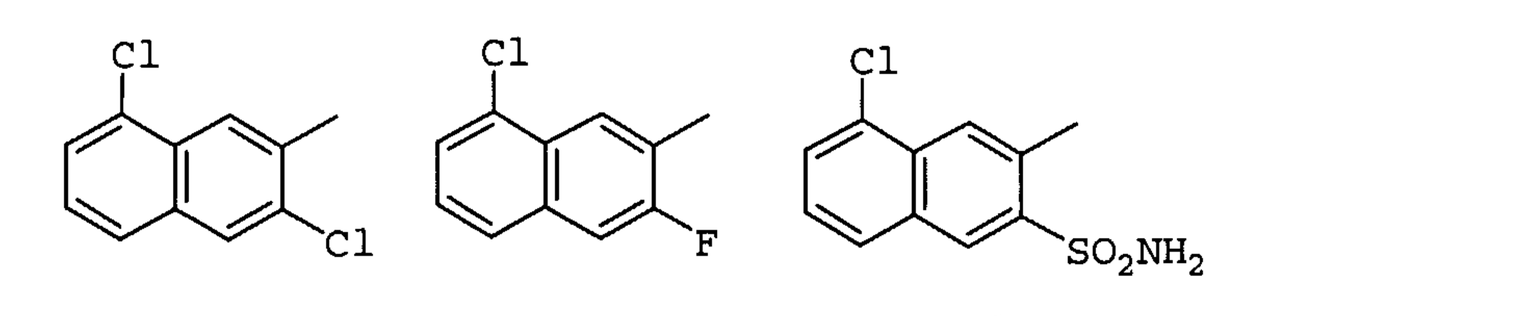
5. A compound of Claim 4, wherein:

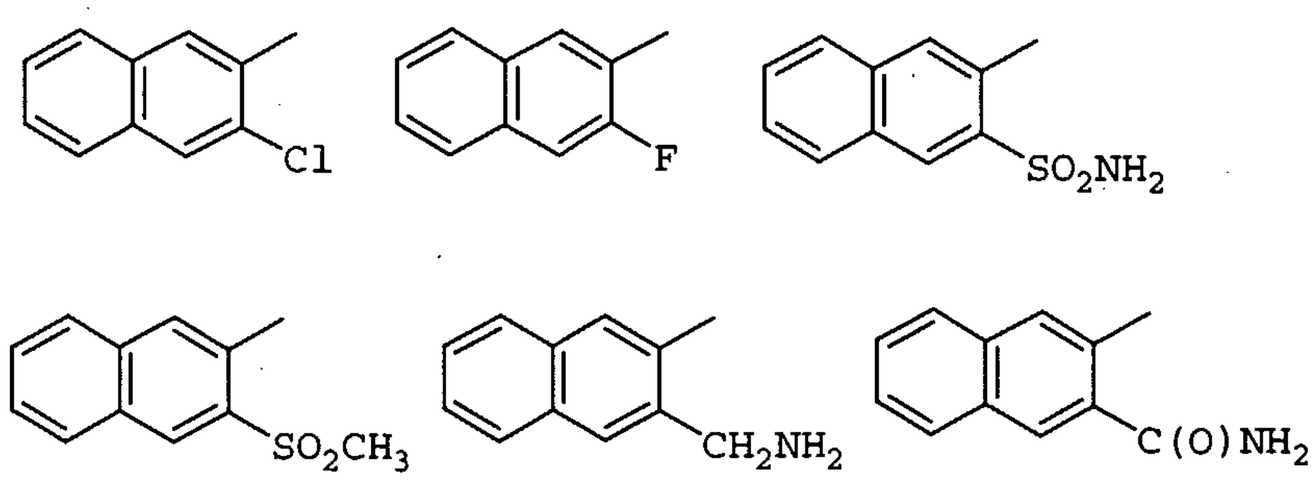
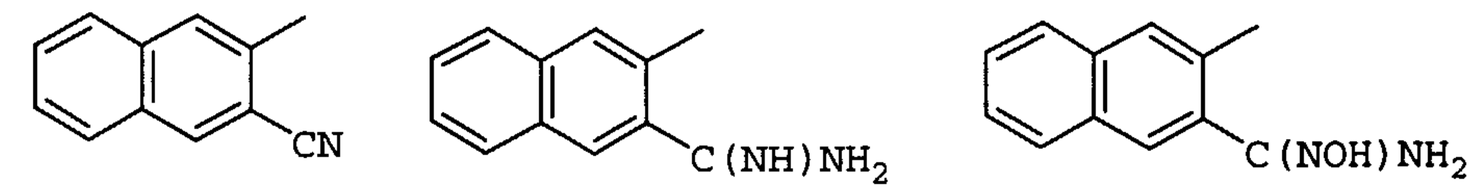
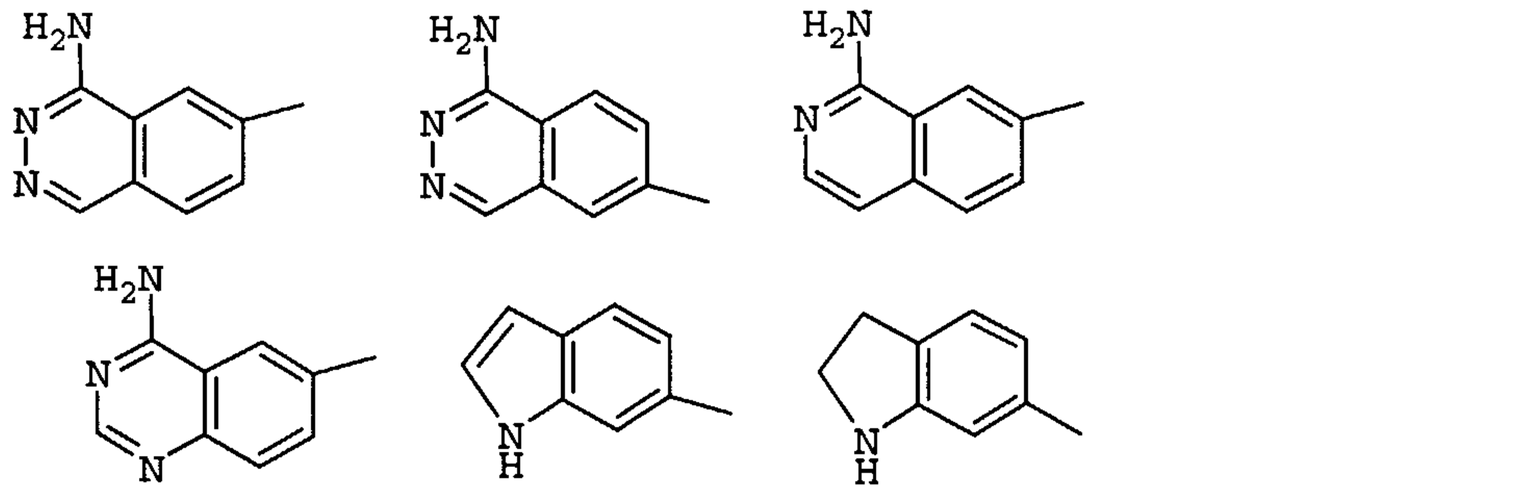
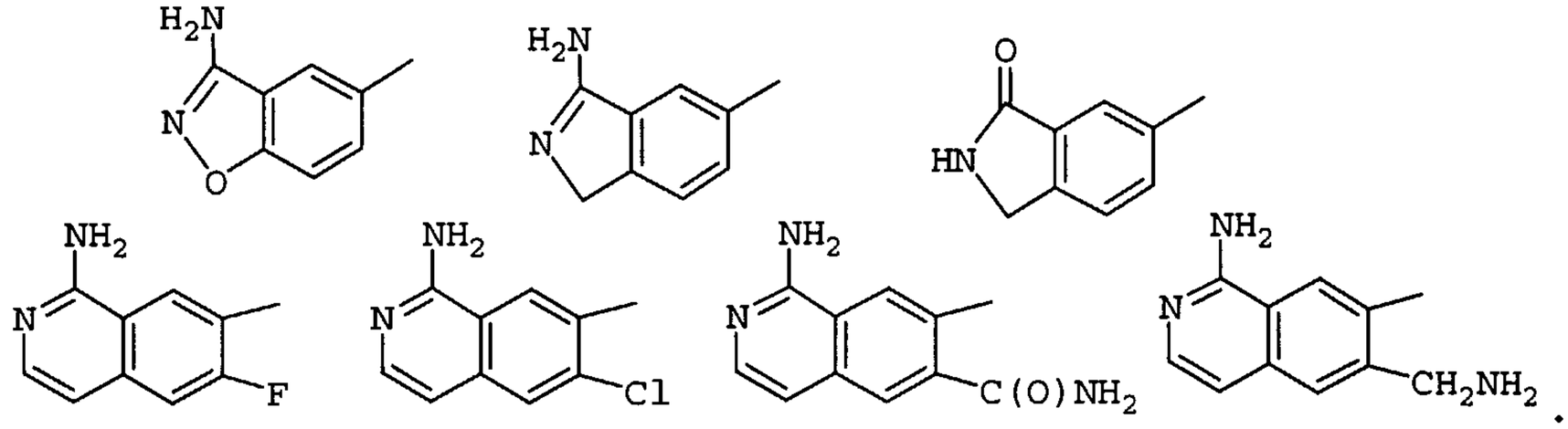
rings P-M are substituted with 0-1 R^{1a} and are selected from the group:

G_1 is absent; and

ring G is selected from:

6. A compound of Claim 5, wherein:

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl and is substituted with 0-1 R^{4a};

X is CH_2 or C(O);

Y is selected from pyrrolidino and morpholino;

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R^{2a}, at each occurrence, is H or CH_3;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, $(CH_2)_rOR^2$, $(CH_2)_rNR^2R^{2a}$, $S(O)_pR^{5a}$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^{4b}, at each occurrence, is selected from H, CH_3, and OH;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and

r, at each occurrence, is selected from 0, 1, and 2.

7. A compound of Claim 6, wherein:

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N,N-diethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(N,N-dimethylaminomethyl)-1-imidazolyl, 2-(N-methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl, and 2-(N-(2-hydroxyethyl)methylamino)-methyl)phenyl.

8. A compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

4-(4-methoxyphenyl)-1-methyl-6-{2'-[(methylamino)methyl]-1,1'-biphenyl-4-yl}-1,2,4,6-tetrahydropyrido[3,4-*b*]pyrazine-3,5-dione;

4-(4-methoxyphenyl)-1-methyl-6-[2'-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl}-1,2,4,6-tetrahydropyrido[3,4-*b*]pyrazine-3,5-dione;

6-[2'-(methylsulfonyl)-1-1'-biphenyl-4-yl]- 4-(4-methoxy-phenyl)-2,3,4,6-tetrahydropyrido[3,4-b]pyrazin-5(1*H*)-one;

3-{5-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-2,4-dioxo-1,2,4,5-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-3-yl}benzenecarboximidamide;

3-[7-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-8-oxo-3,4,7,8-tetrahydro-1,7-naphthyridin-1(2-*H*)-yl]}benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-5-oxo-2,3,5,6-tetrahydropyrido[3,4-*b*]-pyrazin-4(*1H*)-yl]benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-5-oxo-2,3,5,6-tetrahydropyrido-4*H*-pyrido[4,3-*b*][1,4]-oxazin-4-yl}benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-2,5-dioxo-2,3,5,6-tetrahydropyrido[3,4-b]pyrazin-4(1*H*)-yl]benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-3,5-dioxo-2,3,5,6-tetrahydropyrido-4*H*-pyrido[4,3-*b*][1,4]-oxazin-4-yl}benzenecarboximidamide;

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-3,5-dioxo-2,3,5,6-tetrahydropyrido[3,4-b]pyrazin-4(1*H*)-yl]benzenecarboximidamide; and

3-[6-[2'-(methylsulfonyl)-1,1'-biphenyl-4-yl]-2,2-dioxido-5-oxo-5,6-dihydro-1*H*-pyrido[4,3-*c*][1,2,5]thiadiazin-4(3*H*)-yl]benzenecarboximidamide.

9. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7 or 8 or a pharmaceutically acceptable salt thereof.

10. A method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7 or 8 or a pharmaceutically acceptable salt thereof.

11. A method according to Claim 10, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, and venous cerebrovascular thromboembolic disorders.

12. A method according to Claim 11, wherein the thromboembolic disorder is selected from unstable angina, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and

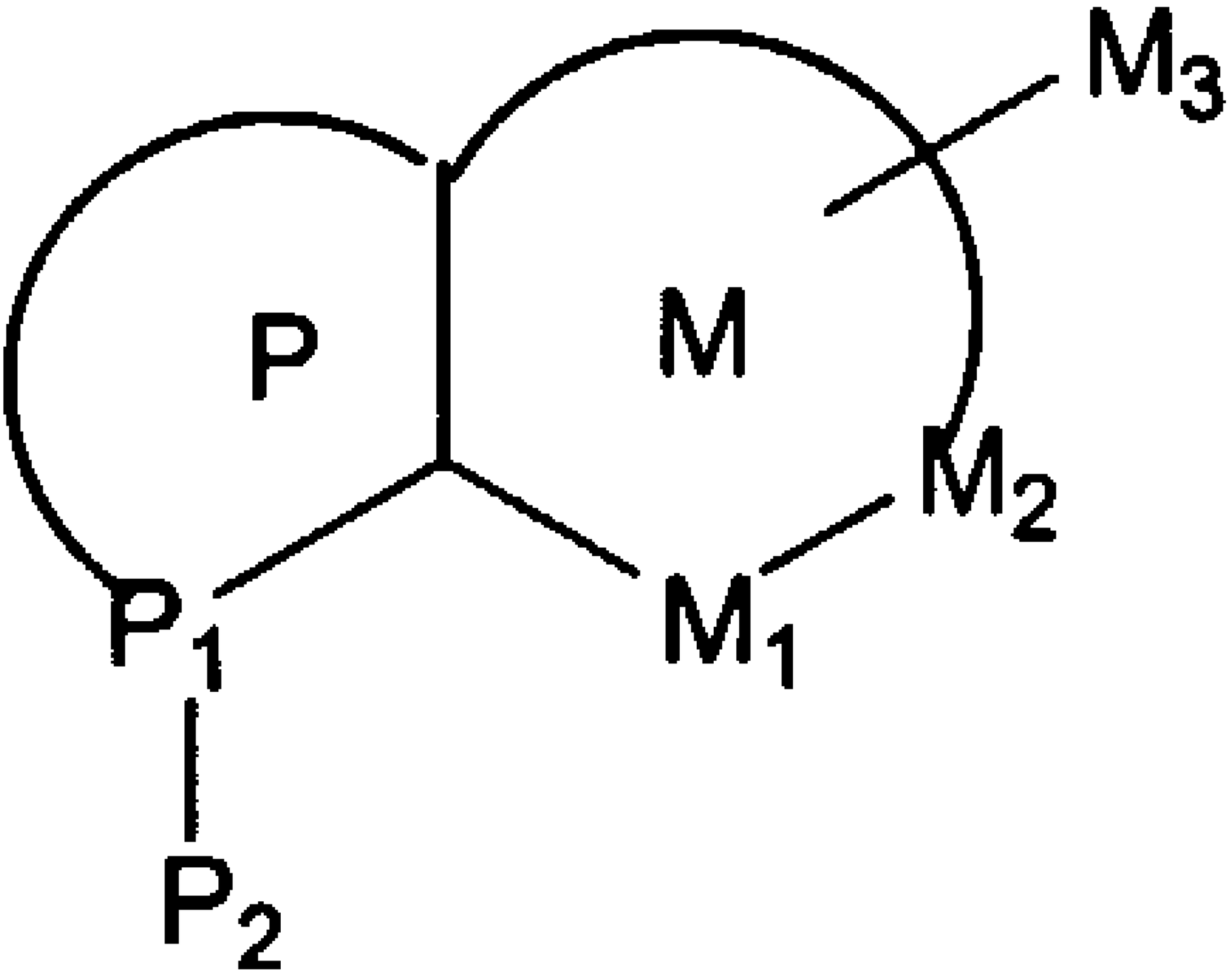
thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, and (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

13. A method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of Claim 1, 2, 3, 4, 5, 6, 7, or 8 or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

14. A method, comprising: administering a compound of Claim 1, 2, 3, 4, 5, 6, 7, or 8 or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

15. A compound of Claim 1, 2, 3, 4, 5, 6, 7 or 8 for use in therapy.

16. Use of a compound of Claim 1, 2, 3, 4, 5, 6, 7 or 8 for the manufacture of a medicament for the treatment of a thromboembolic disorder.



(I)