VIRAL POLYMERASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The invention relates to inhibitors of RNA dependent RNA polymerases, particularly those viral polymerases within the Flaviviridae family, more particularly to HCV polymerase.

BACKGROUND OF THE INVENTION

About 30,000 new cases of hepatitis C virus (HCV) infection are estimated to occur in the United States each year (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051). HCV is not easily cleared by the hosts' immunological defences; as many as 85% of the people infected with HCV become chronically infected. Many of these persistent infections result in chronic liver disease, including cirrhosis and hepatocellular carcinoma (Hoofnagle, J.H.; 1997; *Hepatology* **26**: 15S-20S*). There are an estimated 170 million HCV carriers world-wide, and HCV-associated end-stage liver disease is now the leading cause of liver transplantation. In the United States alone, hepatitis C is responsible for 8,000 to 10,000 deaths annually. Without effective intervention, the number is expected to triple in the next 10 to 20 years. There is no vaccine to prevent HCV infection. Prolonged treatment of chronically infected patients with interferon or interferon and ribavirin is the only currently approved therapy, but it achieves a sustained response in fewer than 50% of cases (Lindsay, K.L.; 1997; *Hepatology* **26**: 71S-77S*, and Reichard, O.; Schvarcz, R.; Weiland, O.; 1997 *Hepatology* **26**: 108S-111S*).

HCV belongs to the family *Flaviviridae*, genus *hepacivirus*, which comprises three genera of small enveloped positive-strand RNA viruses (Rice, C.M.; 1996; "*Flaviviridae*: the viruses and their replication"; pp. 931-960 in *Fields Virology*; Fields, B.N.; Knipe, D.M.; Howley, P.M. (eds.); Lippincott-Raven Publishers, Philadelphia Pa. *). The 9.6 kb genome of HCV consists of a long open reading frame (ORF) flanked by 5' and 3' non-translated regions (NTR's). The HCV 5' NTR is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation (Lemon, S.H.; Honda, M.; 1997; *Semin. Virol.* **8**: 274-288). The HCV polyprotein is cleaved co- and post-translationally into at least 10 individual polypeptides (Reed, K.E.; Rice, C.M.; 1999; *Curr. Top. Microbiol. Immunol.* **242**: 55-84*). The structural proteins result from signal peptidases in the N-

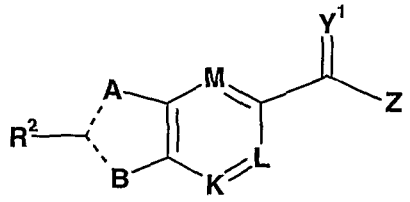
terminal portion of the polyprotein. Two viral proteases mediate downstream cleavages to produce non-structural (NS) proteins that function as components of the HCV RNA replicase. The NS2-3 protease spans the C-terminal half of the NS2 and the N-terminal one-third of NS3 and catalyses *cis* cleavage of the NS2/3 site. The same portion of NS3 also encodes the catalytic domain of the NS3-4A serine protease that cleaves at four downstream sites. The C-terminal two-thirds of NS3 is highly conserved amongst HCV isolates, with RNA-binding, RNA-stimulated NTPase, and RNA unwinding activities. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are unknown. The C-terminal polyprotein cleavage product, NS5B, is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity (Behrens, S.E.; Tomei, L.; DeFrancesco, R.; 1996; *EMBO J.* **15**: 12-22*; and Lohmann, V.; Körner, F.; Herian, U.; Bartenschlager, R.; 1997; *J. Virol.* **71**: 8416-8428*). It has been recently demonstrated that mutations destroying NS5B activity abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051*).

The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for drug development. The absence of RNA dependent RNA polymerases in mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics.
WO 00/06529 reports inhibitors of NS5B which are α, γ-diketoacids.
WO 00/13708, WO 00/10573, WO 00/18231, and WO 01/47883 report inhibitors of NS5B proposed for treatment of HCV.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a novel series of compounds having improved inhibitory activity against HCV polymerase.

In a first aspect of the invention, there is provided an isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I:



(I)

wherein:

A is O, S, NR^1, or CR^1, wherein R^1 is selected from the group consisting of: H, (C_{1-6})alkyl optionally substituted with:

-halogen, OR^{11}, SR^{11} or $N(R^{12})_2$, wherein R^{11} and each R^{12} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, said aryl or **Het** optionally substituted with R^{10}; or

both R^{12} are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;

----- represents either a single or a double bond;

R^2 is selected from: halogen, R^{21}, OR^{21}, SR^{21}, $COOR^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})_2$, , $CON(R^{22})_2$, $NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said R^{21} and R^{22} being optionally substituted with R^{20};

or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

B is NR^3 or CR^3, with the proviso that one of **A** or **B** is either CR^1 or CR^3, wherein R^3 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, cycloakenyl, bicycloalkyl, bicycloalkenyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- OR^{31} or SR^{31} wherein R^{31} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl,

(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or

- $N(\mathbf{R}^{32})_2$ wherein each $\mathbf{R}^{32}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both $\mathbf{R}^{32}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) $O\mathbf{R}^{33}$ wherein $\mathbf{R}^{33}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) $S\mathbf{R}^{34}$ wherein $\mathbf{R}^{34}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(\mathbf{R}^{35})_2$ wherein each $\mathbf{R}^{35}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both $\mathbf{R}^{35}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

K is N or $C\mathbf{R}^4$, wherein $\mathbf{R}^4$ is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or $\mathbf{R}^4$ is $O\mathbf{R}^{41}$ or $S\mathbf{R}^{41}$, $CO\mathbf{R}^{41}$ or $N\mathbf{R}^{41}CO\mathbf{R}^{41}$ wherein each $\mathbf{R}^{41}$ is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or $\mathbf{R}^4$ is $N\mathbf{R}^{42}\mathbf{R}^{43}$ wherein $\mathbf{R}^{42}$ and $\mathbf{R}^{43}$ are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both $\mathbf{R}^{42}$ and $\mathbf{R}^{43}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or $C\mathbf{R}^5$, wherein $\mathbf{R}^5$ has the same definition as $\mathbf{R}^4$ defined above;

M is N or $C\mathbf{R}^7$, wherein $\mathbf{R}^7$ has the same definition as $\mathbf{R}^4$ defined above;

$\mathbf{Y}^1$ is O or S;

Z is $O\mathbf{R}^6$ wherein $\mathbf{R}^6$ is C_{1-6}alkyl substituted with:

- 1 to 4 substituents selected from: OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$,

$C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or

- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{150}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is $(C_{1-6}$alkyl) substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, provided that when $\mathbf{R^{111}}$ is H or unsubstituted alkyl, $\mathbf{R^{112}}$ is not H or unsubstituted alkyl,

or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150};

wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted

with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$, or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to

which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or **Z** is OR^6 wherein R^6 is (C_{1-6}alkyl)aryl substituted with:

- 1 to 4 substituents selected from: OPO_3H, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108a}, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl,

or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-}

$_7$)cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{115a}}$ is the same as $\mathbf{R^{115}}$ but is not H or unsubstituted alkyl, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$; or $\mathbf{R^{122}}$ is $\mathbf{OR^{123}}$ or $N(\mathbf{R^{124}})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is *OH or O*(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-}

$_7$)cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) CON$\mathbf{R^{129}R^{130}}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when $\mathbf{R^{129}}$ is H or unsubstituted alkyl, $\mathbf{R^{130}}$ is not H or unsubstituted alkyl,

or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; and

wherein $\mathbf{R^{150}}$ is

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido;
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) O$\mathbf{R^{104}}$ wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) OCO$\mathbf{R^{105}}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) S$\mathbf{R^{108}}$, $SO_2N(\mathbf{R^{108}})_2$ or $SO_2N(\mathbf{R^{108}})C(O)\mathbf{R^{108}}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) N$\mathbf{R^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-}

$_{6}$)alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or **Z** is OR^6 wherein R^6 is, (C_{3-6})cycloalkyl, (C_{2-6})alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-**Het**, wherein said cycloalkyl, alkenyl, aryl, **Het** or alkyl-**Het**, is optionally substituted with R^{60};

or **Z** is $N(R^{6a})R^6$, wherein R^{6a} is H or (C_{1-6}alkyl) and

R^6 is (C_{1-6})alkyl optionally substituted with:

- 1 to 4 substituents selected from: OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl substituted with R^{150a}, haloalkyl substituted with R^{150}, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not halogen, OH, O(C_{1-6}alkyl), COOH, COO(C_{1-6}alkyl), NH_2, NH(C_{1-6}alkyl) and N(C_{1-6}alkyl)$_2$;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-}

$_6$alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-}

$_7$)cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle

being optionally substituted with R^{160};

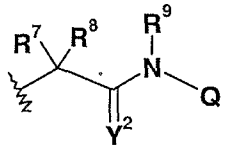
j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or **Z** is $N(R^{6a})R^6$ wherein R^{6a} is as defined above and R^6 is (C_{3-6})cycloalkyl, (C_{2-6})alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with R^{60};

or **Z** is OR^6 or $N(R^{6a})R^6$ wherein R^{6a} is as defined above and R^6 is:



wherein R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{70}; or

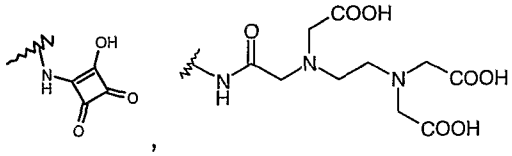
R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a

nitrogen-containing 5-or 6-membered heterocycle;

Y^2 is O or S;

R^9 is H, (C_{1-6} alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het,** all of which optionally substituted with R^{90}; or
R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle;

Q is a 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, (C_{1-6}) alkyl-CONH-aryl or (C_{1-6}) alkyl-CONH-**Het**, all of which being optionally substituted with:



, or R^{100};

or a salt or a derivative thereof;

wherein **Het** is defined as 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms selected from O, N and S; and

R^{10}, R^{20}, R^{60}, R^{70}, R^{90} and R^{100} is each defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are

covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; and

wherein $\mathbf{R^{150}}$ is defined as:

- 1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl,

aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$, or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or $O(C_{1-6}$alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

i) $CO\mathbf{R^{127}}$ wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

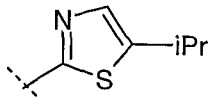
j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

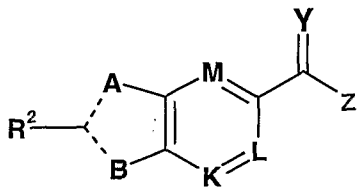
wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein $\mathbf{R^{161}}$ and each $\mathbf{R^{162}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both $\mathbf{R^{162}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

or a salt thereof,

with the proviso that, when **A** is CH, $\mathbf{R^2}$ is phenyl or N-butyl, **B** is NR^3, $\mathbf{R^3}$ is Me, **K** is

CH, **L** is CH, **M** is CH, Y^1 is O, and **Z** is NHR^6, then R^6 is not  .

Alternatively, in a first aspect of the invention, there is provided a compound represented by Formula Ia:



(Ia)

wherein:

A is O, S, NR^1, or CR^1;

B is NR^3 or CR^3;

R^1 is selected from the group consisting of: H, (C_{1-6})alkyl, benzyl, $(C_{1-6}$ alkyl)-$(C_{6-10}$aryl), $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, $COO(C_{1-6}$ alkyl), halogen, and $(C_{1-6}$ alkyl);

R^2 is selected from the group consisting of: H, halogen, (C_{1-6})alkyl; (C_{3-7})cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide , and 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S,

said phenyl, heterocycle and heterobicycle being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, $C(halogen)_3$, (C_{1-6})alkyl, OH, $O(C_{1-6}$ alkyl), NH_2, and $N(C_{1-6}$ alkyl)$_2$;

R^3 is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-$(C_{1-6}$ alkyl);

M is N, CR^4, or COR^5, wherein R^4 is selected from the group consisting of: H,

halogen, and (C_{1-6} alkyl); and R^5 is selected from the group consisting of: H and (C_{1-6} alkyl);

K and **L** is N or CH;

----- represents either a single or a double bond;

Y is O or S;

Z is OR^6 or NR^6R^{6a}

R^6 is selected from the group consisting of: H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl(C_{2-6})alkenyl, (C_{6-10})aryl(C_{2-6})alkenyl, N{(C_{1-6}) alkyl}$_2$, NHCOO(C_{1-6})alkyl(C_{6-10})aryl, NHCO(C_{6-10})aryl, (C_{1-6})alkyl-5- or 6-atom heterocycle, having 1 to 4 heteroatoms selected from O, N and S, and 9- or 10-atom heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

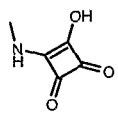
wherein said alkyl, cycloalkyl, aryl, alkenyl, heterocycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said alkyl, cycloalkyl, aryl, alkenyl and heterocycle being optionally substituted with from 1 to 4 substituents selected from: (C_{1-6} alkyl), CF_3, OH, COOH, NHC(C_{1-6}alkyl)$_2$, NHCO(C_{1-6} alkyl), NH_2, NH(C_{1-6} alkyl), and N(C_{1-6} alkyl)$_2$;

9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S, said heterobicycle being optionally substituted with from 1 to 4 substituents selected from:

halogen, OPO_3H, sulfonamido, SO_3H, SO_2CH_3, -$CONH_2$, -$COCH_3$, (C_{1-3})alkyl, (C_{2-4}alkenyl)COOH, tetrazolyl, COOH, -$CONH_2$, triazolyl, OH, NO_2, NH_2, -O(C_{1-6} alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, NHCO(C_{1-}

$_6$ alkyl), -NHCOCOOH, -NHCOCONHOH,-NHCOCONH$_2$, -NHCOCONHCH$_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -NHCH$_2$COOH, -NHCONH$_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,



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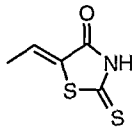
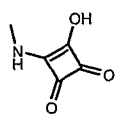


, -NHCN, -NHCHO, -NHSO$_2$CH$_3$, and -NHSO$_2$CF$_3$;

6- or 10-membered aryl being optionally substituted with from 1 to 4 substituents selected from:

halogen, OPO$_3$H, sulfonamido, SO$_3$H, SO$_2$CH$_3$, -CONH$_2$, -COCH$_3$, (C_{1-3})alkyl, (C_{2-4}alkenyl)COOH , tetrazolyl, COOH, -CONH$_2$, triazolyl, OH, NO$_2$, NH$_2$, -O(C_{1-6} alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, NHCO(C_{1-6} alkyl), -NHCOCOOH, -NHCOCONHOH,-NHCOCONH$_2$, -NHCOCONHCH$_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -NHCH$_2$COOH, -NHCONH$_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,



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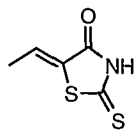


, -NHCN, -NHCHO, -NHSO$_2$CH$_3$, and

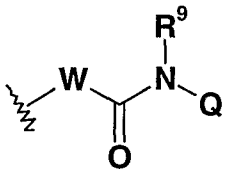
$-NHSO_2CF_3$;

coumarin, (C_{1-6})alkyl-amino, $NH(C_{1-6}$ alkyl), $C(halogen)_3$,

$-NH(C_{2-4})$acyl, $-NH(C_{6-10})$aroyl, $-O(C_{1-6}$alkyl)-**Het**;

R^{6a} is H or $(C_{1-6}$ alkyl) covalently bonded to either R^7 or R^8 to form pyrrolidine;

or **Z** is



wherein

W is CR^7R^8 wherein R^7 and R^8 are each independently H, $(C_{1-6}$ alkyl), $(C_{3-7}$ cycloalkyl), $(C_{1-6}$ alkyl)phenyl, $(C_{1-6}$ alkyl)-$(C_{3-7}$ cycloalkyl), $(C_{3-7}$ cycloalkyl)-$(C_{1-6}$ alkyl), $(C_{3-7}$ cycloalkyl)-$(C_{2-4}$ alkenyl), $(C_{1-6}$ alkyl)-OH, phenyl, CH_2biphenyl, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, or $(C_{1-6}$ alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S,

or R^7 and R^8 are covalently bonded together to form $(C_{3-7}$ cycloalkyl), 4-, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S;

or one of R^7 or R^8 is covalently bonded to R^9 to form a pyrrolidine;

wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from the group consisting of: OH, COOH, $(C_{1-6}$ alkyl), $(C_{2-4}$ alkenyl), $CONH_2$, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, NHCOCOOH, $NHCOCON(C_{1-6}$ alkyl)$_2$, $NHCOCONH(C_{1-6}$ alkyl), SH, $S(C_{1-6}$ alkyl), $NHC(=NH)NH_2$, halogen, and $COO(C_{1-6}$alkyl);

R^9 is H or $(C_{1-6}$ alkyl); and

Q is selected from the group consisting of: $(C_{1-3}$alkyl)CONHaryl, 6-, 9-, or 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

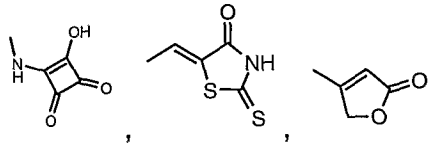
wherein said aryl, biphenyl, heterocycle and heterobicycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $COO(C_{1-6})$alkyl, (C_{1-6})alkyl, (C_{1-6})alkylCOOH, $(C_{1-6}$ alkyl$)(C_{2-4}$ alkynyl), (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4 heteroatoms selected from O, N and S, NH-5- or 6- membered second heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: $(C_{1-6}$ alkyl), CF_3, OH, $(C_{1-6}$alkyl) COOH, $O(C_{1-6}$alkyl)COOH, $(C_{1-6}$alkyl) $COO(C_{1-6}$alkyl), CH_2phenyl, $COO(C_{1-6}$ alkyl), $(C_{1-6}$alkyl)$O(C_{1-6}$alkyl), COOH, $NCH(C_{1-6}$alkyl$)_2$, $NCO(C_{1-6}$ alkyl), NH_2, $NH(C_{1-6}$ alkyl), halogen, and $N(C_{1-6}$ alkyl$)_2$;

halogen, OPO_3H, benzyl, sulfonamido, SH, $SOCH_3$, SO_3H, SO_2CH_3, $S(C_{1-6}$ alkyl)COOH, $-CONH_2$, $-COCH_3$, (C_{1-3})alkyl, $(C_{2-4}$alkenyl)COOH

wherein said alkenyl is optionally substituted with from 1 to 2 $(C_{1-6}$ alkyl) substituents,

$(C_{2-4}$alkenyl)$COO(C_{1-6}$alkyl), tetrazolyl, COOH, triazolyl, OH, NO_2, NH_2, , -$O(C_{1-6}$ alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, (C_{1-4})alkoxy$(C_{1-6}$ alkyl)COOH, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, -NHCOCOOH, -NHCOCONHOH,-$NHCOCONH_2$, $-NHCOCONHCH_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, $-NHCH_2COOH$, $-NHCONH_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,



, -NHCN, -NHCHO, $-NHSO_2CH_3$, $-NHSO_2CF_3$, coumarin, (C_{1-6})alkyl-amino, $NH(C_{1-6}$alkyl$)_2$, C(halogen)$_3$, -NH(C_{2-4})acyl, -NH(C_{6-10})aroyl, -CONH$(C_{1-6}$alkyl), -CO(C_{1-6})alkyl-COOH, -CONH(C_{1-6})alkyl-COOH, -CO-NH-alanyl, -CONH(C_{2-4})alkylN$(C_{1-6}$alkyl$)_2$, -CONH(C_{2-4}) alkyl-**Het**,

-CONH(C_{2-4}) alkyl-(COOH)-**Het**, -CONH(C_{1-2} alkyl) (OH)(C_{1-2} alkyl)OH,
-CONH(C_{1-6}) alkyl-COOH, -CONH(C_{6-10} aryl), -CONH-**Het**,
-CONH(C_{6-10}) aryl-COOH, -CONH(C_{6-10}) aryl-COO(C_{1-6}) alkyl,
-CONH(C_{1-6}) alkyl-COO(C_{1-6}) alkyl, -CONH(C_{6-10}) aryl-(C_{1-6})alkyl-COOH, and
-CONH(C_{6-10}) aryl-(C_{2-6})alkenyl-COOH,

or a salt thereof.

In a third aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV.

In a fourth aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

In a fifth aspect of the invention, there is provided a method of treating or preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a sixth aspect of the invention, there is provided a pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

According to a specific embodiment, the pharmaceutical compositions of this invention comprise an additional immunomodulatory agent. Examples of additional immunomodulatory agents include but are not limited to, α-, β-, δ- γ-, and ω-interferons.

According to an alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an antiviral agent. Examples of antiviral agents include, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise other inhibitors of HCV protease.

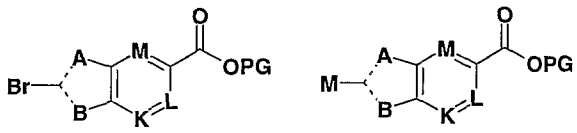
According to yet another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an inhibitor of other targets in the HCV life cycle, such as helicase, polymerase, metalloprotease or IRES.

In a seventh aspect of the invention, there is provided a use of a compound of formula I, for the manufacture of a medicament for the treatment of HCV infection.

In a eighth aspect of the invention, there is provided a use of a compound of formula I, to prevent HCV infection.

In an ninth aspect of the invention, there is provided a use of a compound of formula I, as an HCV polymerase inhibitor.

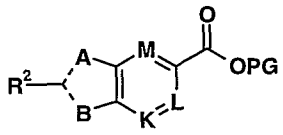
In a tenth aspect of the invention, there is provided an intermediate of formula (1a) or (1b):



1a or 1b

wherein **A, B, K, L**, and **M** are as described herein and **PG** is H or a carboxy protecting group.

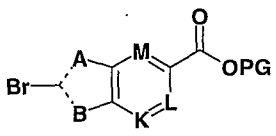
In a eleventh aspect of the invention, there is provided a process for producing compounds of formula (iii),



(iii)

wherein **A**, R^2, **B**, **K**, **L**, **M**, and **PG** are as described herein,
comprising:

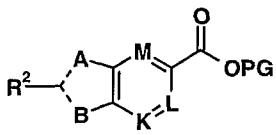
a) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1a)



1a

with R^2-X, wherein R^1, R^3, K, L, M and PG are as described herein and X is (bt not limited to): $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, metal halide, $B(OH)_2$, and $B(O(C_{1-6})alkyl)_2$ to produce compounds of formula (iii).

In an alternative to the eleventh aspect of the invention, there is provided a process for producing compounds of formula (iii),

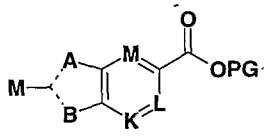


(iii)

wherein A, R^2, B, K, L, M, and PG are as described herein,

comprising:

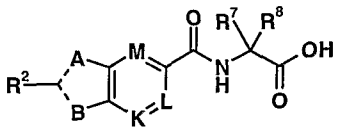
b) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1b)



1b

with R^2-X', wherein X' is halide, $OSO_2(C_{1-6}alkyl)$, OSO_2Ar, OSO_2CF_3 and the like, and M is a metal such as Li, $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, $B(OH)_2$, $B(OC_{1-6}alkyl)_2$, metal halide, to produce compounds of formula (iii).

In an thirteenth aspect of the invention, there is provided an intermediate compound represented by formula 1c:



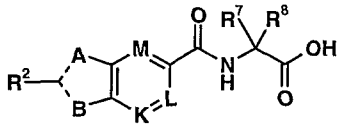
1c

wherein A, R^2, B, K, L, M, R^7 and R^8 are as defined herein, or a salt, or a derivative

thereof.

In an fourteenth aspect of the invention, there is provided a process for producing compounds of formula I, comprising:

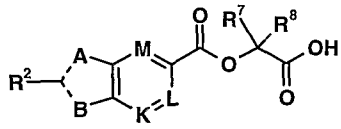
a) coupling, in a mixture containing an aprotic solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1c:



1c

with amine **Q**-NH_2 so as to produce compounds of formula I, wherein **A**, R^2, **B**, R^7, R^8, **Q**, **K**, **L**, and **M** are as defined herein.

In an fifteenth aspect of the invention, there is provided an intermediate compound represented by formula 1d:

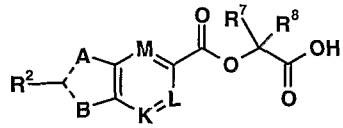


1d

wherein **A**, R^2, **B**, **K**, **L**, **M**, R^7 and R^8 are as defined herein or a salt or a derivative thereof.

In a sixteenth aspect of the invention, there is provided a process for producing compounds of formula I, comprising:

a) coupling, in a mixture containing an appropriate solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1d:



1d

with amine **Q**-NH_2 so as to produce compounds of formula I, wherein **A**, R^2, **B**, R^7, R^8, **Q**, **K**, **L**, and **M** are as defined herein.

In a seventeenth aspect of the invention, there is provided a method of treating or

preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in combination with another anti-HCV agent.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following definitions apply unless otherwise noted:

As used herein, the terms "(C_{1-3}) alkyl", "(C_{1-4}) alkyl" or "(C_{1-6}) alkyl", either alone or in combination with another radical, are intended to mean acyclic straight or branched chain alkyl radicals containing up to three, four and six carbon atoms respectively. Examples of such radicals include methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl.

As used herein, the term "(C_{2-6}) alkenyl", either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight chain radical containing two to six carbon atoms.

As used herein, the term (C_{2-6}) alkynyl" either alone or in combination with another group, is intended to mean an unsaturated, acyclic straight chain sp hybridized radical containing 2 to six carbon atoms.

As used herein. the term "(C_{3-7}) cycloalkyl", either alone or in combination with another radical, means a cycloalkyl radical containing from three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "(C_{5-7})cycloalkenyl", either alone or in combination with another radical, means an unsaturated cyclic radical containing five to seven carbon atoms.

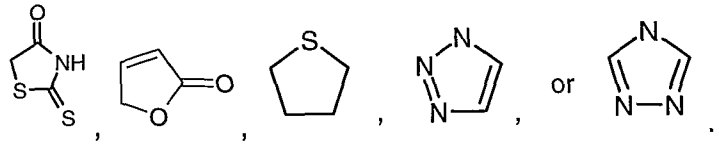
As used herein, the term "carboxy protecting group" defines protecting groups that can be used during coupling and are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of which are hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and *t*-butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters.

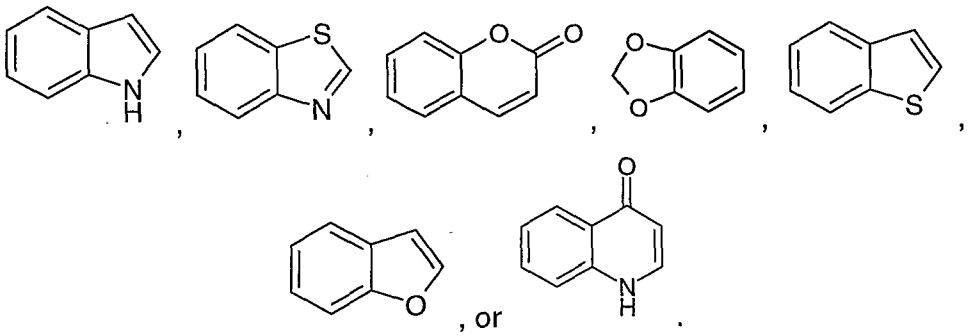
As used herein, the term "aryl", or "6- or 10-membered aryl" either alone or in combination with another radical means aromatic radical containing six or ten carbon atoms, for example phenyl or naphthyl.

As used herein the term heteroatom means O, S or N.

As used herein, the term "heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Furthermore, "heterobicyclic" as used herein, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterocycles include, but are not limited to, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, coumarin, hydantoin, diazepine, 1H-imidazole, isoxazole, thiazole, tetrazole, piperidine, 1,4-dioxane, 4-morpholine, pyridine, pyridine-N-oxide, pyrimidine, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following heterocycles:



As used herein, the term "9- or 10-membered heterobicycle" or "heterobicycle" either alone or in combination with another radical, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterobicycles include, but are not limited to, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following:



As used herein, the term "**Het**" defines a 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms wherever possible, selected from O, N and S.

As used herein, the term "halo" means a halogen atom and includes fluorine, chlorine, bromine and iodine.

As used herein, the term "haloalkyl" is intended to mean an alkyl that is described above in which each hydrogen atom may be successively replaced by a halogen atom, for example CH_2Br or CF_3.

As used herein, the term "metal halide" is intended to mean any metal that is bonded to a halogen atom for use in a metal-catalyzed cross-coupling reaction. Examples of such metal halides include, but are not limited to, -MgCl, -CuCl, or -ZnCl and the like.

As used herein, the term "OH" refers to a hydroxyl group. It is well known to one skilled in the art that hydroxyl groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, ethers, sulfhydryls, and primary, secondary or tertiary amines.

As used herein, the term "SH" refers to a sulfhydryl group. It is intended within the scope of the present invention that , whenever a "SH" or "S**R**" group is present, it can also be substituted by any other appropriate oxidation state such as S**O**R, SO_2**R**, or SO_3**R**.

It is intended that the term "substituted" when applied in conjunction with a radical

having more than one moiety such as C_{1-6}alkyl-aryl, or C_{1-6}alkyl-**Het**, such substitution applies to both moieties i.e. both the alkyl and aryl or **Het** moieties can be substituted with the defined substituents.

As used herein, the term "COOH" refers to a carboxylic acid group. It is well known to one skilled in the art that carboxylic acid groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, esters, amides, boronic acids or tetrazole.

As used herein, the term "functional group equivalent" is intended to mean an element or a substituted derivative thereof, that is replaceable by another element that has similar electronic, hybridization or bonding properties.

As used herein, the term "metal catalyst" is intended to mean a metal such as palladium (0) or palladium (2) that is bonded to a leaving group for use in a cross-coupling reaction. Examples of such palladium catalysts include, but are not limited to, $Pd(Ph_3)_4$, Pd/C, $Pd(OAc)_2$, $PdCl_2$, and the like. Alternative metals that can catalyze cross-coupling reactions include, but are not limited to: $Ni(acac)_2$, $Ni(OAc)_2$, or $NiCl_2$.

As used herein, the term "derivative" is intended to mean "detectable label", "affinity tag" or "photoreactive group". The term "detectable label" refers to any group that may be linked to the polymerase or to a compound of the present invention such that when the compound is associated with the polymerase target, such label allows recognition either directly or indirectly of the compound such that it can be detected, measured and quantified. Examples of such "labels" are intended to include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes and affinity tags such as biotin. Such labels are attached to the compound or to the polymerase by well known methods. The term "affinity tag" means a ligand (that is linked to the polymerase or to a compound of the present invention) whose strong affinity for a receptor can be used to extract from a solution the entity to which the ligand is attached. Examples of such ligands include biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety or a defined epitope recognizable by a

specific antibody. Such affinity tags are attached to the compound or to the polymerase by well-known methods.

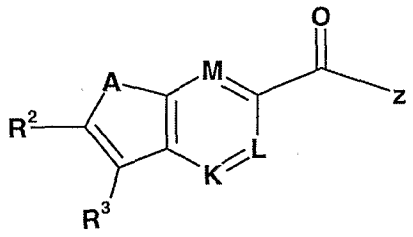
The term "photoreactive group" means a group that is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Examples of such groups include, but are not limited to, benzophenones, azides, and the like.

As used herein, the term "pharmaceutically acceptable salt" includes those derived from pharmaceutically acceptable bases and is non-toxic. Examples of suitable bases include choline, ethanolamine and ethylenediamine. Na^+, K^+, and Ca^{++} salts are also contemplated to be within the scope of the invention (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19, incorporated herein by reference).

Preferred embodiments

Core:

Preferably, compounds of the present invention have the following formula (II):

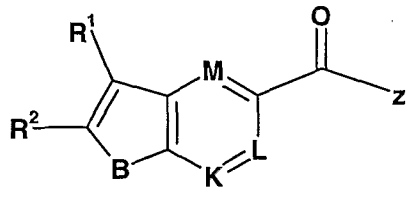


(II)

wherein, preferably, **A** is O, S, or NR^1.

More preferably, **A** is NR^1.

Preferably, compounds of the present invention have the following formula (III):



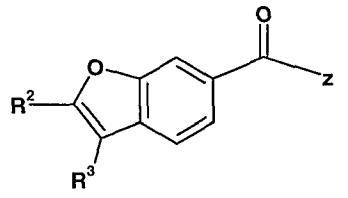
(III)

wherein, preferably, **B** is NR^3.

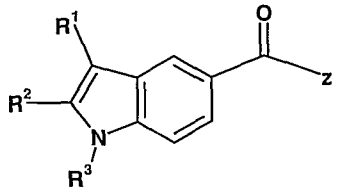
With respect to compounds of formula (II) and (III), preferably, **M, K** and **L** is CH or

N. More preferably, **M, K** and **L** is CH.

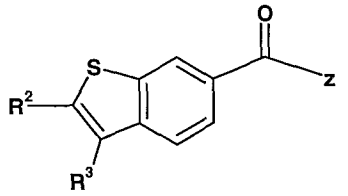
More preferably, compounds of the present invention have the following formulae:



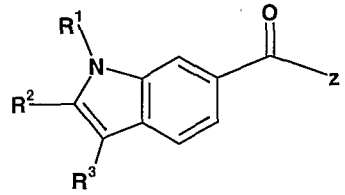
IIa



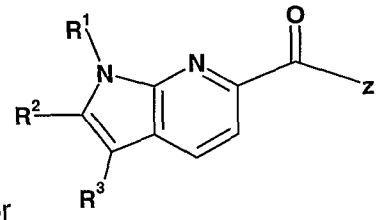
IIIa



IIb



IIc



or

IId

R^1:

Preferably $\mathbf{R^1}$ is selected from the group consisting of: H or (C_{1-6})alkyl. More preferably, $\mathbf{R^1}$ is H, CH_3, isopropyl, or isobutyl. Even more preferably, $\mathbf{R^1}$ is H or CH_3. Most preferably, $\mathbf{R^1}$ is CH_3.

R^2:

Preferably, $\mathbf{R^2}$ is $CON(\mathbf{R^{22}})_2$, wherein each $\mathbf{R^{22}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, or both $\mathbf{R^{22}}$ are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

or $\mathbf{R^2}$ is selected from: H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**; wherein each of said alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, aryl or **Het** is optionally substituted with $\mathbf{R^{20}}$, wherein

R^{20} is defined as:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, $(C_{3-}$

$_7$)cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is preferably:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl optionally substituted with $\mathbf{R^{160}}$;

d) $\mathbf{SR^{108}}$, SO_3H, $SO_2N(\mathbf{R^{108}})_2$ or $SO_2N(\mathbf{R^{108}})C(O)\mathbf{R^{108}}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $\mathbf{NR^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, or (C_{3-7})cycloalkyl, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, $\mathbf{COOR^{115}}$ or $\mathbf{SO_2R^{115}}$ wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $\mathbf{NR^{116}COR^{117}}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with $\mathbf{R^{160}}$;

g) $\mathbf{NR^{118}CONR^{119}R^{120}}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $\mathbf{NR^{121}COCOR^{122}}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with $\mathbf{R^{160}}$; or $\mathbf{R^{122}}$ is $\mathbf{OR^{123}}$ or $N(\mathbf{R^{124}})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

i) $\mathbf{COR^{127}}$ wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl

and cycloalkyl being optionally substituted with R^{160};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, R^2 is selected from: aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3, or

a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}$ alkyl);

b) (C_{1-6})alkoxy;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; being optionally substituted with halogen or:

- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6})alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;

f) $NHCOR^{117}$ wherein R^{117} is (C_{1-6})alkyl, $O(C_{1-6})$alkyl or $O(C_{3-7})$cycloalkyl;

i) CO-aryl; and

k) $CONH_2$, $CONH(C_{1-6}alkyl)$, $CON(C_{1-6}alkyl)_2$, CONH-aryl, or $CONHC_{1-6}alkyl$ aryl.

Still, more preferably, R^2 is aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or

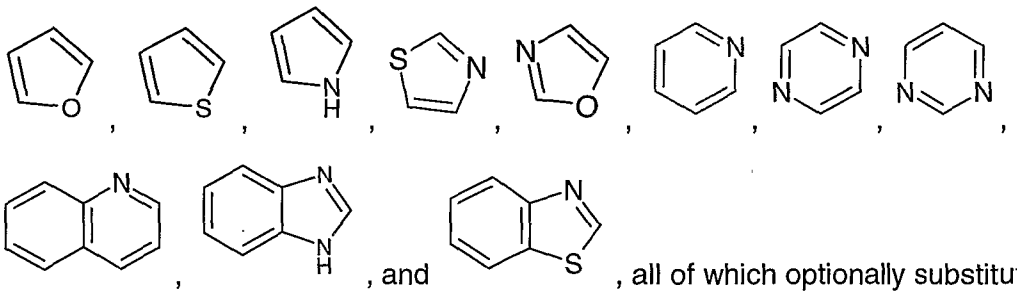
a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}alkyl)$;

b) (C_{1-6})alkoxy; and

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; or being optionally substituted with halogen or:

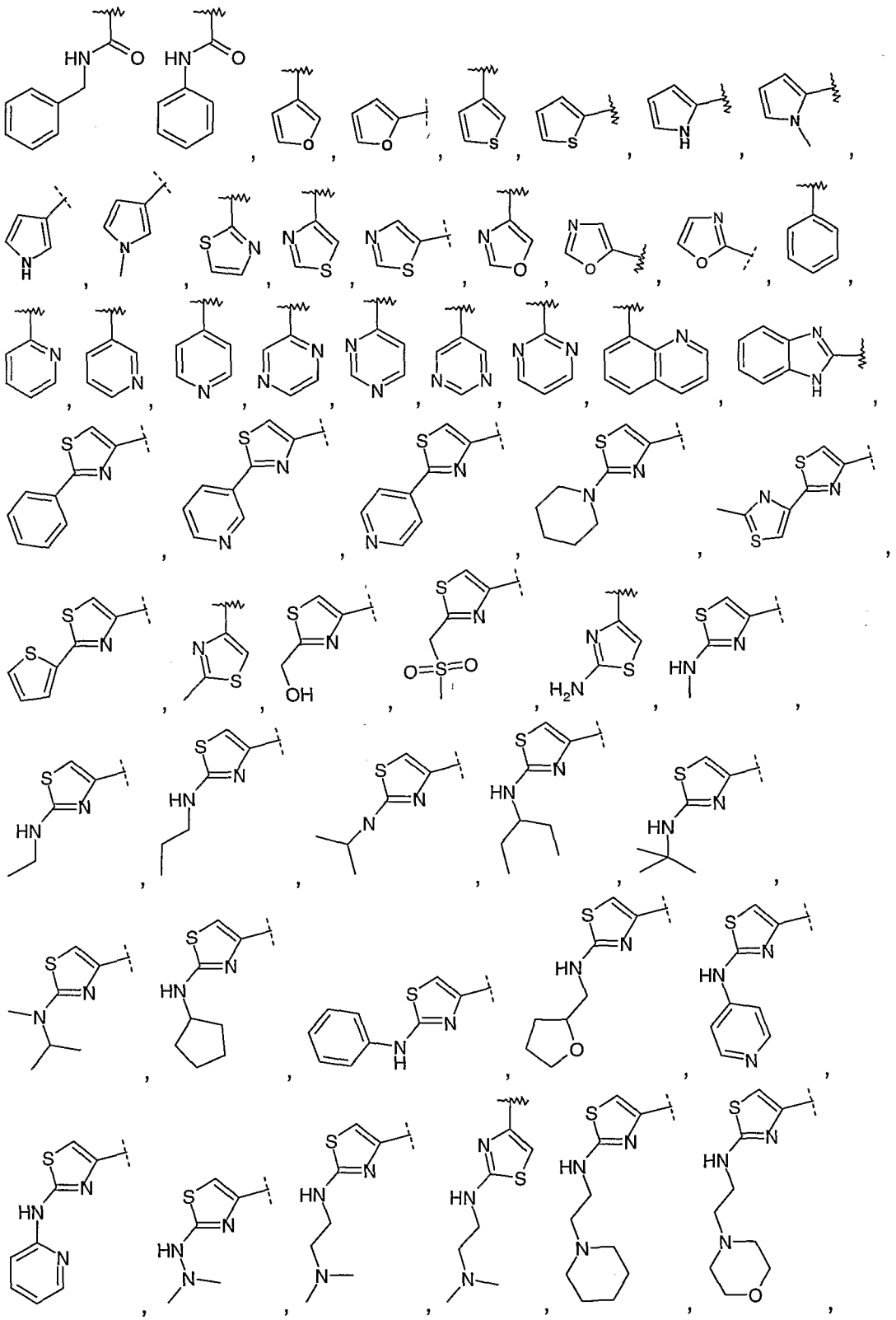
- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6})alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle.

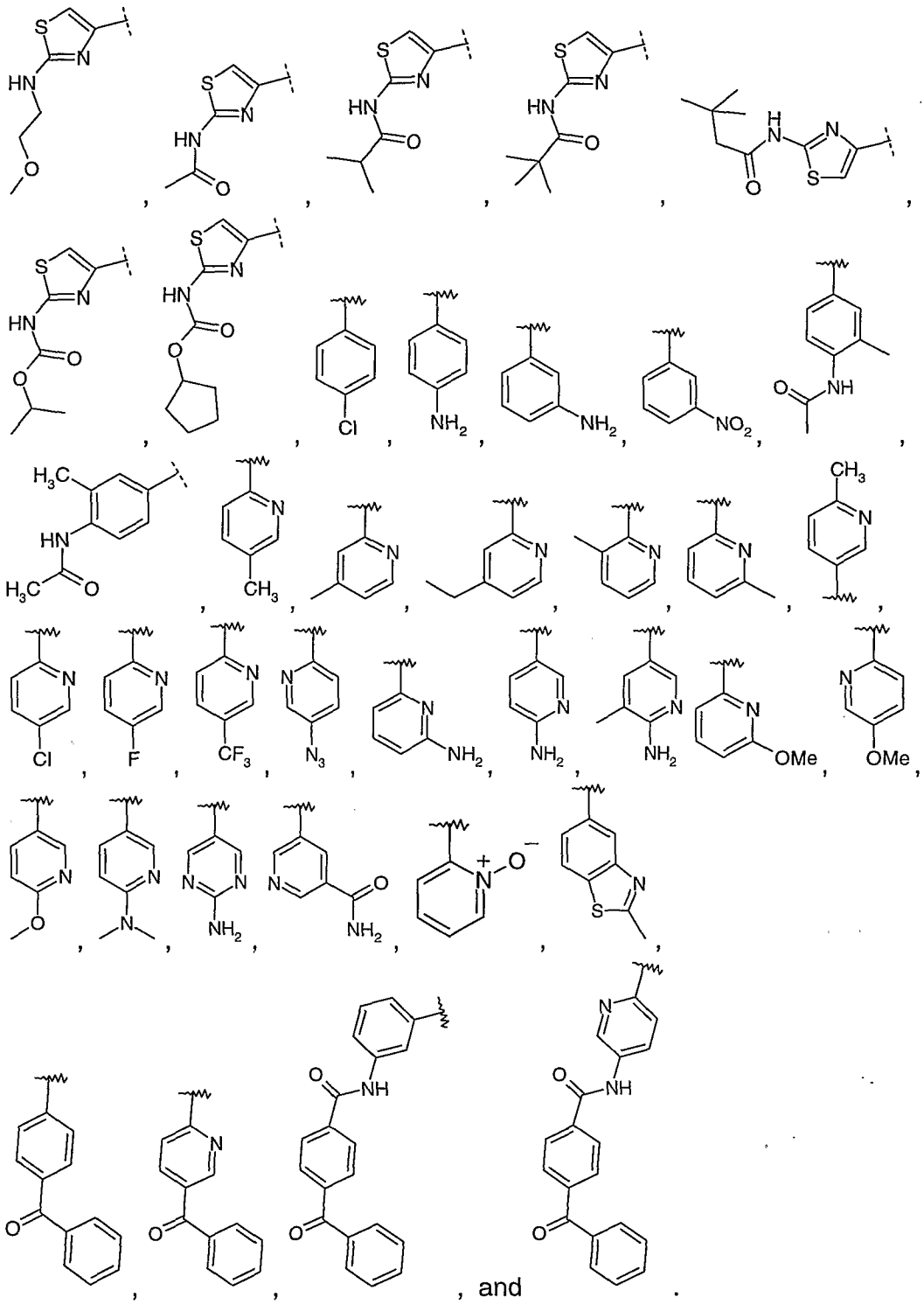
Even more preferably, R^2 is phenyl or a heterocycle selected from:



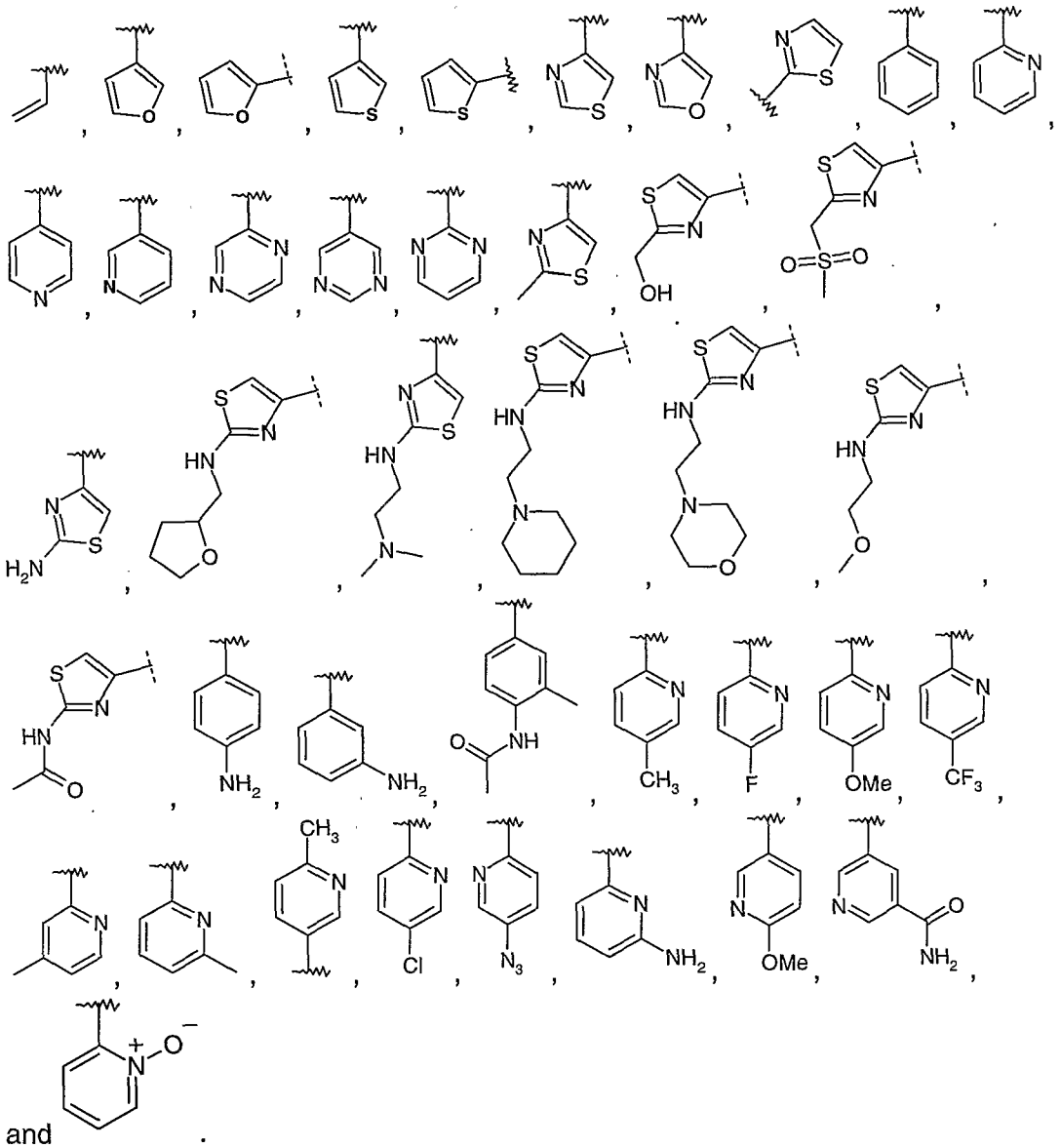
, all of which optionally substituted as defined above.

Even more preferably, R^2 is selected from the group consisting of:
H, Br, $CONHCH_3$, $CON(CH_3)_2$, $CONH_2$, $CH=CH_2$,



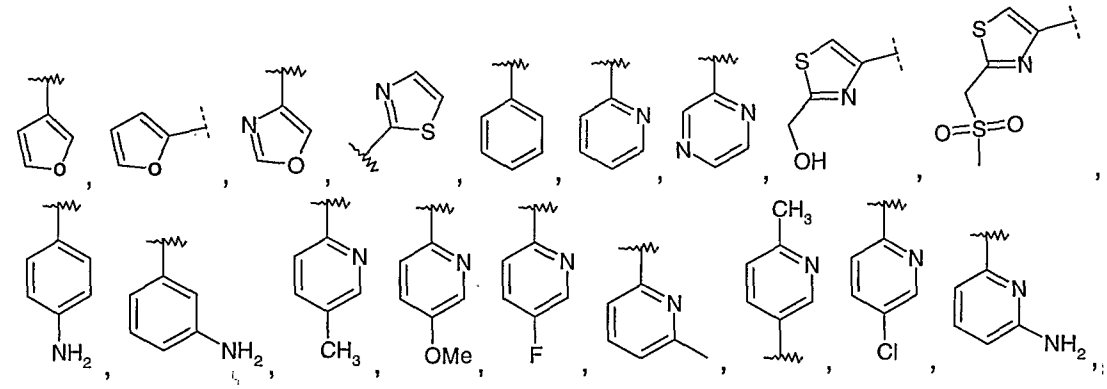


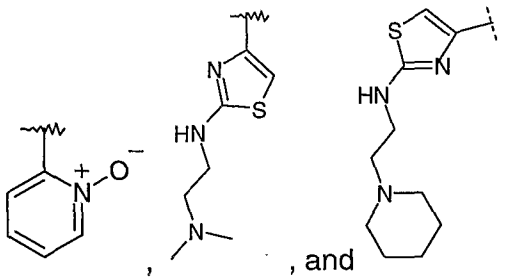
Still more preferably, R^2 is selected from:



and

Most preferably, R^2 is selected from:





, and .

R^3:

Preferably, R^3 is selected from (C_{3-7})cycloalkyl, (C_{3-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, or **Het**. More preferably, R^3 is (C_{3-7})cycloalkyl. Most preferably, R^3 is cyclopentyl, or cyclohexyl.

Y:

Preferably Y^1 is O.

Z:

Preferably, **Z** is OR^6 wherein R^6 is $(C_{1-6}$alkyl)aryl substituted with:

- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is $(C_{1-6}$alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108a}, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with

R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** and R^{115a} is the same as R^{115} but is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6}alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-}

$_6$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}; wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are

attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and

heterocycle being optionally substituted with R^{160};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

More preferably, **Z** is OR^6 wherein R^6 is (C_{1-6}alkyl)aryl substituted with:

- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SO_3H, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl and aryl, said alkyl and aryl being optionally substituted with R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl or (C_{1-6}alkyl)aryl, and R^{115a} is C_{1-6}alkyl substituted with R^{150} or (C_{1-6}alkyl)aryl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, aryl, **Het**, said (C_{3-7})cycloalkyl, aryl, **Het** being optionally

substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl, **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6}alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, said alkyl, aryl and **Het** being optionally substituted with R^{150};

l) aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150}; wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6})alkenyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, aryl or **Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, said alkyl, aryl or **Het** being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being

optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

Even more preferably, **Z** is OR^6 wherein R^6 is (C_{2-6})alkenyl, (C_{1-6})alkyl-**Het**, wherein said alkenyl or alkyl-**Het**, is optionally substituted with R^{60}, wherein preferably R^{60} is:

- 1 to 4 substituents selected from: halogen; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-}$

$_6$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{150}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated

heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{150}}$ is defined as:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted

with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H,

(C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Even more preferably, R^{60} is:

- 1 to 4 substituents selected from: halogen; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl or aryl, said alkyl and aryl being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or $(C_{1-6}$alkyl)aryl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or **Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or **Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H or (C_{1-6})alkyl optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** said alkyl, aryl and **Het** being optionally substituted with R^{150};

l) aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6})alkenyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, aryl or **Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or aryl, said alkyl, aryl and **Het** being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H or (C_{1-6})alkyl optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** said alkyl, aryl and **Het** being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H,

SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Most preferably, **Z** is $N(R^{6a})R^6$ wherein R^{6a} is H or C_{1-6}alkyl. More preferably, R^{6a} is H.

Preferably, R^6 is (C_{2-6})alkenyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2NH(C_{1-6}$alkyl) or $SO_2NHC(O)C_{1-6}$alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or

(C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein, preferably, R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H or (C_{1-6})alkyl optionally substituted with $\mathbf{R^{160}}$; and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein $\mathbf{R^{161}}$ and each $\mathbf{R^{162}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both $\mathbf{R^{162}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, $\mathbf{R^6}$ is (C_{2-6})alkenyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein

said alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{150}}$;

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SH, $S(C_{1-6}$alkyl), SO_3H, $SO_2NH(C_{1-6}$alkyl) or $SO_2NHC(O)C_{1-6}$alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, said alkyl, cycloalkyl being optionally substituted with $\mathbf{R^{150}}$, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, $(C_{3-}$

$_7$)cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein, preferably, $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SH, S(C_{1-6}alkyl), SO_3H, $SO_2N(\mathbf{R^{108}})_2$ or $SO_2N(\mathbf{R^{108}})C(O)\mathbf{R^{108}}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $\mathbf{NR^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $\mathbf{COOR^{115}}$ or $\mathbf{SO_2R^{115}}$ wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein, preferably, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl,

$COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6})alkyl.

Most preferably, R^6 is C_{2-6}alkenyl, phenyl, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, phenyl and the alkyl portion of said alkyl-aryl, or alkyl-**Het**, are optionally substituted with 1 to 3 of:

a) (C_{1-6}) alkyl C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, all of which optionally substituted with C_{1-6}alkyl or C_{1-6}alkoxy;

NH_2, NH(Me) or $N(Me)_2$

e) NHR^{112} wherein R^{112} is aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het**, said aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, being optionally substituted with R^{150};

j) COOH;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl, and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

l) phenyl or **Het,** both optionally substituted with R^{150}, wherein, preferably, R^{150} is selected from:

- 1 or 2 substituents selected from: halogen, NO_2, cyano or azido;
- 1 or 2 substituents selected from:

a) (C_{1-6}) alkyl or (C_{2-6})alkenyl, both optionally substituted with COOH or $CONH_2$;

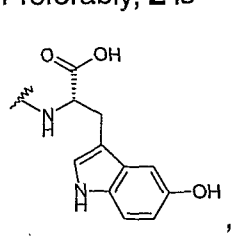
b) OR^{104} wherein R^{104} is H or $(C_{1-6}$alkyl) optionally substituted with COOH;

h) NHCOCOOH;

j) COOH; and

k) $CONH_2$.

Preferably, **Z** is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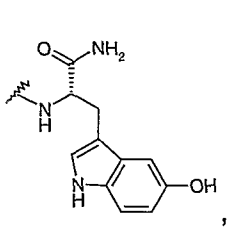
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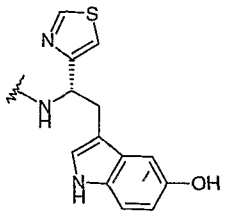
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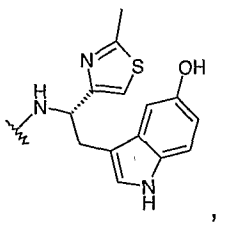
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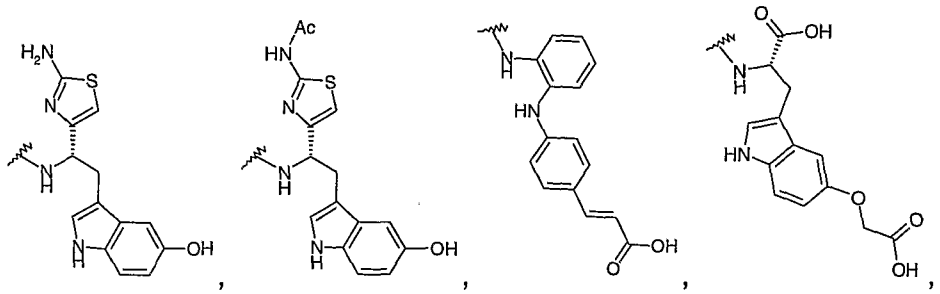
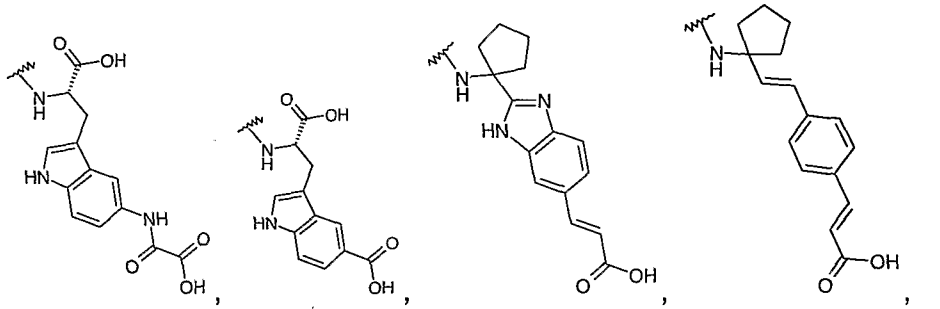
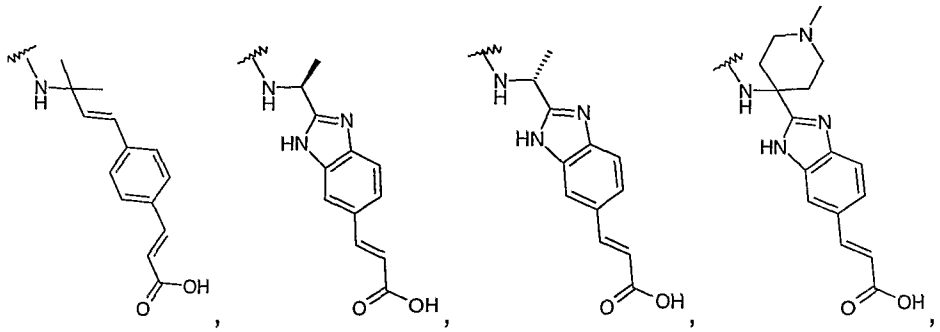
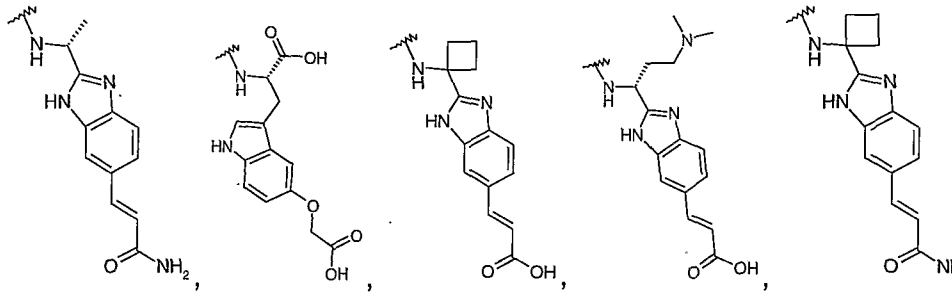
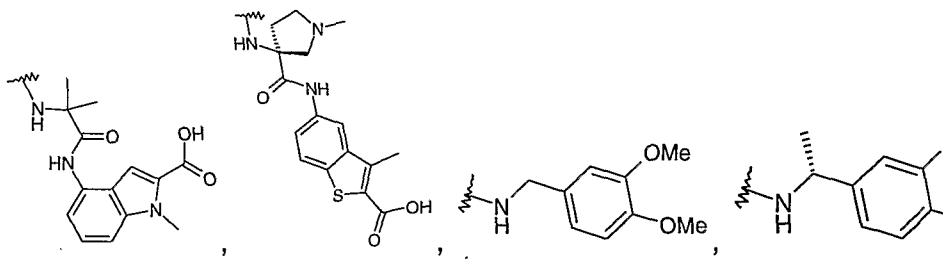
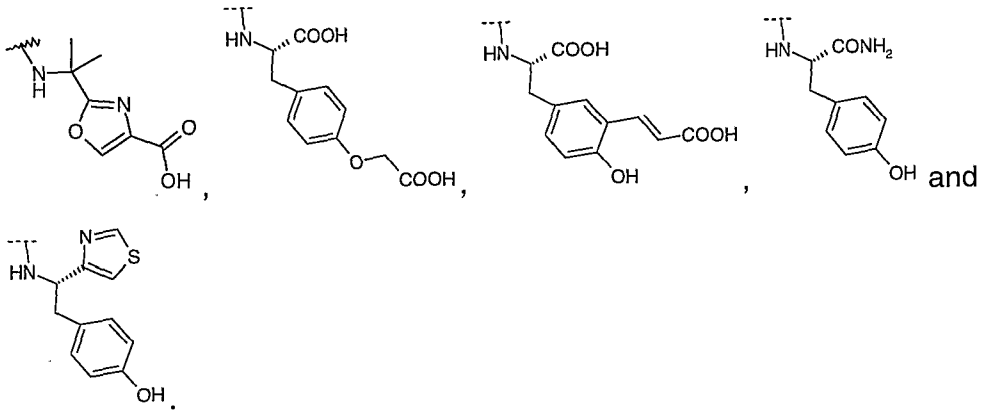
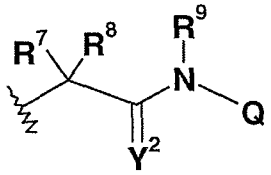








Diamides:

Most preferably, R^6 is:



wherein, preferably, R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{70}; or

R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a nitrogen-containing 5-or 6-membered heterocycle; wherein, preferably, R^{70} is selected from:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded

together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein, preferably, $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ wherein $\mathbf{R^{108}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl,

cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl or (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R^{160};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6})alkyl.

More preferably, R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, all of which optionally substituted with from 1 to 4 substituents selected from halogen or:

a) (C_{1-6})alkyl; and

b) $N(R^{8a'})_2$, COR^{8a}, or $SO_2R^{8a''}$ $COOR^{8a}$, $COCOOR^{8a}$, $CON(R^{8a'})_2$, $COCON(R^{8a'})_2$, wherein each R^{8a} or $R^{8a'}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or each $R^{8a'}$ are independently covalently bonded together and to the nitrogen to which they are both bonded to form a 5, 6 or 7-membered saturated heterocycle; or $R^{8a''}$ is independently (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl.

or R^7 and R^8 are covalently bonded together to form (C_{3-7})cycloalkyl, 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S.

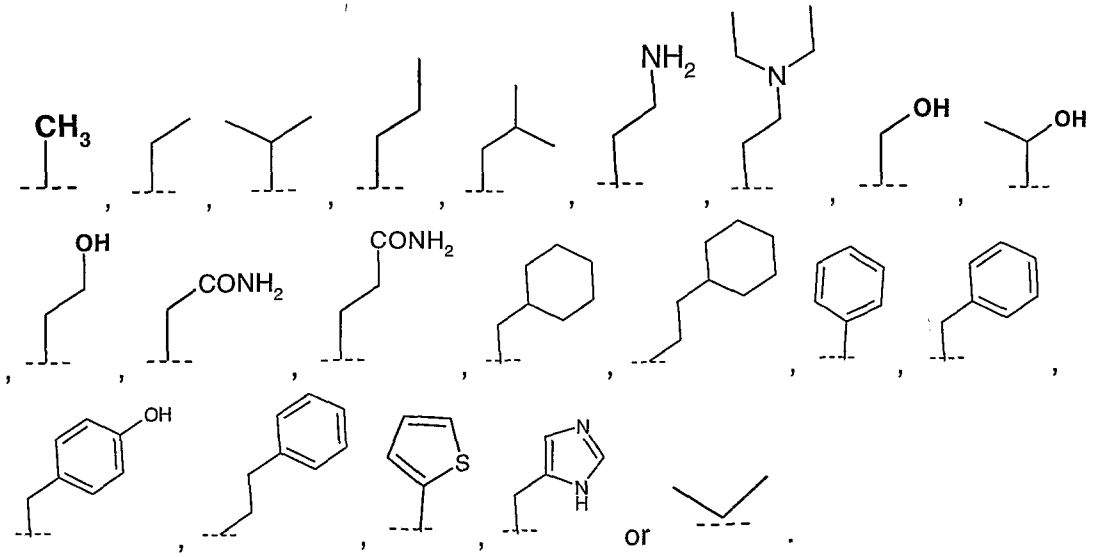
Most preferably, R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**; or R^7 and R^8 are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide;

wherein said alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide are optionally monosubstituted with substituents selected from:

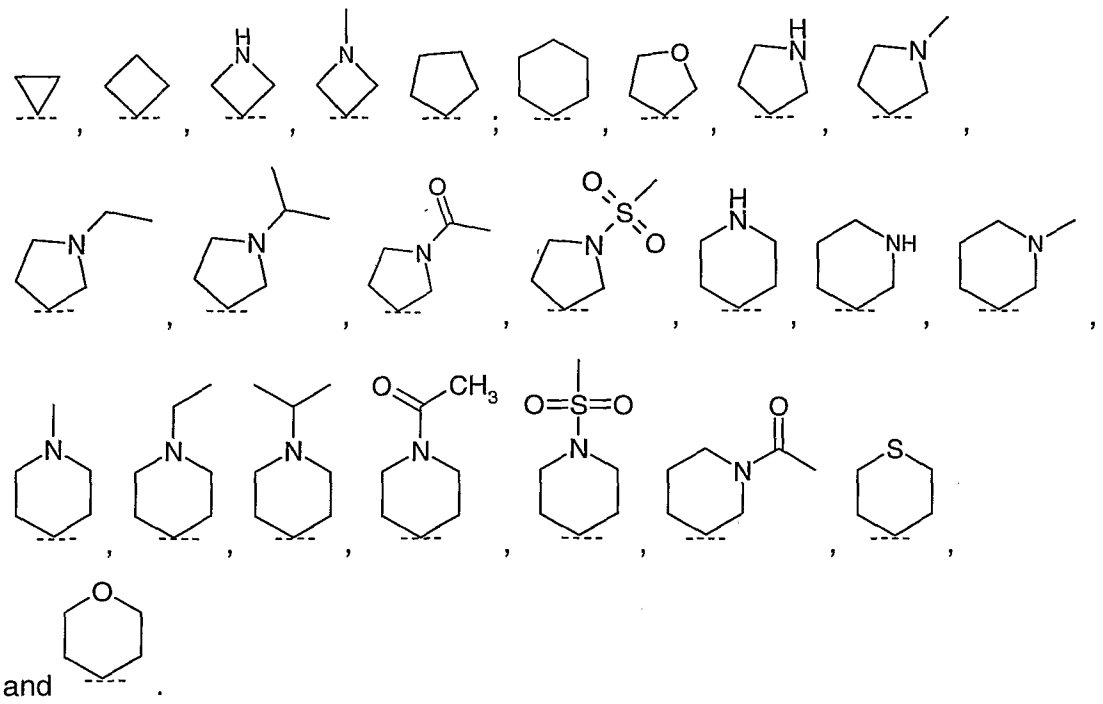
a) (C_{1-6})alkyl; and

c) NH_2, $N(CH_2CH)_2$, $COCH_3$, or SO_2CH_3.

Even more preferably, R^7 and R^8 are selected from:

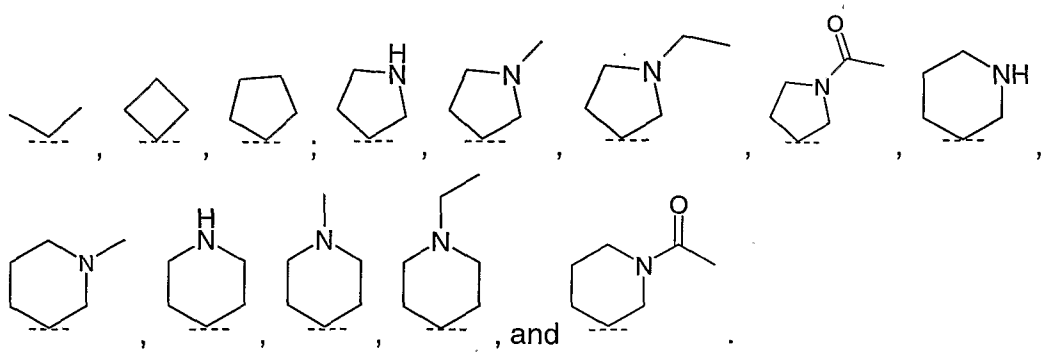


R^7 and R^8 together form:



and .

Most preferably, R^7 and R^8 are selected from the group consisting of:



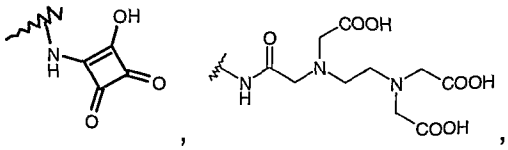
, and .

R^9:

Preferably R^9 is H; or R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle. More preferably, R^9 is H.

Q:

Preferably, **Q** is a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)-Het, all of which being optionally substituted with:



, or R^{100};

wherein R^{100} is:

- 1 to 4 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108} wherein R^{108} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-}

$_{7}$)cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$;

wherein $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are

covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl optionally substituted with $\mathbf{R^{160}}$, and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-

cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein $\mathbf{R^{161}}$ and each $\mathbf{R^{162}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both $\mathbf{R^{162}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, **Q** is a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)-Het, all of which being optionally substituted with:

- 1 to 4 substituents selected from: halogen,NO_2, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{150}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{150}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-}

$_7$)cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) CON$\mathbf{R^{129}R^{130}}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{150}}$ is preferably selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) O$\mathbf{R^{104}}$ wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, said alkyl, cycloalkyl, aryl and **Het** being optionally substituted with $\mathbf{R^{160}}$;

c) OCO$\mathbf{R^{105}}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) S$\mathbf{R^{108}}$, $SO_2N(\mathbf{R^{108}})_2$ or $SO_2N(\mathbf{R^{108}})C(O)\mathbf{R^{108}}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) N$\mathbf{R^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, COO$\mathbf{R^{115}}$ or $SO_2\mathbf{R^{115}}$ wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted

with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or $O(C_{1-6}$alkyl), or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Most preferably, **Q** is a 6- or 10-membered aryl or **Het**, both being optionally substituted with:

- 1 to 3 halogen, NO_2, cyano, azido; or
- 1 to 3 substituents selected from:

a) first (C_{1-6}) alkyl or haloalkyl, first (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which are optionally substituted with $\mathbf{R}^{150}$;

b) OR^{104} wherein $\mathbf{R}^{104}$ is H, (C_{1-6}alkyl);

d) SO_2NHR^{108} wherein $\mathbf{R}^{108}$ is H or (C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein both $\mathbf{R}^{111}$ and $\mathbf{R}^{112}$ are independently H or (C_{1-6})alkyl;

f) $NHCOR^{117}$ wherein $\mathbf{R}^{116}$ is H or (C_{1-6})alkyl;

g) $NHCONR^{119}R^{120}$, wherein $\mathbf{R}^{119}$ and $\mathbf{R}^{120}$ is each independently H or (C_{1-6})alkyl;

h) $NHCOCOR^{122}$ wherein $\mathbf{R}^{122}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R}^{123}$ and each $\mathbf{R}^{124}$ is independently H or (C_{1-6}alkyl);

j) $COOR^{128}$ wherein $\mathbf{R}^{128}$ is H, (C_{1-6})alkyl;

k) $CONHR^{130}$ wherein $\mathbf{R}^{130}$ is H, (C_{1-6})alkyl;

l) 6- or 10-membered aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R}^{150}$; and

wherein, preferably, $\mathbf{R}^{150}$ *is selected from:*

- 1 to 3 halogens; or
- 1 to 3 substituents selected from:

a) first (C_{1-6}) alkyl or haloalkyl, first (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which are optionally substituted with tetrazole, OR^{102}, $COOR^{102}$, wherein $\mathbf{R}^{102}$ is H or (C_{1-6})alkyl;

b) OR^{104} wherein $\mathbf{R}^{104}$ is H, (C_{1-6}alkyl);

d) SO_2NHR^{108} wherein $\mathbf{R}^{108}$ is H or (C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein both $\mathbf{R}^{111}$ and $\mathbf{R}^{112}$ are independently H or (C_{1-6})alkyl;

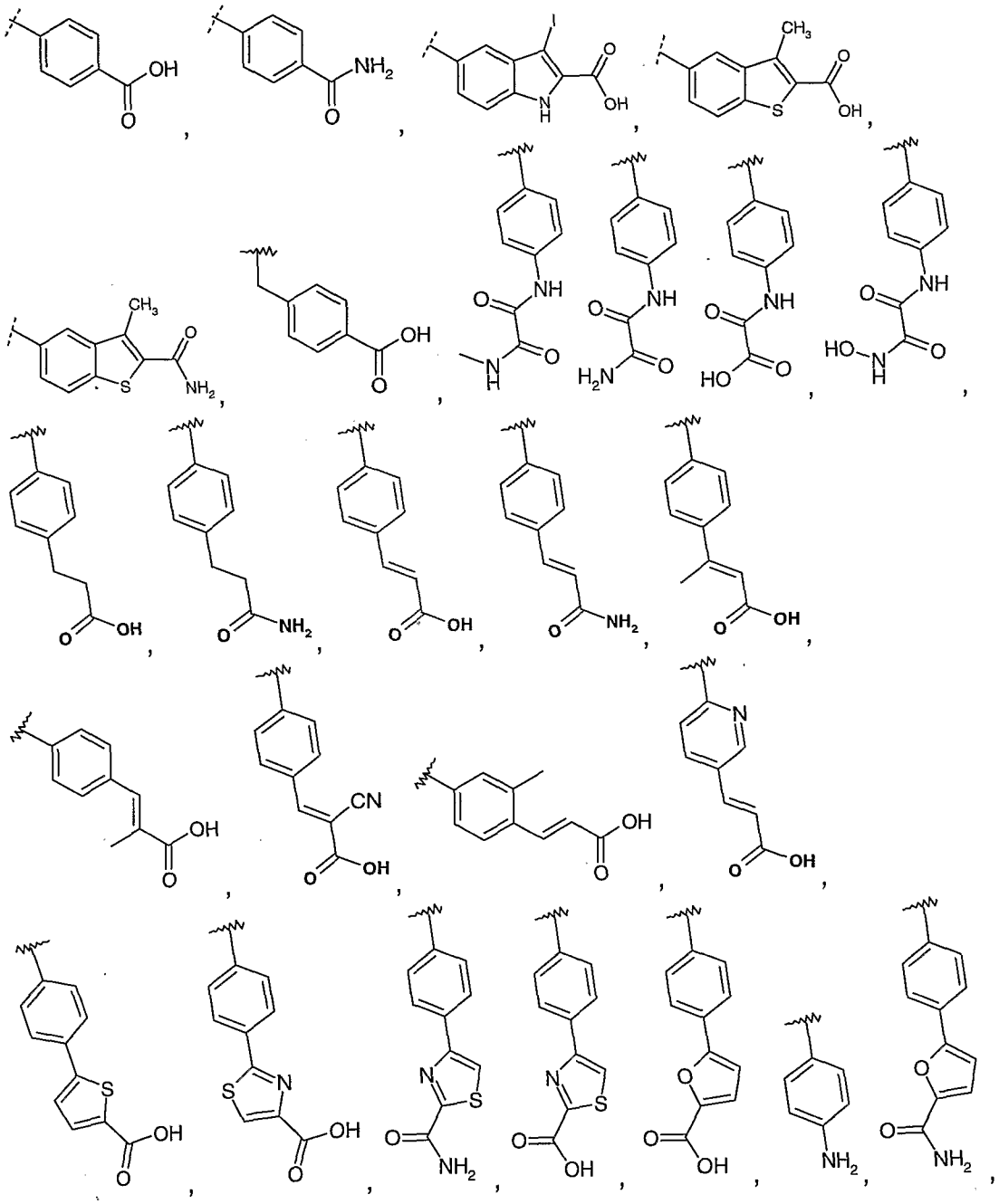
f) $NHCOR^{117}$ wherein $\mathbf{R}^{116}$ is H or (C_{1-6})alkyl; and

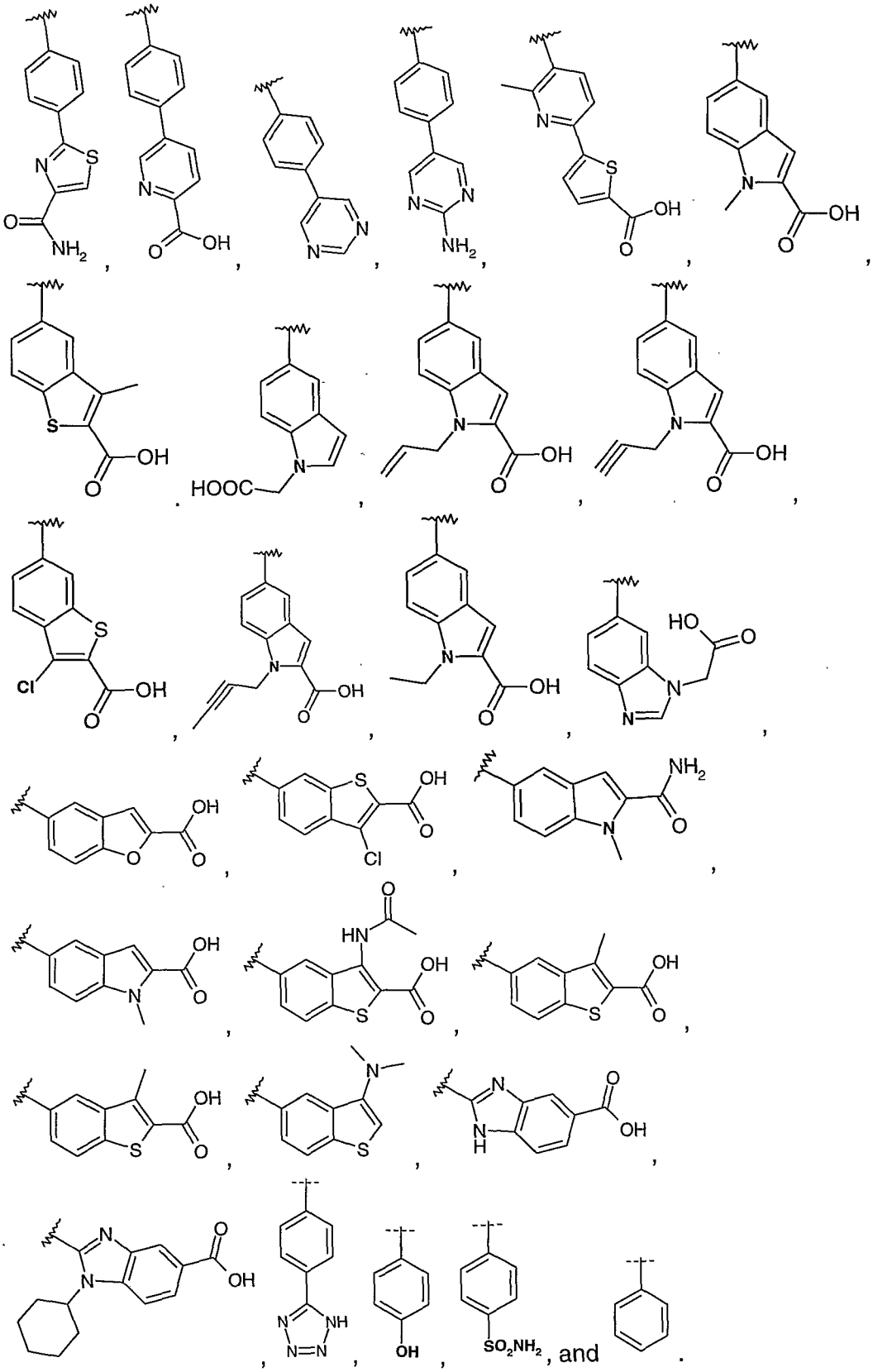
h) $NHCOCOR^{122}$ wherein $\mathbf{R}^{122}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R}^{123}$ and each $\mathbf{R}^{124}$ is independently H or (C_{1-6}alkyl);

j) $COOR^{128}$ wherein $\mathbf{R}^{128}$ is H, (C_{1-6})alkyl; and

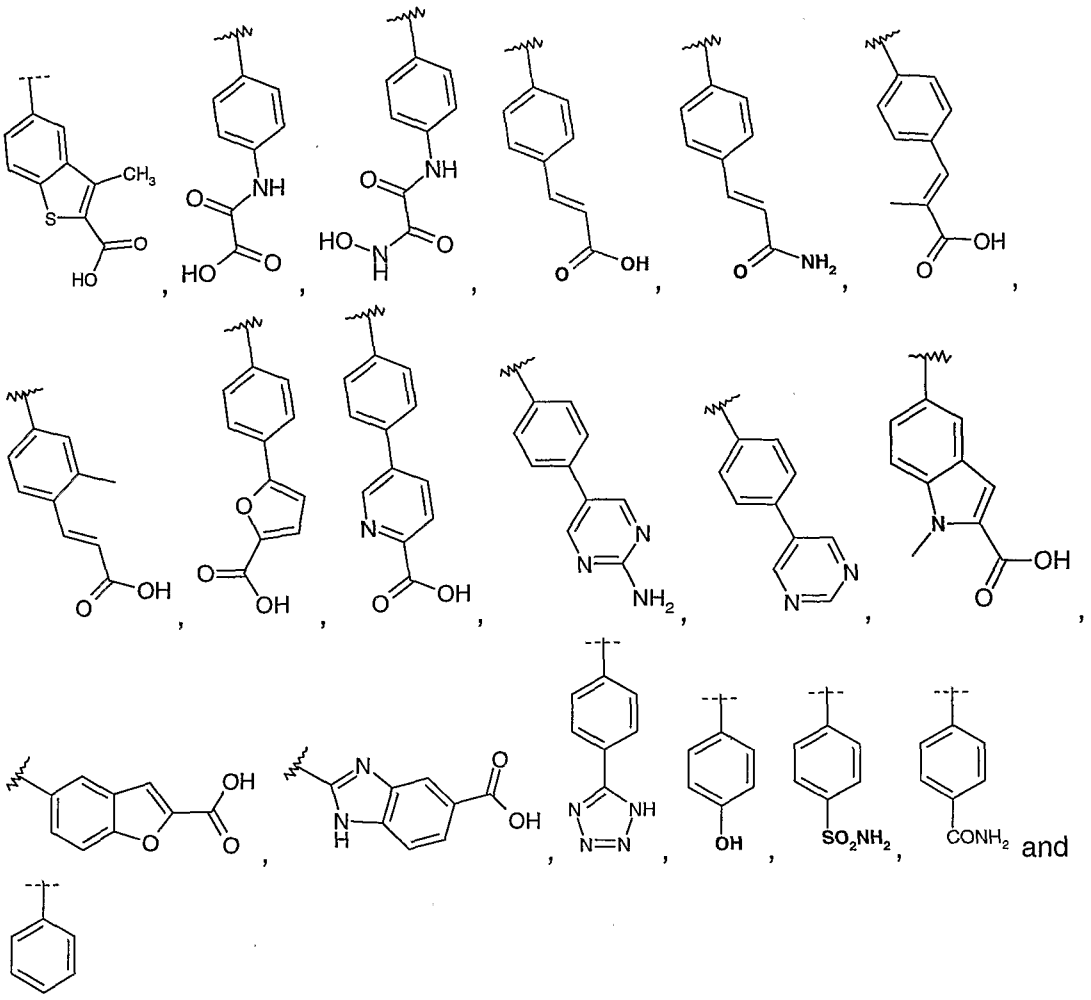
k) $CONHR^{130}$ wherein $\mathbf{R}^{130}$ is H, (C_{1-6})alkyl.

More preferably **Q** is selected from:





Most preferably, **Q** is selected from:



and

Specific embodiments

Included within the scope of this invention are all compounds of formula I as presented in Tables 1 to 9.

Polymerase activity

The ability of the compounds of formula (I) to inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV can be demonstrated by any assay capable of measuring RNA dependent RNA polymerase activity. A suitable assay is described in the examples.

Specificity for RNA dependent RNA polymerase activity

To demonstrate that the compounds of the invention act by specific inhibition of HCV polymerase, the compounds may be tested for inhibitory activity in a DNA dependent RNA polymerase assay.

When a compound of formula (I), or one of its therapeutically acceptable salts, is employed as an antiviral agent, it is administered orally, topically or systemically to mammals, e.g. humans, rabbits or mice, in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice.

For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier.

For topical administration, the compound can be formulated in pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula (I) is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the compound of formula I is

most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a therapeutically acceptable salt is administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

For systemic administration, the compound of formula (I) is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. A dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

When the compositions of this invention comprise a combination of a compound of formula I and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

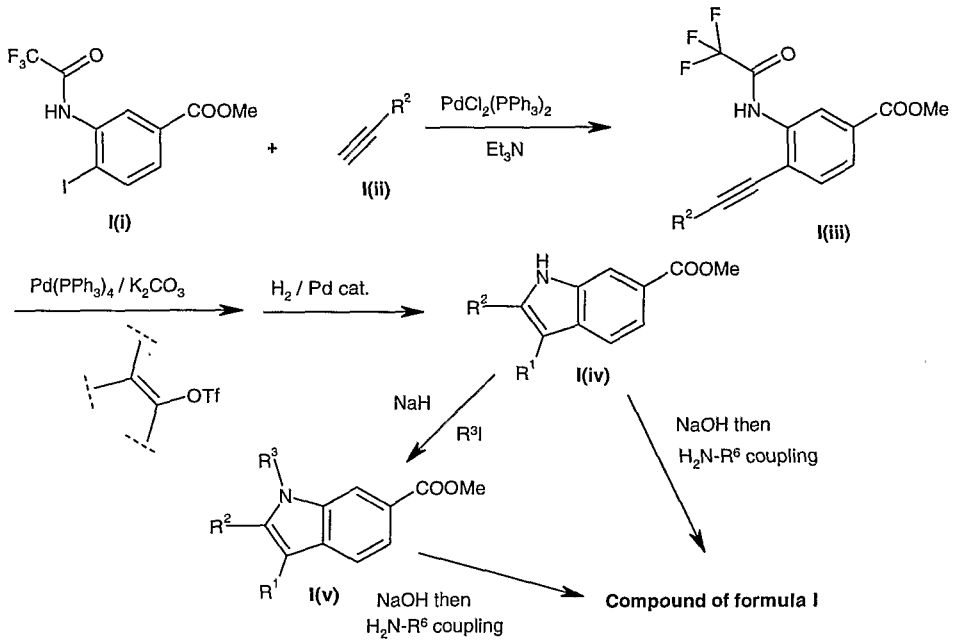
When these compounds or their pharmaceutically acceptable salts are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV polymerase or to treat or prevent HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as α-, β-, or γ-interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS5B polymerase; inhibitors of other targets in the HCV life cycle, which include but not limited to, helicase, NS2/3 protease, NS3 protease, or internal ribosome entry site (IRES); or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Methodology and Synthesis

Indole derivatives or analogs according to the present invention can be prepared from known monocyclic aromatic compounds by adapting known literature sequences such as those described by J.W. Ellingboe et al. (*Tet. Lett.* **1997**, *38*,

7963) and S. Cacchi et al. (*Tet. Lett.* **1992**, *33*, 3915). Scheme 1, shown below wherein R^1, R^2, R^3, R^6, **K**, **L**, and **M** are as described herein illustrate how these procedures can be adapted to the synthesis of compounds of formula **1** of this invention.

Scheme 1



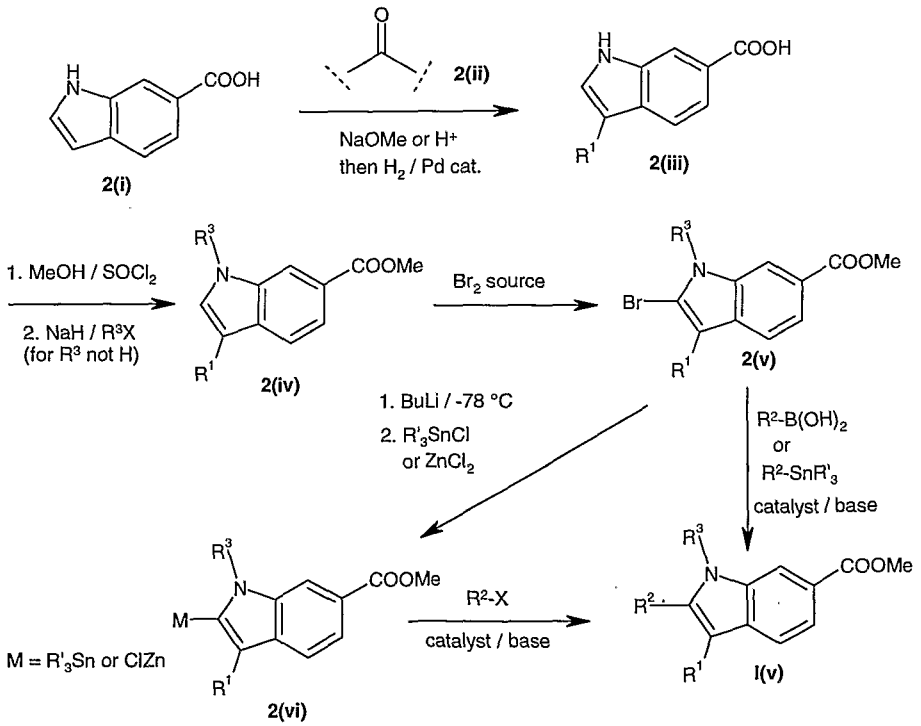
In carrying out the route illustrated in Scheme 1, a suitably protected form of 3-trifluoroacetamido-4-iodobenzoic acid **I(i)** is reacted with an alkyne **I(ii)** in the presence of a metal catalyst (e.g. a palladium metal complex such as $PdCl_2(PPh_3)_2$, Pd_2dba_3, $Pd(PPh_3)_4$ and the like), a base (Et_3N, DIEA and the like or an inorganic basic salt including metal carbonates, fluorides and phosphates), and optionally in the presence of an additional phosphine ligand (triaryl or heteroarylphosphine, dppe, dppf, dppp and the like). Suitable solvents for this reaction include DMF, dioxane, THF, DME, toluene, MeCN, DMA and the like at temperatures ranging from 20 °C to 170 °C, or alternatively without solvent by heating the components together. Alternatively, the cross-coupling reaction can be carried out on a suitably protected form of 3-amino-4-iodobenzoate and the amino group can be trifluoroacetylated in the subsequent step as described by J.W. Ellingboe et al. (*Tet. Lett.* **1997**, *38*, 7963). Reaction of the above diarylalkynes **I(iii)** with an enol triflate under cross-coupling conditions similar to those described above gives after hydrogenation of the douple bond, indole derivatives **I(iv)**. Enol triflates are known and can be prepared from the corresponding ketones by following known literature methods (for example, cyclohexene triflate can be prepared from cyclohexanone, triflic anhydride and a

hindered organic base such as 2,6-di-*tert*-butyl-4-methylpyridine). The hydrogenation of the double bond originally present in R^1 can be carried out with hydrogen gas or a hydrogen donor (ammonium formate, formic acid and the like) in the presence of a metal catalyst (preferably Pd) in a suitable solvent (lower alkyl alcohols, THF etc.).

Finally, following hydrolysis of the ester protecting group in **I(iv),** the resulting 6-carboxyindole derivative **I(v)** is converted to compounds of formula **1** by coupling with the appropriate amine of formula $H_2N\text{-}R^6$. Condensation of the 6-indolecarboxylic acid with amines $H_2N\text{-}R^6$ can be accomplished using standard amide bond forming reagents such as TBTU,HATU, BOP,BroP, EDAC, DCC, isobutyl chloroformate and the like, or by activation of the carboxyl group by conversion to the corresponding acid chloride prior to condensation with an amine. Any remaining protecting group is removed following this step to give compounds of formula **1**.

Alternatively, compounds of formula **1** can be prepared by elaboration from a pre-exisitng indole core by following adaptations of literature procedures as described, for example, by P. Gharagozloo et al. (*Tetrahedron* **1996**, *52*, 10185) or K. Freter (*J. Org. Chem.* **1975**, *40*, 2525). Such a methodology is illustrated in Scheme 2:

Scheme 2



In carrying the route illustrated in Scheme 2, commercially available 6-indolecarboxylic acid **2(i),** which can also be prepared according to the method of S. Kamiya et al. (*Chem. Pharm. Bull.* **1995**, *43*, 1692) is used as the starting material. The indole **2(i)** is reacted with a ketone **2(ii)** under basic or acidic aldol-type conditions. Suitable conditions to affect this condensation include strong bases such as alkali metal hydroxides, alkoxides and hydrides in solvents such as lower alkyl alcohols (MeOH, EtOH, *tert*BuOH etc.), THF, dioxane, DMF, DMSO, DMA and the like at reaction temperature ranging from –20 °C to 120 °C. Alternatively, the condensation can be carried out under acid conditions using organic or mineral acids or both. Appropriate conditions include mixtures of AcOH and aqueous phosphoric acid at temperatures ranging from 15°C to 120 °C.

Following protection of the carboxylic acid group in the form of an ester (usually lower alkyl) using known methods, the indole nitrogen can be alkylated with R^3 if desired. Reaction conditions to alkylate the nitrogen of an indole derivative are well known to those skilled in the art and include the use of strong bases such as alkali metal hydrides, hydroxides, amides, alkoxides and alkylmetals, in the appropriate solvent (such as THF, dioxane, DME, DMF, MeCN, DMSO, alcohols and the like) at temperatures ranging from –78 °C to 140 °C. An electrophilic form of R^3 is used for the alkylation of the indole anion. Such electrophilic species include iodides, bromides, chlorides and sulfonate esters (mesylates, tosylate, brosylate or triflate).

Halogenation (usually bromination, but also iodination) of the 2-position of the indole **2(iv)** gives **2(v)**. Suitable halogenating agents include, for example, elemental bromine, *N*-bromosuccinimide, pyridine tribromide, dibromohydantoin and the corresponding iodo derivatives. Suitable solvents for this reaction are inert to reactive halogenating agents and include for example hydrocarbons, chlorinated hydrocarbons (DCM, CCl_4, $CHCl_3$), ethers (THF, DME, dioxane), acetic acid, ethyl acetate, IPA, and mixtures of these solvents. Reaction temperature ranges from –40 °C to 100 °C. A method of choice to carry out the bromination of indoles as shown in Scheme 2 was described by L. Chu (*Tet. Lett.* **1997**, *38*, 3871).

The 2-bromoindole derivatives **2(v)** can be converted directly to fully substituted key intermediates **I(v)** through a cross-coupling reaction with aryl or heteroaryl boronic acids, boronate esters or trialkylstannane derivatives. These boron or tin organometallic species are from commercial sources or can be prepared by standard literature procedures. Cross-coupling with organoboron reagents can be

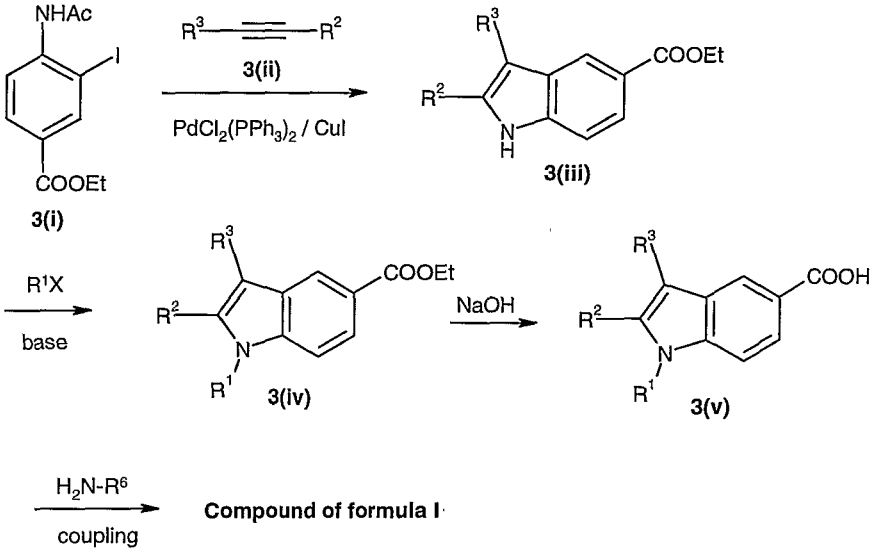
carried out by any variations of the Suzuki cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd°), triaryl or triheteroarylphosphine ligands, an additive such as an inorganic chloride (e.g. LiCl), and a base (usually an aqueous inorganic base such as sodium or potassium carbonate or phosphate). The reaction is usually carried out in an alcoholic solvent (EtOH), DME, toluene, THF and the like at temperatures ranging from 25 °C to 140 °C.

Cross-coupling with tin reagents can be carried out by any variations of the Stille cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd°), triaryl or triheteroaryl phosphine ligands, and an additive such as an inorganic chloride (e.g. LiCl) or iodide (e.g. CuI). Suitable solvents for this reaction include toluene, DMF, THF, DME and the like at temperatures ranging from 25 °C to 140 °C. Intermediate **I(v)** is then converted to compounds of formula **1** as described for Scheme 1.

Alternatively, the 2-bromoindole intermediate **2(v)** can be trans-metallated to an organotin species (or organozinc) and used in Stille-type cross-coupling reactions under conditions described above. In this case, aromatic and heteroaromatic halides (chlorides, bromides, iodides) or triflates are used to introduce R^2. The conversion of 2-bromoindole derivatives **2(v)** to the corresponding organotin species **2(vi)** is carried out via initial low-temperature (usually –78 ° to –30 °C) halogen-metal exchange using an alkyllithium reagent (e.g. nBuLi or *tert*-BuLi) or using lithium metal. The transient 2-lithioindole species is then trapped with a trialkyltin halide (e.g. nBu_3SnCl or Me_3SnCl). Alternatively, the lithioindole intermediate can be trapped with zinc chloride to form the corresponding organozincate which can also undergo transition metal-catalyzed cross-coupling with aromatic and heteroaromatic halides or triflates as described, for example, by M. Rowley (*J. Med. Chem.* **2001**, *44*, 1603).

The present invention also encompasses compounds of formula **1** where the carboxylic group is in the 5-position of the indole system. The synthesis of such compounds is based on adaptation of literature procedures and is depicted in Scheme 3:

Scheme 3



In carrying out the synthetic route illustrated in Scheme 3, ethyl 4-acetamido-3-iodobenzoate **3(i)** undergoes metal catalyzed cross-coupling with an alkyne **3(ii)** to give a 2,3-disubstituted-5-indolecarboxylate **3(iii)** according to an adaptation of a procedure described by A. Bedeschi et al. (*Tet. Lett.* **1997**, *38*, 2307). The indole derivative **3(iii)** is then alkylated on nitrogen with electrophilic R^1 groups (halides, sulfonate esters) under the action of a base such as alkali metal hydroxides, fluorides, hydrides amides, alkyllithium, phosphabases and the like, to give **3(iv).** Suitable solvents for this alkylation include DMF, DMA, DMSO, MeCN, THF, dioxane, DME and the like. Following saponification of the ester group with an alkaline solution, the resulting 5-indolecarboxylic acid derivative **3(v)** is coupled to H_2N-$\mathbf{R^6}$ using an amide bond forming reagent as described previously (Scheme 1), to give compounds of formula I.

EXAMPLES

The present invention is illustrated in further detail by the following non-limiting examples. All reactions were performed in a nitrogen or argon atmosphere. Temperatures are given in degrees Celsius. Flash chromatography was performed on silica gel. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Mass spectral analyses were recorded using electrospray mass spectrometry. Abbreviations or symbols used herein include:

DIEA: diisopropylethylamine;

DMAP: 4-(dimethylamino)pyridine;

DMSO: dimethylsulfoxide;

DMF: N,N-dimethylformamide;

Et: ethyl;

EtOAc: ethyl acetate;

Et_2O: diethyl ether;

HPLC: high performance liquid chromatography;

^{i}Pr: isopropyl

Me: methyl;

MeOH: Methanol;

MeCN: acetonitrile;

Ph: phenyl;

TBE: tris-borate-EDTA;

TBTU: 2-(*1H*-benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate;

TFA: trifluoroacetic acid;

TFAA: trifluoroacetic anhydride;

THF: tetrahydrofuran;

MS (ES): electrospray mass spectrometry;

PFU: plaque forming units;

DEPC: diethyl pyrocarbonate;

DTT: dithiothreitol

EDTA: ethylenediaminetetraacetate

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate

BOP: benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate

EDAC: see ECD

DCC: 1,3-Dicyclohexyl carbodiimide

HOBt: 1-Hydroxybenzotriazole

ES^+: electro spray (positive ionization)

ES^-: electro spray (negative ionization)

DCM: dichloromethane

TBME: *tert*-butylmethyl ether

TLC: thin layer chromatography

AcOH: acetic acid

EtOH: ethanol

DBU: 1,8-diazabicyclo[5.4.0]under-7-ene

BOC: *tert*-butyloxycarbonyl

Cbz: carbobenzyloxy carbonyl

^{i}PrOH: isopropanol

NMP: N-methylpyrrolidone

EDC: 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

RNAsin: A ribonuclease inhibitor marketed by Promega Corporation

Tris: 2-amino-2-hydroxymethyl-1,3-propanediol

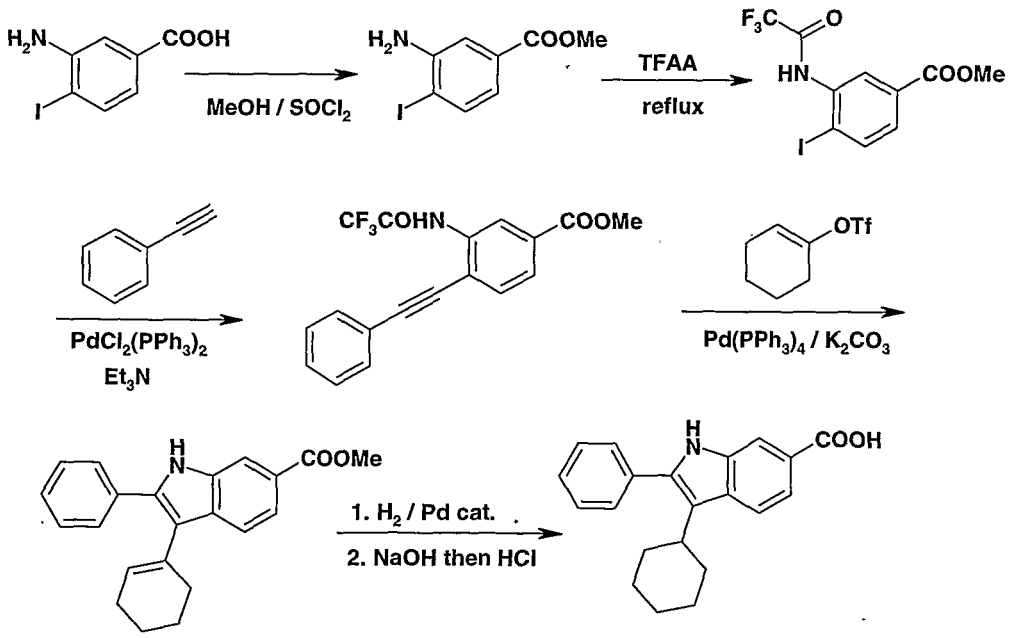
UMP: uridine 5'-monophosphate

UTP: uridine 5'-triphosphate

IPA: isopropyl acetate

Examples 1-45 illustrate methods of synthesis of representative compounds of this invention.

EXAMPLE 1



Methyl 3-amino-4-iodobenzoate:

3-Amino-4-iodobenzoic acid (13.35 g, 50.8 mmol) was added to MeOH (150mL) and $SOCl_2$ (4.8 mL, 65.8 mmol, 1.3 equivalent) was added. The mixture was refluxed for

3 h and then volatiles were removed under reduced pressure. The residue was co-evaporated three times with MeOH and dried in vacuo (15.23 g).

Methyl 3-trifluoroacetamido-4-iodobenzoate:

The aniline derivative from above (14.53 g, 52 mmol) was dissolved in DCM (200 mL) and TFAA (15 mL, 104 mmol) was added. The dark purple solution was refluxed overnight. Volatiles were removed under reduced pressure and the residue was passed through a short pad of silica gel using DCM as eluent. The desired product was obtained as a pink solid (13.81 g).

4-Phenylethynyl-3-(2,2,2-trifluoro-ethanoylamino)-benzoic acid methyl ester:

The iodide from above (0.742 g, 2 mmol), phenylacetylene (0.37 mL, 3.9 mmol, 1.7 equivalent) and Et_3N (6 mL) were charged in a dry flask under argon. $PdCl_2(PPh_3)_2$ (0.241 g, 0.3 mmol) was added and the mixture was stirred at room temperature until judged complete by HPLC analysis (~5 h). The reaction mixture was concentrated to half volume under reduced pressure and diluted with water (80 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the organic extract washed with 5% HCl (100 mL), after (100 mL) and brine (40 mL). After drying over $MgSO_4$, the residue was purified by flash chromatography using 20% EtOAc – hexane as eluent to give the desired cross-coupled alkyne as a tan solid (0.442 g).

Methyl 3-(cyclohexenyl)-2-phenylindole 6-carboxylate:

A flame-dried flask was charged with finely powdered anhydrous K_2CO_3 (0.153 g, 1.1 mmol) and the alkyne derivative from above (0.390 g, 1.1 mmol). Dry DMF (4 mL) was added and the suspension degassed with a stream of argon. The enol triflate derived from cyclohexanone, prepared following the procedure described by A.G. Martinez, M. Hanack et al. (*J. Heterocyclic Chem.* **1988**, *25*, 1237 or equivalent methods described in the literature, (0.802 g, 3.3 mmol, 3 equivalents) was added followed by $Pd(PPh_3)_4$ (0.086 g, 0.07 mmol) and the mixture was stirred for 8 h at room temperature. DMF was removed under vacuum and the residue purified by flash chromatography using DCM as eluent (0.260 g).

Methyl 3-cyclohexyl-2-phenylindole-6-carboxylate:

The material from above was hydrogenated (1 atm H_2 gas) over 20% $Pd(OH)_2$ in the usual manner, using MeOH as solvent. The desired cyclohexane indole was

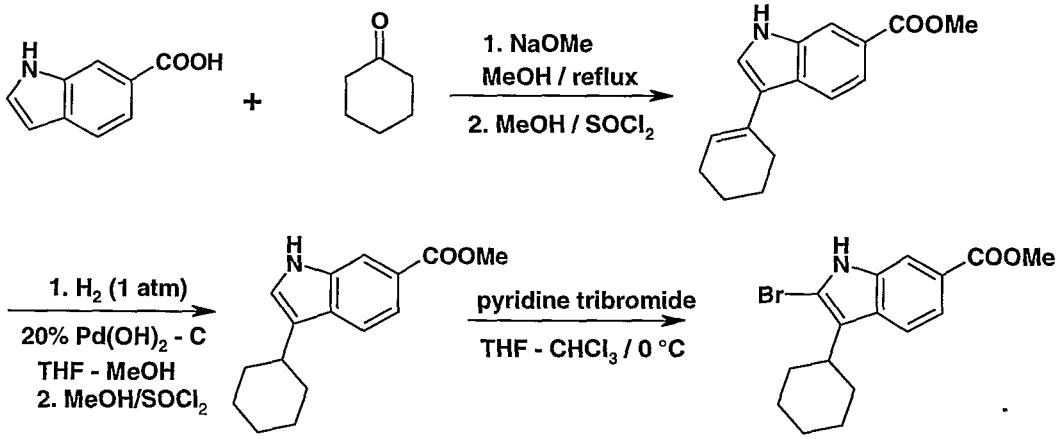
isolated after filtration of the catalyst.

3-Cylohexyl-2-phenylindole-6-carboxylic acid:

The methyl ester from above (0.154 g, 0.15 mmol) was refluxed overnight in a mixture of MeOH (10 mL) and 2N NaOH (6 mL) until complete hydrolysis had occurred as shown by HPLC analysis. After cooling to room temperature, 2N HCl (5 mL) was added followed by AcOH to pH 7. MeOH was removed under reduced pressure, water (50 mL) was added and the product extracted with EtOAc. The extract was washed with water an brine, and dried ($MgSO_4$). Removal of volatiles under reduced pressure gave the title indole carboxylic acid as a light-orange solid (0.149 g).

Following the same procedure but using 2-ethynylpyridine instead of phenylacetylene, 3-cyclohexane-2-(2-pyridyl)indole-6-carboxylic acid was obtained.

EXAMPLE 2:



3-Cyclohexenyl-6-indole carboxylic acid:

A 12 L round-bottomed flask was equipped with a reflux condenser and a mechanical stirrer, and the system was purged with nitrogen gas. 6-Indole carboxylic acid (300.00 g, 1.86 mole, 3 equivalents) was charged into the flask, followed by MeOH (5.5 L). After stirring for 10 min at room temperature, cyclohexanone (579 mL, 5.58 mole) was added. Methanolic sodium methoxide (25% w/w, 2.6 L, 11.37 mole, 6.1 equivalents) was added in portions over 10 min. The mixture was then refluxed for 48 h. After cooling to room temperature, water (4

L) was added and methanol removed under reduced pressure. The residual aqueous phase was acidified to pH 1 with concentrated HCl (~1.2 L). The resulting yellowish precipitate was collected by filtration, washed with water and dried under vacuum at 50 °C. The desired cyclohexane derivative was obtained as a beige solid (451.0g, 100% yield).

3-Cyclohexyl-6-indole carboxylic acid:

The unsaturated derivative from above was hydrogenated for 20 h under 55 psi hydrogen gas pressure over 20% $Pd(OH)_2/C$ (10.25 g) using 1:1 THF – MeOH (2.5 L) as solvent. After filtration of the catalyst, volatiles were removed under reduced pressure and the residue was triturated with hexane. The beige solid was collected by filtration, washed with hexane and dried under vacuum (356.4 g, 78% yield).

Methyl 3-cyclohexyl-6-indole carboxylate:

A 5 L three-necked flask was equipped with a reflux condenser and a mechanical stirrer, and the system was purged with nitrogen gas. The indole carboxylic acid from above (300.00 g, 1.233 mole) was charged into the flask and suspended in MeOH (2 L). Thionyl chloride (5 mL, 0.0685 mole, 0.05 equivalent) was added dropwise and the mixture was refluxed for 48 h. Volatiles were removed under reduced pressure and the residue was triturated with hexane to give a beige solid that was washed with hexane and dried under vacuum (279.6 g, 88% yield).

Methyl-2-bromo-3-cyclohexyl-6-indole carboxylate:

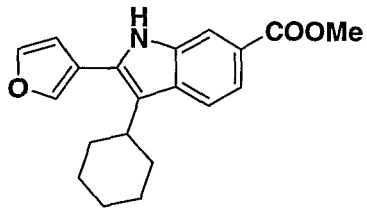
Adapting the procedure of L. Chu (*Tet. Lett.* **1997**, *38*, 3871) methyl 3-cyclohexyl-6-indole carboxylate (4.65 g, 18.07 mmol) was dissolved in a mixture of THF (80 mL) and $CHCl_3$ (80 mL). The solution was cooled in an ice bath and pyridinium bromide perbromide (pyridine tribromide, 7.22 g, 22.6 mmol, 1.25 equivalent) was added. After stirring for 1.5 h at 0 °C, the reaction was judged complete by TLC. It was diluted with $CHCl_3$ (200 mL), washed with 1M $NaHSO_3$ (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL) and brine (50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue crystallized from TBME – hexane. The desired 2-bromoindole derivative was collected by filtration, washed with hexane and dried (3.45 g). Evaporation of mother liquors gave a red solid that was purified by flash chromatography using 15% EtOAc in hexane yielding an additional 3.62 g of pure material. Total yield was 5.17 g (85% yield).

EXAMPLE 3:

General procedure for the Suzuki cross-coupling of aryl and heteroarylboronic acids with 2-bromoindole derivatives:

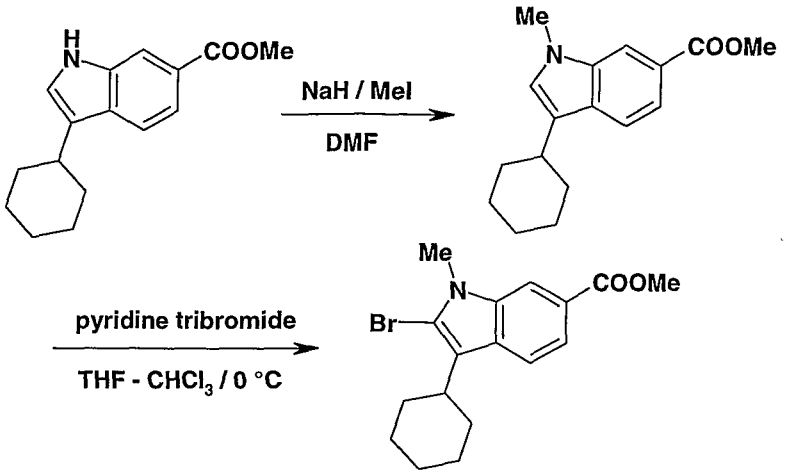
Cross-coupling of aromatic/heteroaromatic boronic acid or ester derivatives with 2-bromoindoles such as the one described in example 2 can be performed using any variations of the standard metal-catalyzed Suzuki cross-coupling reaction as described in the literature and well known to those skilled in the art. The following example serves to illustrate such a process and is non-limiting.

3-Cyclohexyl-2-furan-3-yl-1H-indole-6-carboxylic acid methyl ester:



The 2-bromoindole of example 2 (8.92 g, 26.5 mmol), 3-furanboronic acid (B.P. Roques et al. *J. Heterocycl. Chem.* **1975**, *12*, 195; 4.45 g, 39.79 mmol, 1.5 equivalent) and LiCl (2.25 g, 53 mmol, 2 equivalents) were dissolved in a mixture of EtOH (100 mL) and toluene (100 mL). A 1M aqueous Na_2CO_3 solution (66 mL, 66 mmol) was added and the mixture was degassed with argon for 45 min. $Pd(PPh_3)_4$ (3.06 g, 2.65 mmol, 0.1 equivalent) was added and the mixture stirred overnight at 75-85 °C under argon. Volatiles were removed under reduced pressure and the residue re-dissolved in EtOAc (500 mL). The solution was washed with water, saturated $NaHCO_3$ (100 mL) and brine (100 mL). After drying over a mixture of $MgSO_4$ and decolorizing charcoal, the mixture was filtered and concentrated under reduced pressure. The residual oil was triturated with a mixture of TBME (20 mL) and hexane (40 mL), cooled in ice and the precipitated solid collected by filtration, washed with cold 25% TBME in hexane, and dried (3.09 g). The filtrate and washings from the above trituration were combined, concentrated and purified by flash chromatography using 10-25% EtOAc in hexane to give an additional 4.36 g of product. The total yield of the 2-(3-furyl)indole of example 3 was 8.25 g.

EXAMPLE 4:



Methyl 3-cyclohexyl-1-methyl-6-indole carboxylate:

Methyl 3-cyclohexyl-6-indole carboxylate from example 2 (150.00 g, 0.583 mole) was charged into a 3 L three-necked flask equipped with a mechanical stirrer and purged with nitrogen gas. DMF (1 L) was added and the solution was cooled in an ice-bath. NaH (60% oil dispersion, 30.35 g, 0.759 mole, 1.3 equivalent) was added in small portions (15 min) and the mixture was stirred for 1 h in the cold. Iodomethane (54.5 mL, 0.876 mole, 1.5 equivalent) was added in small portions, maintaining an internal temperature between 5 – 10 °C. The reaction mixture was then stirred overnight at room temperature. The reaction was quenched by pouring into ice-water (3 L), resulting in the formation of a cream-colored precipitate. The material was collected by filtration, washed with water and dried in vacuum at 45 °C (137.3 g, 86% yield).

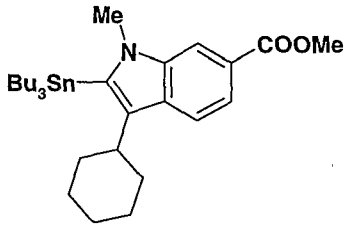
Methyl 2-bromo-3-cyclohexyl-1-methyl-6-indole carboxylate:

The 1-methylindole derivative from above (136.40 g, 0.503 mole) was charged into a 5 L three-necked flask equipped with a mechanical stirrer and purged with nitrogen gas. $CHCl_3$ (750 mL) and THF (750 mL) were added and the solution was cooled to 0 °C. Pyridine tribromide (pyridinium bromide perbromide, 185.13 g, 0.579 mole, 1.15 equivalent) was added in small portions and the mixture was stirred for 1 h at 0 °C. The solvent was removed under reduced pressure at room temperature and the residue dissolved in EtOAc (3 L). The solution was washed with water and brine, dried (decolourising charcoal / $MgSO_4$) and concentrated under reduced pressure.

The residue was suspended in TBME and heated to 50 °C. The suspension was stored overnight in the refrigerator and the cream-coloured crystalline product was collected by filtration. It was washed with TBME and dried in vacuum (134.3 g, 76% yield).

EXAMPLE 5:

Cyclohexyl-methyl-tributylstannanyl-1H-indole-6-carboxylic acid methyl ester:



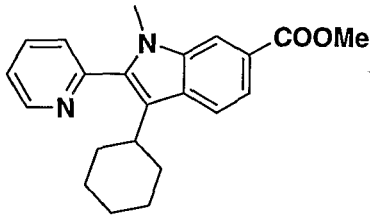
The bromoindole derivative of example 4 (2.70 g, 7.71 mmol) was dissolved in dry THF (40 mL) and the solution was cooled to –78 °C under an argon atmosphere. A solution of nBuLi in hexane (1.4 M, 6.90 mL, 9.64 mmol, 1.25 equivalent) was added dropwise over 15 min and stirring at low temperature was continued for 75 min. To the resulting suspension was added nBu_3SnCl (2.93 mL, 10.8 mmol, 1.4 equivalent) over 5 min. The suspension dissolved and the solution was stirred for 1 h at –78 °C. The reaction mixture was warmed to room temperature and THF removed under reduced pressure. The residue was dissolved in TBME (150 mL), washed with 1:1 brine – water and dried over $MgSO_4$. The material was purified by chromatography on silica gel that was previously deactivated by mixing with a solution of 5% Et_3N in hexane. The same solvent was used as eluent for the chromatography. The title stannane was isolated as a yellow oil (3.42 g, 79 % yield).

EXAMPLE 6:

General procedure for Stille cross-coupling of the 2-stannane indole of example 5 with aromatic/heteroaromatic halides:

Cross-coupling of aromatic/heteroaromatic halides or pseudohalides (preferably bromides, iodides and triflates) with the stannane derivative of example 5 can be performed using any variations of the standard metal-catalyzed Stille cross-coupling reaction as described in the literature. The following example serves to illustrate such a process.

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:

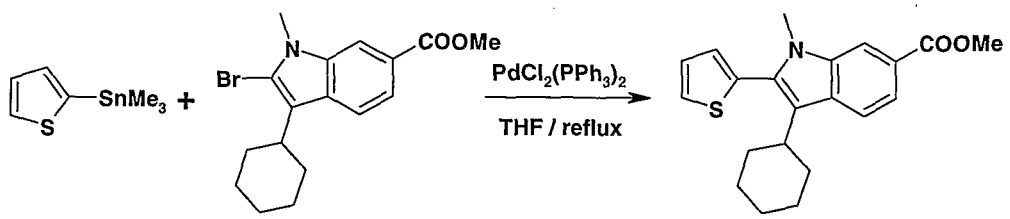


The stannane derivative of example 5 (3.42 g, 6.1 mmol) was dissolved in DMF (10 mL) and CuI (0.116 g, 0.61 mmol, 0.1 equivalent), LiCl (0.517 g, 12.21 mmol, 2 equivalent), triphenylphosphine (0.320 g, 1.22 mmol, 0,2 equivalent) and 2-bromopyridine (0.757 mL, 7.94 mmol, 1.3 equivalent) were added. The solution was degassed with a stream of argon (30 min) and $Pd(PPh_3)_4$ (0.352 g, 0.31 mmol, 0.05 equivalent) was added. After purging with argon for an additional 10 min, the solution was heated and stirred at 100 °C overnight under argon. The DMF was then removed under vacuum and the residue dissolved in EtOAc (150 mL). The solution was washed with 1N NaOH (25 mL) and brine (25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography eluting with $CHCl_3$ then 5-10% EtOAc in $CHCl_3$ (1.516 g, 71% yield).

EXAMPLE 7:

General procedure for Stille cross-coupling of 2-bromoindoles with aryl or heteroarylstannanes:

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:



The 2-bromoindole derivative of example 4 (0.150 g, 0.428 mmol) and 2-trimethylstannylthiophene (S.F. Thames et al. J. Organometal. Chem. 1972, 38, 29; 0.150 g, 0.61 mmol, 1.4 equivalent) were dissolved in dry THF (7 mL) in a sealed

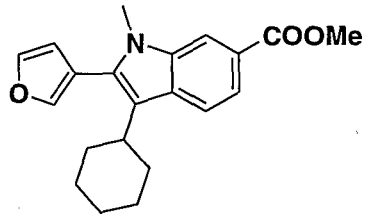
tube, and the solution was degassed with a stream or argon for 30 min. $Pd(Cl)_2(PPh_3)_2$ (0.018 g, 0.026 mmol, 0.06 equivalent was added and the tube sealed. The solution was heated to 80 °C for 40 h. The reaction mixture was cooled to room temperature, EtOAc (10 mL) was added and the suspension filtered. After evaporation of the solvent, the residue was re-submitted to the reaction conditions for an additional 20 h, with fresh 2-stannylthiophene (0.150 g, 0.61 mmol) and catalyst (0.020 g). After cooling to room temperature and filtration of solids, the solvent was evaporated and the residue purified by flash chromatography using 15-100% $CHCl_3$ in hexane as eluent (0.133 g, 88% yield).

The same procedure can be used to couple stannane derivatives to the 2-bromoindole of Example 2.

EXAMPLE 8:

General procedure for the N-alkylation of 2-aryl and 2-heteroaryl-6-indole carboxylates:

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:



NaH (60% oil dispersion, 0.186 g, 4.64 mmol, 1.5 equivalent) was washed with hexane (20 mL) to remove the oil and then re-suspended in DMF (5 mL). After cooling to 0 °C in an ice bath, the indole derivative of example 3 (1.000 g, 3.09 mmol) was added dropwise as a solution in DMF (3 mL + 2 mL rinse). After stirring for 15 min, iodomethane (0.385 mL, 6.18 mmol, 2 equivalents) was added in one portion and the mixture was stirred for 2 h in the cold and an additional 2 h at room temperature. The reaction was then quenched by addition of 1N HCl (1 mL) and diluted with TBME (100 mL). The solution was washed with 1N HCl (25 mL) and dried ($MgSO_4$). After removal of volatiles under reduced pressure, the residue was purified by flash chromatography using 5-10% EtOAc in hexane as eluent to give the title compound as a white solid (0.903 g, 86% yield).

Other *N*-alkylindole derivatives within the scope of this invention could be prepared from the appropriate electrophiles (e.g. EtI, iPrI, iBuI, BnBr) using a similar

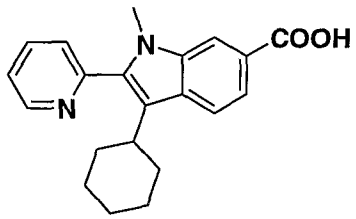
procedure.

EXAMPLE 9:

General procedure for the saponification of 6-indolecarboxylates to the corresponding free carboxylic acids:

This procedure applies to both indole and *N*-methylindole carboxylates.

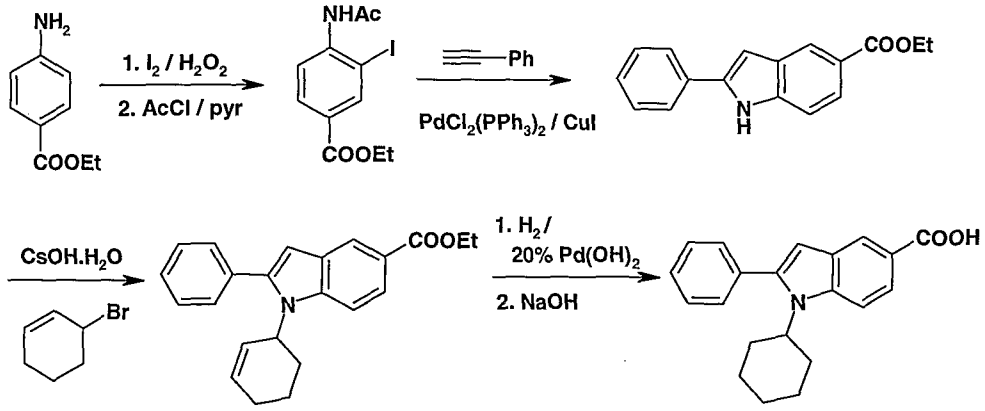
3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid:



The 6-indole carboxylate of example 6 (1.517 g, 4.35 mmol) was dissolved in DMSO (8 mL) and 5N NaOH (4.4 mL) was added. The mixture was stirred at 50 °C for 30 min. The solution was then cooled to room temperature and added dropwise to water (15 mL). Insoluble black impurities were removed by filtration and AcOH (2 mL) was added dropwise to the filtrate. The white precipitate that formed was collected by filtration, washed with water and dried (1.37 g, 94% yield).

EXAMPLE 10:

1-Cyclohexyl-2-phenyl-1H-indole-5-carboxylic acid:



Ethyl 4-amino-3-iodobenzoate:

Ethyl 4-aminobenzoate (15.00 g, 91 mmol) and iodine (11.80 g, 46.5 mmol) were mixed with water (80 mL) and chlorobenzene (4.60 g, 41 mmol). The mixture was stirred while the temperature was gradually raised to 90 °C over 30 min. Hydrogen peroxide (30%, 50 mL) was added over 10 h at 90 °C. After stirring at that temperature for an additional 6 h, the mixture was cooled and the solution decanted from the residual solids. The solids were dissolved in DCM and the solution washed successively with sodium thiosulfate and brine. After drying ($MgSO_4$), the solvent was removed under reduced pressure and the resulting brown solid was triturated with hexane to remove di-iodinated by-products. The desired compound was obtained as a brown solid (22.85 g, 86% yield).

Ethyl 4-acetamido-3-iodobenzoate:

The aniline from above (1.00 g, 3.44 mmol) was dissolved in pyridine (5 mL) and the solution was cooled in ice. AcCl (0.32 mL, 4.47 mmol, 1.3 equivalent) was added dropwise and the mixture was stirred for 1 h at 0 °C and 2 h at room temperature. The reaction mixture was then diluted with 1 N HCl and the product was extracted with TBME (100 mL). The organic phase was washed with 1N HCl (50 mL), dried ($MgSO_4$) and concentrated to give the desired material as a tan-colored solid (1.121 g, 97% yield).

Ethyl 2-phenyl-indole-5-carboxylate:

Following the procedure of A. Bedeschi et al. (*Tet. Lett.* **1997**, *38*, 2307), the acetanilide derivative from above (0.900 g, 2.7 mmol) was reacted with phenylacetylene (0.385 mL, 3.5 mmol, 1.3 equivalent) in the presence of $PdCl_2(PPh_3)_2$ (10 mole %) and CuI (10 mole %) in a mixture of dioxane (5 mL) and tetramethylguanidine (5 mL). The desired 2-phenylindole (0.589 g, 82% yield) was isolated as a yellow solid after flash chromatography with 15% EtOAc in hexane.

1-Cyclohex-1-enyl-2-phenyl-1H-indole-5-carboxylic acid ethyl ester:

The 2-phenylindole derivative from above (0.265 g, 1.0 mmol) was dissolved in DMF (2 mL) and cesium hydroxide monohydrate (0.208 g, 1.2 mmol, 1.2 equivalent) was added. The solution was cooled in an ice bath and 3-bromocyclohexene (0.193 g, 1.2 mmol, 1.2 equivalent) was added dropwise (5 min) as a solution in DMF (1 mL). The mixture was stirred for 30 min at 0 °C. The reaction was diluted with water (25 mL), extracted with Et_2O (2 x 50 mL) and the extract dried over $MgSO_4$. The solvent

was evaporated under reduced pressure to give a white foam (0.095 g) that was used without purification in the next step.

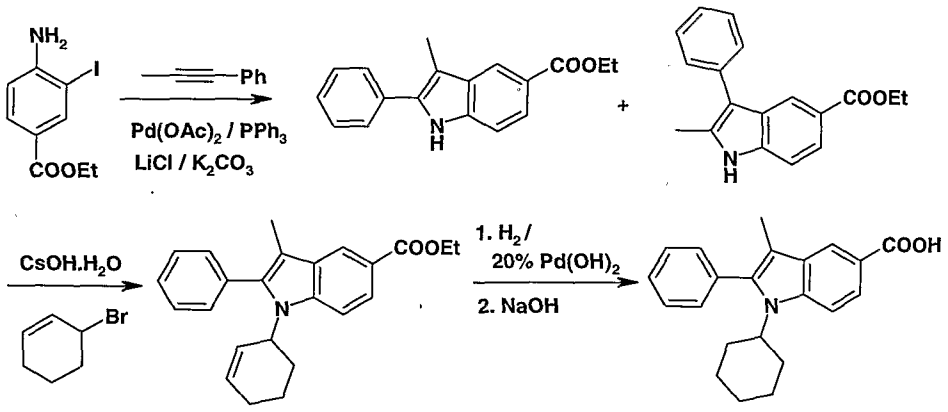
1-Cyclohexyl-2-phenyl-1H-indole-5-carboxylic acid:

The crude indole from above was hydrogenated in the usual way (1 atm H_2 gas) in EtOH over 20% $Pd(OH)_2$ on carbon for 20 h at room temperature. After filtration of the catalyst, the EtOH was removed under reduced pressure.

The residue was dissolved in a mixture of MeOH (1 mL) and DMSO (1 mL) and 5N NaOH (0.5 mL) was added. The mixture was stirred overnight at 50 °C. The reaction mixture was cooled and water (10 mL) was added. After acidification with 1N HCl, the product was extracted into Et_2O (70 mL) and the solution dried (Na_2SO_4). Evaporation of the solvent gave a green residue consisting of a 2:1 mixture (85 mg) of the desired 1-cyclohexyl-2-phenylindole-5-carboxylic acid and 1,3-dicyclohexyl-2-phenylindole-5-carboxylic acid.

EXAMPLE 11:

1-Cyclohexyl-3-methyl-2-phenyl-1H-indole-5-carboxylic acid:



Ethyl 2-phenyl-3-methyl-indole-5-carboxylate:

Adapting the procedure of H.-C. Zhang (*Tet. Lett.* **1997**, *38*, 2439) ethyl 4-amino-3-iodobenzoate (from example 10, 0.500 g, 1.72 mmol) was dissolved in DMF (5 mL) and LiCl (0.073 g, 1.72 mmol, 1 equivalent), PPh_3 (0.090 g, 0.34 mmol, 0.2 equivalent), K_2CO_3 (1.188 g, 8.6 mmol, 5 equivalents) and phenylpropyne (0.645 mL, 5.76 mmol, 3 equivalents) were added. The solution was degassed by purging with argon for 1 h and palladium acetate (0.039 g, 0.17 mmol, 0.1 equivalent) was added. The mixture was stirred at 80 °C under argon for 20 h. The reaction mixture was

diluted with water (25 mL) and extracted with EtOAc (50 mL). The extract was washed with brine (3 x 25 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography with 10-15% EtOAc – hexane gave the desired 2-phenyl-3-methyl indole (0.275 g, least polar component) and the 3-phenyl-2-methyl isomer (0.109 g, more polar component).

Ethyl 1-(3-cyclohexenyl)-3-methyl-2-phenylindole-5-carboxylate:

The less polar isomer from above (0.264 g, 0.95 mmol) was dissolved in DMSO (2 mL) and cesium hydroxide monohydrate (0.191 g, 1.14 mmol, 1.2 equivalent) was added followed by 3-bromocyclohexene (0.183 g, 1.14 mmol, 1.2 equivalent in 0.7 mL of DMSO). The mixture was stirred at room temperature for 30 min. Additional CsOH monohydrate (0.400 g, 2.4 equivalents) and 3-bromocyclohexene (0.400 g, 2.4 equivalents) were added and stirring continued for an additional 30 min. Similar amounts of the two reagents were again added and after another 30 min of stirring at room temperature, the reaction was diluted with 1N HCl (6 mL) and water (20 mL). The product was extracted with TBME (100 mL), dried ($MgSO_4$) and after concentration under reduced pressure, the residue was purified by flash chromatography using 5-10% EtOAc in hexane as eluent. The desired *N*-alkylated indole was obtained (0.130 g).

Ethyl 1-cyclohexyl-3-methyl-2-phenylindole-5-carboxylate:

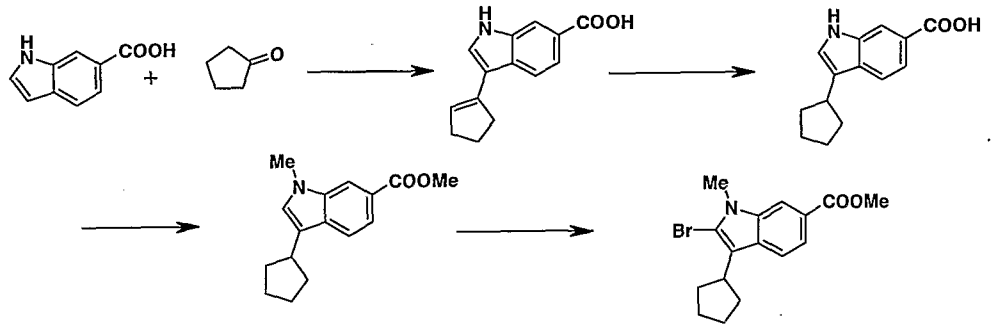
The unsaturated product from above was hydrogenated (1 atm H_2 gas) in the usual way over 20% $Pd(OH)_2$ in EtOH at room temperature for 3 h.

1-Cyclohexyl-3-methyl-2-phenyl-1H-indole-5-carboxylic acid:

The hydrogenated material from above was dissolved in a mixture of DMSO (2 mL) and MeOH (2 mL). 5N NaOH (0.5 mL) was added and the mixture was stirred overnight at 60 °C. After dilution with water (40 mL), the product aqueous phase was washed with a 1:1 mixture of Et_2O – hexane (50 mL) and then acidified with 1N HCl to pH 1. The liberated free acid was extracted with diethyl ether (2 x 50 mL) and the extract dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the desired indole as a light brown solid (0.074 g).

EXAMPLE 12:

2-Bromo-3-cyclopentyl-1-methyl-1H-indole-6-carboxylic acid methyl ester:



A 3 L three-necked flask equipped with a mechanical stirrer was charged with indole 6-carboxylic acid (220 g, 1.365 mole) and KOH pellets (764.45 g, 13.65 mole, 10 equivalents). Water (660 mL) and MeOH (660 mL) were added and the mixture heated to 75 °C. Cyclopentanone (603.7 mL, 6.825 mole, 5 equivalents) was added dropwise over 18 h using a pump. The reaction mixture was heated for an additional 3 h (after which the reaction was judged complete by HPLC) and cooled to 0 °C for 1 h. The precipitated potassium salt is collected by filtration, and washed with TBME (2 X 500 mL) to remove cyclopentanone self-condensation products. The brown solid was re-dissolved in water (2.5 L) and the solution washed with TBME (2 X 1 L). Following acidification to pH 3 with conc. HCl (425 mL), the beige precipitate was collected by filtration, washed with water (2 X 1 L) and dried under vacuum at 70 °C. The crude product weighed 275.9 g (88.9 % mass recovery) and had an homogeneity of 85% (HPLC).

The crude product from above (159.56 g, 0.70 mole) was dissolved in MeOH (750 mL) and 20% $Pd(OH)_2$ on charcoal (8.00 g) was added. The mixture was hydrogenated in a Parr apparatus under 50 psi hydrogen gas for 18 h. After completion, the catalyst was removed by filtration through celite and the solvent removed under reduced pressure. The resulting brown solid was dried at 70 °C under vacuum for 12 h. The crude product (153.2 g) was obtained as a brown solid and was 77% homogeneous by HPLC.

The crude 3-cyclopentylindole-6-carboxylic acid (74.00 g, 0.323 mole) was charged in a 3 L three-necked flask equipped with a mechanical stirrer and a thermometer. The system was purged with nitrogen gas and anhydrous DMF (740 mL) was added. After dissolution on the starting material, anhydrous potassium carbonate (66.91 g, 0.484 mole, 1.5 equivalent) was added and the mixture stirred for 5 minutes. Iodomethane (50 mL, 0.807 mole, 2.5 equivalents) was added and the mixture

stirred for 5 h after which HPLC analysis of the reaction mixture indicated 97% conversion to the methyl ester.

The reaction mixture was cooled in an ice bath and sodium hydride (95%, oil-free, 10.10 g, 0.420 mole, 1.3 equivalent) was added in small portions over 3 min (exothermic: 8 °C to 30 °C internal temperature raise). After stirring for an additional 15 min, the cooling bath was removed and stirring continued for 1.5 h at room temperature after which no further progression was observed (HPLC). Additional NaH (1.55 g, 65 mmol, 0.2 equivalent) and iodomethane (1.0 mL, 16 mmol, 0.05 equivalent) were added and after stirring for 15 min, the reaction was judged complete by HPLC (96% N-methylated).

The reaction mixture was slowly (2 min) poured into water (4 L) with vigorous stirring and after 10 min, acidified to pH <2 with conc. HCl (85 mL). The mixture was stirred for 5 min to allow complete conversion of any remaining potassium carbonate and bicarbonate to the more soluble chloride. The pH was adjusted to ~7 with 4N NaOH (40 mL) and the mixture stirred overnight at room temperature. The precipitated material was collected by filtration, washed with water (600 mL) and dried at 60 °C under vacuum. The crude product (79% homogeneity by HPLC) was obtained as a brown solid (72.9 g).

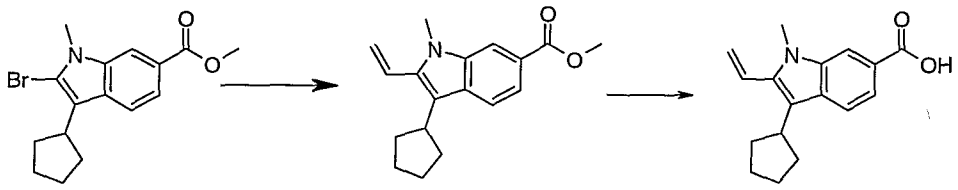
The crude material from above is triturated with a minimal amount of MeOH to remove a series of minor impurities. The solid was then collected by filtration and dissolved in a minimal amount of hot EtOAc. After cooling to room temperature, hexane was added (5 X volume) and the mixture cooled in ice and filtered. The filtrate was then evaporated to dryness to give the desired product.

The *N*-methylindole from above (10.60 g, 41.2 mmol) was dissolved in isopropyl acetate (150 mL) and sodium acetate (5.07 g, 62 mmol, 1.5 equivalent) was added. The suspension was cooled in an ice bath and bromine (2.217 mL, 43.3 mmol, 1.05 equivalent) was added dropwise over 2 min. The pale amber suspension turned dark red (exotherm from 5 °C to 13 °C). It was stirred for 1 h at 0 °C. The reaction was completed by adding additional bromine (0.21 mL, 4.2 mmol, 0.10 equivalent) as shown by HPLC analysis. The reaction was then quenched by addition of 10% aqueous sodium sulfite solution (15 mL), followed by water (50 mL) and K_2CO_3 (10.6 g, 1.8 equivalent) to neutralize HBr. The organic layer was separated, washed with 10% aqueous sodium sulfite and aqueous K_2CO_3 and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue co-evaporated with TBME (75

mL) to give a beige solid that was dried under vacuum overnight (13.80 g). The crude material was triturated with boiling MeOH (80 mL) for 30 min, cooled in ice and the beige solid collected by filtration. The product was dried at 60 °C under vacuum (10.53 g, 76% recovery).

EXAMPLE 13

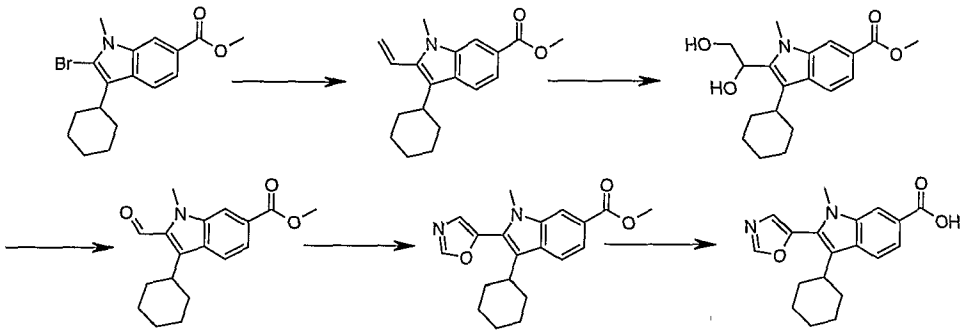
3-Cyclopentyl-1-methyl-2-vinyl-1H-indole-6-carboxylic acid:



To the 2-bromoindole derivative of example 12 (2.044 g, 6.08 mmol) in dry dioxane (20 mL) was added vinyltributyltin (1.954 mL, 6.69 mmol). The solution was degassed by bubbling nitrogen for 15 min. Then bis(triphenylphosphine) palladium (II) chloride (213.4 mg, 0.304 mmol) was added and the reaction mixture was heated at 100 °C overnight. The reaction mixture was diluted with ether and successively washed with water and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (5 cm, 10% AcOEt-hexane) to afford the desired compound (1.32 g, 4.70 mmol, 77 % yield) as a white solid. To the ester from above (153 mg, 0.54 mmol) in a mixture of THF (2.8 mL) and methanol (1.4 mL) was added an aqueous solution of lithium hydroxide (226.6 mg, 5.40 mmol in 1.6 mL of water). The reaction mixture was stirred at 50 °C for 1.5 h and diluted with water. The aqueous layer was acidified with 1M aq. HCl and extracted three times with CH_2Cl_2. The combined organic layers were successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the desired crude acid was isolated (150 mg).

EXAMPLE 14

3-Cyclohexyl-1-methyl-2-oxazol-5-yl-1H-indole-6-carboxylic acid:



To the bromide of example 4 (1.00 g, 2.855 mmol) in dry dioxane (10 mL) was added vinyltributyltin (917.8 µL, 3.141 mmol). The solution was degassed by bubbling nitrogen through for 15 min. Then bis(triphenylphosphine) palladium (II) chloride (101 mg, 0.144 mmol) was added and the solution was refluxed for 7 hrs. The reaction mixture was diluted with ether and successively washed with water and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (5 cm, hexane to 2.5% AcOEt to 5% AcOEt to 10% AcOEt-hexane) to afford the desired compound (773 mg, 2.60 mmol, 91 % yield) as a pale yellow solid.

To the olefinic derivative from above (100 mg, 0.336 mmol) in a mixture of acetone (690 µL), *tert*-butanol (690 µL) and water (690 µL) were successively added *N*-methylmorpholine *N*-oxide (NMMO; 48 mg, 0.410 mmol) and a 2.5 % solution of osmium tetroxide in *tert*-butanol (33 µL). The reaction mixture was stirred at room temperature for three days and then concentrated. The residue was dissolved in EtOAc and successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude diol (117 mg) was isolated.

To the crude diol obtained above (*ca.* 0.336 mmol) in a mixture of THF (3.2 mL) and water (3.2 mL) at 0 °C was added sodium periodate (86.2 mg, 0.403 mmol). The cooling bath was then removed and the reaction mixture was stirred at room temperature for 1h 45 min. AcOEt was then added. The resulting solution was successively washed with 10% aq. citric acid, water, satd aq. $NaHCO_3$, water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude desired aldehyde was isolated (92 mg, 0.307 mmol, 91 % yield).

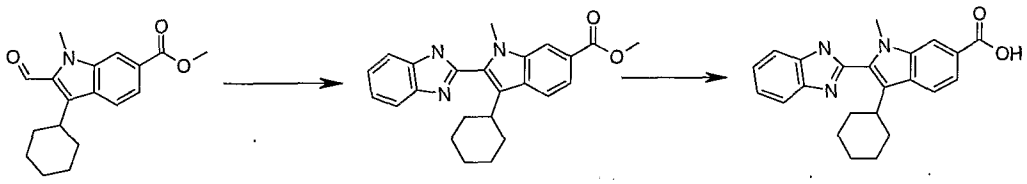
A mixture of the aldehyde from above (25.8 mg, 0.086 mmol), anhydrous potassium

carbonate (12.4 mg, 0.090 mmol) and Tosmic (17.57 mg, 0.090 mmol) in absolute MeOH (500 µL) was refluxed for 2 h. AcOEt was then added and the mixture was successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude desired oxazole was isolated (28 mg, 0.083 mmol, 96 % yield).

To the ester from above (28 mg, 0.083 mmol) in a mixture of THF (425 µL), MeOH (210 µL) and water (250 µL) was added lithium hydroxide (34.8 mg, 0.830 mmol). The reaction mixture was stirred overnight at room temperature, then diluted with water and acidified with a 1N aq. HCl solution. The aqueous layer was extracted with dichloromethane (3X) and successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the title crude acid was isolated (30 mg).

EXAMPLE 15

2-(1H-Benzimidazol-2-yl)-3-cyclohexyl-1-methyl-1H-indole-6-carboxylic acid:



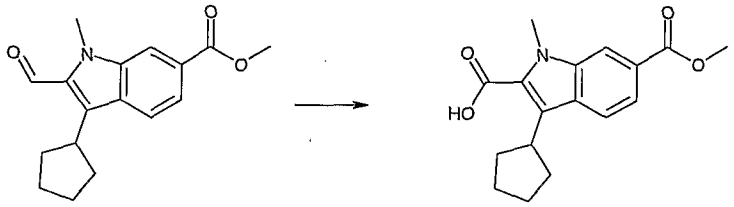
To a mixture of the aldehyde from example 14 (28 mg, 0.094 mmol) and 1,2-diaminobenzene (10.9 mg, 0.101 mmol) in acetonitrile (500 µL) and DMF (200 µL) was added chloranil (24.8 mg, 0.101 mmol). The reaction mixture was stirred at room temperature for three days. AcOEt was added and the reaction mixture was successively washed with a 1N aq. NaOH solution (2X), water (4X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (1 cm, 30% AcOEt-hexane) to afford the desired benzimidazole ester derivative (11 mg, 0.028 mmol, 30 % yield).

To the ester from above (11 mg, 0.028 mmol) in a mixture of THF (240 µL), MeOH (120 µL) and water (140 µL) was added lithium hydroxide (11.7 mg, 0.280 mmol). The reaction mixture was stirred overnight at room temperature, then diluted with water and acidified with a 1N aq. HCl solution. The aqueous layer was extracted with dichloromethane (3X) and successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the title crude acid was isolated

(9 mg, 0.0241 mmol, 86 % yield).

EXAMPLE 16

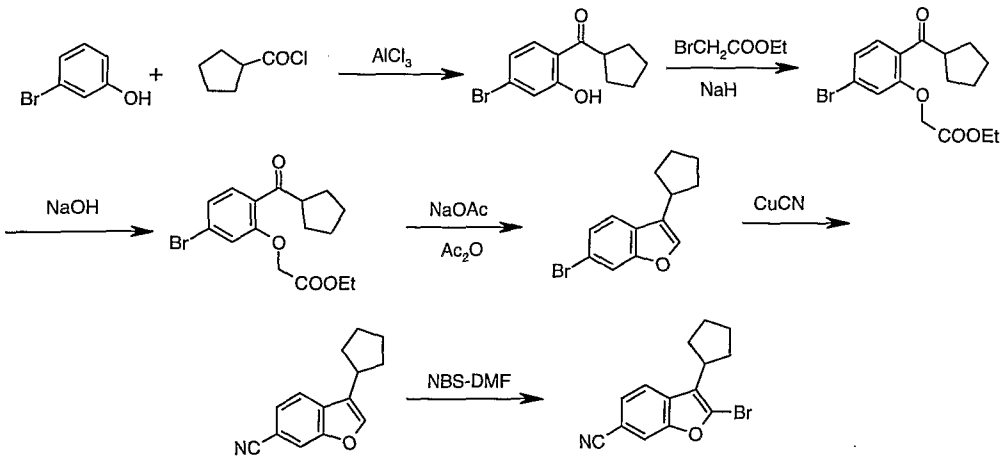
3-Cyclopentyl-1-methyl-1H-indole-2,6-dicarboxylic acid 6-methyl ester:



To the 3-cyclopentyl aldehyde prepared in a similar fashion to that described in example 15 (20 mg. 0.07 mmol) and 2-methyl-2-butene (541 µL, 5.11 mmol) in tert-butanol (500 µL) at 0 °C was added a freshly prepared solution of sodium chlorite (64.2 mg, 0.711 mmol) in phosphate buffer (98 mg of NaH_2PO_4 in 150 µL of water). The reaction mixture was stirred for 45 min. at room temperature then brine was added. The aqueous layer was extracted twice with EtOAc. The combined organic layer was successively washed with a 0.5 N aq. HCl solution and brine. After the usual treatment ($MgSO_4$, filtration and concentration) 23.1 mg of the desired crude acid were isolated as a yellow solid.

EXAMPLE 17

2-Bromo-3-cyclopentyl-benzofuran-6-carbonitrile:



To a solution of 3-bromophenol (10 g, 57.8 mmol) in 1,2-dichloroethane (50 mL) was added $AlCl_3$ (11.5 g, 86.2 mmol), cautiously, in two equal portions at room temperature. Cyclopentanecarbonyl chloride (7.7 g, 58.1 mmol) was then added dropwise via syringe at room temperature. The reaction solution was then heated to

reflux under N_2 for a period of 2 hours. The reaction solution was cooled to room temperature and carefully poured into 100 ml of 1N HCl ice slush. After a few minutes of gentle stirring, the phases were separated and the aqueous phase was extracted with 1,2-dichloroethane. The organic phases were combined and washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified on a pad of silica gel by hexanes. 17.2 g (78%) of the product was collected as a yellow liquid / low melting solid.

To a solution of the above phenol (12.2 g, 45.3 mmol) in 80 mL DMF at 0°C was added 60% NaH (2.67 g, 66.7 mmol). The ice bath was removed and the reaction solution was allowed to stir for 30 minutes. Ethyl Bromoacetate (11.4 g, 68.3 mmol) was then added dropwise via syringe. A mild exotherm (~40 °C) was observed, and the reaction solution was allowed to stir at room temperature for 1 hour. The reaction mixture was carefully poured into 150 ml of ice water, then acidified to pH 4-5 with 1N HCl. The reaction mixture was then extracted with EtOAc. The phases were separated and the organic fraction was washed with saturated $NaHCO_3$, water and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude material was taken to next step as is and treated as theoretical in yield.

16.1 g (45.3 mmol) of the above crude ester was combined with 61 mL of 1N NaOH and 137 mL of THF and stirred at room temperature overnight (additional 1N NaOH may be added if starting material persists.) Upon hydrolysis the THF was stripped off and the aqueous phase was extracted with EtOAc, which was discarded. The aqueous phase was then acidified to pH 2-3 with 1N HCl and extracted with EtOAc. The phases were separated and the organic phase was washed with water and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude material was taken to the next step as is and treated as theoretical in yield.

13.3 g (40.7 mmol) of the crude acid from above was dissolved in 200 mL Ac_2O. NaOAc (6.7 g, 81.7 mmol) was added and the resulting mixture was refluxed for 5 hours under N_2. The heat was removed and the reaction mixture was allowed to cool to room temperature. The reaction solution was then diluted with 100 mL toluene and neutralized with ice / 6N NaOH (STRONG EXOTHERM!). The phases were separated and the aqueous phase was extracted with EtOAc. The organic fractions were combined and washed with water and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified on a

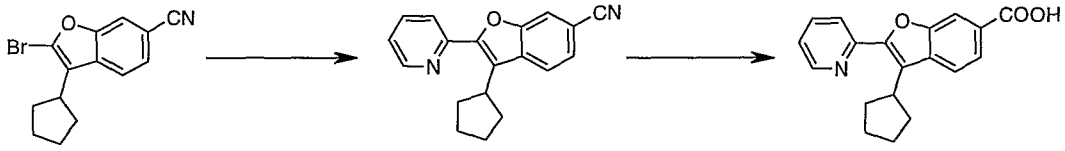
pad of silica gel by petroleum ether. 7.8 g (72%) of product was collected as a clear liquid / low melting solid.

The bromobenzofuran from above (29.6 g, 111.6 mmol) was dissolved in 60 mL DMF. CuCN (12.0 g, 134.0 mmol) was added and the resulting mixture was refluxed under N_2 for 7 hours. The heat was removed and the reaction mixture was allowed to cool to room temperature. The reaction solution was poured into 300 mL of 5% aqueous NaCN, and 200 mL of EtOAc was added. The resulting solution was stirred gently until all solids went into solution. The layers were separated and the aqueous fraction was extracted with EtOAc. The organic fractions were combined and washed with 5% aqueous NaCN, water and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude brown solid was cleaned up on a pad of silica gel by 10% EtOAc / Hexanes, and then purified by recrystallization in hexanes.

A solution of *N*-bromosuccinimide (5.340 g, 30 mmol) in DMF (20 mL) was added dropwise to a solution of the above benzofuran derivative (2.00 g, 9.47 mmol) in DMF (20 mL). The mixture was stirred overnight at room temperature after which the bromination was judged complete (HPLC). The reaction mixture was diluted with EtOAc and washed successively with water (3 X) and brine. After drying ($MgSO_4$), the solvent was removed under reduced pressure and the residue purified by flash chromatography using 3 % EtOAc in hexane to give the title 2-bromobenzofuran derivative as a white solid (1.45 g, 53 % yield).

EXAMPLE 18

3-Cyclopentyl-2-pyridin-2-yl-benzofuran-6-carboxylic acid:

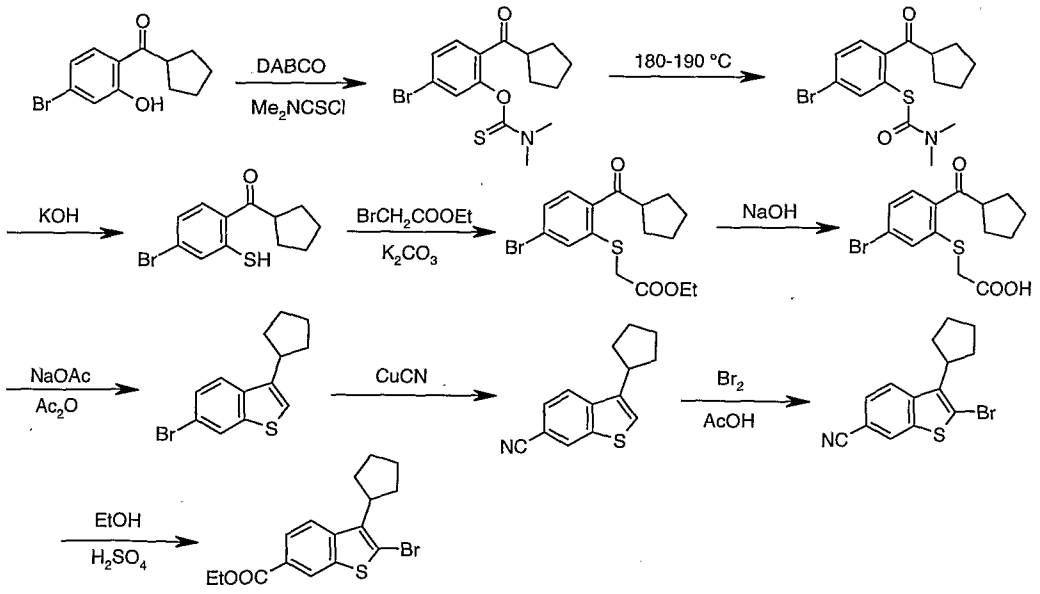


The 2-bromobenzofuran derivative of example 17 (0.850 g, 2.93 mmol), 2-tri(n-butyl)stannylpyridine (1.362 g, 3.7 mmol), triphenylphosphine (0.760 g, 2.90 mmol), lithium chloride (0.250 g, 5.9 mmol) and CuI (0.057 g, 0.3 mmol) were dissolved in DMF (30 mL) and the mixture was degassed by bubbling argon for 30 min. Tetrakis (triphenylphosphine)palladium (0.208 g, 0.18 mmol) was added and the mixture stirred at 100 °C under an argon atmosphere. After 19 h, the reaction was cooled to room temperature, poured into water (70 mL) and extracted with TBME. The organic

phase was washed with water (2 X) and brine, dried ($MgSO_4$) and concentrated to give a residue that was purified by flash chromatography. The desired 2(2-pyridyl)benzofuran derivative (0.536 g, 63 % yield) was obtained as a white solid. The nitrile from above (0.200 g, 0.694 mmol) was suspended in a mixture of conc. H_2SO_4 (5 mL), AcOH (4 mL) and water (2 mL). After refluxing for 1.5 h, TLC showed complete hydrolysis. The mixture was cooled in ice and the 10 N NaOH was added dropwise to pH 9. The aqueous layer was washed with dichloromethane and then acidified to pH 6 with 5 N HCl. The product was extracted with EtOAc, dried ($MgSO_4$) and solvents removed under reduced pressure. The desired carboxylic acid was obtained as a white solid.

EXAMPLE 19

2-Bromo-3-cyclopentyl-benzo[b]thiophene-6-carboxylic acid ethyl ester



To a solution of 3-bromo-6-cyclopentanecarbonylphenol of Example 17 (5.194 g, 19.30 mmol) in DMF (58.0 mL) was added 1,4-diazabicyclo[2.2.2]octane (4.33 g, 38.60 mmol) and dimethylthiocarbamyl chloride (4.77 g, 38.6 mmol) at room temperature. The mixture was stirred at room temperature for 3 hr. The mixture was acidified with 1 N HCl to pH 3 and then extracted with EtOAc. The organic layers were combined and washed with brine and dried over $MgSO_4$. The crude mixture was purified through a plug of silica gel with 3%EtOAc/hexanes to provide 6.976 g (100%) of the desired thiocarbamate as a colorless oil.

The neat *O*-3-bromo-6-cyclopentanecarbonyl N,N-dimethylthiocarbamate from

above (43.147 g, 121.1 mmol) was heated to internal temperature of 180-190°C for 5 hr. TLC (20% EtOAc/hexanes: R_f 0.6 (starting material), 0.5 (product)) was used to monitor the reaction progress. The crude material was used for the next reaction without further purification.

The crude *S*-3-bromo-6-cyclopentanecarbonyl *N,N*-dimethylthiocarbamate from above was dissolved in MeOH (600 mL), KOH (40.0 g, 714 mmol) was added and the mixture was heated to reflux for 1.5 h. The mixture was cooled to room temperature and the solvent was removed by rotary evaporation. The residue was dissolved in water and acidified by 6 N HCl to pH 3. It was extracted with EtOAc and the crude product was purified by a silica gel chromatography with 1-5% EtOAc/hexanes. 31.3 g (91%) of the desired thiophenol derivative was obtained as a yellow oil.

To a solution of the 3-bromo-6-cyclopentanecarbonylthiophenol from above (0.314 g, 1.105 mmol) in acetone (5.0 mL) was added K_2CO_3 (0.477 g, 3.45 mmol) followed by addition of ethyl bromoacetate (0.221 g, 0.147 mL, 1.33 mmol). The mixture was stirred overnight. The reaction mixture was filtered through filter paper and the filtrate was concentrated. Purification by silica gel with 5% EtOAc/hexanes provided 0.334 g (82%) of the product as a colorless oil.

The crude ester from above was dissolved in THF (12.0 mL), 1 N NaOH (5.0 mL) was added at room temperature. The mixture was stirred at room temperature for 2-3 hr, or until TLC indicated complete reaction. The solvent was removed by rotary evaporation. Water was added and the mixture was acidified with 6 N HCl to pH 3 and extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was used without further purification.

To the crude acid from above was added acetic anhydride (16.0 mL), and then NaOAc (0.573 g) and the mixture was heated to reflux overnight. The mixture was cooled to room temperature and poured into a mixture of ice and toluene. 6 N NaOH was added until pH to about 7, and extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by silica gel with hexanes to provide 0.795 g (80%) of 6-bromo-3-cyclopentyl benzothiophene as a colorless oil.

A mixture of the 6-bromo-3-cyclopentylbenzothiophene from above (0.723 g, 2.57 mmol), and copper cyanide (0.272 g, 3.04 mmol) in DMF (1.4 mL) was heated to reflux overnight. The mixture was cooled to room temperature and diluted with

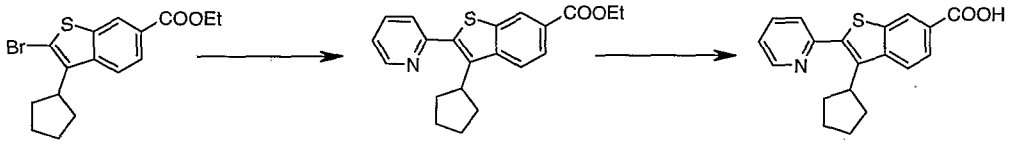
EtOAc. 2 N NH_4OH was added and the mixture was stirred for 10 minutes and filtered through Celite. The aqueous layer was extracted with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was used without further purification.

3-cyclopentyl-6-cyanobenzothiophene (17.65 g, 77.65 mmol) was dissolved in acetic acid (310 mL), bromine (49.64 g, 310.6 mmol) was added at room temperature. The mixture was stirred at room temperature overnight and HPLC was used to monitor the reaction progress. After the reaction was complete, toluene was added to the reaction mixture to remove acetic acid (3 x 100 mL). The crude product was dried under reduced pressure and used without further purification.

The crude cyano derivative from above was added to ethanol (150 mL, denatured) and conc. H_2SO_4 (45 mL) and the mixture heated to reflux for 1-2 days. After completion (HPLC) the reaction mixture was cooled to room temperature and poured into ice-water and extracted with dichloromethane (5 x 100 mL), the organic layers were combined and washed with 5% $NaHCO_3$, and brine. The solvent was removed under reduced pressure and the residue was purified with silica gel by 1% EtOAc/hexanes. The collected fractions were concentrated and the residue was slurried in methanol. The solid was filtered and washed with ice-cold methanol to provide 15.9 g (58%, two steps) of pure ethyl ester as a slight yellow solid.

EXAMPLE 20

3-Cyclopentyl-2-pyridin-2-yl-benzo[b]thiophene-6-carboxylic acid:



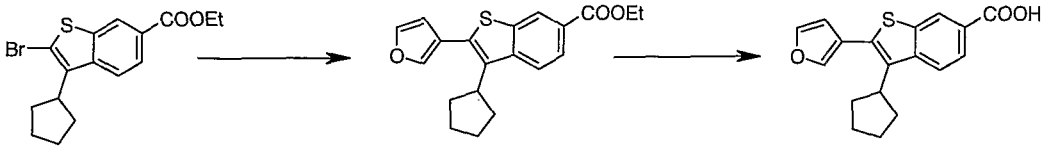
The 2-bromobenzothiophene of example 19 (0.354 g, 1.00 mmol), 2-tri(n-butyl)stannylpyridine (0.442 g, 1.2 mmol), triphenylphosphine (0.262 g, 1.00 mmol), lithium chloride (0.085 g, 2.0 mmol) and CuI (0.019 g, 0.1 mmol) were dissolved in DMF (10 mL) and the mixture was degassed by bubbling argon for 30 min. Tetrakis (triphenylphosphine)palladium (0.069 g, 0.06 mmol) was added and the mixture stirred at 100 °C under an argon atmosphere. After 24 h, the reaction was cooled to room temperature, poured into water (70 mL) and extracted with TBME. The organic phase was washed with water (2 X) and brine, dried ($MgSO_4$) and concentrated to

give a residue that was purified by flash chromatography. The desired 2(2-pyridyl)benzothiophene ester (0.197 g, 56 % yield) was obtained as a pale yellow waxy solid.

The ester from above was hydrolyzed in the usual manner using NaOH, to give the title acid that could be used directly or purified by HPLC and flash chromatography. The acid could be coupled to amine derivatives following the general procedure described in example 37.

EXAMPLE 21

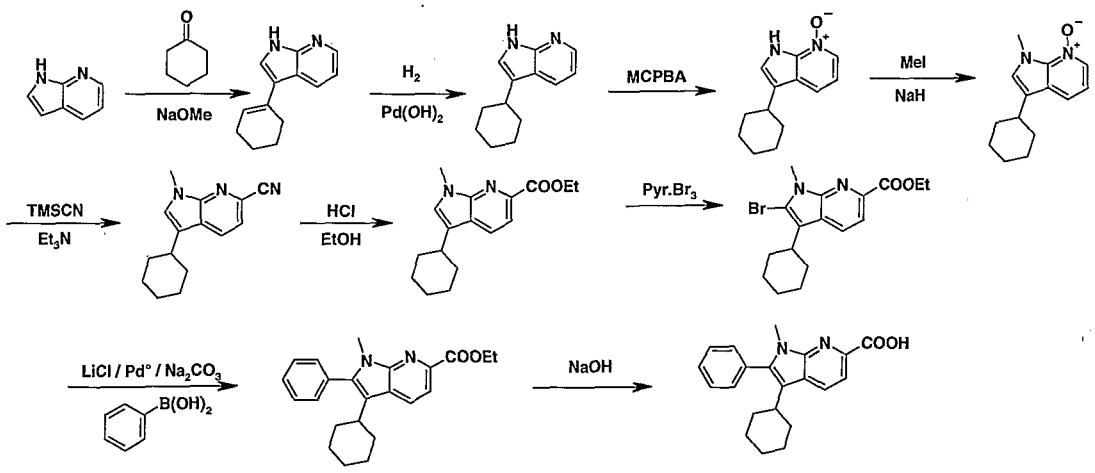
3-Cyclopentyl-2-furan-3-yl-benzo[b]thiophene-6-carboxylic acid:



The 2-bromobenzothiophene ester of example 19 was coupled to 3-furanboronic acid as described in example 3 to give the desired 2(3-furyl)benzothiophene ester in 85 % yield. Saponification of the ethyl ester was carried out with NaOH at room temperature to give the title carboxylic acid derivative.

EXAMPLE 22

3-Cyclohexyl-1-methyl-2-phenyl-1H-pyrrolo[2,3,b]pyridine-6-carboxylic acid:



7-Azaindole (15.00 g, .127 mole) was dissolved in MeOH (330 mL) and sodium methoxide (25% w/w in MeOH, 172 mL, 0.753 mole) and cyclohexanone (52.86 mL, 0.51 mole) were added. The mixture was refluxed for 60 h and then concentrated under reduced pressure. After cooling in ice-water, the reaction mixture was

acidified to pH 8 with 3N HCl and the precipitated solid was collected by filtration. The product was washed with water, triturated with TBME-hexane and dried by azeotroping with toluene (19.8 g).

The material from above (15.00 g, 75.65 mmol) was dissolved in a mixture of EtOH (130 mL) and THF (30 mL) and 20% $Pd(OH)_2$ on carbon (1.30 g) was added. The mixture was hydrogenated under 1 atm of H_2 gas for 24 h, after which point additional catalyst (1.30 g) was added. After stirring under H_2 gas for an additional 16 h, the catalyst was removed by filtration and the solution evaporated under reduced pressure to give a residue that was triturated with TBME to give an amber solid (13.9 g).

The azaindole derivative from above (7.50 g, 37.45 mmol) was dissolved in DME (130 mL) and *meta*-chloroperbenzoic acid (12.943 g, 60.0 mmol) was added. After stirring for 2 h, volatiles were removed under reduced pressure and the residue suspended in water (100 mL). The mixture was basified to pH 10 by addition of saturated aqueous Na_2CO_3 solution under vigorous stirring. The solid was then collected by filtration, washed with water and a small amount of TBME, and dried (7.90 g).

The crude N-oxide from above (4.00 g, 18.49 mmol) was dissolved in DMF (350 mL) and NaH (60% dispersion, 1.52 g, 38 mmol) was added in small portions over 5 min. The mixture was stirred for 30 min and iodomethane (1.183 mL, 19 mmol) was added dropwise over 20 min to the suspension. After stirring for 3 h at room temperature, no more progress was measured by HPLC analysis. The reaction mixture was poured into water and extracted 3 times with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and evaporated to give an amber solid (3.65 g, 60% homogeneity by NMR) that was used immediately without purification.

The crude product from above (0.80 g, 3.47 mmol) was dissolved in MeCN (10 mL). Triethylamine (1.13 mL, 8.1 mmol) was added followed by trimethylsilyl cyanide (2.13 mL, 16 mmol). The solution was then refluxed for 19 h. After cooling to room temperature, the reaction was quenched by slow addition of aqueous $NaHCO_3$ and the product extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated to a residue that was purified by flash chromatography on silica gel using 15% EtOAc-hexane (0.285 g).

The nitrile (0.300 g, 1.254 mmol) was suspended in EtOH (15 mL) and hydrogen chloride gas was bubbled through for 15 min to give a clear solution. The solution was then refluxed for 1.5 h until TLC showed complete conversion of starting

material. After cooling to room temperature, volatiles were removed under reduced pressure and the residue was dissolved in EtOAc. The solution was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (15-20% EtOAc-hexane) to give the desired ethyl ester as a pale yellow gum (0.227 g).

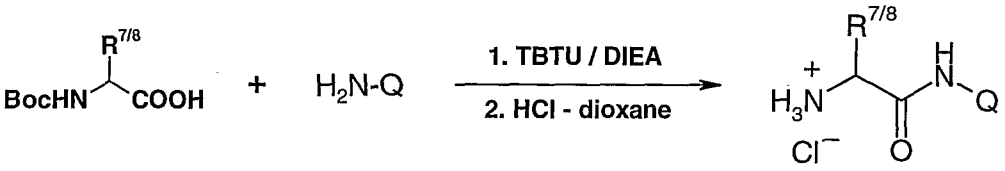
The ester from above (0.100 g, 0.35 mmol) was dissolved in THF (4 mL) and pyridinium hydrobromide perbromide (0.200 g, 0.532 mmol) was added. The mixture was stirred at 65 °C in a sealed vial for 16 h (>80% conversion). The solution was evaporated and the residue taken up into EtOAc. The solution was washed with water and brine, dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography on silica gel (15% EtOAc-hexane).

The bromide from above (0.100 g, 0.274 mmol), phenylboronic acid (0.049 g, 0.4 mmol) and lithium chloride (0.019 g, 0.45 mmol) were dissolved in a mixture of toluene (2 mL), EtOH (2 mL) and 1M Na_2CO_3 (0.43 mL). The mixture was degassed by passing argon gas through the solution for 30 min, and tetrakistriphenylphosphine palladium (0.035 g, 0.03 mmol) was added. The mixture was refluxed for 18 h after which point more catalyst (0.035 g, 0.03 mmol) was added. After refluxing for an additional 2 h, the EtOH was removed under reduced pressure. The residue was dissolved in EtOAc and the solution washed with 10% aqueous HCl and brine, and dried ($MgSO_4$). Removal of volatiles under reduced pressure gave an orange gum that was purified by flash chromatography on silica gel using 20% EtOAc-hexane (0.105 g, crude).

The partially purified ester from above (0.100 g, 0.276 mmol) was dissolved in a mixture of THF (2 mL) and EtOH (2 mL). 1N NaOH (2.8 mL) was added and the mixture stirred for 4 h at room temperature. Volatiles were removed under reduced pressure and the residue diluted with 10% aqueous HCl. The product was extracted with EtOAc (3 X), dried ($MgSO_4$), evaporated and purified by reversed-phase preparative HPLC to give the title compound.

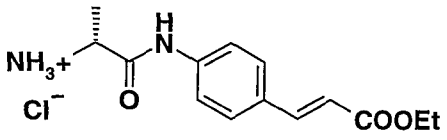
EXAMPLE 23:

General procedure for the preparation of aromatic amide derivatives from α-monosubstituted N-Boc-amino acids:



N-Boc protected α-monosubstituted amino acids were coupled to aromatic amine derivatives using standard amide bond coupling reagents. The *N*-Boc protecting group was then cleaved under acidic conditions and the appropriate amine derivatives were isolated as hydrochloride salts. The following procedure for coupling *N*-Boc-D-alanine to ethyl 4-aminocinnamate is representative:

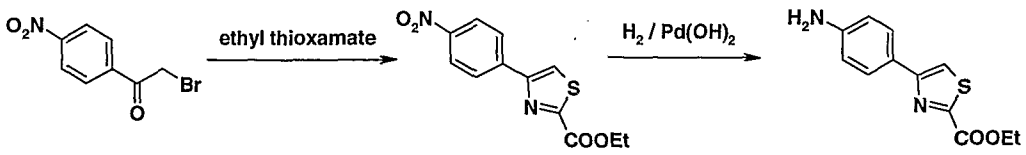
(R)-1-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenylcarbamoyl]-ethyl-ammonium chloride:



N-Boc-D-alanine (0.284 g, 1.5 mmol) was dissolved in DMSO (2 mL) and DIEA (1.04 mL, 6 mmol, 4 equivalents) was added. Ethyl 4-aminocinnamate (0.287 g, 1.5 mmol) was added followed by TBTU (0.578 g, 1.80 mmol) and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with EtOAc (75 mL) and the solution washed with water (40 mL), 1N NaOH (3 x 25 mL), 1M $KHSO_4$ (2 x 25 mL) and 5% $NaHCO_3$ (25 mL). The extract was dried ($MgSO_4$) and concentrated to give the desired *N*-Boc-protected anilide as a yellow solid (0.411 g). The material from above was stirred for 1 h with 4N HCl in dioxane (10 mL). Removal of volatiles under reduced pressure and trituration of the residue with TBME gave the title hydrochloride salt as a brown solid.

EXAMPLE 24:

4-(4-Amino-phenyl)-thiazole-2-carboxylic acid ethyl ester:



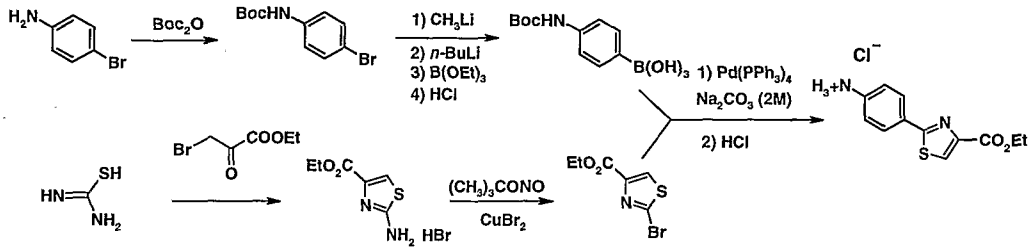
4'-Nitro-2-bromoacetophenone (6.100 g, 25 mmol) and ethyl thioxamate (3.460 g, 26 mmol) were dissolved in MeOH (20 mL) and the solution was refluxed for 1 h. After

cooling to room temperature, the precipitated solid was collected by filtration, washed with cold MeOH and dried under vacuum (5.15 g, 75% yield).

A suspension of the nitroester from above (2.50 g, 8.98 mmol) and 20% $Pd(OH)_2$ on carbon (200 mg) in 2:1 EtOH – THF (60 mL) was stirred for 3 h under 1 atm of hydrogen gas. The suspension was filtered to remove the catalyst and volatiles removed under reduced pressure to give the title compound as a reddish foam (2.05 g, 92% yield).

EXAMPLE 25:

4-(4-Ethoxycarbonyl-thiazol-2-yl)-phenyl-ammonium chloride:



p-Bromoaniline (13.0 g, 76 mmol) and Boc_2O (19.8 g, 91 mmol) were dissolved in toluene (380 mL) and stirred at 70 °C for 15 h. The reaction mixture was cooled to RT, evaporated to dryness, re-dissolved in EtOAc and washed with 0.1M HCl and brine. The organic solution was dried over anhydrous $MgSO_4$, evaporated to dryness and purified by flash column chromatography, using 5% to 10% EtOAc in hexane as the eluent, to obtain the Boc-protected aniline (23 g). The Boc-protected bromoaniline (10.7 g, 39.2 mmol) was dissolved in anhydrous THF (75 mL) in a flask equipped with an overhead stirrer. The solution was cooled to 0 °C and MeLi (1.2 M in Et_2O, 33 mL, 39.2 mmol) was added drop wise while maintaining the internal temperature below 7 °C. The reaction mixture was stirred at 0 °C for 15 min and then cooled to –78 °C before *N*-BuLi (2.4 M in hexane, 17 mL, 39.2 mmol) was added drop wise, maintaining the internal temperature below –70 °C). The reaction mixture was stirred at –78 °C for 1h, $B(OEt)_3$ (17 mL, 98 mmol) was added drop wise (internal temperature < -65 °C) and stirring was continued for 45 min at –78 °C and at 0 °C for 1 h. The reaction mixture was then treated with 5% aqueous HCl (~100 mL, to pH ~1) for 15 min and NaCl(s) was added to saturate the aqueous layer. The aqueous layer was extracted with 0.5 M NaOH (4 x 100 mL) and the combined

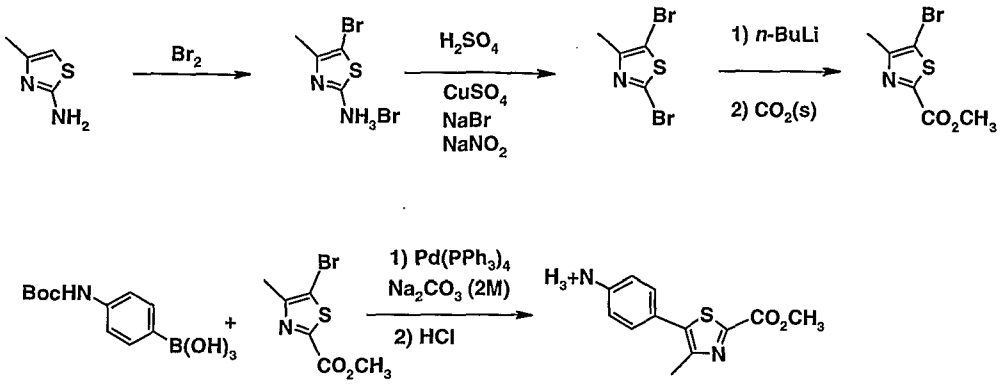
aqueous layers were acidified with 5% HCl (150 mL, to pH ~1) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give the *N*-Boc carbamate of 4-aminophenylboronic acid as a solid (7.5 g).

Thiourea (7.60 g, 100 mmol) and ethyl bromopyruvate (12.6 mL, 100 mmol) were mixed and heated to 100 °C for 45 min. After cooling of the reaction mixture, the solid obtained was triturated with acetone, filtered and recrystallized from EtOH to obtain the desired aminothiazole product (10.6 g, 40 mmol). The aminothiazole was then added slowly (over a period of 20 min) to a solution of *t*-butylnitrite (6.2 g, 60 mmol) and $CuBr_2$ (10.7 g, 48 mmol) in MeCN (160 mL) at 0 °C. The reaction mixture was allowed to warm-up to RT and to stirred for 2.5 h. The mixture was then added to an aqueous HCl solution (20%) and extracted with Et_2O (2 x 400 mL). The organic layer was washed with aqueous HCl (10%), dried over anhydrous $MgSO_4$ and evaporated to dryness. The desired bromothiazole product was isolated in ~85% yield (4.3 g) after flash column chromatography using 15% EtOAc in hexane as the eluent.

To a de-gassed solution of the bromothiazole product (230 mg, 0.97 mmol), the boronic acid derivative from above (230 mg, 0.97 mmol) and aqueous Na_2CO_3 (2M, 3 mL) in DME (3mL), a catalytic amount of $Pd(PPh_3)_4$ (56 mg, 0.049 mmol) was added and the reaction mixture was stirred at 80 °C under argon for 20 h. The reaction mixture was then cooled to RT, diluted with EtOAc and extracted with brine, aqueous $NaHCO_3$ (2 x) and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The carbamate-ester product was isolated after flash column chromatography using 20% to 30% EtOAc in hexane: 180 mg. The aniline hydrochloride was isolated after removal of the Boc protecting group with 4N HCl in dioxane for 30 min.

EXAMPLE 26:

4-(2-Methoxycarbonyl-4-methyl-thiazol-5-yl)-phenyl-ammonium chloride:

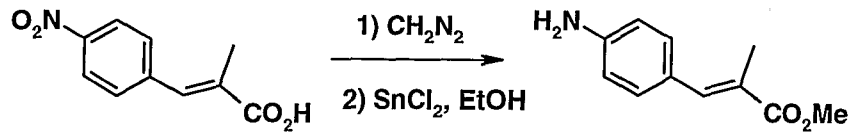


To a solution of 2-amino-4-methylthiazole (7.90 g, 69 mmol) in Et_2O (70 mL) at 15 °C, Br_2 was added slowly over a period of 30 min while stirring vigorously. The solid material formed was filtered and recrystallized from EtOH. The crystalline product was filtered and dried under vacuum to give the 5-bromo derivative as the HBr salt (10.3 g). This product was then dissolved in a solution of $CuSO_4$ (11.4 g) and NaBr (9.9 g) in H_2O (115 mL) and H_2SO_4 (5M, 360 mL) was added at 0 °C. An aqueous solution of $NaNO_2$ (6.10 g in 20 mL of H_2O) was then added drop wise to the reaction mixture over a period of 25 min, maintaining the temperature below 3 °C. The reaction mixture was stirred at 3 °C for 20 min and then at RT for 1 h. The reaction mixture was diluted with brine (280 mL) and extracted with Et_2O (3 x 300 mL). The ether layers were combined, washed with a saturated, aqueous solution of sodium thiosulfate to eliminate any unreacted Br_2, dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel (~200 mL). The solvent was evaporated and the desired product isolated by distillation (bp = 80-81 °C at 15mm Hg).

A solution of the dibromo intermediate (500 mg, 1.94 mmol) in hexane (5 mL) was added to a cooled solution (-70 °C) of *n*-BuLi (870 µL of 2.2M in hexane), diluted with 10 mL of hexane. The reaction was stirred at –70 °C for 1 h and then added to CO_2(s). The mixture was partitioned between H_2O and Et_2O. The aqueous layer was acidified with 1N HCl (pH ~2) and extracted with EtOAc (2 x), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was re-dissolved in MeOH / DCM, treated with CH_2N_2 (until the solution remained yellow) and evaporated to dryness to give the desired 5-bromo-4-methylthiazole-2-carboxylate ester as a yellow solid (230 mg). Suzuki cross-coupling of this product with the *N*-Boc protected 4-aminophenylboronic acid, as previously described (example 25), gave the building block 5-(4-amino-phenyl)-4-methyl-thiazole-2-carboxylate methyl ester. This product was treated with 4N HCl in dioxane for 30 min to remove the Boc protecting group and obtain the desired compound.

EXAMPLE 27:

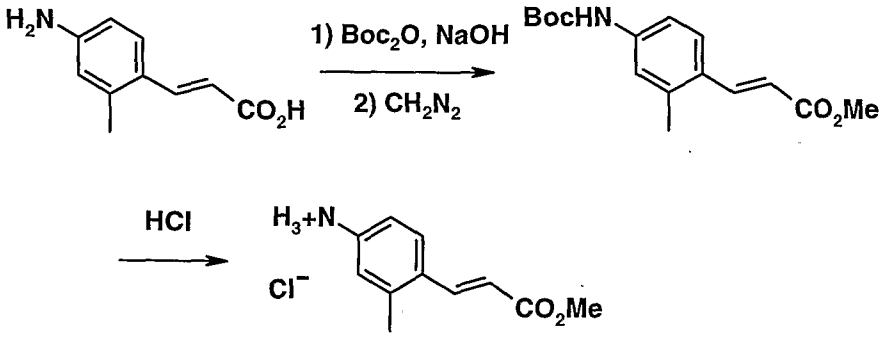
(E)-3-(4-Amino-phenyl)-2-methyl-acrylic acid methyl ester:



α-Methyl-4-nitrocinnamic acid (53 mg, 0.25 mmol) was dissolved in EtOAc and MeOH and a solution of CH_2N_2 in Et_2O was added until a persistent yellow color was observed. A couple of drops of AcOH were added to destroy the excess CH_2N_2. The mixture was diluted with EtOAc and the organic layer was washed with H_2O, aqueous NaOH (1N) and brine, dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was re-dissolved in EtOH (2 mL), $SnCl_2 \cdot 2H_2O$ (289 mg, 1.28 mmol) was added and the reaction mixture was heated to reflux for 1h. The mixture was cooled to RT, diluted with EtOAc and quenched by the addition of aqueous, saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$ and concentrated to dryness to give the title compound (40 mg) as a yellow solid.

EXAMPLE 28:

4-((E)-2-Methoxycarbonyl-vinyl)-3-methyl-phenyl-ammonium chloride:

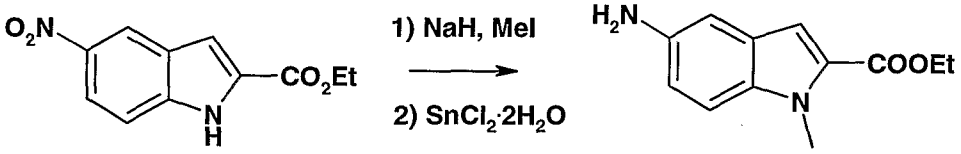


4-Amino-2-methyl cinnamic acid (0.090 g, 0.51 mmol) and NaOH (1M, 1.1 mL, 1.1 mmol) were dissolved in dioxane (4 mL), Boc_2O (117 mg, 0.53 mmol) was added and the mixture was stirred at RT for 15 h. The reaction mixture was partitioned between EtOAc and H_2O, the pH of the aqueous layer was adjusted to be basic using 1N NaOH, and extracted with EtOAc (3 x). The aqueous layer was then

acidified to pH ~2 and extracted with EtOAc (3 x). The new organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give an orange gum (118 mg). The crude Boc-protected 4-amino-2-methyl cinnamic acid was re-dissolved in EtOAc and a solution of CH_2N_2 in Et_2O was added until a persistent yellow color was observed. A few drops of AcOH were added to destroy the excess CH_2N_2 and the reaction mixture was washed with 10% aqueous HCl, saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography, using 10% EtOAc in hexane as the eluent, led to the isolation of the Boc-protected methyl ester as a yellow solid (36 mg). Finally, the Boc protecting group was removed after acid treatment with HCl in dioxane (as described previously) to give the title compound.

EXAMPLE 29:

5-Amino-1-methyl-1H-indole-2-carboxylic acid ethyl ester



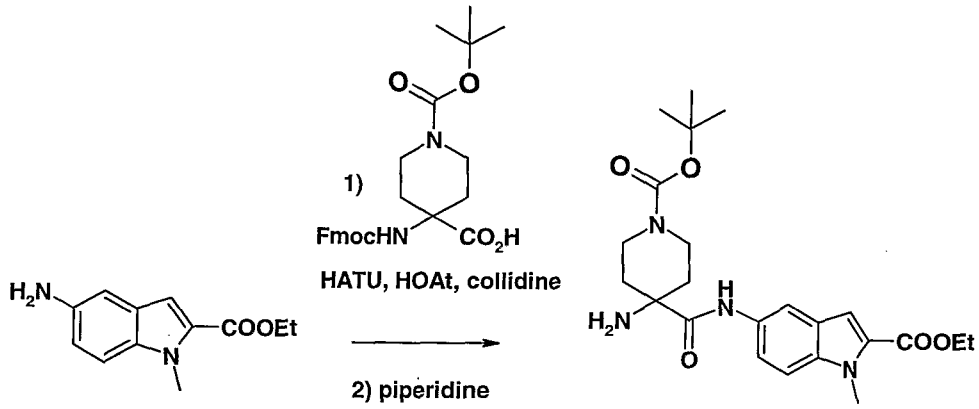
The ethyl ester of 5-nitroindole-2-carboxylic acid (0.300 g, 1.28 mmol) was dissolved in anhydrous DMF (6 mL) and NaH (0.078 g, 60%, 1.92 mmol) was added. The reaction was stirred at RT for 20 min, then MeI (160 µL, 2.56 mmol) was added and stirring was continued for 3 h. The reaction was quenched with the addition of aqueous $NaHCO_3$ (~1%) while stirring vigorously. The brown solid formed (0.096 g) was filtered and dried in air overnight.

The *N*-methyl nitro derivative (196 mg, 0.79 mmol) was then dissolved in DMF (4 mL), H_2O (400 µL) and $SnCl_2 \cdot 2H_2O$ (888 mg, 3.95 mmol) were added, and the mixture was stirred at 60 °C for 3 h. The mixture was then partitioned between 10% aqueous $NaHCO_3$ and EtOAc and stirred vigorously. The aqueous layer was re-extracted with EtOAc and the combined EtOAc layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by flash column chromatography, using 1:1 ration EtOAc/hexane as the eluent, to obtain the pure 5-aminoindole derivative (118 mg).

N-Alkylation of 5-nitroindole-2-carboxylate with other alkylating agents (such as EtI, propargyl bromide, benzyl bromide) under the conditions described above gave the corresponding 5-amino-1-alkyl-*1H*-indole-2-carboxylates.

EXAMPLE 30:

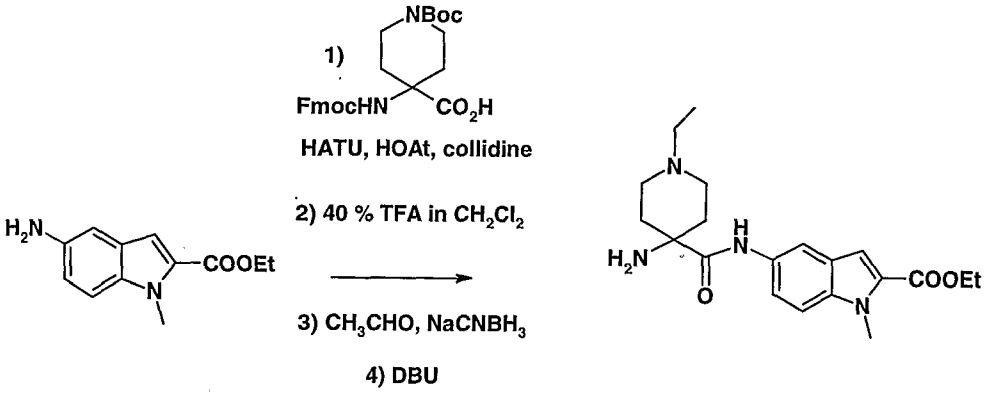
5-{[1-(4-Amino-1-t-butoxycarbonyl-piperidin-4-yl)-methanoyl]-amino}-1-methyl-1H-indole-2-carboxylic acid ethyl ester:



A solution of amine from example 29 (70 mg, 0.32 mmol), *N*-Fmoc-amino-(4-*N*-Boc-piperidinyl)carboxylic acid (150 mg, 0.32 mmol), HATU (139 mg, 0.35 mmol), HOAt (48 mg, 0.35 mmol) and collidine (155 mg, 1.28 mmol) in DMF (2 mL) was stirred at RT for 15 h. The reaction mixture was diluted with EtOAc, washed with 1% aqueous citric acid (2 x), saturated $NaHCO_3$ (2 x) and brine, dried over anhydrous $MgSO_4$ and concentrated to dryness to give an orange solid (210 mg) which was used in the next reaction without purification. A solution of the crude solid (210 mg) in DMF (3 mL) and piperidine (95 mL, 0.95 mmol) was stirred at RT for 3 h. The reaction mixture was concentrated to dryness and purified by flash column chromatography, using a solvent gradient from 50% EtOAc in hexane to 100% EtOAc as the eluent, to give the compound as a brown solid (110 mg).

EXAMPLE 31:

5-{[1-(4-Amino-1-ethyl-piperidin-4-yl)-methanoyl]-amino}-1-methyl-1H-indole-2-carboxylic acid ethyl ester:



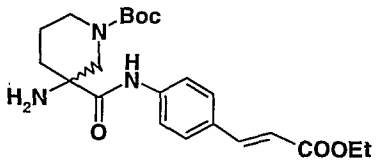
The 5-aminoindole derivative of example 29 was coupled to N-Fmoc-amino-(4-N-Boc-piperidinyl)carboxylic acid as described in example 30.

The Boc protecting group was removed with 25% TFA in CH_2Cl_2 in the usual way, and the product was then dissolved in EtOH (6 mL). AcOH (133 mg), acetaldehyde (33 mg, 0.74 mmol) and $NaCNBH_3$ (23mg, 0.37 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to remove most of the solvent, the residue was re-dissolved in EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the N-ethyl derivative as an orange solid.

This solid was dissolved in THF (2.5 mL), DBU (113 mg, 0.74 mmol) was added and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, the remaining residue was dissolved in EtOAc and the organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was further extracted with 1N HCl and H_2O (2 x), and the pH of the combined aqueous layers was adjusted to pH ~10 with 1N NaOH. The aqueous layer was then extracted with EtOAc (3 x), the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated to dryness to give the title amine derivative (44 mg).

EXAMPLE 32:

(E)-3-(4-{[1-(3-Amino-piperidin-3-yl)-methanoyl]-amino}-phenyl)-acrylic acid ethyl ester:



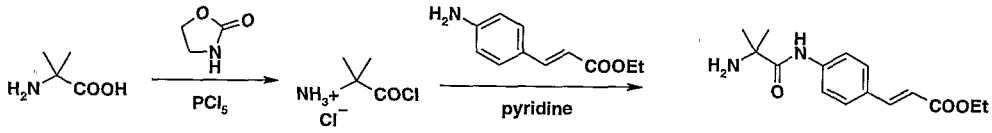
Following a similar procedure to that described in example 31, commercially available N-Fmoc-amino-(3-N-Boc-piperidinyl)carboxylic acid was coupled to the ethyl ester of 4-aminocinnamic acid and the Fmoc protecting group was removed to give the title compound of example 32 in racemic form.

The racemic starting material, N-Fmoc-amino-(3-N-Boc-piperidinyl)carboxylic acid, could also be resolved into its two enantiomers by preparative HPLC on a chiral support (Chiralcel OD, 10 micron, 2.00 cm I.D. x 25 cm), using 35% H_2O in MeCN as the eluent.

EXAMPLE 33:

General procedure for coupling α,α-disubstituted amino acids to aromatic amines:

(E)-3-[4-(2-Amino-2-methyl-propanoylamino)-phenyl]-acrylic acid ethyl ester:

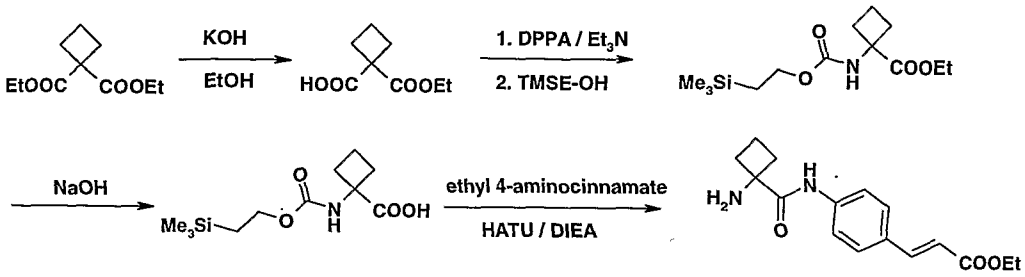


Adapting the procedure described by E. S. Uffelman et al. (*Org. Lett.* **1999**, *1*, 1157), 2-aminoisobutyric acid was converted to the corresponding amino acid chloride hydrochloride: 2-oxazolidinone (12.30 g, 0.141 mole) was dissolved in MeCN (150 mL) and phosphorous pentachloride (49.02 g, 0.235 mole, 1.7 equivalent) was added in one portion. The homogeneous mixture was stirred for 24 h at room temperature. 2-Aminoisobutyric acid (14.55 g, 0.141 mole) was added and the suspension was stirred for 48 h at room temperature. The desired acid chloride hydrochloride was collected by filtration, washed with MeCN and dried under vacuum.

The acid chloride (12.778 g, 80 mmol, 1.4 equivalent) was suspended in DCM (200 mL) and ethyl 4-aminocinnamate (11.045 g, 57.7 mmol, 1 equivalent) was added. Pyridine (7.01 mL, 86.6 mmol, 1.5 equivalent) was added drop wise and the mixture was stirred for 3.5 h at room temperature. The reaction was then poured into a mixture of 1N NaOH (25 mL) and saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc. The organic phase was washed with aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure gave the title compound as a white solid (15.96 g, 101% yield).

EXAMPLE 34:

(E)-3-(4-{[1-(1-Amino-cyclobutyl)-methanoyl]-amino}-phenyl)-acrylic acid ethyl ester:



Diethyl 1,1-cyclobutanedicarboxylate (20.00 g, 100 mmol) and KOH (6.60 g, 100 mmol) were refluxed in EtOH (100 mL) for 2 h. After cooling to room temperature, volatiles were removed under reduced pressure and the residue partitioned between Et_2O and 4N HCl. The organic extract was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the monoester as a clear oil (14.45 g, 84% yield).

The monoester from above (14.45 g, 84 mmol), Et_3N (14.1 mL, 100 mmol) and diphenylphosphoryl azide (24.05 g, 87.4 mmol) were dissolved in dry toluene (114 mL) and the mixture heated at 80 °C for 1 h and 110 °C for an additional hour. Trimethylsilylethanol (9.94 g, 100 mmol) was added in one portion and the mixture refluxed for 48 h. Toluene was then removed under reduced pressure and the residue dissolved in DCM. The solution was washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure gave a dark oil which was purified by passage through a pad of silica gel using 30% EtOAc in hexane as eluent. The desired carbamate was obtained as a clear yellow liquid (21.0 g).

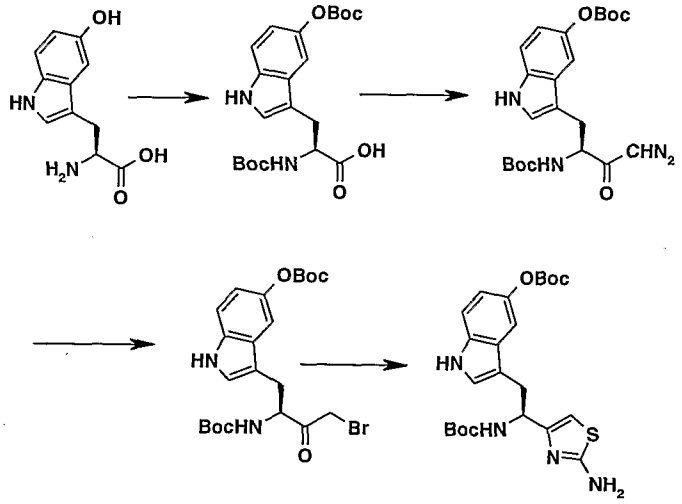
The carbamate from above (1.50 g, 5.22 mmol) was dissolved in THF (5 mL) and 2N NaOH (5 mL) was added. The mixture was stirred at 70 °C for 1 h. Following dilution with water, the aqueous phase was washed with Et_2O to remove unreacted starting material. The aqueous phase was then acidified with $KHSO_4$ and the product extracted with EtOAc. The desired free carboxylic acid was obtained as an oil (1.25 g).

The acid from above (0.519 g, 2.0 mmol) was dissolved in DCM (10 mL). DIEA (1.39 mL, 8.0 mmol, 4 equivalents) was added, followed by ethyl 4-aminocinnamate (0.573 g, 3.0 mmol, 1.5 equivalent) and HATU (1.143 g, 3.0 mmol, 1.5 equivalents).

The mixture was stirred at room temperature for 3 days. The reaction was poured into TBME (100 mL) and the solution washed successively with 10% aqueous citric acid (2 x 25 mL) and saturated aqueous $NaHCO_3$ (25 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue stirred with TFA (10 mL) for 30 min. Volatiles were then removed under reduced pressure and the residue was co-evaporated twice with hexane. The crude product was dissolved in TBME (60 mL) and the solution washed with 1N NaOH (2 x 25 mL). After drying (Na_2SO_4), volatiles were removed in vacuum to give the title compound as a light brown solid (0.500 g).

EXAMPLE 35:

Carbonic acid 3-[(S)-2-tert-butoxycarbonylamino-2-(2-amino-thiazol-4-yl)-ethyl]-1H-indol-5-yl ester tert-butyl ester:



(*S*)-5-Hydroxytryptophan was converted to the bis-Boc derivative by the method of V. F. Pozdnev, *Chem. Nat. Compd. (Engl. Transl.)* **1982**, *18 (1)*, 125) which was isolated as the free carboxylic acid. This material (1.0377 g, 2.47 mmol) was dissolved in THF (5 mL), DIEA (0.645 mL, 3.7 mmol) was added and the mixture cooled in ice. Isobutyl chloroformate (0.384 mL, 2.96 mmol) was added and the mixture stirred at 0-5 °C for 18 h. Excess diazomethane in Et_2O (0.6 M, 15 mL) was then added and the mixture stirred for 1 h. Another portion of diazomethane (10 mL) was added and after 40 min, the reaction was diluted with Et_2O (75 mL). The solution was washed successively with 10% aqueous citric acid (25 mL) and saturated aqueous $NaHCO_3$ (25 mL), and dried ($MgSO_4$). Volatiles were removed under reduced pressure and the residue purified by flash chromatography with 40% EtOAc / hexane. The diazomethylketone was obtained as a yellow foam (0.783 g).

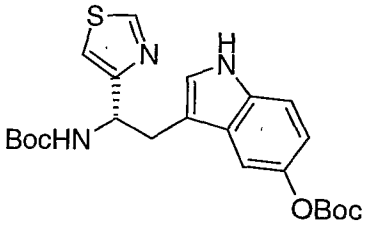
The diazomethylketone from above was dissolved in EtOAc (10 mL) and the solution cooled to –30 °C. A solution of HBr in AcOH (48% w/w, 0.384 mL) was added dropwise over 60 min. The cold reaction mixture was then diluted with Et_2O (100 mL) and washed successively with 10% aqueous citric acid (2 X 25 mL) and saturated aqueous $NaHCO_3$ (25 mL), and dried ($MgSO_4$). Volatiles were removed under reduced pressure and the residue coevaporated with hexane to give the bromomethylketone as a white foam (0.870 g).

The bromomethylketone from above was reacted with thiourea (2 equivalents) in MeCN at room temperature for 18 h. The solvent was then removed under reduced pressure and the residue dissolved in minimal DMSO. This solution was added dropwise with stirring to a mixture of water (15 mL) and DIEA (0.2 mL). The precipitate that formed was collected by filtration, washed with water and dried to give the title compound.

This method is general and can be applied to the preparation of other 2-alkyl and 2-alkylaminothiazole derivatives by reacting the appropriate thioamide or thiourea derivative with the bromomethylketone compound described above.

EXAMPLE 36:

Carbonic acid 3-((S)-2-tert-butoxycarbonylamino-2-thiazol-4-yl-ethyl)-1H-indol-5-yl ester tert-butyl ester:

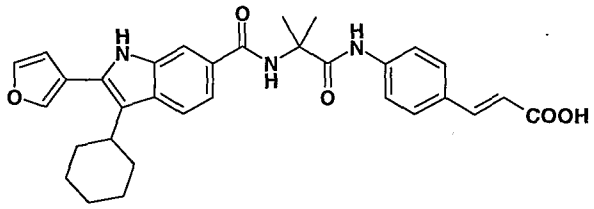


To a stirred suspension of P_2S_5 (0.89 g, 2.0 mmol) in dry dioxane (5 mL) was added dry formamide (433 µL, 10.9 mmol). The mixture was heated at 90°C for 2.5 h (to maintain a free suspension occasional trituration was needed). The suspension was allowed to cool to room temperature, the solid filtered off and the bromoketone from example 29 (0.5 mmol) was added to the filtrate. The solution was heated to 80 °C for 2 h then diluted with EtOAC (25 mL), washed with 5% aqueous citric acid (2 X 20 mL), 5% aqueous sodium bicarbonate (2 X 20 mL) and brine. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, the title compound was obtained.

EXAMPLE 37 (ENTRY 2050):

General procedure for coupling 5- or 6-indolecarboxylic acids to α,α-disubstituted amino amides:

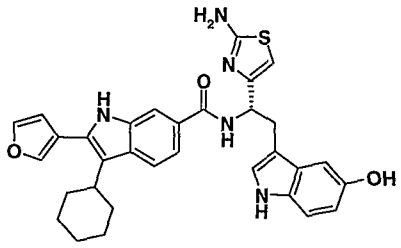
(E)-3-[4-(2-{[1-(3-Cyclohexyl-2-furan-3-yl-1H-indol-6-yl)-methanoyl]-amino}-2-methyl-propanoylamino)-phenyl]-acrylic acid:



The indole carboxylic acid derived from the methyl ester of example 3 (0.050 g, 0.16 mmol), the amino amide derivative of example 33 (0.053 g, 0.019 mmol, 1.2 equivalent) and HATU (0.122 g, 0.32 mmol, 2 equivalents) were dissolved in DMSO (1 mL). DIEA (0.14 mL, 0.8 mmol, 5 equivalents) was added. The mixture was stirred for 1 h at room temperature then treated with 2.5N NaOH (0.3 mL) for 1 h at 50 °C to affect hydrolysis of the cinnamate ester function. The mixture was then acidified to pH 1 with TFA and the title compound was isolated by preparative reversed-phase HPLC (0.033 g).

EXAMPLE 38 (ENTRY 1010):

General procedure for coupling thiazole derivatives (Examples 35, 36) to 6-indolecarboxylic acids:

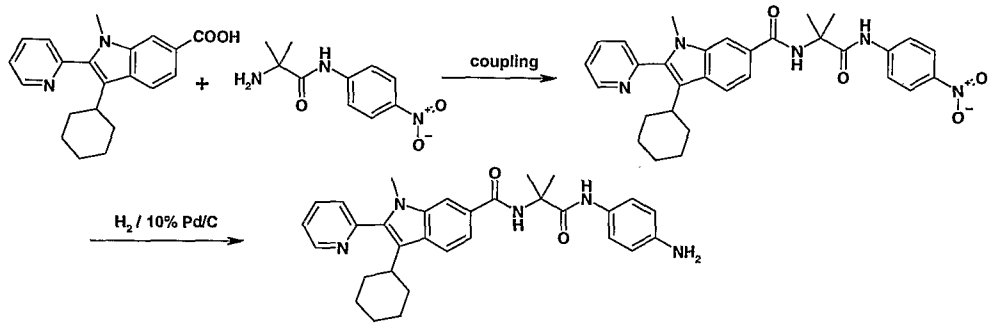


The thiazole derivative of example 35 was deprotected by stirring with 4 N HCl in dioxane and coupled to the 6-indole carboxylic acid derived from the methyl ester of

example 3 using TBTU/DIEA in DMSO as described in example 37. Following coupling, the title compound was isolated directly by preparative reversed-phase HPLC.

EXAMPLE 39

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid [1-(4-amino-phenylcarbamoyl)-1-methyl-ethyl]-amide (Entry 2072):

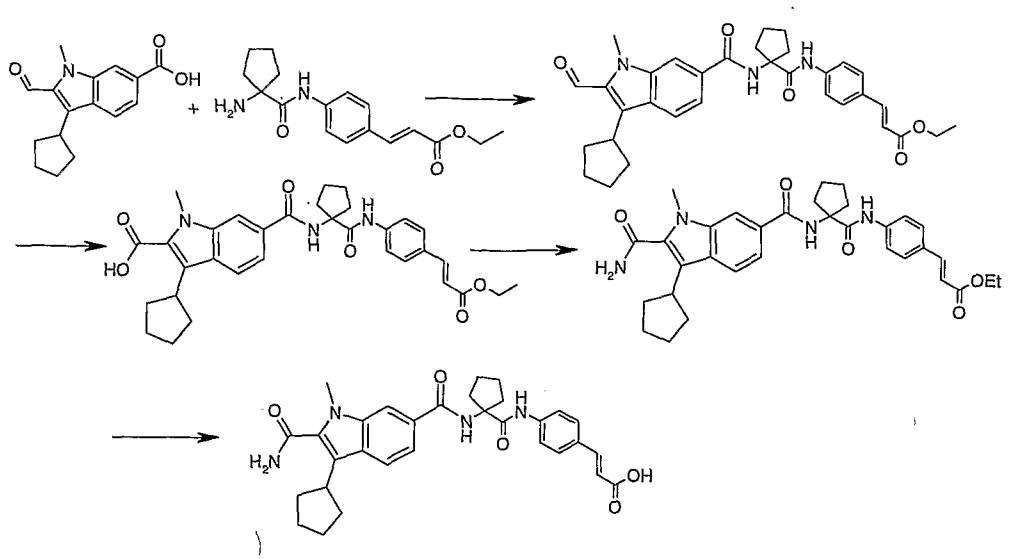


The amino amide derivative prepared from α-aminoisobutyryl chloride and 4-nitroaniline following the procedure of example 33 was coupled in the usual way (example 37) to the indole derivative of example 9.

The nitro derivative was hydrogenolyzed (1 atm H_2 gas, 10% Pd/C) in MeOH for 5 h to give the title compound after purification by preparative reversed-phase HPLC.

EXAMPLE 40

(E)-3-(4-{[1-(1-{[1-(2-Carbamoyl-3-cyclopentyl-1-methyl-1H-indol-6-yl)-methanoyl]-amino}-cyclopentyl)-methanoyl]-amino}-phenyl)-acrylic acid:



To a mixture of the acid aldehyde, derived by saponification of the ester aldehyde of example 16, (50 mg, 0.184 mmol) and an amine, prepared adapting the procedure described in example 33, (55.7 mg, 0.184 mmol) in CH_2Cl_2 were successively added HATU (84 mg, 0.221 mmol) and DIEA (128 µL, 0.736 mmol). The reaction mixture was stirred overnight at room temperature and then concentrated. The residue was dissolved in EtOAc and successively washed with a 10 % aq. citric acid solution (2X), a satd aq. $NaHCO_3$ solution, water and then with brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (2 cm, 35 % AcOEt-hexane) to afford the desired amide-aldehyde derivative (83.5 mg, 0.150 mmol, 81.5 % yield).

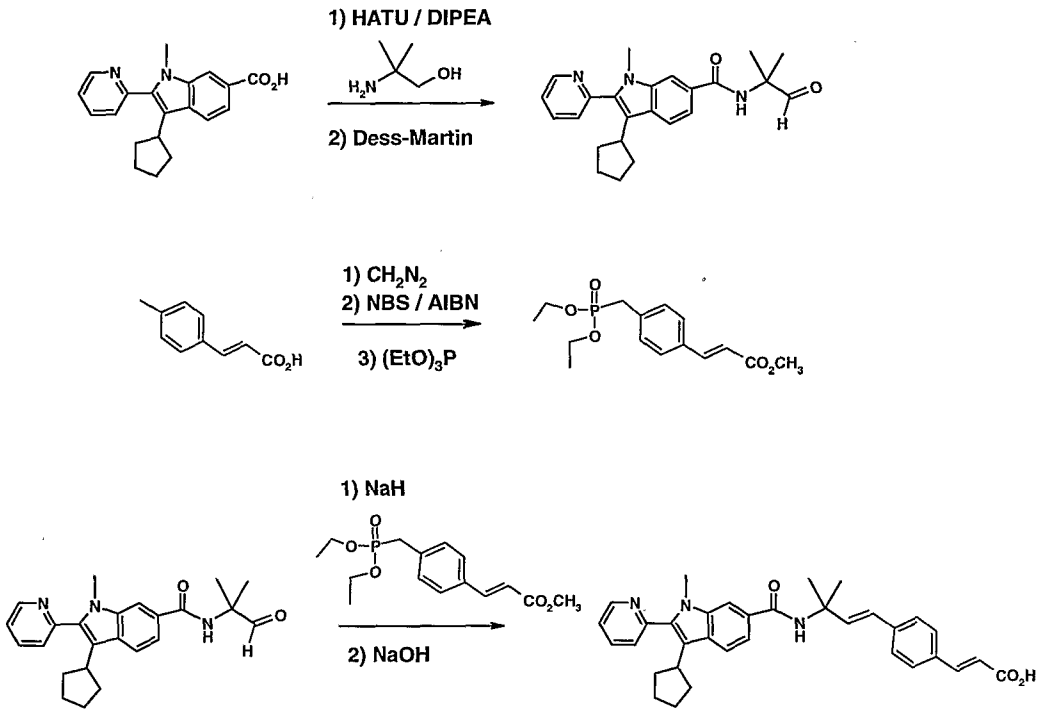
To the aldehyde from above (87 mg, 0.157 mmol) in a mixture of *tert*-butanol (2 mL) and 2-methyl-2-butene (1.2 mL) at 0 °C was added a freshly prepared solution of sodium chlorite (141.6 mg, 1.57 mmol) in phosphate buffer (216 mg of NaH_2PO_4, 1.57 mmol, in 600 µL of water). The reaction mixture was stirred for 10 min. at room temperature then brine was added. The mixture was extracted with EtOAc (2X) and the combined organic layers were successively washed with a 0.5 N aq. solution and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude desired acid was isolated as a white solid (82.6 mg, 92.3 % yield).

To the acid (15 mg, 0.0275 mmol) in DMF at 0 °C were successively added DIEA (7.2 µL, 0.0413 mmol) and isobutyl chloroformate (10.7 µL, 0.0413 mmol). The reaction mixture was stirred for 30 min at this temperature then ammonium hydroxide (7.5 µL, 0.056 mmol) was added. After the addition the mixture was slowly allowed to warm to room temperature and stirred overnight. 1N aq. NaOH was added (275 µL, 0.275 mmol) and the reaction mixture was heated at 60 °C for 1.5 h. Glacial acetic acid was finally added to destroy the excess hydroxide and the mixture was HPLC purified. After lyophilization the desired amide was isolated (2.6 mg, 0.005 mmol, 18 % yield) as a white solid.

Other 2-carboxamide derivatives were prepared in a similar fashion by replacing ammonia with the desired amine.

EXAMPLE 41

(E)-3-[4-((E)-3-{[1-(3-Cyclopentyl-1-methyl-2-pyridin-2-yl-1H-indol-6-yl)-methanoyl]-amino}-3-methyl-but-1-enyl)-phenyl]-acrylic acid:



3-Cyclopentyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid (0.100 g, 0.31 mmol), 2-amino-2-methyl-1-propanol (0.028 g, 0.31 mmol) and HATU (0.154 g, 0.41 mmol) were dissolved in DMSO (5 mL). To this mixture, DIEA (0.22 mL, 1.2 mmol) was added and the solution was stirred at room temperature for 3 h. The reaction mixture was poured into EtOAc (100 mL) and the solution washed successively with saturated aqueous $NaHCO_3$ (2 x 25 mL) and brine (25 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (using 60-70% EtOAc in hexane) to give the primary alcohol intermediate as a yellow oil (0.048 g). This product was dissolved in CH_2Cl_2 (2 mL), Dess-Martin periodinane (0.063 g, 0.15 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with CH_2Cl_2 (100 mL), the organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (using 60% EtOAc in hexane) to give the aldehyde intermediate (0.011 g).

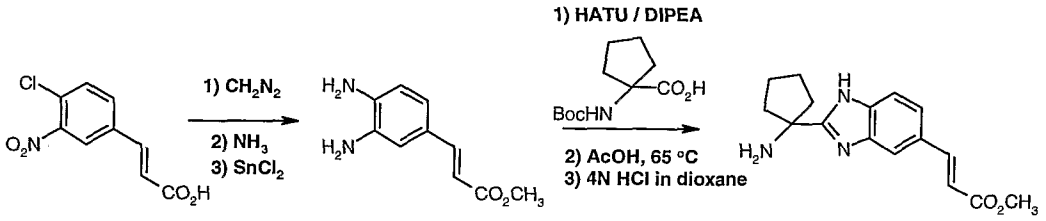
Diazomethane was slowly added to a solution of 4-methylcinnamic acid (3.0 g, 18.5 mmol) in CH_3OH/CH_2Cl_2 (5 mL/15 mL) until the yellow color persisted, indicating the presence of excess diazomethane. The solution was evaporated to dryness under reduced pressure and the residue was re-dissolved in CCl_4 (15 mL). *N*-Bromosuccinimide (3.62 g, 20.4 mmol) and AIBN (0.304 g, 1.85 mmol) were added

and the mixture was stirred at reflux for 3 hours. The solution was then cooled to room temperature and filtered. The organic layer was washed with aqueous NaOH (0.5 N, 2 x 50 mL) and water (50 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum and the residue was purified by flash column chromatography (0-40% EtOAc in hexane) to obtain the bromide intermediate as a white solid (2.4 g). This product was dissolved in $(EtO)_3P$ (37.7 mL, 220 mmol) and heated to reflux at 160 °C. The ethyl bromide formed was collected in a Dean-Stark distillation apparatus over a period of 2.5 hours. The reaction mixture was condensed under vacuum to a yellow solid, which was then purified by flash column chromatography (70-100% EtOAc in hexane) to give the phosphonate as a white solid (1.9 g).

A solution of phosphonate (20 mg, 0.06 mmol) and NaH (60%, 3.5 mg, 0.087 mmol) in anhydrous THF (300 µL) was stirred at RT for 30 min. A solution of the aldehyde intermediate (11 mg, 0.029 mmol) in THF was added and stirring was continued for 4 hours. After that period, aqueous NaOH (2.5 N, 50 µL) was added and the mixture was stirred at 40 °C for 15 hours. The mixture was acidified with glacial acetic acid (~1 mL), concentrated and purified by reversed HPLC to obtain the title compound (3.7 mg) as a yellow solid.

EXAMPLE 42:

(Z)-3-[2-(1-Amino-cyclopentyl)-1H-benzoimidazol-5-yl]-acrylic acid methyl ester:



Diazomethane was slowly added to a solution of 4-chloro-3-nitrocinnamic acid in CH_3OH/CH_2Cl_2 until the yellow color persisted, indicating the presence of excess diazomethane. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in DMSO. The solution was heated to 140 °C and ammonia gas was bubbled through for a period of 4 hours. The mixture was cooled to room temperature and degassed with N_2, and poured onto ice. The precipitate formed was filtered, washed with cold water and dried under vacuum for 16 hours to give the crude 4-amino-3-nitrocinnamic ester as a yellow solid (2.05 g). The solid

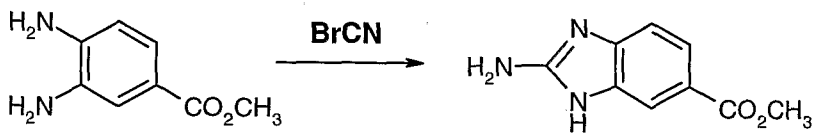
was dissolved in ethanol (40 mL), $SnCl_2$.dihydrate (9.91 g, 43.9 mmol) was added and the reaction mixture was heated to reflux for 4 hours. The solution was concentrated to remove most of the ethanol, diluted with EtOAc and saturated aqueous $NaHCO_3$ was added slowly. The mixture was stirred for 20 min, the organic layer was extracted with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (using 50% to 70% EtOAc in hexane) to give the diamino intermediate as a yellow solid (1.03 g).

A portion of the 3,4-diaminocinnamate ester (186 mg, 0.970 mmol) and N-Boc-1-aminocyclopentane-1-carboxylic acid (222 mg, 0.970 mmol) were coupled in the presence of HATU / DIEA (in the usual way) and the amide product formed was dehydrated by heating at 65 °C in a solution of acetic acid (4 mL). The reaction residue was purified by reversed HPLC to give the N-Boc protected (Z)-3-[2-(1-amino-cyclopentyl)-1*H*-benzoimidazol-5-yl]-acrylic acid ethyl ester.

The Boc protecting group was removed with 4N HCl in dioxane in the usual way to give (Z)-3-[2-(1-amino-cyclopentyl)-1*H*-benzoimidazol-5-yl]-acrylic acid ethyl ester as yellow foam (200 mg).

EXAMPLE 43:

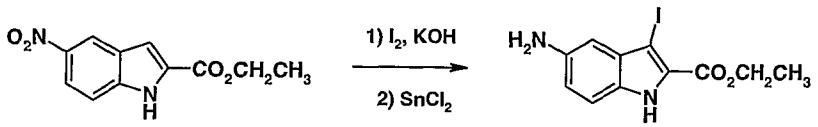
2-Amino-3H-benzoimidazole-5-carboxylic acid:



A solution of cyanogen bromide (5M, 1.44 mL, 7.22 mmol) was slowly added to a suspension of 3,4-diaminobenzoate (1.0 g, 6.02 mmol) in water (10 mL). The mixture was stirred at room temperature for 24 hours. An aqueous solution of Na_2CO_3 (10%) was added slowly until the product had precipitated as a brown solid (890 mg).

EXAMPLE 44:

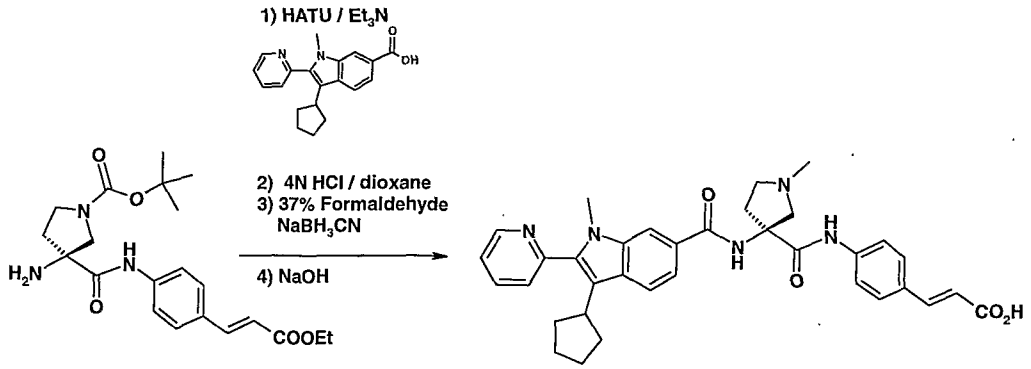
5-Amino-3-iodo-1H-indole-2-carboxylic acid ethyl ester:



Ethyl 5-nitroindole-2-carboxylate (1.00 g, 4.27 mmol) was dissolved in DMF (15 mL), KOH (0.84 g, 14.9 mmol) was added and the mixture was stirred at room temperature for 10 min. Iodine (1.084 g, 4.27 mmol) was added and stirring was continued for 3 hours. The reaction mixture was poured into a solution of water (150 mL) containing $NaHSO_3$ (1 g) and concentrated NH_4OH (2.5 mL). The precipitate formed was filtered, washed with water and dried to give the 3-iodo intermediate as a beige solid (1.49 g). A portion of this solid (503 mg, ~1.4 mmol) was dissolved in ethanol (15 mL), $SnCl_2$.dihydrate (1.58 g, 6.99 mmol) was added and the reaction mixture was heated to reflux for 4 hours. The solution was concentrated to remove most of the ethanol, diluted with EtOAc and saturated aqueous $NaHCO_3$ was added slowly to pH=8-9. The mixture was stirred for 20 min, the organic layer was extracted with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue (431 mg of brown solid) contained the desired product 5-amino-3-iodo-1*H*-indole-2-carboxylic acid ethyl ester in reasonable purity to be used in the synthesis of inhibitors without further purification.

EXAMPLE 45:

(E)-3-(4-{[1-((S)-3-{[1-(3-Cyclopentyl-1-methyl-2-pyridin-2-yl-1H-indol-6-yl)-methanoyl]-amino}-1-methyl-pyrrolidin-3-yl)-methanoyl]-amino}-phenyl)-acrylic acid:



3-Cyclopentyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid (0.197 mg, 0.589 mmol), the appropriate amine (0.170 g, 0.420 mmol) and HATU (0.320 g, 0.840 mmol) were dissolved in DMSO (4 mL). To this mixture, Et_3N (0.300 mL, 2.15 mmol) was added and the solution was stirred at room temperature for 5 hours. The

reaction mixture was poured into EtOAc (100 mL) and the solution washed successively with 1% aqueous citric acid (2 x 25 mL), saturated aqueous $NaHCO_3$ (2 x 25 mL) and brine (25 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (using hexane/EtOAc in 1:1 ratio) to give the intermediate product as a slightly colored foam (280 mg). This product was stirred in 4N HCl in dioxane (3.0 mL) for 1 hour (to remove the Boc protecting group) and then all volatile components were removed under reduced pressure.

A portion of the residue (41 mg, 0.060 mmol) was dissolved in ethanol (2 mL), acetic acid (31 mg, 0.530 mmol) was added, 37% aqueous formaldehyde (15 µL, ~0.2 mmol) and $NaBH_3CN$ (5.6 mg, 0.090 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residue was re-dissolved in DMSO (1 mL), aqueous NaOH (2.5 N, 230 µL, 0.58 mmol) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified by the addition of acetic acid (~1 mL) and purified by C18 reversed phase preparative HPLC to give the final product as a light yellow solid (11 mg).

EXAMPLE 46: INHIBITION OF NS5B RNA DEPENDENT RNA POLYMERASE ACTIVITY

The compounds of the invention were tested for inhibitory activity against the hepatitis C virus RNA dependant polymerase (NS5B), according to the following assay:

The substrates are:

a 12 nucleotide RNA oligo-uridylate (or oligo-uridine-monophosphate) (oligo-U) primer modified with biotin at the free 5'C position;

a complementary poly-adenylate (or adenosine monophospahte) (polyA) template of heterogeneous length (1000-10000 nucleotides); and

UTP-[5,6 ^{3}H].

Polymerase activity is measured as the incorporation of UMP-[5,6 ^{3}H] into the chain elongated from the oligo-U primer. The ^{3}H-labelled reaction product is captured by SPA-beads coated with streptavidin and quantified on the TopCount.

All solutions were made from DEPC treated MilliQ water [2 ml of DEPC is added to 1 L of MilliQ water; the mixture is shaken vigorously to dissolve the DEPC, then autoclaved at 121°C for 30 minutes].

Enzyme: The full length HCV NS5B (**SEQ ID NO.1**) was purified as an N-terminal hexa-histidine fusion protein from baculovirus infected insect cells. The enzyme can be stored at –20°C in storage buffer (see below). Under these conditions, it was found to maintain activity for at least 6 months.

Substrates: The biotinylated oligo-U_{12} primer, the Poly(A) template, and the UTP-[5,6 ^3H] were dissolved in water. The solutions can be stored at –80°C.

Assay buffer:	20 mM Tris-HCl pH 7.5
	5 mM $MgCl_2$
	25 mM KCl
	1 mM EDTA
	1 mM DTT
NS5B storage buffer:	0.1 µM NS5B
	25 mM Tris-HCl pH 7.5
	300 mM NaCl
	5 mM DTT
	1 mM EDTA
	0.1 % n-Dodecyl maltoside
	30 % glycerol

Test compound cocktail: Just prior to assay, test compounds of the invention were dissolved in assay buffer containing 15% DMSO.

Substrate cocktail: Just prior to assay, the substrates were mixed in assay buffer to the following concentrations:

Component	Concentration in substrate cocktail	Final Concentration in assay
RNAsin™	0.5 U/ µL	1.67 U/ µL
Biotin-oligo-U_{12}	3 ng/µL	1 ng/ µL

primer		
PolyA template	30 ng/ µL	10 ng/ µL
UTP-[5,6-^{3}H] 35 Ci/mmol	0.025 µCi/ µL	0.0083 µCi/ µL 0.25 µM
UTP	2.25 µM	0.75 µM

Enzyme cocktail: Just prior to assay, the RNA polymerase (NS5B) cocktail was prepared in assay buffer to the following specifications:

Component	Concentration in cocktail
Tris-HCl at **pH 7.5**	20 mM
$MgCl_2$	5 mM
KCl	25 mM
EDTA	1 mM
DTT	1 mM
n- Dodecyl maltoside	1%
NS5B	30 nM

Protocol:

The assay reaction was performed in a Microfluor™ white "U" bottom plate (Dynatech™ #7105), by successively adding:

20 µL of test compound cocktail;

20 µL of substrate cocktail; and

20 µL of enzyme cocktail

(final [NS5B] in assay = 10 nM; final [n-dodecyl maltoside] in assay = 0.33%; final DMSO in assay = 5%).

The reaction was incubated at room temperature for 1.5 hours. STOP solution (20 µL; 0.5 M EDTA, 150 ng/ µl tRNA) was added, followed by 30 µl streptavidin coated PVT beads (8mg/ml in 20 mM Tris-HCl, pH 7.5, 25 mM KCl, 0.025% NaN_3). The plate was then shaken for 30 minutes. A solution of CsCl was added (70 µL, 5 M), to bring the CsCl concentration to 1.95 M. The mixture was then allowed to stand for 1 hour. The beads were then counted on a Hewlett Packard TopCount™ instrument using the following protocol:

Data mode: counts per minute

Scintillator: liq/plast
Energy range: low
Efficiency mode: normal
Region: 0-50
Count delay: 5 minutes
Count time: 1 minute
Expected results: 6000 cpm/well
200 cpm/well no enzyme control.

Based on the results at ten different concentrations of test compound, standard concentration-% inhibition curves were plotted and analysed to determine IC_{50}'s for the compounds of the invention. For some compounds the IC_{50} was estimated from two points.

EXAMPLE 47: SPECIFICITY OF NS5B RNA DEPENDENT RNA POLYMERASE INHIBITION

The compounds of the invention were tested for inhibitory activity against polio virus RNA dependent RNA polymerase and calf thymus DNA dependent RNA polymerase II in the format that is described for the HCV polymerase with the exception that another polymerase was used in place of the HCV NS5B polymerase.

EXAMPLE 48: CELL BASED HCV RNA REPLICATION ASSAY

Cell Culture

Huh7 cells that stably maintain a subgenomic HCV replicon were established as previously described (Lohman et al., 1999. Science **285**: 110-113) and designated as the S22.3 cell-line. S22.3 cells are maintained in Dulbecco's Modified Earle Medium (DMEM) supplemented with 10% FBS and 1mg/mL neomycin (Standard Medium). During the assay, DMEM medium supplemented with 10% FBS, containing 0.5% DMSO and lacking neomycin was used (Assay Medium). 16 hours prior to compound addition, S22.3 cells are trypsinized and diluted to 50 000 cells/ml in Standard Medium. 200µL (10 000 cells) are distributed into each well of a 96-well plate. The plate was then incubated at 37°C with 5% $C0_2$ until the next day.

Reagents and Materials:

Product	Company	Catalog #	Storage
DMEM	Wisent Inc.	10013CV	4°C
DMSO	Sigma	D-2650	RT
Dulbecco's PBS	Gibco-BRL	14190-136	RT
Fetal Bovine Serum	Bio-Whittaker	14-901F	-20°C/4°C
Neomycin (G418)	Gibco-BRL	10131-027	-20°C/4°C
Trypsin-EDTA	Gibco-BRL	25300-054	-20°C/4°C
96-well plates	Costar	3997	RT
PVDF 0.22µm Filter Unit	Millipore	SLGV025LS	RT
Deep-Well Titer Plate Polypropylene	Beckman	267007	RT

Preparation of Test Compound

10µL of test compound (in 100% DMSO) was added to 2 ml of Assay Medium for a final DMSO concentration of 0.5% and the solution was sonicated for 15 min and filtered through a 0.22µM Millipore Filter Unit. 900µl was transfered into row A of a Polypropylene Deep-Well Titer Plate. Rows B to H, contain 400µL aliquots of Assay Medium (containing 0.5% DMSO), and are used to prepare serial dilutions (1/2) by transferring 400µl from row to row (no compound was included in row H).

Application of test compound to cells

Cell culture medium was aspirated from the 96-well plate containing the S22.3 cells. 175µL of assay medium with the appropriate dilution of test compound was transferred from each well of the compound plate to the corresponding well of the cell culture plate (row H was used as the "No inhibition control"). The cell culture plate was incubated at 37°C with 5% $C0_2$ for 72 hours.

Extraction of Total Cellular RNA

Following the 72 hour incubation period, the total cellular RNA was extracted from the S22.3 cells of the 96-well plate using the RNeasy 96 kit (Qiagen®, RNeasy Handbook. 1999.). Briefly, assay medium was completely removed from cells and 100 µL of RLT buffer (Qiagen®) containing 143 mM β-mercaptoethanol was added to each well of the 96-well cell-culture plate. The microplate was gently shaken for 20 sec. 100 µL of 70% ethanol was then added to each microplate well, and mixed by

pipetting. The lysate was removed and applied to the wells of a RNeasy 96 (Qiagen®) plate that was placed on top of a Qiagen® Square-Well Block. The RNeasy 96 plate was sealed with tape and the Square-Well Block with the RNeasy 96 plate was loaded into the holder and placed in a rotor bucket of a 4K15C centrifuge. The sample was centrifuged at 6000 rpm (~5600 x g) for 4 min at room temperature. The tape was removed from the plate and 0.8 ml of Buffer RW1 (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The RNeasy 96 plate was placed on top of another clean Square-Well Block, the tape removed and 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The tape was removed and another 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 10 min at room temperature. Tape was removed, the RNeasy 96 plate was placed on top of a rack containing 1.2-mL collection microtubes. The RNA was eluted by adding 50 µL of RNase-free water to each well, sealing plate with a new piece of tape and incubated for 1 min at room temperature. The plate was then centrifuged at 6000 rpm for 4 min at room temperature. The elution step was repeated with a second volume of 50 µl RNase-free water. The microtubes with total cellular RNA are stored at –70°C.

Quantification of Total Cellular RNA

RNA was quantified on the STORM® system (Molecular Dynamics®) using the RiboGreen® RNA Quantification Kit (Molecular Probes®). Briefly, the RiboGreen reagent was diluted 200-fold in TE (10mM Tris-HCl pH =7.5, 1mM EDTA). Generally, 50µL of reagent was diluted in 10mL TE. A Standard Curve of ribosomal RNA was diluted in TE to 2µg/mL and pre-determined amounts (100, 50, 40, 20, 10, 5, 2 and 0µL) of the ribosomal RNA solution are then transferred in a new 96-well plate (COSTAR # 3997) and the volume was completed to 100µL with TE. Generally, column 1 of the 96-well plate was used for the standard curve and the other wells are used for the RNA samples to be quantified. 10µL of each RNA sample that was to be quantified, was transferred to the corresponding well of the 96-well plate and 90µL of TE was added. One volume (100µL) of diluted RiboGreen reagent was

added to each well of the 96-well plate and incubated for 2 to 5 minutes at room temperature, protected from light (a 10 µL RNA sample in a 200 uL final volume generates a 20 X dilution). The fluorescence intensity of each well was measured on the STORM® system (Molecular Dynamics®). A standard curve was created on the basis of the known quantities of the ribosomal RNA and the resulting fluorescent intensities. The RNA concentration in the experimental samples was determined from the standard curve and corrected for the 20X dilution.

Reagents and Materials:

Product	Company	Catalog #	Storage
DEPC	Sigma	D5758	4°C
EDTA	Sigma	E5134	RT
Trizma-Base	Sigma	T8524	RT
Trizma-HCl	Sigma	T7149	RT
Collection Tube Strips	Qiagen	19562	RT
Ribogreen RNA Quantitation Kit	Molecular Probe	R11490	-20°C
Rneasy 96 Kit	Qiagen	74183	RT
Square-Well Blocks	Qiagen	19573	RT

Real-Time RT-PCR

The Real-Time RT-PCR was performed on the ABI Prism 7700 Sequence Detection System using the TaqMan EZ RT-PCR Kit from (Perkin-Elmer Applied Biosystems®). RT-PCR was optimized for the quantification of the 5' IRES of HCV RNA by using the Taqman technology (Roche Molecular Diagnostics Systems) similar to the technique previoulsy described (Martell et al., 1999. J. Clin. Microbiol. 37: 327-332). The system exploits the 5'-3' nucleolytic activity of AmpliTaq DNA polymerase. Briefly, the method utilizes a dual-labeled fluorogenic hybridization probe (PUTR Probe) that specifically anneals to the template between the PCR primers (primers 8125 and 7028). The 5' end of the probe contains a fluorescent reporter (6-carboxyfluorescein [FAM]) and the 3' end contains a fluorescent quencher (6-carboxytetramethylrhodamine [TAMRA]). The FAM reporter's emission spectrum was suppressed by the quencher on the intact hybridization probe. Nuclease degradation of the hybridization probe releases the reporter, resulting in an increase

in fluorescence emission. The ABI Prism 7700 sequence detector measures the increase in fluorescence emission continuously during the PCR amplification such that the amplified product was directly proportion to the signal. The amplification plot was analysed early in the reaction at a point thatrepresents the logarithmic phase of product accumulation. A point representing a defined detection threshold of the increase in the fluorescent signal associated with the exponential growth of the PCR product for the sequence detector was defined as the cycle threshold (C_T). C_T values are inversely proportional to the quantity of input HCV RNA; such that under identical PCR conditions, the larger the starting concentration of HCV RNA, the lower the C_T. A standard curve was created automatically by the ABI Prism 7700 detection system by plotting the C_T against each standard dilution of known HCV RNA concentration. Reference samples for the standard curve are included on each RT-PCR plate. HCV Replicon RNA was synthesized (by T7 transcription) *in vitro*, purified and quantified by OD_{260}. Considering that 1µg of this RNA = 2.15 X 10^{11} RNA copies, dilutions are made in order to have 10^8, 10^7, 10^6, 10^5, 10^4, 10^3 or 10^2 genomic RNA copies / 5µL. Total cellular Huh-7 RNA was also incorporated with each dilution (50ng / 5µL). 5µL of each reference standard (HCV Replicon + Huh-7 RNA) was combined with 45µL of Reagent Mix, and used in the Real-Time RT-PCR reaction.

The Real-Time RT-PCR reaction was set-up for the experimental samples that were purified on RNeasy 96 –well plates by combining 5µl of each total cellular RNA sample with 45µL of Reagent Mix.

Reagents and Materials:

Product	Company	Catalog #	Storage
TaqMan EZ RT-PCR Kit	PE Applied Biosystems	N808-0236	-20°C
MicroAmp Optical Caps	PE Applied Biosystems	N801-0935	RT
MicroAmp Optical 96-Well Reaction Plate	PE Applied Biosystems	N801-0560	RT

Reagent Mix preparation:

Component	Volume for one sample (µL)	Volume for One Plate (µL) (91 samples + Dead Volume)	Final conc.
Rnase-free water	16.5	1617	

5X TaqMan EZ buffer	10	980	1X
$Mn(OAc)_2$ (25mM)	6	588	3mM
dATP (10mM)	1.5	147	300µM
dCTP (10mM)	1.5	147	300µM
dGTP (10mM)	1.5	147	300µM
dUTP (20mM)	1.5	147	600µM
Forward Primer (10µM)	1	98	200nM
Reverse Primer (10µM)	1	98	200nM
PUTR probe (5µM)	2	196	200nM
rTth DNA polymerase (2.5 U/µL)	2	196	0.1 U/µL
AmpErase UNG (1U/µL)	0.5	49	0.01 U/µL
Total Volume	45	4410	

Forward Primer Sequence (SEQ ID. 2): 5' - ACG CAG AAA GCG TCT AGC CAT GGC GTT AGT - 3'

Reverse Primer Sequence (SEQ ID NO. 3): 5' - TCC CGG GGC ACT CGC AAG CAC CCT ATC AGG - 3'

Note: Those primers amplify a region of 256-nt present within the 5' untranslated region of HCV.

PUTR Probe Sequence (SEQ ID NO. 4): [6FAM] - TGG TCT GCG GAA CCG GTG AGT ACA CC - [TAMRA]

No Template Controls (NTC): On each plate, 4 wells are used as "NTC". For these controls, 5µl of water are added to the well in place of RNA.

Thermal Cycling Conditions:

50°C 2 min

60°C 30 min

95°C 5 min

95°C 15 sec } for 2 cycles

60°C 1 min

90°C 15 sec
60°C 1 min } for 40 cycles

Following the termination of the RT-PCR reaction the data analysis requires setting of threshold fluorescence signal for the PCR plate and a standard curve was constructed by plotting the Ct value versus RNA copy number used in each reference reaction. The Ct values obtained for the assay samples are used to interpolate an RNA copy number based on the standard curve.
Finally, the RNA copy number was normalized (based on the RiboGreen RNA quantification of the total RNA extracted from the cell culture well) and expressed as genome equivalents / µg of total RNA [ge/µg].

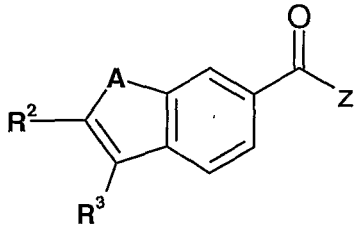
The RNA copy number [g.e./µg] from each well of the cell culture plate was a measure of the amount of replicating HCV RNA in the presence of various concentrations of inhibitor. The % inhibition was calculated with the following equation:

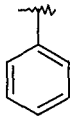
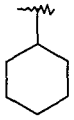
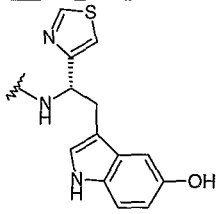
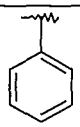
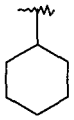
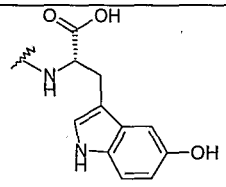
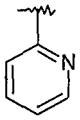
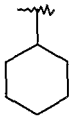
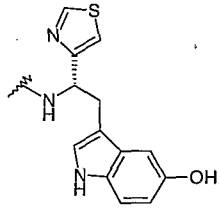
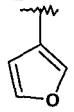
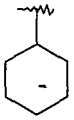
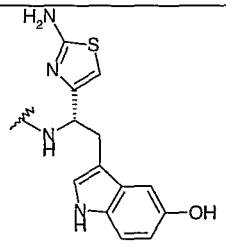
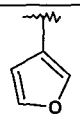
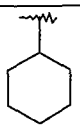
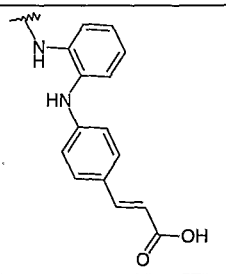
100 - [(g.e./µg inh)/(g.e./µg ctl)x 100].

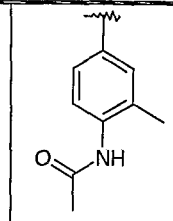
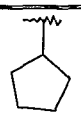
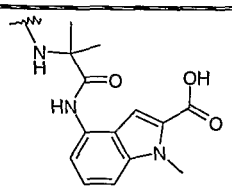
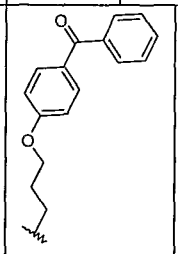
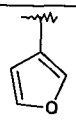
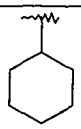
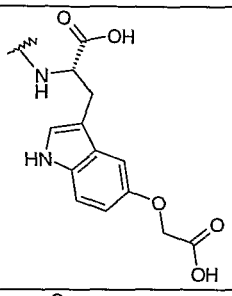
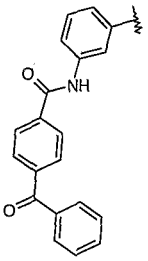
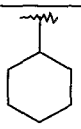
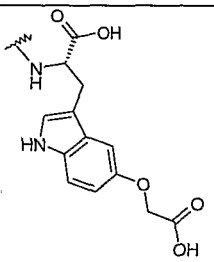
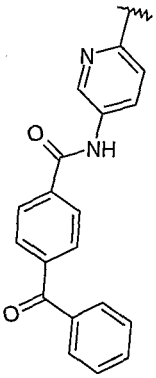
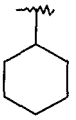
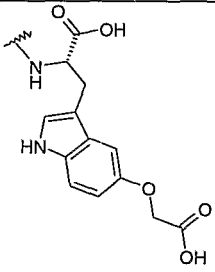
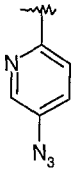
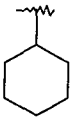
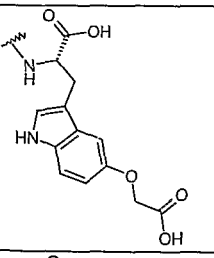
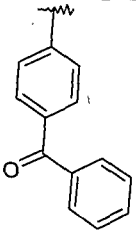
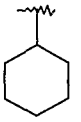
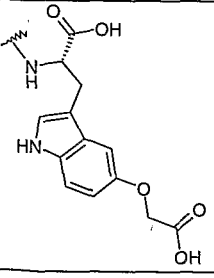
A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (EC_{50}) was calculated by the use of SAS software (Statistical Software System; SAS Institute, Inc. Cary, N.C.).

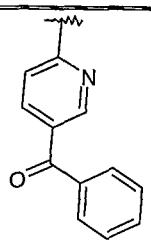
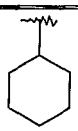
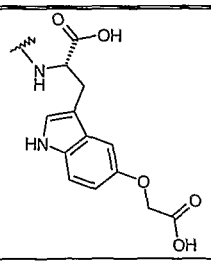
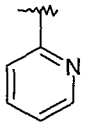
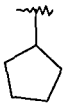
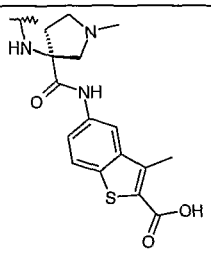
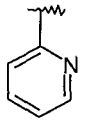
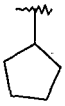
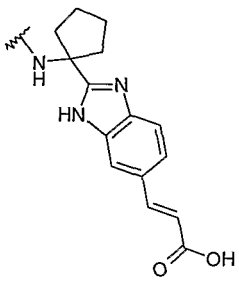
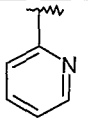
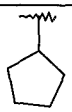
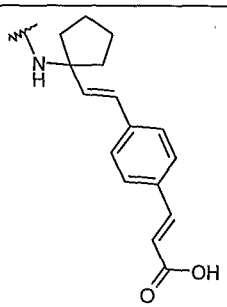
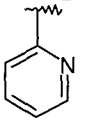
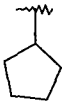
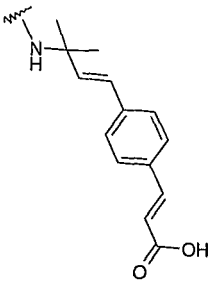
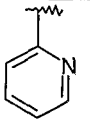
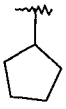
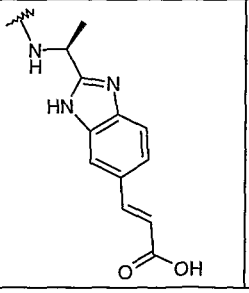
In Tables 1 to 9 below, the following ranges apply:
IC_{50}: A = 10µM-1µM; B = 1µM-500nM; and C<500nM.
Ec_{50}: A = 5µM-500nM; and B = ≤500nM

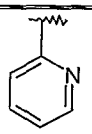
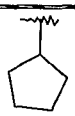
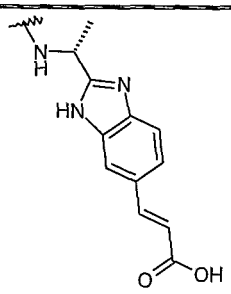
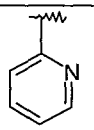
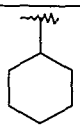
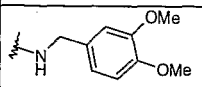
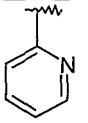
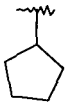
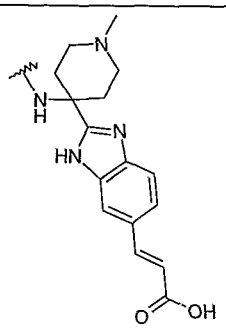
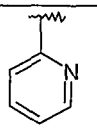
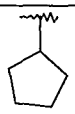
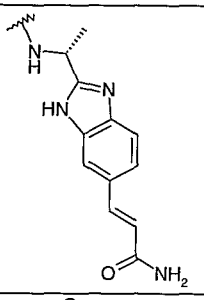
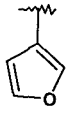
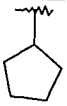
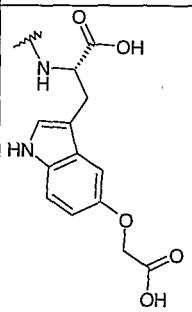
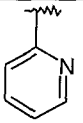
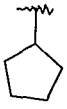
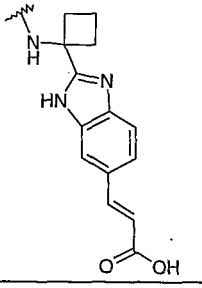
TABLE 1

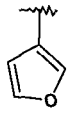
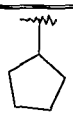
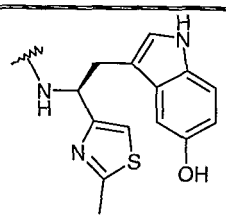
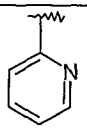
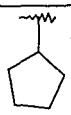
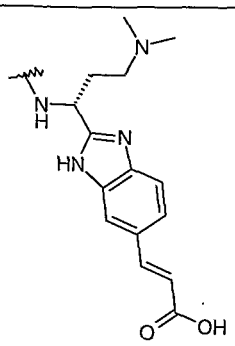
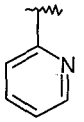
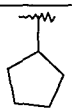
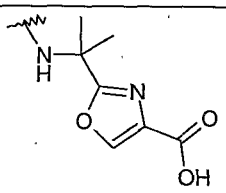
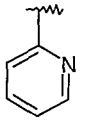
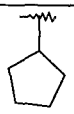
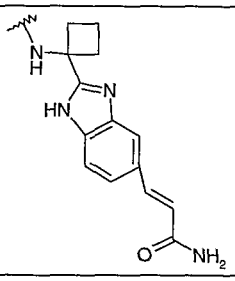
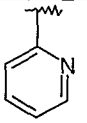
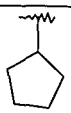
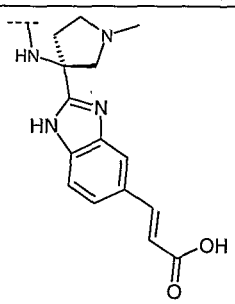
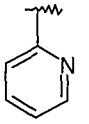
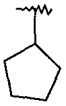
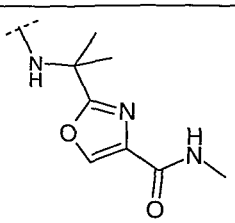


Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
1001	NH				A	B	561.2
1002	NH				C	--	522.2
1003	NH				A	A	562.2
1004	NH				B	B	566.2
1005	NH				A	--	546.3

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
1006	NMe				C	B	648.3
1007					A	--	808.3
1008	NMe				B	--	815.3 (M-H)
1009	NMe				A	--	818.1
1010	NMe				C	--	636.3
1011	NMe				B	--	698.3

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
1012	NMe				C	--	699.3
1013	NMe				C	B	636.3
1014	NMe				C	B	574.4
1015	NMe				C	B	560.3
1016	NMe				C	B	534.2
1017	NMe				C	A	534.3

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
1018	NMe				C	B	534.3
1019	NH				A	--	470.3
1020	NMe				C	B	603.4
1021	NMe				C	B	533.4
1022	S				C	--	573.3
1023	NMe				C	C	560.4

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
1024	S				C	A	568.3
1025	NMe				C	A	591.4
1026	NMe				B	--	473.3
1027	NMe				C	B	559.4
1028	NMe				C	B	589.4
1029	NMe				B	--	486.4

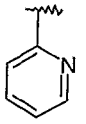
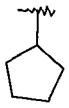
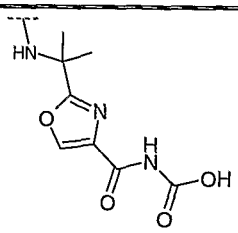
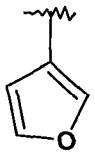
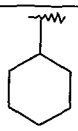
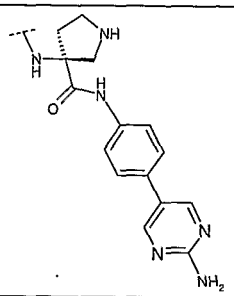
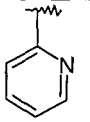
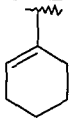
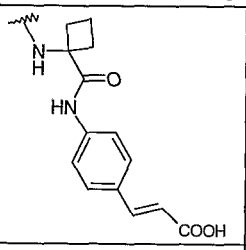
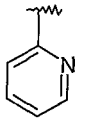
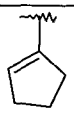
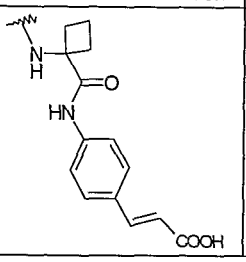
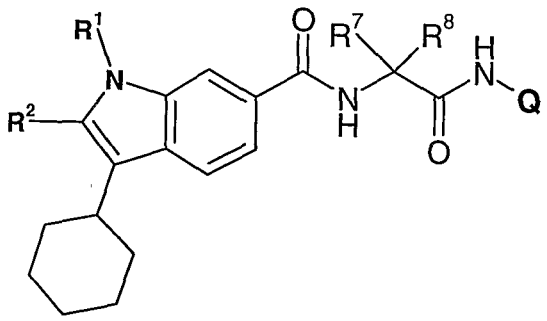
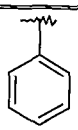
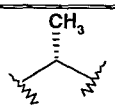
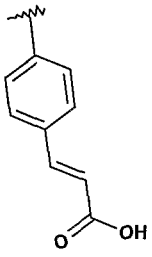
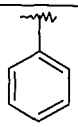
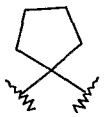
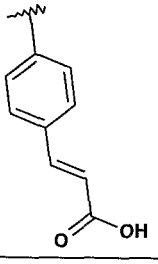
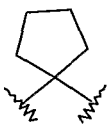
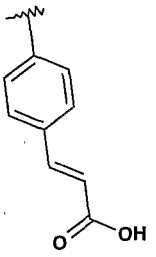
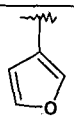
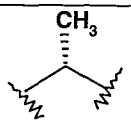
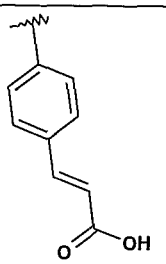
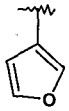
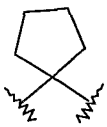
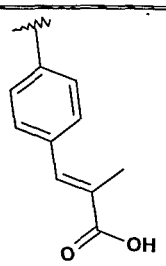
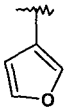
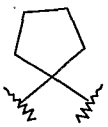
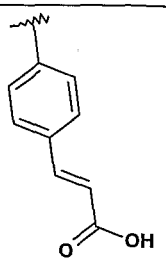
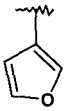
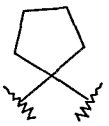
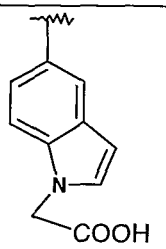
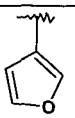
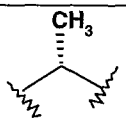
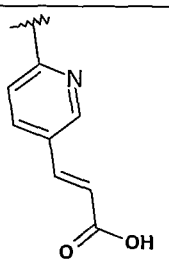
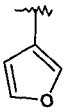
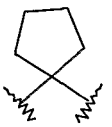
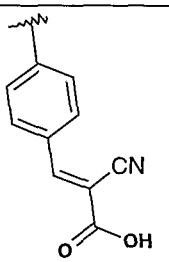
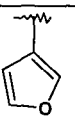
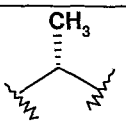
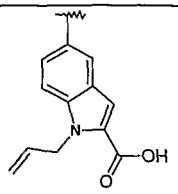
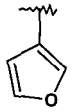
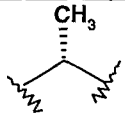
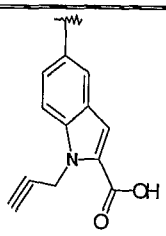
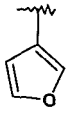
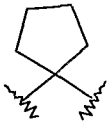
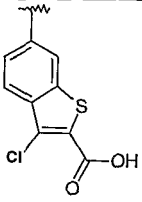
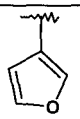
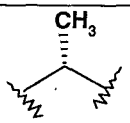
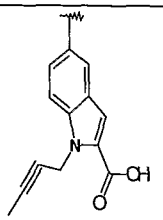
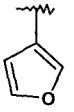
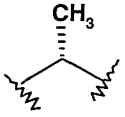
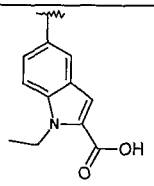
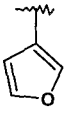
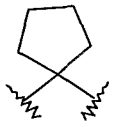
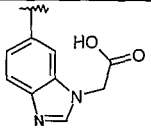
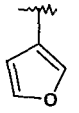
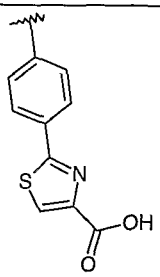
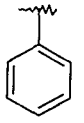
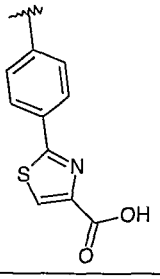
Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
1030	NMe				B	--	530.4
1031	NMe				C	--	604.5
1032	NMe				C	C	575.5
1033	NMe				B		561.3

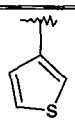
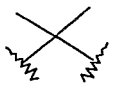
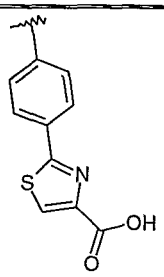
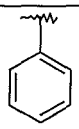
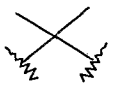
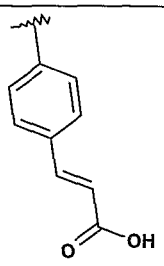
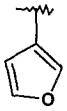
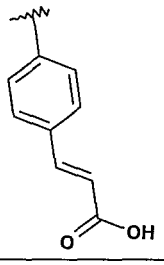
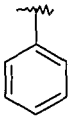
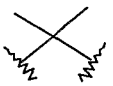
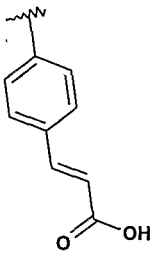
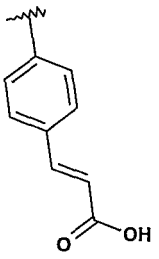
TABLE 2

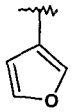
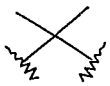
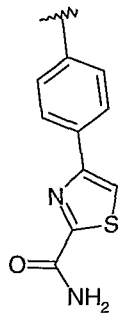
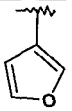
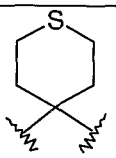
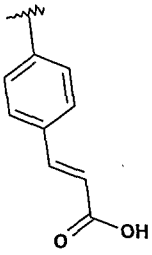
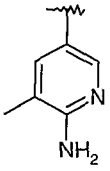
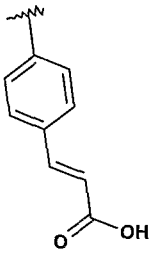
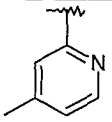
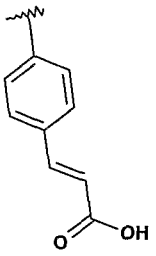
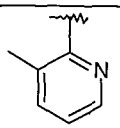
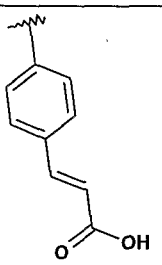
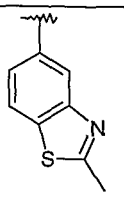
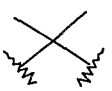
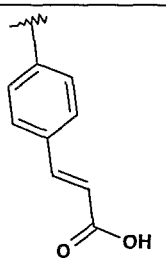


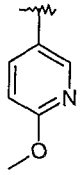
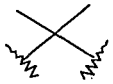
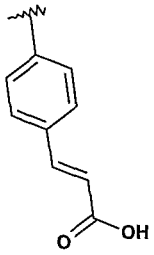
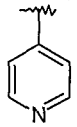
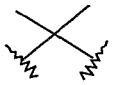
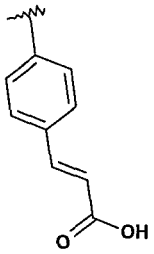
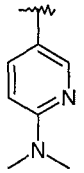
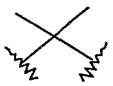
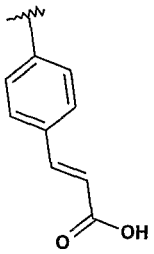
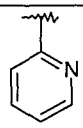
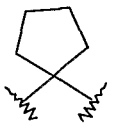
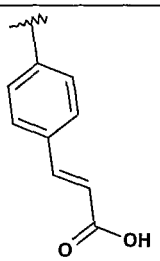
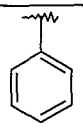
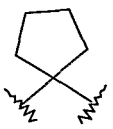
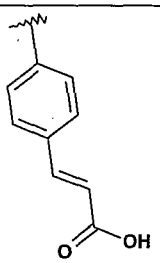
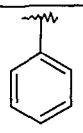
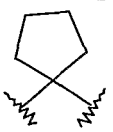
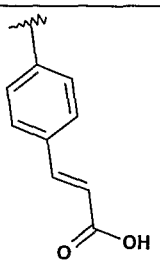
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2001	H				B	B	534.2
2002	H				B	B	576.2
2003	H	Br			A	A	578.6 (MH^+)/ 580 (MH^+)
2004	H				B	B	526.2

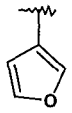
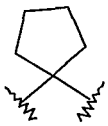
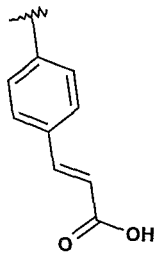
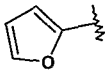
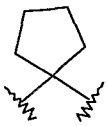
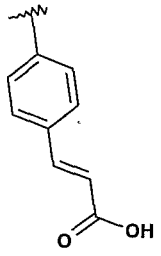
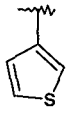
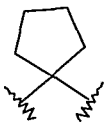
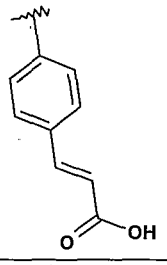
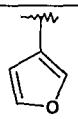
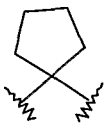
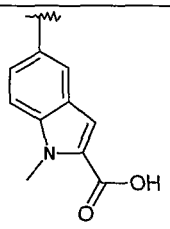
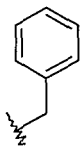
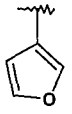
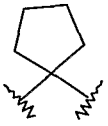
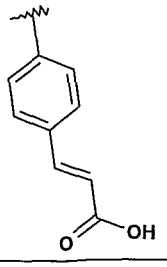
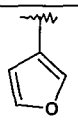
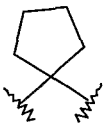
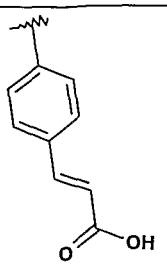
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2005	H				B	B	580.3
2006	Me				B	B	580.3
2008	H				B	A	593.2
2009	H				B	A	527.2
2010	H				B	A	589.3
2011	H				B	A	579.3

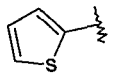
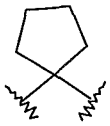
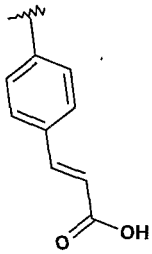
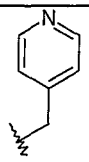
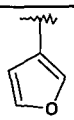
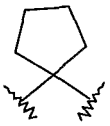
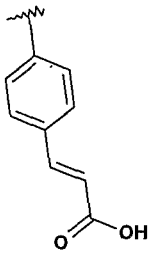
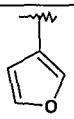
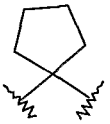
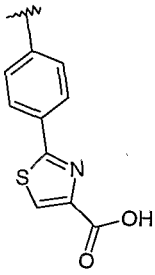
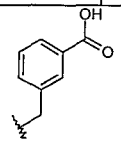
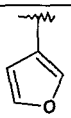
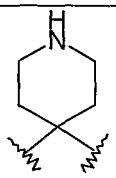
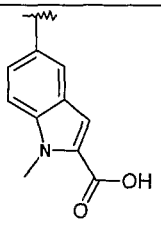
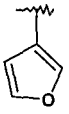
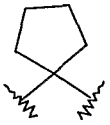
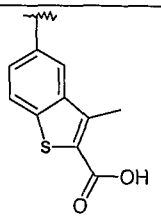
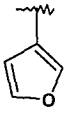
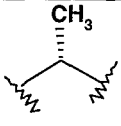
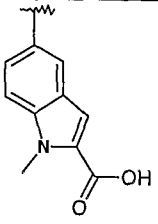
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2012	H				B	A	577.2
2013	H				B	B	630.2
2014	H				A	A	591.3
2015	H				B	B	567.2
2016	H				A	--	594.2
2017	H				B	B	597.2
2018	H				B	B	607.2

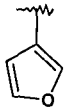
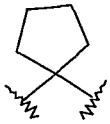
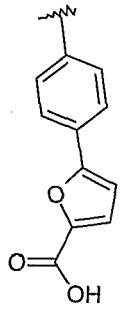
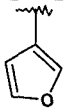
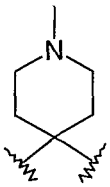
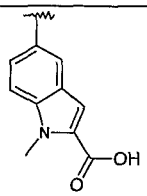
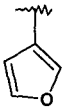
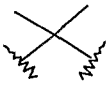
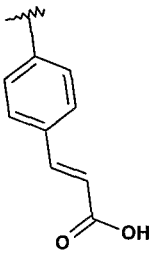
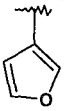
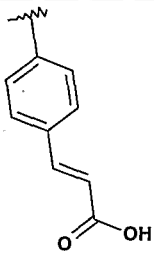
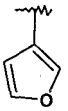
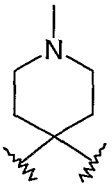
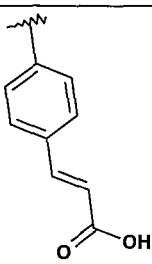
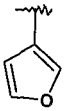
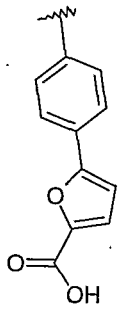
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2019	H				B	A	613.1
2020	Et				B	B	578.2
2021					B	A	596.4
2022					A	--	592.3
2023	Me	H			A	--	488.2

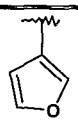
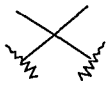
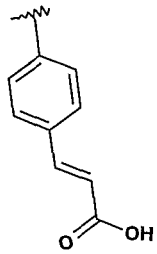
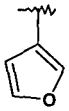
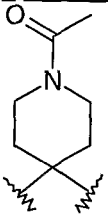
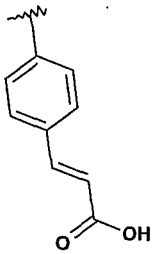
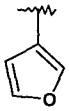
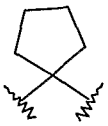
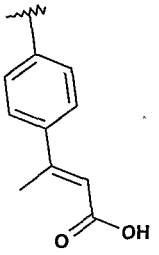
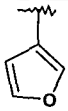
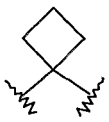
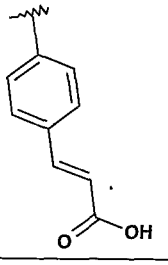
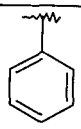
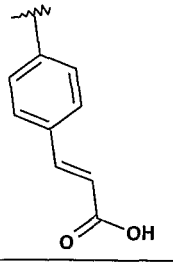
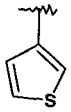
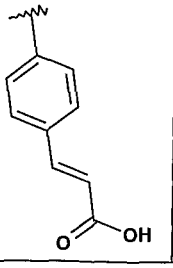
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2024	H				B	B	596.3
2025	H				B	B	596.3 (M-H)
2026	Me				B	--	594.4
2027	Me				B	--	579.3
2028	Me				A	--	579.3
2029	Me				B	--	635.3

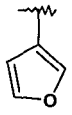
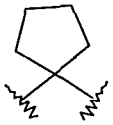
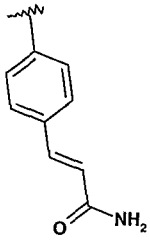
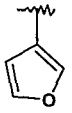
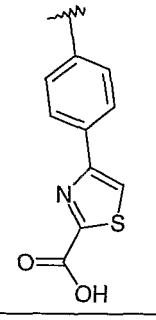
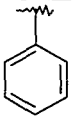
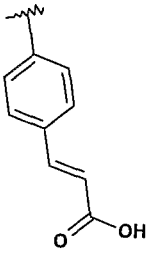
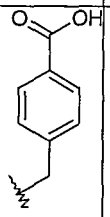
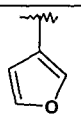
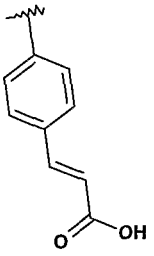
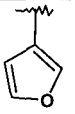
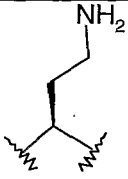
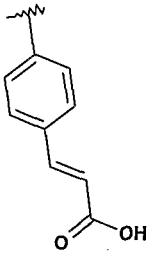
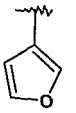
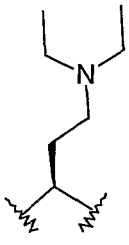
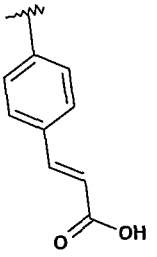
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2030	Me				C	B	565.3
2031	Me				C	B	595.3
2032	Me				B	B	608.4
2033	H				B	B	577.2
2034	Me				C	B	590.2
2035	H				C	B	576.2

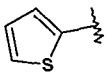
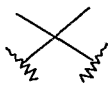
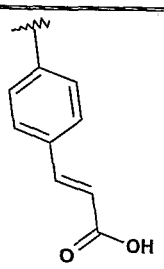
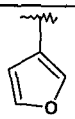
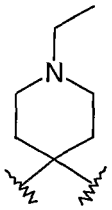
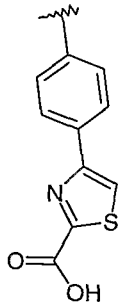
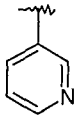
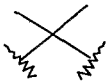
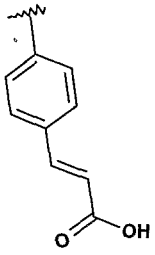
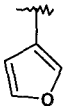
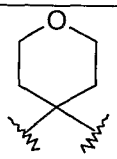
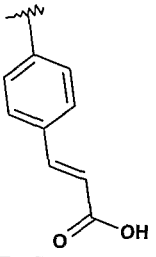
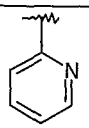
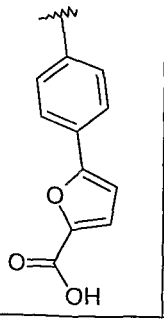
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2036	H				C	B	566.3
2037	H				C	B	566.2
2038	H				C	B	582.2
2039	H				C	B	593.3
2040					C	B	656.3
2041	Me				B	B	580.3

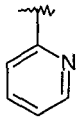
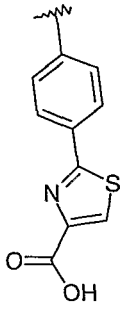
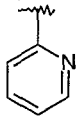
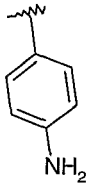
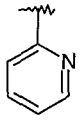
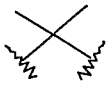
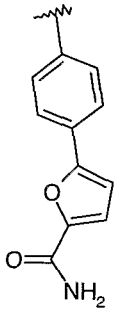
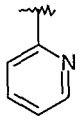
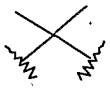
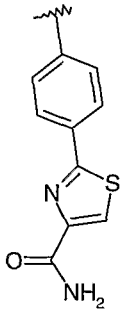
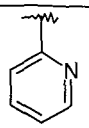
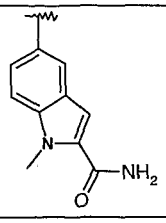
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2042	H				C	B	582.3
2043					C	B	657.3
2044	H				C	B	621.2
2045					C	--	742.3
2046	H				C	B	610.2
2047	H				C	B	553.2

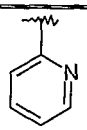
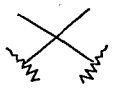
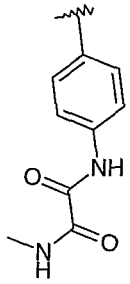
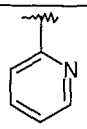
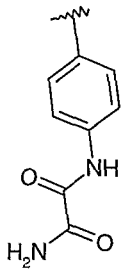
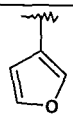
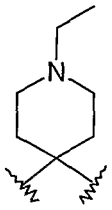
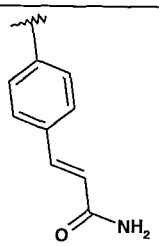
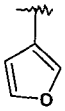
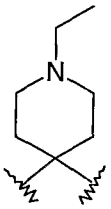
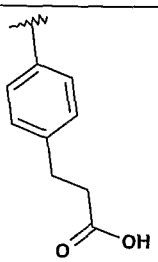
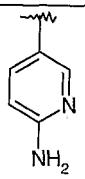
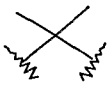
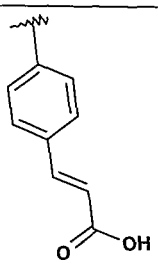
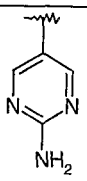
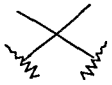
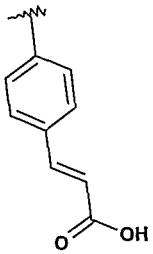
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2048	H				C	B	606.2
2049	H				C	A	620.3 (M-H)
2050	H				C	B	540.3
2051	Me				C	B	554.3
2052	H				C	B	595.4
2053	H				C	B	580.2

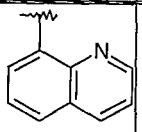
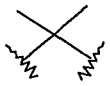
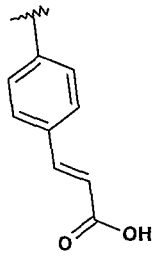
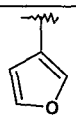
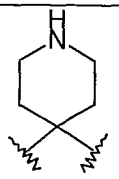
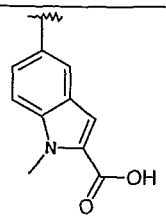
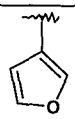
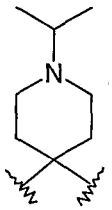
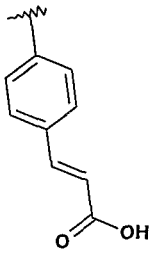
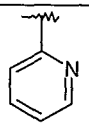
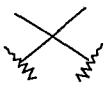
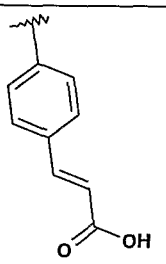
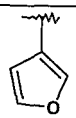
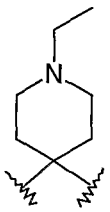
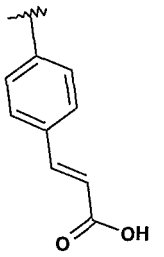
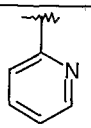
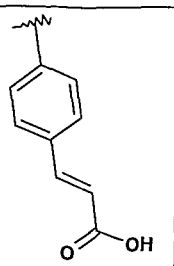
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2054	Et				C	B	568.2
2055	H				C	B	623.2
2056	H				C	B	580.2
2057	H				C	B	552.2
2058	H				C	B	550.2
2059	H				C	B	556.2

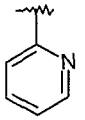
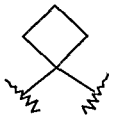
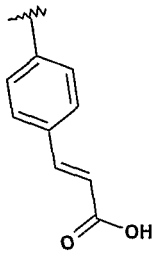
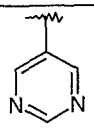
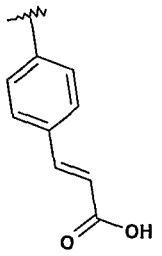
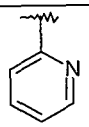
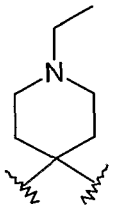
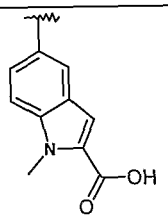
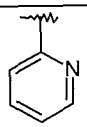
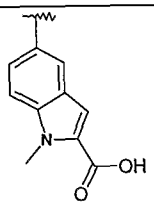
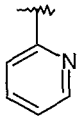
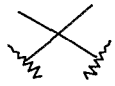
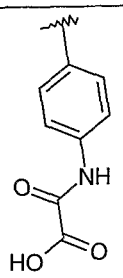
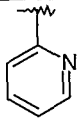
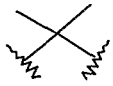
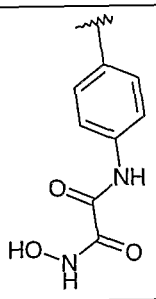
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2060	H				C	B	565.2
2061	H				C	A	597.1
2062	Me				C	B	564.2
2063					C	--	674.3
2064	H				C	--	555.2
2065	H				C	--	611.3

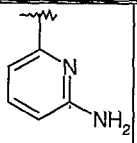
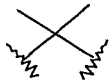
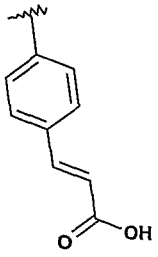
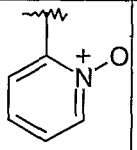
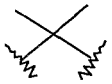
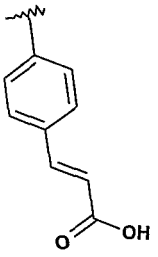
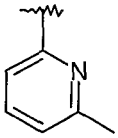
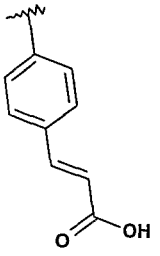
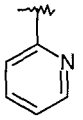
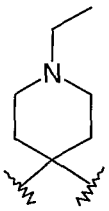
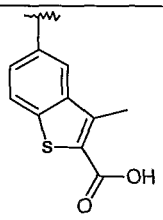
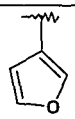
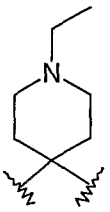
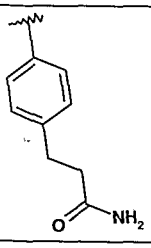
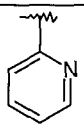
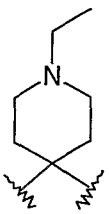
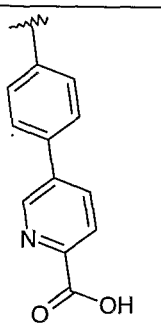
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2066	Me				C	B	570.2
2067	H				C	A	666.2
2068	Me				C	B	565.3
2069	H				C	B	582.3
2070	Me				C	B	605.2

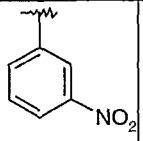
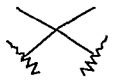
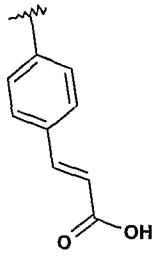
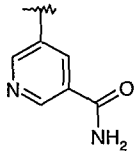
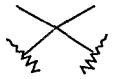
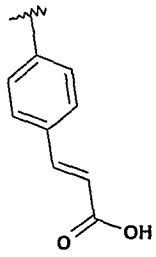
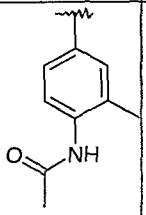
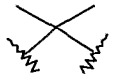
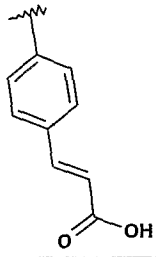
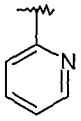
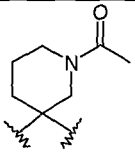
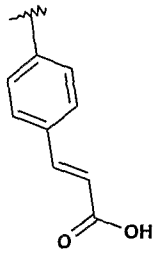
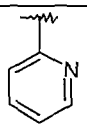
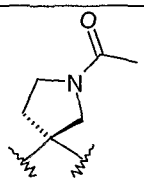
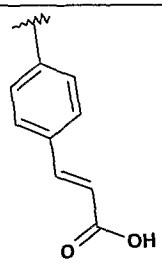
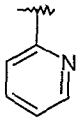
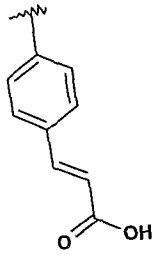
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2071	Me				C	B	622.2
2072	Me				C	B	510.2
2073	Me				C	B	604.2
2074	Me				C	B	621.2
2075	Me				C	B	591.3

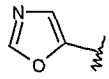
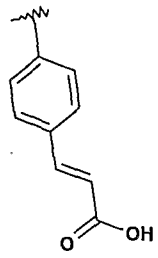
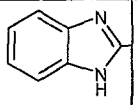
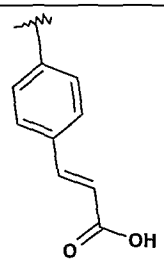
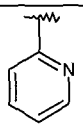
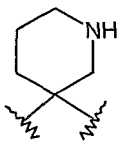
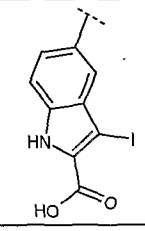
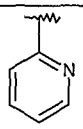
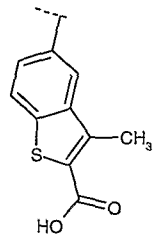
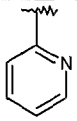
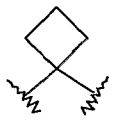
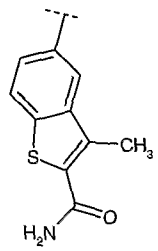
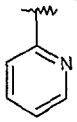
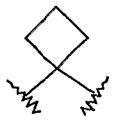
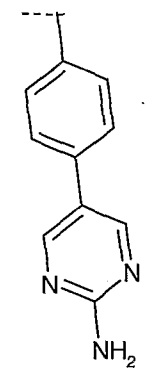
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2076	Me				C	B	595.3
2077	Me				C	B	581.3
2078	H				C	A	608.4
2079	H				C	A	611.4
2080	Me				C	B	580.3
2081	Me				C	B	581.3

Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2082	Me				C	B	615.3
2084	H				C	A	608.2
2086	H				C	B	623.3
2087	Me				C	B	565.2
2088	H				C	B	609.3
2089	H				C	B	551.2

Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2090	Me				C	B	577.2
2091	Me				C	B	566.3
2092	Me				C	B	661.3
2093	Me				C	B	592.3
2094	Me				C	A	582.2
2095	Me				C	B	597.3

Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2096	Me				C	B	580.3
2097	Me				C	A	581.3
2098	Me				C	B	579.3
2099	Me				C	B	678.4
2100	H				A	B	610.4
2101	Me				C	B	685.4

Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2102	Me				C	B	609.3
2103	Me				C	B	608.3
2104	Me				C	B	635.4
2105	Me				C	B	648.3
2106	Me				C	B	634.3
2107	Me				C	B	648.2

Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2108	Me				C	B	555.4
2109	Me				B	A	604.4
2110	Me				C	B	745.2
2111	Me				C	B	621.3
2112	Me				C	B	620.3
2113	Me				B	B	600.5

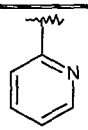
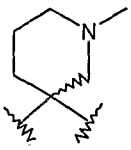
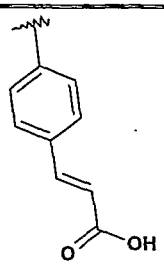
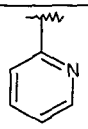
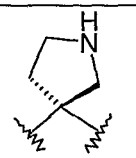
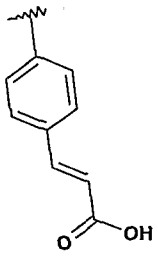
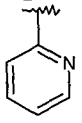
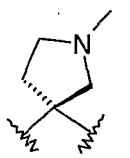
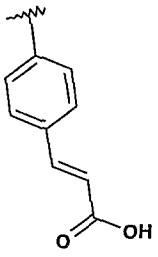
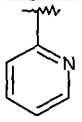
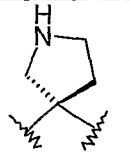
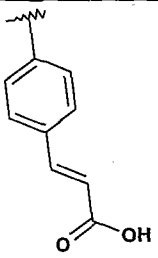
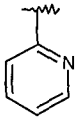
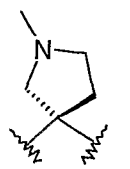
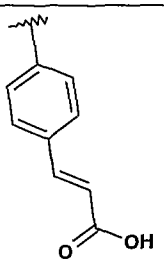
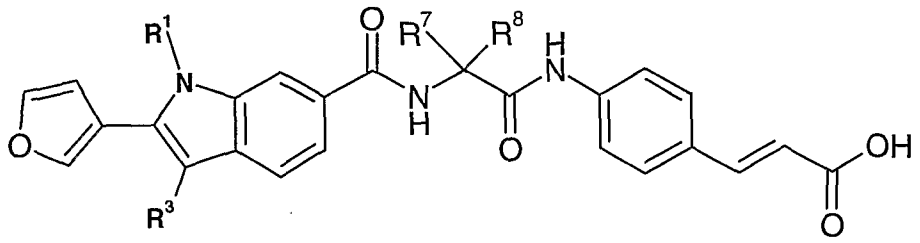
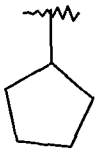
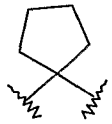
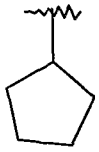
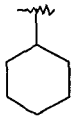
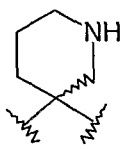
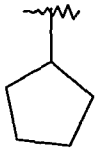
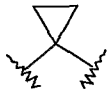
Cpd. #	R^1	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
2114	Me				C	B	620.3
2115	Me				C	B	592.3
2116	Me				C	B	606.3
2117	Me				C	B	592.3
2118	Me				C	B	606

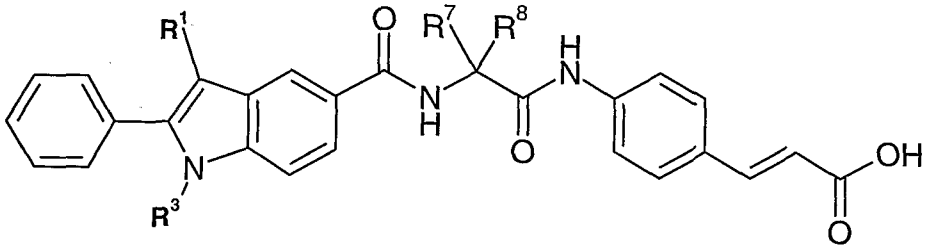
TABLE 3



cpd. #	R^1	R^3	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
3001	H			C	B	567.3
3002	H			C	B	552.2
3003	Me			C	B	526.2
3004	Me			C	C	538.3

5

TABLE 4



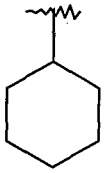
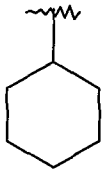
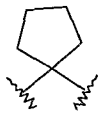
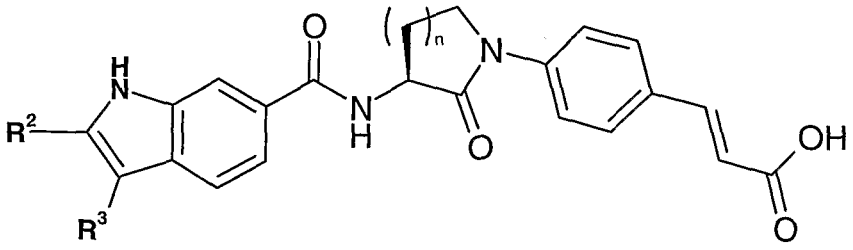
cpd. #	R^1	R^3		IC_{50}	EC_{50}	m/z $(M+H)^+$
4001	Me			B	B	590.3
4002	H			B	B	576.3

TABLE 5



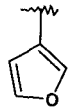
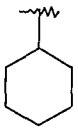
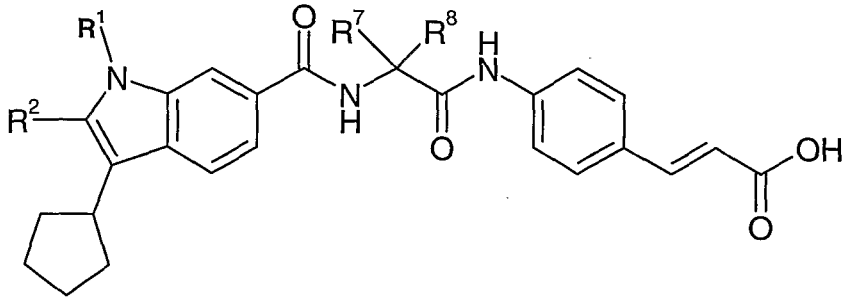
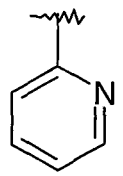
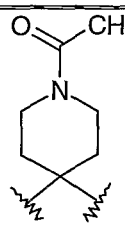
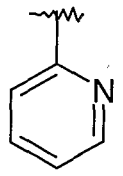
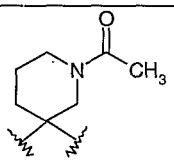
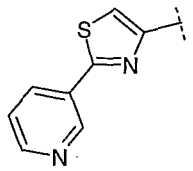
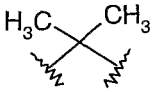
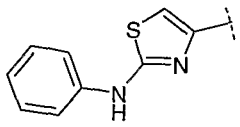
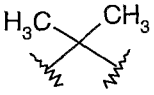
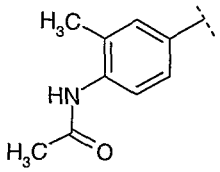
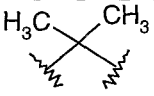
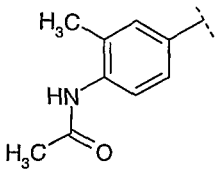
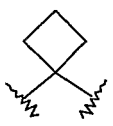
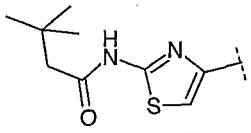
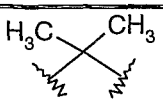
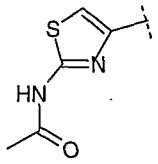
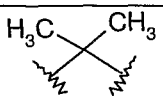
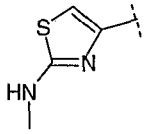
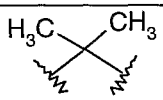
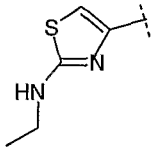
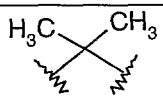
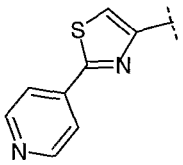
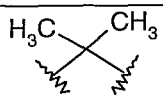
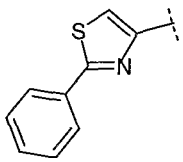
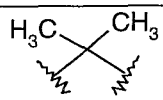
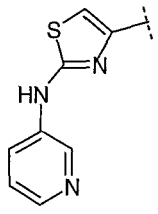
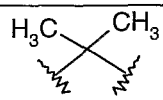
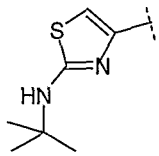
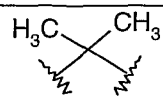
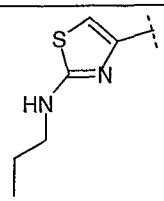
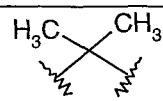
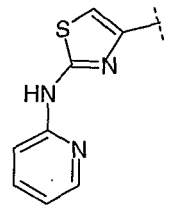
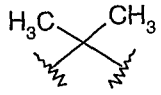
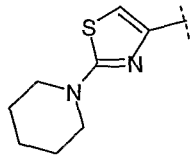
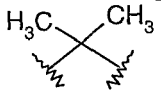
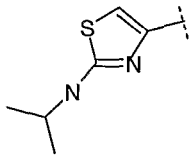
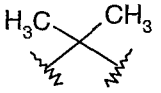
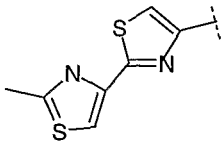
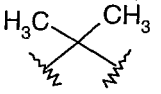
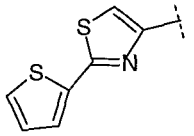
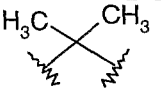
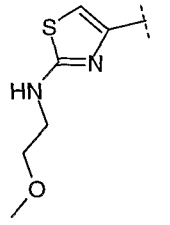
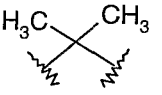
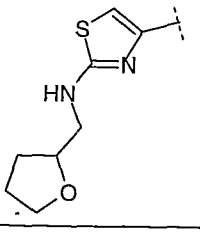
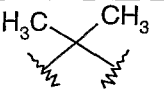
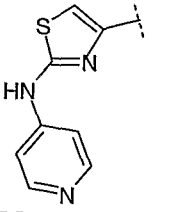
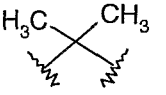
cpd. #	R^2	R^3	n	IC_{50}	EC_{50}	m/z $(M+H)^+$
5001			1	A	--	538.2

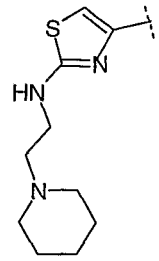
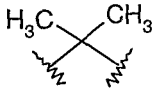
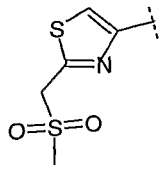
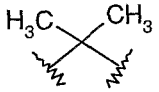
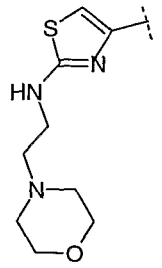
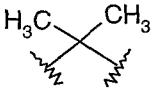
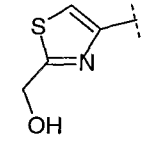
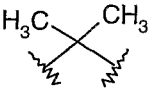
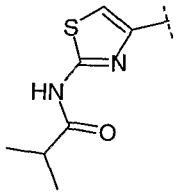
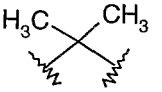
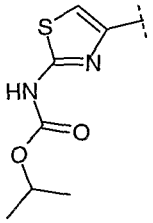
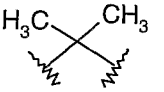
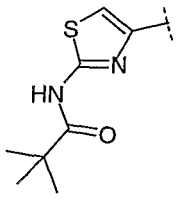
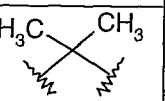
TABLE 6

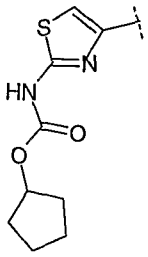
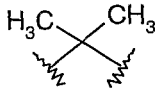
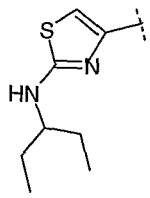
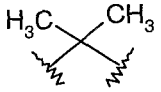
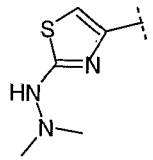
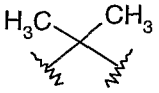
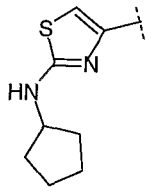
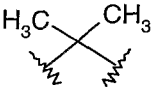
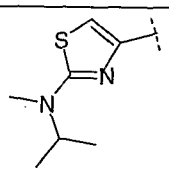
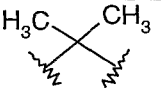
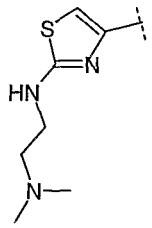
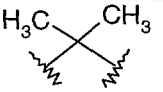
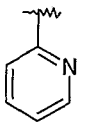
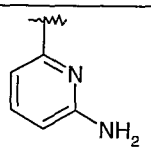


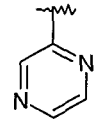
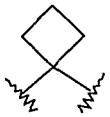
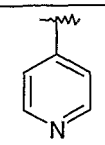
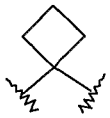
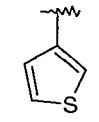
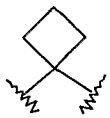
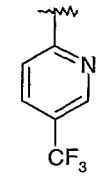
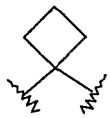
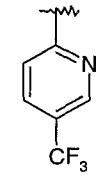
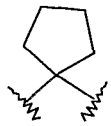
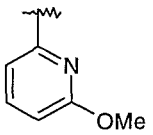
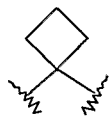
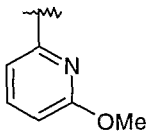
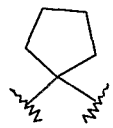
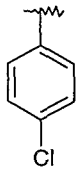
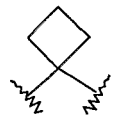
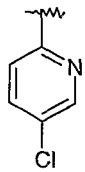
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6001	CH_3			C	B	634.3
6002	CH_3			C	B	634.3
6003	CH_3			C	B	634.2
6004	CH_3			B	--	648.2
6005	CH_3			C	B	621.3
6006	CH_3			C	B	633.3

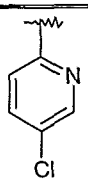
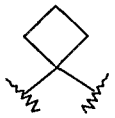
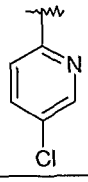
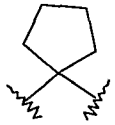
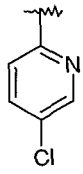
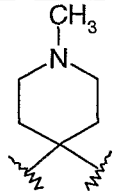
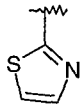
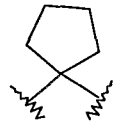
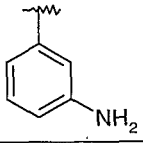
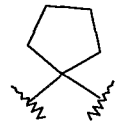
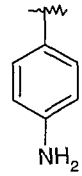
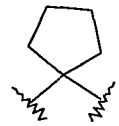
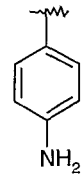
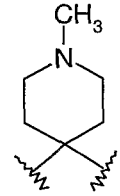
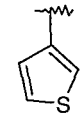
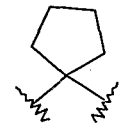
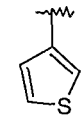
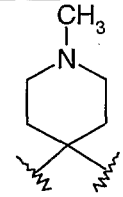
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6007	CH_3			C	B	670.3
6008	CH_3			C	B	614.3
6009	CH_3			C	B	586.3
6010	CH_3			C	B	600.3
6011	CH_3			C	B	634.3
6012	CH_3			B	B	633.3
6013	CH_3			C	B	649.3
6013	CH_3			C	B	628.3
6014	CH_3			C	B	614.3

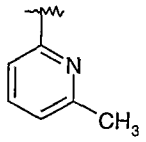
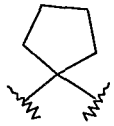
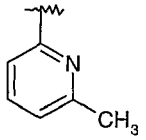
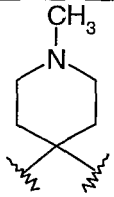
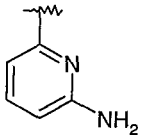
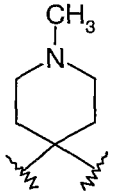
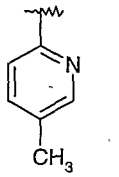
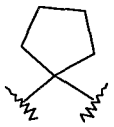
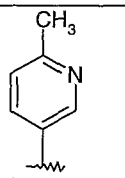
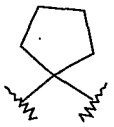
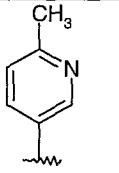
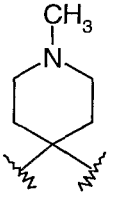
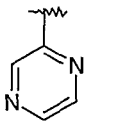
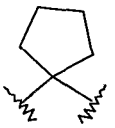
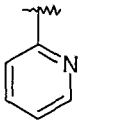
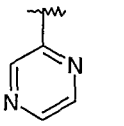
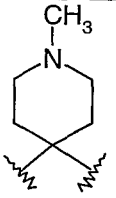
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6015	CH_3			B	B	649.3
6016	CH_3			C	B	640.4
6017	CH_3			C	B	614.3
6018	CH_3			C	B	654.3
6019	CH_3			B	B	639.3
6020	CH_3			C	B	630.3
6021	CH_3			C	B	656.4
6022	CH_3			B	B	649.3

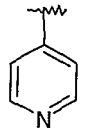
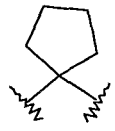
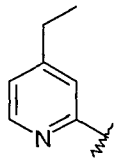
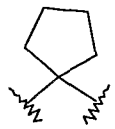
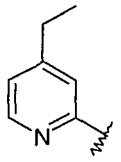
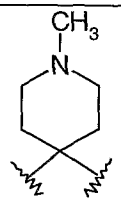
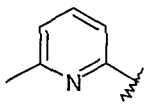
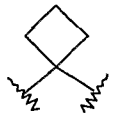
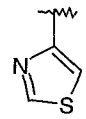
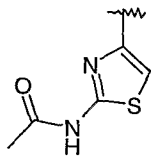
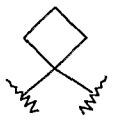
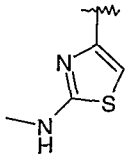
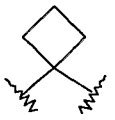
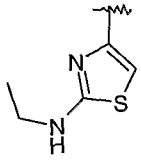
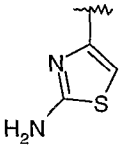
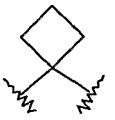
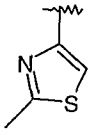
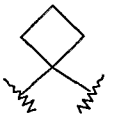
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6023	CH_3			C	B	683.4
6024	CH_3			C	B	649.3
6025	CH_3			C	B	685.4
6026	CH_3			C	B	587.3
6027	CH_3			C	B	642.3
6028	CH_3			C	B	658.3
6029	CH_3			C	B	656.4

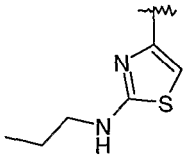
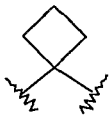
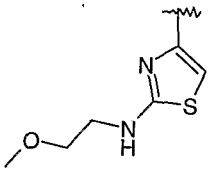
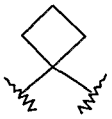
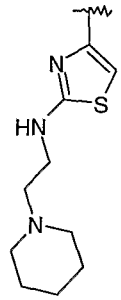
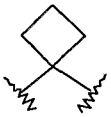
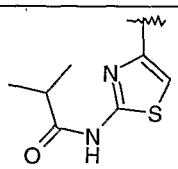
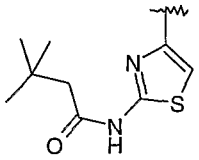
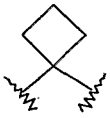
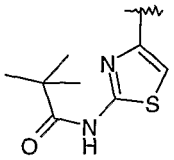
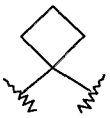
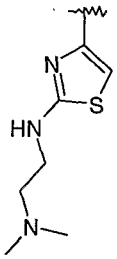
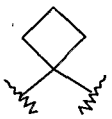
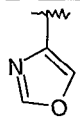
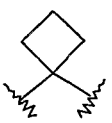
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6030	CH_3			B	B	684.4
6031	CH_3			B	B	642.4
6032	CH_3			C	B	615.3
6033	CH_3			B	B	640.4
6034	CH_3			C	B	628.4
6035	CH_3			C	B	643.4
6036	CH_3			C	B	549.3
6037	CH_3			C	B	564.3

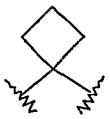
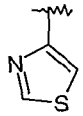
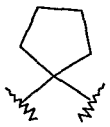
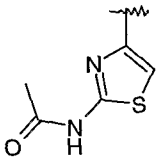
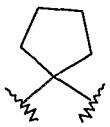
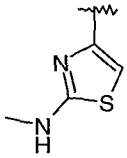
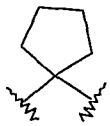
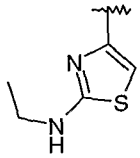
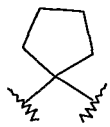
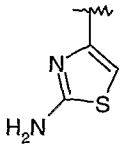
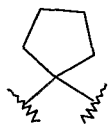
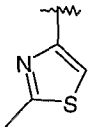
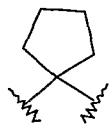
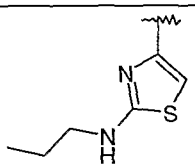
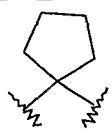
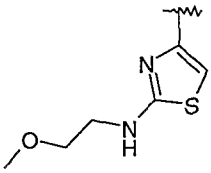
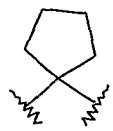
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6038	CH_3			C	B	564.3
6039	CH_3			C	B	563.3
6040	CH_3			C	B	568.3
6041	CH_3			C	B	631.3
6042	CH_3			C	B	645.3
6043	CH_3			C	B	593.3
6044	CH_3			C	B	607.3
6045	CH_3			B	B	596.3
6046	CH_3			C	B	500.2
6047	CH_3			C	B	285.2

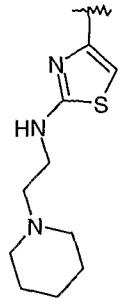
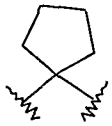
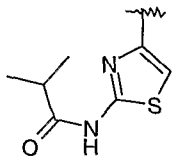
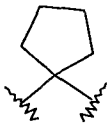
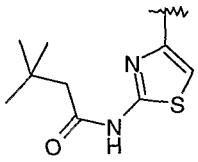
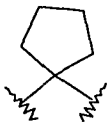
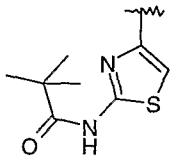
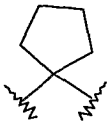
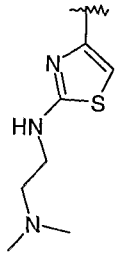
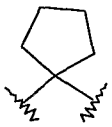
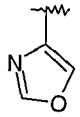
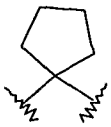
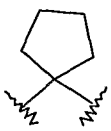
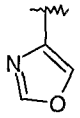
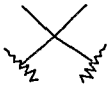
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6048	CH_3			C	B	597/2
6049	CH_3			C	B	611.2
6050	CH_3			C	B	640.3
6051	CH_3			C	B	583.3
6052	CH_3			C	B	591.3
6053	CH_3			C	B	591.3
6054	CH_3			C	B	620.4
6055	CH_3			C	B	582.3
6056	CH_3			C	B	611.3

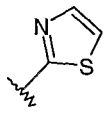
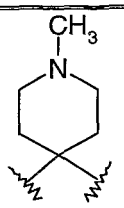
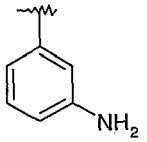
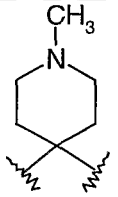
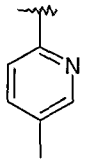
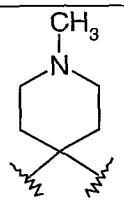
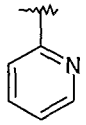
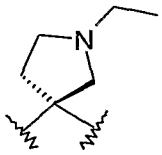
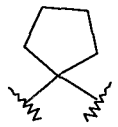
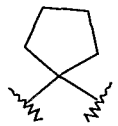
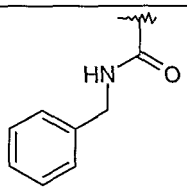
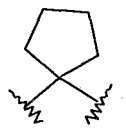
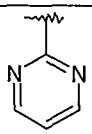
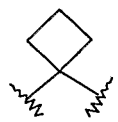
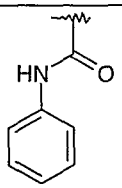
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6057	CH_3			C	B	591.4
6058	CH_3			C	B	620.4
6059	CH_3			C	B	621.4
6060	CH_3			C	B	591.4
6061	CH_3			C	B	591.3
6062	CH_3			C	B	620.4
6063	CH_3			C	B	578.3
6064	CH_3			C	B	563.3
6065	CH_3			C	A	607.3

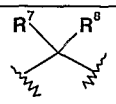
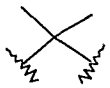
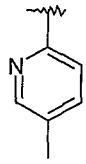
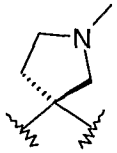
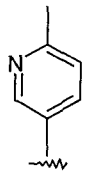
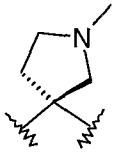
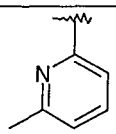
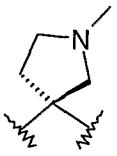
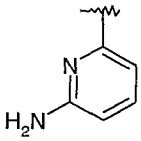
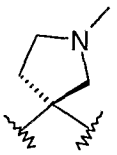
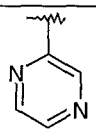
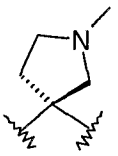
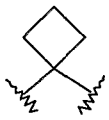
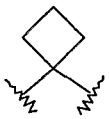
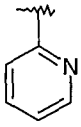
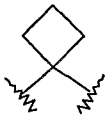
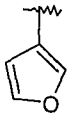
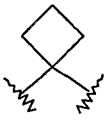
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6066	CH_3			C	B	577.3
6067	CH_3			A	A	605.4
6068	CH_3			C	A	634.4
6069	CH_3			C	B	577.3
6070	CH_3			C	B	569.2
6071	CH_3			C	B	626.2
6072	CH_3			C	B	598.3
6073	CH_3			C	B	612.3
6074	CH_3			C	B	584.3
6075	CH_3			C	B	583.3

cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6076	CH_3			C	B	626.3
6077	CH_3			C	B	642.3
6078	CH_3			C	B	695.4
6079	CH_3			C	B	654.3
6080	CH_3			C	B	682.4
6081	CH_3			C	B	668.4
6082	CH_3			C	B	655.4
6083	CH_3			C	B	553.3

cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6084	CH_3			C	B	512.3
6085	CH_3			C	B	583.3
6086	CH_3			C	B	640.3
6087	CH_3			C	B	612.3
6088	CH_3			C	B	626.3
6089	CH_3			C	B	598.3
6090	CH_3			C	B	597.3
6091	CH_3			C	B	640.4
6092	CH_3			C	B	656.4

cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6093	CH_3			C	B	709.4
6094	CH_3			C	B	668.4
6095	CH_3			C	B	696.4
6096	CH_3			C	B	682.4
6097	CH_3			C	B	669.4
6098	CH_3			C	B	567.3
6099	CH_3			C	B	526.4
6100	CH_3			C	B	541.3

cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6101	CH_3			C	B 0.165	612.3
6102	CH_3			C	B	620.4
6103	CH_3			C	B	620.4
6105	CH_3			C	B	620.4
6106	CH_3	$CONHCH_3$		B	--	557.3
6107	CH_3	$CON(CH_3)_2$		A	--	571.3
6110	CH_3			A	--	633.3
6111	CH_3			C	B	564.3
6112	CH_3			B	--	593.3

cpd. #	R^1	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
6113	CH_3	$CONH_2$		B	--	517.3
6114	CH_3			C	B	606.3
6115	CH_3			C	B	606.3
6116	CH_3			C	B	606.3
6117	CH_3			C	B	607.3
6118	CH_3			C	B	593.3
6119	CH_3	H		A	--	486.3
6120	CH_3	Br		B	--	566.2
6121	H			B	B	549.3
6122	CH_3			C	B	581.3

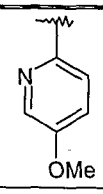
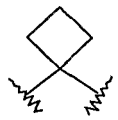
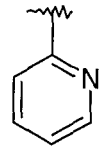
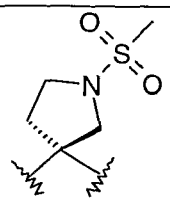
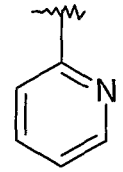
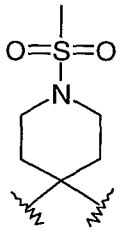
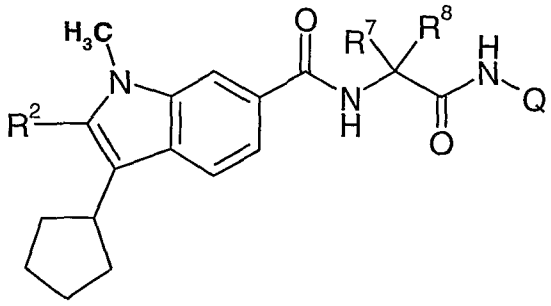
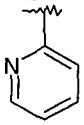
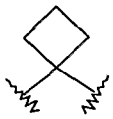
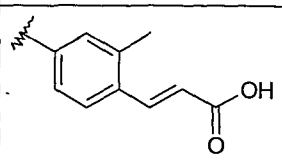
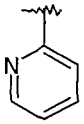
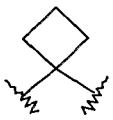
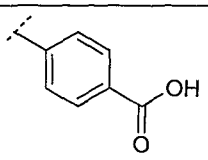
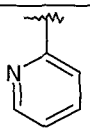
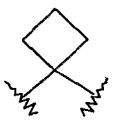
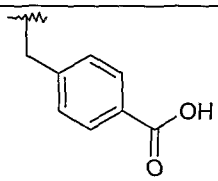
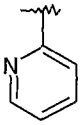
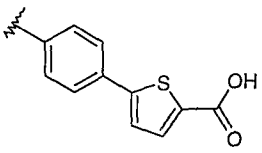
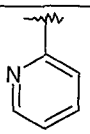
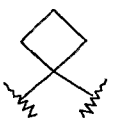
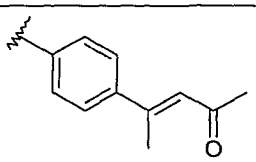
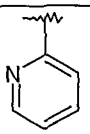
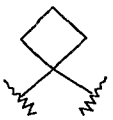
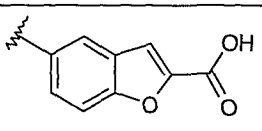
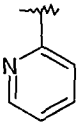
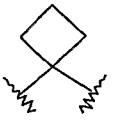
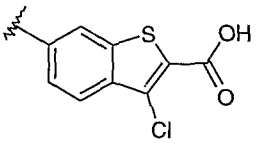
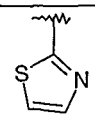
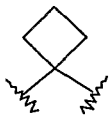
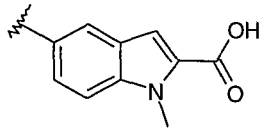
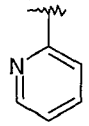
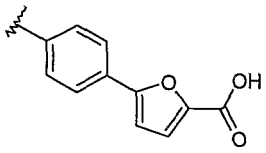
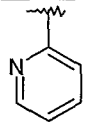
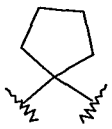
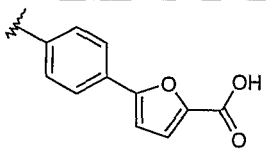
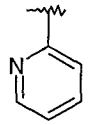
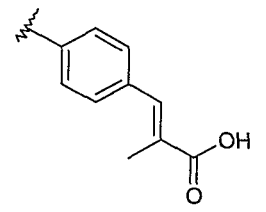
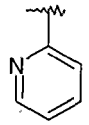
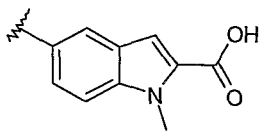
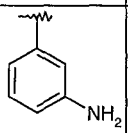
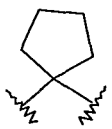
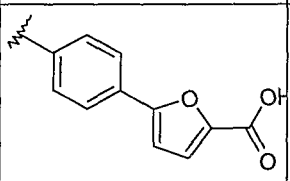
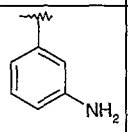
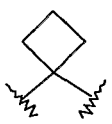
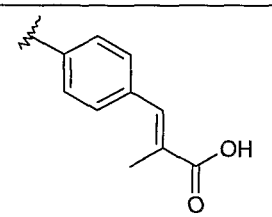
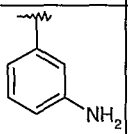
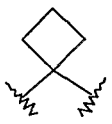
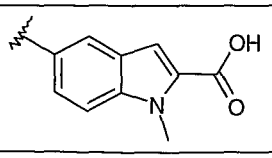
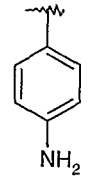
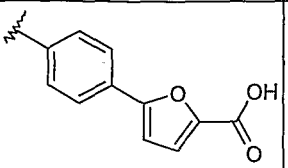
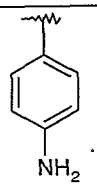
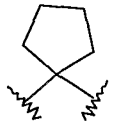
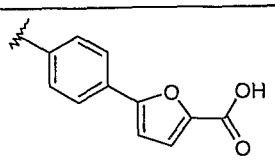
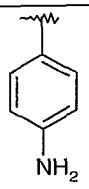
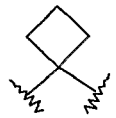
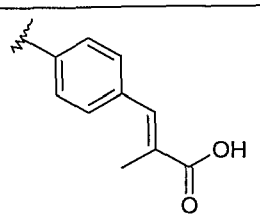
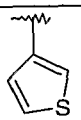
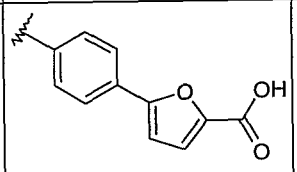
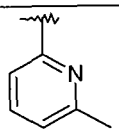
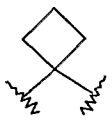
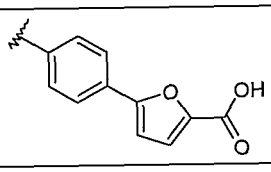
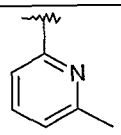
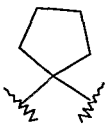
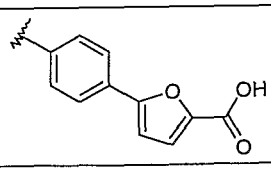
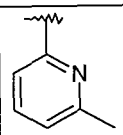
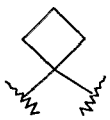
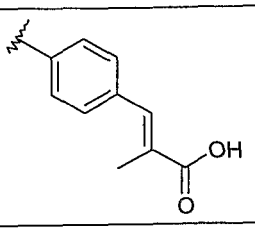
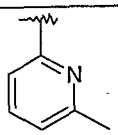
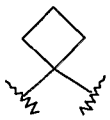
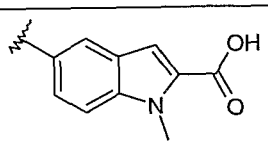
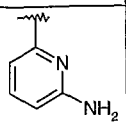
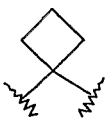
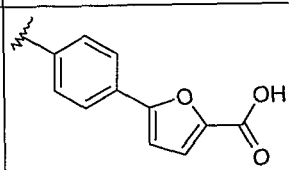
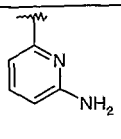
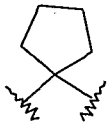
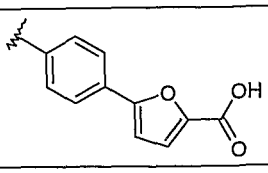
cpd. #	R^1	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
6123	CH_3			C	B	593.4
6124	CH_3			C	B	656.4
6125	CH_3			C	B	670.4

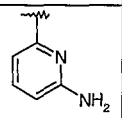
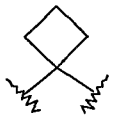
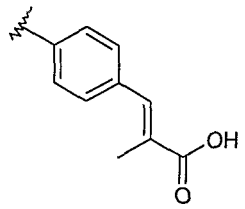
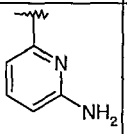
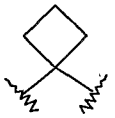
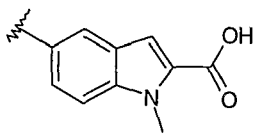
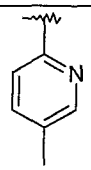
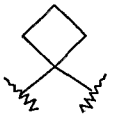
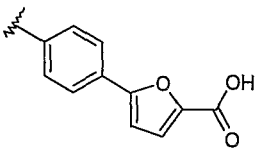
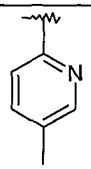
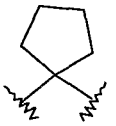
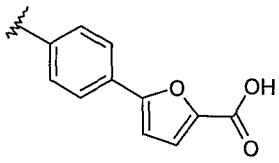
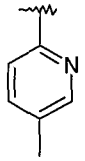
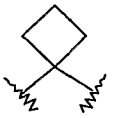
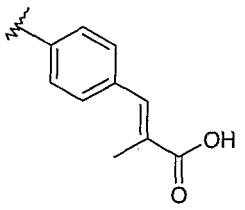
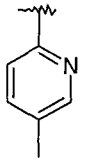
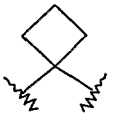
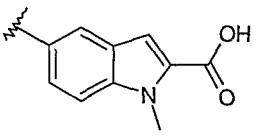
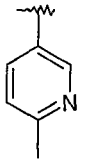
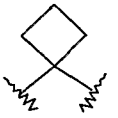
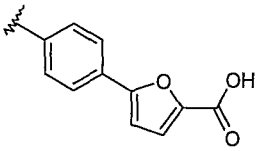
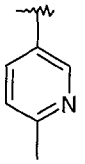
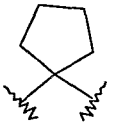
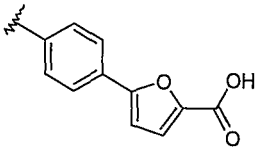
TABLE 7

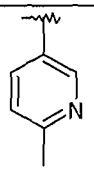
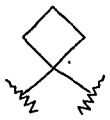
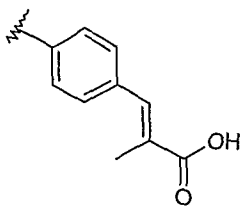
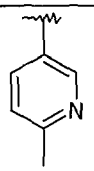
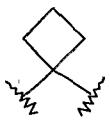
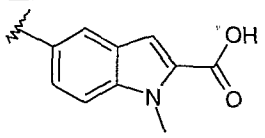
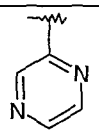
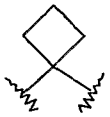
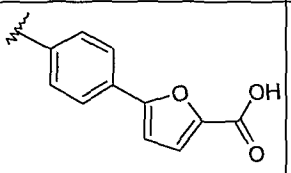
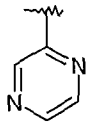
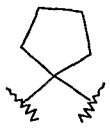
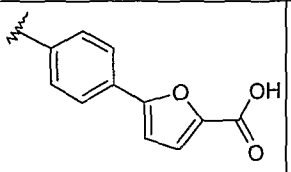
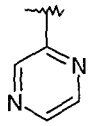
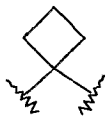
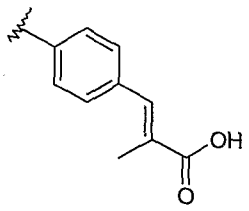
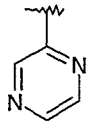
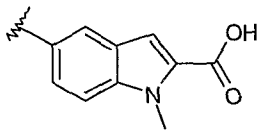
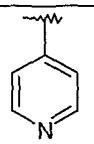
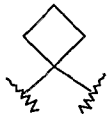
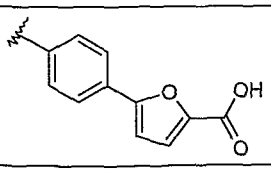
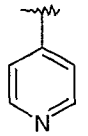
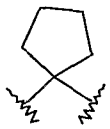
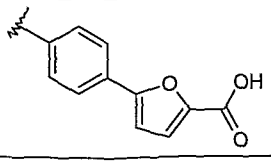
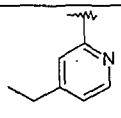
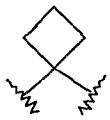
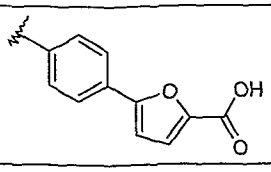


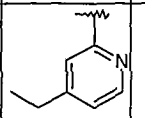
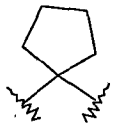
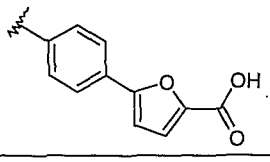
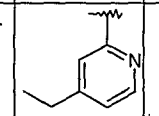
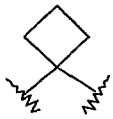
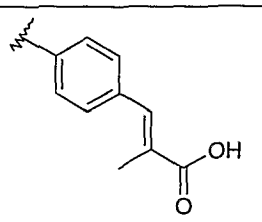
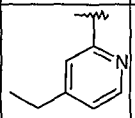
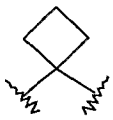
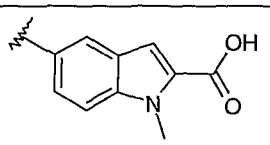
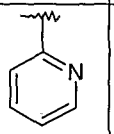
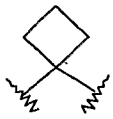
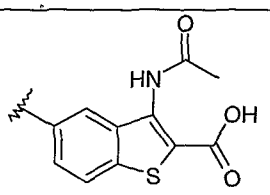
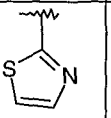
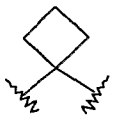
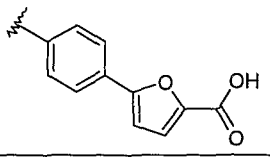
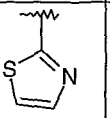
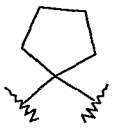
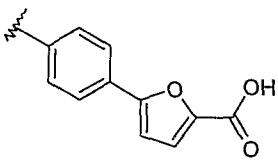
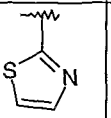
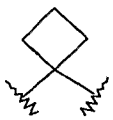
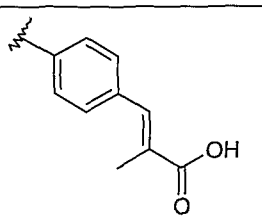
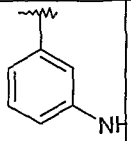
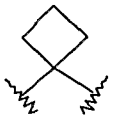
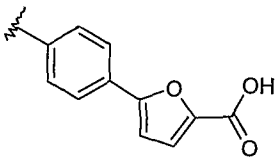
cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7001				C	B	577.3
7002				A	A	552.3
7003				A	A	551.3
7004				B	B	619.2
7005				C	B	577.3
7006				C	B	577.2
7007				C	B	627.2

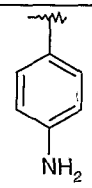
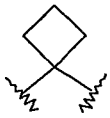
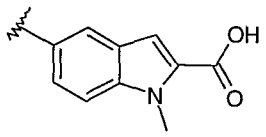
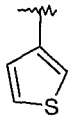
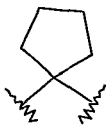
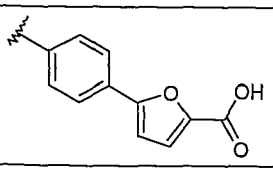
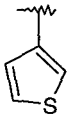
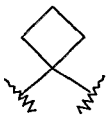
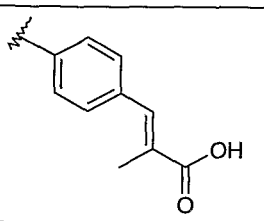
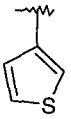
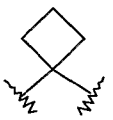
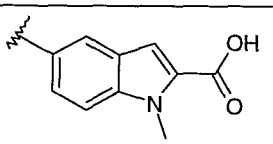
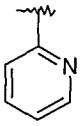
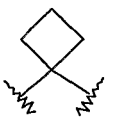
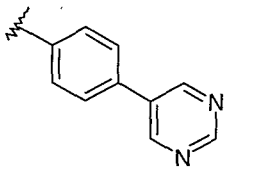
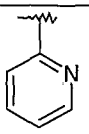
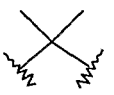
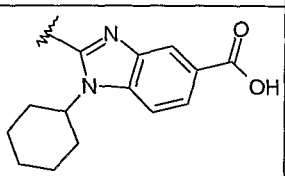
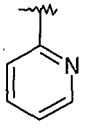
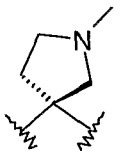
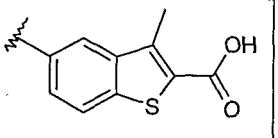
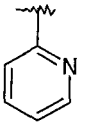
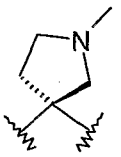
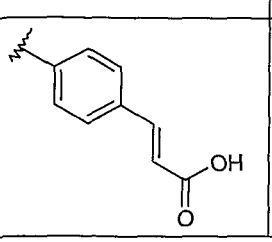
cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7008				C	B	596.2
7009				C	B	603.3
7010				C	B	617.3
7011				C	B	577.3
7012				C	B	590.3
7013				C	B	631.3
7014				C	B	591.3
7015				C	B	604.3
7016				C	B	617.3

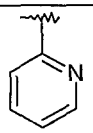
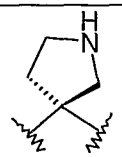
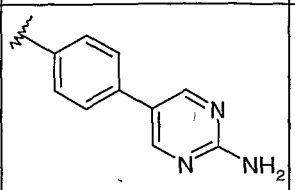
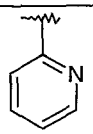
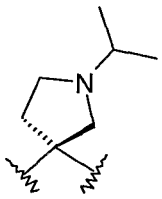
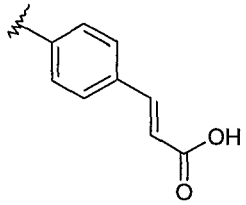
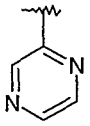
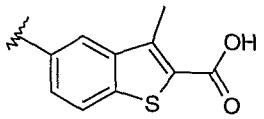
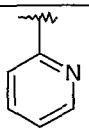
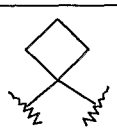
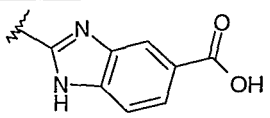
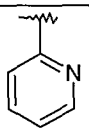
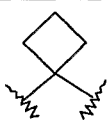
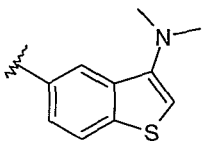
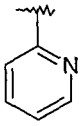
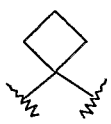
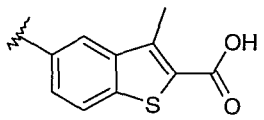
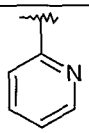
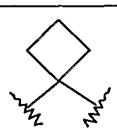
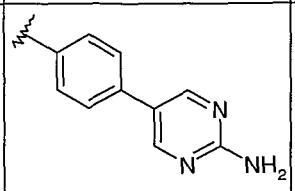
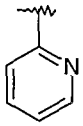
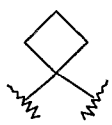
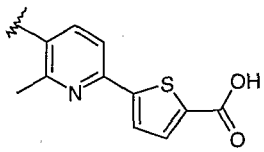
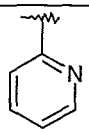
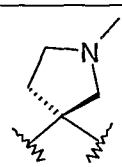
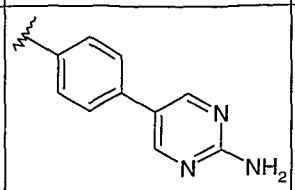
cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7017				C	B	631.3
7018				C	B	591.4
7019				C	B	608.3
7020				C	B	617.3
7021				C	B	631.3
7022				C	B	591.3
7023				C	B	604.4
7024				C	B	618.3
7025				C	B	632.3

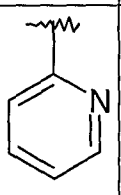
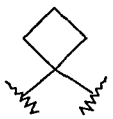
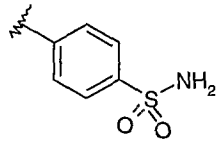
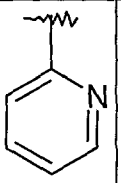
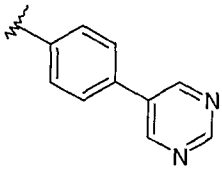
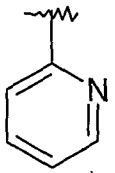
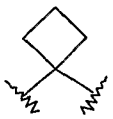
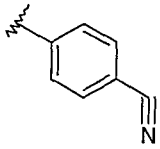
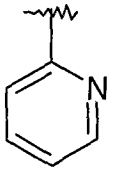
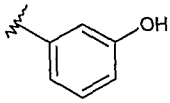
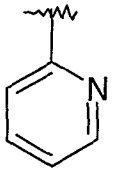
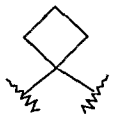
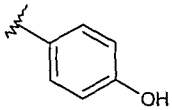
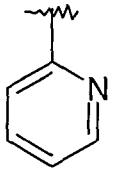
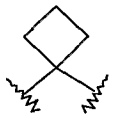
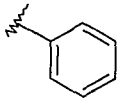
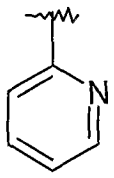
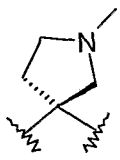
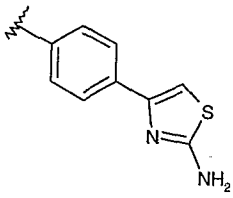
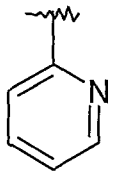
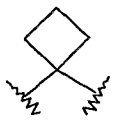
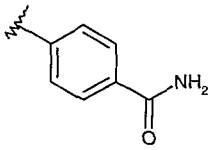
cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7026				C	B	592.3
7027				C	B	605.3
7028				C	B	617.3
7029				C	B	631.3
7030				C	B	591.4
7031				C	B	604.3
7032				C	B	617.3
7033				C	B	631.4

cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7034				C	B	591.4
7035				C	B	604.3
7036				C	B	604.3
7037				C	B	618.3
7038				C	B	578.3
7039				C	B	613.3
7040				C	B	603.3
7041				C	B	617.3
7042				A	A	631.3

cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7043				A	A	645.4
7044				A	A	605.4
7045				A	A	618.4
7046				C	--	650.2
7047				C	B	609.3
7048				C	B	623.3
7049				C	B	583.3
7050				C	B	617.4

cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7051				C	B	604.4
7052				C	B	622.3
7053				C	B	582.3
7054				C	B	595.3
7055				B	A	571.3
7056				A	--	647.4
7057				C	B	636.3
7058				C	B	592.4

cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7059				C	A	601.4
7060				C	B	620.5
7061				C	B	637.3
7062				C	--	577.4
7063				B	--	592.4
7064				C	B	607.3
7065				B	A	586.4
7066				A	A	634.4
7067				C	--	615.4

cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7068				C	B	572.4
7069				C	B	600.4
7070				B	--	518.4
7071				C	--	509.3
7072				C	--	509.4
7073				B	--	493.4
7075				C	--	620.5
7076				C		536.4

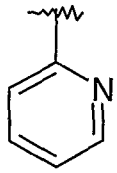
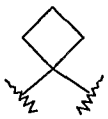
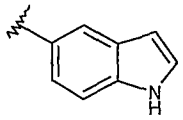
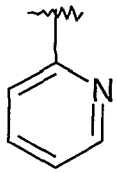
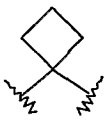
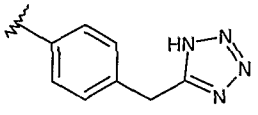
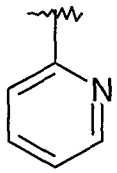
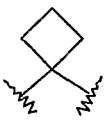
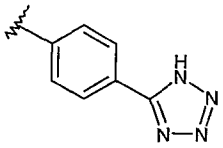
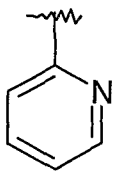
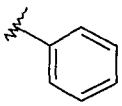
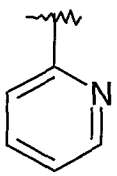
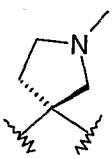
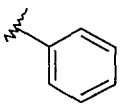
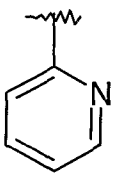
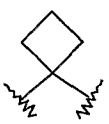
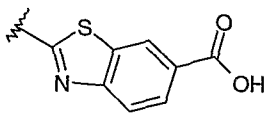
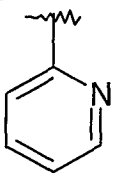
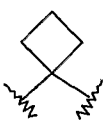
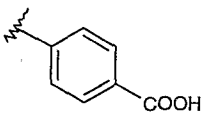
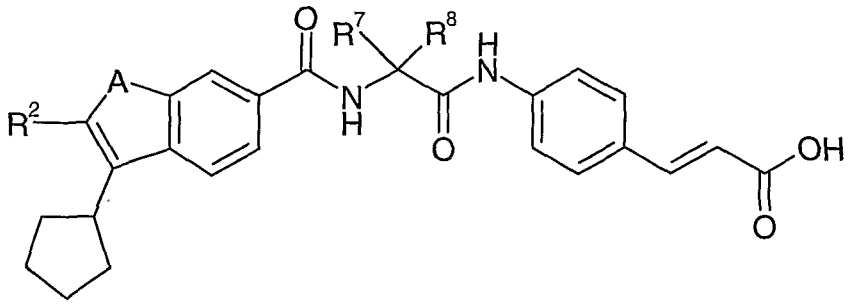
cpd #	R^2	R^7 R^8	Q	IC_{50}	EC_{50}	m/z $(M+H)^+$
7077				C	B	532.4
7078				B	--	575.3
7079				C	B	561.3
7080				C	A	508.5
7081				C	A	522.3
7082				C	--	594.2
7083				C	--	537.3

TABLE 8



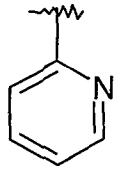
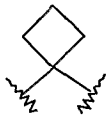
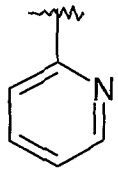
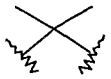
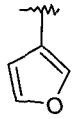
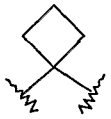
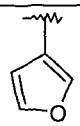
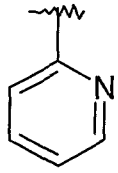
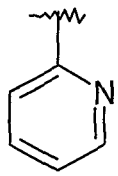
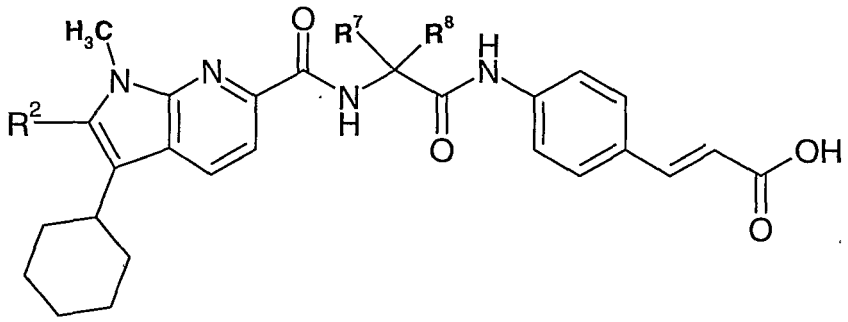
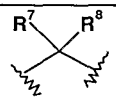
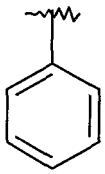
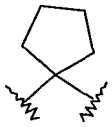
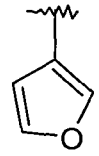
cpd. #	A	R^2	R^7 R^8	IC_{50}	EC_{50}	m/z $(M+H)^+$
8001	S			A	A	566.3
8002	S			A	A	554.3
8003	S			B	--	555.3
8004	S			C	--	543.3
8005	O			A	--	550.3
8006	O			A	--	538.3

TABLE 9

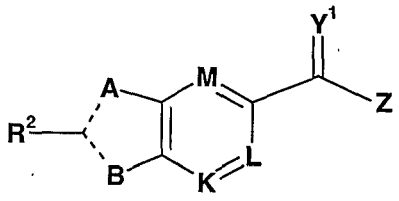


cpd. #	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
9001			B	--	591.4
9002			C	B	567.4

5

CLAIMS

1. An isomer, enantiomer, diastereoisomer, or tautomer of a compound, represented by formula I:



(I)

wherein:

A is O, S, NR^1, or CR^1, wherein R^1 is selected from the group consisting of: H, (C_{1-6})alkyl optionally substituted with:

-halogen, OR^{11}, SR^{11} or $N(R^{12})_2$, wherein R^{11} and each R^{12} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, said aryl or **Het** optionally substituted with R^{10}; or

both R^{12} are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;

----- represents either a single or a double bond;

R^2 is selected from: halogen, R^{21}, OR^{21}, SR^{21}, $COOR^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})_2$, , $CON(R^{22})_2$, $NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said R^{21} and R^{22} being optionally substituted with R^{20};

or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

B is NR^3 or CR^3, with the proviso that one of **A** or **B** is either CR^1 or CR^3, wherein R^3 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, cycloakenyl, bicycloalkyl, bicycloalkenyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- OR^{31} or SR^{31} wherein R^{31} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or
- $N(R^{32})_2$ wherein each R^{32} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{32} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR^{33} wherein R^{33} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) SR^{34} wherein R^{34} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(R^{35})_2$ wherein each R^{35} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{35} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

K is N or CR^4, wherein R^4 is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^4 is OR^{41} or SR^{41}, COR^{41} or $NR^{41}COR^{41}$ wherein each R^{41} is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^4 is $NR^{42}R^{43}$ wherein R^{42} and R^{43} are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both R^{42} and R^{43} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or CR^5, wherein R^5 has the same definition as R^4 defined above;

M is N or CR^7, wherein R^7 has the same definition as R^4 defined above;

Y^1 is O or S;

Z is OR^6 wherein R^6 is C_{1-6}alkyl substituted with:

- 1 to 4 substituents selected from: OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or

(C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted

with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$, or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to

which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or **Z** is OR^6 wherein R^6 is (C_{1-6}alkyl)aryl substituted with:

- 1 to 4 substituents selected from: OPO_3H, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108a}, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-}

$_6$alkyl)aryl or (C_{1-6}alkyl)**Het,** and $\mathbf{R^{115a}}$ is the same as $\mathbf{R^{115}}$ but is not H or unsubstituted alkyl, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$; or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-}

$_6$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl,

aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-}

$_6$alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or **Z** is OR^6 wherein R^6 is, (C_{3-6})cycloalkyl, (C_{2-6})alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-**Het**, wherein said cycloalkyl, alkenyl, aryl, **Het** or alkyl-**Het**, is optionally substituted with R^{60};

or **Z** is $N(R^{6a})R^6$, wherein R^{6a} is H or (C_{1-6}alkyl) and

R^6 is (C_{1-6})alkyl optionally substituted with:

- 1 to 4 substituents selected from: OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl substituted with R^{150a}, haloalkyl substituted with R^{150}, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not halogen, OH, O(C_{1-6}alkyl), COOH, COO(C_{1-6}alkyl), NH_2, NH(C_{1-6}alkyl) and N(C_{1-6}alkyl)$_2$;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated

heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are

attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**; (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl optionally substituted with $\mathbf{R^{160}}$, and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl,

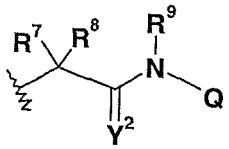
or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein $\mathbf{R^{161}}$ and $\mathbf{R^{162}}$ are as defined above;

or **Z** is $N(R^{6a})R^6$ wherein $\mathbf{R^{6a}}$ is as defined above and $\mathbf{R^6}$ is (C_{3-6})cycloalkyl, (C_{2-6})alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with $\mathbf{R^{60}}$;

or **Z** is OR^6 or $N(R^{6a})R^6$ wherein $\mathbf{R^{6a}}$ is as defined above and $\mathbf{R^6}$ is:



wherein $\mathbf{R^7}$ and $\mathbf{R^8}$ are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with $\mathbf{R^{70}}$; or

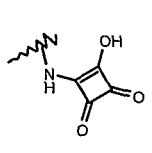
$\mathbf{R^7}$ and $\mathbf{R^8}$ are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is $N(R^{6a})R^6$, either of $\mathbf{R^7}$ or $\mathbf{R^8}$ is covalently bonded to $\mathbf{R^{6a}}$ to form a nitrogen-containing 5-or 6-membered heterocycle;

Y^2 is O or S;

R^9 is H, (C_{1-6} alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het,** all of which optionally substituted with R^{90}; or

R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle;

Q is a 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, (C_{1-6}) alkyl-CONH-aryl or (C_{1-6}) alkyl-CONH-**Het**, all of which being optionally substituted with:



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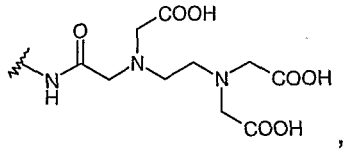


, or R^{100};

or a salt or a derivative thereof;

wherein **Het** is defined as 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms selected from O, N and S; and

R^{10}, R^{20}, R^{60}, R^{70}, R^{90} and R^{100} is each defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or

(C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{150}}$ is defined as:

- 1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are

covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$, or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-}

$_7$)cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

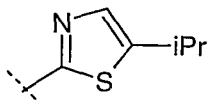
i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$; and

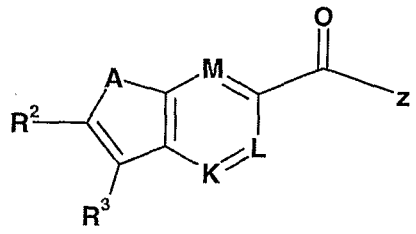
wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein $\mathbf{R^{161}}$ and each $\mathbf{R^{162}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both $\mathbf{R^{162}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

or a salt thereof,

with the proviso that, when **A** is CH, $\mathbf{R^2}$ is phenyl or N-butyl, **B** is NR^3, $\mathbf{R^3}$ is Me, **K** is CH, **L** is CH, **M** is CH, $\mathbf{Y^1}$ is O, and **Z** is NHR^6, then $\mathbf{R^6}$ is not 

.

2. A compound of formula (II):



(II)

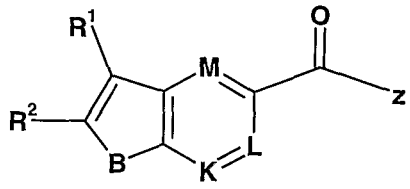
wherein, **A** is O, S, or NR^1 and R^1, R^2, R^3, **K**, **L**, **M** and **Z** are as defined in claim 1.

3. The compound according to claim 2, wherein **A** is NR^1.

4. The compound according to claim 2, wherein **M, K** and **L** is CH or N.

5. The compound according to claim 4, wherein **M, K** and **L** is CH.

6. A compound of formula (III):



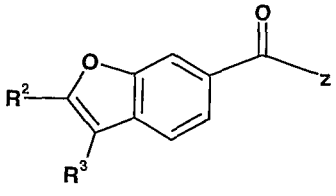
(III)

wherein, **B** is NR^3 and R^1, R^2, R^3, **K**, **L**, **M** and **Z** are as defined in claim 1.

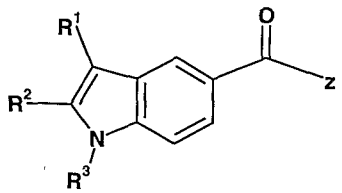
7. The compound according to claim 6, wherein **M, K** and **L** is CH or N.

8. The compound according to claim 7, wherein **M, K** and **L** is CH.

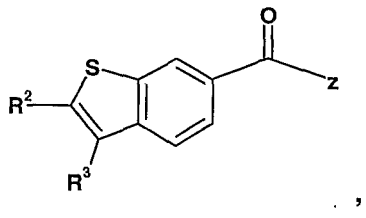
9. A compound of the formula:



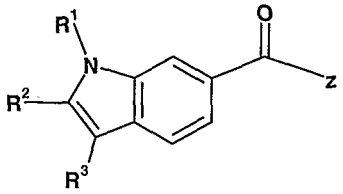
IIa



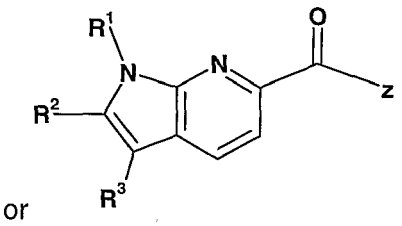
IIIa



IIb



IIc



or

IId

wherein R^1, R^2, R^3 and **Z** are as defined in claim 1.

10. The compound according to claim 1, wherein R^1 is selected from: H or (C_{1-6})alkyl.

11. The compound according to claim 10, wherein R^1 is H, CH_3, isopropyl, or isobutyl.

12. The compound according to claim 11, wherein R^1 is H or CH_3.

13. The compound according to claim 12, wherein R^1 is CH_3.

14. The compound according to claim 1, wherein R^2 is $CON(R^{22})_2$, wherein each R^{22} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached; or R^2 is selected from: H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**; wherein each of said alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, aryl or **Het** is optionally substituted with R^{20}, wherein R^{20} is defined as:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{150}}$;

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which

they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$; or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or $O(C_{1-6}$alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het**, (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; wherein $\mathbf{R^{150}}$ is:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het** and heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, or (C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, and heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

15. The compound according to claim 14, wherein R^2 is selected from: aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3, or

a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}$ alkyl);

b) (C_{1-6})alkoxy;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; being optionally substituted with halogen or:

- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6})alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;

f) $NHCOR^{117}$ wherein R^{117} is (C_{1-6})alkyl, $O(C_{1-6})$alkyl or $O(C_{3-7})$cycloalkyl;

i) CO-aryl; and

k) $CONH_2$, $CONH(C_{1-6}$alkyl), $CON(C_{1-6}$alkyl)$_2$, CONH-aryl, or $CONHC_{1-6}$alkyl aryl.

16. The compound according to claim 15, wherein R^2 is aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or

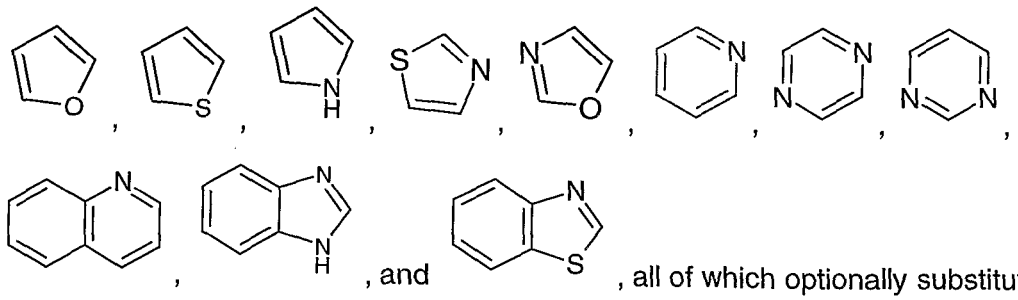
a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}$alkyl);

b) (C_{1-6})alkoxy; and

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; or being optionally substituted with halogen or:

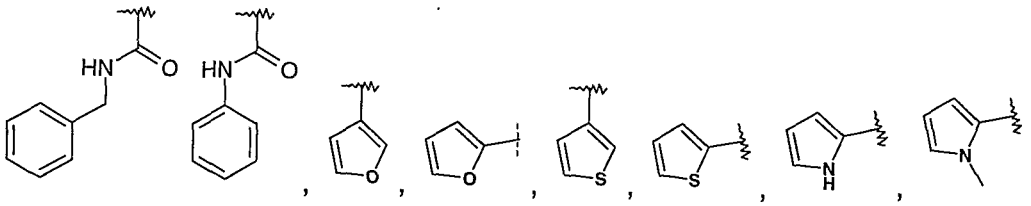
- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6})alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle.

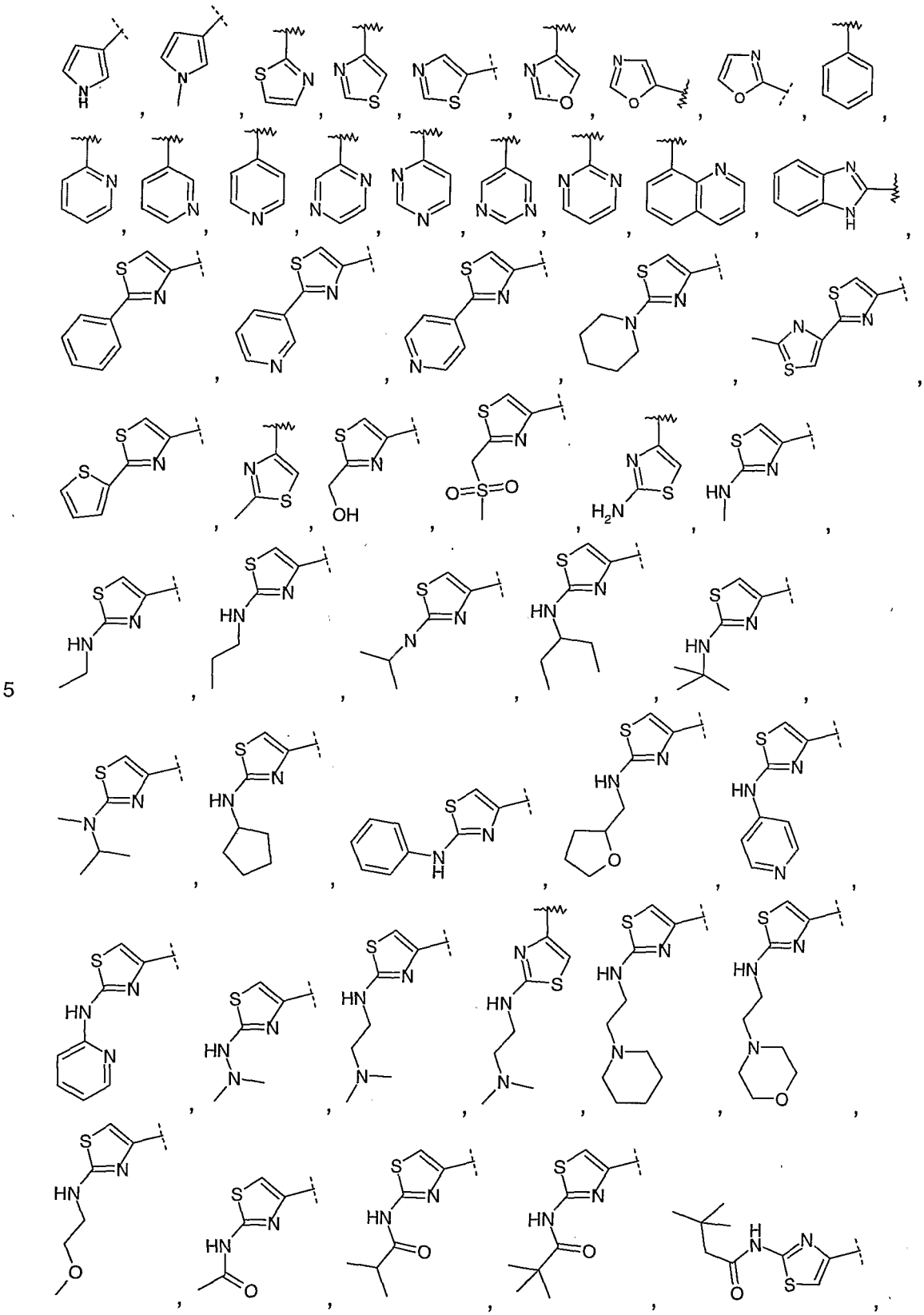
17. The compound according to claim 16, wherein R^2 is phenyl or a heterocycle selected from:

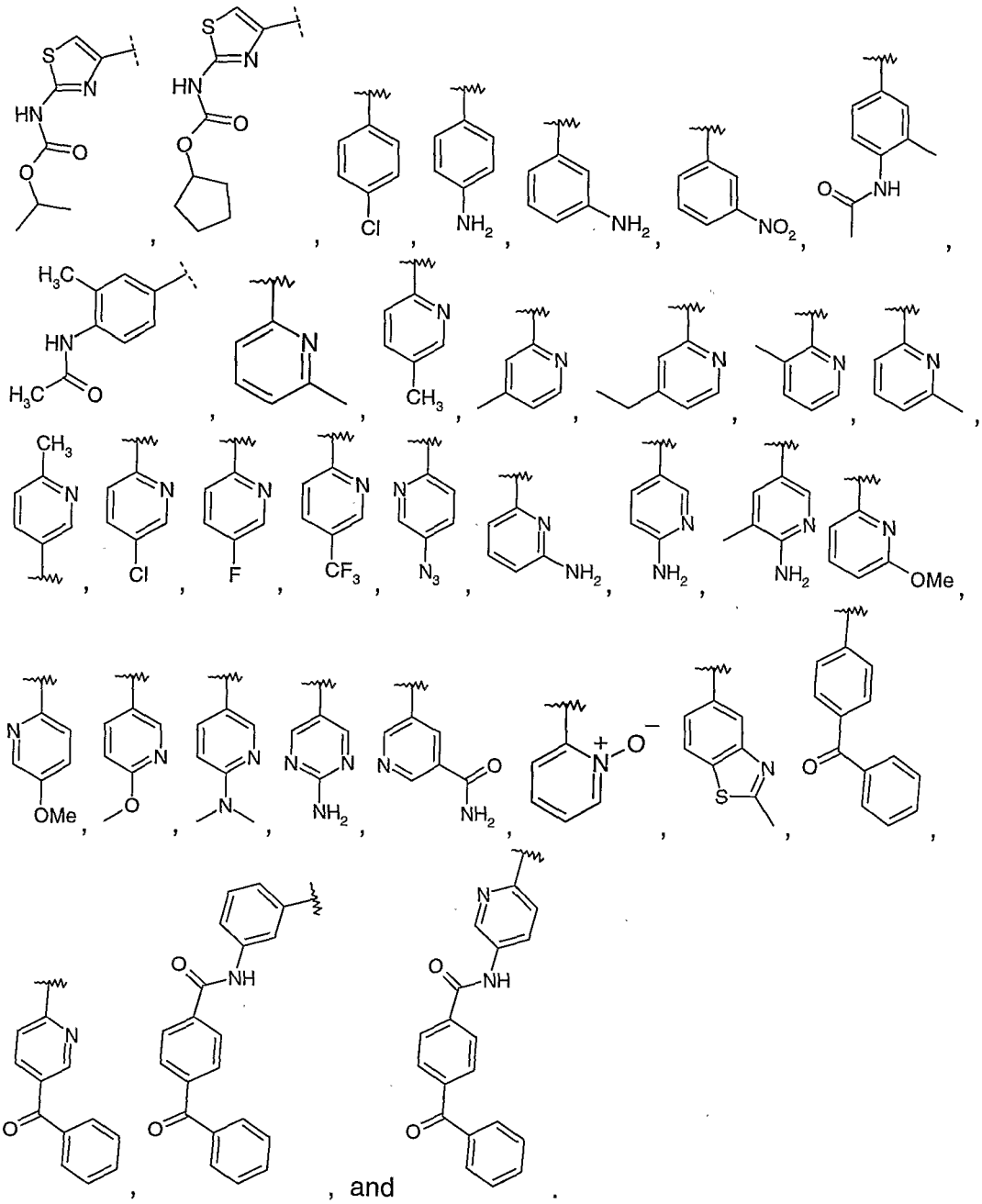


, and , all of which optionally substituted as defined in claim 16.

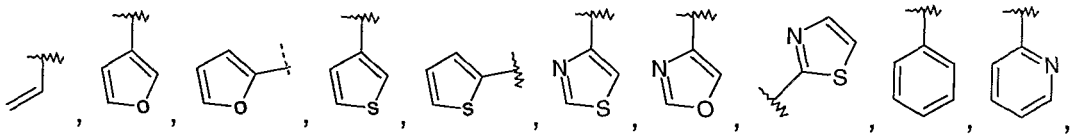
18. The compound according to claim 17, wherein R^2 is selected from the group consisting of: H, Br, $CONHCH_3$, $CON(CH_3)_2$, $CONH_2$, $CH=CH_2$,

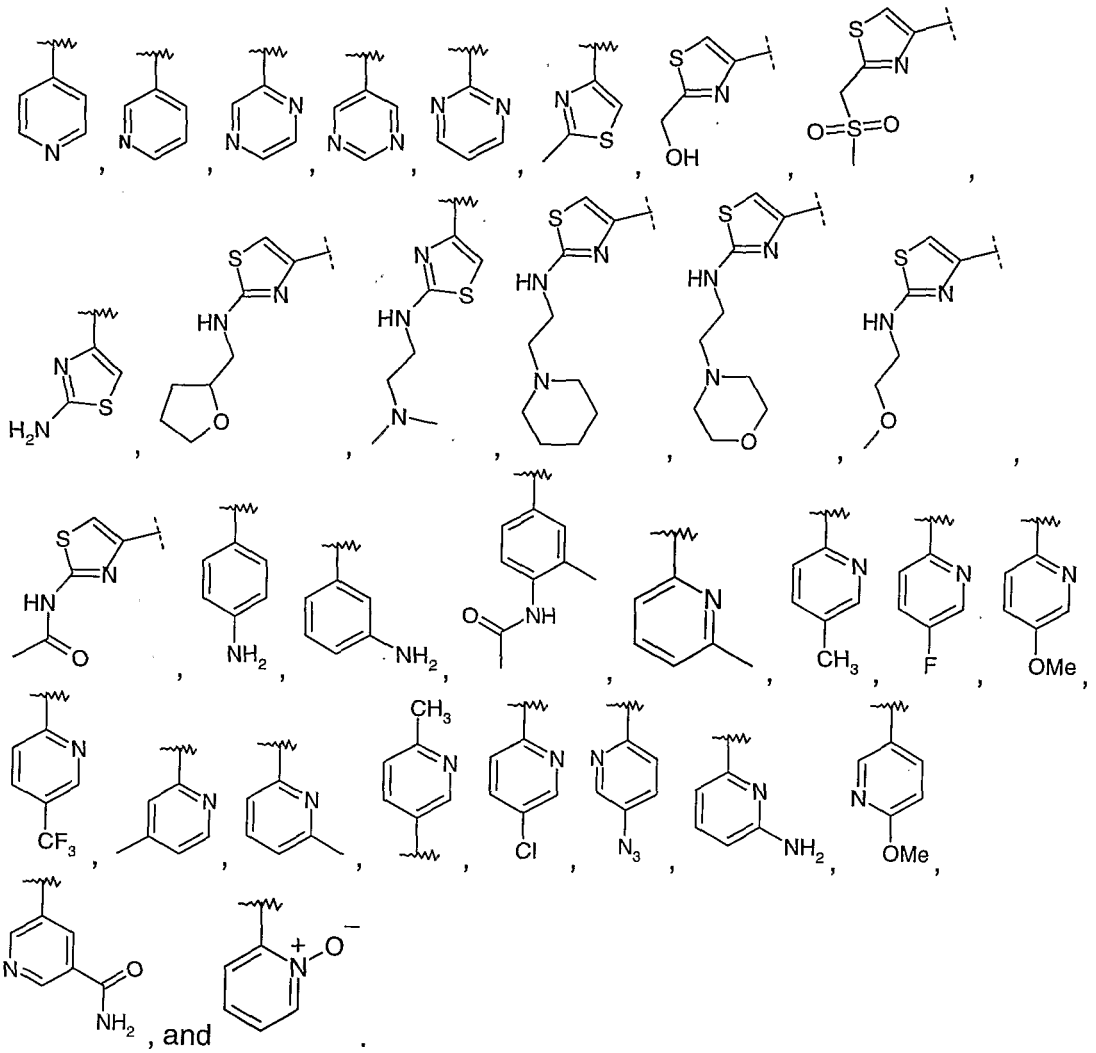






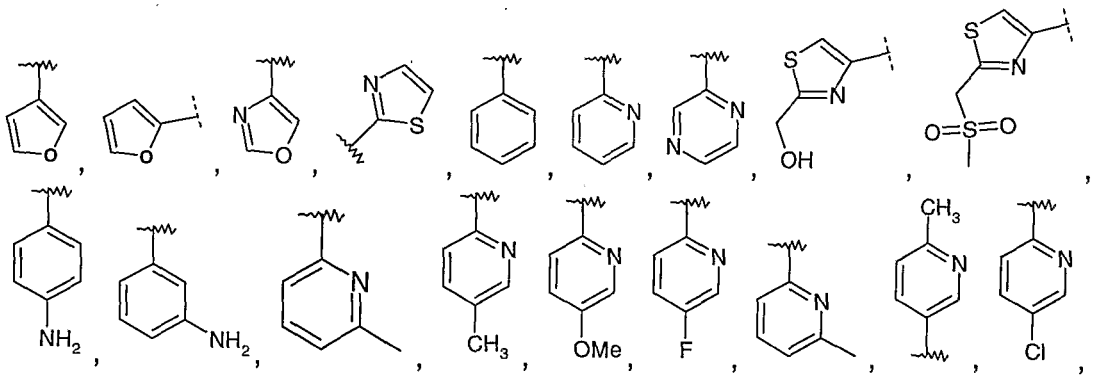
19. The compound according to claim 18, wherein R^2 is selected from:

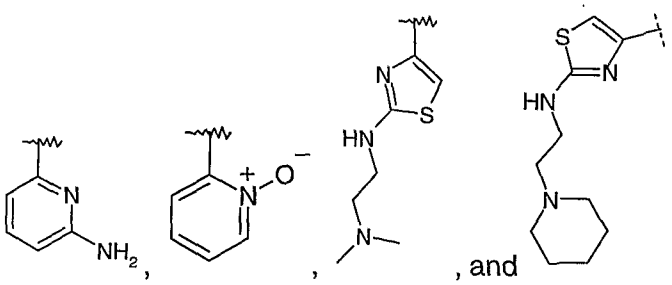




, and .

20. The compound according to claim 19, wherein R^2 is selected from:





21. The compound according to claim 1, wherein R^3 is selected from (C_{3-7})cycloalkyl, (C_{3-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, or **Het**.

22. The compound according to claim 21, wherein R^3 is (C_{3-7})cycloalkyl.

23. The compound according to claim 22, wherein R^3 is cyclopentyl, or cyclohexyl.

24. The compound according to claim 1, wherein Y^1 is O.

25. The compound according to claim 1, wherein **Z** is OR^6 wherein R^6 is $(C_{1-6}$alkyl)aryl substituted with 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is $(C_{1-6}$alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108a}, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-

membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{108a}}$ is the same as $\mathbf{R^{108}}$ but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , provided that when $\mathbf{R^{111}}$ is H or unsubstituted alkyl, $\mathbf{R^{112}}$ is not H or unsubstituted alkyl, or $\mathbf{R^{112}}$ is also $COOR^{115}$ or SO_2R^{115a} wherein $\mathbf{R^{115}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** and $\mathbf{R^{115a}}$ is the same as $\mathbf{R^{115}}$ but is not H or unsubstituted alkyl, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H or C_{1-6}alkyl and $\mathbf{R^{122}}$ is OR^{123} or $N(\mathbf{R^{124}})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is (C_{1-6})alkyl substituted with $\mathbf{R^{150}}$, (C_{3-7})cycloalkyl,

or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when $\mathbf{R^{129}}$ is H or unsubstituted alkyl, $\mathbf{R^{130}}$ is not H or unsubstituted alkyl, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein $\mathbf{R^{150}}$ is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl,

Het, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to

form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein, $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

26. The compound according to claim 25, wherein **Z** is OR^6 wherein R^6 is (C_{1-6}alkyl)aryl substituted with 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SO_3H, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl and aryl, said alkyl and aryl being optionally substituted with R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl or (C_{1-6}alkyl)aryl, and R^{115a} is C_{1-6}alkyl substituted with R^{150} or (C_{1-6}alkyl)aryl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, aryl, **Het**, said (C_{3-7})cycloalkyl, aryl, **Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl, **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6}alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, said alkyl, aryl and **Het** being optionally substituted with R^{150};

l) aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6})alkenyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, aryl or **Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, said alkyl, cycloalkyl, aryl or **Het** being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl and R^{122} is OR^{123} or

$N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), aryl or **Het**, or R^{124} is OH or O(C_{1-6}alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160}; and

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

27. The compound according to claim 1, wherein **Z** is OR^6 wherein R^6 is (C_{2-6})alkenyl, (C_{1-6})alkyl-**Het**, wherein said alkenyl or alkyl-**Het**, is optionally substituted with R^{60}, wherein R^{60} is:

- 1 to 4 substituents selected from: halogen; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-}

$_6$)alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , COO$\mathbf{R^{115}}$ or $SO_2\mathbf{R^{115}}$ wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) N$\mathbf{R^{116}}$CO$\mathbf{R^{117}}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) N$\mathbf{R^{118}}$CON$\mathbf{R^{119}}\mathbf{R^{120}}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) N$\mathbf{R^{121}}$COCO$\mathbf{R^{122}}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl optionally substituted with $\mathbf{R^{150}}$, and $\mathbf{R^{122}}$ is O$\mathbf{R^{123}}$ or N($\mathbf{R^{124}}$)$_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) CO$\mathbf{R^{127}}$ wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) COO$\mathbf{R^{128}}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) CON$\mathbf{R^{129}}\mathbf{R^{130}}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-}

$_7$)cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}; wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-}

$_7$)cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H or (C_{1-6})alkyl optionally substituted with $\mathbf{R^{160}}$, and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from:

tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

28. The compound according to claim 27, wherein R^{60} is:

- 1 to 4 substituents selected from: halogen; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl or aryl, said alkyl and aryl being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or $(C_{1-6}$alkyl)aryl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or **Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or **Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl, and R^{122} is OR^{123} or

$N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), aryl or **Het**, or R^{124} is OH or O(C_{1-6}alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H or (C_{1-6})alkyl optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** said alkyl, aryl and **Het** being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}; wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6})alkenyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, aryl or **Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or aryl, said alkyl, aryl and **Het** being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), aryl or **Het**, or R^{124} is OH or O(C_{1-6}alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H or (C_{1-6})alkyl optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** said alkyl, aryl and **Het** being optionally substituted

with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

29. The compound according to claim 1, wherein **Z** is $N(R^{6a})R^6$ wherein R^{6a} is H or C_{1-6}alkyl and R^6 is (C_{2-6})alkenyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2NH(C_{1-6}$alkyl) or $SO_2NHC(O)C_{1-6}$alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl,

(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or $O(C_{1-6}$alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$;wherein, $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) $\mathbf{SR^{108}}$, $SO_2N(\mathbf{R^{108}})_2$ or $SO_2N(\mathbf{R^{108}})C(O)\mathbf{R^{108}}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $\mathbf{NR^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $\mathbf{COOR^{115}}$ or $\mathbf{SO_2R^{115}}$ wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $\mathbf{NR^{116}COR^{117}}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $\mathbf{NR^{118}CONR^{119}R^{120}}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-}

$_{6}$)alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

30. The compound according to claim 29, wherein R^{6a} is H.

31. The compound according to claim 29, wherein R^6 is (C_{2-6})alkenyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SH, $S(C_{1-6}$alkyl), SO_3H, $SO_2NH(C_{1-6}$alkyl) or $SO_2NHC(O)C_{1-6}$alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, said alkyl, cycloalkyl being optionally substituted with R^{150};

or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are

covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl, and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

l) aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150}; and

wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido;
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

d) SH, $S(C_{1-6}$alkyl), SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein

R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently

bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6})alkyl.

32. The compound according to claim 31, wherein $\mathbf{R^6}$ is C_{2-6}alkenyl, phenyl, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, phenyl and the alkyl portion of said alkyl-aryl or alkyl-**Het**, are optionally substituted with 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, all of which optionally substituted with C_{1-6}alkyl or C_{1-6}alkoxy, NH_2, NH(Me) or $N(Me)_2$;

e) NHR^{112} wherein R^{112} is aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, said aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, being optionally substituted with $\mathbf{R^{150}}$;

j) COOH;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

l) phenyl or **Het,** both optionally substituted with $\mathbf{R^{150}}$ and

wherein $\mathbf{R^{150}}$ is selected from:

- 1 or 2 substituents selected from: halogen, NO_2, cyano or azido;
- 1 or 2 substituents selected from:

a) (C_{1-6}) alkyl or (C_{2-6})alkenyl, both optionally substituted with COOH or $CONH_2$;

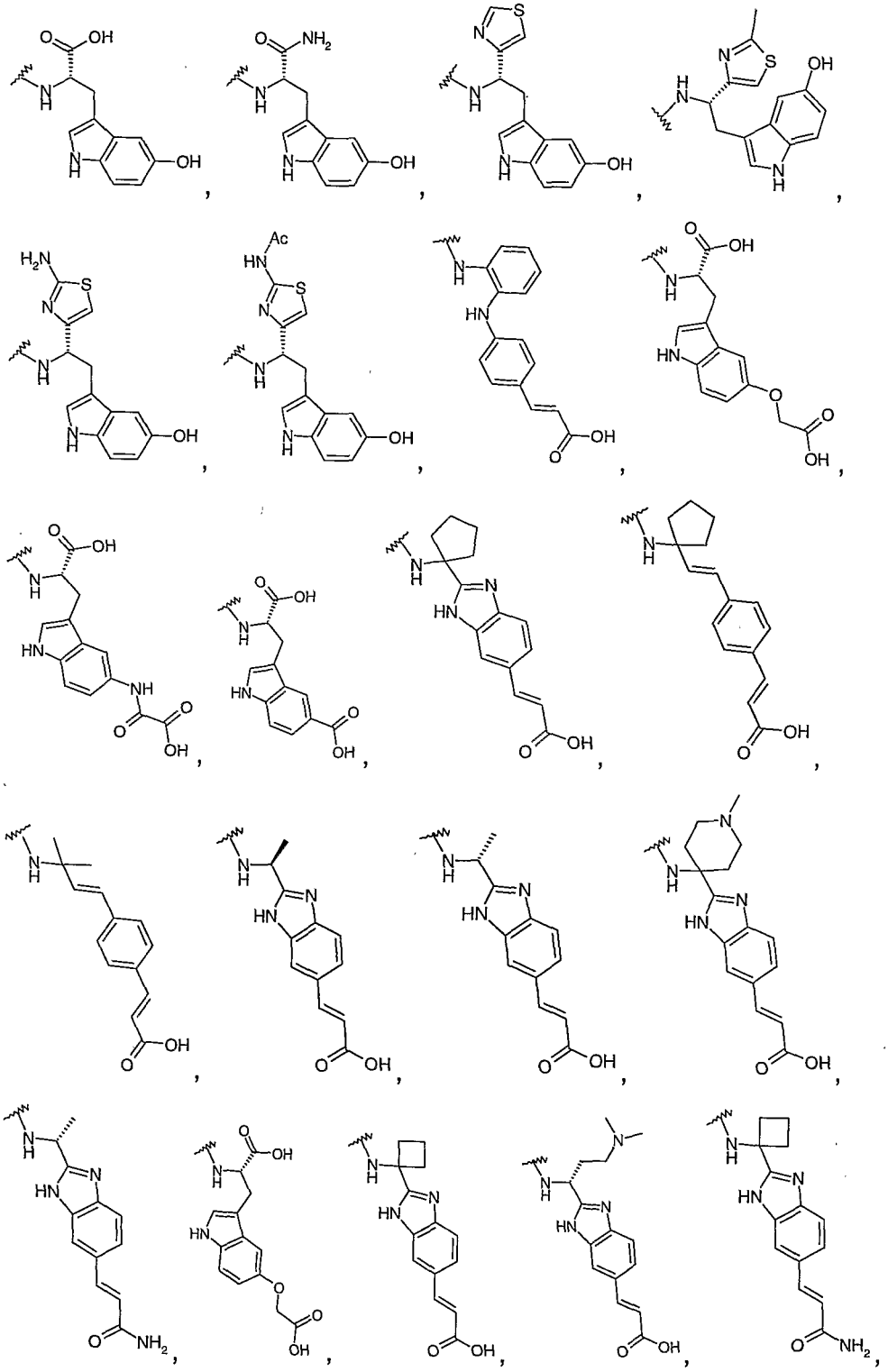
b) OR^{104} wherein R^{104} is H or (C_{1-6}alkyl) optionally substituted with COOH;

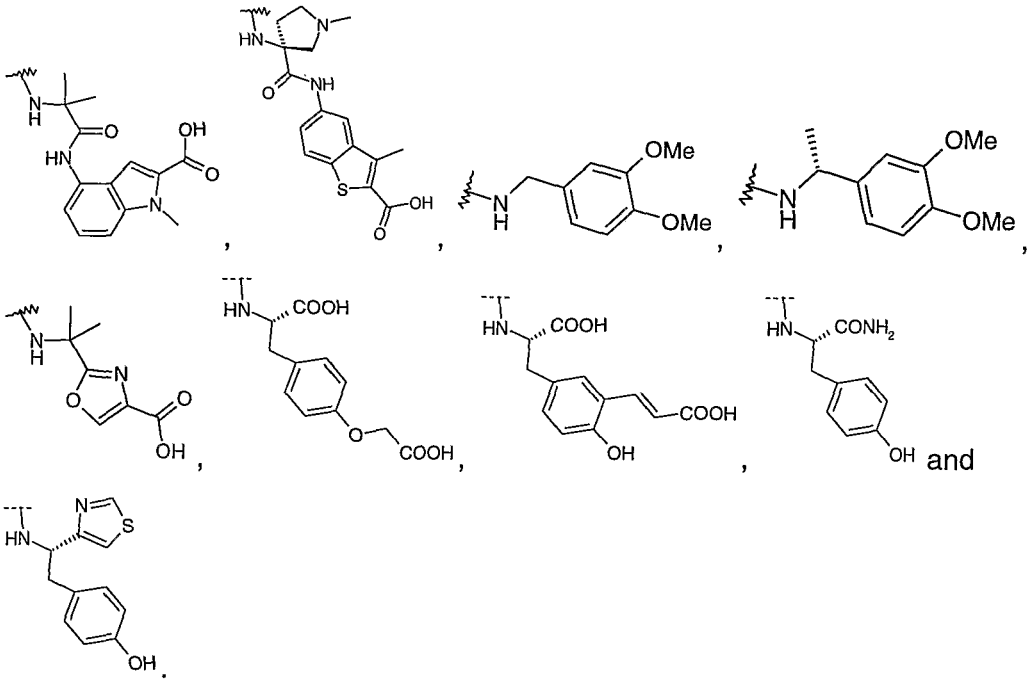
h) NHCOCOOH;

j) COOH; and

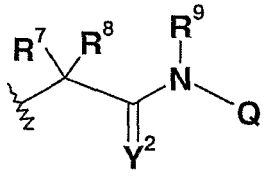
k) $CONH_2$.

33. The compound according to claim 32, wherein **Z** is selected from:





34. The compound according to claim 29, wherein R^6 is:



wherein R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{70}; or

R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a nitrogen-containing 5-or 6-membered heterocycle;

wherein R^{70} is selected from:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-}

$_6$alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$, and $\mathbf{R^{122}}$ is $\mathbf{OR^{123}}$ or $\mathbf{N(R^{124})_2}$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) $\mathbf{COR^{127}}$ wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $\mathbf{COOR^{128}}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $\mathbf{CONR^{129}R^{130}}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$, wherein, $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with $\mathbf{R^{160}}$;

d) $\mathbf{SR^{108}}$, $\mathbf{SO_2N(R^{108})_2}$ wherein $\mathbf{R^{108}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl being optionally substituted with $\mathbf{R^{160}}$;

e) $\mathbf{NR^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, and $\mathbf{R^{112}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,**

(C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl or (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R^{160};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6})alkyl.

35. The compound according to claim 34, wherein R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, all of which optionally substituted with from 1 to 4 substituents selected from halogen or:

a) (C_{1-6})alkyl; and

b) $N(R^{8a'})_2$, COR^{8a}, or $SO_2R^{8a''}$ $COOR^{8a}$, $COCOOR^{8a}$, $CON(R^{8a'})_2$, $COCON(R^{8a'})_2$, wherein each R^{8a} or $R^{8a'}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or each $R^{8a'}$ are independently covalently bonded together and to the nitrogen to which they are both bonded to form a 5, 6 or 7-membered saturated heterocycle; or $R^{8a''}$ is independently (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl.

or R^7 and R^8 are covalently bonded together to form (C_{3-7})cycloalkyl, 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S.

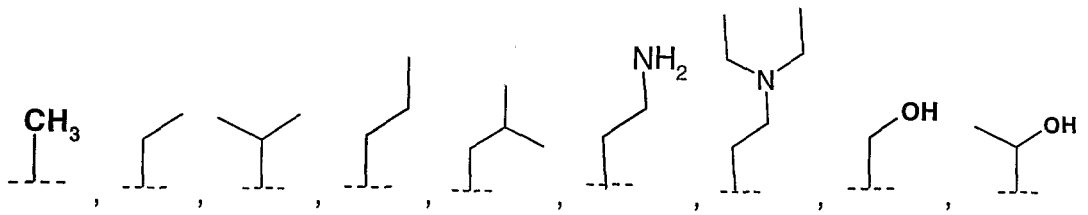
36. The compound according to claim 35, wherein R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**; or R^7 and R^8 are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide;

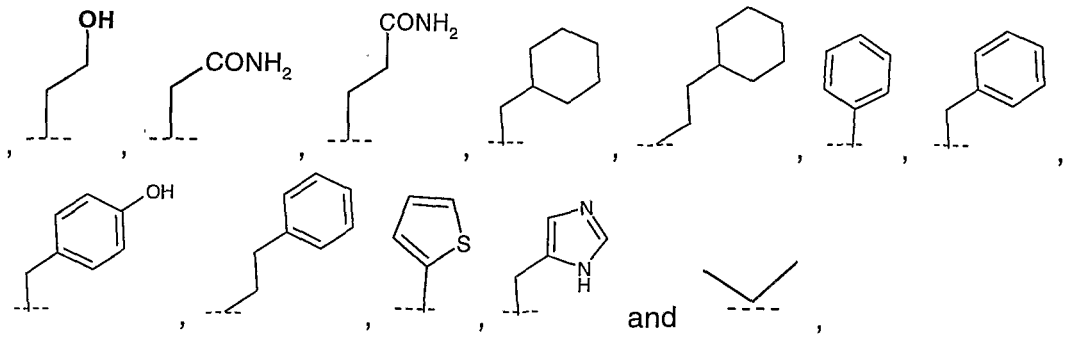
wherein said alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide are optionally monosubstituted with substituents selected from:

a) (C_{1-6})alkyl; and

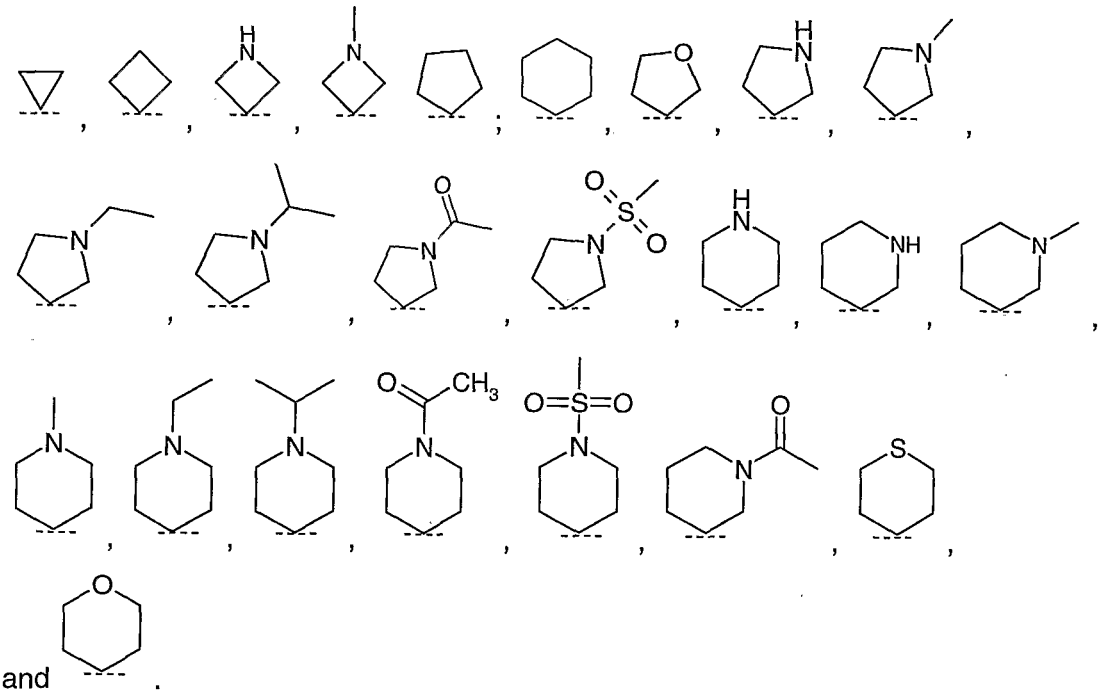
b) NH_2, $N(CH_2CH)_2$, $COCH_3$, or SO_2CH_3.

37. The compound according to claim 36, wherein R^7 and R^8 are selected from:

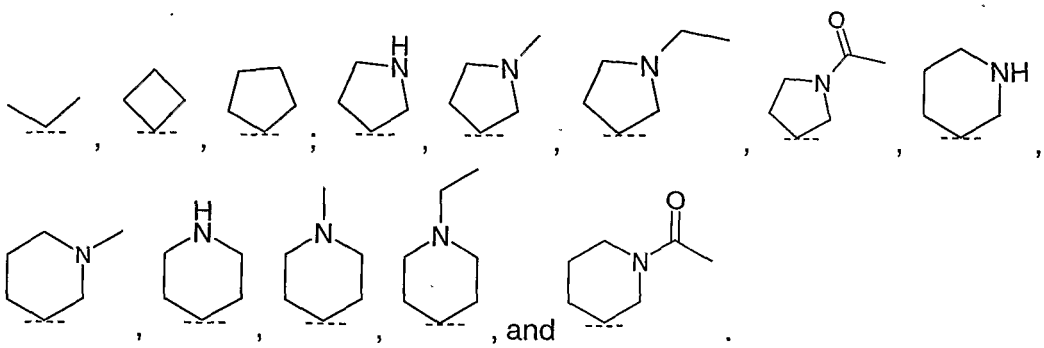




or R^7 and R^8 together form:



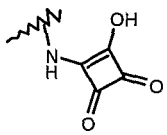
38. The compound according to claim 37, wherein R^7 and R^8 are selected from:



39. The compound according to claim 34, wherein $\mathbf{R^9}$ is H, or $\mathbf{R^9}$ is covalently bonded to either of $\mathbf{R^7}$ or $\mathbf{R^8}$ to form a 5- or 6-membered heterocycle.

40. The compound according to claim 39, wherein $\mathbf{R^9}$ is H.

41. The compound according to claim 34, wherein **Q** is a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)-**Het**, all of which being optionally substituted with: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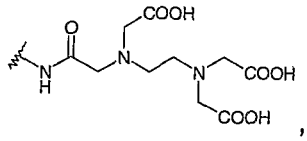

, or $\mathbf{R^{100}}$;

wherein $\mathbf{R^{100}}$ is:

- 1 to 4 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{150}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108} wherein $\mathbf{R^{108}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-}

$_6$)alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$; or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; wherein $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl optionally substituted with $\mathbf{R^{160}}$, and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein $\mathbf{R^{161}}$ and each $\mathbf{R^{162}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both $\mathbf{R^{162}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

42. The compound according to claim 41, wherein **Q** is a 6- or 10-membered

aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)-Het, all of which being optionally substituted with:

- 1 to 4 substituents selected from: halogen,NO_2, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated

heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ is H, (C_{1-6})alkyl optionally substituted with $\mathbf{R^{150}}$, and $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or $O(C_{1-6}$alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het**, (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; wherein $\mathbf{R^{150}}$ is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, said alkyl, cycloalkyl, aryl and **Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or O(C_{1-6}alkyl), or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6

or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

43. The compound according to claim 42, wherein **Q** is a 6- or 10-membered aryl or **Het**, both being optionally substituted with:

- 1 to 3 halogen, NO_2, cyano, azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, first (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which are optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl);

d) SO_2NHR^{108} wherein R^{108} is H or (C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H or (C_{1-6})alkyl;

f) $NHCOR^{117}$ wherein R^{116} is H or (C_{1-6})alkyl;

g) $NHCONR^{119}R^{120}$, wherein R^{119} and R^{120} is each independently H or (C_{1-6})alkyl;

h) $NHCOCOR^{122}$ wherein R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H or $(C_{1-6}$alkyl);

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl;

k) $CONHR^{130}$ wherein R^{130} is H, (C_{1-6})alkyl;

l) 6- or 10-membered aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150}; wherein R^{150} is selected from:

- 1 to 3 halogens; or
- 1 to 3 substituents selected from:

a) first (C_{1-6}) alkyl or haloalkyl, first (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which are optionally

substituted with tetrazole, OR^{102}, $COOR^{102}$, wherein R^{102} is H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl);

d) SO_2NHR^{108} wherein R^{108} is H or (C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H or (C_{1-6})alkyl;

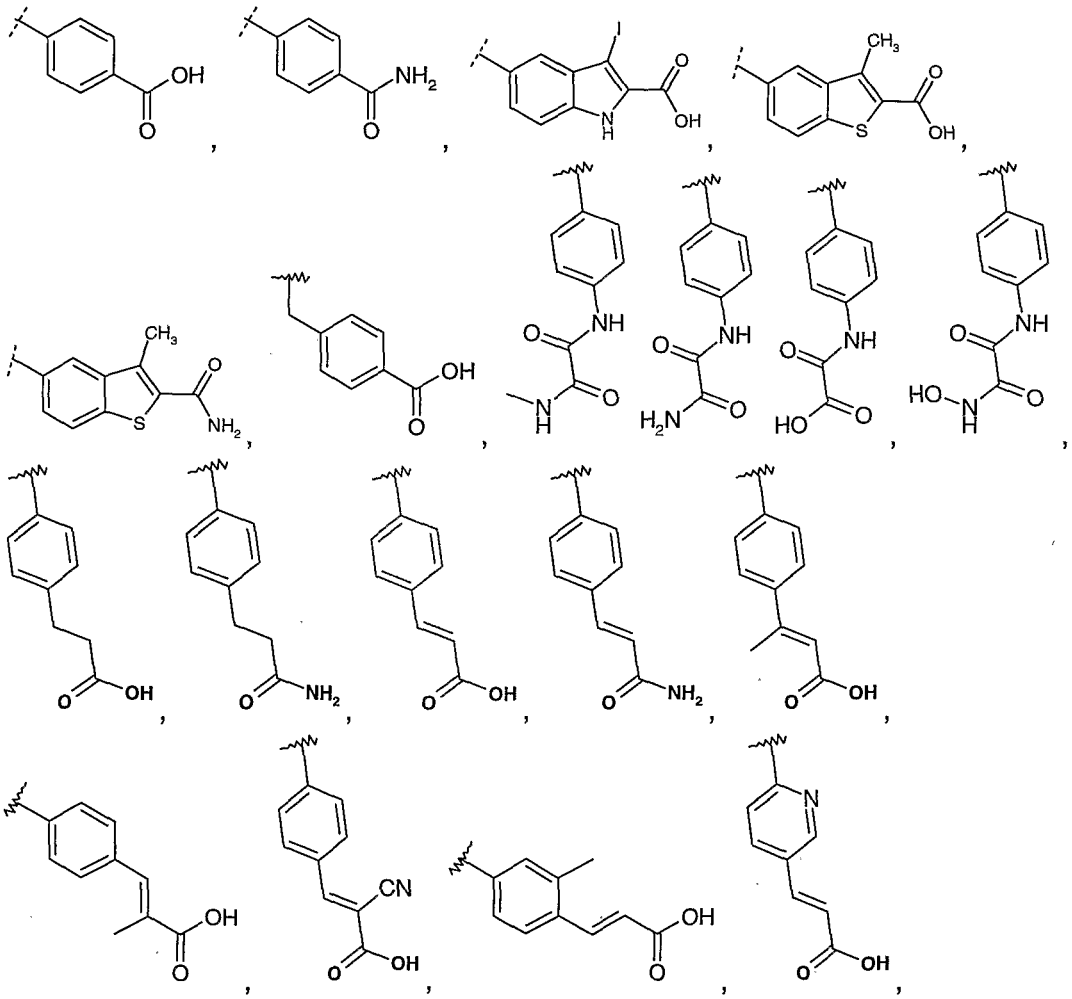
f) $NHCOR^{117}$ wherein R^{116} is H or (C_{1-6})alkyl; and

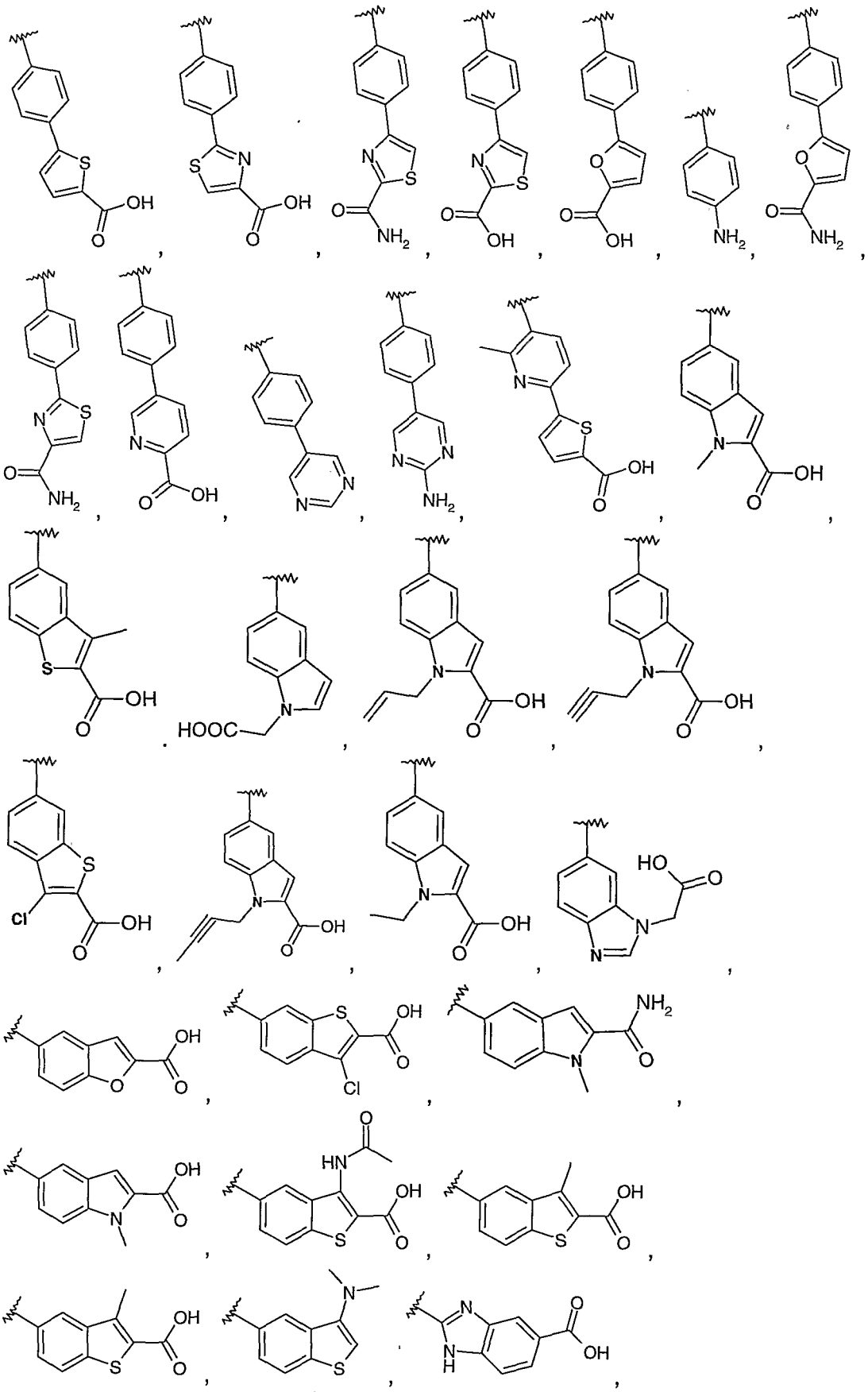
h) $NHCOCOR^{122}$ wherein R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H or $(C_{1-6}$alkyl);

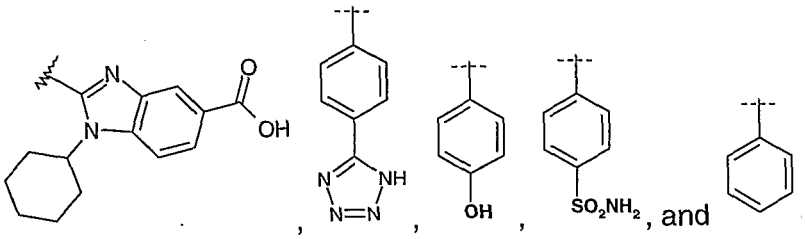
j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl; and

k) $CONHR^{130}$ wherein R^{130} is H, (C_{1-6})alkyl.

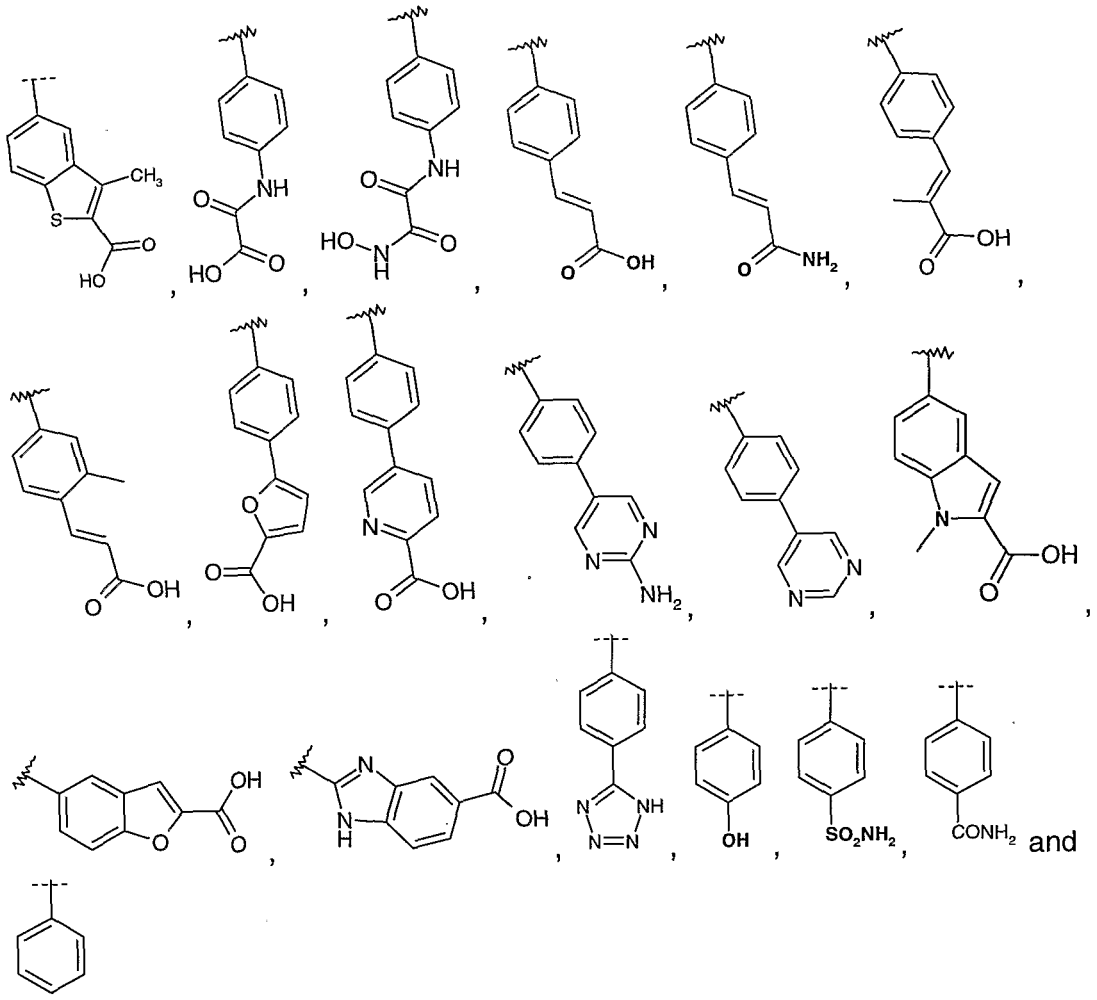
44. The compound according to claim 43, wherein **Q** is selected from:



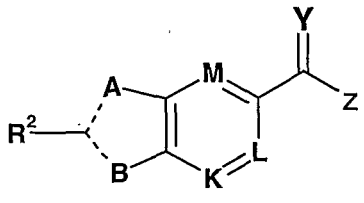




45. The compound according to claim 44, wherein **Q** is selected from:



46. A compound represented by Formula Ia:



(Ia)

wherein:

A is O, S, NR^1, or CR^1;

B is NR^3 or CR^3;

R^1 is selected from the group consisting of: H, (C_{1-6})alkyl, benzyl, $(C_{1-6}$ alkyl)-$(C_{6-10}$aryl), $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, $COO(C_{1-6}$ alkyl), halogen, and $(C_{1-6}$ alkyl);

R^2 is selected from the group consisting of: H, halogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide , and 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S,

said phenyl, heterocycle and heterobicycle being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, $C(halogen)_3$, (C_{1-6})alkyl, OH, $O(C_{1-6}$ alkyl), NH_2, and $N(C_{1-6}$ alkyl$)_2$;

R^3 is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-$(C_{1-6}$ alkyl);

M is N, CR^4, or COR^5, wherein R^4 is selected from the group consisting of: H, halogen, and $(C_{1-6}$ alkyl); and R^5 is selected from the group consisting of: H and $(C_{1-6}$ alkyl);

K and **L** is N or CH;

----- represents either a single or a double bond;

Y is O or S;

Z is OR^6 or NR^6R^{6a}

R^6 is selected from the group consisting of: H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-6})alkyl, (C_{2-6})alkenyl,

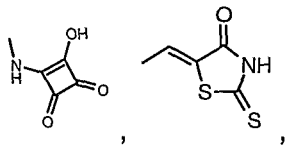
(C_{3-6})cycloalkyl(C_{2-6})alkenyl, (C_{6-10})aryl(C_{2-6})alkenyl, N{(C_{1-6}) alkyl}$_2$, NHCOO(C_{1-6})alkyl(C_{6-10})aryl, NHCO(C_{6-10})aryl, (C_{1-6})alkyl-5- or 6-atom heterocycle, having 1 to 4 heteroatoms selected from O, N and S, and 9- or 10-atom heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

wherein said alkyl, cycloalkyl, aryl, alkenyl, heterocycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said alkyl, cycloalkyl, aryl, alkenyl and heterocycle being optionally substituted with from 1 to 4 substituents selected from: $(C_{1-6}$ alkyl), CF_3, OH, COOH, NHC$(C_{1-6}$alkyl$)_2$, NHCO$(C_{1-6}$ alkyl), NH_2, NH$(C_{1-6}$ alkyl), and N$(C_{1-6}$ alkyl$)_2$;

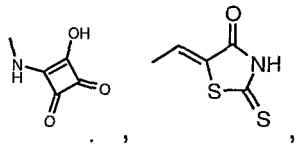
9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S, said heterobicycle being optionally substituted with from 1 to 4 substituents selected from:

halogen, OPO_3H, sulfonamido, SO_3H, SO_2CH_3, -$CONH_2$, -$COCH_3$, (C_{1-3})alkyl, $(C_{2-4}$alkenyl)COOH, tetrazolyl, COOH, -$CONH_2$, triazolyl, OH, NO_2, NH_2, -O$(C_{1-6}$ alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, NHCO$(C_{1-6}$ alkyl), -NHCOCOOH, -NHCOCONHOH,-$NHCOCONH_2$, -$NHCOCONHCH_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -$NHCH_2COOH$, -$NHCONH_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,


, -NHCN, -NHCHO, $-NHSO_2CH_3$, and $-NHSO_2CF_3$;

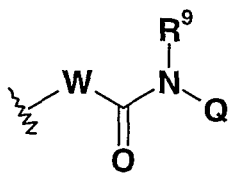
6- or 10-membered aryl being optionally substituted with from 1 to 4 substituents selected from:

halogen, OPO_3H, sulfonamido, SO_3H, SO_2CH_3, $-CONH_2$, $-COCH_3$, (C_{1-3})alkyl, $(C_{2-4}$alkenyl)COOH , tetrazolyl, COOH, $-CONH_2$, triazolyl, OH, NO_2, NH_2, $-O(C_{1-6}$ alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, cyano, azido, $-O-(C_{1-6})$alkyl COOH, $-O-(C_{1-6})$alkyl COO-(C_{1-6})alkyl, $NHCO(C_{1-6}$ alkyl), -NHCOCOOH, -NHCOCONHOH,$-NHCOCONH_2$, $-NHCOCONHCH_3$, $-NHCO(C_{1-6})$alkyl-COOH, $-NHCOCONH(C_{1-6})$alkyl-COOH, $-NHCO(C_{3-7})$cycloalkyl-COOH, $-NHCONH(C_{6-10})$aryl-COOH, - $NHCONH(C_{6-10})$aryl-$COO(C_{1-6})$alkyl, - $NHCONH(C_{1-6})$alkyl-COOH,- $NHCONH(C_{1-6})$alkyl-$COO(C_{1-6})$alkyl, - $NHCONH(C_{1-6})$alkyl-(C_{2-6})alkenyl-COOH, - $NH(C_{1-6})$alkyl-(C_{6-10})aryl-$O(C_{1-6})$alkyl COOH, - $NH(C_{1-6})$alkyl-(C_{6-10})aryl-COOH, $-NHCH_2COOH$, $-NHCONH_2$, $-NHCO(C_{1-6})$hydroxyalkyl COOH, $-OCO(C_{1-6})$hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,


, -NHCN, -NHCHO, $-NHSO_2CH_3$, and $-NHSO_2CF_3$;

coumarin, (C_{1-6})alkyl-amino, $NH(C_{1-6}$ alkyl), $C(halogen)_3$, $-NH(C_{2-4})$acyl, $-NH(C_{6-10})$aroyl, $-O(C_{1-6}$alkyl)-**Het**;

R^{6a} is H or $(C_{1-6}$ alkyl) covalently bonded to either R^7 or R^8 to form pyrrolidine; or **Z** is



wherein

W is CR^7R^8 wherein R^7 and R^8 are each independently H, (C_{1-6} alkyl), (C_{3-7} cycloalkyl), (C_{1-6} alkyl)phenyl, (C_{1-6} alkyl)-(C_{3-7} cycloalkyl), (C_{3-7} cycloalkyl)-(C_{1-6} alkyl), (C_{3-7} cycloalkyl)-(C_{2-4} alkenyl), (C_{1-6} alkyl)-OH, phenyl, CH_2biphenyl, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, (C_{1-6} alkyl)-5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, or (C_{1-6} alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S,

or R^7 and R^8 are covalently bonded together to form (C_{3-7} cycloalkyl), 4-, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S; or one of R^7 or R^8 is covalently bonded to R^9 to form a pyrrolidine;

wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from the group consisting of: OH, COOH, (C_{1-6} alkyl), (C_{2-4} alkenyl), $CONH_2$, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, NHCOCOOH, $NHCOCON(C_{1-6}$ alkyl)$_2$, $NHCOCONH(C_{1-6}$ alkyl), SH, $S(C_{1-6}$ alkyl), $NHC(=NH)NH_2$, halogen, and $COO(C_{1-6}$alkyl);

R^9 is H or (C_{1-6} alkyl); and

Q is selected from the group consisting of: (C_{1-3}alkyl)CONHaryl, 6-, 9-, or 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

wherein said aryl, biphenyl, heterocycle and heterobicycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $COO(C_{1-6})$alkyl, (C_{1-6})alkyl, (C_{1-6})alkylCOOH, (C_{1-6} alkyl)(C_{2-4} alkynyl), (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4 heteroatoms selected from O, N and S, NH-5- or 6- membered second heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

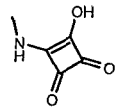
wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: (C_{1-6} alkyl), CF_3, OH, (C_{1-6}alkyl) COOH, O(C_{1-6}alkyl)COOH, (C_{1-6}alkyl) $COO(C_{1-6}$alkyl), CH_2phenyl, $COO(C_{1-6}$ alkyl), (C_{1-6}alkyl)O(C_{1-6}alkyl), COOH,

$NCH(C_{1-6}alkyl)_2$, $NCO(C_{1-6}$ alkyl), NH_2, $NH(C_{1-6}$ alkyl), halogen, and $N(C_{1-6}$ alkyl$)_2$;

halogen, OPO_3H, benzyl, sulfonamido, SH, $SOCH_3$, SO_3H, SO_2CH_3, $S(C_{1-6}$ alkyl)COOH, $-CONH_2$, $-COCH_3$, (C_{1-3})alkyl, $(C_{2-4}$alkenyl)COOH

wherein said alkenyl is optionally substituted with from 1 to 2 $(C_{1-6}$ alkyl) substituents,

$(C_{2-4}$alkenyl)$COO(C_{1-6}$alkyl), tetrazolyl, COOH, triazolyl, OH, NO_2, NH_2, , -$O(C_{1-6}$ alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, (C_{1-4})alkoxy$(C_{1-6}$ alkyl)COOH, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, -NHCOCOOH, -NHCOCONHOH,-$NHCOCONH_2$, -$NHCOCONHCH_3$, -$NHCO(C_{1-6})$alkyl-COOH, -$NHCOCONH(C_{1-6})$alkyl-COOH, -$NHCO(C_{3-7})$cycloalkyl-COOH, -$NHCONH(C_{6-10})$aryl-COOH, - $NHCONH(C_{6-10})$aryl-$COO(C_{1-6})$alkyl, - $NHCONH(C_{1-6})$alkyl-COOH,- $NHCONH(C_{1-6})$alkyl-$COO(C_{1-6})$alkyl, - $NHCONH(C_{1-6})$alkyl-(C_{2-6})alkenyl-COOH, - $NH(C_{1-6})$alkyl-(C_{6-10})aryl-$O(C_{1-6})$alkyl COOH, - $NH(C_{1-6})$alkyl-(C_{6-10})aryl-COOH, $-NHCH_2COOH$, $-NHCONH_2$, -$NHCO(C_{1-6})$hydroxyalkyl COOH, -$OCO(C_{1-6})$hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,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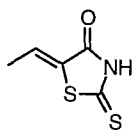
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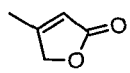
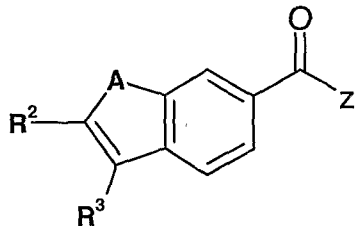
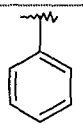
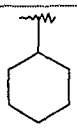
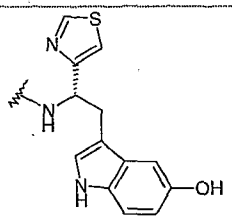
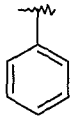
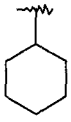
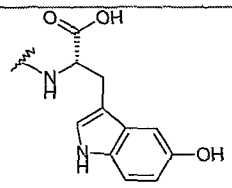
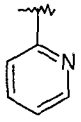
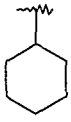
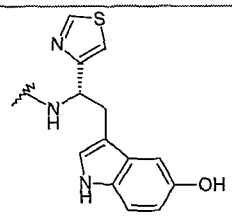
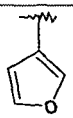
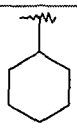
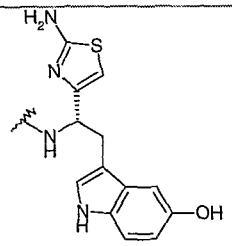
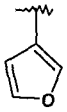
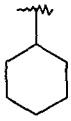
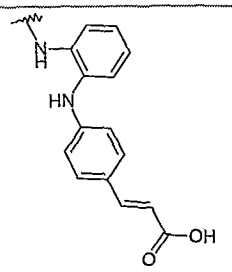
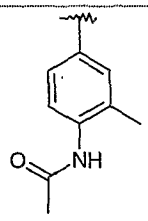
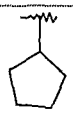
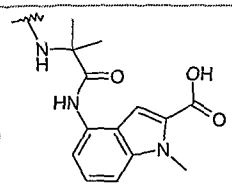

, -NHCN, -NHCHO, $-NHSO_2CH_3$, $-NHSO_2CF_3$, coumarin, (C_{1-6})alkyl-amino, $NH(C_{1-6}alkyl)_2$, $C(halogen)_3$, -$NH(C_{2-4})$acyl, -$NH(C_{6-10})$aroyl, -$CONH(C_{1-6}$alkyl), -$CO(C_{1-6})$alkyl-COOH, -$CONH(C_{1-6})$alkyl-COOH, -CO-NH-alanyl, -$CONH(C_{2-4})$alkyl$N(C_{1-6}alkyl)_2$, -$CONH(C_{2-4})$ alkyl-**Het**, -$CONH(C_{2-4})$ alkyl-(COOH)-**Het**, -$CONH(C_{1-2}$ alkyl) (OH)$(C_{1-2}$ alkyl)OH, -$CONH(C_{1-6})$ alkyl-COOH, -$CONH(C_{6-10}$ aryl), -CONH-**Het**, -$CONH(C_{6-10})$ aryl-COOH, -$CONH(C_{6-10})$ aryl-$COO(C_{1-6})$ alkyl, -$CONH(C_{1-6})$ alkyl-$COO(C_{1-6})$ alkyl, -$CONH(C_{6-10})$ aryl-(C_{1-6})alkyl-COOH, and -$CONH(C_{6-10})$ aryl-(C_{2-6})alkenyl-COOH,

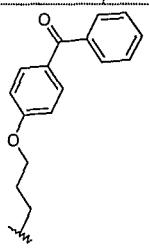
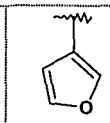
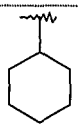
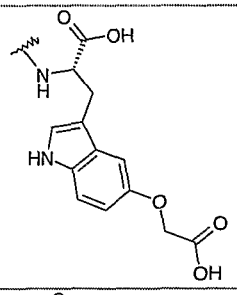
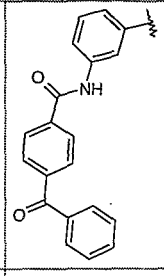
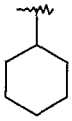
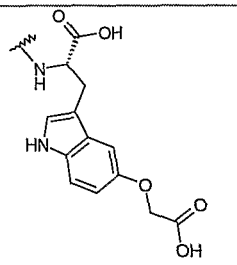
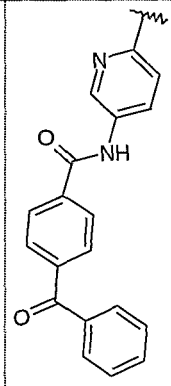
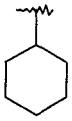
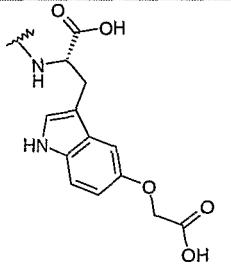
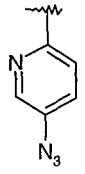
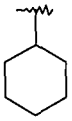
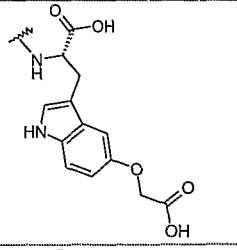
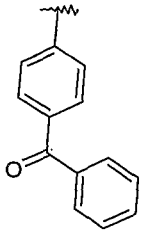
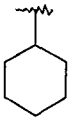
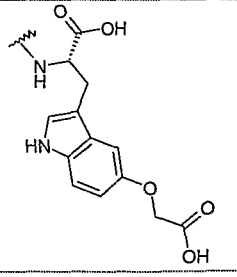
or a salt thereof.

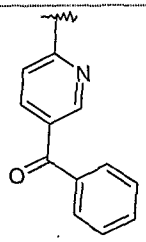
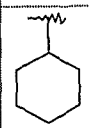
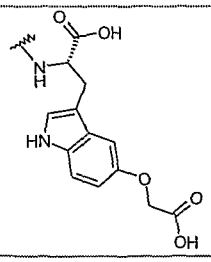
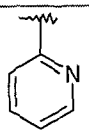
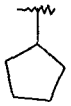
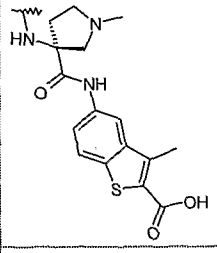
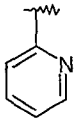
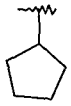
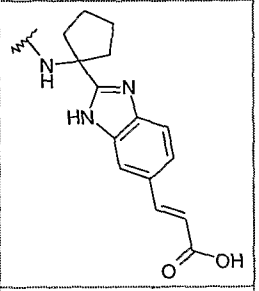
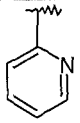
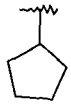
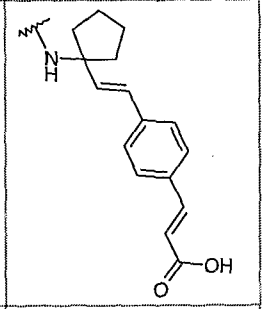
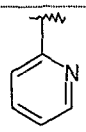
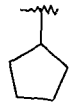
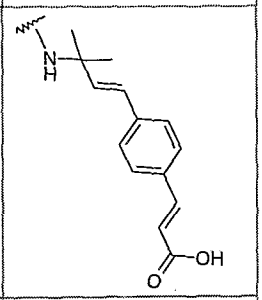
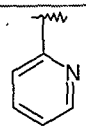
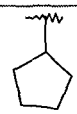
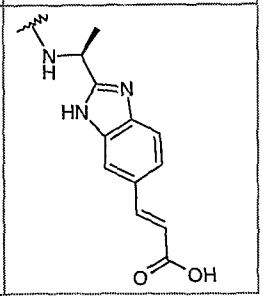
47. A compound of the formula:

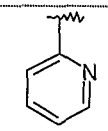
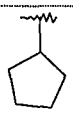
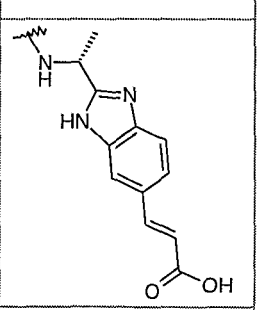
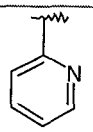
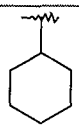
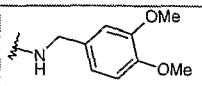
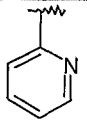
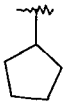
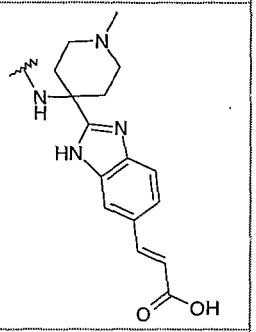
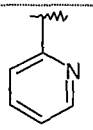
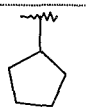
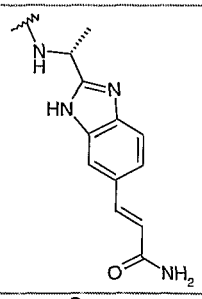
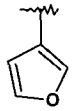
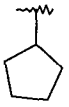
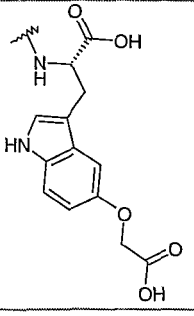
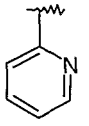
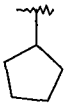
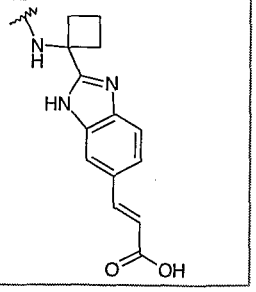


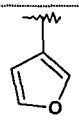
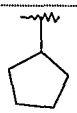
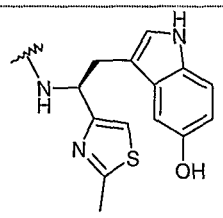
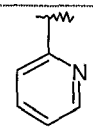
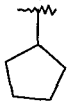
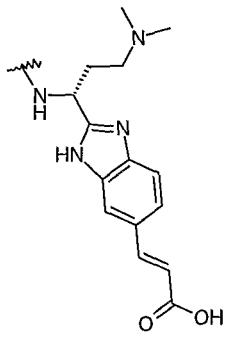
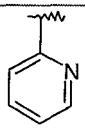
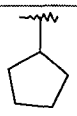
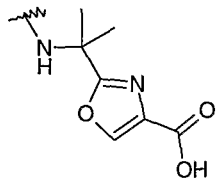
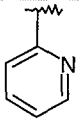
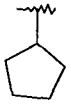
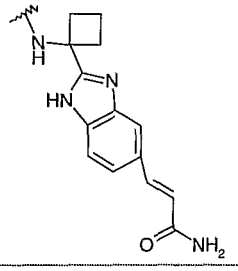
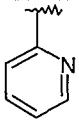
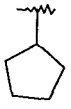
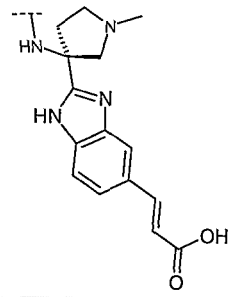
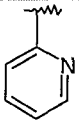
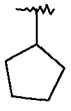
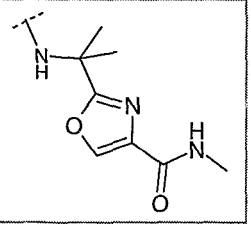
wherein **A**, R^2, R^3 and **Z** are defined as follows:

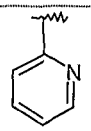
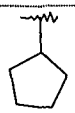
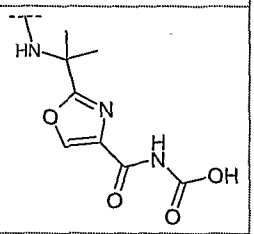
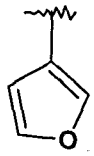
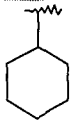
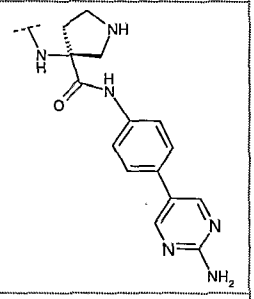
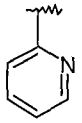
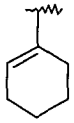
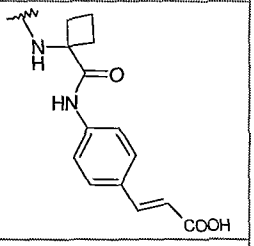
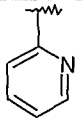
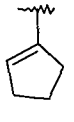
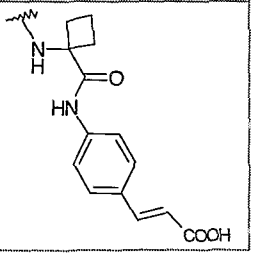
Cpd. #	A	R^2	R^3	Z
1001	NH			 ;
1002	NH			 ;
1003	NH			 ;
1004	NH			 ;
1005	NH			 ;
1006	NMe			 ;

Cpd. #	A	R^2	R^3	Z
1007				 ;
1008	NMe			 ;
1009	NMe			 ;
1010	NMe			 ;
1011	NMe			 ;

Cpd. #	A	R^2	R^3	Z
1012	NMe			 ;
1013	NMe			 ;
1014	NMe			 ;
1015	NMe			 ;
1016	NMe			 ;
1017	NMe			 ;

Cpd. #	A	R^2	R^3	Z
1018	NMe			
1019	NH			
1020	NMe			
1021	NMe			
1022	S			
1023	NMe			

Cpd. #	A	R^2	R^3	Z
1024	S			
1025	NMe			
1026	NMe			
1027	NMe			
1028	NMe			
1029	NMe			

Cpd. #	A	R^2	R^3	Z
1030	NMe			
1031	NMe			
1032	NMe			
1033	NMe			

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;

;

and

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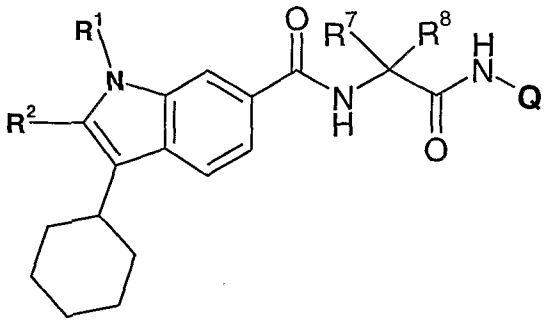
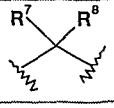
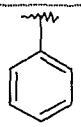
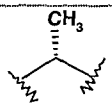
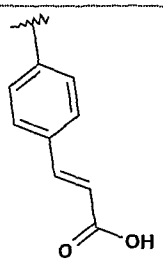
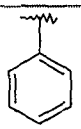
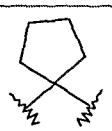
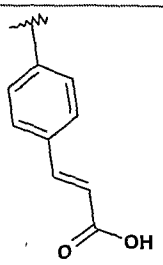
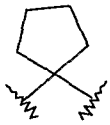
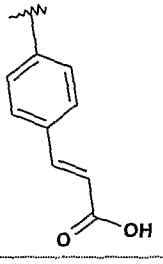
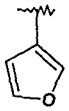
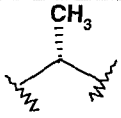
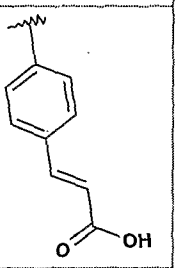
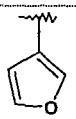
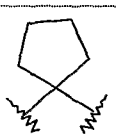
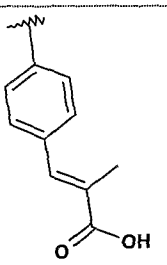
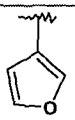
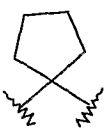
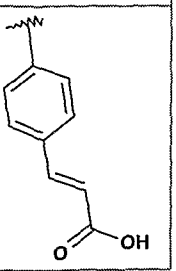
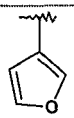
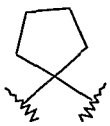
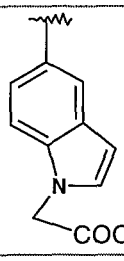
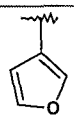
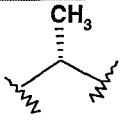
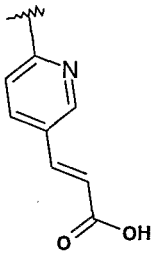
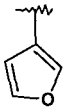
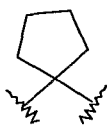
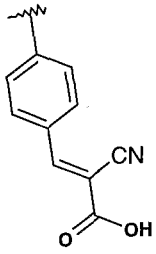
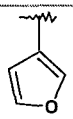
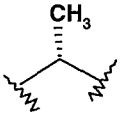
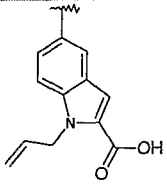
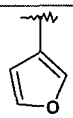
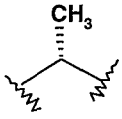
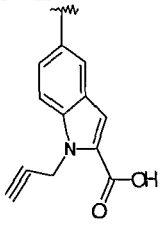
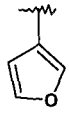
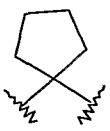
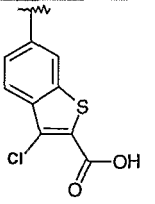
48. A compound of the formula:

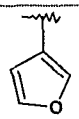
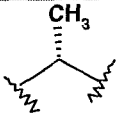
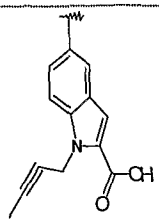
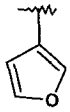
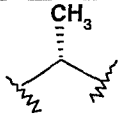
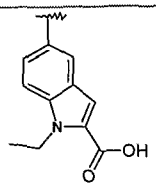
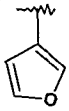
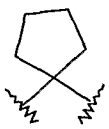
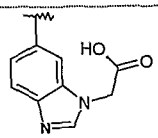
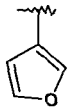
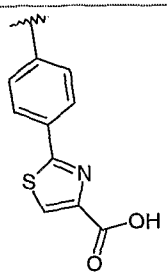
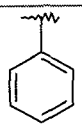
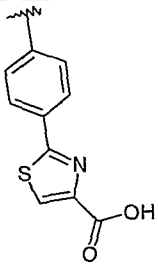
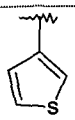
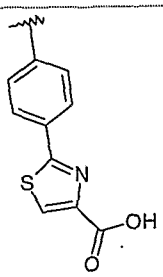
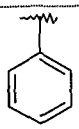
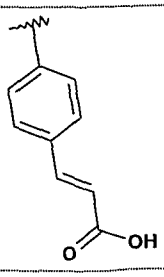


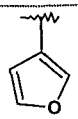
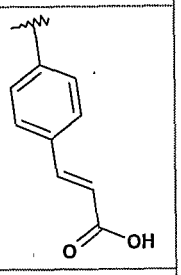
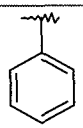
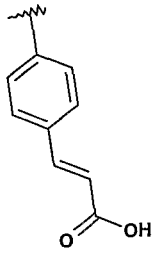
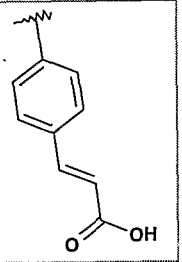
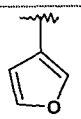
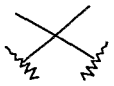
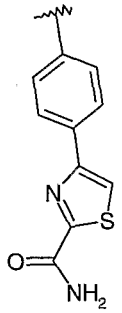
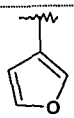
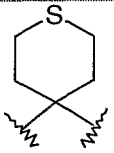
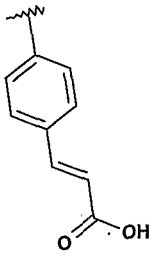
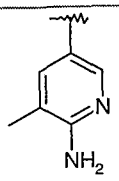
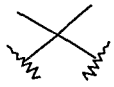
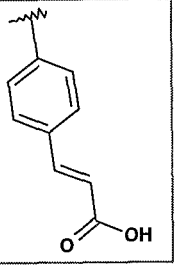
wherein R^1, R^2, R^7, R^8 and **Q** are defined as follows:

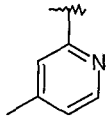
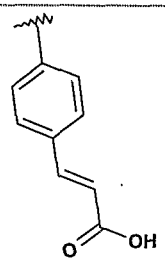
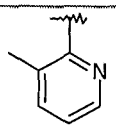
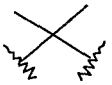
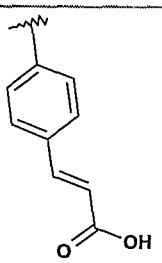
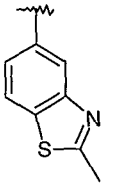
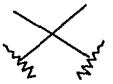
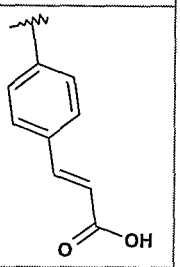
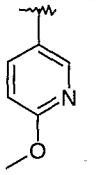
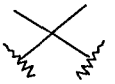
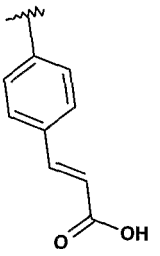
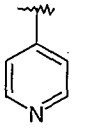
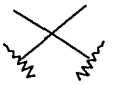
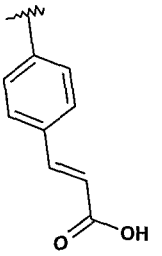
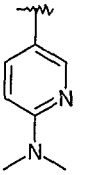
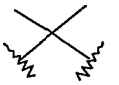
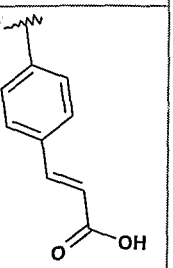
Cpd. #	R^1	R^2		Q

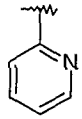
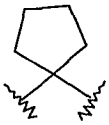
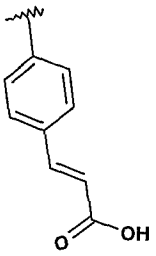
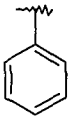
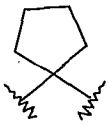
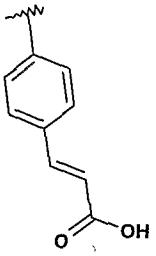
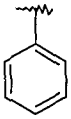
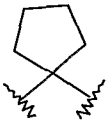
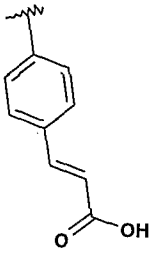
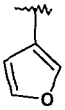
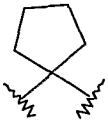
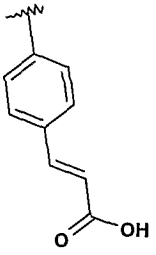
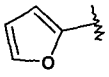
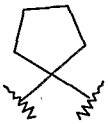
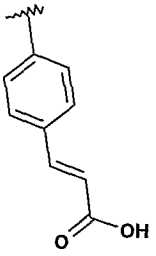
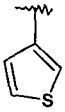
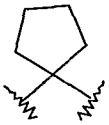
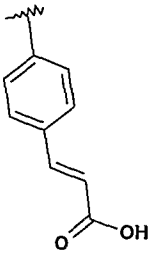
Cpd. #	R^1	R^2	R^7 R^8	Q
2001	H			 ;
2002	H			 ;
2003	H	Br		 ;
2004	H			 ;
2005	H			 ;
2006	Me			 ;

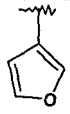
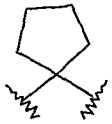
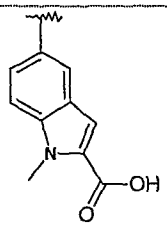
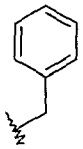
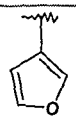
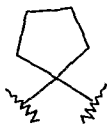
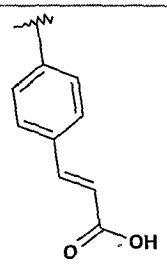
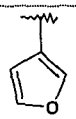
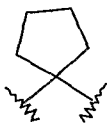
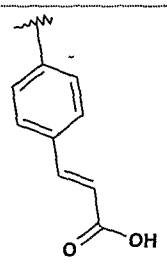
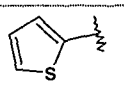
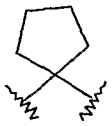
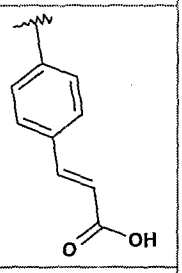
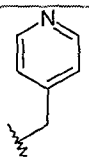
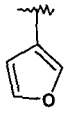
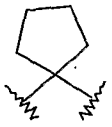
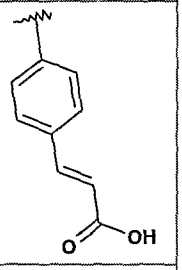
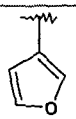
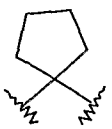
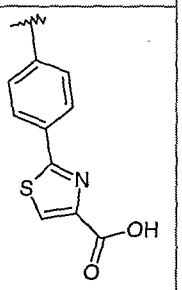
Cpd. #	R^1	R^2	R^7 R^8	Q
2008	H			
2009	H			
2010	H			
2011	H			
2012	H			
2013	H			

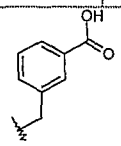
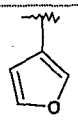
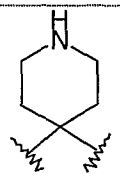
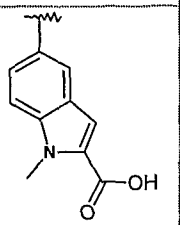
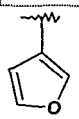
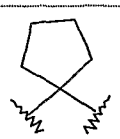
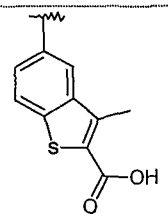
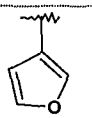
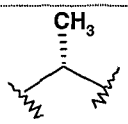
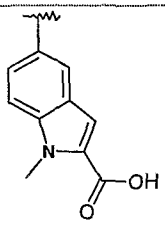
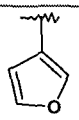
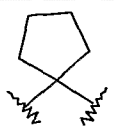
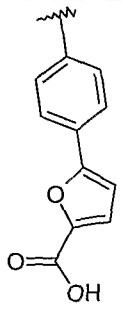
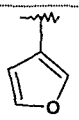
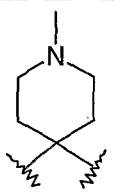
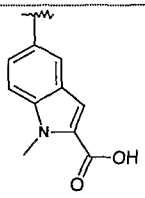
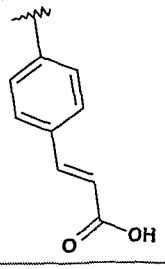
Cpd. #	R^1	R^2	R^7 R^8	Q
2014	H			 ;
2015	H			 ;
2016	H			 ;
2017	H			 ;
2018	H			 ;
2019	H			 ;
2020	Et			 ;

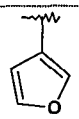
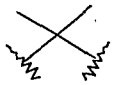
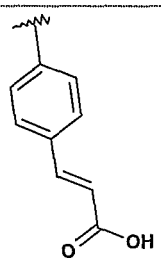
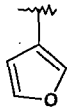
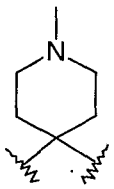
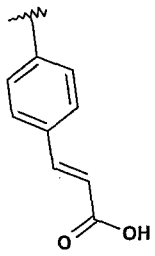
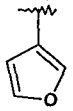
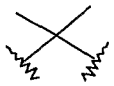
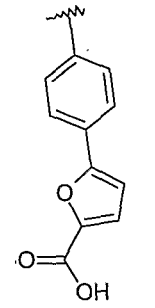
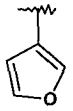
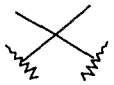
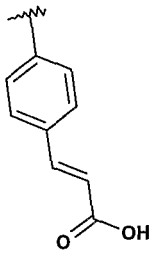
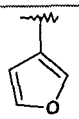
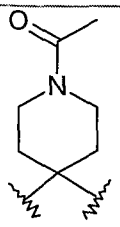
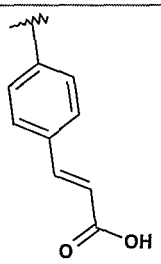
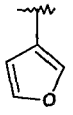
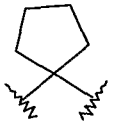
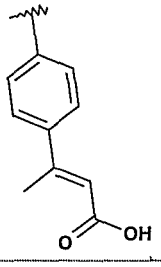
Cpd. #	R^1	R^2	R^7 R^8	Q
2021				
2022				
2023	Me	H		
2024	H			
2025	H			
2026	Me			

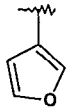
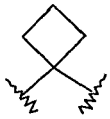
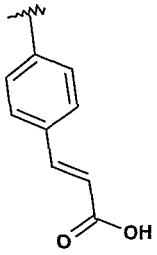
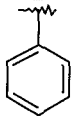
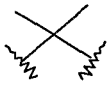
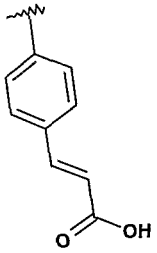
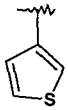
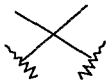
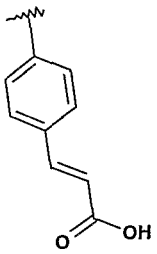
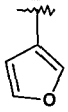
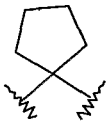
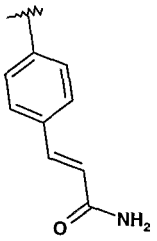
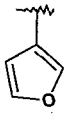
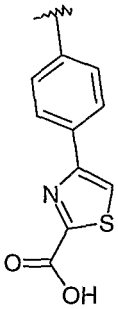
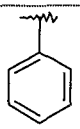
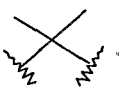
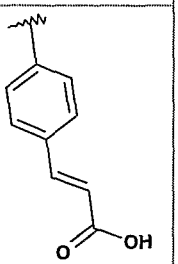
Cpd. #	R^1	R^2	R^7 R^8	Q
2027	Me			 ;
2028	Me			 ;
2029	Me			 ;
2030	Me			 ;
2031	Me			 ;
2032	Me			 ;

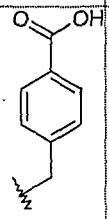
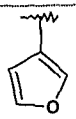
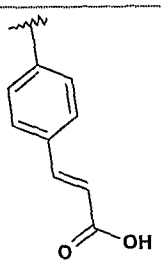
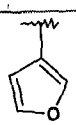
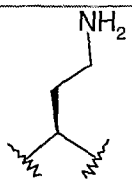
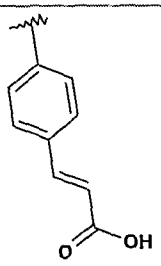
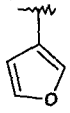
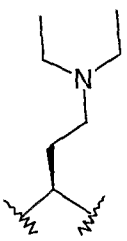
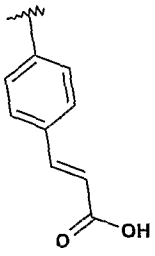
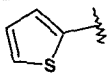
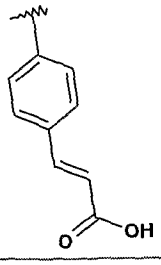
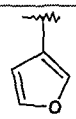
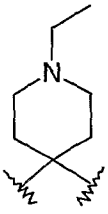
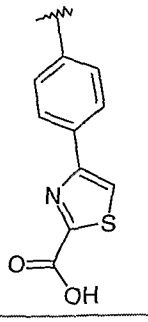
Cpd. #	R^1	R^2	R^7 R^8	Q
2033	H			 ;
2034	Me			 ;
2035	H			 ;
2036	H			 ;
2037	H			 ;
2038	H			 ;

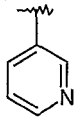
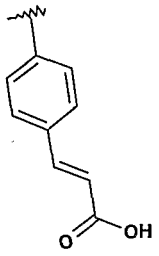
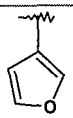
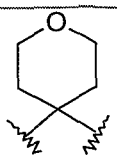
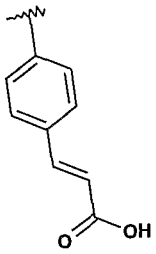
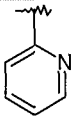
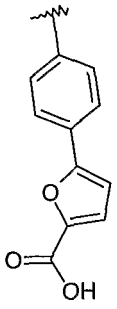
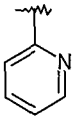
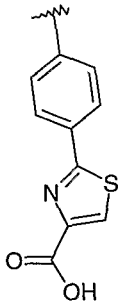
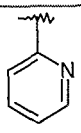
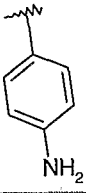
Cpd. #	R^1	R^2	R^7 R^8	Q
2039	H			
2040				
2041	Me			
2042	H			
2043				
2044	H			

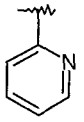
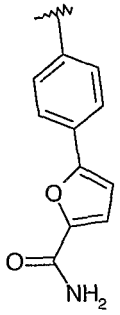
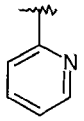
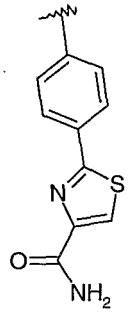
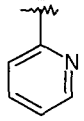
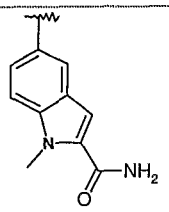
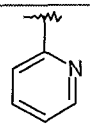
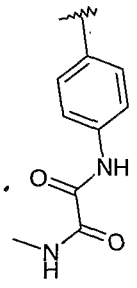
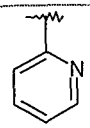
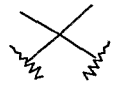
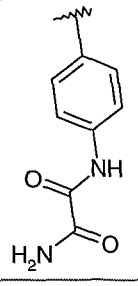
Cpd. #	R^1	R^2	R^7 R^8	Q
2045				 ;
2046	H			 ;
2047	H			 ;
2048	H			 ;
2049	H			 ;
2050	H			 ;

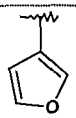
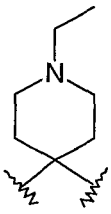
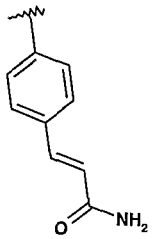
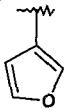
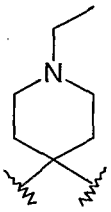
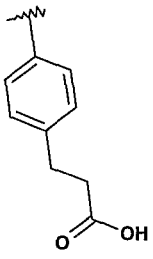
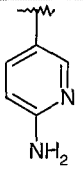
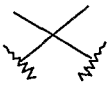
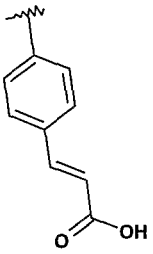
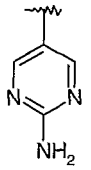
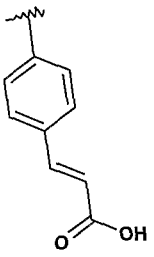
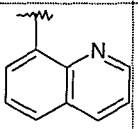
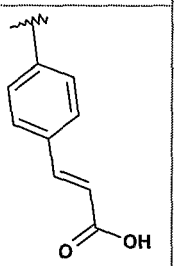
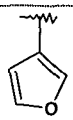
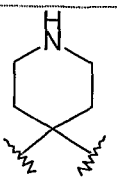
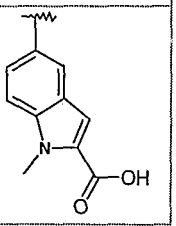
Cpd. #	R^1	R^2	R^7 R^8	Q
2051	Me			
2052	H			
2053	H			
2054	Et			
2055	H			
2056	H			

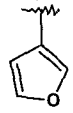
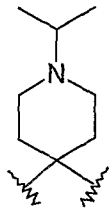
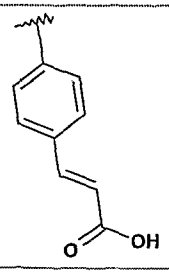
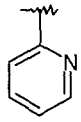
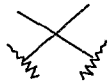
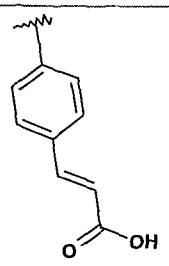
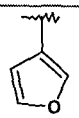
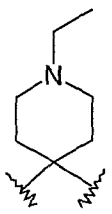
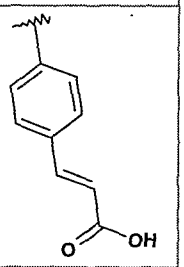
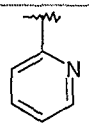
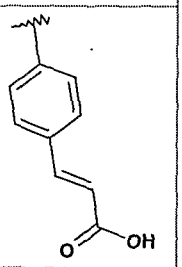
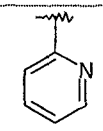
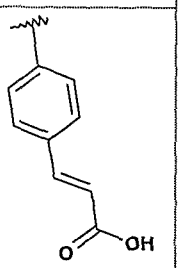
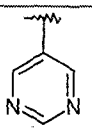
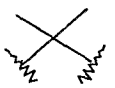
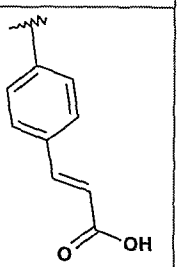
Cpd. #	R^1	R^2	R^7 R^8	Q
2057	H			 ;
2058	H			 ;
2059	H			 ;
2060	H			 ;
2061	H			 ;
2062	Me			 ;

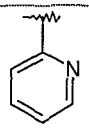
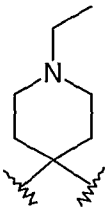
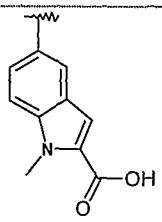
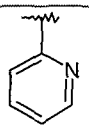
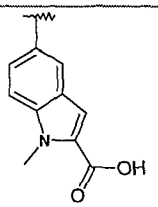
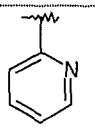
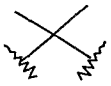
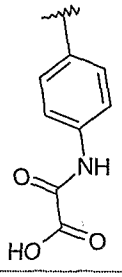
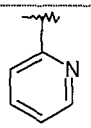
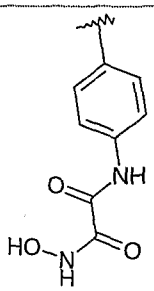
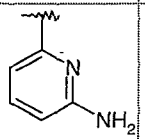
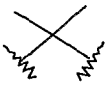
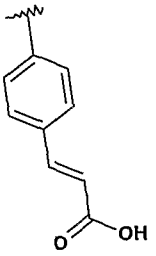
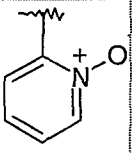
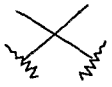
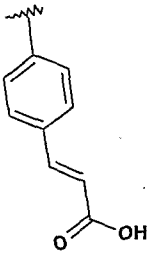
Cpd. #	R^1	R^2	R^7 R^8	Q
2063				 ;
2064	H			 ;
2065	H			 ;
2066	Me			 ;
2067	H			 ;

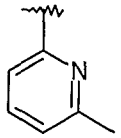
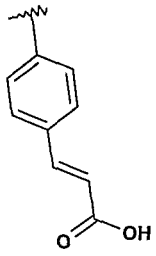
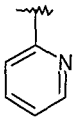
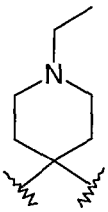
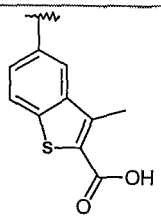
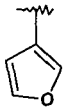
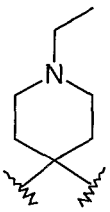
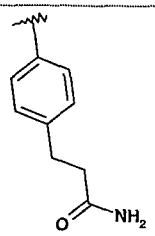
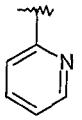
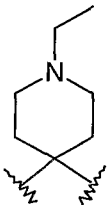
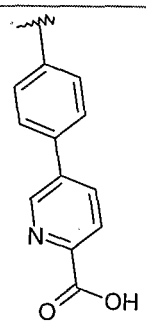
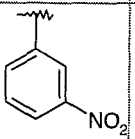
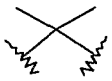
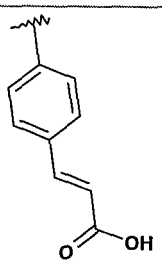
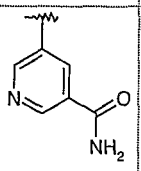
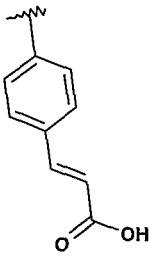
Cpd. #	R^1	R^2	R^7 R^8	Q
2068	Me			
2069	H			
2070	Me			
2071	Me			
2072	Me			

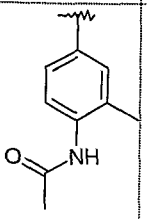
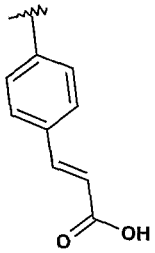
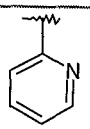
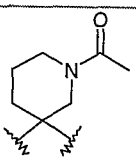
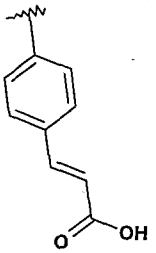
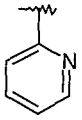
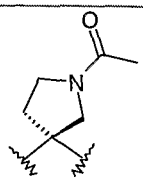
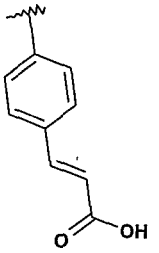
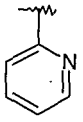
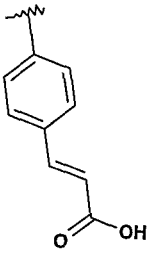
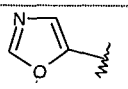
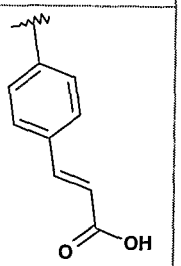
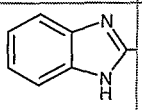
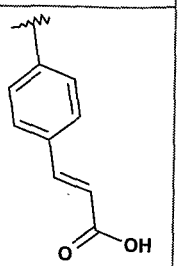
Cpd. #	R^1	R^2	R^7 R^8	Q
2073	Me			 ;
2074	Me			 ;
2075	Me			 ;
2076	Me			 ;
2077	Me			 ;

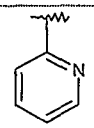
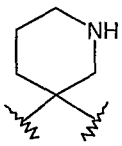
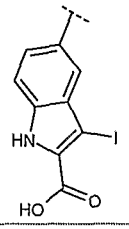
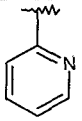
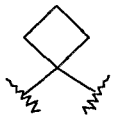
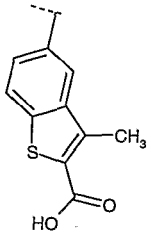
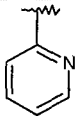
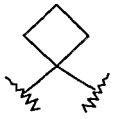
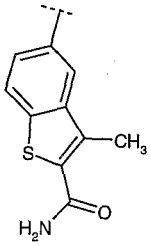
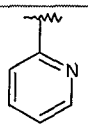
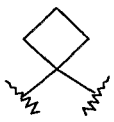
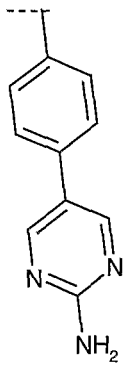
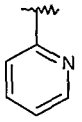
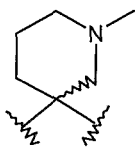
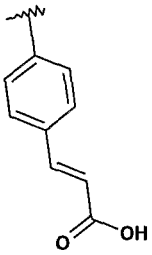
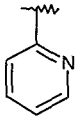
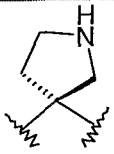
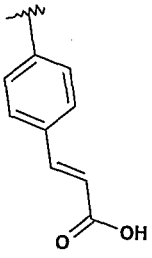
Cpd. #	R^1	R^2	R^7 R^8	Q
2078	H			 ;
2079	H			 ;
2080	Me			 ;
2081	Me			 ;
2082	Me			 ;
2084	H			 ;

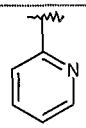
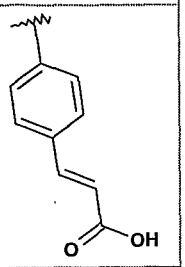
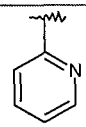
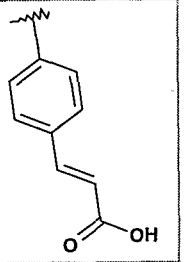
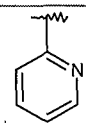
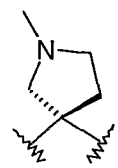
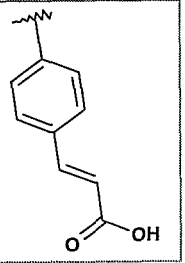
Cpd. #	R^1	R^2	R^7 R^8	Q
2086	H			
2087	Me			
2088	H			
2089	H			
2090	Me			
2091	Me			

Cpd. #	R^1	R^2	R^7 R^8	Q
2092	Me			
2093	Me			
2094	Me			
2095	Me			
2096	Me			
2097	Me			

Cpd. #	R^1	R^2	R^7 R^8	Q
2098	Me			
2099	Me			
2100	H			
2101	Me			
2102	Me			
2103	Me			

Cpd. #	R^1	R^2	R^7 R^8	Q
2104	Me			 ;
2105	Me			 ;
2106	Me			 ;
2107	Me			 ;
2108	Me			 ;
2109	Me			 ;

Cpd. #	R^1	R^2	R^7 R^8	Q
2110	Me			 ;
2111	Me			 ;
2112	Me			 ;
2113	Me			 ;
2114	Me			 ;
2115	Me			 ;

Cpd. #	R^1	R^2	R^7 R^8	Q
2116	Me			
2117	Me			
2118	Me			

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and

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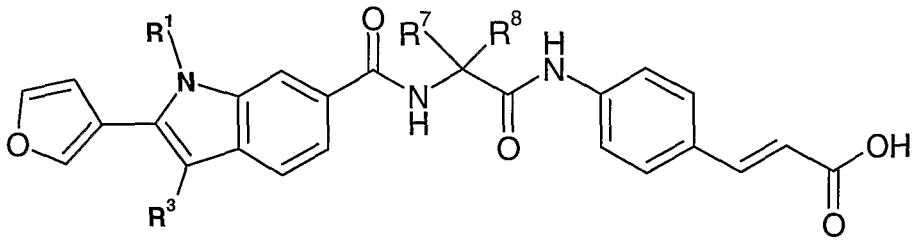
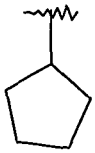
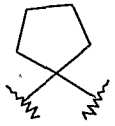
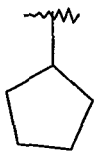
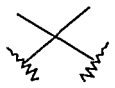
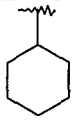
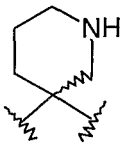
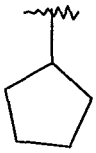
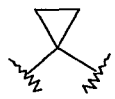
49. A compound of the formula:



wherein R^1, R^3, R^7 and R^8 are defined as follows:

cpd. #	R^1	R^3	R^7 R^8
3001	H		

;

3002	H		
3003	Me		
3004	Me		

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and

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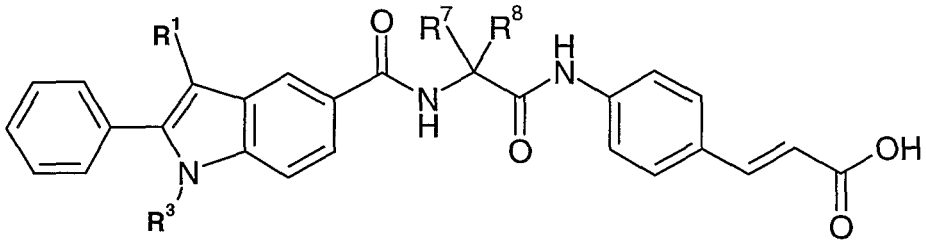
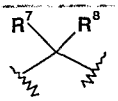
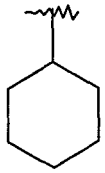
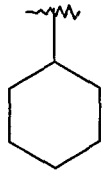
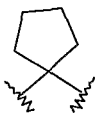
50. A compound of the formula:



wherein R^1, R^3, R^7 and R^8 are defined as follows:

cpd. #	R^1	R^3	
4001	Me		
4002	H		

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and

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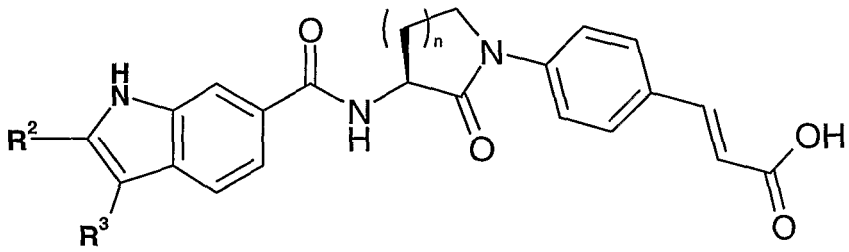
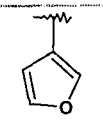
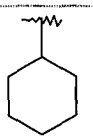
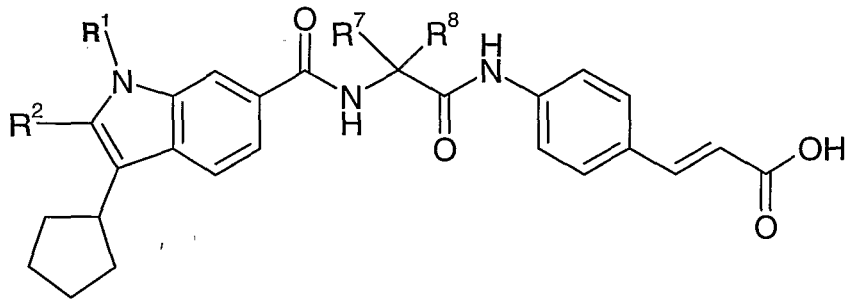
51. A compound of the formula:



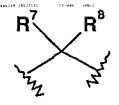
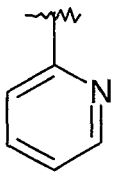
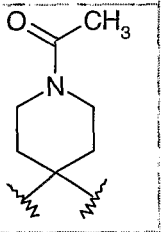
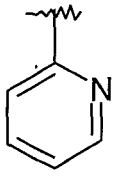
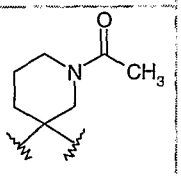
wherein R^2, R^3 and n are defined as follows:

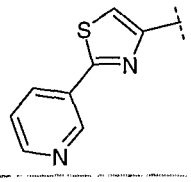
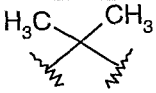
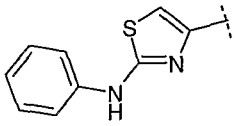
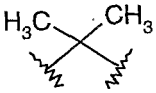
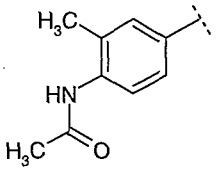
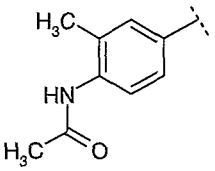
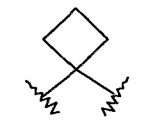
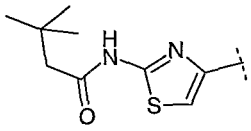
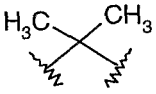
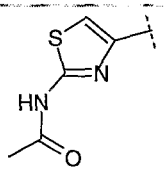
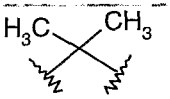
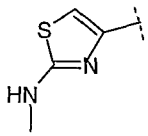
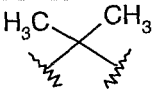
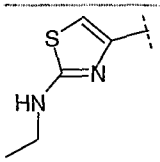
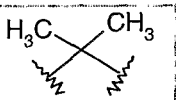
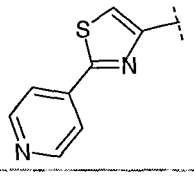
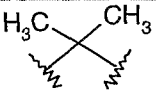
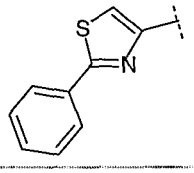
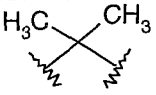
cpd. #	R^2	R^3	n
5001			1

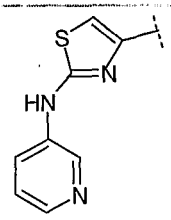
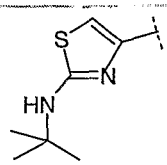
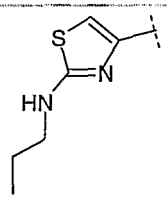
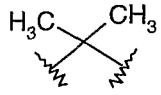
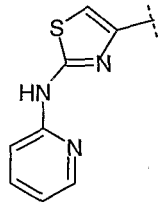
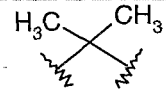
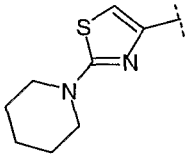
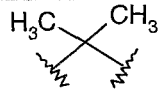
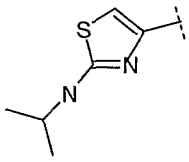
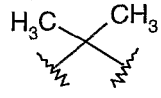
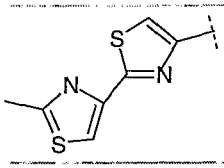
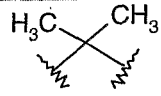
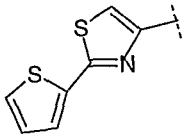
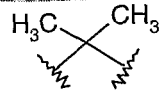
52. A compound of the formula:

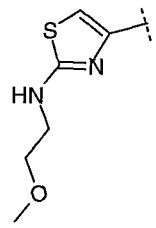
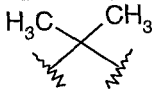
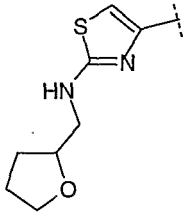
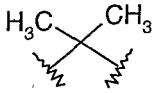
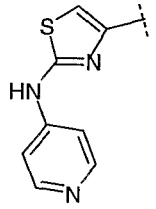
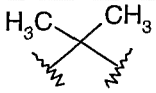
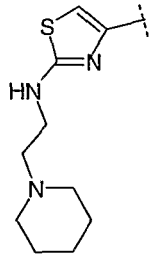
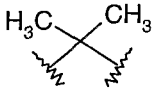
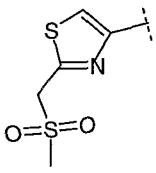
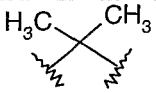
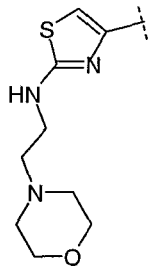
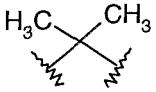
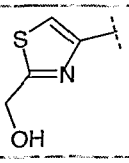
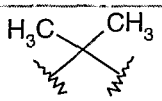


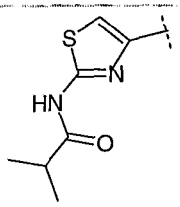
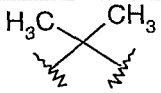
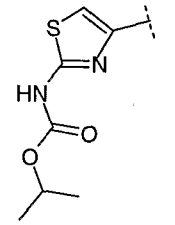
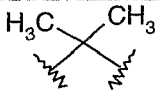
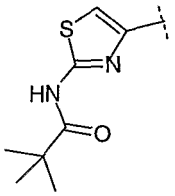
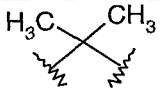
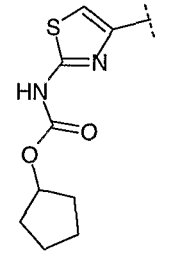
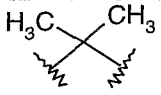
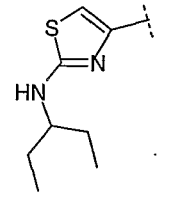
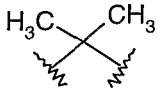
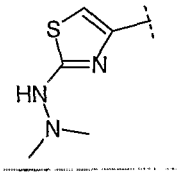
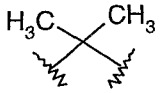
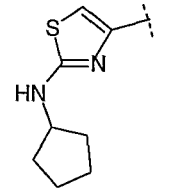
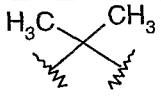
wherein R^1, R^2, R^7 and R^8 are defined as follows:

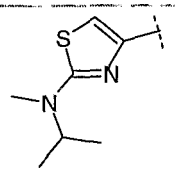
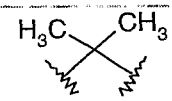
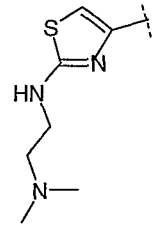
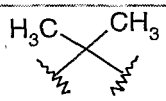
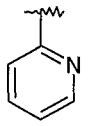
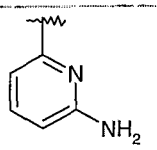
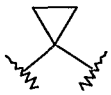
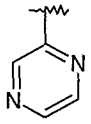
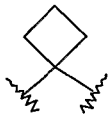
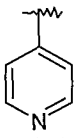
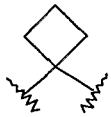
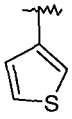
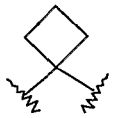
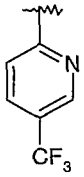
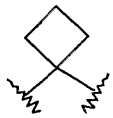
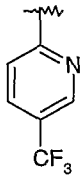
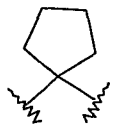
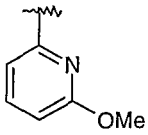
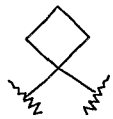
cpd. #	R^1	R^2	
6001	CH_3		 ;
6002	CH_3		 ;

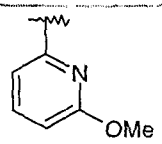
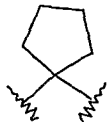
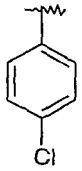
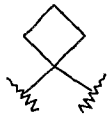
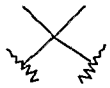
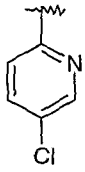
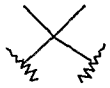
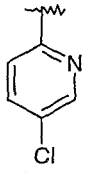
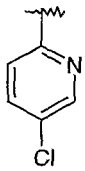
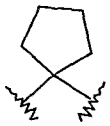
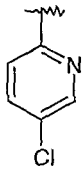
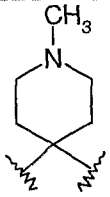
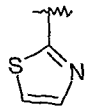
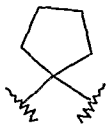
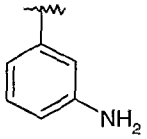
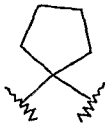
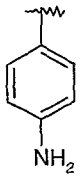
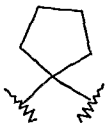
cpd. #	R^1	R^2	R^7 R^8	
6003	CH_3			;
6004	CH_3			;
6005	CH_3			;
6006	CH_3			;
6007	CH_3			;
6008	CH_3			;
6009	CH_3			;
6010	CH_3			;
6011	CH_3			;
6012	CH_3			;

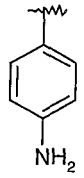
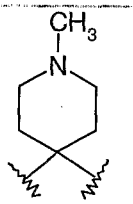
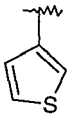
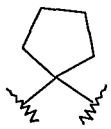
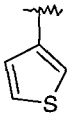
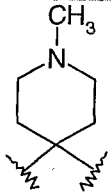
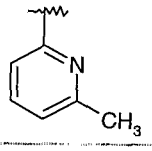
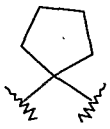
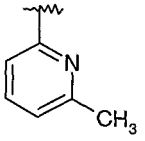
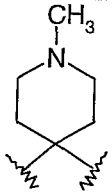
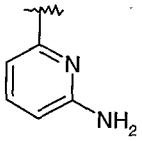
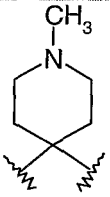
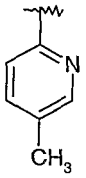
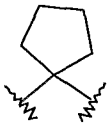
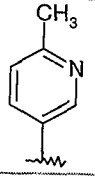
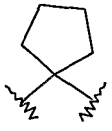
cpd. #	R^1	R^2	R^7 R^8	
6013	CH_3			;
6013	CH_3			;
6014	CH_3			;
6015	CH_3			;
6016	CH_3			;
6017	CH_3			;
6018	CH_3			;
6019	CH_3			;

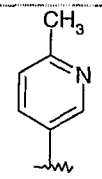
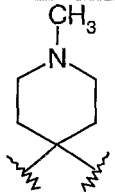
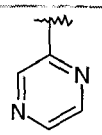
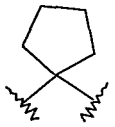
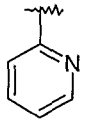
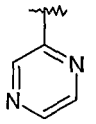
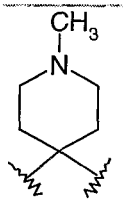
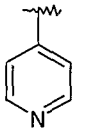
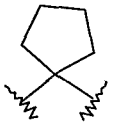
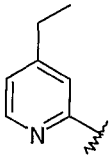
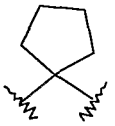
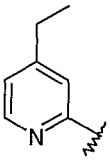
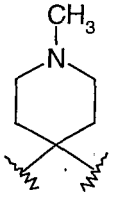
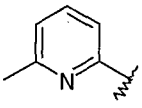
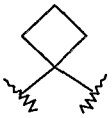
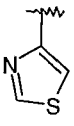
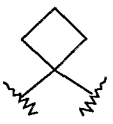
cpd. #	R^1	R^2	R^7 R^8	
6020	CH_3			;
6021	CH_3			;
6022	CH_3			;
6023	CH_3			;
6024	CH_3			;
6025	CH_3			;
6026	CH_3			;

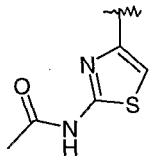
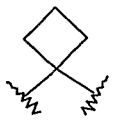
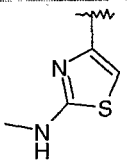
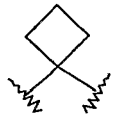
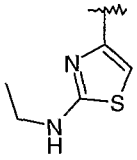
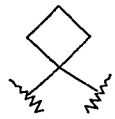
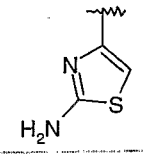
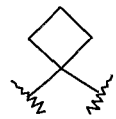
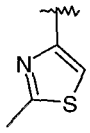
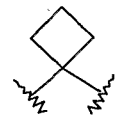
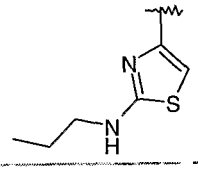
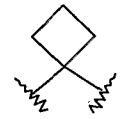
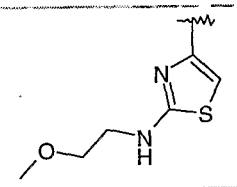
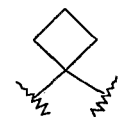
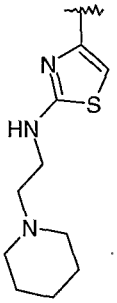
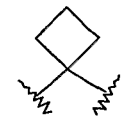
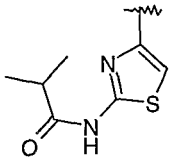
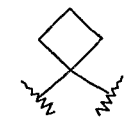
cpd. #	R^1	R^2	R^7 R^8	
6027	CH_3			;
6028	CH_3			;
6029	CH_3			;
6030	CH_3			;
6031	CH_3			;
6032	CH_3			;
6033	CH_3			;

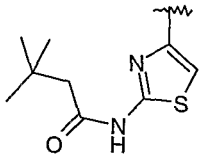
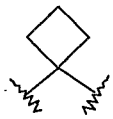
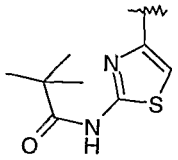
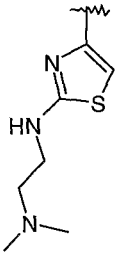
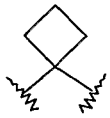
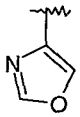
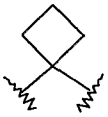
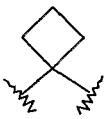
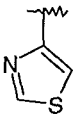
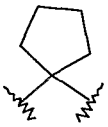
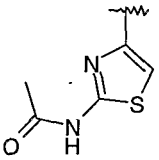
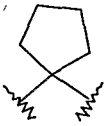
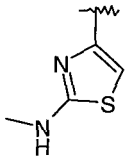
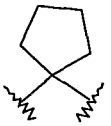
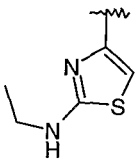
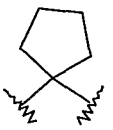
cpd. #	R^1	R^2	R^7 R^8
6034	CH_3		 ;
6035	CH_3		 ;
6036	CH_3		;
6037	CH_3		 ;
6038	CH_3		 ;
6039	CH_3		 ;
6040	CH_3		 ;
6041	CH_3		 ;
6042	CH_3		 ;
6043	CH_3		 ;

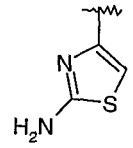
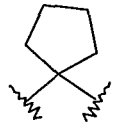
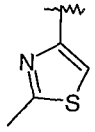
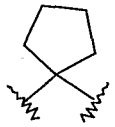
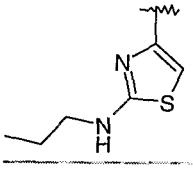
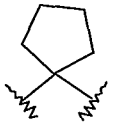
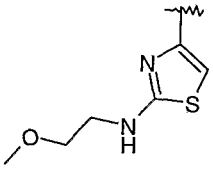
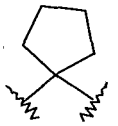
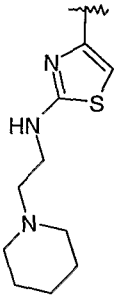
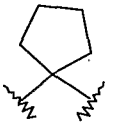
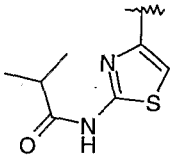
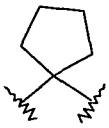
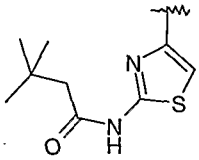
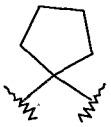
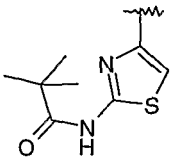
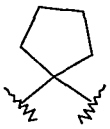
cpd. #	R^1	R^2	R^7 R^8	
6044	CH_3			;
6045	CH_3			;
6046	CH_3			;
6047	CH_3			;
6048	CH_3			;
6049	CH_3			;
6050	CH_3			;
6051	CH_3			;
6052	CH_3			;
6053	CH_3			;

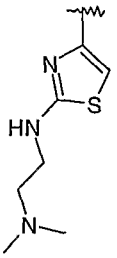
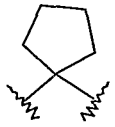
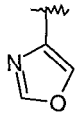
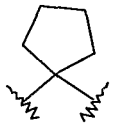
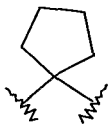
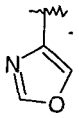
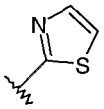
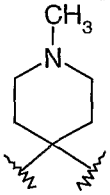
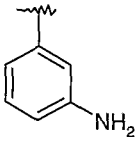
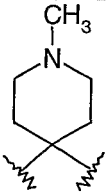
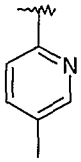
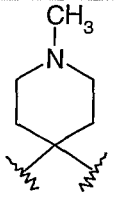
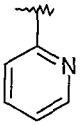
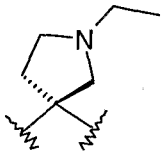
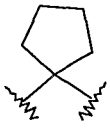
cpd. #	R^1	R^2	R^7 R^8
6054	CH_3		 ;
6055	CH_3		 ;
6056	CH_3		 ;
6057	CH_3		 ;
6058	CH_3		 ;
6059	CH_3		 ;
6060	CH_3		 ;
6061	CH_3		 ;

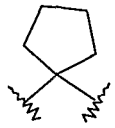
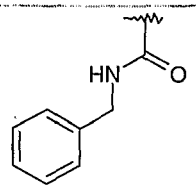
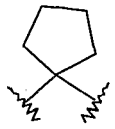
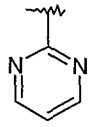
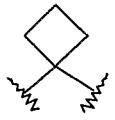
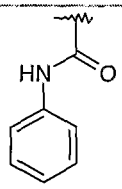
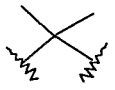
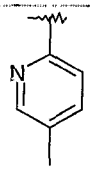
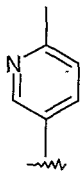
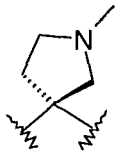
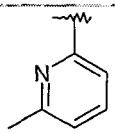
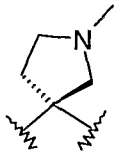
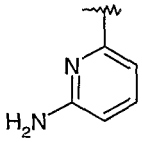
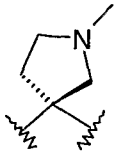
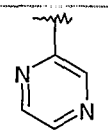
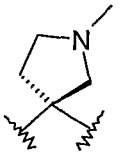
cpd. #	R^1	R^2	R^7 R^8	
6062	CH_3			;
6063	CH_3			;
6064	CH_3			;
6065	CH_3			;
6066	CH_3			;
6067	CH_3			;
6068	CH_3			;
6069	CH_3			;
6070	CH_3			;

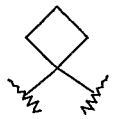
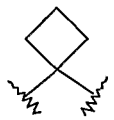
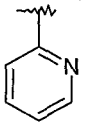
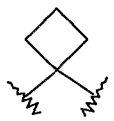
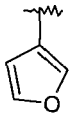
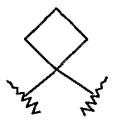
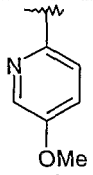
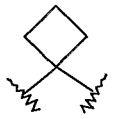
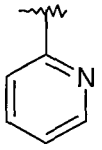
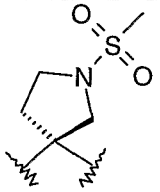
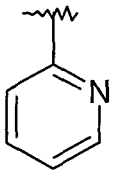
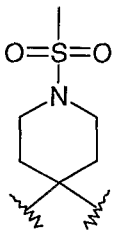
cpd. #	R^1	R^2	R^7 R^8
6071	CH_3		 ;
6072	CH_3		 ;
6073	CH_3		 ;
6074	CH_3		 ;
6075	CH_3		 ;
6076	CH_3		 ;
6077	CH_3		 ;
6078	CH_3		 ;
6079	CH_3		 ;

cpd. #	R^1	R^2	R^7 R^8	
6080	CH_3			;
6081	CH_3			;
6082	CH_3			;
6083	CH_3			;
6084	CH_3			;
6085	CH_3			;
6086	CH_3			;
6087	CH_3			;
6088	CH_3			;

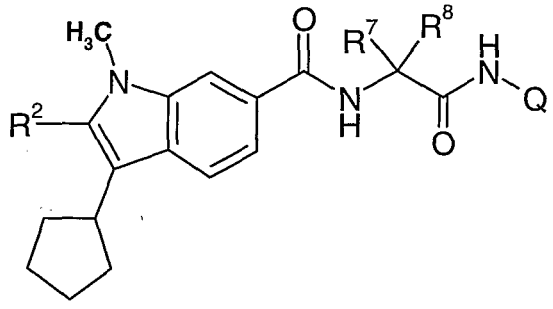
cpd. #	R^1	R^2	R^7 R^8
6089	CH_3		 ;
6090	CH_3		 ;
6091	CH_3		 ;
6092	CH_3		 ;
6093	CH_3		 ;
6094	CH_3		 ;
6095	CH_3		 ;
6096	CH_3		 ;

cpd. #	R^1	R^2	R^7 R^8	
6097	CH_3			;
6098	CH_3			;
6099	CH_3			;
6100	CH_3			;
6101	CH_3			;
6102	CH_3			;
6103	CH_3			;
6105	CH_3			;
6106	CH_3	$CONHCH_3$		;

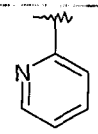
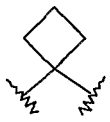
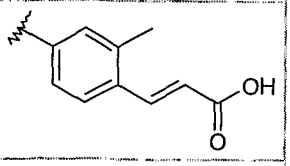
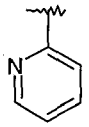
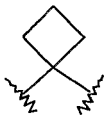
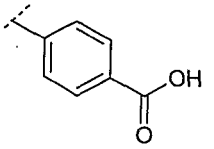
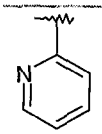
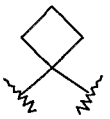
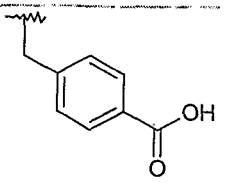
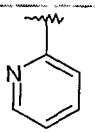
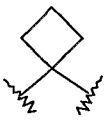
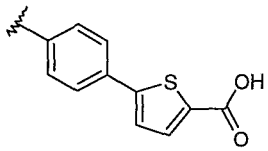
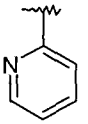
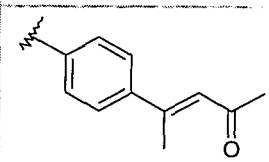
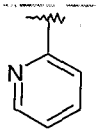
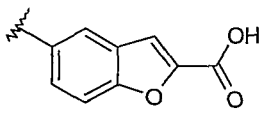
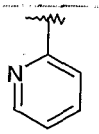
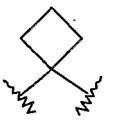
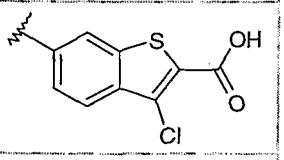
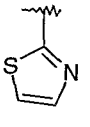
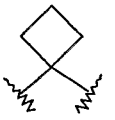
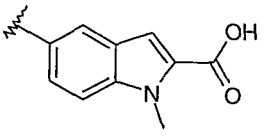
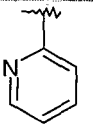
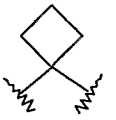
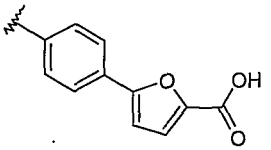
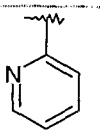
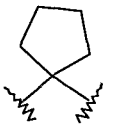
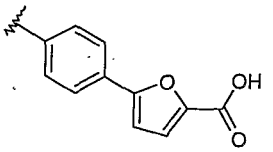
cpd. #	R^1	R^2	R^7 R^8	
6107	CH_3	$CON(CH_3)_2$		;
6110	CH_3			;
6111	CH_3			;
6112	CH_3			;
6113	CH_3	$CONH_2$		;
6114	CH_3			;
6115	CH_3			;
6116	CH_3			;
6117	CH_3			;
6118	CH_3			;

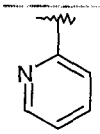
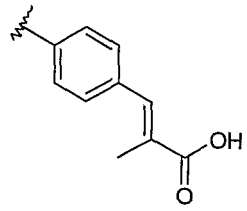
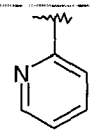
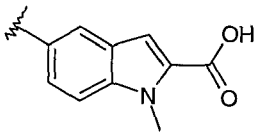
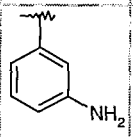
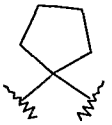
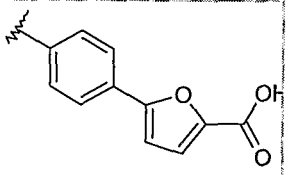
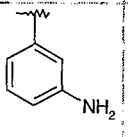
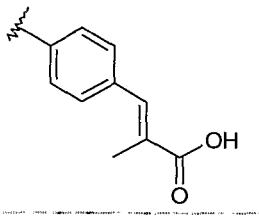
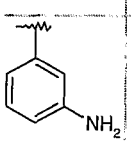
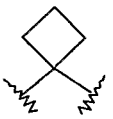
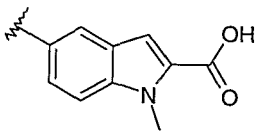
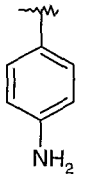
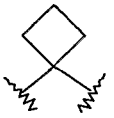
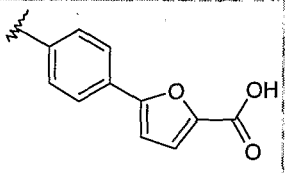
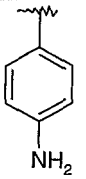
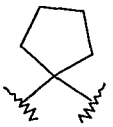
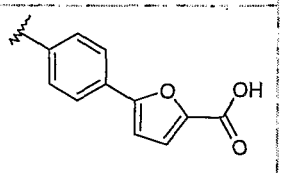
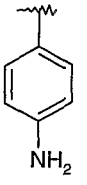
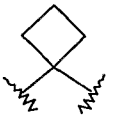
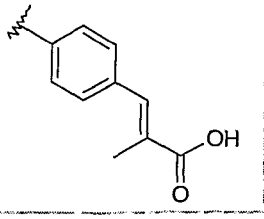
cpd. #	R^1	R^2	R^7 R^8	
6119	CH_3	H		;
6120	CH_3	Br		;
6121	H			;
6122	CH_3			;
6123	CH_3			;
6124	CH_3			; and
6125	CH_3			.

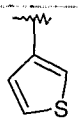
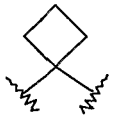
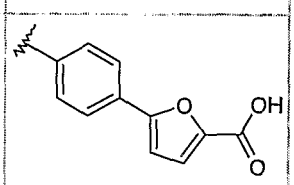
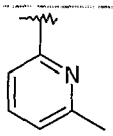
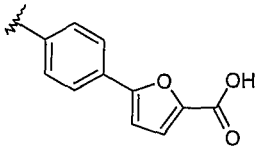
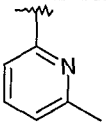
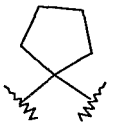
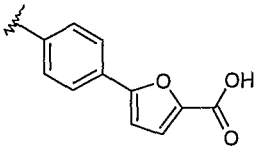
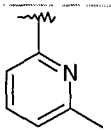
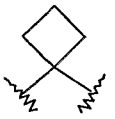
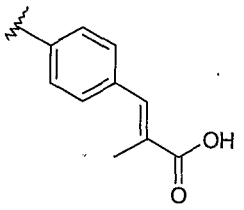
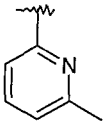
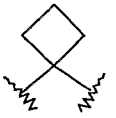
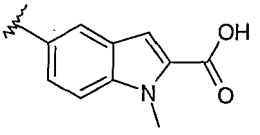
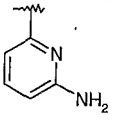
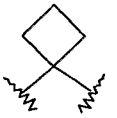
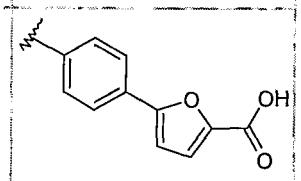
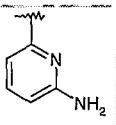
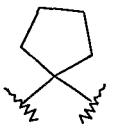
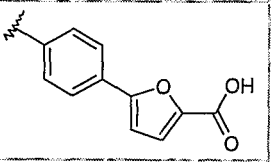
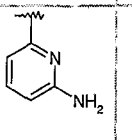
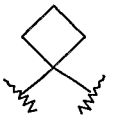
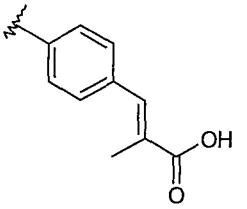
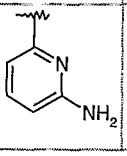
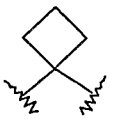
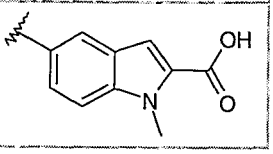
53. A compound of the formula:



wherein R^2, R^7, R^8 and **Q** are defined as follows:

cpd #	R^2	R^7 R^8	Q
7001			 ;
7002			 ;
7003			 ;
7004			 ;
7005			 ;
7006			 ;
7007			 ;
7008			 ;
7009			 ;
7010			 ;

cpd #	R^2	R^7 R^8	Q
7011			 ;
7012			 ;
7013			 ;
7014			 ;
7015			 ;
7016			 ;
7017			 ;
7018			 ;

cpd #	R^2	R^7 R^8	Q
7019			 ;
7020			 ;
7021			 ;
7022			 ;
7023			 ;
7024			 ;
7025			 ;
7026			 ;
7027			 ;

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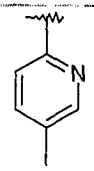
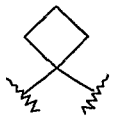
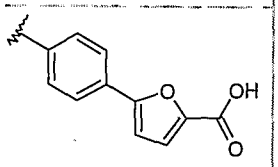
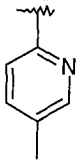
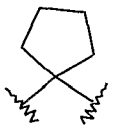
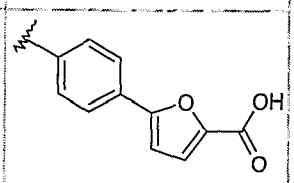
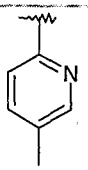
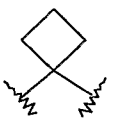
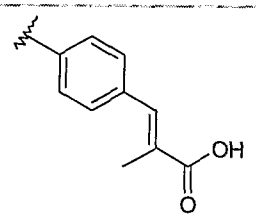
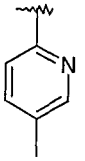
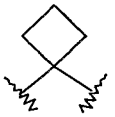
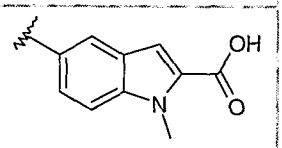
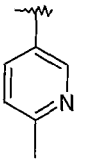
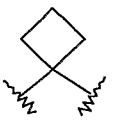
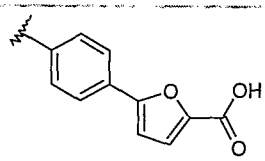
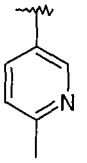
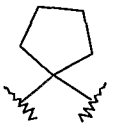
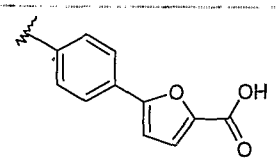
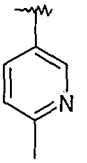
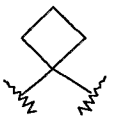
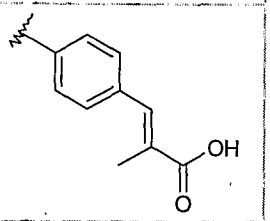
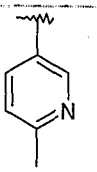
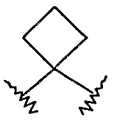
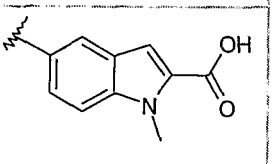
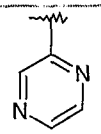
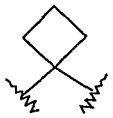
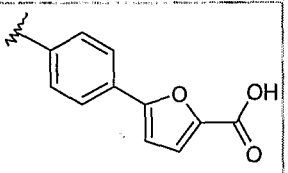
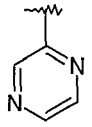
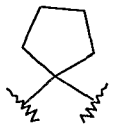
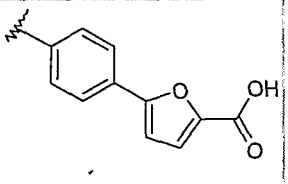
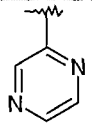
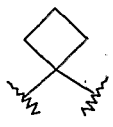
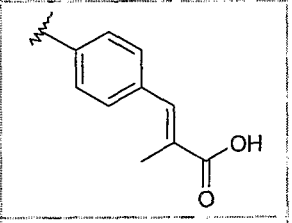
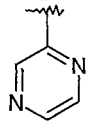
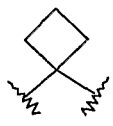
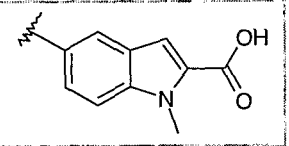
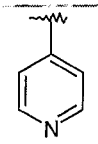
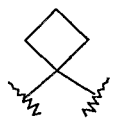
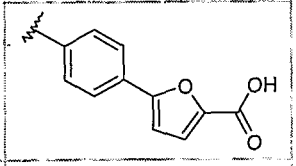
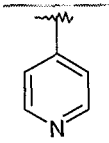
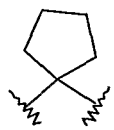
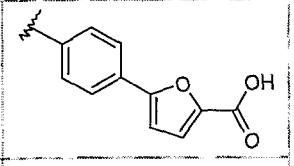
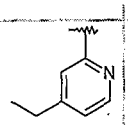
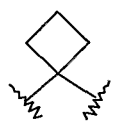
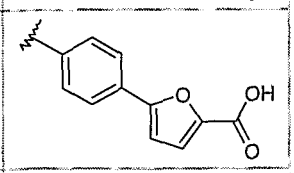
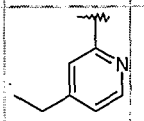
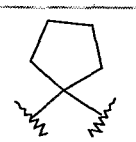
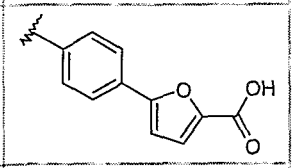
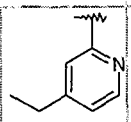
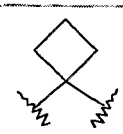
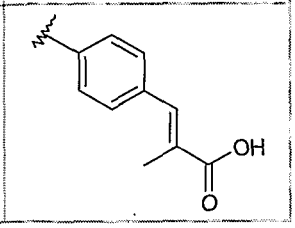
7028			 ;
7029			 ;
7030			 ;
7031			 ;
7032			 ;
7033			 ;
7034			 ;
7035			 ;

cpd #	R^2	R^7 R^8	Q
7036			 ;
7037			 ;
7038			 ;
7039			 ;
7040			 ;
7041			 ;
7042			 ;
7043			 ;
7044			 ;

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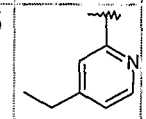
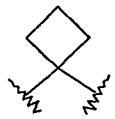
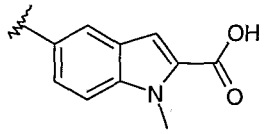
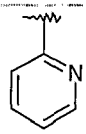
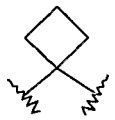
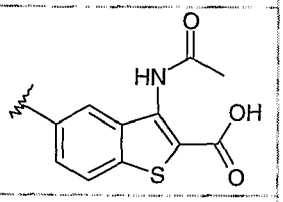
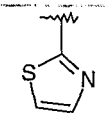
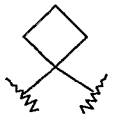
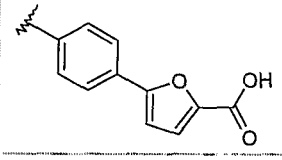
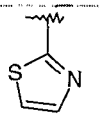
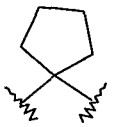
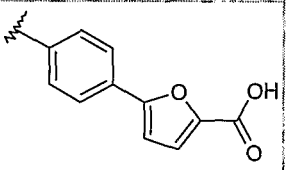
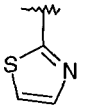
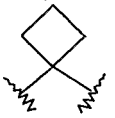
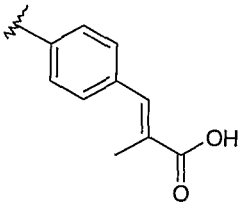
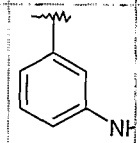
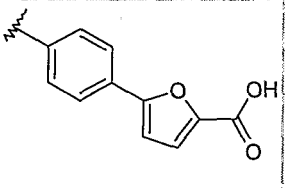
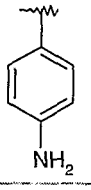
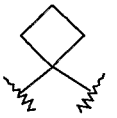
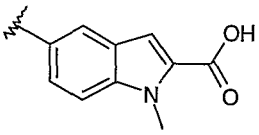
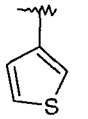
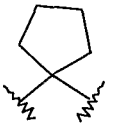
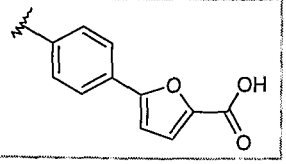
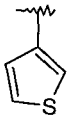
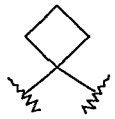
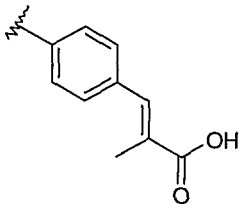
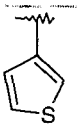
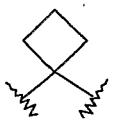
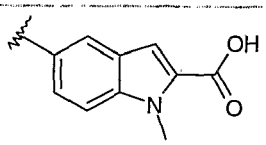
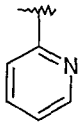
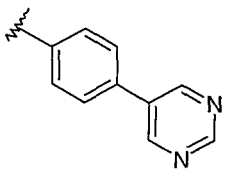
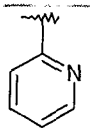
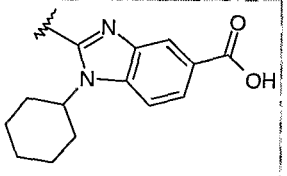
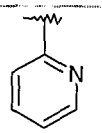
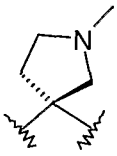
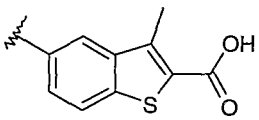
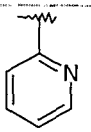
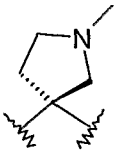
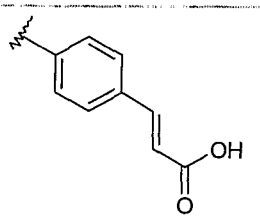
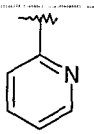
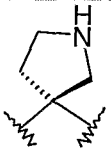
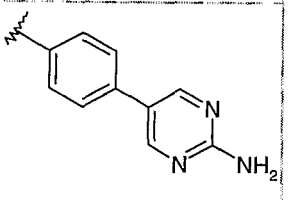
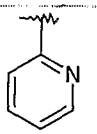
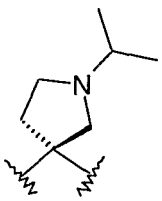
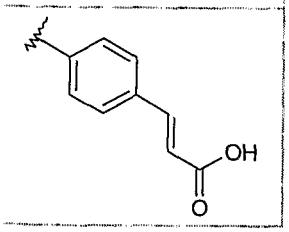
7045			
7046			
7047			
7048			
7049			
7050			
7051			
7052			

cpd #	R^2	R^7 R^8	Q
7053			 ;
7054			 ;
7055			 ;
7056			 ;
7057			 ;
7058			 ;
7059			 ;
7060			 ;

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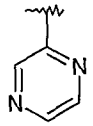
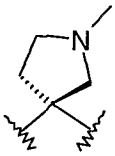
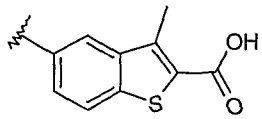
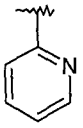
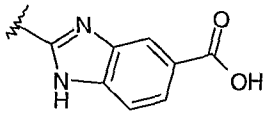
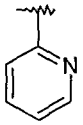
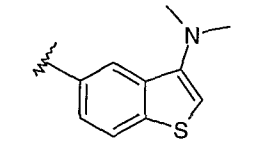
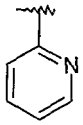
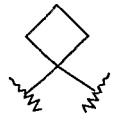
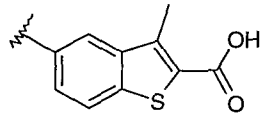
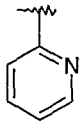
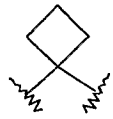
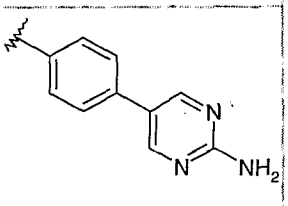
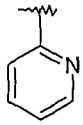
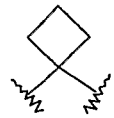
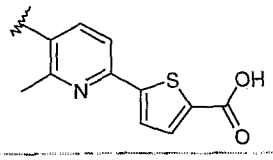
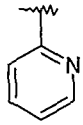
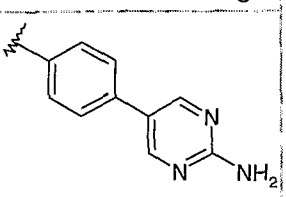
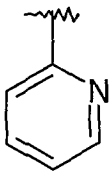
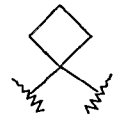
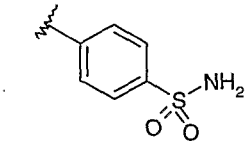
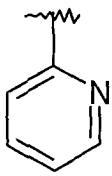
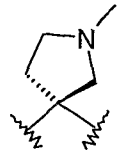
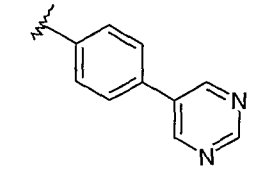
7061			 ;
7062			 ;
7063			 ;
7064			 ;
7065			 ;
7066			 ;
7067			 ;
7068			 ;
7069			 ;

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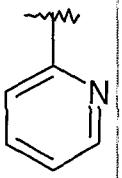
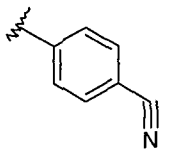
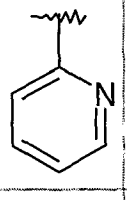
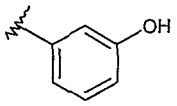
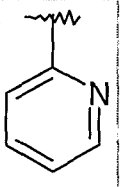
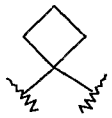
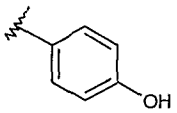
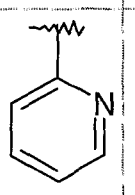
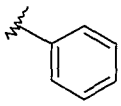
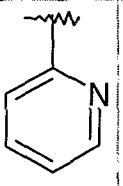
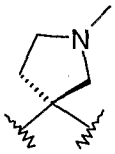
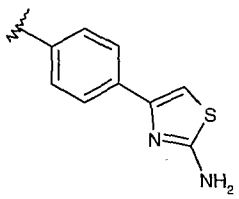
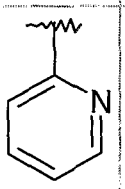
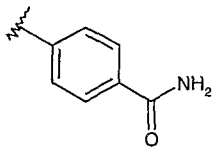
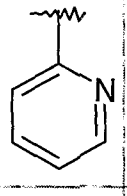
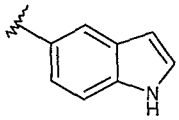
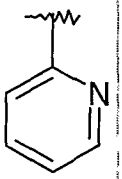
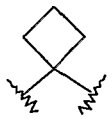
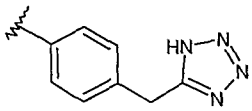
7070			 ;
7071			 ;
7072			 ;
7073			 ;
7075			 ;
7076			 ;
7077			 ;
7078			 ;

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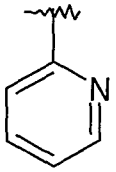
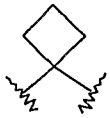
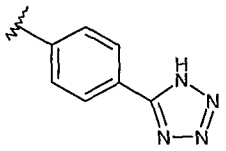
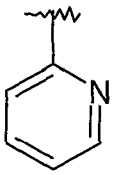
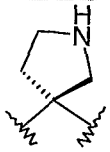
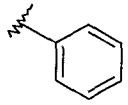
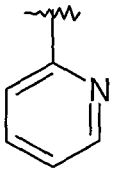
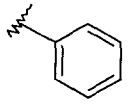
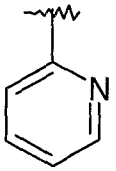
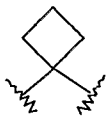
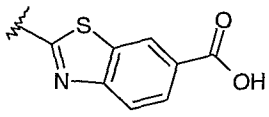
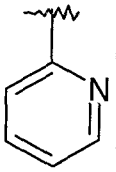
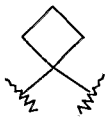
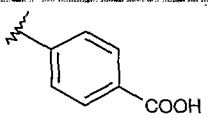
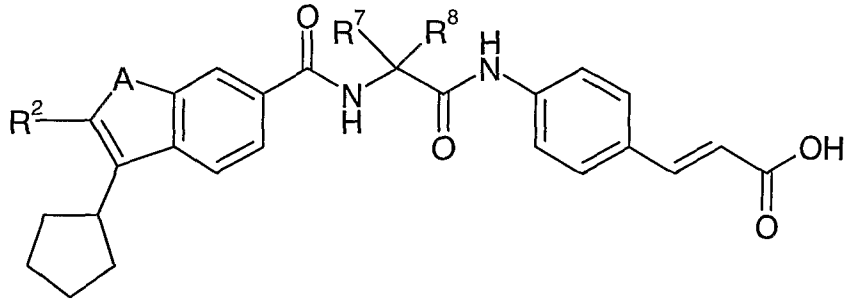
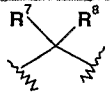
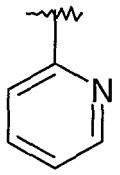
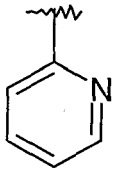
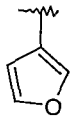
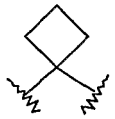
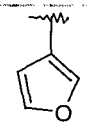
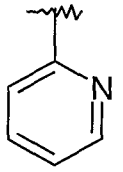
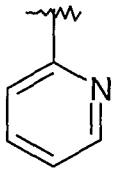
7079			 ;
7080			 ;
7081			 ;
7082			 ; and
7083			 .

54. A compound of the formula:

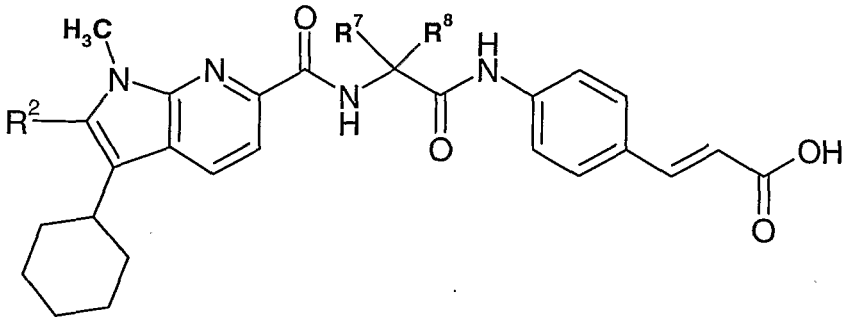


wherein **A**, R^2, R^7 and R^8 are defined as follows:

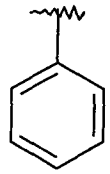
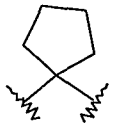
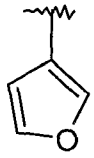
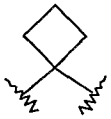
cpd. #	A	R^2	R^7 R^8
			

cpd. #	A	R^2	R^7 R^8	
8001	S			;
8002	S			;
8003	S			;
8004	S			;
8005	O			; and
8006	O			.

55. A compound of the formula:



wherein R^2, R^7 and R^8 are defined as follows:

cpd. #	R^2	R^7 R^8
9001		
9002		

; and

56. A compound of the formula I according to claim 1, or a pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV.

57. A compound of the formula I according to claim 1, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

58. A pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

59. A composition according to claim 58, further comprising an immunomodulatory agent.

60. A composition according to claim 59, wherein said immunomodulatory agents is selected from: α-, β-, δ- γ-, and ω-interferon.

61. A composition according to claim 58, further comprising another antiviral agent.

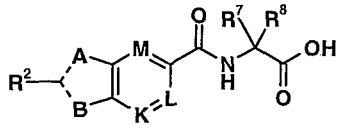
62. A composition according to claim 61, wherein said antiviral agent is selected from: ribavirin and amantadine.

63. A composition according to claim 58, further comprising another inhibitor of HCV polymerase.

64. A composition according to claim 58, further comprising an inhibitor of: HCV helicase, HCV protease, HCV metalloprotease or HCV IRES.

65. Use of a compound of formula I according to claim 1, for the manufacture of a medicament for the treatment of HCV infection.

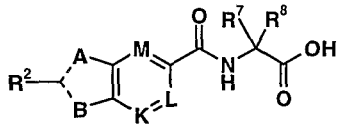
66. An intermediate compound represented by formula 1c:



1c

wherein **A**, R^2, **B**, **K**, **L**, **M**, R^7 and R^8 are as defined in claim 1, or a salt, or a derivative thereof.

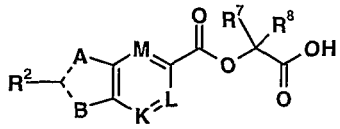
67. A process for producing compounds of formula I, comprising:
a) coupling, in a mixture containing an aprotic solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1c:



1c

with amine **Q**-NH_2 so as to produce compounds of formula I, wherein **A**, R^2, **B**, R^7, R^8, **Q**, **K**, **L**, **M** and **Q** are as defined in claim 1.

68. An intermediate compound represented by formula 1d:

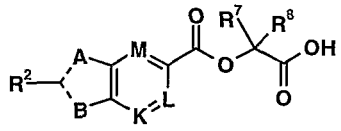


1d

wherein **A**, R^2, **B**, **K**, **L**, **M**, R^7 and R^8 are as defined in claim 1, or a salt or a derivative thereof.

69. A process for producing compounds of formula I, comprising:

a) coupling, in a mixture containing an appropriate solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1d:



1d

with amine **Q**-NH_2 so as to produce compounds of formula I, wherein **A**, $\mathbf{R^2}$, **B**, $\mathbf{R^7}$, $\mathbf{R^8}$, **Q**, **K**, **L**, and **M** are as defined in claim 1.