QUINOLINE DERIVATIVES AS INHIBITORS OF MEK ENZYMES

The present invention relates to certain novel quinoline derivatives as well as to their use as pharmaceuticals, in particular as inhibitors of specific kinase enzymes, such as MEK enzymes. Further aspects of the invention include pharmaceutical compositions and methods of treatment of proliferative disease such as cancer using said compounds.

Cancer is a disease in which cells grow and divide in an uncontrolled fashion. This uncontrolled growth arises from abnormalities in signal transduction pathways that are used by normal cells to regulate cell growth and division in response to various signalling molecules. Normal cells do not proliferate unless stimulated to do so by specific signal molecules located outside the cell derived from nearby cells or tissues. Growth factors bind to the cell membrane via specific receptors which have intrinsic enzyme activity. These receptors relay the growth signal to the cell nucleus via a series of signalling proteins. In cancer, a number of defects in signal pathways are apparent. For example, cancer cells may produce their own growth factors which bind to their cognate receptors, resulting in an autocrine loop, or receptors may be mutated or overexpressed leading to an increased, continuous signal to proliferate. In addition, negative regulators of cell growth may be lost.

Oncogenes are cancer related genes which often encode abnormal versions of signal pathway components, such as receptor tyrosine kinases, serine-threonine kinases, or downstream signaling molecules such as the ras genes, which code for closely related small guanine nucleotide binding proteins which hydrolyse bound guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Ras proteins are active in promoting cell growth and transformation when they are bound to GTP and inactive when they are bound to GDP. Transforming mutants of p21ras are defective in their GTPase activity and hence remain in the active GTP bound state. The ras oncogene is known to play an integral role in certain cancers, and has been found to contribute to the formation of over 20% of all cases of human cancer.

When activated by ligand, cell surface receptors which are coupled to the mitogenic response, such as growth factor receptors, initiate a chain of reactions which leads to the activation of guanine nucleotide exchange activity on ras. When in its active GTP-bound state, a number of proteins interact directly with ras at the plasma membrane

resulting in signal transmission through several distinct pathways. The best characterised effector protein is the product of the raf proto-oncogene. The interaction of raf and ras is a key regulatory step in the control of cell proliferation. Ras-mediated activation of the raf serine-threonine kinase in turn activates the dual-specificity MEK (MEK1 and MEK2), which is the immediate upstream activator of mitogen activated protein kinase (MAPKs known as extracellular signal regulated protein kinases or ERK1 and ERK2). To date, no substrates of MEK other than MAPK have been identified, though recent reports indicate that MEK may also be activated by other upstream signal proteins such as MEK kinase or MEKK1 and PKC. Activated MAPK translocates and accumulates in the nucleus, where it can phosphorylate and activate transcription factors such as Elk-1 and Sap1a, leading to the enhanced expression of genes such as that for c-fos.

The ras-dependent raf-MEK-MAPK cascade is one of the key signalling pathways responsible for transmitting and amplifying mitogenic signals from cell surface to the nucleus resulting in changes in gene expression and cell fate. This ubiquitous pathway appears essential for normal cell proliferation and constitutive activation of this pathway is sufficient to induce cellular transformation. Transforming mutants of p21ras are constitutively active, resulting in raf, MEK and MAPK activity and cell transformation. Inhibition of MEK activity using either antisense raf, a dominant negative MEK mutant or the selective inhibitor PD098059 have been shown to block the growth and morphological transformation of ras-transformed fibroblasts.

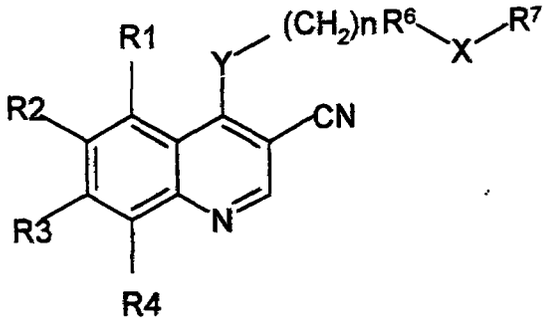
The mechanism of activation of raf, MEK and MAPK is through phosphorylation on specific serine, threonine or tyrosine residues. Activated raf and other kinases phosphorylate MEK1 on S218 and S222 and MEK2 on S222 and S226. This results in MEK activation and subsequent phosphorylation and activation of ERK1 on T190 and Y192 and ERK2 on T183 and Y185 by the dual specificity MEKs. Whilst MEK can be activated by a number of protein kinases, and active MAPKs phosphorylate and activate a number of substrate proteins including transcription factors and other protein kinases, MEKs appear specific and sole activators of MAPKs and could act as a focal point for cross-cascade regulation. MEK1 and MEK2 isoforms show unusual specificity and also contain a proline-rich insert between catalytic subdomains IX and X which is not present in any of the other known MEK family members. These differences between MEK and other protein kinases, together with the known role of MEK in proliferative signalling

suggest that it may be possible to discover and employ selective MEK inhibitors as therapeutic agents for use in proliferative disease.

WO 98/43960 discloses a range of 3-cyano quinoline compounds and their use in the treatment of cancer. Certain of the compounds are demonstrated as being inhibitors of Epidermal Growth Factor Receptor Kinase, and to inhibit cancer cell growth. Other quinoline derivatives which inhibit the effect of growth factors such as VEGF are described in WO98/13350.

This invention provides compounds which are inhibitors of the kinase activity of MEK and as a result, can produce therapeutically useful effects in the treatment of proliferative disease and in particular cancer.

According to the present invention there is provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

wherein:

n is 0-1;

X and Y are independently selected from –NH-, -O-, -S-, or $-NR^8-$ where R^8 is alkyl of 1-6 carbon atoms and X may additionally comprise a CH_2 group;

R^7 is a group $(CH_2)_mR^9$ where m is 0,or an integer of from 1-3 and R^9 is a substituted aryl group, an optionally substituted cycloalkyl ring of up to 10 carbon atoms, or an optionally substituted heterocyclic ring or an N-oxide of any nitrogen containing ring;

R^6 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen,

alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

R_1, R_2, R_3 and R_4 are each independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or a group R^{13}-X^1-$(CH_2)_x$ wherein x is 0 to 3, X^1 represents -O-, $-CH_2-$, -OCO-, carbonyl, -S-, -SO-, $-SO_2-$, $-NR^{14}CO-$, $-CONR^{15}-$, $-SO_2NR^{16}-$, $-NR^{17}SO_2-$ or $-NR^{18}-$ (wherein R^{14}, R^{15}, R^{16}, R^{17} and R^{18} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{13} is selected from one of the following sixteen groups:

1) C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^2COR^{19} (wherein X^2 represents -O- or $-NR^{20}-$ (wherein R^{20} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{19} represents $-NR^{21}R^{22}-$ or $-OR^{23}-$ (wherein R^{21}, R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{24} (wherein X^3 represents -O-, -S-, -SO-, $-SO_2-$, -OCO-, $-NR^{25}CO-$, $-CONR^{26}-$, $-SO_2NR^{27}-$, $-NR^{28}SO_2-$ or $-NR^{29}-$ (wherein R^{25}, R^{26}, R^{27}, R^{28} and R^{29} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{24} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{30} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{31}CO-$, $-CONR^{32}-$, $-SO_2NR^{33}-$, $-NR^{34}SO_2-$ or $-NR^{35}-$

(wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{30} represents hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{36} (wherein R^{36} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) $(CH_2)_qX^6R^{37}$ (wherein q is an integer from 0 to 5, X^6 represents a direct bond, -O-, -S-, -SO-, $-SO_2-$, $-NR^{38}CO-$, $-CONR^{39}-$, $-SO_2NR^{40}-$, $-NR^{41}SO_2-$ or $-NR^{42}-$ (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is a phenyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl, pyridone or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}hydroxyalkoxy, C_{1-4}aminoalkyl, C_{1-4}alkylamino, carboxy, cyano, $-CONR^{43}R^{44}$ and $-NR^{45}COR^{46}$ (wherein R^{43}, R^{44}, R^{45} and R^{46}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

7) C_{2-6}alkenylR^{36} (wherein R^{36} is as defined hereinbefore);

8) C_{2-6}alkynylR^{36} (wherein R^{36} is as defined hereinbefore);

9) X^7R^{47} (wherein X^7 is $-SO_2-$, -O- or $-CONR^{48}R^{49}-$ (wherein R^{48} and R^{49}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{47} represents C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X^7 is $-SO_2-$, X^1 is -O-, when X^7 is -O-, X^1 is carbonyl, when X^7 is $-CONR^{48}R^{49}-$, X^1 is -O- or NR^{18} (wherein R^{48}, R^{49} and R^{18} are as defined hereinbefore);

10) C_{2-6}alkenylR^{37} (wherein R^{37} is as defined hereinbefore);

11) C_{2-6}alkynylR^{37} (wherein R^{37} is as defined hereinbefore);

12) C_{2-6}alkenylX^8R^{37} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{50}CO-$, $-CONR^{51}-$, $-SO_2NR^{52}-$, $-NR^{53}SO_2-$ or $-NR^{54}-$ (wherein R^{50}, R^{51}, R^{52}, R^{53} and R^{54} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

13) C_{2-6}alkynylX^9R^{37} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{55}CO-$, $-CONR^{56}-$, $-SO_2NR^{57}-$, $-NR^{58}SO_2-$ or $-NR^{59}-$ (wherein R^{55}, R^{56}, R^{57}, R^{58} and R^{59} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

14) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{37} (wherein X^{10} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{60}CO-$, $-CONR^{61}-$, $-SO_2NR^{62}-$, $-NR^{63}SO_2-$ or $-NR^{64}-$ (wherein R^{60}, R^{61}, R^{62}, R^{63} and R^{64} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

15) R^{36} (wherein R^{36} is as defined hereinbefore); and

16) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{36} (wherein X^{10} and R^{36} are as defined hereinbefore).

Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. A preferred pharmaceutically acceptable salt is a hydrochloride salt.

The alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkoxymethyl, alkanoyloxymethyl, alkylsuphinyl, alkylsulphonyl, alkylsulfonamido, carboalkoxy, carboalkyl, alkanoylamino aminoalkyl, alkylaminoalkyl, N,N-dicycloalkylaminoalkyl, hydroxyalkyl, and alkoxyalkyl substituents include both straight chain as well as branched carbon chains. The cycloalkyl portions of N-cycloalkyl-N-alkylaminoalkyl and N,N-dicycloalkylaminoalkyl substituents include both simple carbocycles as well as carbocycles containing alkyl substituents. The alkenyl portion of the alkenyl, alkenoyloxymethyl, alkenyloxy, alkenylsulfonamido, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. The alkynyl portion of the alkynyl, alkynoyloxymethyl, alkynylsulfonamido, alkynyloxy, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. Carboxy is defined as a $-CO_2H$ radical. Carboalkoxy of 2-7 carbon atoms is defined as a $-CO_2R"$ radical, where R" is an alkyl radical of 1-6 carbon atoms. Carboalkyl is defined as a –COR" radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkanoyloxy is defined as a –OCOR" radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkanoyloxymethyl is defined as $R"CO_2CH_2-$ radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkoxymethyl is defined at $R"OCH_2-$ radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphinyl is defined as R"SO- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphonyl is defined as $R"SO_2-$ radical, where R" is alkyl radical of 1-6 carbon atoms. Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are defined as $R"SO_2NH-$ radical, where R" is an alkyl radical of 1-6 carbon atoms, an alkenyl radical of 2-6 carbon atoms, or an alkynyl radical of 2-6 carbon

atoms, respectively. N-alkylcarbamoyl is defined as R"NHCO- radical, where R" is an alkyl radical of 1-6 carbon atoms. N,N-dialkylcarbamoyl is defined as R" R'NCO- radical, where R" is an alkyl radical of 1-6 carbon atoms, R' is an alkyl radical of 1-6 carbon atoms and R', and R" may be the same or different. When X is substituted, it is preferred that it is mono-, di-, or tri-substituted, with monosubstituted being most preferred. It is preferred that of the substituents, R_1, R_2, R_3 and R_4 at least one is hydrogen and it is most preferred that two or three be hydrogen. An azacycloalkyl-N-alkyl substituent refers to a monocyclic heterocycle that contains a nitrogen atom on which is substituted a straight or branched chain alkyl radical. A morpholino-N-alkyl substituent is a morpholine ring substituted on the nitrogen atom with a straight or branch chain alkyl radical. A pipeazino-N-alkyl substituent is a piperazine ring substituted on one of the nitrogen atoms with a straight or branch chain alkyl radical. A N-alkyl-piperidino-N-alkyl substituent is a piperidine ring substituted on one of the nitrogen atoms with a straight or branched chain alkyl group and on the other nitrogen atom with a straight or branch chain alkyl radical.

When any group contains an alkyl portion, the alkyl portion contains preferably 1-6 carbon atoms, more preferably 1-4 carbon atoms, particularly methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl or tert-butyl. When any group contains an alkenyl or alkynyl portion, the alkenyl or alkynyl portion contains preferably 2-6 carbon atoms, more preferably 2-4 carbon atoms.

The compounds of this invention may contain an asymmetric carbon; in such cases, the compounds of this invention cover the racemate and the individual R and S entantiomers, and in the case were more than one asymmetric carbon exists, the individual diasteromers, their racemates and individual entantiomers.

Examples of substituents for aryl groups R^9 or optional substituents for carbocyclic or heterocyclic groups R^9 include one or more groups selected from hydroxy; halo; nitro; cyano; carboxy; C_{1-6}alkoxy; C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{2-6}alkenyloxy; C_{2-6}alkynyloxy; C_{3-6}cycloalkyl; amino; mono- or di-C_{1-6}alkyl amino; heterocyclyl optionally substituted with C_{1-6}alkyl or oxo; $C(O)R^a$, $C(O)OR^a$, $S(O)_dR^a$; $NR^aC(O)R^b$; $C(O)NR^aS(O)_dR^b$, $C(O)NR^aR^b$; $NR^aC(O)NR^bR^c$; $NR^aS(O)_dR^b$ or $N(S(O)_dR^b)S(O)_dR^c$ where d is 0, 1 or 2 and R^a, R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, aryl, C_{3-6}cycloalkyl or heterocylcyl, and wherein any alkyl, alkenyl or alkynyl group

or moiety contained within the substituent one R^9 may themselves be optionally substituted with one or more groups selected from hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms, C_{3-6}cycloalkyl, heterocyclyl optionally substituted with C_{1-6}alkyl or oxo; $C(O)R^d$, $C(O)OR^d$ NR^dR^e, $S(O)_eR^d$, $NR^dC(O)R^e$; $C(O)NR^dR^e$; $NR^dC(O)NR^eR^f$; $NR^dS(O)_eR^e$ where e is 0, 1 or 2 and R^d, R^e and R^f are independently selected from hydrogen or C_{1-6}alkyl optionally substituted with one or more groups selected from hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms, C_{3-6}cycloalkyl, heterocyclyl optionally substituted with C_{1-6}alkyl or oxo; $C(O)R^g$, $C(O)OR^g$ NR^gR^h, $S(O)_eR^g$, $NR^hC(O)R^g$; $C(O)NR^gR^h$; $NR^gC(O)NR^hR^i$; $NR^gS(O)_eR^h$ where e is as defined above and R^g, R^h and R^i are independently selected from hydrogen or C_{1-6}alkyl. Alternatively, two substituents on adjacent atoms may be joined to form the second ring of a bicyclic ring system wherein the said second ring is optionally substituted with one or more of the groups listed above for R^9 and optionally contains one or more heteroatoms.

In some embodiments, the level of substitution on the group R^9 is a chain substituted with complex. Thus, for example, a substituent may comprise an subsituted alkyl chain which is optionally interposed with heteroatoms such as groups of sub-formula (i)

$$-X^a-R^{70}-(X^b-R^{71})_q-(X^c)_s-R^{72} \qquad (i)$$

where X^a , X^b and X^c are independently selected from any of the groups listed above for X^1,

R^{70} and R^{71} are independently selected from C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene groups any of which may be optionally substituted with hydroxy; cyano; nitro; halo; carboxy, carboalkoxy of 2-7 carbon atoms or C_{3-6}cycloalkyl;

R^{72} is hydrogen or an C_{1-6}alkyl, C_{2-6} alkenyl or C_{2-6}alkynyl group any of which may be optionally substituted with hydroxy; cyano; nitro; halo; carboxy or C_{3-6}cycloalkyl;

and q and s are independently 0 or 1.

Preferably R^9 is an optionally substituted alkoxy group and most preferably, R^9 is a substituted alkoxy group.

A particular example of compounds of formula (I) are compounds of formula (IA) which are compounds of formula (I) as defined above provided that R^7 is a group $(CH_2)_mR^9$ where m is 0,or an integer of from 1-3 and R^9 is a substituted aryl or substituted cycloalkyl ring of up to 10 carbon atoms, wherein the substituents comprise at

least one alkoxy group of 1-6 carbon atoms and optionally one or more further substituents, or R^9 is a heterocyclic ring containing 1 or 2 oxygen atoms and optionally one or more substituents, and where R^1, R^2, R^3 or R^4 are a group R^{13}-X^1-$(CH_2)_x$ wherein x is 0 to 3, X^1 represents -O-, -CH_2-, -OCO-, carbonyl, -S-, -SO-, -SO_2-, -NR^{14}CO-, SO_2NR^{16}-, -$NR^{17}SO_2$- or -NR^{18}- (wherein R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{13} are as defined above).

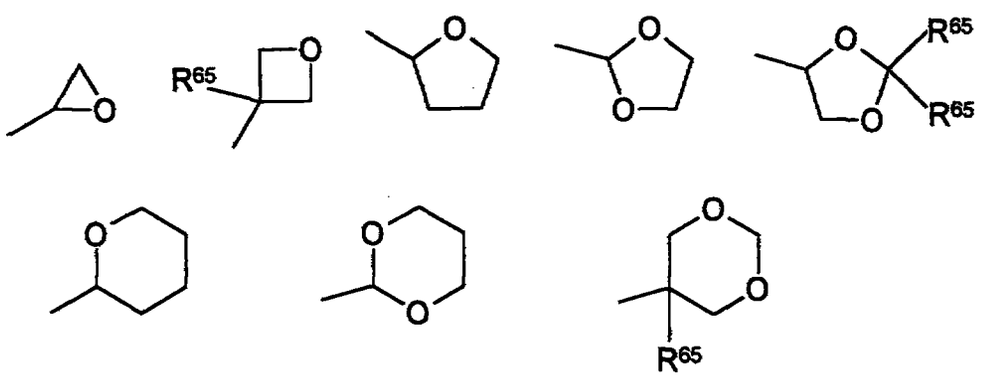
Suitable examples of groups Y are -NH-. Suitably X is oxygen.

Preferably n is 0.

Particular examples of groups R^9 include phenyl or cycloalkyl of from 3-8 and preferably of 6 carbon atoms which are substituted at the position alpha with a alkoxy group, in particular methoxy.

When R^9 is subsituted phenyl or cycloalkyl, m is preferably 0.

Examples of heterocyclic rings R^9 include 3- 7 membered rings, up to two of which may be oxygen atoms. Such groups include:

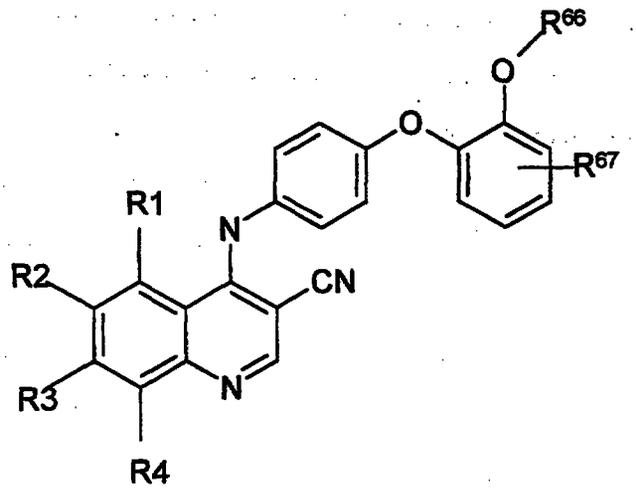


where each R^{65} is independently selected from hydrogen or C_{1-6}alkyl and especially methyl. In such compounds, m is suitably 1, 2 or 3.

Other examples of heterocyclic groups R^9 include pyridyl, thiazolyl, pyrazinyl, pyrimidinyl, oxadiazole.

Suitable further substituents for R^7 include those listed above for pyridyl, pyrimidinyl and phenyl groups R^6.

Thus a preferred sub-group of compounds of formula (I) are compounds of formula (II)



(II)

where R^1, R^2, R^3 and R^4 are as defined above and R^{66} is C_{1-6} alkyl in particular methyl and R^{67} is selected from hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino.

Suitably R^{66} is C_{1-6} alkyl such as methyl. Preferably however it is a substituted C_{1-4} alkyl group, wherein the substitutents are selected from hydroxy, NR^dR^e, $S(O)_eR^d$, $NR^dC(O)R^e$; $C(O)NR^dR^e$; $NR^dC(O)NR^eR^f$; $NR^dS(O)_eR^e$ where e, R^d, R^e and R^f are as defined above.

Preferably R^{67} is hydrogen.

Examples of preferred groups for R^1, R^2, R^3 and R^4 are set out in WO 98/43960. Preferably x is 0. Conveniently R^{13} is selected from one of the following sixteen groups:

1) C_{1-5}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or

C_{2-5}alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) C_{2-3}alkylX^2COR^{19} (wherein X^2 is as defined hereinbefore and R^{19} represents -$NR^{21}R^{22}$- or -OR^{23}- (wherein R^{21}, R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl));

3) C_{2-4}alkylX^3R^{24} (wherein X^3 is as defined hereinbefore and R^{24} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-3}alkoxy and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}hydroxyalkyl and C_{1-3}alkoxy);

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{30} (wherein X^4 and X^5 are as defined hereinbefore and R^{30} represents hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{70} (wherein R^{70} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C_{1-5}alkyl through a carbon atom and which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}hydroxyalkyl and C_{1-3}alkoxy) or C_{2-5}alkylR^{71} (wherein R^{71} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms of which one is N and the other is selected independently from O, S and N, which heterocyclic group is linked to C_{2-5}alkyl through a nitrogen atom and which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}hydroxyalkyl and C_{1-3}alkoxy);

6) $(CH_2)_qX^6R^{37}$ (wherein X^6 is as defined hereinbefore; q is an integer from 0 to 4 if X^6 is a direct bond and q is 0, 2 or 3 if X^6 is other than a direct bond; and R^{37} is a phenyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, of which preferably one is N, which phenyl group, pyridone group or aromatic heterocyclic group may be substituted as hereinbefore defined, advantageously substituted with up to 2 substituents as hereinbefore defined, more preferably substituted with one substituent selected from the group of substituents as hereinbefore defined);

7) C_{4-5}alkenylR^{72} (wherein R^{72} represents R^{70} or R^{71} as defined hereinbefore);

8) C_{4-5}alkynylR^{72} (wherein R^{72} represents R^{70} or R^{71} as defined hereinbefore);

9) X^7R^{47} (wherein X^7 is as defined hereinbefore and R^{47} represents C_{1-3}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino);

10) C_{3-5}alkenylR^{37} (wherein R^{37} is as defined hereinbefore);

11) C_{3-5}alkynylR^{37} (wherein R^{37} is as defined hereinbefore);

12) C_{4-5}alkenylX^8R^{37} (wherein X^8 and R^{37} are as defined hereinbefore);

13) C_{4-5}alkynylX^9R^{30} (wherein X^9 and R^{30} are as defined hereinbefore);

14) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{37} (wherein X^{10} and R^{37} are as defined hereinbefore);

15) R^{36} (wherein R^{36} is as defined hereinbefore); and

16) C_{1-3}alkyl$X^{11}C_{1-3}$alkylR^{36} (wherein X^{11} and R^{36} are as defined hereinbefore).

Advantageously R^{13} is selected from one of the following eleven groups:

1) C_{1-4}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or

C_{2-4}alkyl which may be unsubstituted or substituted with one or two groups selected from hydroxy and amino;

2) C_{2-3}alkylX^2COR^{19} (wherein X^2 is as defined hereinbefore and R^{19} represents $-NR^{21}R^{22}$- or $-OR^{23}$- (wherein R^{21}, R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl));

3) C_{2-3}alkylX^3R^{24} (wherein X^3 is as defined hereinbefore and R^{24} is a group selected from C_{1-3}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X^3 through a carbon atom and which C_{1-3}alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy);

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{30} (wherein X^4 and X^5 are as defined hereinbefore) and R^{30} represents hydrogen or C_{1-2}alkyl);

5) C_{1-4}alkylR^{70} (wherein R^{70} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C_{1-4}alkyl through a carbon atom and which group may carry one or two substituents selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy) or C_{2-4}alkylR^{71} (wherein R^{71} is a group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may carry one

or two substituents selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy); and

6) $(CH_2)_qX^6R^{37}$ (wherein X^6 is as defined hereinbefore; q is an integer from 1 to 3 if X^6 is a direct bond and q is 2 or 3 if X^6 is other than a direct bond; and R^{37} is a phenyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 2 heteroatoms selected from O, N and S, of which preferably one is N, which phenyl group, pyridone group or aromatic heterocyclic group may be substituted as hereinbefore defined, preferably substituted with one substituent selected from hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}alkoxy, C_{1-2}hydroxyalkyl, C_{1-2}hydroxyalkoxy, carboxy, cyano, $-CONR^{43}R^{44}$ and $-NR^{45}COR^{46}$ (wherein R^{43}, R^{44}, R^{45} and R^{46}, which may be the same or different, each represents hydrogen or C_{1-2}alkyl));

7) C_{4-5}alkenylR^{71} (wherein R^{71} is as defined hereinbefore);

8) C_{4-5}alkynylR^{71} (wherein R^{71} is as defined hereinbefore);

9) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{37} (wherein X^{10} and R^{37} are as defined hereinbefore);

10) R^{36} (wherein R^{36} is as defined hereinbefore); and

11) C_{1-3}alkyl$X^{11}C_{1-3}$alkylR^{36} (wherein X^{11} and R^{36} are as defined hereinbefore).

Preferably R^{13} is selected from one of the following nine groups:

1) C_{1-3}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or

C_{2-3}alkyl which may be unsubstituted or substituted with one or two groups selected from hydroxy and amino;

2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl;

3) C_{2-3}alkylX^3R^{24} (wherein X^3 is as defined hereinbefore and R^{24} is a group selected from C_{1-2}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X^3 through a carbon atom and which C_{1-2}alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy);

4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{32}$ (wherein X^4 and X^5 are as defined hereinbefore) and R^{30} represents hydrogen or $C_{1-2}alkyl$);

5) $C_{1-2}alkylR^{70}$ (wherein R^{70} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-2}alkyl$ through a carbon atom and which group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$ and $C_{1-2}alkoxy$) or $C_{2-3}alkylR^{59}$ (wherein R^{59} is a group selected from morpholino, thiomorpholino, piperidino, piperazin-1-yl and pyrrolidin-1-yl which group may carry one or two substituents selected from oxo, hydroxy, halogeno, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$ and $C_{1-2}alkoxy$);

6) $(CH_2)_qX^6R^{37}$ (wherein X^6 is as defined hereinbefore; q is an integer from 1 to 3 if X^6 is a direct bond and q is 2 or 3 if X^6 is other than a direct bond; and R^{37} is a group selected from phenyl, a pyridone group, pyridyl, imidazolyl, thiazolyl, thienyl, triazolyl and pyridazinyl, preferably selected from phenyl, a pyridone group, pyridyl, imidazolyl, thiazolyl and triazolyl which group may be substituted with one substituent selected from hydroxy, halogeno, $C_{1-2}alkyl$, $C_{1-2}alkoxy$, $C_{1-2}hydroxyalkyl$, $C_{1-2}hydroxyalkoxy$, carboxy, cyano, $-CONR^{43}R^{44}$ and $-NR^{45}COR^{46}$ (wherein R^{43}, R^{44}, R^{45} and R^{46} are as defined hereinbefore);

7) $C_{1-3}alkylX^{10}C_{1-3}alkylR^{37}$ (wherein X^{10} and R^{37} are as defined hereinbefore);

8) R^{36} (wherein R^{36} is as defined hereinbefore); and

9) $C_{1-3}alkylX^{11}C_{1-3}alkylR^{36}$ (wherein X^{11} and R^{36} are as defined hereinbefore).

More preferably R^{13} represents 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 2-(4-oxidomorpholino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 3-(4-oxo-1,4-dihydro-1-pyridyl)propyl, methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 3-(1,2,4-triazol-1-yl)propyl, 3-(1,2,4-triazol-4-yl)propyl, 2-(4-pyridyloxy)ethyl, 3-(4-pyridyloxy)propyl, 2-(4-pyridylamino)ethyl, 3-(4-

pyridylamino)propyl, 2-(2-methylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, 3-(5-methyl-1,2,4-triazol-1-yl)propyl, morpholino, N-methylpiperazinyl, piperazinyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, 2-methoxyethyl, 3-methoxypropyl, 2-(imidazol-1-yl)ethyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 3-(imidazol-1-yl)propyl, 3-(1,2,3-triazol-1-yl)propyl, 3-(1,2,3-triazol-2-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 2-(methylsulphinyl)ethyl, benzyl, 2-sulphamoylethyl or 2-(methylsulphonyl)ethyl.

Especially R^{13} represents methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 3-(3-pyridyl)propyl, benzyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, or 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl.

More especially R^{13} represents methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, 2-(pyrrolidin-1-yl)ethyl,

3-(pyrrolidin-1-yl)propyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, benzyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, or 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl.

In particular R^1 and R^4 are suitably hydrogen.

Examples of preferred groups for R^2 include C_{1-6} alkoxy such as methoxy.

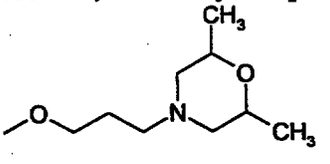
The group R^3 is suitably selected from hydrogen or C_{1-6}alkoxy.

Preferably both R^2 and R^3 are C_{1-6} alkoxy and are preferably methoxy.

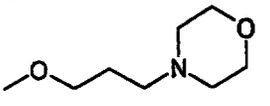
A further preferred group for R^2 or R^3 is 3-morpholinopropyloxy.

Particular examples of compounds of formula (I) are listed in Tables 1, 2 and 3.

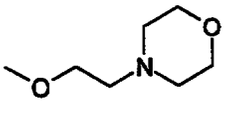
In these tables "DMMPO" indicates a 1,6-dimethylmorpholinopropoxy group of formula:



"MPO" is morpholinopropoxy group of formula:

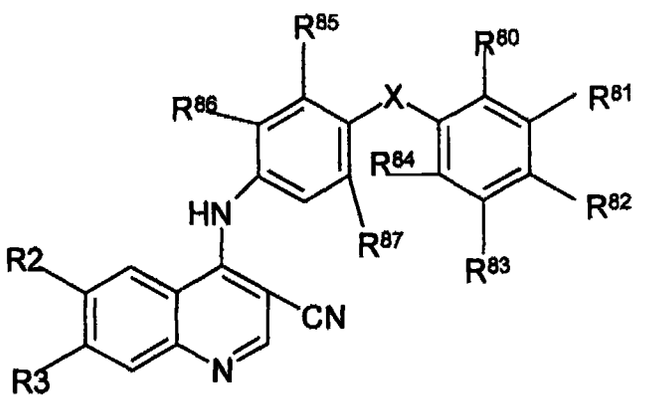


"MEO" is a morpholinoethoxygroup of formula:

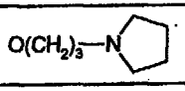
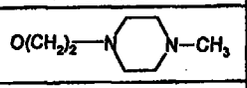
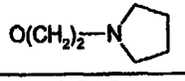
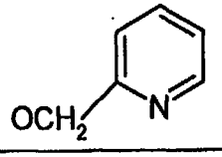
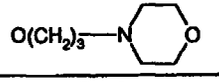
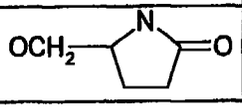


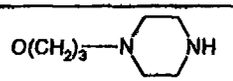
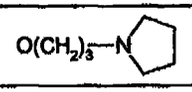
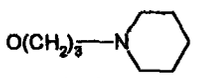
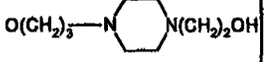
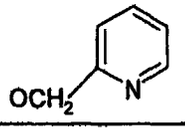
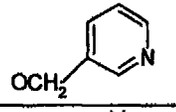
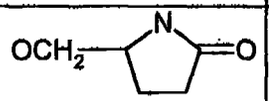
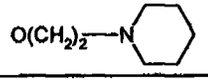
and Me is CH_3

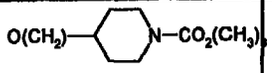
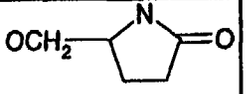
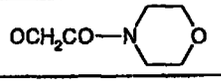
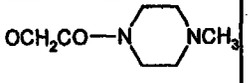
Table 1

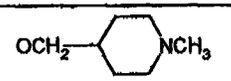
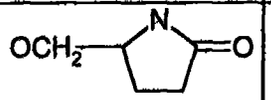
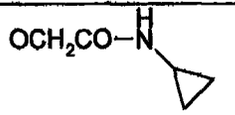


No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
1	OMe	OMe	O	OMe	H	H	H	H	H	H	H
2	OMe	OMe	NH	H	H	OMe	H	H	H	H	H
3	OMe	OMe	O	H	OMe	H	H	H	H	Cl	H
4	OMe	OMe	O	OMe	H	H	H	H	H	Cl	H
5	OMe	OMe	O	OMe	H	H	H	OMe	H	H	H
6	OMe	OMe	O	OMe	H	H	H	Me	H	H	H
7	OMe	OMe	O	H	OMe	H	H	H	H	H	H
8	OMe	OMe	O	H	H	OMe	H	H	H	H	H
9	OMe	$OCH_2C_6H_5$	O	OMe	H	H	H	H	H	H	H
10	OMe	OMe	O	OMe	OMe	H	H	H	H	H	H
11	OMe	OMe	O	H	OMe	H	OMe	H	H	H	H
12	OMe	OMe	O	$OCH_2(Me)_2$	H	H	H	H	H	H	H
13	OMe	OMe	O	CO_2Me	H	H	OMe	H	H	H	H
14	MPO	OMe	O	OMe	H	H	H	H	H	H	H
15	OMe	OMe	O	H	OMe	H	Cl	H	H	H	H

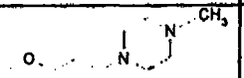
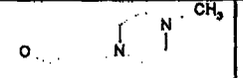
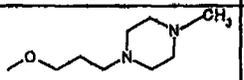
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
16	OMe	MPO	O	OMe	H	H	H	H	H	H	H
17	MPO	OMe	O	OMe	H	H	H	H	H	H	H
18		OMe	O	OMe	H	H	H	H	H	H	H
19	MPO	OMe	O	OMe	H	H	H	H	H	H	H
20	$O(CH_2)_3N(Me)_2$	OMe	O	OMe	H	H	H	H	H	H	H
21	MPO	OMe	O	OMe	H	H	H	H	H	H	H
22		OMe	O	OMe	H	H	H	H	H	H	H
23		OMe	O	OMe	H	H	H	H	H	H	H
24	MPO	OMe	O	OMe	H	H	H	H	H	H	H
25	$O(CH_2)_2N(Me)_2$	OMe	O	OMe	H	H	H	H	H	H	H
26	OH	OMe	O	OMe	H	H	H	H	H	H	H
27	OMe	OH	O	OMe	H	H	H	H	H	H	H
28		OMe	O	OMe	H	H	H	H	H	H	H
29	2-thiazolyloxy	OMe	O	OMe	H	H	H	H	H	H	H
30	2-pyrimidinyloxy	OMe	O	OMe	H	H	H	H	H	H	H
31	2-pyridyloxy	OMe	O	OMe	H	H	H	H	H	H	H
32	OMe	OMe	O	OMe	H	H	H	H	H	H	H
33	OMe		O	OMe	H	H	H	H	H	H	H
34		OMe	O	OMe	H	H	H	H	H	H	H

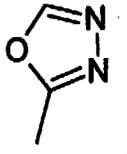
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
35	OMe		O	OMe	H	H	H	H	H	H	H
36	OMe		O	OMe	H	H	H	H	H	H	H
37	OMe		O	OMe	H	H	H	H	H	H	H
38	OMe		O	OMe	H	H	H	H	H	H	H
39	OMe		O	OMe	H	H	H	H	H	H	H
40	OMe		O	OMe	H	H	H	H	H	H	H
41	OMe		O	OMe	H	H	H	H	H	H	H
42	$O(CH_2)_2OMe$	$O(CH_2)_2OMe$	O	OMe	H	H	H	H	H	H	H
43	OMe	OMe	O	OMe	H	H	H	H	H	Me	H
44	OMe		O	OMe	H	H	H	H	H	H	H
45	$O(CH_2)_2OMe$	$O(CH_2)_2OMe$	O	H	OMe	H	H	H	H	H	H
46	$O(CH_2)_2OMe$	$O(CH_2)_2OMe$	O	H	OMe	H	OMe	H	H	H	H
47	$O(CH_2)_2OMe$	$O(CH_2)_2OMe$	O	OCH_2Me	H	H	H	H	H	H	H

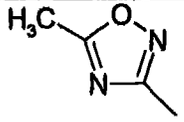
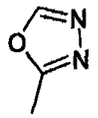
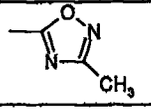
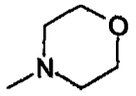
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
48	OMe		O	OMe	H	H	H	H	H	H	H
49	$OCH_2CO_2CH_2Me$	OMe	O	OMe	H	H	H	H	H	H	H
50	OCH_2CF_3	OMe	O	OMe	H	H	H	H	H	H	H
51	$OCH_2CH=CH_2$	OMe	O	OMe	H	H	H	H	H	H	H
52	OCH_2COOH	OMe	O	OMe	H	H	H	H	H	H	H
53		OMe	O	OMe	H	H	H	H	H	H	H
54	$OCH_2C\equiv CH$	OMe	O	OMe	H	H	H	H	H	H	H
55	OCH_2CH_2OMe	OMe	O	OMe	H	H	H	H	H	H	H
56	OMe	OMe	O	OCH_2Me	H	H	H	H	H	Me	H
57		OMe	O	OMe	H	H	H	H	H	H	H
58		OMe	O	OMe	H	H	H	H	H	H	H
59	$OCH_2C(O)NH$ $CH_2CH=CH_2$	OMe	O	OMe	H	H	H	H	H	H	H
60	$OCH_2C(O)NH$-Me	OMe	O	OMe	H	H	H	H	H	H	H
61	$OCH_2C(O)NH$-$(CH_2)_2OMe$	OMe	O	OMe	H	H	H	H	H	H	H
62	OMe	OH	O	OCH_2Me	H	H	H	H	H	H	H

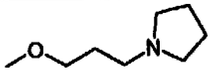
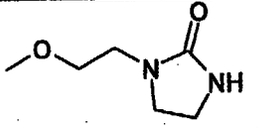
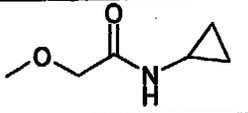
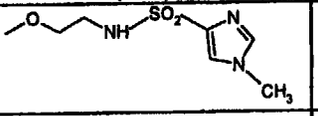
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
63	OMe		O	OMe	H	H	H	H	H	H	H
64	OMe		O	OMe	H	H	H	H	H	H	H
65	OMe	$OCH_2CO_2CH_2Me$	O	OMe	H	H	H	H	H	H	H
66	OMe	OCH_2CO_2H	O	OMe	H	H	H	H	H	H	H
67	OMe	$CCH_2C{\equiv}CH$	O	OMe	H	H	H	H	H	H	H
68	OMe		O	OMe	H	H	H	H	H	H	H
69	OMe	MPO	O	H	OMe	H	H	H	H	H	H
70	OMe	MPO	O	OCH_2Me	H	H	H	H	H	H	H
71	$NHCO_2CH(Me)_2$	OMe	O	OMe	H	H	H	H	H	H	H
72	NH_2	OMe	O	OMe	H	H	H	H	H	H	H
73	$NHSO_2Me$	OMe	O	OMe	H	H	H	H	H	H	H
74	OMe	OMe	O	F	H	H	H	OMe	H	H	H
75	OMe	OMe	O	H	H	Cl	H	H	H	H	H
76	OMe	OMe	O	H	H	NO_2	H	H	H	H	H
77	OMe	OMe	O	F	H	F	H	H	H	H	H
78	OMe	OMe	S	Me	H	H	H	H	H	Cl	H
79	OMe	OMe	S	H	H	Cl	H	H	H	H	H
80	OMe	OMe	O	H	H	Me	H	H	H	Cl	H
81	OMe	OMe	O	F	H	H	H	H	H	H	H
82	OMe	OMe	O	Me	H	H	H	H	H	H	H
83	OMe	OMe	O	H	H	Cl	H	H	Cl	H	Cl
84	OMe	OMe	S	H	CO_2Me	H	H	H	H	H	H

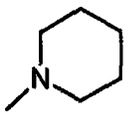
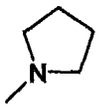
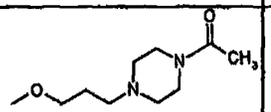
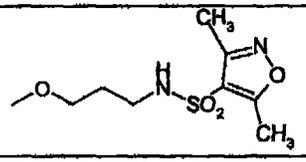
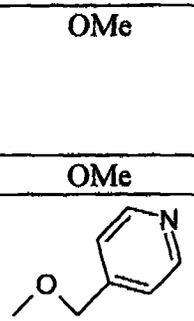
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
85	OMe	OMe	O	SMe	H	H	H	H	H	H	H
86	OMe	OMe	O	CN	H	H	H	H	H	H	H
87	OMe	OMe	O	H	I	H	H	H	H	H	H
88	OMe	OMe	O	Br	H	H	H	H	H	H	H
89	OMe	OMe	O	H	Br	H	H	H	H	H	H
90	OMe	OMe	O	H	F	H	H	H	H	H	H
91	OMe	OMe	O	H	Cl	H	H	H	H	H	H
92	OMe	OMe	O	I	H	H	H	H	H	H	H
93	OMe	OMe	O	Cl	H	H	Cl	H	H	H	H
94	OMe	OMe	O	Cl	H	H	H	H	H	H	H
95	OMe	OMe	O	H	NHC(O)Me	H	H	H	H	H	H
96	OMe	OMe	O	OH	H	H	H	H	H	H	H
97	OMe	OMe	O	$C(O)_2CH_2C_6H_5$	H	H	H	H	H	H	H
98	OMe	OMe	O	OCF_3	H	H	H	H	H	H	H
99	OMe	OMe	O	H	CF_3	H	H	H	H	H	H
100	OMe	OMe	O	$C(O)_2H$	H	H	H	H	H	H	H
101	OMe	OMe	O	H	$NHCH_2Me$	H	H	H	H	H	H
102	COOH	OMe	O	OMe	H	H	H	H	H	H	H
103	OMe	OMe	O	$C(O)_2Me$	H	H	H	H	H	H	H
104	OMe	OMe	O	H	$N(CH_2Me)_2$	H	H	H	H	H	H
105	OMe	OMe	O	H	CN	H	H	H	H	H	H
106	OMe	OMe	O	H	NHC(O)Me	H	H	H	Me	H	H
107	OMe	OMe	O	H	CN	H	H	H	Me	H	H
108	OH	OMe	O	H	$OCF_2.CHF_2$	H	H	H	H	H	H
109	OH	OMe	O	OCH_2CCH	H	H	H	H	H	H	H
110	OH	OMe	O	CN	H	H	H	H	H	H	H

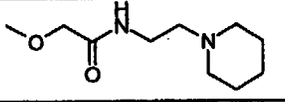
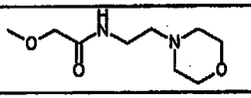
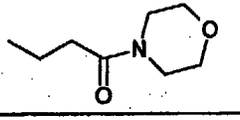
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
111	OMe	OMe	O	$N(Me)_2$	H	H	H	H	H	H	H
112	OMe	OMe	O	H	$N(Me)_2$	H	H	H	H	H	H
113	OMe	OH	O	H	OCF_2CF_2H	H	H	H	H	H	H
114		OMe	O	$OCH_2C{\equiv}CH$	H	H	H	H	H	H	H
115	MPO	OMe	O	H	OCF_2CF_2H	H	H	H	H	H	H
116	OMe	OMe	O	$CONH_2$	H	H	H	H	H	H	H
117	OMe	OMe	O	H	NH(Me)	H	H	H	H	H	H
118		OMe	O	H	OCF_2CF_2H	H	H	H	H	H	H
119	$O(CH_2)_3N(Me)_2$	OMe	O	H	OCF_2CF_2H	H	H	H	H	H	H
120	MPO	OMe	O	OH	H	H	H	H	H	H	H
121	$O(CH_2)_3N(Me)_2$	OMe	O	OH	H	H	H	H	H	H	H
122	OH	OMe	O	OCH_2CN	H	H	H	H	H	H	H
123	OH	OMe	O	OCH_2CH_2OH	H	H	H	H	H	H	H
124	OMe	OH	O	OCH_2CN	H	H	H	H	H	H	H
125	OMe	OH	O	OCH_2CH_2OH	H	H	H	H	H	H	H
126	OMe	OH	O	$OCH_2CH{=}CH_2$	H	H	H	H	H	H	H
127		OMe	O	$OCH_2CH{=}CH_2$	H	H	H	H	H	H	H
128	$O(CH_2)_3N(Me)_2$	OMe	O	$OCH_2CH{=}CH_2$	H	H	H	H	H	H	H
129	OH	OMe	O	$OCH_2CONHMe$	H	H	H	H	H	H	H
130	OMe	OH	O	CN	H	H	H	H	H	H	H
131	$OCH_2C{\equiv}CH$	OMe	O	CN	H	H	H	H	H	H	H
132	OMe	$OCH_2C{\equiv}CH$	O	CN	H	H	H	H	H	H	H

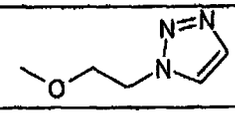
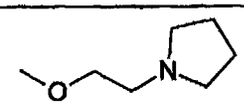
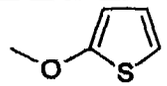
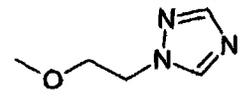
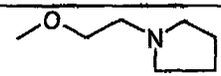
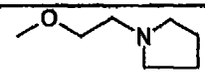
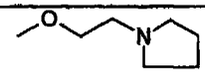
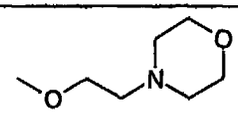
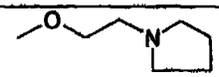
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
133	$O(CH_2)_2OMe$	$O(CH_2)_2OMe$	O	H	$NHCH_2Me$	H	H	H	H	H	H
134	OMe	MPO	O	H	$NHCH_2Me$	H	H	H	H	H	H
135	OMe	OMe	O		H	H	H	H	H	H	H
136	OMe	OMe	O	S(O)Me	H	H	H	H	H	H	H
137	MPO	OMe	O	OCH_2CH_2OH	H	H	H	H	H	H	H
138	OMe	MPO	O	OCH_2CH_2OH	H	H	H	H	H	H	H
139	OMe	MPO	O	CN	H	H	H	H	H	H	H
140	OMe	OMe	O	$S(O)_2Me$	H	H	H	H	H	H	H
141	OMe	MPO	O	F	H	H	H	H	H	H	H
142	OMe	MPO	O	$OCH_2CONHMe$	H	H	H	H	H	H	H
143	MPO	OMe	O	$OCH_2CONHMe$	H	H	H	H	H	H	H
144	OMe	OMe	O	F	F	H	H	H	H	H	H
145	OMe	MPO	O	H	F	H	H	H	H	H	H
146	OMe	OMe	O	H	OCF_2CF_2H	H	H	H	H	H	H
147	OMe	OMe	O	F	H	H	H	F	H	H	H
148	OMe	OMe	O	F	H	H	F	H	H	H	H
149	OMe	OMe	O	H	F	H	F	H	H	H	H
150	OMe	OH	O	$OCH_2CO_2(CH_2)_2Me$	H	H	H	H	H	H	H
151	OMe	OH	O	$OCH_2CONH(CH_2)_2Cl$	H	H	H	H	H	H	H
152	OMe	OH	O	$OCH_2CONH(CH_2)_2$-OH	H	H	H	H	H	H	H
153	OMe	OMe	O	$OCH_2CONH(CH_2)_2$-OH	H	H	H	H	H	H	H
154	OMe	MPO	O	OCF_2CF_2H	H	H	H	H	H	H	H

No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
155	OMe	OH	O	F	H	H	H	H	Me	H	H
156	OMe	OMe	O	H	NCONH-Me	H	H	H	H	H	H
157	OMe	OMe	O	H	OCF_3	H	H	H	H	H	H
158	OMe	OMe	O	CO_2Me	F	H	H	H	H	H	H
159	OMe	OMe	O	OCH_2CH_2OH	H	H	H	H	H	H	H
160	OMe	OMe	O	F	F	H	H	F	H	H	H
161	OMe	OMe	O	$OCH_2CONHMe$	H	H	H	H	H	H	H
162	OMe	OMe	O	OCF_3	H	H	H	H	H	H	H
163	OMe	MPO	O	H	H	F	H	H	H	H	H
164	OMe	MPO	O	F	H	F	H	H	H	H	H
165	OMe	MPO	O	CN	H	H	H	H	Me	H	H
166	OMe	OMe	O		H	H	H	H	H	H	H
167	OMe	OMe	O	H		H	H	H	H	H	H
168	OMe	MPO	O	$CH_2CONHMe$	H	H	H	H	H	H	H
169	OMe	MPO	O	$CH_2CO_2(CH_2)_2Me$	H	H	H	H	H	H	H
170	OMe	MPO	O	OCH_2CO_2H	H	H	H	H	H	H	H
171	OMe	OMe	O		H	H	H	H	H	H	H
172	OMe	OMe	O		H	H	H	H	H	H	H

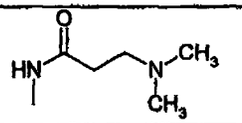
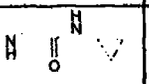
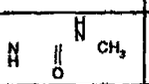
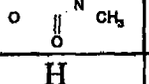
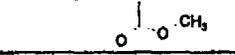
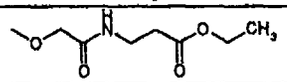
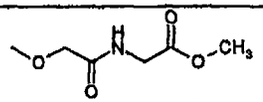
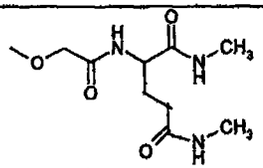
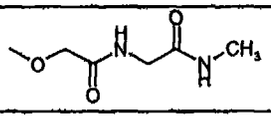
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
173	OMe	MPO	O	CH_2CO_2H	H	H	H	H	H	H	H
174	OMe	OMe	O	NHC(O)Me	H	H	H	H	H	H	H
175	OMe	MPO	O	$OCH_2CONH(CH_2)_2$-OH	H	H	H	H	H	H	H
176	OMe		O	$OCH_2CONH(CH_2)_2$-OH	H	H	H	H	H	H	H
177	OMe	DMMPO	O	$OCH_2CONH(CH_2)_2$-OH	H	H	H	H	H	H	H
178	OMe	MPO	O	$OCH_2CH_2NHS(O)_2$-Me	H	H	H	H	H	H	H
179	OMe	MPO	O	$O(CH_2)_2N(Me)CON(CH_2Me)_2$	H	H	H	H	H	H	H
180	OMe	MPO	O	$O(CH_2)_3NHCOMe$	H	H	H	H	H	H	H
181	OMe	MPO	O	$O(CH_2)_3NHCOCH(Me)_2$	H	H	H	H	H	H	H
182	OMe	MPO	O		H	H	H	H	H	H	H
183	OMe	MPO	O		H	H	H	H	H	H	H
184	OMe	MPO	O	$O(CH_2)_2NHCOCH(Me)_2$	H	H	H	H	H	H	H
185	OMe	OMe	O		H	H	H	H	H	H	H
186	OMe	OMe	O	$OCH_2CH_2NHSO_2Me$	H	H	H	H	H	H	H

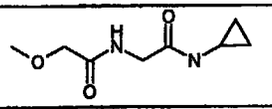
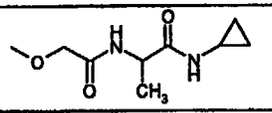
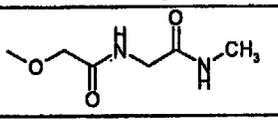
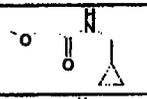
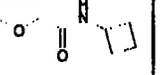
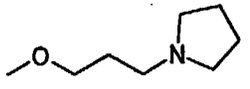
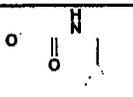
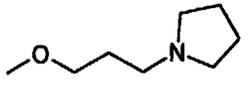
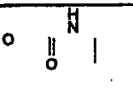
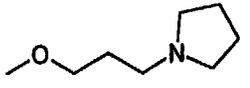
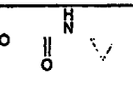
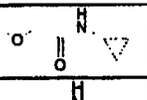
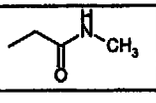
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
187	OMe	OMe	O	H		H	H	H	H	H	H
188	OMe	OMe	O		H	H	H	H	H	H	H
189	OMe	OMe	O		H	H	H	H	H	H	H
190	OMe	OMe	O		H	H	H	H	H	H	H
191	OMe	OMe	O	$O(CH_2)_3NHS(O)_2Me$	H	H	H	H	H	H	H
192	OMe	OMe	O	$O(CH_2)_3NHCOCH(Me)_2$	H	H	H	H	H	H	H
193	OMe	MPO	O	$O(CH_2)_3NHS(O)_2Me$	H	H	H	H	H	H	H
194	OMe		O	$OCH_2CONH(CH_2)_2OH$	H	H	H	H	H	H	H
195	OMe	OMe	O		H	H	H	H	H	H	H
196	OMe	OMe	O	H	Me	H	H	H	H	H	H
197	OMe		O	OMe	H	H	H	H	H	H	H

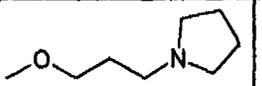
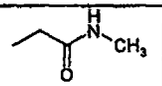
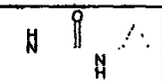
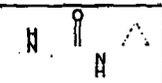
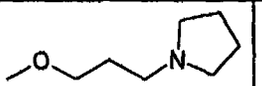
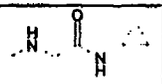
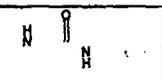
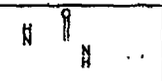
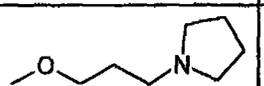
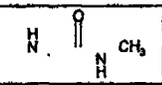
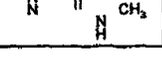
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
198	OMe	OMe	O	NHMe	H	H	H	H	H	H	H
199	OMe	OMe	O	$NHCH_2Me$	H	H	H	H	H	H	H
400	OMe	OMe	O	$N(SO_2Me)_2$	H	H	H	H	H	H	H
401	OMe	OMe	O	$OCH_2C(O)NHCH_2$-$C(O)NH_2$	H	H	H	H	H	H	H
402	OMe	OMe	O	$OCH_2C(O)NHCH$-(Me) $C(O)NHMe$	H	H	H	H	H	H	H
403	OMe	OMe	O	$OCH_2C(O)NHCH_2$ $C(O)NHMe$	H	H	H	H	H	H	H
404	OMe	OMe	O	$OCH_2C(O)N(CH_2Me)$ $C(O)NH(CH_2)_3N(Me)_2$	H	H	H	H	H	H	H
405	OMe	OMe	O		H	H	H	H	H	H	H
406	OMe	OMe	O		H	H	H	H	H	H	H
407	OMe	OMe	O	$O(CH_2)_2N(Me)C(O)N($ $CH_2Me)_2$	H	H	H	H	H	H	H
408	OMe	MPO	O	$O(CH_2)_2NHCOCH$-$(Me)_2$	H	H	H	H	H	H	H
409	OMe	OMe	O	$O(CH_2)_2NHC(O)Me$	H	H	H	H	H	H	H
410	OMe	OMe	O	$(CH_2)_2C(O)NHMe$	H	H	H	H	H	H	H
411	OMe	OMe	O	$(CH_2)_2C(O)NHS(O)_2Me$	H	H	H	H	H	H	H
412	OMe	OMe	O		H	H	H	H	H	H	H
413	OMe	OMe	O	$(CH_2)_2C(O)NHCH_2$ $CHCH_2$	H	H	H	H	H	H	H

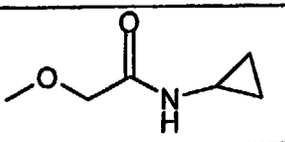
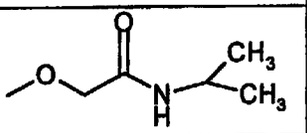
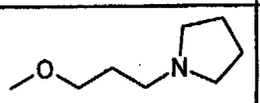
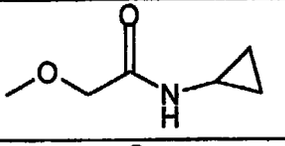
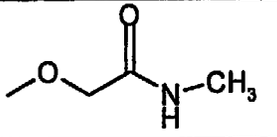
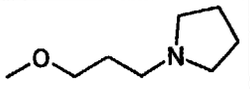
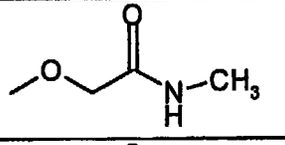
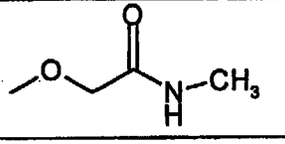
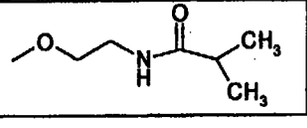
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
414	OMe	OMe	O		H	H	H	H	H	H	H
415	OMe	OMe	O		H	H	H	H	H	H	H
416		OMe	O	CN	H	H	H	H	H	H	H
417	OMe	OMe	O		H	H	H	H	H	H	H
418	OMe		O	H	$NHCH_2Me$	H	H	H	H	H	H
419	OMe		O	F	H	H	H	H	H	H	H
420	OMe		O	CN	H	H	H	H	H	H	H
421	OMe		O	OMe	H	H	H	H	H	H	H
422	OMe		O	H	OMe	H	H	H	H	H	H
423	OH	OMe	O	H	OCF_2CF_2H	H	H	H	H	H	H
424	$OCH_2C_6H_5$	OMe	O	OMe	H	H	H	H	H	H	H
425	COOMe	OMe	O	OMe	H	H	H	H	H	H	H
426	OH	OMe	O	$OCH_2CH=CH_2$	H	H	H	H	H	H	H
427	OMe	OH	O	$OCH_2CONHMe$	H	H	H	H	H	H	H

No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
428	H	OMe	O	H		H	H	H	H	H	H
429	H	OMe	O	OMe	H	H	H	H	H	H	H
430	OMe	OMe	O		H	H	H	H	H	H	H
431	OMe		O	H	OMe	H	H	H	H	H	H
432	OMe	OMe	O		H	H	H	H	H	H	H
433	OMe	OMe	O		H	H	H	H	H	H	H
434	OMe	OMe	O		H	H	H	H	H	H	H
435	OMe	OMe	O		H	H	H	H	H	H	H

No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
436	OMe	OMe	O		H	H	H	H	H	H	H
437	OMe	OMe	O		H	H	H	H	H	H	H
438	OMe	OMe	O	H		H	H	H	H	H	H
439	OMe	OMe	O	H		H	H	H	H	H	H
440	OMe	OMe	O	H		H	H	H	H	H	H
441	OMe	OMe	O		H	H	H	H	H	H	H
442	OMe	OMe	O		H	H	H	H	H	H	H
443	OMe	OMe	O		H	H	H	H	H	H	H
444	OMe	OMe	O		H	H	H	H	H	H	H
445	OMe	OMe	O		H	H	H	H	H	H	H

No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
446	OMe	OMe	O		H	H	H	H	H	H	H
447	OMe	OMe	O		H	H	H	H	H	H	H
448	OMe	OMe	O		H	H	H	H	H	H	H
449	OMe	DMMPO	O	H		H	H	H	H	H	H
450	OMe	DMMPO	O	H		H	H	H	H	H	H
451	OMe		O	H		H	H	H	H	H	H
452	OMe		O	H		H	H	H	H	H	H
453	OMe		O	H		H	H	H	H	H	H
454	OMe	DMMPO	O	H		H	H	H	H	H	H
455	OMe	DMMPO	O	H		H	H	H	H	H	H

No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
456	OMe		O	H		H	H	H	H	H	H
457	OMe	DMMPO	O	H	OMe	H	H	H	H	H	H
458	OMe	MPO	O	H		H	H	H	H	H	H
459	OMe	DMMPO	O	H		H	H	H	H	H	H
460	OMe		O	H		H	H	H	H	H	H
461	OMe	MPO	O	H		H	H	H	H	H	H
462	OMe	DMMPO	O	H		H	H	H	H	H	H
463	OMe		O	H		H	H	H	H	H	H
464	OMe	MPO	O	H		H	H	H	H	H	H
465	OMe	DMMPO	O	H		H	H	H	H	H	H

No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
466	OMe	DMMPO	O		H	H	H	H	H	H	H
467	OMe	MPO	O		H	H	H	H	H	H	H
468	OMe		O		H	H	H	H	H	H	H
469	OMe	DMMPO	O		H	H	H	H	H	H	H
470	OMe		O		H	H	H	H	H	H	H
471	OMe	MPO	O		H	H	H	H	H	H	H
472	OMe	OMe	O	$O(CH_2)_2NHCO$-$(CH_2)_2CN$	H	H	H	H	H	H	H
473	OMe	OMe	O		H	H	H	H	H	H	H

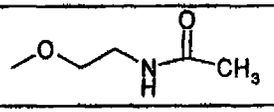
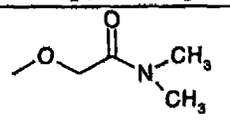
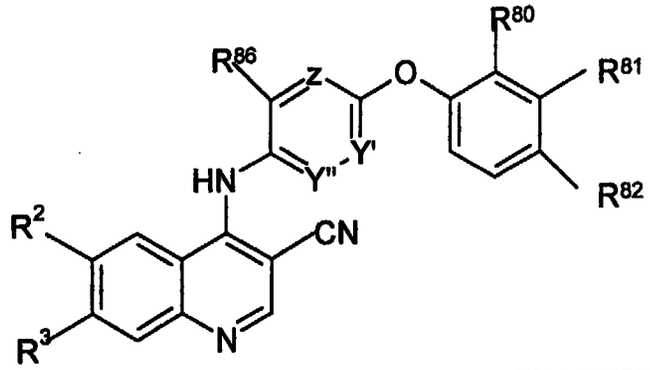
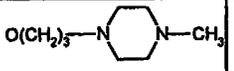
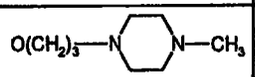
No.	R^2	R^3	X	R^{80}	R^{81}	R^{82}	R^{83}	R^{84}	R^{85}	R^{86}	R^{87}
474	OMe	OMe	O		H	H	H	H	H	H	H
475	OMe	OMe	O	$O(CH_2)_2NHCOO$ $CH_2CH=CH_2$	H	H	H	H	H	H	H
476	OMe	OMe	O		H	H	H	H	H	H	H
477	OMe	OMe	O	H	OCH_2-C(O)NH-Me	H	H	H	H	H	H
478	OMe	MEO	O	F	H	H	H	H	H	H	H
479	OMe	MEO	O	CN	H	H	H	H	H	H	H
480	OMe	MEO	O	H	$NHCH_2$-Me	H	H	H	H	H	H
481	OMe	DMMPO	O	H	OCH_2 C(O) NH-Me	H	H	H	H	H	H
482	OMe	OMe	O	H	OCH_2 C(O) NH-$CH(Me)_2$	H	H	H	H	H	H

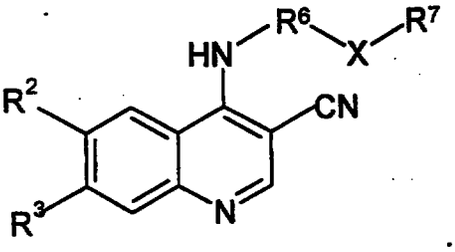
Table 2

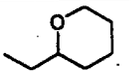
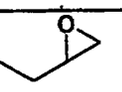
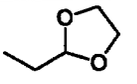
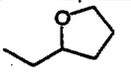
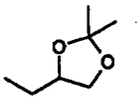
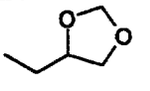
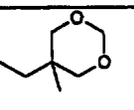
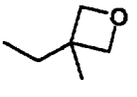
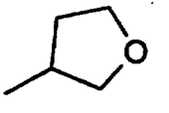
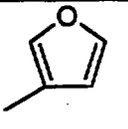
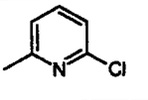


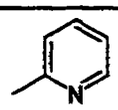
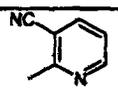
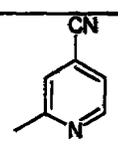
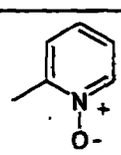
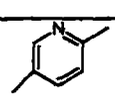
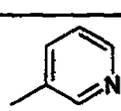
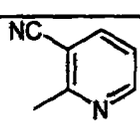
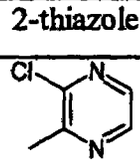
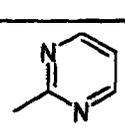
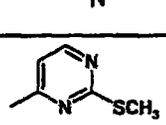
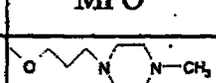
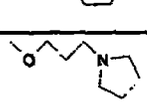
No.	R^2	R^3	Y'	Y"	Z	R^{80}	R^{81}	R^{82}	R^{86}
200	OMe	OMe	CH	CH	N	H	H	OMe	H
201	OMe	OMe	CH	CH	N	H	OMe	H	H
202	OMe	OMe	CH	CH	N	OMe	H	H	H
203	OMe	OH	N	CH	N	OMe	H	H	H
204		OMe	CH	CH	N	OMe	H	H	H
205	OMe		CH	CH	N	OMe	H	H	H
206	$O(CH_2)_3N(Me)_2$	OMe	CH	CH	N	OMe	H	H	H
207	OMe	$O(CH_2)_3N(Me)_2$	CH	CH	N	OMe	H	H	H
208	MPO	OMe	CH	CH	N	OMe	H	H	H
209	OMe	MPO	CH	CH	N	OMe	H	H	Me
210	OMe	MPO	N	CH	N	OMe	H	H	H
211	OMe	OH	N	CH	CH	OMe	H	H	Me
212	OMe	OMe	CH	CH	N	H	CF_3	H	H

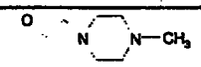
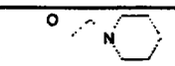
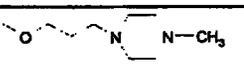
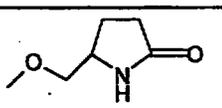
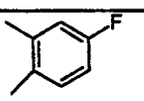
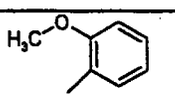
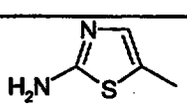
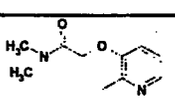
No.	R^2	R^3	Y'	Y"	Z	R^{80}	R^{81}	R^{82}	R^{86}
213	OMe	MPO	N	CH	CH	F	H	H	H
214	OMe	MEO	N	CH	CH	H	OMe	H	H
215	OMe	MPO	CH	N	CH	OMe	H	H	H
216	OMe	MPO	CH	N	CH	$OCH_2CONHMe$	H	H	H
217	OMe	MPO	N	CH	CH	H	OMe	H	H
218	OMe	OH	N	CH	CH	F	H	H	Me
219	OMe	$OCH_2C_6H_5$	N	CH	CH	F	H	H	Me
220	OH	OMe	N	CH	CH	OMe	H	H	H
221	OMe	OH	N	CH	CH	OMe	H	H	H
222	OMe	$OCH_2C_6H_5$	N	CH	CH	OMe	H	H	Me
223	OMe	DMMPO	N	CH	CH	H		H	H
224	OMe		N	CH	CH	H		H	H
225	OMe	DMMPO	N	CH	CH	H		H	H

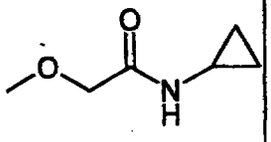
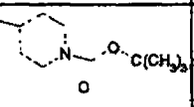
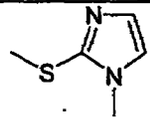
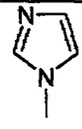
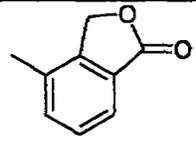
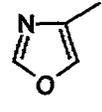
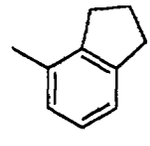
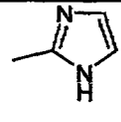
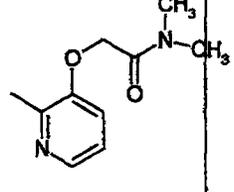
Table 3

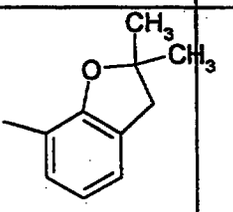
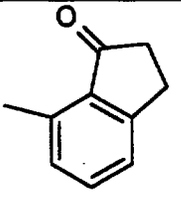
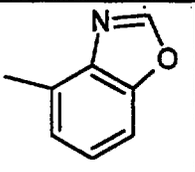
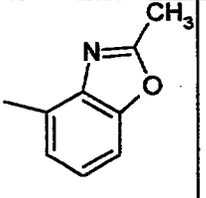
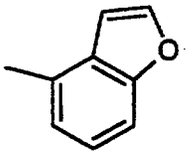
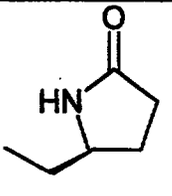
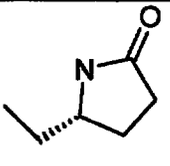
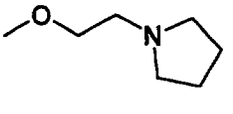


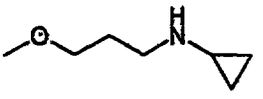
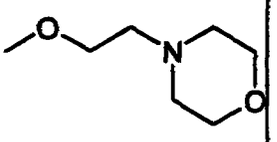
NO.	R^2	R^3	R^6	R^7	X
250	OMe	OMe	p-Ph		O
251	OMe	OMe	p-Ph		O
252	OMe	OMe	p-Ph		O
253	OMe	OMe	p-Ph		O
254	OMe	OMe	p-Ph		O
255	OMe	OMe	p-Ph		O
256	OMe	OMe	p-Ph		O
257	OMe	OMe	p-Ph		O
258	OMe	OMe	p-Ph		O
259	OMe	OMe	p-Ph		O
260	OMe	DMMPO	p-Ph	2-thiazole	O
261	OMe	OMe	p-Ph		O

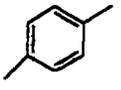
NO.	R^2	R^3	R^6	R^7	X
262	OMe	OMe	p-Ph		O
263	OMe	OMe	p-Ph		O
264	OMe	OMe	p-Ph		O
265	OMe	OMe	p-Ph		O
266	OMe	OMe			O
267	OMe	OMe	p-Ph		S
268	OMe	OMe	p-Ph	2-thiazole	O
269	OMe	OMe	p-Ph		O
270	OMe	OMe	p-Ph		O
271	OMe	OMe	p-Ph		O
272	$OCH_2C_6H_5$	OMe	p-Ph	2-thiazole	O
273	OH	OMe	p-Ph	2-thiazole	O
274	MPO	OMe	p-Ph	2-thiazole	O
275		OMe	p-Ph	2-thiazole	O
276		OMe	p-Ph	2-thiazole	O
277	MPO	OMe	p-Ph	2-thiazole	O
278	MEO	OMe	p-Ph	2-thiazole	O

NO.	R^2	R^3	R^6	R^7	X
279		OMe	p-Ph	2-thiazole	O
280		OMe	p-Ph	2-thiazole	O
281	$O(CH_2)_2N(Me)_2$	OMe	p-Ph	2-thiazole	O
282	OMe	OH	p-Ph	2-thiazole	O
283	OMe	MPO	p-Ph	2-thiazole	O
284	OMe		p-Ph	2-thiazole	O
285	OMe		p-Ph	2-thiazole	O
286	OMe	$O(CH_2)_3N(Me)_2$	p-Ph	2-thiazole	O
287	OMe	OMe			O
288	OMe	OCH_2COOCH_2Me	p-Ph	2-thiazole	O
289	OMe	OCH_2COOH	p-Ph	2-thiazole	O
290	$O(CH_2)_2OMe$	$O(CH_2)_2OMe$	p-Ph	2-thiazole	O
291	OMe	$OCH_2CONHMe$	p-Ph	2-thiazole	O
292	OMe	$OCH_2CONHCH_2$ $CHCH_2$	p-Ph	2-thiazole	O
293	NH_2	OMe	p-Ph	2-thiazole	O
294	OMe	MPO	p-Ph	2-pyridyl	O
295	OMe	OMe	p-Ph	2-thiazole	S
296	OMe	OMe	p-Ph		S
297	OMe	OMe	p-Ph	cyclopentyl	O
298	OMe	OMe	p-Ph	cyclohexyl	O
299	OMe	OMe	p-Ph		O
300	OMe	$OCH_2C_6H_5$	p-Ph	2-thiazole	O
301	$NHCO_2C$ $(Me)_3$	OMe	p-Ph	2-thiazole	O

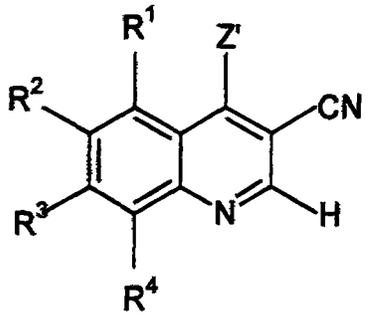
NO.	R^2	R^3	R^6	R^7	X
302	OMe		p-Ph	2-thiazole	O
303	OMe	OMe	p-Ph		O
304	OMe	OMe	p-Ph		CH_2
305	OMe	OMe	p-Ph		CH_2
306	OMe	OMe	p-Ph		O
307	OMe	OMe	p-Ph		O
308	OMe	OMe	p-Ph		O
309	OMe	OMe	p-Ph		S
310	OMe	MEO	p-Ph		O

NO.	R^2	R^3	R^6	R^7	X
311	OMe	OMe	p-Ph		O
312	OMe	OMe	p-Ph		O
313	OMe	OMe	p-Ph		O
314	OMe	OMe	p-Ph		O
315	OMe	OMe	p-Ph		O
316	OMe	OMe	p-Ph		O
317	OMe	OMe	p-Ph		O
318	OMe		p-Ph	2-thiazole	O

NO.	R^2	R^3	R^6	R^7	X
319	OMe		p-Ph	2-thiazole	O
320	OMe		p-Ph	2-thiazole	O

where p-Ph represents a para-phenylene group of formula 

Compounds of formula (I) are suitably prepared by reacting a compound of formula (III)



(III)

where $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ represent R^1, R^2, R^3 and R^4 respectively as defined in relation to formula (I) or a precursor thereof, and Z' is a leaving group, with a compound of formula (IV)

$$H\text{-}\ Y(CH_2)_nR^6XR^{7'}$$

(IV)

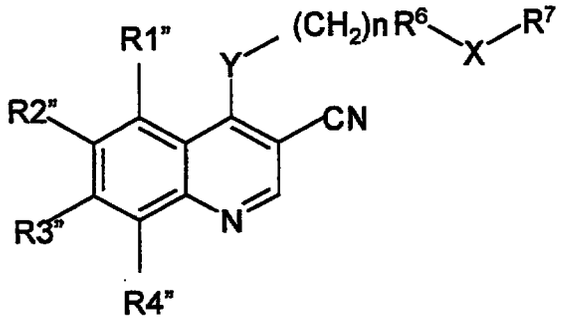
where R^6, Y, X, and n are as defined in relation to formula (I), and $R^{7'}$ is a group R^7 or a precursor thereof; and thereafter if necessary or desired converting precursor groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $R^{7'}$ to groups of formula R^1, R^2, R^3, R^4 and R^7 respectively, or converting a group R^1, R^2, R^3, R^4 and R^7 to a different such group.

Suitable leaving groups for Z' include halogen such as bromo or chloro, or a mesylate or tosylate group or a substituted phenoxy group.

The reaction is suitably carried out in an organic solvent such as an alcohol for example propanol or cyclohexanol at elevated temperatures, for example of from 50 to 150°C, for example at about 105°C.

Conversion reactions in which precursor groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are converted to groups of formula R^1, R^2, R^3 and R^4 respectively, or groups R^1, R^2, R^3 and R^4 are converted to different such group can be carried out using conventional chemistry as outlined hereinafter. Particular precursor groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are groups of formula $R^{13'}$-X^1-$(CH_2)_x$ wherein x and X^1 are as defined hereinafter, and $R^{13'}$ is C_{1-5}alkyl which is substituted with halo other than fluoro, and in particular chloro or bromo. The chloro or bromo group may readily be converted into many other groups R^{13} as defined in relation to claim 1. Such compounds are novel and form a further aspect of the invention. They may have activity similar to that of compounds of formula (I) in their own right and therefore may be used in place of a compound of formula (I).

Thus the invention further provides a compound of formula (IB)

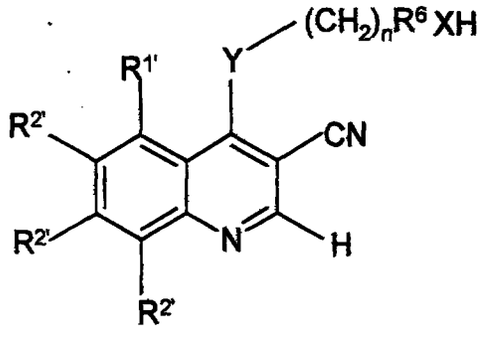


(IB)

where Y, n, R^6, X and R^7 are as defined in claim 1 and at least one of $R^{1"}$, $R^{2"}$, $R^{3"}$ or $R^{4"}$ is a group $R^{13'}$-X^1-$(CH_2)_x$ wherein X^1 and x are as defined in claim 1 and $R^{13'}$ is alkyl substituted by chloro or bromo; and the remainder are groups R^1, R^2, R^3 and R^4 respectively.

Similarly conversion reactions involving groups R^7 may be effected using conventional chemistry. For example substitutent groups on a group R^9 within the group R^7 may be changed, for example by changing acids to esters or amides etc.

Alternatively, compounds of formula (I) are prepared by reacting a compound of formula (V)



(V)

where $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are as defined in relation to fomula (III) R^6, X, Y and n are as defined in relation to formula (I), with a compound of formula (VI)

$$R^{7'}\text{-}Z'' \qquad \text{(VI)}$$

where R^7 is as defined in relation to formula (IV) and Z" is a leaving group;

and thereafter if necessary or desired converting precursor groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $R^{7'}$ to groups of formula R^1, R^2, R^3, R^4 and R^7 respectively, or converting a group R^1, R^2, R^3, R^4 and R^7 to a different such group. Suitable leaving groups for Z" include halogen such a bromo or chloro, or a mesylate or tosylate group. Conversion reactions are as described above.

The reaction is suitably carried out in an organic solvent such as DMF at elevated temperatures, for example of from 40 to 120°C, for example at about 80°C.

Compounds of formula (III) and (V) are either known compounds or they can be prepared from known compounds by conventional methods, for example as described in WO 98/43960, WO 98/13350. Exemplary preparations of compounds of formula (III) are included hereinafter.

Compounds of formula (IV) are also known compounds (see for example Rev. Chim. (Bucharest) (1988), 39(6), 477-82 and DD 110651: 74.01.05) or they can be prepared from known compounds using conventional methods. For example, where Y is NH, compounds of formula (IV) are suitably prepared by reduction of a compound of formula (VII)

$O_2N(CH_2)_nR^6XR^{7'}$

(VII)

where X, R^6, R^7 and n are as defined above. It may be convenient to convert precursor groups $R^{7'}$ to groups R^7 or groups R^7 to other such groups at the level of compound of formula (VII) or (IV) using conventional chemistry.

Compounds of formula (VI) are also known compounds or they can be prepared from known compounds by conventional methods.

Compounds of the invention are useful in the inhibition of MEK enzyme activity and can be used in the treatment of proliferative disease. They will suitably be in the form of a pharmaceutical composition, in combination with a pharmaceutically acceptable carrier. Such compositions form a further aspect of the invention.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient

within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable

dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or

more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects MEK enzymes.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for

intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

In a further aspect, the invention provides a method of treating proliferative disease by administering a compound of formula (I) as described above, or a pharmaceutical composition as described above.

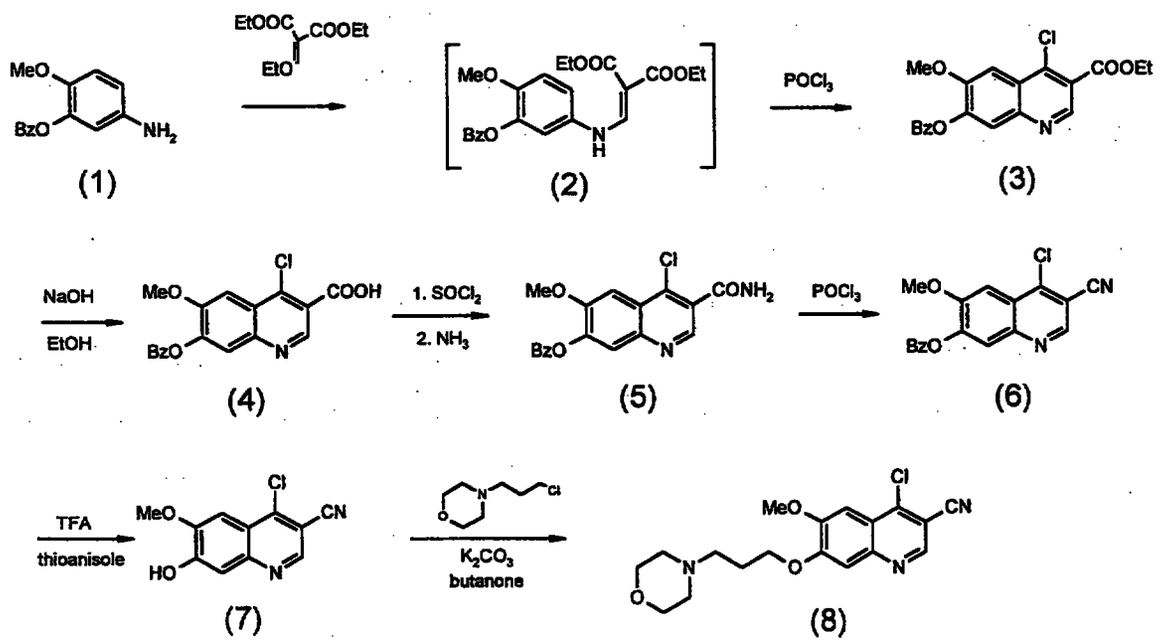
Yet a further aspect of the invention provides the use of a compound of formula (I) as defined above, in the preparation of a medicament for use in the inhibition of MEK enzyme activitiy and in particular for the treatment of proliferative disease such as cancer.

The invention will now be particularly described by way of Example. The preparation of various intermediates used in the Examples is described in the Preparations.

Preparation 1

Chloroquinoline intermediates

These can be prepared for example using the following scheme where "Bz" represents benzyl.



A mixture of (1) (10.36g., 45.3 mmole) and diethylethoxymethylene malonate (9mL, 45.3 mmole) was heated at 110°C for 1 hour and then allowed to cool overnight. The mixture was evaporated and the product (2) used in the next step without further purification.

Mass Spectrum m/e 400 (M^++H).

Preparation of (3)

A mixture of (2) (assumed 45.3 mmole) and phosphoryl chloride (83.3mL, 906 mmole) was heated at 115 °C for 18 hours. After cooling, the solution was evaporated to remove excess phosphoryl chloride. The residue was treated with ice and aqueous ammonia to hydrolyse the remaining phosphoryl chloride. The solid product was filtered off and dried in a vacuum oven to give a cream coloured solid, 9.0g (53% yield).

Mass Spectrum m/e 372 (M^++H).

Preparation of (4)

A mixture of (3) (9.0g, 24.2 mmole) was stirred in ethanol (48.3mL) for 15 minutes at ambient temperature to give a smooth suspension. Aqueous sodium hydroxide solution (2.0M, 48.3mL, 96.7 mmole) was added and the mixture stirred for 18 hours at ambient temperature. The ethanol was removed by rotary evaporation and the resulting solution was acidified to pH 2 with hydrochloric acid while stirring. The precipitate was filtered off and dried in a vacuum oven to give an orange solid, 7.19g (86% yield).

Mass Spectrum m/e 344 (M^++H).

Preparation of (5)

A mixture of (4) (7.18g, 20.9 mmole) and thionyl chloride (90 mL) was refluxed for 2 hours. After cooling the excess thionyl chloride was removed by rotary evaporation and the residue was suspended in acetone (175mL) and the resulting suspension cooled in an ice-bath. Aqueous ammonia (S.G. 0.880, 20mL) was added gradually, keeping the temperature below 10 °C. The resulting suspension was filtered off, washed with water and air-dried to give a solid, 5.15g (75% yield).

Mass Spectrum m/e 343 (M^++H).

Preparation of (6)

A mixture of (5) (20.55g, 60 mmole) and phosphoryl chloride (250mL) was heated and stirred at 120 °C for 4 hours when the starting material had dissolved. Heating and stirring

was continued at 110 °C for 18 hours. After cooling, the solution was evaporated to remove excess phosphoryl chloride. Last traces of phosphoryl chloride were removed by azeotroping with toluene. The residue was treated with ice and aqueous ammonia to remove acidity. The solid product was filtered off and dried in a vacuum oven to give a grey solid, 19.23g (99% yield).

(This may also be prepared as described in WO 9843960)

Mass Spectrum m/e 325 (M^++H).

Preparation of (7)

A mixture of **(6)** (19.23g, 60.0 mmole) and trifluoroacetic acid (300 mL) and thioanisole (35mL) was refluxed in a nitrogen atmosphere for 3 hours. After cooling the trifluoroacetic acid was removed by rotary evaporation and the oily residue was stirred with ice and water and basified with aqueous ammonia (S.G. 0.880). The resulting suspension was filtered and the solid was washed successively with water, ethyl acetate and diethyl ether and then dried to give a khaki solid, 13.74g (97% yield).

Mass Spectrum m/e 235 (M^++H).

Preparation of (8)

(4-chloro-6-methoxy-7-[3-(1-morpholino)propoxy]-3-quinolinecarbonitrile)

A mixture of (7) (2.34g, 10.0 mmole) and 1-(3-chloropropyl)morpholine (2.45g, 15.0 mmole) and anhydrous potassium carbonate (2.07g, 15.0 mmole) suspended in butanone (150mL) was stirred in a oil-bath at 88 °C for 96 hours. The suspension was filtered hot to remove inorganics and the filtrate was allowed to cool and then evaporated to ca. 100mL. A solid precipitated on standing for 72 hours. The solid was filtered off and washed with a little acetone and then dried to give a white solid, 0.54g (15% yield).

Mass Spectrum m/e 362 (M^++H).

Preparation 2

By similar processes the following analogues were also prepared:-

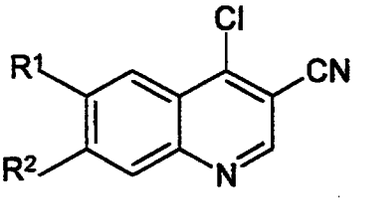
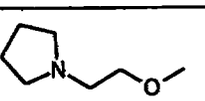


Table 4

R^1	R^2	Mass Spectrum
OCH_2CH_2OMe	OCH_2CH_2OMe	m/e 337 (M^++H).
OMe	MPE	m/e 348 (M^++H)
OMe		m/e 332 (M^++H).
$OCH_2C_6H_5$	OMe	m/e 324 (M^++H).
OH	OMe	m/e 234 (M^++H).
$OCH_2C(O)_2CH_2Me$	OMe	m/e 321 (M^++H).
OMe	$OCH_2C(O)_2CH_2Me$	m/e 321 (M^++H).
$OCH_2C(O)_2Me$	OMe	
OMe	$O(CH_2)_3Cl$	m/e 310 (M^++H).

Example 1

A mixture of 4-chloro-3-cyano-6,7-dimethoxyquinoline (1.5 g), prepared as described in WO 9843960, and 4-(2-methoxyphenoxy)-aniline (2.58 g), prepared as described in Rev. Chim. (Bucharest) (1988), 39(6),477-82, in 1-propanol (90 ml) was stirred and heated at 105°C for 6 hours. The mixture was cooled to ambient temperature and then filtered. The crystals were washed with a small volume of 1-propanol and then dried to give 4-(2-methoxyphenoxy)-anilino-3-cyano-6,7-dimethoxyquinoline (Compound 1 in Table 1) (2.19 g, 85%).

Mass Spectrum m/e 428 (M^++H).

NMR Spectrum (d-6-DMSO, d values) 3.75 (s, 3H), 4.00 (s, 6H), 6.95 (m, 3H), 7.05 (m, 1H), 7.20 (m, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.85 (s, 1H), 11.10 (broad, 1H).

Example 2

Preparation of Compound 253 in Table 3

Step 1

A mixture of 4-chloro-3-cyano-6,7-dimethoxy-quinoline (2.49 g) and 4-aminophenol (2.4 g) in n-propanol (150 ml) was stirred and heated at 110°C for 4 hours. The mixture was

cooled to ambient temperature and then filtered. The crystals were washed with a small volume of diethyl ether and then dried to give 3-cyano-6,7-dimethoxy-4-(4-hydroxy)-anilino-quinoline (2.68 g, 83%).

Mass Spectrum m/e 322 (M^++H).

NMR Spectrum (d-6-DMSO, d values) 3.85 (s, 3H), 3.9 (s, 3H), 6.8 (d, 2H), 7.1 (d, 2H), 7.25 (s, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.3 (broad s, 1H).

Step 2

3-Cyano-6,7-dimethoxy-4-(4-hydroxy)-anilino-quinoline (160.5 mg) was dissolved in DMF (5 ml) and potassium carbonate (138 mg) was added. The mixture was stirred under an atmosphere of nitrogen for 5 minutes and then 2-bromomethyl-tetrahydrofuran (180 ml) was added. The mixture was stirred and heated at 80°C for 18 hours. The mixture was cooled to ambient temperature and then diluted with ethyl acetate and then extracted with water. The aqueous phase was re-extracted with ethyl acetate and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was then purified by column chromatography using 2-3% methanol/dichloromethane mixtures as eluent. There was thus obtained 3-cyano-6,7-dimethoxy-4-(2-tetrahyrofuranyl-methoxy)-anilino-quinoline (70 mg, 34%).

Mass Spectrum m/e 406 (M^++H).

NMR Spectrum ($CDCl_3$, d values) 1.8 (m, 1H), 1.95 (m, 2H), 2.05 (m, 1H), 3.6 (s, 3H), 3.85 (dd, 1H), 3.9 (m, 1H), 3.95 (m, 1H), 4.0 (s, 3H), 4.25 (m, 1H), 6.8 (broad s, 1H), 6.85 (s, 1H), 6.95 (d, 2H), 7.1 (d, 2H), 7.35 (s, 1H), 8.6 (s, 1H).

Example 3

By an analogous procedure to that described for Example 2, step 2, but using an alternative bromide, the compounds listed in Table 5 were prepared:

Table 5

No	bromide	mass spec	nmr	Notes
250	2-bromo-methyltetra-hydropyran	m/e 420 (M^++H)	(d-6-DMSO, d values) 1.2-1.7 (m, 6H), 3.40 (m, 1H), 3.60 (m, 1H), 3.90 (s, 3H), 3.90 (s, 3H), 3.9 (m, 3H), 6.95 (d, 2H), 7.20 (d, 2H), 7.25 (d, 1H), 7.75 (d, 1H), 8.30 (d, 1H), 9.35 (broad s, 1H).	
251	epibromohydrin	m/e 378 (M^++H)	(d-6-DMSO, d values) 2.70 (dd, 1H), 2.83 (dd, 1H), 3.35 (m, 1H), 3.85 (dd, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.35 (dd, 1H), 7.00 (d, 2H), 7.20 (d, 2H), 7.26 (s, 1H), 7.75 (s, 1H), 8.30 (s, 1H), 9.35 (broad s, 1H).	RT/ 48hrs/ DMF/ K_2CO_3
252	2-bromomethyl-1,3-dioxolane	m/e 408 (M^++H)	($CDCl_3$, d values) 3.60 (s, 3H), 3.95 (m, 3H), 4.00 (s, 3H), 4.05 (m, 3H), 5.30 (t, 1H), 6.80 (broad s, 1H), 6.85 (s, 1H), 6.95 (d, 2H), 7.15 (d, 2H), 7.35 (s, 1H), 8.60 (s, 1H).	

Example 4

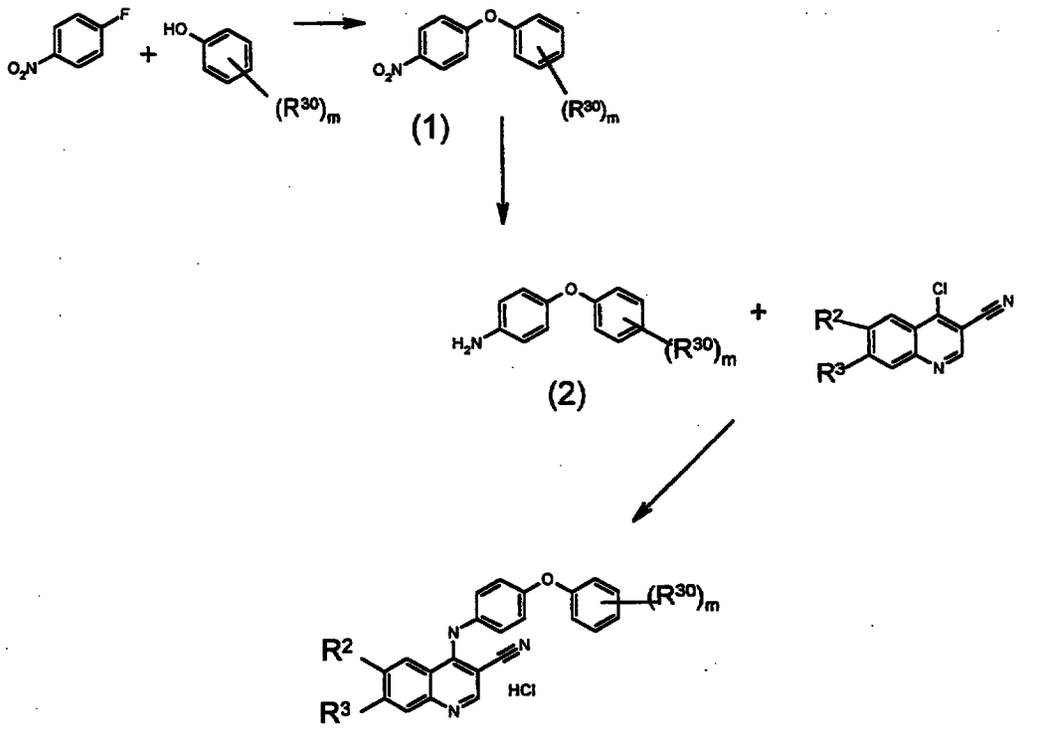
By an analogous procedure to that described for Example 2, step 2, but using a tosylate instead of a bromide, the following compounds were prepared.

Table 6

No	intermediate	mass	nmr
254	2,2-dimethyl-4-(4-toluenesulphonyloxymethyl)-1,3-dioxolane	m/e 436 (M^++H)	($CDCl_3$, d values) 1.4 (s, 3H), 1.45 (s, 3H), 3.65 (s, 3H), 3.90 (dd, 1H), 3.95 (m, 1H), 4.00 (s, 3H), 4.05 (m, 1H), 4.15 (dd, 1H), 4.50 (m, 1H), 6.80 (broad s, 1H), 6.90 (s, 1H), 6.95 (d, 2H), 7.10 (d, 2H), 7.35 (s, 1H), 8.60 (s, 1H).
255	4-(4-toluenesulphonyloxymethyl)-1,3-dioxolane	m/e 408 (M^++H)	($CDCl_3$, d values) 3.60 (s, 3H), 3.85 (m, 1H), 3.95 (m, 1H), 4.00 (s, 3H), 4.05 (m, 2H), 4.40 (m, 1H), 4.95 (s, 1H), 5.10 (s, 1H), 6.80 (broad s, 1H), 6.85 (s, 1H), 6.95 (d, 2H), 7.10 (d, 2H), 7.35 (s, 1H), 8.60 (s, 1H).
256	5-bromo-5-(4-toluenesulphonyloxymethyl)-1,3-dioxane	m/e 436 (M^++H)	($CDCl_3$, d values) 0.95 (s, 3H), 3.50 (d, 2H), 3.65 (s, 3H), 4.00 (d, 2H), 4.00 (s, 3H), 4.10 (s, 1H), 4.70 (d, 1H), 5.00 (d, 1H), 6.80 (broad s, 1H), 6.85 (s, 1H), 6.95 (d, 2H), 7.15 (d, 2H), 7.35 (s, 1H), 8.60 (s, 1H).

Example 5

Using a method analogous to that described in Example 1 (except that in some instances, intermediates (1) and (2) were modified prior to further reaction as described in Examples 14 and 15 hereinafter) i.e. as set out in the following scheme:



but with the appropriate aniline intermediate (2) (where $(R^{30})_m$ are substitutents R^{20}, R^{21}, R^{22}, R^{23} and R^{24} are as set out in Table 1) and quinoline where R^2 and R^3 are as defined in Table 1, the following compounds set out in Table 7 were prepared.

Table 7

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
2	m/e 427 (M^++H)	(d-6-DMSO, d values) 3.72 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 6.87 (d, 2H), 6.98 (d, 2H), 7.10 (d, 2H), 7.18 (d, 2H), 7.46 (s, 1H), 8.04 (s, 1H), 8.67 (s, 1H), 2NH assumed under H_2O, (2.5-3.6).	165°C/2.5h/ cyclohexanol				
3	m/e 462/ 464 (M^++H)		160°C/5h/ cyclohexanol				
4	m/e 462/ 464 (M^++H)		160°C/5h/ cyclohexanol				
5	m/e 458 (M^++H)	(d-6-DMSO, d values) 3.70 (s, 6H), 3.90 (s, 3H), 3.95 (s, 3H), 6.80 (d, 2H), 6.85 (d, 2H), 7.10 (t, 1H), 7.25 (d, 1H), 7.40 (s, 1H), 8.05 (s, 1H), 8.85 (s, 1H), 10.80 (broad s, 1H)	110°C/4h/ 1-PrOH	m/e 276 (M^++H)	KOtBu, MeOH	m/e 246 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
6	m/e 442 (M^++H)	(d-6-DMSO, d values) 2.05 (s, 3H), 3.65 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 6.80 (d, 2H), 6.90 (d, 1H), 7.00 (d, 1H), 7.15 (t, 1H), 7.35 (d, 2H), 7.40 (s, 1H), 8.05 (s, 1H), 8.80 (s, 1H), 10.90 (broad s, 1H)	110°C/4h/ 1-PrOH	m/e 230 (M^++H)	KOtBu, MeOH	m/e 260 (M^++H)	H_2, Pd/C, EtOAc
7	m/e 428 (M^++H)	(d-6-DMSO, d values) 3.70 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 6.55 (s, 1H), 6.60 (m, 1H), 6.65 (dd, 1H), 7.15 (d, 2H), 7.25 (t, 1H), 7.45 (s, 1H), 7.50 (d, 2H), 8.05 (s, 1H), 8.85 (s, 1H), 11.10 (broad s, 1H)	110°C/4h/1-PrOH	m/e 216 (M^++H)			
8	m/e 428 (M^++H)	(d-6-DMSO, d values) 3.70 (s, 3H), 4.00 (s, 6H), 6.55 (s, 1H), 6.95 (m, 2H), 7.00 (d, 2H), 7.05 (d, 2H), 7.40 (d, 2H), 7.40 (s, 1H), 8.05 (s, 1H), 8.85 (s, 1H), 10.90 (broad s, 1H)	110°C/4h/1-PrOH	m/e 246 (M^++H)	KOtBu, MeOH	m/e 216 (M^++H)	H_2, Pd/C, EtOAc
9	m/e 504 (M^++H)	(d-6-DMSO, d values) 3.73 (s, 3H), 3.97 (s, 3H), 5.32 (s, 2H), 6.95 (m, 3H), 7.05 (d, 1H), 7.18 (m, 2H), 7.38 (m, 5H), 7.51 (d, 2H), 7.58 (s, 1H), 8.17 (s, 1H), 8.87 (s, 1H), 11.13 (broad, 1H)	1-PrOH / 115° / 5 h				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
10	m/e 458 (M^++H)	(d-6-DMSO, d values) 3.65 (s, 3H), 3.80 (s, 3H), 4.00 (s, 6H), 6.65 (d, 1H), 6.90 (d, 1H), 7.05 (m, 3H), 7.40 (d, 2H), 7.45 (m, 1H), 8.15 (m, 1H), 8.90 (s, 1H)	110°C/18h/1 -PrOH	m/e 276 (M^++H)	KOtBu, DMA	m/e 246 (M^++H)	H_2, Pd/C, EtOAc
11	m/e 458 (M^++H)	(d-6-DMSO, d values) 3.70 (s, 6H), 4.00 (s, 6H), 6.20 (d, 2H), 6.25 (t, 1H), 7.20 (d, 2H), 7.45 (s, 1H), 7.50 (d, 2H), 8.15 (s, 1H), 8.90 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1 -PrOH	m/e 276 (M^++H)	KOtBu, DMA	m/e 246 (M^++H)	H_2, Pd/C, EtOAc
12	m/e 456 (M^++H)	(d-6-DMSO, d values) 1.20 (d, 6H), 4.00 (s, 6H), 4.6 (m, 1H), 6.95 (m, 3H), 7.05 (d, 1H), 7.20 (d, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1 -PrOH	m/e 274 (M^++H)	KOtBu, DMA	m/e 244 (M^++H)	H_2, Pd/C, EtOAc
13	m/e 486 (M^++H)	(d-6-DMSO, d values) 3.70 (s, 3H), 3.75 (s, 3H), 4.05 (s, 6H), 6.55 (d, 1H), 6.85 (dd, 1H), 7.15 (d, 2H), 7.50 (s, 1H), 7.55 (d, 2H), 7.85 (d, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1 -PrOH	m/e 304 (M^++H)	KOtBu, DMA	m/e 274 (M^++H	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
15	m/e 462 (M^++H)	(d-6-DMSO, d values) 3.75 (s, 3H), 4.00 (s, 6H), 6.55 (t, 1H), 6.60 (t, 1H), 6.80 (t, 1H), 7.20 (d, 2H), 7.50 (s, 1H), 7.55 (d, 2H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 250 (M^++H)	$SnCl_2.2H_2O$, HCl, EtOAc
32	m/e 442 (M^++H)	(d-6-DMSO, d values) 1.20 (t, 3H), 3.95 (s, 6H), 4.00 (q, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.15 (m, 2H), 7.35 (d, 2H), 7.45 (s, 1H), 8.10 (s, 1H), 8.85 (s, 1H), 10.95 (broad s, 1H)	110°C/4h/1-PrOH	m/e 260 (M^++H)	KOtBu, MeOH	m/e 230 (M^++H)	H_2, Pd/C, EtOAc
42	m/e 516 (M^++H)	(d-6-DMSO, d values), 3.35 (s, 6H), 3.74 (s, 3H), 3.76 (m, 4H), 4.32 (m, 4H), 6.97 (m, 3H), 7.05 (d, 1H), 7.07 (m, 2H), 7.39 (d, 2H), 7.47 (s, 1H), 8.14 (s, 1H), 8.89 (s, 1H), 10.96 (broad, 1H)	1-PrOH / reflux / 18h	m/e 337 (M^++H)	$POCl_3$ / 120° / 2h		
43	m/e 442 (M^++H)	($CDCl_3$, d values) 2.25 (s, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 4.00 (s, 3H), 6.60 (broad s, 1H), 6.80 (m, 2H), 7.00 (m, 5H), 7.15 (td, 1H), 7.30 (s, 1H), 8.60 (s, 1H)	110°C/36h/1-PrOH	m/e 260 (M^++H)	KOtBu, DMA	m/e 230 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
45	m/e 516 (M^++H)	(d-6-DMSO, d values), 3.49 (m, 6H), 3.71 (s, 3H), 3.77 (m, 4H), 4.33 (m, 4H), 6.60 (m, 2H), 6.70 (d, 1H), 7.17 (d, 2H), 7.28 (t, 1H), 7.47 (d, 2H), 7.50 (s, 1H), 8.16 (s, 1H), 8.90 (s, 1H), 11.02 (broad, 1H)	1-PrOH / reflux / 18 h				
46	m/e 546 (M^++H)	(d-6-DMSO, d values), 3.35 (m, 6H), 3.69 (s, 6H), 3.77 (m,4H), 4.33 (m,4H),6.19 (d, 2H),6.26 (t 1H),7.19 (m,2H), 7.49 (m, 3H), 8.19 (s, 1H), 8.91 (s, 1H), 11.12 (broad, 1H)	1-PrOH / reflux / 18 h				
47	m/e 530 (M^++H)	(d-6-DMSO, d values), 1.21 (t, 3H), 3.35 (m, 6H), 3.77 (m, 4H), 4.03 (q, 2H), 4.32 (m, 4H), 6.97 (m, 3H), 7.05 (d, 1H), 7.18 (m, 2H), 7.39 (d, 2H), 7.47 (s, 1H), 8.14 (s, 1H), 8.89 (s, 1H), 10.95 (broad, 1H)	1-PrOH / reflux / 18 h				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
49	m/e 500 $(M+H)^+$	(d-6-DMSO, d values) 1.21 (t, 3H), 3.72 (s, 3H), 4.01 (s, 3H), 4.17 (q, 2H), 4.98 (s, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.19 (m, 2H), 7.42 (m, 3H), 8.06 (s, 1H), 8.89 (s, 1H)	100°C/6h/1-PrOH			m/e 321, 323 $(M+H)^+$	RT/30mins /ethylbromoacetate/KOtBu/n-Bu_4NI/DMA
56	m/e 456 (M^+H)	($CDCl_3$, d values) 1.30 (q, 3H), 2.25 (s, 3H), 3.60 (s, 3H), 4.00 (s, 3H), 4.05 (t, 2H), 6.60 (m, 1H), 6.75 (m, 2H), 6.90 (m, 1H), 7.00 (m, 4H), 7.15 (m, 1H), 7.30 (s, 1H), 8.55 (s, 1H)	110°C/36h/1-PrOH	m/e 274 (M^+H)	KOtBu, DMA	m/e 244 (M^+H)	H_2, Pd/C, EtOAc
62	m/e 428 $(M+H)^+$	(d-6-DMSO, d values) 1.21 (t, 3H), 3.97 (s, 3H), 4.03 (q, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.37 (m, 2H), 7.40 (s, 1H), 8.05 (s, 1H), 8.88 (s, 1H)	100°C/18h/1-PrOH				
65	m/e 500 $(M+H)^+$	(d-6-DMSO, d values) 1.24 (t, 3H), 3.72 (s, 3H), 3.97 (s, 3H), 4.20 (q, 2H), 5.05 (s, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.18 (m, 2H), 7.27 (s, 1H), 7.37 (d, 2H), 8.07 (s, 1H), 8.84 (s, 1H)	100°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
69	m/e 541 (M^++H)	(d-6-DMSO, d values) 2.34 (m, 2H), 3.12 (m, 2H), 3.50 (m, 4H), 3.73 (s, 3H), 3.85 (m, 2H), 3.98 (s, 2H), 4.02 (s, 3H), 4.33 (t, 2H), 6.62 (m, 2H), 6.72 (m, 1H), 7.20 (d, 2H), 7.30 (t, 1H), 7.49 (d, 2H), 7.54 (s, 1H), 8.21 (s, 1H), 8.89 (s, 1H), 11.08 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 3 h				
74	m/e 446 (M^++H)	(d-6-DMSO, d values) 3.75 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 6.90 (d, 2H), 7.00 (m, 2H), 7.25 (dd, 1H), 7.40 (d, 2H), 7.45 (s, 1H), 8.15 (s, 1H), 8.90 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 234 (M^++H)	H_2, Pd/C, EtOAc
75	m/e 432 (M^++H)	(d-6-DMSO, d values) 3.98 (s, 6H), 7.05 (d, 2H), 7.15 (d, 2H), 7.40 (s, 1H), 7.42 (d, 2H), 7.50 (d, 2H), 8.10 (s, 1H), 8.85 (s, 1H)					
76	m/e 443 (M^++H)	(d-6-DMSO, d values) 3.99 (s, 6H), 7.15-7.30 (m, 4H), 7.48-7.52 (m, 3H), 8.05 (s, 1H), 8.11 (d, 2H), 8.68 (s, 1H), NH assumed under H_2O, (3.2-3.4).	165°C/2.5h/ cyclohexanol				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
77	m/e 434 (M^++H)	(d-6-DMSO, d values) 3.92 (s, 3H), 3.94 (s, 3H), 6.95 (m, 1H), 7.05 (d, 2H), 7.05 - 7.25 (m, obscured), 7.29 (d, 2H), 7.4 - 7.5 (m, 1H), 7.75 (s, 1H), 8.40 (s, 1H), 9.43 (s, 1H)	150°C/16h/ Dowtherm A				
78	m/e 462/ 464 (M^++H)		150°C/16h/ Dowtherm A				
79	m/e 448/ 450 (M^++H)	(d-6-DMSO, d values) 3.96 (s, 3H), 3.98 (s, 3H), 7.30 (d, 2H), 7.37 (d, 4H), 7.45 (m, 3H), 8.04 (s, 1H), 8.7 (s, obscured).	160°C/5h/ cyclohexanol				
80	m/e 446/ 448 (M^++H)		160°C/5h/ cyclohexanol				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
81	m/e 416 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.10 (d, 2H), 7.15 (m, 1H), 7.20 (m, 2H), 7.40 (m, 1H), 7.45 (m, 3H), 8.20 (s, 1H), 8.90 (s, 1H), 11.12 (broad s, 1H)	110°C/4h/1-PrOH		KOtBu, MeOH	m/e 204 (M^++H)	H_2, Pd/C, EtOAc
82	m/e 412 (M^++H)	(d-6-DMSO, d values) 2.10 (s, 3H), 4.00 (s, 6H), 6.95 (m, 3H), 7.10 (t, 1H), 7.20 (t, 1H), 7.40 (d, 2H), 7.45 (s, 1H), 8.15 (s, 1H), 8.85 (s, 1H), 11.05 (broad s, 1H)	110°C/4h/1-PrOH		KOtBu, MeOH	m/e 200 (M^++H)	H_2, Pd/C, EtOAc
83	m/e 514 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 5.05 (s, 2H), 7.45 (d, 2H), 7.45 (s, 1H), 7.55 (d, 2H), 7.60 (s, 2H), 8.05 (s, 1H), 8.95 (s, 1H)	110°C/18h/1-PrOH				
84	m/e 486 (M^++H)	(d-6-DMSO, d values) 3.80 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.35 (s, 2H), 7.35 (d, 2H), 7.45 (m, 4H), 7.60 (d, 1H), 7.80 (d, 1H), 8.00 (s, 1H), 8.05 (s, 1H), 8.90 (s, 1H), 10.90 (broad s, 1H)	110°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
85	m/e 444 (M^++H)	(d-6-DMSO, d values) 2.4 (s, 3H), 4.00 (s, 6H), 6.90 (dd, 1H), 7.05 (d, 2H), 7.20 (m, 2H), 7.35 (dd, 1H), 7.45 (m, 3H), 8.10 (s, 1H), 8.85 (s, 1H) 10.90 (broad s, 1H)	110°C/5.5h/1 -PrOH		KOtBu, MeOH, DMA	m/e 232 (M^++H)	H_2, Pd/C, EtOAc
86	m/e 423 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.95 (d, 1H), 7.25 (t, 1H), 7.30 (d, 2H), 7.45 (s, 1H), 7.55 (d, 2H), 7.60 (m, 1H), 7.90 (dd, 1H), 8.15 (s, 1H), 8.90 (s, 1H)	110°C/5.5h/1 -PrOH	m/e 239 (M-H)	KOtBu, MeOH, DMA	m/e 211 (M^++H)	H_2, Pd/C, EtOAc
87	m/e 524 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.05 (dd, 1H), 7.15 (m, 3H), 7.35 (t, 1H), 7.40 (s, 1H), 7.45 (m, 3H), 8.05 (s, 1H), 8.80 (s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 312 (M^++H)	$SnCl_2.2H_20$, EtOAc
88	m/e 476 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.10 (m, 4H), 7.40 (td, 1H), 7.45 (s, 1H), 7.45 (d, 2H), 7.75 (dd, 1H), 8.05 (s, 1H), 8.90 (s, 1H), 11.05 (broad s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 264 (M^++H)	$SnCl_2.2H_20$, EtOAc
89	m/e 476 (M^++H)	(d-6-DMSO, d values) 3.95 (s, 3H), 3.95 (s, 3H), 7.00 (m, 1H), 7.20 (m, 3H), 7.30 (m, 3H), 7.40 (d, 2H), 7.90 (s, 1H), 8.60 (s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 264 (M^++H)	$SnCl_2$. $2H_20$, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
90	m/e 476 (M^++H)	(d-6-DMSO, d values) 3.95 (s, 3H), 3.95 (s, 3H), 7.00 (m, 1H), 7.20 (m, 3H), 7.30 (m, 3H), 7.40 (d, 2H), 7.90 (s, 1H), 8.60 (s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 264 (M^++H)	$SnCl_2.2H_20$, EtOAc
91	m/e 432 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.00 (m, 2H), 7.20 (dd, 1H), 7.20 (d, 2H), 7.40 (t, 1H), 7.45 (s, 1H), 7.50 (d, 2H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 220 (M^++H)	$SnCl_2.2H_20$, EtOAc
92	m/e 524 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.95 (d, 2H), 7.05 (m, 2H), 7.40 (m, 1H), 7.45 (s, 1H), 7.45 (d, 2H), 7.90 (d, 1H), 8.15 (s, 1H), 8.90 (s, 1H), 11.05 (broad s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 312 (M^++H)	$SnCl_2.$ $2H_20$, EtOAc
93	m/e 466 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.05 (d, 1H), 7.15 (m, 3H), 7.45 (s, 1H), 7.55 (d, 2H), 7.60 (d, 1H), 8.15 (s, 1H), 8.95 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1 -PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
94	m/e 432 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.10 (t, 3H), 7.20 (t, 1H), 7.35 (t, 1H), 7.50 (s, 1H), 7.55 (d, 2H), 7.60 (d, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH	m/e 243 (M^++H)	KOtBu, DMA	m/e 220 (M^++H)	$SnCl_2.2H_20$, HCl, EtOAc
95	m/e 455 (M^++H)	(d-6-DMSO, d values) 2.05 (s, 3H), 4.00 (s, 6H), 6.65 (m, 1H), 7.15 (d, 2H), 7.30 (d, 2H), 7.45 (m, 4H), 8.20 (s, 1H), 8.95 (s, 1H), 10.10 (broad s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH	m/e 273 (M^++H)	KOtBu, DMA		H_2, Pd/C, EtOAc
96	m/e 414 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.80 (m, 1H), 6.95 (m, 5H), 7.35 (d, 2H), 7.40 (s, 1H), 8.00 (s, 1H), 8.75 (s, 1H), 9.60 (broad s, 1H), 10.50 (broad s, 1H)	110°C/18h/1-PrOH				H_2, Pd/C, EtOAc
97	m/e 532 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 5.25 (s, 2H), 7.05 (m, 3H), 7.30 (m, 6H), 7.50 (m, 3H), 7.60 (m, 1H), 7.90 (dd, 1H), 8.15 (s, 1H), 8.90 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1-PrOH	m/e 350 (M^++H)	KOtBu, DMA	m/e 320 (M^++H)	$SnCl_2.2H_2O$, HCl, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
98	m/e 466 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.00 (d, 1H), 7.20 (d, 2H), 7.30 (t, 1H), 7.50 (s, 1H), 7.55 (d, 2H), 7.60 (t, 1H), 7.80 (d, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 254 (M^++H)	$SnCl_2.2H_2O$, HCl, EtOAc
99	m/e 466 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 7.30 (m, 3H), 7.35 (d, 1H), 7.50 (m, 2H), 7.55 (d, 2H), 7.60 (t, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 254 (M^++H)	$SnCl_2.2H_2O$, HCl, EtOAc
100	m/e 442 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.95 (d, 1H), 7.05 (d, 2H), 7.20 (t, 1H), 7.45 (d, 2H), 7.50 (s, 1H), 7.55 (m, 1H), 7.80 (dd, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH	m/e 350 (M^++H	KOtBu, DMA	m/e 230 (M^++H)	H_2, Pd/C, EtOAc
101	m/e 441 (M^++H)	(d-6-DMSO, d values) 1.15 (t, 3H), 3.00 (q, 2H), 4.00 (s, 6H), 6.25 (dd, 1H), 6.30 (t, 1H), 6.40 (dd, 1H), 7.10 (m, 3H), 7.45 (d, 2H), 7.50 (s, 1H), 8.15 (s, 1H), 8.85 (s, 1H), 11.00 (broad s, 1H)	110°C/18h/1-PrOH	m/e 259 (M^++H	KOtBu, DMA	m/e 229 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
103	m/e 456 (M^++H)	(d-6-DMSO, d values) 3.75 (s, 3H), 4.00 (s, 6H), 7.10 (s, 1H), 7.10 (d, 2H), 7.30 (t, 1H), 7.50 (m, 3H), 7.60 (t, 1H), 7.90 (d, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1 -PrOH	m/e 274 (M^++H	KOtBu, DMA	m/e 244 (M^++H)	H_2, Pd/C, EtOAc
104	m/e 469 (M^++H)	(d-6-DMSO@373K, d values) 1.10 (t, 6H), 3.30 (q, 4H), 4.00 (s, 6H), 6.35 (dd, 1H), 6.50 (s, 1H), 6.60 (dd, 1H), 7.10 (d, 2H), 7.20 (t, 1H), 7.40 (d, 2H), 7.50 (s, 1H), 8.05 (s, 1H), 8.65 (s, 1H)	110°C/18h/1 -PrOH	m/e 287 (M^++H	KOtBu, DMA	m/e 257 (M^++H)	H_2, Pd/C, EtOAc
105	m/e 423 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 7.30 (d, 2H), 7.40 (m, 2H), 7.50 (m, 5H), 8.30 (s, 1H), 8.95 (s, 1H), 11.60 (broad s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 211 (M^++H)	$SnCl_2.2H_2O$, HCl, EtOAc
106	m/e 469 (M^++H)	($CDCl_3$, d values) 2.10 (s, 3H), 2.25 (s, 3H), 3.80 (s, 3H), 4.00 (s, 3H), 6.80 (dd, 1H), 6.90 (m, 2H), 7.00 (d, 1H), 7.10 (m, 3H), 7.30 (m, 1H), 7.35 (s, 1H), 7.50 (broad s, 1H), 8.55 (s, 1H)	110°C/36h/1 -PrOH	m/e 287 (M^++H	KOtBu, DMA	m/e 257 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
107	m/e 437 (M^++H)	(d-6-DMSO, d values) 2.25 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 7.00 (d, 1H), 7.15 (dd, 1H), 7.25 (m, 2H), 7.50 (m, 2H), 7.60 (td, 1H), 7.90 (dd, 1H), 8.30 (s, 1H), 8.90 (s, 1H), 11.20 (broad s, 1H)	110°C/60h/1-PrOH	m/e 255 (M^++H	KOtBu, DMA	m/e 225 (M^++H)	$SnCl_2.2H_20$, HCl, EtOAc
108	m/e 500 $(M+H)^+$	(d-6-DMSO, d values) 4.02 (s, 3H), 6.74 (tt, 1H), 6.89 (m, 1H), 7.03 (m, 2H), 7.22 (d, 2H), 7.46 (m, 3H), 7.50 (1H, s), 7.95 (s, 1H), 8.88 (s, 1H)	100°C/18h/1-PrOH				
109	m/e 438 $(M+H)^+$	(d-6-DMSO, d values) 3.54 (m, 1H), 4.01 (s, 3H), 4.80 (m, 2H), 6.99 (m, 4H), 7.18 (m, 1H), 7.25 (m, 1H), 7.38 (d, 2H), 7.48 (1H, s), 7.94 (s, 1H), 8.88 (s, 1H)	100°C/18h/1-PrOH		60°C/1h/K_2CO_3/$HCCCH_2$Br/acetone	m/e 240 $(M+H)^+$	90°C/2h/$SnCl_2.2H_2O$/EtOAc
110	m/e 409 (M^++H)	(d-6-DMSO, d values) 4.0 (s, 3H), 6.97 (d, 1H), 7.23-7.35 (m, 3H), 7.47 (s, 1H), 7.51 (d, 2H), 7.63 (t, 1H), 7.9 (d, 1H), 7.95 (s, 1H), 8.89 (s, 1H), 10.5 (br.s, 1H), 10.85 (br.s, 1H)	82°C/20h/iso-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
111	m/e 441	(d-6-DMSO, d values) 2.80 (s, 6H), 4.00 (s, 6H), 6.95 (m, 2H), 7.05 (d, 2H), 7.20 (m, 2H), 7.40 (d, 2H), 7.40 (s, 1H), 8.10 (s, 1H), 8.85 (s, 1H), 10.90 (broad s, 1H)	110°C/18h/1-PrOH	m/e 259 (M^++H	KOtBu, DMA/ HCHO, AcOH, $NaBH_3CN$, EtOH	m/e 229 (M^++H)	H_2, Pd/C, EtOAc
112	m/e 441	(d-6-DMSO, d values) 2.90 (s, 6H), 4.00 (s, 6H), 6.35 (m, 2H), 6.50 (d, 1H), 7.15 (m, 3H), 7.45 (d, 2H), 7.50 (s, 1H), 8.15 (s, 1H), 8.90 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1-PrOH	m/e 259 (M^++H	HCHO, AcOH, $NaBH_3CN$, EtOH	m/e 229 (M^++H)	H_2, Pd/C, EtOAc
113	m/e 500 $(M+H)^+$	(d-6-DMSO, d values) 3.97 (s, 3H), 6.74 (tt, 1H), 6.89 (m, 1H), 7.03 (m, 2H), 7.24 (d, 2H), 7.34 (s, 1H), 7.45 (d, 1H), 7.51 (d, 2H), 8.04 (s, 1H), 8.87 (s, 1H)	100°C/18h/1-PrOH				
116	m/e 441 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.95 (d, 1H), 7.00 (d, 1H), 7.40 (m, 4H), 7.85 (d, 2H), 7.95 (dd, 1H), 8.15 (s, 1H), 8.95 (s, 1H), 10.55 (broad s, 1H), 11.10 (broad s, 1H), 11.70 (broad s, 1H)	110°C/70h/1-PrOH	m/e 257 (M-H)	KOtBu, DMA	m/e 229 (M^++H)	$SnCl_2.2H_2O$, HCl, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
117	m/e 427 (M^++H)	(d-6-DMSO, d values) 2.63 (s, 3H), 3.97 (d, 6H), 6.24 (m, 3H), 6.38 (d, 1H), 7.10 (m, 3H), 7.45 (t, 3H), 8.19 (s, 1H), 8.90 (s, 1H), 11.17 (broad, 1H)	1-PrOH / 110 deg / 18h			m/e 215 (M^++H)	H_2 / Pd/C / EtOAc / RT / ambient pressure
122	m/e 439 $(M+H)^+$	(d-6-DMSO, d values) 4.00 (s, 3H), 5.14 (s, 2H), 7.01 (d, 2H), 7.09 (m, 2H), 7.23 (m, 1H), 7.33 (d, 1H), 7.40 (d, 2H), 7.45 (s, 1H), 7.94 (s, 1H), 8.87 (s, 1H)	100°C/18h/1-PrOH		60°C/1h/ K_2CO_3/bromoacetonitrile/acetone	m/e 241 $(M+H)^+$	90°C/2h/$SnCl_2.2H_2O$/EtOAc
123	m/e 444 $(M+H)^+$	(d-6-DMSO, d values) 3.60 (t, 2H), 4.00 (m, 5H), 6.98 (m, 4H), 7.17 (m, 2H), 7.27 (d, 2H), 7.46 (s, 1H), 7.93 (s, 1H), 8.87 (s, 1H)	100°C/18h/1-PrOH				
124	m/e 439 $(M+H)^+$	(d-6-DMSO, d values) 3.95 (s, 3H), 5.15 (s, 2H), 7.03 (d, 2H), 7.10 (m, 2H), 7.24 (m, 1H), 7.31 (m, 1H), 7.41 (m, 2H), 7.45 (m, 1H), 8.08 (s, 1H), 8.83 (s, 1H)	100°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
125	m/e 444 $(M+H)^+$	(d-6-DMSO, d values) 3.60 (t, 2H), 3.96 (s, 3H), 3.98 (t, 2H), 7.00 (m, 4H), 7.16 (m, 2H), 7.37 (s, 1H), 7.42 (m, 2H), 8.10 (s, 1H), 8.84 (s, 1H)	100°C/18h/1-PrOH				
126	m/e 440 $(M+H)^+$	(d-6-DMSO, d values) 3.89 (s, 3H), 4.55 (m, 2H), 5.17 (dd, 1H), 5.29 (dd, 1H), 5.92 (m, 1H), 6.89 (d, 2H), 6.93 (m, 1H), 7.02 (m, 1H), 7.13 (m, 2H), 7.16 (s, 1H), 7.21 (d, 2H), 7.72 (s, 1H), 8.29 (s, 1H), 9.34 (s, 1H)	100°C/18h/1-PrOH		60°C/1h/ K_2CO_3/ allyl bromide/ acetone	m/e 242 $(M+H)^+$	90°C/3h/$SnCl_2.2H_2O$/ EtOAc
129	m/e 471 $(M+H)^+$	(d-6-DMSO, d values) 2.61 (d, 3H), 3.98 (s, 3H), 4.46 (s, 2H), 7.00 (m, 4H), 7.04 (m, 1H), 7.12 (m, 2H), 7.33 (d, 2H), 7.41 (s, 1H), 7.49 (bs, 1H), 7.86 (s, 1H), 8.74 (s, 1H)	100°C/18h/1-PrOH				
130	m/e 409.2 $(M^+ + H)$	(d-6-DMSO, d values) 3.98 (s, 3H), 6.95 (d, 1H), 7.22-7.4 (m, 3H), 7.42 (s, 1H), 7.5-7.7 (m, 3H), 7.9 (d, 1H), 8.09 (s, 1H), 8.89 (s, 1H), 11.1 (br.s, 1H), 11.7 (br.s, 1H)	82°C/20h/iso-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
133	m/e 529 (M^++H)	(d-6-DMSO, d values) 1.19 (t, 3H), 3.12 (q, 2H), 3.37 (s, 6H), 3.79 (m, 4H), 4.36 (m, 4H), 6.66 (m, 3H), 7.18 (d, 2H), 7.26 (m, 1H), 7.51 (d, 2H), 7.56 (s, 1H), 8.31 (s, 1H), 8.99 (s, 1H), 11.39 (s, 1H)	EtOH / reflux / 18 h				
134	m/e 554 (M^++H)	(d-6-DMSO, d values) 1.13 (t, 3H), 2.30 (m, 2H), 3.12 (q, 2H), 3.16 (broad, 2H), 3.49 (broad, 2H), 3.80 (broad, 4H), 3.95 (s, 3H), 4.31 (t, 2H), 6.32 (m, 2H), 6.48 (m, 1H), 7.13 (m, 3H), 7.42 (m, 3H), 8.07 (s, 1H), 8.90 (s, 1H), 10.80 (broad, 1H), 10.95 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / reflux / 48 h				
135	m/e 466	($CDCl_3$, d values) 3.80 (s, 3H), 4.05 (s, 3H), 7.00 (m, 5H), 7.15 (d, 2H), 7.25 (m, 1H), 7.40 (s, 1H), 7.50 (td, 1H), 8.05 (dd, 1H), 8.45 (s, 1H), 8.60 (s, 1H)	110°C/18h/1-PrOH	m/e 284 (M^++H	KOtBu, DMA	m/e 254 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
141	m/e 529 (M^++H)	(d-6-DMSO, d values) 2.34 (m, 2H), 3.08 (m, 2H), 3.48 (m, 4H), 3.90 (m, 4H), 4.01 (s, 3H), 4.30 (t, 2H), 7.12 (d, 2H), 7.21 (m, 3H), 7.40 (m, 1H), 7.48 (d, 2H), 7.57 (s, 1H), 8.34 (s, 1H), 8.90 (s, 1H), 11.28 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 60deg / 72 h				
144	m/e 434 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.95 (m, 1H), 7.20 (m, 4H), 7.50 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.25 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 222 (M^++H)	H_2, Pd/C, EtOAc
145	m/e 529 (M^++H)		1-PrOH / 1.0M ethereal HCl (1 equiv.) / 60deg / 72 h				
146	m/e 514 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 6.75 (tt, 1H), 6.90 (t, 1H), 7.00 (m, 2H), 7.20 (d, 2H), 7.45 (s, 1H), 7.50 (d, 1H), 7.55 (d, 2H), 8.20 (s, 1H), 8.95 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
147	m/e 434 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 6H), 7.05 (d, 2H), 7.35 (m, 3H), 7.45 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.25 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 222 (M^++H)	H_2, Pd/C, EtOAc
148	m/e 434 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 7.00 (m, 2H), 7.20 (d, 2H), 7.45 (m, 1H), 7.50 (s, 1H), 7.55 (d, 2H), 8.20 (s, 1H), 8.95 (s, 1H), 11.35 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 222 (M^++H)	H_2, Pd/C, EtOAc
149	m/e 434 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 6.75 (dd, 2H), 6.95 (tt, 1H), 7.30 (d, 2H), 7.50 (s, 1H), 7.55 (d, 2H), 8.25 (s, 1H), 8.95 (s, 1H), 11.45 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 222 (M^++H)	H_2, Pd/C, EtOAc
150	m/e 500 (M^++H)	(d-6-DMSO, d values) 0.83 (t, 3H), 1.57 (m, 2H), 3.9 (s, 3H), 4.05(t, 2H), 4.8 (s, 2H), 6.9-7.04 (m, 7H), 7.18 (s, 1H), 7.23 (d, 2H), 7.72 (s, 1H), 8.3 (s, 1H), 9.34 (s, 1H)	100°C/5h/1-PrOH/HCl	m/e 333.51 (M^++H	DMA/ KOtBu, /150°C/0.5h	m/e 303.58 (M^++H)	Hydrogen/ 5% Pd/C/ EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
151	m/e 519,521 (M^++H)	(d-6-DMSO, d values) 3.43 (q, 2H), 3.6 (t, 2H), 3.9 (s, 3H), 4.5(s, 2H), 6.93-7.15 (m, 6H), 7.16 (s, 1H), 7.24 (d, 2H), 7.73 (s, 1H), 7.89 (t, 1H), 8.3 (s, 1H), 9.35 (s, 1H)	100°C/5h/1-PrOH/HCl	m/e 333.51 (M^++H	DMA/ KOtBu, /150°C/0.5h	m/e 303.58 (M^++H)	Hydrogen/ 5% Pd/C/ EtOAc
152	m/e 500.52 (M^++H)	(d-6-DMSO, d values) 3.16 (q, 2H), 3.4 (t, 2H), 3.9 (s, 3H), 4.47(s, 2H), 4.7(t, 1H), 6.94-7.17 (m, 7H), 7.18 (s, 1H), 7.24 (d, 2H), 7.57 (t, 1H), 7.74 (s, 1H), 8.31 (s, 1H), 9.34 (s, 1H)	100°C/5h/1-PrOH/HCl	m/e 333.51 (M^++H	DMA/K-butoxide/ 150°C/0.5h	m/e 303.58 (M^++H)	Hydrogen/ 5% Pd/C/EtOAc
153	m/e 515.44 (M^++H)	(d-6-DMSO, d values) 3.16 (q, 2H), 3.39 (t, 2H), 3.98 (s, 6H), 3.95 (v.br. s, 1H), 4.48(s, 2H), 6.95-7.22 (m, 6H), 7.41 (s, 1H), 7.44 (d, 2H), 7.6 (t, 1H), 8.13 (s, 1H), 8.9 (s, 1H), 11.07 (br.s, 1H)	100°C/2h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
156	m/e 470 (M^++H)	(d-6-DMSO, d values) 2.60 (s, 3H), 4.00 (s, 6H), 6.20 (broad s, 1H), 6.50 (dd, 1H), 7.00 (d, 1H), 7.10 (d, 2H), 7.20 (t, 1H), 7.35 (t, 1H), 7.45 (d, 2H), 7.45 (s, 1H), 8.15 (s, 1H), 8.80 (broad s, 1H), 8.90 (s, 1H), 11.10 (broad s, 1H)	110°C/18h/1-PrOH			m/e 256 (M-H)	H_2, Pd/C, EtOAc
157	m/e 482 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 7.00 (broad s, 1H), 7.05 (m, 2H), 7.25 (d, 2H), 7.50 (m, 4H), 8.25 (s, 1H), 8.95 (s, 1H), 11.40 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 270 (M^++H)	H_2, Pd/C, EtOAc
158	m/e 474 (M^++H)	(d-6-DMSO, d values) 3.80 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 6.80 (d, 1H), 7.15 (t, 1H), 7.20 (d, 2H), 7.50 (m, 4H), 8.20 (s, 1H), 8.95 (s, 1H), 11.25 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 262 (M^++H)	H_2, Pd/C, EtOAc
159	m/e 458 $(M+H)^+$	(d-6-DMSO, d values) 3.61 (m, 2H), 4.00 (bs, 8H), 6.98 (m, 4H), 7.17 (m, 2H), 7.42 (m, 3H), 8.13 (s, 1H), 8.90 (s, 1H)	100°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
160	m/e 452 (M^++H)	($CDCl_3$, d values) 3.80 (s, 3H), 4.00 (s, 3H), 6.75 (s, 1H), 6.80 (broad s, 1H), 6.95 (m, 4H), 7.10 (d, 2H), 7.35 (s, 1H), 8.60 (s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 240 (M^++H)	H_2, Pd/C, EtOAc
161	m/e 485 $(M+H)^+$	(d-6-DMSO, d values) 2.62 (d, 3H), 3.97 (s, 6H), 4.33 (s, 2H), 7.08 (m, 6H), 7.42 (m, 3H), 7.52 (m, 1H), 8.13 (s, 1H), 8.92 (s, 1H)	100°C/18h/1-PrOH				
162	m/e 482 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 7.10 (d, 1H), 7.15 (d, 2H), 7.25 (m, 1H), 7.40 (td, 1H), 7.50 (m, 4H), 8.20 (s, 1H), 8.95 (s, 1H), 11.30 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 270 (M^++H)	H_2, Pd/C, EtOAc
163	m/e 529 (M^++H)	(d-6-DMSO, d values) 2.33 (m, 2H), 3.12 (m, 2H), 3.50 (m, 4H), 3.83 (t, 2H), 3.99 (s, 2H), 4.02 (s, 3H), 4.36 (t, 2H), 7.12 (m, 4H), 7.26 (m, 2H), 7.48 (d, 2H), 7.52 (s, 1H), 8.18 (s, 1H), 8.88 (s, 1H), 10.92 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 48 h				

WO 00/68201 PCT/GB00/01697

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
164	m/e 529 (M^++H)	(d-6-DMSO, d values) 2.34 (m, 2H), 3.12 (m, 2H), 3.49 (m, 4H), 3.83 (t, 2H), 4.00 (m, 5H), 4.32 (t, 2H), 7.15 (m, 3H), 7.27 (m, 1H), 7.50 (m, 4H), 8.16 (s, 1H), 8.88 (s, 1H), 10.94 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 48h				
165	m/e 550 (M^++H)	(d-6-DMSO, d values) 2.28 (s, 3H), 2.34 (m, 2H), 3.12 (m, 2H), 3.29 (m, 2H), 3.50 (m, 2H), 3.84 (t, 2H), 4.02 (m, 5H), 4.33 (t, 2H), 7.02 (d, 1H), 7.18 (m, 1H), 7.29 (m, 2H), 7.53 (d, 2H), 7.64 (m, 1H), 7.92 (m, 1H), 8.27 (s, 1H), 8.88 (s, 1H), 11.00 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 48h				
166	m/e 480 (M^++H)	(d-6-DMSO@373K, d values) 2.60 (s, 3H), 4.00 (s, 6H), 7.05 (d, 2H), 7.10 (d, 1H), 7.35 (t, 1H), 7.40 (d, 2H), 7.55 (s, 1H), 7.55 (t, 1H), 7.95 (dd, 1H), 8.15 (s, 1H), 8.70 (s, 1H)	110°C/18h/1-PrOH		KOtBu, DMF	m/e 268 (M^++H)	$Na_2S_2O_4$, EtOH, H_2O

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
167	m/e 466 (M^++H)	($CDCl_3$, d values) 3.80 (s, 3H), 4.00 (s, 3H), 7.00 (s, 1H), 7.05 (d, 2H), 7.05 (s, 1H), 7.20 (d, 2H), 7.20 (d, 1H), 7.40 (s, 1H), 7.50 (t, 1H), 7.70 (t, 1H), 7.80 (d, 1H), 8.45 (s, 1H), 8.60 (s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 254 (M^++H)	H_2, Pd/C, EtOAc
169	m/e 611 $(M+H)^+$	(d-6-DMSO, d values) 0.91 (t, 3H), 1.53 (m, 2H), 2.33 (m, 2H), 3.08 (m, 2H), 3.26 (m, 2H), 3.35-3.50 (m, 2H (under H_2O signal)), 3.68 (s, 2H), 3.81 (m, 2H), 3.95 (m, 4H), 3.99 (s, 3H), 4.29 (m, 2H), 6.87 (d, 1H), 7.04 (d, 2H), 7.10 (m, 1H), 7.26 (m, 1H), 7.37 (d, 1H), 7.46 (d, 2H), 7.54 (s, 1H), 8.20 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH				
171	m/e 480 (M^++H)	(d-6-DMSO, d values) 2.40 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 7.05 (d, 1H), 7.10 (d, 2H), 7.35 (t, 1H), 7.50 (d, 2H), 7.50 (s, 1H), 7.60 (t, 1H), 8.10 (d, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.25 (broad s, 1H)	110°C/18h/1-PrOH.		KOtBu, DMF	m/e 268 (M^++H)	$Na_2S_2O_4$, EtOH, H_2O

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
172	m/e 483 (M^++H)	(d-6-DMSO, d values) 3.05 (m, 4H), 3.65 (m, 4H), 4.00 (s, 3H), 4.00 (s, 3H), 6.45 (dd, 1H), 6.55 (d, 1H), 6.65 (dd, 1H), 7.15 (d, 2H), 7.20 (t, 1H), 7.45 (d, 2H), 7.45 (s, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.25 (broad s, 1H)	110°C/5h/1-PrOH	m/e 301 (M^++H	KOtBu, DMA	m/e 271 (M^++H)	H_2, Pd/C, EtOAc
173	m/e 569 $(M+H)^+$	(d-6-DMSO, d values) 1.18 (t, 3H), 2.31 (m, 2H), 3.05 (m, 4H), 3.29 (m, 2H), 3.35-3.50 (m, 2H (under H_2O signal)), 3.63 (s, 2H), 3.81 (m, 2H), 3.97 (m, 5H), 4.28 (m, 2H), 6.86 (d, 1H), 7.06 (d, 2H), 7.12 (m, 1H), 7.24 (m, 1H), 7.37 (m, 1H), 7.43 (d, 2H), 7.46 (s, 1H), 8.10 (s, 1H), 8.82 (bs, 1H), 10.80 (bs, 1H)	100°C/18h/1-PrOH				
174	m/e 455 (M^++H)	(d-6-DMSO, d values) 2.00 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 6.90 (dd, 1H), 7.05 (m, 2H), 7.10 (d, 2H), 7.45 (d, 2H), 7.50 (s, 1H), 7.95 (d, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 9.40 (broad s, 1H), 11.30 (broad s, 1H)	110°C/18h/1-PrOH.	m/e 273 (M^++H	Ac_2O, DMA	m/e 243 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
178	m/e 648.5 $(M-H^+)^-$	(d-6-DMSO, d values) 2.32 (m, 2H), 2.89 (s, 3H), 3.09 (m, 2H), 3.28 (m, 4H), 3.50 (m, 2H), 3.82 (m, 2H), 3.96 (m, 2H), 4.00 (s, 3H), 4.05 (m, 2H), 4.30 (m, 2H), 6.99 (m, 4H), 7.18 (m, 3H), 7.39 (d, 2H), 7.50 (s, 1H), 8.16 (s, 1H), 8.86 (s, 1H)	100°C/18h/1-PrOH		RT/18h/ $MeSO_2Cl$/ $^iPr_2NEt$/ DCM	m/e 323 $(M+H)^+$	RT/18h/H_2 /5% Pd/C/EtOAc
179	m/e 683 $(M+H)^+$	(d-6-DMSO, d values) 0.95 (t, 6H), 2.32 (m, 2H), 2.74 (s, 3H), 3.01 (q, 4H), 3.08 (m, 2H), 3.26 (m, 2H), 3.33 (t, 2H), 3.47 (m, 2H), 3.79 (m, 2H), 3.95 (m, 2H), 3.99 (s, 3H), 4.10 (t, 2H), 4.29 (m, 2H), 6.95 (m, 3H), 7.03 (m, 1H), 7.18 (m, 2H), 7.39 (d, 2H), 7.51 (s, 1H), 8.18 (s, 1H), 8.92 (s, 1H)	100°C/18h/1-PrOH	m/e 388 $M+H)^+$	RT/18h/ DEAD/Ph_3/ DCM	m/e 358 $(M+H)^+$	RT/18h/5 %Pd/C/H_2/ EtOAc
180	m/e 626 $(M+H)^+$	(d-6-DMSO, d values) 1.69 (m, 2H), 1.78 (s, 3H), 2.34 (m, 2H), 3.02 (m, 2H), 3.08 (m, 2H), 3.26 (m, 2H), 3.47 (m, 2H), 3.79 (m, 2H), 3.95 (m, 2H), 3.97 (m, 2H), 4.00 (s, 3H), 4.30 (m, 2H), 6.98 (m, 3H), 7.05 (m, 1H), 7.39 (d, 2H), 7.53 (s, 1H), 7.84 (m, 1H), 8.24 (s, 1H), 8.95 (s, 1H)	100°C/18h/1-PrOH	m/e 331 $M+H)^+$	RT/2h/ acetyl chloride/ iPr_2NEt/ DCM	m/e 301 $(M+H)^+$	RT/18h/H_2 /5%Pd/C/EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
181	m/e 654 $(M+H)^+$	(d-6-DMSO, d values) 0.95 (d, 6H), 1.71 (m, 2H), 2.31 (m, 3H), 3.04 (m, 4H), 3.28 (m, 2H), 3.47 (m, 2H), 3.81 (m, 2H), 3.95 (m, 2H), 3.99 (m, 5H), 4.29 (m, 2H), 6.99 (m, 3H), 7.04 (m, 1H), 7.14 (m, 2H), 7.40 (d, 2H), 7.53 (s, 1H), 7.71 (m, 1H), 8.26 (s, 1H), 8.95 (s, 1H)	100°C/18h/1-PrOH	m/e 359 $M+H)^+$	RT/2h/ iso-butyryl chloride/i-Pr_2NEt DCM	m/e 329 $(M+H)^+$	RT/18h/H_2 /5%Pd/C/EtOAc
182	m/e 639 $(M+H)^+$	(d-6-DMSO, d values) 2.31 (m, 2H), 3.06 (m, 2H), 3.12 (m, 2H), 3.26 (m, 4H), 3.47 (m, 2H), 3.80 (m, 2H), 3.95 (m, 2H), 3.99 (s, 3H), 4.04 (t, 2H), 4.30 (m, 2H), 6.97 (m, 3H), 7.08 (m, 1H), 7.18 (d, 2H), 7.38 (d, 2H), 7.50 (s, 1H), 8.17 (s, 1H), 8.87 (s, 1H)	100°C/18h/1-PrOH	m/e 344 $M+H)^+$	RT/18h/ DEAD/PPh_3/ DCM	m/e 314 $(M+H)^+$	RT/18h/H_2 /5%Pd/C/EtOAc
184	m/e 640.6 $(M+H)^+$	(d-6-DMSO, d values) 0.96 (d, 6H), 2.34 (m, 3H), 3.11 (m, 2H), 3.29 (m, 4H), 3.50 (m, 2H), 3.80 (m, 2H), 3.97 (m, 7H), 4.29 (m, 2H), 6.99 (m, 4H), 7.17 (m, 2H), 7.59 (d, 2H), 7.49 (s, 1H), 7.79 (s, 1H), 8.13 (s, 1H), 8.86 (s, 1H)	100°C/18h/1-PrOH		RT/18h/Iso butyryl chloride/i-Pr_2NEt/ DCM	m/e 315.5 $(M+H)^+$	RT/18h/H_2 /5% Pd/C/EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
185	m/e 601.5 $(M+H)^+$	(d-6-DMSO, d values) 3.09 (m, 2H), 3.67 (s, 3H), 4.97 (m, 8H), 7.00 (m, 4H), 7.14 (m, 2H), 7.40 (m, 3H), 7.50 (m, 1H), 7.72 (d, 2H), 8.05 (s, 1H), 8.88 (s, 1H)	100°C/18h/1-PrOH		RT/18h/ Methyl imid-azole $MeSO_2Cl$ $^iPr_2NEt$/ DCM	m/e 357.5 $(M-H^+)^-$	RT/18h/H_2 /5% Pd/C/EtOAc
186	m/e 535.5 $(M+H)^+$	(d-6-DMSO, d values) 2.89 (s, 3H), 3.26 (m, 2H), 3.97 (m, 6H), 4.05 (m, 2H), 7.00 (m, 4H), 7.17 (m, 3H), 7.41 (m, 3H), 8.09 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH				
187	m/e 483 (M^+H)	(d-6-DMSO, d values) 3.05 (m, 4H), 3.65 (m, 4H), 4.00 (s, 3H), 4.00 (s, 3H), 6.45 (dd, 1H), 6.55 (t, 1H), 6.70 (dd, 1H), 7.15 (d, 2H), 7.20 (t, 1H), 7.45 (d, 2H), 7.45 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.30 (broad s, 1H)	110°C/5h/1-PrOH	m/e 301 $(M^+H$	KOtBu, DMA	m/e 271 (M^+H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
188	m/e 481 (M^++H)	(d-6-DMSO, d values) 1.40 (broad s, 2H), 1.55 (broad s, 4H), 3.00 (broad s, 4H), 4.00 (s, 3H), 4.00 (s, 3H), 7.00 (m, 4H), 7.20 (m, 2H), 7.40 (d, 2H), 7.45 (s, 1H), 8.20 (s, 1H), 8.85 (s, 1H), 11.10 (broad s, 1H)	110°C/5h/1-PrOH	m/e 299 (M^++H	KOtBu, DMA	m/e 269 (M^++H)	H_2, Pd/C, EtOAc
189	m/e 467 (M^++H)	(d-6-DMSO, d values) 1.80 (m, 4H), 3.25 (m, 4H), 3.95 (s, 6H), 6.75 (t, 1H), 6.90 (m, 4H), 7.05 (t, 1H), 7.40 (d, 2H), 7.45 (s, 1H), 8.20 (s, 1H), 8.85 (s, 1H), 11.15 (broad s, 1H)	110°C/5h/1-PrOH	m/e 285 (M^++H	KOtBu, DMA	m/e 255 (M^++H)	H_2, Pd/C, EtOAc
190	m/e 525 $(M+H)^+$	(d-6-DMSO, d values) 3.13 (m, 2H), 3.30 (m, 4H), 3.97 (d, 6H), 4.04 (m, 2H), 6.98 (m, 3H), 7.06 (m, 1H), 7.18 (m, 2H), 7.37 (m, 2H), 8.06 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
191	m/e 548 $(M+H)^+$	(d-6-DMSO, d values) 1.79 (m, 2H), 2.84 (s, 3H), 2.97 (m, 2H), 3.97 (s, 6H), 4.03 (m, 2H), 6.97 (m, 4H), 7.05 (m, 1H), 7.18 (m, 2H), 7.42 (m, 3H), 8.13 (s, 1H), 8.91 (s, 1H)	100°C/18h/1-PrOH	m/e 367 $M+H)^+$	RT/2h/ $MeSO_2$-Cl /iPr_2NEt/ DCM	m/e 336 $(M+H)^+$	RT/18h/H_2 /5%Pd/C/EtOAc
192	m/e 541 $(M+H)^+$	(d-6-DMSO, d values) 0.96 (d, 6H), 1.71 (m, 2H), 2.31 (m, 1H), 3.05 (m, 2H), 3.97 (s, 8H), 6.97 (m, 3H), 7.04 (m, 1H), 7.16 (m, 2H), 7.40 (m, 3H), 7.71 (bs, 1H), 8.11 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH				
193	m/e 660 $(M+H)^+$	(d-6-DMSO, d values) 1.79 (m, 2H), 2.31 (m, 2H), 2.84 (s, 3H), 2.98 (m, 2H), 3.10 (m, 2H), 3.28 (m, 2H), 3.4-3.6 (m, 2H (under H_2O peak)), 3.78 (m, 2H), 3.98 (bs, 5H), 4.02 (m, 2H), 4.28 (m, 2H), 6.97 (m, 4H), 7.05 (m, 1H), 7.16 (m, 2H), 7.37 (d, 2H), 7.46 (s, 1H), 8.10 (s, 1H), 8.84 (s, 1H)	100°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
195	m/e 630 $(M+H)^+$	(d-6-DMSO, d values) 1.75 (t, 2H), 2.27 (s, 3H), 2.53 (s, 3H), 2.87 (m, 2H), 3.98 (m, 8H), 6.95 (m, 3H), 7.01 (m, 1H), 7.13 (m, 2H), 7.38 (m, 3H), 7.87 (m, 1H), 8.06 (s, 1H), 8.85 (s, 1H)	100°C/18h/1-PrOH	m/e 448 $M+H)^+$	RT/18h/ DMSO chloride/ iPr_2NEt/ DCM	m/e 418 $(M+H)^+$	80°C/18h/ $SnCl_2.2H_2O$/EtOAc
196	m/e 412 (M^+H)	(d-6-DMSO, d values) 2.30 (s, 3H), 4.00 (s, 6H), 6.80 (d, 1H), 6.80 (s, 1H), 6.95 (d, 1H), 7.15 (d, 2H), 7.25 (t, 1H), 7.45 (d, 2H), 7.45 (s, 1H), 8.15 (s, 1H), 8.90 (s, 1H) 11.10 (broad s, 1H)	110°C/18h/1-PrOH	m/e 230 $(M^+H$	KOtBu, DMA	m/e 200 (M^+H)	H_2, Pd/C, EtOAc
198	m/e 427	(d-6-DMSO, d values) 2.65 (s, 3H), 4.00 (s, 3H), 4.00 (s, 3H), 6.60 (t, 1H), 6.75 (m, 2H), 7.00 (m, 1H), 7.05 (d, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH	m/e 243 (M-H)	HCHO, AcOH, $BH_3.SMe_2$, THF	m/e 215 (M^+H)	H_2, Pd/C, EtOAc
199	m/e 441 (M^+H)	(d-6-DMSO, d values) 1.15 (t, 3H), 3.10 (q, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 6.60 (t, 1H), 6.80 (m, 2H), 7.00 (m, 1H), 7.05 (d, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.85 (s, 1H), 11.15 (broad s, 1H)	110°C/12h/1-PrOH	m/e 259 $(M^+H$	BH_3. SMe_2, THF	m/e 229 (M^+H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
200	m/e 429.4 $(M+H)^+$.	(d-6-DMSO, δ values) 3.76 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 6.94 - 7.00 (m, 2H), 7.03 - 7.09 (m, 2H), 7.14 (d, 1H), 7.47 (s, 1H), 7.94 (dd, 1H), 8.21 (s, 1H), 8.27 (d, 1H), 8.93 (s, 1H), 11.23 (bs, 1H)	95°C/16h/1-PrOH	m/e 247.2 $M+H)^+$	115°C/ 2h/ K_2CO_3/ DMA	m/e 217.2 $(M+H)^+$	10% Pd on C/EtOAc
201	m/e 429.4 $(M+H)^+$	(d-6-DMSO, δ values) 3.74 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 6.66 - 6.72 (m, 2H), 6.77 (dd, 1H), 7.19 (d, 1H), 7.31 (t, 1H), 7.48 (s, 1H), 7.98 (dd, 1H), 8.21 (s, 1H), 8.32 (d, 1H), 8.94 (s, 1H), 11.24 (bs, 1H)	95°C/16h/ 1-PrOH	m/e 247.2 $M+H)^+$	115°C/ 2h/ K_2CO_3/ DMA	m/e 217.2 $(M+H)^+$.	10% Pd on C/EtOAc
202	m/e 429.4 $(M+H)^+$	(d-6-DMSO, δ values) 3.68 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.98 (m, 1H), 7.09 - 7.16 (m, 3H), 7.21 (m, 1H), 7.48 (s, 1H), 7.92 (dd, 1H), 8.17 - 8.22 (m, 2H), 8.94 (s, 1H), 11.14 (bs, 1H)	95°C/16h/ 1-PrOH		115°C/ 2h/ K_2CO_3/ DMA		10% Pd on C/EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
203		(d-6-DMSO, δ values) 3.67 (s, 3H), 3.99 (s, 3H), 7.00 (t, 1H), 7.12 - 7.29 (m, 3H), 7.42 (s, 1H), 8.16 (s, 1H), 8.77 (s, 2H), 8.95 (s, 1H)	100°C/16h/ 1-PrOH	m/e 247 $M+H)^+$	RT/1h/ KOtBu/ MeO-phenol/ DMA 135°C/ 5h/	m/e 217.9 $(M+H)^+$	RT/4h/5% Pd on C/H_2/ EtOAc
212	m/e 467.4 $(M+H)^+$	(d-6-DMSO, δ values) 3.99 (s, 3H), 4.00 (s, 3H), 7.32 (d, 1H), 7.44 - 7.49 (m, 2H), 7.57 (d, 1H), 7.68 (t, 1H), 8.03 (dd, 1H), 8.19 (s, 1H), 8.35 (d, 1H), 8.94 (s, 1H)	100°C/7h/1-PrOH				
217	m/e 542 (M^+H)	(d-6-DMSO, d values) 2.34 (m, 2H), 3.14 (m, 2H), 3.50 (m, 4H), 3.76 (s, 3H), 3.82 (m, 2H), 3.99 (s, 2H), 4.02 (s, 3H), 4.32 (t, 2H), 6.71 (m, 2H), 6.80 (m, 1H), 7.20 (d, 2H), 7.33 (t, 1H), 7.50 (s, 1H), 7.96 (m, 1H), 8.16 (s, 1H), 8.32 (d, 1H), 8.81 (s, 1H), 10.86 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 3 h				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
219	m/e 507.4 $(M+H)^+$		RT/15min/ NaH/ DMA RT2h		100°C/ 3h/ K_2CO_3/ DMA	m/e 219.3 $(M+H)^+$	RT/5h/10 %Pd on C/H_2/ EtOAc
220		(d-6-DMSO, δ values) 3.68 (s, 3H), 4.00 (s, 3H), 6.98 (t, 1H), 7.08 - 7.16 (m, 3H), 7.22 (m, 1H), 7.52 (s, 1H), 7.88 (dd, 1H), 7.96 (s, 1H), 8.17 (dd, 1H), 8.91 (s, 1H), 10.80 (bs, 1H)	100°C/16h/1 -PrOH				
222	m/e 519.4 (M^+H)		RT/15min/ NaH//DMA then ii) RT2h		100°C/ 3h/ K_2CO_3/ DMA	m/e 230.6 (M^+H)	RT/5h/10 %Pd on C/H_2/ EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
226	m/e 528 (M^++H)	(d-6-DMSO, d values) 3.58 (m, 4H), 3.70 (m, 2H), 3.76 (s, 3H), 3.86 (m, 2H), 4.00 (m, 2H), 4.03 (s, 3H), 4.70 (t, 2H), 6.71 (m, 3H), 6.80 (m, 1H), 7.20 (d, 1H), 7.34 (t, 1H), 7.54 (s, 1H), 7.97 (m, 1H), 8.21 (s, 1H), 8.33 (d, 1H), 8.86 (s, 1H), 10.95 (broad, 1H), 11.28 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 6 h			
258	m/e 392 (M^++H)	($CDCl_3$, d values) 2.10 (m, 2H), 3.65 (s, 3H), 3.95 (m, 4H), 4.00 (s, 3H), 4.95 (m, 1H), 6.90 (d, 2H), 6.90 (s, 1H), 7.15 (d, 2H), 7.25 (s, 1H), 7.35 (s, 1H), 8.60 (s, 1H)	110°C/5h/1-PrOH		KOtBu, DMA	m/e 180 (M^++H)	H_2, Pd/C, EtOAc
259	m/e 406 (M^++H)	(d-6-DMSO, d values) 1.60 (m, 2H), 2.00 (m, 2H), 3.50 (m, 2H), 3.85 (m, 2H), 4.00 (s, 6H), 4.65 (m, 1H), 7.05 (d, 2H), 7.35 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (broad s, 1H)	110°C/3h/1-PrOH		KOtBu, DMA	m/e 194 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
261	m/e 433, 435 $(M+H)^+$	(d-6-DMSO, d values) 3.98 (d, 6H), 7.2 (m, 2H), 7.28 (m, 2H) 7.42 (m, 3H), 8.10 (m, 3H), 8.95 (s, 1H)	85°C/18h/ DME			m/e 220 $(M+H)^+$	iKF-Al_2O_3, 18-C-6, DMSO then TFA, Et_3SiH
262	m/e 397 $(M+H)^+$	(d-6-DMSO, d values) 3.90 (s, 3H), 3.95 (s, 3H), 6.98 (d, 1H), 7.16 (m, 1H) 7.19 (d, 1H), 7.28 (d, 1H), 7.31 (m, 1H), 7.74 (s, 1H), 7.82 (m, 1H), 8.19 (m, 1H), 8.41 (s, 1H), 9.42 (s, 1H)	100°C/24h/1 -PrOH		m/e 187 $(M+H)^+$	TFA, Et_3SiH	
263	m/e 424 $(M+H)^+$	(d-6-DMSO, d values) 3.98 (d, 6H), 7.31 (m, 2H), 7.38 (d, 2H) 7.42 (s, 1H), 7.51 (d, 2H), 8.11 (s, 1H), 8.4 (m, 2H), 8.95 (1H, s).	100°C/18h/1 -PrOH			m/e $(M+H)^+$	TFA, Et_3SiH
264	m/e 424 $(M+H)^+$	(d-6-DMSO, d values) 3.98 (d, 6H), 7.32 (m, 2H), 7.41 (s, 1H) 7.50 (m, 2H), 7.61 (d, 1H), 8.12 (s, 1H), 8.42 (d, 1H), 8.96 (s, 1H)	100°C/18h/1 -PrOH			m/e 212 $(M+H)^+$	TFA, Et_3SiH

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
265	m/e 415 $(M+H)^+$	(d-6-DMSO, d values) 4.00 (d, 6H), 7.18 (m, 2H), 7.22 (m, 2H) 7.36 (m, 1H), 7.46 (d, 2H), 7.50 (s, 1H), 8.10 (s, 1H), 8.38 (dd, 1H), 8.90 (s, 1H)	100°C/18h/1-PrOH			m/e $(M+H)^+$	TFA, Et_3SiH
266	m/e 400.3 $(M+H)^+$.	(d-6-DMSO, δ values) 3.98 (s, 3H), 4.00 (s, 3H), 7.34 (d, 1H), 7.50 (s, 1H), 7.54 (dd, 1H), 7.68 (dd, 1H), 8.02 (dd, 1H), 8.26 (s, 1H), 8.31 (d, 1H), 8.46 (d, 1H), 8.50 (d, 1H), 8.92 (s, 1H)	100°C/7h/1-PrOH				
267	m/e 440 $(M+H)^+$	(d-6-DMSO, d values) 3.99 (ap.d, 6H), 7.08 (d, 1H), 7.42 (s, 1H) 7.52 (d, 2H), 7.70 (d, 2H), 8.00 (m, 2H), 8.80 (m, 1H), 8.90 (s, 1H)	100°C/18h/1-PrOH				
268	m/e 405 $(M+H)^+$	(d-6-DMSO, d values) 3.99 (s, 6H), 7.22 (d, 1H), 7.32 (d, 1H) 7.46 (m, 3H), 7.52 (d, 2H), 8.15 (s, 1H), 8.95 (s, 1H)	100°C/18h/1-PrOH				
269	m/e 434, 436 $(M+H)^+$	(d-6-DMSO, d values) 3.98 (ap.d, 6H), 7.40 (m, 3H), 7.53 (d, 2H) 8.12 (s, 1H), 8.20 (d, 1H), 8.25 (d, 1H), 8.96 (s, 1H)	100°C/18h/1-PrOH		K_2CO_3, DMA		$SnCl_2.2H_2O$, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
270	m/e 400 $(M+H)^+$	(d-6-DMSO, d values) 4.00 (s, 6H), 7.30 (d, 1H), 7.33 (d, 2H), 7.45 (m, 2H), 7.52 (s, 1H), 8.18 (s, 1H), 8.66 (d, 2H), 8.96 (s, 1H)	100°C/18h/1-PrOH	m/e 218 $M+H)^+$	K_2CO_3, DMA		10%Pd/C, EtOAc
271	m/e 446 $(M+H)^+$	(d-6-DMSO, d values) 2.40 (s, 3H), 4.00 (s, 6H), 6.78 (d, 1H), 7.40 (bd, 2H), 7.51 (s, 1H), 7.57 (d, 2H), 8.19 (s, 1H), 8.53 (d, 1H), 8.98 (s, 1H)	100°C/18h/1-PrOH	m/e 264 $M+H)^+$	K_2CO_3, DMA		$SnCl_2.2H_2O$, EtOAc
272	m/e 481 $(M+H)^+$	(d-6-DMSO, d values) 3.97 (s, 3H), 5.29 (s, 2H), 7.29 (d, 1H), 7.33 (d, 1H), 7.35 (m, 2H), 7.42 (m, 2H), 7.43-7.54 (m, 6H), 8.41 (s, 1H), 8.95 (s, 1H)	100°C/18h/1-PrOH			m/e 193 $(M+H)^+$	120°C/18h/KOH/DMA
287	m/e 446 (M^+H)	(d-6-DMSO, d values) 3.60 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 6.55 (dd, 1H), 6.95 (td, 1H), 7.00 (d, 1H), 7.05 (d, 1H), 7.10 (td, 1H), 7.15 (td, 1H), 7.45 (s, 1H), 7.60 (dd, 1H), 8.00 (s, 1H), 9.00 (s, 1H), 10.90 (broad s, 1H)	110°C/60h/1-PrOH	m/e 264 $M^+H)$	KOtBu, DMA	m/e 234 (M^+H)	$SnCl_2.2H_2O$, EtOAc
288	m/e 477 $(M+H)^+$	(d-6-DMSO, d values) 1.23 (t, 3H), 4.00 (s, 3H), 4.20 (q, 2H), 5.06 (s, 2H), 7.26 (d, 1H), 7.33 (m, 3H), 7.50 (m, 4H), 8.16 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
290	m/e 493 (M^++H)	(d-6-DMSO, d values), 3.36 (m, 6H), 3.77 (m, 4H), 4.33 (m, 4H), 7.27 (d, 1H), 7.33 (d, 1H), 7.48 (m, 2H), 7.52 (m, 3H), 8.21 (s, 1H), 8.91 (s, 1H), 11.12 (broad, 1H)	EtOH / reflux / 18 h				
294	m/e 511 $(M+H)^+$	(d-6-DMSO, d values) 2.33 (m, 2H), 3.08 (m, 2H), 3.28 (m, 2H), 3.47 (m, 2H), 3.81 (m, 2H), 3.93 (m, 2H), 3.99 (s, 3H), 4.29 (m, 2H), 7.01 (d, 1H), 7.14 (m, 1H), 7.26 (d, 2H), 7.34 (d, 2H), 7.54 (s, 1H), 7.85 (m, 1H), 8.18 (s, 1H), 8.91 (s, 1H)	100°C/18h/1 -PrOH				
295	m/e 421 (M^++H)	(d-6-DMSO, d values) 3.90 (s, 3H), 3.95 (s, 3H), 7.25 (d, 2H), 7.40 (s, 1H), 7.65 (m, 4H), 7.75 (d, 1H), 8.60 (s, 1H), 9.60 (broad s, 1H)	110°C/18h/1 -PrOH		KOtBu, DMA	m/e 209 (M^++H)	$SnCl_2.2H_2$ 0, HCl, MeOH,
296	m/e 434 (M-H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 7.35 (d, 2H), 7.40 (d, 2H), 7.50 (s, 1H), 7.55 (s, 1H), 8.25 (s, 1H), 8.95 (s, 1H), 11.40 (broad s, 1H)	110°C/18h/1 -PrOH/HCl			m/e 224 (M^++H)	$SnCl_2.2H_2$ 0HCl, MeOH,

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
297	m/e 390 (M^++H)	(d-6-DMSO, d values) 1.60 (m, 2H), 1.70 (m, 4H), 1.90 (m, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 4.85 (m, 1H), 7.00 (d, 2H), 7.35 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (broad s, 1H)	110°C/5h/1-PrOH	m/e 208 (M^++H	KOtBu, DMA	m/e 178 (M^++H)	H_2, Pd/C, EtOAc
298	m/e 404 (M^++H)	(d-6-DMSO, d values) 1.40 (m, 6H), 1.70 (m, 2H), 1.95 (m, 2H), 4.00 (s, 6H), 4.40 (m, 1H), 7.00 (d, 2H), 7.35 (d, 2H), 7.45 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.15 (broad s, 1H)	110°C/3h/1-PrOH		KOtBu, DMA	m/e 192 (M^++H)	H_2, Pd/C, EtOAc
299	m/e 500 $(M+H)^+$	(d-6-DMSO, d values) 2.83 (s, 3H), 2.99 (s, 3H), 3.98 (s, 6H), 4.96 (s, 2H), 7.10 (m, 1H), 7.20 (d, 2H), 7.42 (m, 1H), 7.48 (m, 3H), 7.69 (m, 1H), 8.16 (s, 1H), 8.95 (s, 1H)	100°C/18h/1-PrOH				
300	m/e 391 $(M+H)^+$	(d-6-DMSO, d values) 3.90 (s, 3H), 7.21 (d, 2H), 7.30 (m, 3H), 7.37 (m, 2H), 7.69 (s, 1H), 8.40 (s, 1H)	75°C/2h/TFA thioanisole				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
303	m/e 505 (M^++H)	(d-6-DMSO, d values) 1.40 (s, 9H), 1.55 (m, 2H), 1.90 (m, 2H), 3.2 (m, 2H), 3.65 (m, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 4.60 (m, 1H), 7.05 (d, 2H), 7.35 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.85 (s, 1H), 11.25 (broad s, 1H)	110°C/18h/1-PrOH				
304	m/e 432 (M^++H)	(d-6-DMSO, d values) 2.45 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 5.15 (s, 2H), 6.95 (s, 1H), 7.20 (s, 4H), 7.30 (s, 1H), 7.35 (s, 1H), 7.65 (s, 1H), 8.45 (s, 1H), 9.40 (broad s, 1H)	110°C/18h/1-PrOH/HCl			m/e 220 (M^++H)	$SnCl_2.2H_2$0 HCl, MeOH
305	m/e 386 (M^++H)	(d-6-DMSO, d values) 3.85 (s, 3H), 3.95 (s, 3H), 5.20 (s, 2H), 6.90 (s, 1H), 7.15 (s, 1H), 7.20 (d, 2H), 7.25 (s, 1H), 7.30 (s, 1H), 7.35 (s, 1H), 7.70 (d, 2H), 8.45 (s, 1H), 9.40 (broad s, 1H)	110°C/18h/1-PrOH/HCl			m/e 174 (M^++H)	$SnCl_2.2H_2$0HCl, MeOH
306	m/e 454 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 5.30 (s, 2H), 7.25 (d, 2H), 7.30 (t, 1H), 7.55 (m, 5H), 8.25 (s, 1H), 8.95 (s, 1H), 11.35 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 242 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
307	m/e 389 (M^++H)	(d-6-DMSO, d values) 3.95 (s, 3H), 4.00 (s, 3H), 6.35 (d, 1H), 7.40 (d, 2H), 7.50 (s, 1H), 7.55 (d, 2H), 8.25 (s, 1H), 8.80 (d, 1H), 8.95 (s, 1H), 11.40 (broad s, 1H)	90°C/18h/1-PrOH		KOtBu, DMA		$SnCl_2$. $2H_2O$ HCl, MeOH
308	m/e 438 (M^++H)	(d-6-DMSO, d values) 2.00 (m, 2H), 2.75 (t, 2H), 2.90 (t, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 6.80 (d, 1H), 7.00 (d, 2H), 7.05 (d, 1H), 7.15 (t, 1H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH		KOtBu, DMA	m/e 226 (M^++H)	H_2, Pd/C, EtOAc
309	m/e 404 (M^++H)	(d-6-DMSO, d values) 3.95 (s, 3H), 4.00 (s, 3H), 7.45 (d, 2H), 7.55 (d, 2H), 7.60 (s, 1H), 7.80 (s, 2H), 8.40 (s, 1H), 8.95 (s, 1H), 11.70 (broad s, 1H)	110°C/18h/1-PrOH, HCl	m/e 222 (M^++H	KOtBu, DMA	m/e 192 (M^++H)	$SnCl_2$. $2H_20$, HCl, MeOH,

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
310	m/e 611 $(M+H)^+$	(d-6-DMSO, d values) 2.31 (m, 2H), 2.84 (s, 3H), 2.99 (s, 3H), 3.10 (m, 2H), 3.25-3.55 (m, 4H (under H_2O signal)), 3.80 (s, 2H), 3.96 (m, 2H), 3.98 (s, 3H), 4.31 (m, 2H), 4.95 (s, 2H), 7.09 (m, 1H), 7.17 (d, 2H), 7.41 (m, 3H), 7.50 (s, 1H), 7.68 (m, 1H), 8.16 (s, 1H), 8.87 (s, 1H)	100°C/18h/1-PrOH				
311	m/e 468 (M^+H)	(d-6-DMSO, d values) 1.40 (s, 6H), 3.05 (s, 2H), 3.95 (s, 6H), 6.80 (m, 2H), 7.00 (d, 2H), 7.05 (t, 1H), 7.40 (d, 2H), 7.50 (s, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.20 (broad s, 1H)	110°C/18h/1-PrOH			m/e 256 (M^+H)	H_2, Pd/C, EtOAc
316	m/e 419.4 $(M+H)^+$	(d-6-DMSO, δ values) 1.82 - 1.90 (m, 1H), 2.09 - 2.31 (m, 3H), 3.86 - 4.04 (m, 9H), 7.05 (d, 2H), 7.37 (d, 2H), 7.45 (s, 1H), 7.82 (s, 1H), 8.14 (s, 1H), 8.90 (s, 1H)	100°C/3h/1-PrOH	m/e 237.1 $M+H)^+$	RT/18h/ PPh_3/DEAD/THF	m/e 207.4 $(M+H)^+$.	RT/18h/10% Pd on C/EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
317	m/e 419.4 $(M+H)^+$	(d-6-DMSO, δ values) 1.80 - 1.92 (m, 1H), 2.08 - 2.30 (m, 3H), 3.85 - 4.04 (m, 9H), 7.06 (d, 2H), 7.38 (d, 2H), 7.46 (s, 1H), 7.84 (s, 1H), 8.14 (s, 1H), 8.90 (s, 1H)	100°C/3h/ 1-PrOH	m/e 237.1 $M+H)^+$	RT/18h/ PPh_3/ DEAD/ THF	m/e 207.4 $(M+H)^+$	RT/4h/10 % Pd on C/EtOAc
318	m/e 488 (M^+H)	(d-6-DMSO, d values) 1.89 (m, 2H), 2.03 (m, 2H), 3.14 (m, 2H), 3.61 (m, 2H), 3.71 (m, 2H), 4.03 (s, 3H), 4.62 (t, 2H), 7.27 (d, 1H), 7.33 (d, 1H), 7.47 (d, 1H), 7.55 (d, 1H), 7.60 (s, 1H), 8.34 (s, 1H), 8.93 (s, 1H), 11.29 (broad, 1H), 11.44 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 105 °C / 20 h				
320	m/e 504 (M^+H)	(d-6-DMSO, d values) 3.57 (m, 4H), 3.70 (m, 2H), 3.85 (m, 2H), 4.00 (m, 2H), 4.02 (s, 3H), 4.71 (t, 2H), 7.30 (m, 1H), 7.36 (m, 1H), 7.50 (m, 5H), 8.19 (s, 1H), 8.90 (s, 1H), 10.96 (broad, 1H), 11.38 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110°/ 6 h				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
400	m/e 569 (M^++H)	(d-6-DMSO, d values) 3.55 (s, 6H), 3.95 (s, 3H), 4.00 (s, 3H), 6.90 (d, 1H), 7.10 (t, 1H), 7.15 (d, 2H), 7.40 (t, 1H), 7.50 (s, 1H), 7.55 (d, 2H), 7.60 (d, 1H), 8.20 (s, 1H), 8.90 (s, 1H), 11.40 (broad s, 1H)	110°C/3h/1-PrOH.		MsCl, NEt_3, CH_2Cl_2	m/e 357 (M^++H)	H_2, Pd/C, EtOAc
401	m/e 528.32 (M^++H)	(d-6-DMSO, d values) 3.68 (d, 2H), 3.98 (d, 6H), 4.53(s, 2H), 6.94-7.2 (m, 7H), 7.33 (br.s, 1H),7.4 (s, 1H), 7.42 (d, 2H), 7.95 (br.t, 1H), 8.09 (s, 1H), 8.92(s, 1H), 10.99(br.s, 1H)	100°C/2h/1-PrOH				
402	m/e 556.38 (M^++H)	(d-6-DMSO, d values) 1.2 (d, 3H), 2.56 (d, 3H), 3.98 (d, 6H), 4.28(m, 1H), 4.52 (s, 2H), 6.96-7.2 (m, 6H), 7.4 (s, 1H), 7.42 (s, 2H), 7.85 (br.d, 1H), 7.92 (br.q, 1H), 8.08 (s, 1H), 8.9(s, 1H), 10.98(br.s, 1H)	100°C/2h/1-PrOH	m/e 374.15 M^++H)	EDC/DMAP/HOBT/DMA	m/e 344.24 (M^++H)	Hydrogen/ 5% Pd/C/EtOAc
403	m/e 542.35 (M^++H)	(d-6-DMSO, d values) 2.57 (d, 3H), 3.7 (d, 2H), 3.98 (s, 6H), 4.54(s, 2H), 6.94-7.2 (m, 6H), 7.4 (s, 1H), 7.43 (s, 2H), 7.8 (br.q, 1H), 7.92 (br.t, 1H), 8.09 (s, 1H), 8.9(s, 1H), 11.0(br.s, 1H)	100°C/2h/1-PrOH		EDC/DMAP/HOBT/DMA	m/e 330.22 (M^++H)	Hydrogen/ 5% Pd/C

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
404	m/e 627.49 (M^++H)	(d-6-DMSO, d values) 1.06 (t, 3H), 1.7 (t, 2H), 3.0 (q, 1H), 3.12 (m, 2H), 3.28 (s, 6H), 3.36 (q, 1H), 3.6 (t, 2H), 3.92 (d, 6H), 5.05(s, 2H), 6.85-7.03 (m, 6H), 7.25 (d, 2H), 7.3 (s, 1H), 7.78 (s, 1H), 8.36 (s, 1H), 8.72 (br.s, 1H) 9.52 (s, 1H)	100°C/2h/1-PrOH	m/e 445.35 M^++H)	EDC/N-Methyl morpho-line/ DCM	m/e 415.32 (M^++H)	Hydrogen/ 5% Pd/C
405	m/e 582.42 (M^++H)	(d-6-DMSO, d values) 1.25-1.45 (m, 1H), 1.6-1.8 (m, 5H), 2.74-2.94 (m, 2H), 3.0-3.14 (m, 2H), 3.27-3.56 (m, 4H), 3.97 (d, 6H), 4.55(s, 2H), 6.97-7.2 (m, 6H), 7.42 (d, 2H), 7.48 (s, 1H), 8.08 (t, 1H), 8.22 (s, 1H), 8.95 (s, 1H), 10.13 (br.s, 1H), 11.2 (br.s, 1H)	100°C/2h/1-PrOH	m/e 400.33 M^++H)	EDC/ NMM/ DCM	m/e 370.2 (M^++H)	Hydrogen/ 5% Pd/C
406	m/e 584.42 (M^++H)	(d-6-DMSO, d values) 2.96-3.7 (m, 8H), 3.7-3.97 (m, 4H), 3.99 (s, 6H), 4.5(s, 2H), 6.95-7.2 (m, 6H), 7.41 (d, 2H), 7.44 (s, 1H), 8.1 (t, 1H), 8.18 (s, 1H), 8.89 (s, 1H)	100°C/2h/1-PrOH	m/e 402.27 (M^++H	EDC/ NMM/ DCM	m/e 372.25 (M^++H)	Hydrogen/ 5% Pd/C

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
407	m/e 570 $(M+H)^+$	(d-6-DMSO, d values) 0.95 (t, 6H), 2.74 (s, 3H), 3.03 (q, 4H), 3.96 (m, 6H), 4.11 (t, 2H), 6.98 (m, 4H), 7.05 (m, 1H), 7.18 (m, 2H), 7.38 (m, 4H), 8.06 (bs, 1H), 8.87 (bs, 1H)	100°C/18h/1 -PrOH				
409	m/e 513 $(M+H)^+$	(d-6-DMSO, d values) 1.68 (m, 2H), 1.76 (s, 3H), 3.00 (m, 2H), 3.97 (s, 8H), 6.99 (m, 3H), 7.05 (m, 1H), 7.16 (m, 2H), 7.42 (m, 3H), 7.83 (bs, 1H), 8.14 (s, 1H), 8.96 (s, 1H)	100°C/18h/1 -PrOH				
410	m/e 483 $(M+H)^+$	(d-6-DMSO, d values) 2.34 (t, 2H), 2.53 (m, 3H), 2.80 (t, 2H), 3.96 (m, 6H), 6.85 (d, 1H), 7.05 (m, 3H), 7.19 (m, 1H), 7.31 (d, 1H), 7.39 (s, 1H), 7.45 (d, 2H), 7.68 (bs, 1H), 8.05 (s, 1H), 8.89 (s, 1H)	100°C/18h/1 -PrOH	m/e 301 $M+H)^+$	RT/18h/ methyla mine.HC l/EDC/ DMAP/ NMM/ DCM	m/e 271 $(M+H)^+$	RT/18h/5 %PdC/H_2/ EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
411	m/e 547 $(M+H)^+$	(d-6-DMSO, d values) 2.60 (t, 2H), 2.85 (t, 3H), 3.18 (s, 3H), 3.98 (s, 6H), 6.86 (d, 1H), 7.08 (m, 3H), 7.20 (m, 1H), 7.31 (m, 1H), 7.45 (m, 3H), 8.18 (s, 1H), 8.[illegible] (s, 1H)	100°C/18h/1-PrOH	m/e 363 $(M-H^+)^-$	RT/18h/methane sulphonamide/EDC/DMAP/NMM/DCM	m/e 335 $(M+H)^+$	RT/18h/5%PdC/H_2/EtOAc
412	m/e 539 $(M+H)^+$	(d-6-DMSO, d values) 2.58 (m, 2H), 2.83 (m, 2H), 3.47 (m, 4H), 3.95 (m, 6H), 6.88 (d, 1H), 7.08 (d, 2H), 7.11 (m, 1H), 7.20 (m, 1H), 7.35 (m, 2H), 7.43 (d, 2H), 8.02 (s, 1H), 8.94 (s, 1H)	100°C/18h/1-PrOH	m/e 357 $M+H)^+$	RT/18h/morpholine/EDC/DMAP/NMM/DCM	m/e 327 $(M+H)^+$	RT/18h/5%PdC/H_2/EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
413	m/e 509 $(M+H)^+$	(d-6-DMSO, d values) 2.43 (t, 2H), 2.81 (t, 2H), 3.66 (m, 4H), 3.99 (s, 6H), 5.00 (m, 2H), 5.74 (m, 1H), 6.89 (d, 1H), 7.08 (m, 3H), 7.19 (m, 1H), 7.31 (m, 1H), 7.47 (m, 3H), 7.92 (bs, 1H), 8.13 (s, 1H), 8.92 (s, 1H)	100°C/18h/1-PrOH	m/e 327 $M+H)^+$	RT/18h/ allyl amine EDC/D MAP/ NMM/ DCM	m/e 297 $(M+H)^+$	80°C/18h /$SnCl_2$.2 H_2O/EtO Ac
414	m/e 509 $(M+H)^+$	(d-6-DMSO, d values) 3.97 (s, 6H), 4.37 (m, 2H), 4.65 (m, 2H), 6.93 (d, 2H), 7.00 (m, 1H), 7.06 (m, 1H), 7.14 (m, 2H), 7.41 (d, 2H), 7.46 (s, 1H), 7.67 (s, 1H), 7.87 (s, 1H), 8.17 (bs, 1H), 8.91 (s, 1H)	100°C/18h/1-PrOH	m/e 327 $M+H)^+$	RT/18h/ DEAD/ PPh_3/ DCM	m/e 297 $(M+H)^+$	RT/18h/5 %Pd/C/H 2/ EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
415	m/e 510 $(M+H)^+$	(d-6-DMSO, d values) 1.81 (m, 2H), 1.91 (m, 2H), 2.95 (m, 2H), 3.97 (m, 6H), 4.35 (m, 2H), 6.97 (d, 2H), 7.05 (m, 1H), 7.10 (m, 1H), 7.24 (m, 2H), 7.40 (d, 2H), 7.47 (s, 1H), 8.24 (s, 1H), 8.87 (s, 1H)	100°C/18h/1-PrOH	m/e 329 $M+H)^+$	RT/18h/ b-OH-ethylpyrrolidine/ DEAD/ PPh_3/ DCM	m/e 299 $(M+H)^+$	RT/18h/5 %Pd/C/ H_2/ EtOAc
416	m/e 475 $(M+H)^+$		80°C/18h/DME				
417	m/e 509 $(M+H)^+$	(d-6-DMSO, d values) 3.98 (s, 6H), 4.31 (m, 2H), 4.42 (m, 2H), 6.95 (d, 2H), 7.00 (m, 1H), 7.04 (m, 2H), 7.14 (m, 2H), 7.40 (m, 4H), 7.95 (s, 1H), 8.11 (s, 1H), 8.28 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH	m/e 327 $M+H)^+$	RT/18h/ DEAD/ PPh_3/ DCM	m/e 297 $(M+H)^+$	RT/18h/ 5%Pd/C/ H_2/ EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
418	m/e 524 (M^++H)	(d-6-DMSO, d values) 1.12 (t, 3H), 1.88 (m, 2H), 2.04 (m, 2H), 2.97 (q, 2H), 3.16 (m, 2H), 3.68 (m, 4H), 3.95 (s, 3H), 4.54 (t, 2H), 5.66 (broad, 1H), 6.14 (q, 1H), 6.21 (t, 1H), 6.33 (q, 1H), 7.05 (m, 3H), 7.30 (d, 2H), 7.43 (s, 1H), 7.89 (s, 1H), 8.48 (s, 1H), 9.73 (broad, 1H), 10.33 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 105 °C / 20 h			
419	m/e 499 (M^++H)	(d-6-DMSO, d values) 1.90 (m, 2H), 2.04 (m, 2H), 3.15 (m, 2H), 3.62 (m, 2H), 3.71 (m, 2H), 3.99 (s, 3H), 4.59 (t, 2H), 7.17 (m, 5H), 7.44 (m, 3H), 7.52 (s, 1H), 8.16 (s, 1H), 8.86 (s, 1H), 10.91 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) 105 °C /20h				
420	m/e 506 (M^++H)	(d-6-DMSO, d values) 1.89 (m, 2H), 2.04 (m, 2H), 3.17 (m, 2H), 3.64 (m, 2H), 3.71 (m, 2H), 4.01 (s, 3H), 4.59 (t, 2H), 6.96 (d, 2H), 7.31 (m, 3H), 7.52 (m, 3H), 7.64 (m, 1H), 7.91 (m, 1H), 8.13 (s, 1H), 8.82 (s, 1H), 10.74 (broad, 2H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 105 °C / 20h				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
421	m/e 527 (M^++H)	(d-6-DMSO, d values) 3.55 (m, 4H), 3.70 (m, 2H), 3.76 (s, 3H), 3.85 (m, 2H), 4.00 (m, 2H), 4.01 (s, 3H), 4.70 (t, 2H), 6.99 (m, 2H), 7.07 (d, 1H), 7.21 (m, 2H), 7.40 (d, 2H), 7.54 (s, 1H), 8.18 (s, 1H), 8.88 (s, 1H), 10.94 (broad, 1H), 11.41 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 3 h				
422	m/e 511 (M^++H)	(d-6-DMSO, d values) 1.89 (m, 2H), 2.04 (m, 2H), 3.15 (m, 2H), 3.63 (m, 4H), 3.71 (m, 2H), 3.74 (s, 3H), 3.99 (s, 3H), 4.59 (t, 2H), 6.97 (m, 3H), 7.05 (m, 1H), 7.19 (m, 2H), 7.37 (d, 2H), 7.50 (s, 1H), 8.13 (s, 1H), 8.83 (s, 1H), 10.89 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 105 °C / 20h				
423	m/e 568(M^+ +H)		100°C/18h/ N-PrOH				
424	m/e 504 (M^++H)		100°C/18h/ 1-PrOH				
425	m/e456 (M^++H)		100°C/18h/ 1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
427	m/e471 $(M^+ + H)$		100°C/18h/ 1-PrOH	m/e 303 $M+H)^+$	150°C/2.5h/ DMA/ KO^{t}Bu	m/e 273 $(M+H)^+$	RT/18/ H_2/10% Pd/C/ EtOAc
428	m/e 481.4 $(M+H)^+$	(d-6-DMSO, δ values) 0.47 (m, 2H), 0.61 (m, 2H), 2.69 (m, 1H), 3.98 (s, 3H), 4.40 (s, 2H), 6.59 - 6.65 (m, 2H), 6.71 (d, 1H), 7.15 (d, 2H), 7.28 (t, 1H), 7.43 (s, 1H), 7.49 (d, 3H), 8.08 (m, 1H), 8.70 (d, 1H), 8.99 (s, 1H)	100°C/5h/ 1-PrOH				
429	m/e 398.3 $(M+H)^+$	(d-6-DMSO, δ values) 3.74 (s, 3H), 3.98 (s, 3H), 6.92 - 6.98 (m, 3H), 7.06 (d, 1H), 7.16 - 7.26 (m, 2H), 7.36 - 7.44 (m, 3H), 7.47 (d, 1H), 8.70 (d, 1H), 9.00 (s, 1H), 11.28 (s, 1H)	100°C/3h/ 1-PrOH				Rev. Chim. (1988), 39 (6), 477-82

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
431	m/e 512 (M^++H)	(d-6-DMSO, d values) 1.89 (m, 2H), 2.03 (m, 2H), 3.13 (m, 2H), 3.63 (m, 2H), 3.71 (m, 2H), 3.73 (s, 3H), 4.04 (s, 3H), 4.60 (m, 2H), 6.68 (m, 2H), 6.77 (d, 1H), 7.17 (d, 1H), 7.30 (t, 1H), 7.57 (s, 1H), 7.96 (m, 1H), 8.31 (d, 1H), 8.39 (s, 1H), 8.91 (s, 1H), 11.22 (broad, 1H), 11.47 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 105 °C / 20 h				
432	m/e 554 (M^++H)	(d-6-DMSO, d values) 2.95 (t, 2H), 3.05 (m, 2H), 3.15 (m, 4H), 3.80 (m, 2H), 3.90 (m, 2H), 3.95 (s, 3H), 4.00 (s, 3H), 6.80 (m, 1H), 7.10 (d, 4H), 7.45 (d, 2H), 7.50 (s, 1H), 7.85 (m, 1H), 8.30 (s, 1H), 8.90 (s, 1H), 9.80 (broad s, 1H), 11.20 (broad s, 1H), 11.40 (broad s, 1H)	110°C/18h/ 1-PrOH/ HCl			m/e 342 (M^++H)	H_2, Pd/C, EtOAc
433	m/e 582 (M^++H)	(d-6-DMSO, d values) 1.10 (s, 3H), 1.15 (s, 3H), 2.60 (m, 2H), 2.95 (t, 2H), 3.35 (m, 4H), 4.00 (s, 3H), 4.00 (s, 3H), 6.90 (m, 1H), 7.10 (d, 4H), 7.45 (d, 2H), 7.55 (s, 1H), 7.90 (m, 1H), 8.35 (s, 1H), 8.90 (s, 1H), 9.80 (broad s, 1H), 11.45 (broad s, 2H)	110°C/18h/ 1-PrOH/ HCl			m/e 370 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
434	m/e 552 (M^++H)	(d-6-DMSO, d values) 1.35 (m, 1H), 1.70 (m, 5H), 2.90 (m, 4H), 3.20 (m, 2H), 3.30 (m, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 6.90 (m, 1H), 7.10 (m, 4H), 7.45 (d, 2H), 7.55 (s, 1H), 7.85 (m, 1H), 8.30 (s, 1H), 8.90 (s, 1H), 9.80 (broad s, 1H), 10.35 (broad s, 1H), 11.40 (broad s, 1H)	110°C/2h/1-PrOH/HCl			m/e 340	H_2, Pd/C, EtOAc
435	m/e 498 (M^++H)	NMR Spectrum (d-6-DMSO@373K, d values) 2.55 (s, 3H), 3.10 (m, 2H), 3.70 (m, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 6.95 (m, 1H), 7.05 (d, 2H), 7.10 (m, 2H), 7.40 (d, 2H), 7.55 (s, 1H), 7.85 (m, 1H), 8.25 (s, 1H), 8.65 (s, 1H), 8.90 (broad s, 1H), 9.45 (broad s, 1H)	110°C/2h/1-PrOH/HCl			m/e 286 (M^++H)	H_2, Pd/C, EtOAc
436	m/e 512 (M^++H)	(d-6-DMSO@373K, d values) 2.75 (s, 6H), 2.90 (t, 2H), 3.30 (t, 2H), 4.00 (s, 3H), 4.00 (s, 3H), 6.95 (m, 1H), 7.05 (d, 2H), 7.10 (m, 2H), 7.40 (d, 2H), 7.55 (s, 1H), 7.85 (m, 1H), 8.20 (s, 1H), 8.65 (s, 1H), 9.50 (broad s, 1H)	110°C/2h/1-PrOH/HCl			m/e 300 (M^++H)	H_2, Pd/C, EtOAc

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
437	m/e 497 $(M+H)^+$	(d-6-DMSO, d values) 0.69 (m, 2H), 0.87 (m, 2H), 2.71 (m, 1H), 3.28 (s, 2H), 3.96 (m, 6H), 7.02 (m, 4H), 7.21 (m, 2H), 7.40 (d, 2H), 7.47 (s, 1H), 8.21 (s, 1H), 8.87 (s, 1H), 9.35 (bs, 2H)	100°C/18h/1 -PrOH				
438	m/e 509 $(M+H)^+$	(d-6-DMSO, d values) 0.38 (m, 2H), 0.59 (m, 2H), 2.53 (m, 1H), 3.54 (s, 2H), 3.97 (s, 6H), 6.18 (m, 1H), 6.26 (m, 1H), 6.33 (m, 1H), 7.08 (m, 3H), 7.45 (m, 3H), 7.95 (m, 1H), 8.18 (s, 1H), 8.95 (s, 1H)	100°C/18h/1 -PrOH				
439	m/e 484 $(M+H)^+$	(d-6-DMSO, d values) 2.58 (d, 3H), 3.57 (s, 2H), 3.96 (s, 6H), 6.20 (m, 1H), 6.23 (m, 1H), 6.31 (m, 1H), 7.08 (m, 3H), 7.43 (m, 3H), 7.79 (m, 1H), 8.08 (s, 1H), 8.87 (s, 1H)	100°C/18h/1 -PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
440	m/e 582.54 (M^++H)	(d-6-DMSO, d values) 1.56-1.74 (m, 2H), 2.00 (m, 2H), 2.12(m, 1H), 2.64 (d, 3H), 2.72 (d, 3H), 2.96 (m, 2H), 3.44 (m, 2H), 4.0 (s, 3H), 4.06 (d, 2H), 4.40(s, 2H), 6.60(m, 2H), 6.73 (d, 1H), 7.15 (d, 2H), 7.28 (t, 1H), 7.49 (d, 2H), 7.54 (s, 1H), 8.0(br.s, 1H), 8.2(s, 1H), 8.89 (s, 1H), 10.17 (br.s, 1H), 11.16 (br.s, 1H)	100°C/2.5h/ 1-PrOH/ ethereal HCl				
441	m/e 629.52 (M^++H)	(d-6-DMSO, d values) 1.99 (m, 1H), 2.01 (m, 1H), 2.35(t, 2H), 3.54 (s, 3H), 3.6 (s, 3H),3.96 (2s, 6H), 4.35 (m, 1H), 4.55 (m, 2H), 6.95-7.21 (m, 6H), 7.4(s, 1H), 7.42(s, 2H), 8.08 (s, 1H), 8.28 (d, 1H), 8.9 (s, 1H), 10.96 (br.s, 1H)	100°C/2h/1-PrOH			m/e 417.26 (M^++H)	Hydrogen/ 5% Pd/C
442	m/e 571.47 (M^++H)	(d-6-DMSO, d values) 1.13(t, 2H), 2.45 (t, 2H), 3.32 (t, 2H),3.96 (2s, 6H), 4.0 (q, 2H), 4.46 (s, 2H), 6.96-7.20 (m, 6H), 7.4(s, 2H), 7.42(s, 1H), 7.75 (t, 1H), 8.06 (s, 1H), 8.89 (s, 1H)	100°C/2h/1-PrOH			m/e 359.22(M^++H)	Hydrogen/5% Pd/C

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
443	m/e 543.42 (M^++H)	(d-6-DMSO, d values) 3.60 (s, 3H), 3.90 (d, 2H),3.96 (2s, 6H), 4.55 (s, 2H), 6.96-7.2 (m, 6H), 7.4(s, 1H), 7.42(s, 2H), 8.05 (s, 1H), 8.16 (t, 1H), 8.9 (s, 1H), 10.99 (br.s, 1H)	100°C/2h/1-PrOH			m/e 331.14(M^++H)	Hydrogen/5% Pd/C
444	m/e 629.52 (M^++H)	(d-6-DMSO, d values) 1.70 (m, 1H), 1.86 (m, 1H), 2.0(t, 2H), 2.45 (d, 3H), 2.56 (d, 3H),3.96 (2s, 6H), 4.2 (m, 1H), 4.52 (s, 2H), 6.94-7.21 (m, 6H), 7.39 (s, 1H), 7.41 (s, 2H), 7.7(q, 1H), 7.81(d, 2H), 7.92 (q, 1H), 8.08 (s, 1H), 8.9 (s, 1H), 10.92 (br.s, 1H)	100°C/2h/1-PrOH				
445	m/e 556.45 (M^++H)	(d-6-DMSO, d values) 2.23 (t, 2H), 2.5 (d, 3H),3.29 (t, 2H), 3.97 (2s, 6H), 4.45 (s, 2H), 6.96-7.2 (m, 6H), 7.41(s, 1H), 7.44(s, 2H), 7.62 (t, 1H), 7.8 (q, 1H), 8.13 (s, 1H), 8.9 (s, 1H), 11.03 (br.s, 1H)	100°C/2h/1-PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
446	m/e 568.45 (M^++H)	(d-6-DMSO, d values) 0.4 (m, 2H), 0.56 (m, 2H), 2.47 (m, 1H), 3.66 (d, 2H), 3.98 (d, 6H), 4.54(s, 2H), 6.94-7.2 (m, 6H), 7.4 (s, 1H), 7.42 (s, 2H), 7.85 (br.t, 1H), 7.95 (d, 1H), 8.10 (s, 1H), 8.88 (s, 1H), 11.09(br.s, 1H)	100°C/2h/1-PrOH				
447		(d-6-DMSO, d values) 0.4 (m, 2H), 0.56 (m, 2H), 1.24 (d, 3H), 2.47 (m, 1H), 3.98 (2s, 6H), 4.23 (m, 1H), 4.54(s, 2H), 6.94-7.2 (m, 6H), 7.4 (s, 1H), 7.42 (s, 2H), 7.90 (d, 1H), 8.03 (d, 1H), 8.10 (s, 1H), 8.88 (s, 1H), 10.94(br.s, 1H)	100°C/2h/1-PrOH				
471	m/e 598.5 $(M+H)^+$	(d-6-DMSO D4 Acetic, δ values) 2.24 - 2.35 (m, 2H), 2.62 (s, 3H), 3.03 - 3.10 (m, 4H), 3.29 (t, 2H), 3.73 - 3.78 (m, 4H), 3.98 (s, 3H), 4.28 (t, 2H), 4.41 (s, 2H), 6.59 - 6.65 (m, 2H), 6.73 (dd, 1H), 7.15 (d, 2H), 7.28 (t, 1H), 7.46 (s, 2H), 7.49 (s, 1H), 8.08 (s, 1H), 8.84 (s, 1H)	RT/48h/NaI/ Morpholine				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
472	m/e 538.5 $(M+H)^+$	(d-6-DMSO, d values) 2.42 (m, 2H), 2.58 (m, 2H), 3.34 (m, 2H), 3.97 (m, 8H), 6.99 (m, 4H), 7.17 (m, 2H), 7.38 (m, 2H), 7.41 (s, 1H), 8.08 (s, 1H), 8.11 (m, 1H), 8.87 (s, 1H)	100°C/18h/ 1-PrOH				
473	m/e 527.5 $(M+H)^+$	(d-6-DMSO, d values) 0.97 (d, 6H), 2.34 (m, 1H), 3.30 (m, 2H), 3.97 (m, 8H), 7.00 (m, 4H), 7.30 (m, 2H), 7.41 (m, 3H), 7.78 (m, 1H), 8.13 (s, 1H), 8.96 (s, 1H)	100°C/18h/1 -PrOH				
474	m/e 499.5 $(M+H)^+$	(d-6-DMSO, d values) 1.79 (s, 3H), 3.29 (m, 2H), 3.96 (m, 8H), 6.99 (m, 4H), 7.17 (m, 2H), 7.41 (m, 3H), 7.89 (m, 1H), 8.12 (s, 1H), 8.92 (s, 1H)	100°C/18h/1 -PrOH				
475	m/e 541.5 $(M+H)^+$	(d-6-DMSO, d values) 3.26 (m, 2H), 4.97 (m, 8H), 4.45 (m, 2H), 5.17 (m, 2H), 5.87 (m, 1H), 7.00 (m, 4H), 7.18 (m, 3H), 7.60 (m, 3H), 8.08 (s, 1H), 8.89 (s, 1H)	100°C/18h/1 -PrOH				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1		Intermediate 2	
				Mass	Reaction	Mass	Reaction
476	m/e 610.7 $(M-H^+)^-$	(d-6-DMSO, d values) 2.32 (m, 2H), 2.82 (s, 3H), 2.93 (s, 3H), 3.10 (m, 2H), 3.22-3.53 (m, 4H, under H_2O peak), 3.78 (m, 2H), 3.95 (m, 5H), 4.29 (m, 2H), 4.81 (s, 2H), 7.04 (m, 7H), 7.36 (m, 2H), 7.43 (s, 1H), 8.07 (s, 1H), 8.81 (s, 1H)	RT/18h/ $HNMe_2$.HCl/ DMAP/EDC /NMM/DCM				
477		(d-6-DMSO, δ values) 2.64 (d, 3H), 3.99 (s, 6H), 4.42 (s, 2H), 6.60 - 6.67 (m, 2H), 6.74 (dd, 1H), 7.17 (d, 2H), 7.28 (t, 1H), 7.45 - 7.53 (m, 3H), 7.99 (m, 1H), 8.16 (s, 1H), 8.92 (s, 1H), 11.14 (bs, 1H)	100°C/2h/ 1-PrOH			m/e 273.2 $(M+H)^+$	5% Pd on C/H_2/ EtOAc
478	m/e 515 $(M^+ + H)$	(d-6-DMSO, d values) 3.56 (m, 4H), 3.70 (m, 2H), 3.86 (m, 2H), 4.00 (m, 2H), 4.02 (s, 3H), 4.71 (t, 2H), 7.16 (d, 2H), 7.25 (m, 3H), 7.43 (m, 1H), 7.48 (d, 2H), 7.57 (s, 1H), 8.23 (s, 1H), 8.91 (s, 1H), 11.10 (broad, 1H), 11.52 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 6h				

No.	mass spec	n.m.r.	reaction conditions	Intermediate 1 Mass	Intermediate 1 Reaction	Intermediate 2 Mass	Intermediate 2 Reaction
479	m/e 522 (M^++H)	(d-6-DMSO, d values) 3.57 (m, 4H), 3.71 (m, 2H), 3.85 (m, 2H), 4.00 (m, 2H), 4.04 (s, 3H), 4.71 (t, 2H), 6.99 (d, 2H), 7.32 (m, 3H), 7.57 (m, 3H), 7.67 (m, 1H), 7.93 (m, 1H), 8.23 (s, 1H), 8.91 (s, 1H), 11.11 (broad, 1H), 11.45 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 6h				
480	m/e 540 (M^++H)	(d-6-DMSO, d values) 1.66 (t, 3H), 3.06 (q, 2H), 3.56 (m, 4H), 3.71 (m, 2H), 3.87 (m, 2H), 4.00 (m, 2H), 4.03 (s, 3H), 4.71 (t, 2H), 6.44 (m, 3H), 7.16 (m, 3H), 7.48 (d, 2H), 7.57 (s, 1H), 8.28 (s, 1H), 8.94 (s, 1H), 11.24 (broad, 1H), 11.55 (broad, 1H)	1-PrOH / 1.0M ethereal HCl (1 equiv.) / 110deg / 6 h				
482	m/e 513.5 $(M+H)^+$	(d-6-DMSO, d values) 1.05 (d, 6H), 3.87 (m, 1H), 3.97 (m, 6H), 4.43 (s, 2H), 7.05 (m, 6H), 7.42 (m, 4H), 8.08 (s, 1H), 8.89 (s, 1H)	100°C/18h/1-PrOH			m/e 301.5 (M+H)	RT/18h/ H_2/5% Pd/C/ EtOAc

In the above and other Examples, the following abbreviations have been been used:

- ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;
- nitrogen atoms which are shown as less than trivalent are H substituted to complete the trivalency;
- the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*,*N*-dimethylformamide;
DCM	dichloromethane;
EtOAc	ethyl acetate;
HOBT	N-hydroxybenzotriazole hydrate ;
NMM	*N*-Methylmorpholine;
TFA	Trifluoroacetic acid;
1-Pr-OH	propan-1-ol;
MeOH	methanol;
EtOH	ethanol;
KOtBu	potassium tert-butoxide;
RT	room/ambient temperature.

Example 6

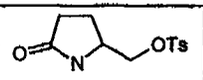
Compounds of formula (I) were also converted to different such compounds by reacting appropriate derivatisation reactions, either directly or by way of certain chloro substituted intermediates. These can be summarised in the following Table 8 with the Intermediates listed in the Intermediate Table 9 below.

Table 8

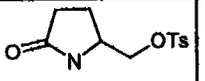
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I8	morpholine	RT/2hrs	14	m/e 541 $(M+H)^+$	(d-6-DMSO, d values) 2.30 (m, 2H), 3.18 (m, 2H), 3.40 (m, 4H), 3.75 (s, 3H), 3.81 (m, 2H), 3.95 (m, 2H), 3.98 (s, 3H), 4.30 (m, 2H), 6.94 (m, 3H), 7.08 (m, 1H), 7.19 (m, 2H), 7.38 (d, 2H), 7.47 (s, 1H), 8.25 (s, 1H), 8.86 (s, 1H).
I18	N-methyl piperazine	EtOH / 80deg / 3.5 hours	16	m/e 554 (M^+H)	(d-6-DMSO, d values) 2.31 (m, 2H), 2.83 (s, 3H), 3.30 (m, 2H), 3.54 (broad, 8H), 3.73 (s, 3H), 3.99 (s, 3H), 4.31 (m, 2H), 6.95 (m, 3H), 7.04 (d, 1H), 7.17 (m, 2H), 7.39 (d, 2H), 7.48 (s, 1H), 8.15 (s, 1H), 8.88 (s, 1H), 11.12 (broad, 1H).
I9	N-methyl piperazine	RT/18hrs/NaI	17	m/e 554 $(M+H)^+$	(d-6-DMSO, d values) 2.25 (m, 2H), 2.80 (m, 3H), 3.38 (m, 2H), 3.60 (m, 8H), 3.78 (s, 3H), 3.99 (s, 3H), 4.35 (m, 2H), 6.96 (m, 3H), 7.08 (m, 1H), 7.19 (m, 2H), 7.39 (d, 2H), 7.50 (s, 1H), 8.25 (bs, 1H), 8.91 (s, 1H).
I9	pyrrolidine	RT/18hrs/NaI	18	m/e 525 $(M+H)^+$	(d-6-DMSO, d values) 1.88 (m, 2H), 2.04 (m, 2H), 2.26 (m, 2H), 3.32 (m, 2H), 3.60 (m, 4H), 3.75 (s, 3H), 4.00 (s, 3H), 4.28 (m, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.10 (m, 2H), 7.38 (m, 3H), 8.15 (s, 1H), 8.60 (bs, 1H), 8.93 (s, 1H).

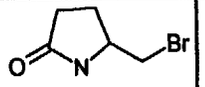
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I9	piperidine	RT/18hrs/NaI	19	m/e 539 $(M+H)^+$	(d-6-DMSO, d values) 1.40 (m, 2H), 1.6-1.8 (m, 4H), 2.28 (m, 2H), 2.95 (m, 2H), 3.21 (m, 2H), 3.45 (m, 2H), 3.72 (s, 3H), 3.97 (s, 3H), 4.28 (m, 2H), 6.94 (m, 3H), 7.07 (m, 1H), 7.20 (m, 2H), 7.39 (d, 2H), 7.45 (s, 1H), 8.24 (s, 1H), 8.92 (s, 1H).
I9	dimethyl-amine	RT/18hrs/NaI/ EtOH	20	m/e 499 $(M+H)^+$	(d-6-DMSO, d values) 2.23 (m, 2H), 2.81 (d, 6H), 3.24 (m, 2H), 3.73 (s, 3H), 3.99 (s, 3H), 4.29 (m, 2H), 6.95 (m, 3H), 7.06 (m, 1H), 7.18 (m, 2H), 7.37 (d, 2H), 7.39 (s, 1H), 8.13 (s, 1H), 8.85 (s, 1H).
I10	morpholine	RT/18hrs/NaI	21	m/e 527 $(M+H)^+$	(d-6-DMSO, d values) 3.06 (m, 2H), 3.39 (m, 2H), 3.64 (m, 2H), 3.71 (s, 3H), 3.75 (m, 2H), 3.90 (m, 2H), 4.00 (s, 3H), 4.68 (m, 2H), 6.94 (m, 3H), 7.05 (m, 1H), 7.19 (m, 2H), 7.37 (d, 2H), 7.50 (s, 1H), 8.38 (s, 1H), 8.87 (s, 1H).
I10	N-methyl piperazine	RT/18hrs/NaI	22	m/e 540 $(M+H)^+$	(d-6-DMSO, d values) 2.80 (s, 3H), 3.24-3.65 (m, 10H), 3.72 (s, 3H), 3.99 (s, 3H), 4.58 (m, 2H), 6.95 (m, 3H), 7.06 (m, 1H), 7.19 (m, 2H), 7.39 (d, 2H), 7.50 (s, 1H), 8.36 (s, 1H), 8.85 (s, 1H).
I10	pyrrolidine	RT/18hrs/NaI	23	m/e 511 $(M+H)^+$	(d-6-DMSO, d values) 1.84 (m, 2H), 2.04 (m, 2H), 3.05 (m, 2H), 3.65-3.72 (m, 4H), 3.75 (s, 3H), 3.98 (s, 3H), 4.60 (m, 2H), 6.96 (m, 3H), 7.07 (m, 1H), 7.18 (m, 2H), 7.39 (d, 2H), 7.47 (s, 1H), 8.32 (s, 1H), 8.89 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I10	piperidine	RT/18hrs/NaI	24	m/e 525 $(M+H)^+$	(d-6-DMSO, d values) 1.5-1.85 (m, 6H), 3.02 (m, 2H), 3.4-3.6 (m, 4H), 3.73 (s, 3H), 3.99 (s, 3H), 4.63 (m, 2H), 6.95 (m, 3H), 7.06 (m, 1H), 7.18 (m, 2H), 7.37 (d, 2H), 7.44 (s, 1H), 8.29 (s, 1H), 8.88 (s, 1H).
I10	dimethyl amine	RT/18hrs/NaI/ EtOH	25	m/e 485 $(M+H)^+$	(d-6-DMSO, d values) 2.91 (m, 6H), 3.63 (m, 2H), 3.74 (s, 3H), 3.99 (s, 3H), 4.54 (m, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.18 (m, 2H), 7.35 (d, 2H), 7.42 (s, 1H), 8.17 (s, 1H), 8.83 (s, 1H).
424		75°C/1hr/thioanisole/TFA	26	m/e 414 $(M+H)^+$	(d-6-DMSO, d values) 3.73 (s, 3H), 3.95 (s, 3H), 6.89 (d, 2H), 6.95 (m, 1H), 7.02 (m, 1H), 7.15 (m, 2H), 7.22 (d, 2H), 7.30 (s, 1H), 7.69 (s, 1H), 8.48 (s, 1H), 9.60 (bs, 1H), 9.94 (bs, 1H).
9		TFA / thioanisole / 90deg / 1.5 hours	27	m/e 414 (M^+H)	(d-6-DMSO, d values) 3.75 (s, 3H), 3.91 (s, 3H), 6.89 (d, 2H), 6.94 (m, 1H), 7.02 (d, 1H), 7.16 (m, 3H), 7.23 (m, 1H), 7.73 (s, 1H), 8.31 (s, 1H), 9.33 (s, 1H), 10.31 (broad, 1H).
26	2-chloromethyl-pyridine	RT/96hr/ KOtBu, /DMA	28	m/e 505 (M^+H)	(d-6-DMSO, d values) 3.74 (s, 3H), 4.01 (s, 3H), 5.39 (s, 2H), 6.95 (m, 3H), 7.04 (d, 1H), 7.17 (m, 2H), 7.41 (m, 3H), 7.50 (s, 1H), 7.63 (d, 1H), 7.93 (m, 1H), 8.34 (s, 1H), 8.61 (d, 1H), 8.97 (s, 1H).

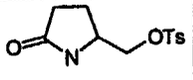
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
26	2-bromo thiazole	120°C/18hrs/ KOH/DMA	29	m/e 499 (M^++H)	(d-6-DMSO, d values) 3.73 (s, 3H), 3.99 (s, 3H), 6.96 (m, 4H), 7.05 (m, 1H), 7.18 (m, 2H), 7.36 (m, 3H), 7.41 (s, 1H), 7.96 (s, 1H), 8.85 (s, 1H).
26	2-chloro pyrimidine	100°C/18hrs/ $K_2C\ O_3$/DMA	30	m/e 492 (M^++H)	(d-6-DMSO, d values) 3.73 (s, 3H), 3.90 (s, 3H), 6.95 (m, 3H), 7.04 (m, 1H), 7.17 (m, 2H), 7.31 (m, 1H), 7.37 (m, 2H), 7.60 (s, 1H), 8.66 (m, 3H), 9.01 (s, 1H).
26	2-bromo pyridine	120°C/18hrs/ $Cs_2C\ O_3$/DMA	31	m/e 491 (M^++H)	(d-6-DMSO, d values) 3.71 (s, 3H), 3.89 (s, 3H), 6.93 (m, 3H), 7.03 (m, 1H), 7.16 (m, 3H), 7.36 (d, 2H), 7.51 (s, 1H), 7.89 (m, 1H), 8.05 (m, 1H), 8.35 (s, 1H), 8.93 (s, 1H)
I18	morpholine	78°C/3hr/ethanol	33	m/e 541 (M^++H)	(d-6-DMSO, d values) 2.35 (m, 2H), 3.10 (m, 2H), 3.48 (d, 4H), 3.74 (s, 3H), 3.92 (m, 4H), 3.98 (s, 3H), 4.31 (t, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.17 (m, 2H), 7.39 (d, 2H), 7.56 (s, 1H), 8.25 (s, 1H), 8.89 (s, 1H), 11.22 (broad, 1H), 11.26 (broad, 1H)
26		RT/18hr/DMA / KOtBu, /18-crown-6	34	m/e 511 (M^++H)	(d-6-DMSO, d values) 1.90 (m, 2H), 2.08-2.40 (m, 3H), 3.73 (s, 3H), 3.98 (s, 3H), 4.15 (m, 2H), 6.98 (m, 3H), 7.08 (m, 1H), 7.18 (m, 3H), 7.39 (d, 2H), 7.58 (s, 1H), 7.78 (s, 1H), 8.18 (s, 1H), 8.92 (s, 1H), 11.0 (bs, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I18	piperazine	EtOH / 80deg / 3.5 hours	35	m/e 540 (M^++H)	(d-6-DMSO, d values) 2.33 (m, 2H), 3.32 (m, 2H), 3.48 (s, 8H), 3.73 (s, 3H), 3.97 (s, 3H), 4.31 (t, 2H), 6.96 (m, 3H), 7.04 (d, 1H), 7.18 (m, 2H), 7.37 (d, 2H), 7.48 (s, 1H), 8.13 (s, 1H), 8.87 (s, 1H), 11.04 (broad, 1H).
I18	pyrrolidine	EtOH / 80deg / 3.5 hours	36	m/e 525 (M^++H)	(d-6-DMSO, d values) 1.95 (broad, 2H), 2.28 (m, 2H), 3.03 (broad, 2H), 3.31 (t, 2H), 3.58 (broad, 2H), 3.73 (s, 3H), 3.97 (s, 3H), 4.29 (t, 2H), 6.96 (m, 3H), 7.05 (d, 1H), 7.18 (m, 2H), 7.39 (d, 2H), 7.47 (s, 1H), 8.14 (s, 1H), 8.86 (s, 1H), 11.06 (broad, 1H).
I18	Piperidine	EtOH / 80deg / 3.5 hours	37	m/e 539 (M^++H)	(d-6-DMSO, d values) 1.74 (m, 4H), 2.30 (m, 2H), 2.44 (m, 2H), 2.90 (m, 2H), 3.20 (t, 2H), 3.47 (m, 2H), 3.72 (s, 3H), 3.95 (s, 3H), 4.28 (t, 2H), 6.94 (m, 3H), 7.04 (d, 1H), 7.17 (m, 2H), 7.38 (d, 2H), 7.49 (s, 1H), 8.11 (s, 1H), 8.84 (s, 1H).
I18	N- (2 hydroxyethyl) piperazine	EtOH / 80deg / 7 hours	38	m/e 584 (M^++H)	(d-6-DMSO, d values @ *373deg K*) 2.27 (m, 2H), 3.18 (m, 4H), 3.43 (s, 4H), 3.53 (s, 4H), 3.77 (s, 3H), 3.82 (t, 2H), 3.98 (s, 3H), 4.33 (t, 2H), 6.97 (m, 3H), 7.04 (d, 1H), 7.16 (m, 2H), 7.35 (d, 2H), 7.56 (s, 1H), 8.09 (s, 1H), 8.67 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
27	2-chloromethyl-pyridine	RT/48hr/DMSO/ KOtBu,(1M in THF)	39	m/e 505 (M^++H)	(d-6-DMSO, d values) 3.73 (s, 3H), 4.01 (s, 3H), 5.41 (s, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.18 (m, 2H), 7.40 (m, 3H), 7.54 (s, 1H), 7.58 (d, 1H), 7.89 (m, 1H), 8.21 (s, 1H), 8.63 (d, 1H), 8.96 (s, 1H), 11.10 (broad, 1H)
27	3-chloromethyl-pyridine	RT/48hr/DMSO/ KOtBu,(1M in THF)	40	m/e 505 (M^++H)	(d-6-DMSO, d values) 3.74 (s, 3H), 3.98 (s, 3H), 5.40 (s, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.18 (m, 2H), 7.38 (m, 2H), 7.58 (m, 1H), 7.63 (s, 1H), 8.09 (m, 1H), 8.19 (s, 1H), 8.65 (d, 1H), 8.82 (d, 1H), 8.86 (s, 1H), 11.04 (broad, 1H)
27		RT/96hr/ DMSO KOtBu,(1M in THF)	41	m/e 511 (M^++H)	(d-6-DMSO, d values) 1.93 (m, 1H), 2.10 (m, 1H), 2.20 (m, 1H), 2.34 (m, 1H), 3.74 (s, 3H), 3.90 (s, 3H), 3.94 (m, 1H), 4.10 (m, 2H), 6.90 (d, 2H), 6.93 (m, 1H), 7.02 (m, 1H), 7.16 (m, 2H), 7.23 (d, 2H), 7.32 (s, 1H), 7.73 (s, 1H), 7.76 (s, 1H), 8.37 (s, 1H), 9.41 (s, 1H).
27	N-(2-chloroethyl) piperidine	RT/96hr/ powdered KOH/DMSO	44	m/e 525 (M^++H)	(d-6-DMSO, d values) 1.77 (m, 6H), 3.06 (m, 2H), 3.56 (m, 4H), 3.74 (s, 3H), 3.98 (s, 3H), 4.63 (t, 2H), 6.95 (m, 3H), 7.04 (m, 1H), 7.18 (m, 2H), 7.36 (d, 2H), 7.50 (s, 1H), 8.11 (s, 1H), 8.81 (s, 1H), 10.47 (broad, 1H), 10.75 (broad, 1H)

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
27	 WO 9965867	RT/120hr/DMSO KOtBu,(1M in THF)	48	m/e 611 (M^++H)	(d-6-DMSO, d values) 1.23 (m, 2H), 1.40 (s, 9H), 1.78 (m, 2H), 2.02 (broad, 1H), 2.77 (m, 2H), 3.75 (s, 3H), 3.91 (s, 3H), 4.00 (m, 4H), 6.91 (m, 3H), 7.02 (m, 1H), 7.15 (m, 2H), 7.23 (d, 2H), 7.30 (s, 1H), 7.75 (s, 1H), 8.36 (s, 1H), 9.38 (s, 1H)
26	F_3CCH_2O-S(O)$_2$.CH_3	120°C/20hr/ DMA/ KOtBu, /18-crown-6	50	m/e 496.1 (M^++H)	(CDCl3, d values) 3.76 (s, 3H), 3.94 (s, 3H), 4.07 (q, 2H), 6.78 (s, 1H), 6.84-7.12 (m, 9H), 7.30 (s, 1H), 8.52 (s, 1H). Intermediate 1. M461666
26	CH_2CHCH_2-Br	23°C/20hr/DMA/ KOtBu, /18-crown-6	51	m/e 454 (M^++H)	(d-6-DMSO, d values) 3.74 (s, 3H), 3.93 (s, 3H), 4.8 (d, 2H), 5.29 (d, 1H), 5.44 (d, 1H), 6.03-6.2 (m, 1H), 6.86-7.26 (m, 8H), 7.3 (s, 1H), 7.77 (s, 1H), 8.37 (s, 1H), 9.36 (s, 1H).
49		RT/18hrs/NaOH/MeOH/water	52	m/e 472 $(M+H)^+$	(d-6-DMSO, d values) 3.77 (s, 3H), 3.97 (s, 3H), 4.85 (s, 2H), 6.92 (d, 2H), 6.96 (m, 1H), 7.03 (m, 1H), 7.18 (m, 2H), 7.25 (d, 2H), 7.33 (s, 1H), 7.77 (s, 1H), 8.39 (s, 1H), 9.44 (s, 1H).
26		RT/4hrs/ KOtBu / 18-C-6/n-Bu_4NI/DMA	53	m/e 511 $(M+H)^+$	(d-6-DMSO, d values) 1.91 (m, 2H), 2.11-2.30 (m, 3H), 3.76 (s, 3H), 4.00 (s, 3H), 4.12 (m, 2H), 6.99 (m, 3H), 7.08 (m, 1H), 7.21 (m, 3H), 7.40 (d, 2H), 7.80 (s, 1H), 8.20 (s, 1H), 8.92 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
26	$CH{\equiv}CCH_2Br$	23°C/20hr/ DMA/ KOtBu, /18-crown-6	54	m/e 452 $(M^+{+}H)$	d-6-DMSO, d values) 3.6 (t, 1H), 3.73 (s, 3H), 3.94 (s, 3H), 4.92 (d, 2H), 6.84-7.3 (m, 8H), 7.33 (s, 1H), 7.84 (s, 1H), 8.38 (s, 1H), 9.38 (s, 1H).
26	CH_3OCH_2 CH_2Br	23°C/20hr/DM A/ KOtBu, /18-crown-6	55	m/e 472 $(M^+{+}H)$	(d-6-DMSO, d values) 3.32 (s, 3H), 3.71 (t, 2H), 3.73 (s, 3H), 3.93 (s, 3H), 4.21 (t, 2H), 6.85-7.28 (m, 8H), 7.3 (s, 1H), 7.75 (s, 1H), 8.36 (s, 1H), 9.36 (s, 1H).
52	morpholine	RT/64hrs/ EDC/DMAP/ DCM	57	m/e 541 $(M+H)^+$	(d-6-DMSO, d values) 3.48 (m, 4H), 3.61 (m, 4H), 3.76 (s, 3H), 4.01 (s, 3H), 5.11 (s, 2H), 6.96 (m, 3H), 7.08 (m, 1H), 7.21 (m, 2H), 7.40 (m, 3H), 8.15 (s, 1H), 8.89 (s, 1H).
52	N-methyl piperazine	RT/18hrs /EDC/DMAP/ DCM	58	m/e 552 $(M+H)^+$	(d-6-DMSO, d values) 2.80 (bs, 3H), 3.00-3.60 (m, 8H (under H_2O peak)), 3.75 (s, 3H), 4.01 (s, 3H), 5.18 (s, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.18 (m, 2H), 7.39 (m, 3H), 7.70 (bs, 1H), 8.33 (bs, 1H), 8.78 (bs, 1H).
52	allylamine	RT/18hrs/EDC /DMAP/DCM	59	m/e 511 $(M+H)^+$	(d-6-DMSO, d values) 3.74 (s, 3H), 3.78 (m, 2H), 4.02 (s, 3H), 4.77 (s, 2H), 5.09 (m, 2H), 5.80 (m, 1H), 6.97 (m, 3H), 7.08 (m, 1H), 7.20 (m, 2H), 7.37 (d, 2H), 7.44 (s, 1H), 8.21 (s, 1H), 8.16 (m, 1H), 8.85 (bs, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
52	methylamine	RT/18hrs/THF/ EDC/DMAP/D CM	60	m/e 485 $(M+H)^+$	(d-6-DMSO, d values) 2.68 (m, 3H), 3.78 (s, 3H), 4.03 (s, 3H), 4.70 (s, 2H), 6.96 (m, 3H), 7.06 (m, 1H), 7.19 (m, 2H), 7.36 (s, 1H), 7.40 (m, 2H), 7.89 (bs, 1H), 8.08 (s, 1H), 8.86 (s, 1H), 10.68 (bs, 1H).
52	methoxy ethanolamine	RT/18hrs/EDC /DMAP/DCM	61	m/e 529 $(M+H)^+$	(d-6-DMSO, d values) 3.25 (s, 3H), 3.75 (s, 3H), 4.01 (s, 3H), 4.73 (s, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.20 (m, 2H), 7.37 (s, 1H), 7.40 (m, 2H), 7.95 (bs, 1H), 8.07 (s, 1H), 8.86 (s, 1H), 10.70 (bs, 1H).
48		95°C/18hr/HC HO(aq.)/HCO OH	63	m/e 525 (M^+H)	(d-6-DMSO, d values) 1.73 (m, 2H), 2.04 (m, 2H), 2.20 (m, 1H), 2.78 (s, 3H), 3.06 (m, 2H), 3.44 (m, 2H), 3.77 (s, 3H), 3.96 (s, 3H), 4.14 (d, 2H), 6.96 (m, 3H), 7.03 (m, 1H), 7.16 (m, 2H), 7.29 (m, 2H), 7.44 (s, 1H), 7.89 (s, 1H), 8.58 (s, 1H)
27		55°C/30hr/DM SO/KOtBu(1M in THF)	64	m/e 511 (M^+H)	(d-6-DMSO, d values) 1.93 (m, 1H), 2.10 (m, 1H), 2.20 (m, 1H), 2.34 (m, 1H), 3.74 (s, 3H), 3.90 (s, 3H), 3.94 (m, 1H), 4.10 (m, 2H), 6.90 (d, 2H), 6.93 (m, 1H), 7.02 (m, 1H), 7.16 (m, 2H), 7.23 (d, 2H), 7.32 (s, 1H), 7.73 (s, 1H), 7.76 (s, 1H), 8.37 (s, 1H), 9.41 (s, 1H).
65		RT/18hrs/ NaOH/MeOH/ water	66	m/e 472 $(M+H)^+$	(d-6-DMSO, d values) 3.74 (s, 3H), 3.92 (s, 3H), 4.88 (s, 2H), 6.89 (d, 2H), 6.95 (m, 1H), 7.01 (m, 1H), 7.16 (m, 3H), 7.24 (d, 2H), 7.76 (s, 1H), 8.35 (s, 1H), 9.43 (bs, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
27	$CH{\equiv}CCH_2Br$	23°C/20hr/DMA/KOtBu	67	m/e 452.2 (M^+H)	(d-6-DMSO, d values) 3.63 (t, 1H), 3.75 (s, 3H), 3.9 (s, 3H), 5.0(d, 2H), 6.84-7.04 (m, 4H), 7.1-7.28 (m, 4H), 7.4 (s, 1H), 7.78 (s, 1H), 8.37(s, 1H), 9.42(s, 1H).
66	cyclopropyl amine	RT/18hrs/EDC / DMAP/DCM	68	m/e 511 $(M+H)^+$	(d-6-DMSO, d values) 0.47 (m, 2H), 0.63 (m, 2H), 2.66 (m, 1H), 3.74 (s, 3H), 3.96 (s, 3H), 4.70 (s, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.17 (m, 2H), 7.21 (m, 1H), 7.37 (d, 2H), 8.03 (s, 1H), 8.29 (m, 1H), 8.81 (s, 1H).
62	Chloropropyl morpholine	60°C/18hrs/ KO^{t}Bu/Bu_4NI/ 18-C-6/DMA	70	m/e 553.6 $(M-H^+)^-$	(d-6-DMSO, d values) 2.33 (m, 2H), 3.12 (m, 2H), 3.29 (m, 2H), 3.49 (m, 2H), 3.83 (m, 2H), 3.83 (m, 2H), 3.95 (m, 2H), 4.00 (s, 3H), 4.03 (m, 2H), 4.30 (m, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.17 (m, 2H), 7.38 (m, 2H), 7.54 (s, 1H), 8.18 (s, 1H), 8.88 (s, 1H).
102	diphenyl phosphoryl azide	100°C/18hrs/NEt3 /t-BuOH	71	m/e 513 $(M+H)^+$	(d-6-DMSO, d values) (broadened due to rotamers) 1.48 (bs, 9H), 3.71 (bs, 3H), 3.99 (bs, 3H), 6.92 (bm, 2H), 6.95 (bm, 3H), 7.03 (bm, 1H), 7.15 (bs, 1H), 7.40 (bm, 3H), 8.66 (bs, 1H), 8.80 (bs, 1H), 8.91 (bs, 1H), 10.93 (bs, 1H).
71		RT/2hrs/Et_3SiH/TFA	72	m/e 413 $(M+H)^+$	(d-6-DMSO, d values) 3.74 (s, 3H), 3.95 (s, 3H), 5.39 (bs, 2H), 6.85 (d, 2H), 6.91 (m, 1H), 6.96 (m, 1H), 7.10 (m, 3H), 7.20 (s, 1H), 7.29 (s, 1H), 8.24 (s, 1H), 9.06 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
27	$CH{\equiv}CCH_2Br$	23°C/20hr/DMA/KOtBu	67	m/e 452.2 $(M^+{+}H)$	(d-6-DMSO, d values) 3.63 (t, 1H), 3.75 (s, 3H), 3.9 (s, 3H), 5.0(d, 2H), 6.84-7.04 (m, 4H), 7.1-7.28 (m, 4H), 7.4 (s, 1H), 7.78 (s, 1H), 8.37(s, 1H), 9.42(s, 1H).
66	cyclopropylamine	RT/18hrs/EDC / DMAP/DCM	68	m/e 511 $(M+H)^+$	(d-6-DMSO, d values) 0.47 (m, 2H), 0.63 (m, 2H), 2.66 (m, 1H), 3.74 (s, 3H), 3.96 (s, 3H), 4.70 (s, 2H), 6.95 (m, 3H), 7.05 (m, 1H), 7.17 (m, 2H), 7.21 (m, 1H), 7.37 (d, 2H), 8.03 (s, 1H), 8.29 (m, 1H), 8.81 (s, 1H).
62	Chloropropylmorpholine	60°C/18hrs/ KO^{t}Bu/Bu_4NI/ 18-C-6/DMA	70	m/e 553.6 $(M\text{-}H^+)^-$	(d-6-DMSO, d values) 2.33 (m, 2H), 3.12 (m, 2H), 3.29 (m, 2H), 3.49 (m, 2H), 3.83 (m, 2H), 3.83 (m, 2H), 3.95 (m, 2H), 4.00 (s, 3H), 4.03 (m, 2H), 4.30 (m, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.17 (m, 2H), 7.38 (m, 2H), 7.54 (s, 1H), 8.18 (s, 1H), 8.88 (s, 1H).
102	diphenylphosphorylazide	100°C/18hrs/NEt3 /t-BuOH	71	m/e 513 $(M+H)^+$	(d-6-DMSO, d values) (broadened due to rotamers) 1.48 (bs, 9H), 3.71 (bs, 3H), 3.99 (bs, 3H), 6.92 (bm, 2H), 6.95 (bm, 3H), 7.03 (bm, 1H), 7.15 (bs, 1H), 7.40 (bm, 3H), 8.66 (bs, 1H), 8.80 (bs, 1H), 8.91 (bs, 1H), 10.93 (bs, 1H).
71		RT/2hrs/Et_3SiH/TFA	72	m/e 413 $(M+H)^+$	(d-6-DMSO, d values) 3.74 (s, 3H), 3.95 (s, 3H), 5.39 (bs, 2H), 6.85 (d, 2H), 6.91 (m, 1H), 6.96 (m, 1H), 7.10 (m, 3H), 7.20 (s, 1H), 7.29 (s, 1H), 8.24 (s, 1H), 9.06 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
72	$MeSO_2Cl$	70°C/12hrs/ pyridine	73	m/e 490 $(M+H)^+$	(d-6-DMSO, d values) 3.06 (s, 3H), 3.74 (s, 3H), 3.99 (s, 3H), 6.89 (d, 2H), 6.95 (m, 1H), 7.01 (m, 1H), 7.13 (m, 2H), 7.22 (d, 2H), 7.37 (s, 1H), 8.21 (s, 1H), 8.44 (s, 1H), 9.24 (bs, 1H), 9.65 (bs, 1H).
425		RT/3days/NaOH/MeOH/ water	102	m/e 442 $(M+H)^+$	(d-6-DMSO, d values) 3.74 (s, 3H), 3.95 (s, 3H), 6.89 (d, 2H), 6.95 (m, 1H), 7.01 (m, 1H), 7.14 (m, 2H), 7.25 (d, 2H), 7.37 (s, 1H), 8.49 (s, 1H), 8.78 (s, 1H), 9.89 (bs, 1H).
I11	1-Methyl piperazine	60°C/3hr/NaI	114	m/e 579 $(M+H)^+$	(d-6-DMSO, δ values) 2.25 (m, 2H), 2.80 (s, 3H), 3.24 - 3.53 (m under H2O, 10H), 3.56 (m, 1H), 3.99 (s, 3H), 4.30 (m, 2H), 4.80 (d, 2H), 6.96 - 7.05 (m, 4H), 7.16 - 7.28 (m, 2H), 7.40 (m, 2H), 7.46 (s, 1H), 8.22 (s, 1H), 8.91 (s, 1H).
108	N-(3chloro-propyl) morpholine	RT/15min/KOtBu/DMA then 60°C/4hr/nBu_4NI/18 crown 6	115		(d-6-DMSO, δ values) 2.23 - 2.36 (m, 2H), 3.03 - 3.16 (m, 2H), 3.24 - 3.34 (m, 2H), 3.42 - 3.51 (m, 2H), 3.71 - 3.83 (m, 2H), 3.92 - 4.03 (m, 5H), 4.35 (t, 2H), 6.75 (tt,), 6.90 (s, 1H), 7.00 - 7.06 (m, 2H), 7.21 - 7.28 (d, 2H), 7.46 - 7.56 (m, 4H), 8.31 (s, 1H), 8.92 (s, 1H).
I12	1-Methyl-piperazine	60°C/3hr/NaI	118	m/e 640 $(M+H)^+$	(d-6-DMSO, δ values) 2.23 - 2.37 (m, 2H), 2.80 (s, 3H), 3.39 - 3.78 (m underH2O, 10H), 4.00 (s, 3H), 4.35 (t, 2H), 6.76 (tt, 1H), 6.90 (m, 1H), 7.02 (dd, 1H), 7.24 (d, 2H), 7.45 (d, 1H), 7.50 - 7.56 (m, 3H), 8.37 (s, 1H), 8.93 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I12	1-Methyl-piperazine	60°C/3hr/NaI	119	m/e 585 $(M+H)^+$	(d-6-DMSO, δ values) 2.20 - 2.30 (m, 2H), 2.81 (s, 6H), 3.25 (m, 2H), 4.00 (s, 3H), 4.32 (t, 2H), 6.74 (tt, 1H), 6.90 (m, 1H), 7.02 (m, 1H), 7.24 (d, 2H), 7.44 - 7.56 (m, 4H), 8.27 (s, 1H), 8.95 (s, 1H).
I11	Morpholine	60°C/3hr/NaI	120	m/e 527 $(M+H)^+$	(d-6-DMSO, δ values) 1.87 - 2.00 (m, 2H), 2.32 - 2.40 (m, 2H), 3.50 - 3.59 (m, 4H), 3.77 - 3.88 (m, 4H), 3.94 (s, 3H), 4.13 (t, 2H), 6.78 (m, 1H), 6.87 - 7.02 (m, 5H), 7.22 (m, 2H), 7.30 (s, 1H), 7.75 (s, 1H), 8.36 (s, 1H), 9.39 (s, 1H), 9.49 (s, 1H).
I11	Dimethylamine	60°C/3hr/NaI/MeOH	121	m/e 485 $(M+H)^+$	(d-6-DMSO, δ values) 2.07 (m, 2H), 2.54 (s, 6H), 2.86 (m, 2H), 3.93 (s, 3H), 4.15 (t, 2H), 6.78 (m, 1H), 6.89 - 7.00 (m, 5H), 7.22 (d, 2H), 7.31 (s, 1H), 7.75 (s, 1H), 8.38 (s, 1H), 9.38 (s, 1H), 9.48 (bs, 1H).
I13	1-Methyl-piperazine	80°C/3hr/NaI	127	m/e 580 $(M+H)^+$	(d-6-DMSO, δ values) 2.21 - 2.32 (m, 2H), 2.79 (s, 3H), 3.19 - 3.65 (m under H2O, 10H), 4.00 (s, 3H), 4.32 (t, 2H), 4.57 (d, 2H), 5.16 (d, 1H), 5.28 (d, 1H), 5.86 - 6.00 (m, 1H), 6.93 - 7.00 (m, 3H), 7.06 (d, 1H), 7.17 (d, 2H), 7.39 (d, 2H), 7.52 (s, 1H), 8.32 (s, 1H), 8.91 (s, 1H), 9.70 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I13	Dimethyl amine	80°C/3hr/NaI/ MeOH	128	m/e 525.4 $(M+H)^+$	(d-6-DMSO, δ values) 2.20 - 2.30 (m, 2H), 2.77 (s, 3H), 2.79 (s, 3H), 3.16 - 3.31 (m under H2O, 2H), 3.99 (s, 3H), 4.30 (t, 2H), 4.57 (d, 2H), 5.17 (d, 1H), 5.29 (d, 1H), 5.86 - 6.00 (m, 1H), 6.92 - 7.00 (m, 3H), 7.06 (d, 1H), 7.16 (d, 2H), 7.39 (d, 2H), 7.49 (s, 1H), 8.29 (s, 1H), 8.89 (s, 1H).
I10	$CH\equiv CCH_2Br$	23°C/20hr/DM A/KOtBu	131	m/e 447 .2 $(M^+ + H)$	(d-6-DMSO, d values) 3.61(t, 1H), 3.94 (s, 3H), 4.93(d, 2H), 6.92 (d, 1H), 7.2-7.3 (m, 3H), 7.35 (s, 1H), 7.38 (d, 2H), 7.62(t, 1H) 7.88(s, 1H), 7.9 (d, 1H), 8.43 (s, 1H), 9.52 (s, 1H),
I30	$CH\equiv CCH_2Br$	23°C/20hr/DM A/KOtBu	132	m/e 447 $(M^+ + H)$	(d-6-DMSO, d values) 3.64(t, 1H), 3.92 (s, 3H), 5.0(d, 2H), 6.93 (d, 1H), 7.2-7.3 (m, 3H), 7.4 (d, 2H), 7.42 (s, 1H), 7.6(t, 1H) 7.8(s, 1H), 7.89 (d, 1H), 8.42 (s, 1H), 9.6 (s, 1H),
I14	Morpholine	RT/18hrs/NaI	137	m/e 570 $(M+H)^+$	(d-6-DMSO, d values) 2.29 (m, 2H), 3.10 (m, 2H), 3.29 (m, 2H), 3.47 (m, 2H), 3.60 (m, 2H), 3.79 (m, 2H), 4.00 (m, 5H), 4.32 (m, 2H), 6.95 (m, 4H), 7.14 (m, 2H), 7.41 (m, 2H), 7.47 (s, 1H), 8.28 (s, 1H), 8.95 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I15	Morpholine	RT/18hrs/NaI	138	m/e 571 $(M+H)^+$	(d-6-DMSO, d values) 2.34 (m, 2H), 3.08 (m, 2H), 3.29 (m, 2H), 3.49 (m, 2H), 3.62 (m, 2H), 3.84 (m, 2H), 3.93 (m, 1H), 4.01 (m, 5H), 4.31 (m, 2H), 6.97 (m, 4H), 7.17 (m, 2H), 7.41 (m, 2H), 7.57 (s, 1H), 8.25 (s, 1H), 8.93 (s, 1H).
130	N-(3-chloropropyl) -morpholine	80^0C/4hr/ KOtBu/tetrabutylammonium iodide/18-crown-6	139	m/e 536. 04 (M^+H)	(d-6-DMSO, d values) 1.94 (m, 2H), 2.3-2.5 (m, 4H), 3.29 (m, 2H), 3.57 (m, 4H), 3.92 (s, 3H), 4.2 (t, 2H), 6.93 (d, 1H), 7.13 (d, 2H), 7.16 (s, 1H), 7.2 (s, 1H), 7.29(d, 2H) 7.62 (t, 1H), 7.76 (s, 1H), 7.89 (d, 1H), 8.4 (s, 1H), 9.54(s, 1H).
427	Chloropropyl morpholine	60°C/18hrs/K O^{t}Bu/Bu_4NI/18 -C-6/DMA	142	m/e 596 $(M-H^+)^-$	(d-6-DMSO, d values) 2.34 (m, 2H), 2.61 (m, 3H), 3.11 (m, 2H), 3.26 (m, 2H), 3.47 (m, 2H), 3.82 (m, 2H), 3.96 (m, 2H), 4.01 (m, 3H), 4.30 (m, 2H), 4.47 (s, 2H), 7.05 (m, 6H), 7.29 (m, 1H), 7.43 (m, 2H), 7.54 (m, 2H), 8.21 (s, 1H), 8.92 (s, 1H).
129	Chloropropyl morpholine	60°C/18hrs/K O^{t}Bu/Bu_4NI/18 -C-6/DMA	143	m/e 596 $(M-H^+)^-$	(d-6-DMSO, d values) 2.31 (m, 2H), 2.62 (m, 3H), 3.13 (m, 2H), 3.29 (m, 2H), 3.46 (m, 2H), 3.82 (m, 2H), 3.92 (m, 2H), 3.99 (m, 3H), 4.34 (m, 2H), 4.47 (s, 2H), 7.06 (m, 6H), 7.43 (m, 2H), 7.54 (m, 2H), 8.37 (s, 1H), 8.93 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
113	Chloropropyl morpholine	60°C/18hrs/K O^{t}Bu/Bu$_4$NI/18 -C-6/DMA	154	m/e 625.5 $(M\text{-}H^+)^-$	(d-6-DMSO, d values) 2.33 (m, 2H), 3.11 (m, 2H), 3.29 (m, 2H), 3.35 (m, 2H), 3.82 (m, 2H), 3.96 (m, 2H), 3.98 (s, 3H), 4.32 (m, 2H), 6.76 (tt, 1H), 7.04 (m, 2H), 7.24 (m, 2H), 7.49 (m, 1H), 7.54 (m, 3H), 8.21 (s, 1H), 8.89 (s, 1H).
219		75°C/1.5hr/TF A/ Thioanisole	218	m/e 417.4 $(M+H)^+$	(d-6-DMSO, δ values) 2.24 (s, 3H), 3.94 (s, 3H), 7.21 - 7.39 (m, 6H), 7.77 (s, 1H), 8.00 (s, 1H), 8.25 (s, 1H), 9.20 (s, 1H), 10.34 (bs, 1H).
I7	Piperidine	RT/18hrs/NaI	170	m/e 581.5 $(M\text{-}H^+)^-$	(d-6-DMSO, d values) 1.51 (m, 2H), 1.71 (m, 4H), 2.18 (m, 2H), 3.08 (m, 6H), 3.91 (s, 3H), 4.24 (m, 2H), 4.66 (s, 2H), 7.03 (m, 6H), 7.24 (m, 2H), 7.33 (s, 1H), 7.76 (s, 1H), 8.37 (s, 1H), 9.46 (s, 1H).
I4 (Ex. 7)	morpholine	23°C/24hr/NaI	175	m/e 628.58 $(M^+\text{+H})$	(d-6-DMSO, d values) 2.32 (m, 2H), 3.0-3.64 (m, 10H), 3.8 (t, 2H), 3.96 (m, 2H), 3.98 (s, 3H), 4.28 (t, 2H), 4.48(s, 2H), 6.94-7.21 (m, 6H), 7.4 (d, 2H), 7.52 (s, 1H), 7.6 (t, 1H), 8.11 (s, 1H), 8.85 (s, 1H).
I4	pyrollidine	23°C/24hr/NaI	176	m/e 612.56 $(M^+\text{+H})$	(d-6-DMSO, d values) 1.89 (m, 2H), 2.0 (m, 2H), 2.28 (m, 2H), 3.02 (m, 2H), 3.15 (q, 2H), 3.2-3.7 (m, 6H), 3.98 (s, 3H), 4.29 (t, 2H), 4.48(s, 2H), 6.95-7.21 (m, 6H), 7.4 (d, 2H), 7.5 (s, 1H), 7.6 (t, 1H), 8.16 (s, 1H), 8.86 (s, 1H).

WO 00/68201 PCT/GB00/01697

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I4	dimethyl-morpholine	23°C/24hr/NaI	177	m/e 656.6 (M^++H)	(d-6-DMSO, d values) 1.14 (d, 6H), 2.22-2.74 (m,4H), 3.1-3.62 (m, 8H), 3.9-4.09 (m, 5H), 4.3 (t, 2H), 4.48 (s, 2H), 6.95-7.21 (m, 6H), 7.4 (d, 2H), 7.47 (s, 1H), 7.6 (t, 1H), 8.1 (s, 1H), 8.85 (s, 1H).
I4	1-acetyl-piperazine	23°C/24hr/NaI	194	m/e 669.59 (M^++H)	(d-6-DMSO, d values) 2.0 (s, 3H), 2.32 (m,2H), 2.84-3.7 (m, 14H), 3.99 (s, 3H), 4.3 (t, 2H), 4.42 (br.d., 1H), 4.48 (s, 2H), 6.95-7.22 (m, 6H), 7.4 (d, 2H), 7.46 (s, 1H), 7.6 (t, 1H), 8.18 (s, 1H), 8.84 (s, 1H), 9.2 (br.s., 1H).
27	4-chloromethyl-pyridine	RT/48hr/DMSO/ KOtBu(1M in THF)	197	m/e 505 (M^++H)	(d-6-DMSO, d values) 3.75 (s, 3H), 4.03 (s, 3H), 5.53 (s, 2H), 6.96 (m, 3H), 7.05 (m, 1H), 7.18 (m, 2H), 7.38 (d, 2H), 7.53 (s, 1H), 7.74 (d, 2H), 8.20 (s, 1H), 8.74 (d, 2H), 8.79 (s, 1H), 10.93 (broad, 1H)
I16	1-Methyl-piperazine	60°C/16hr/NaI	204	m/e 555 $(M+H)^+$	(d-6-DMSO, δ values) 2.24 - 2.37 (m, 2H), 2.78 (s, 3H), 3.19 - 3.62 (m underH2O, 10H), 3.67 (s, 3H), 3.99 (s, 3H), 4.36 (t, 2H), 6.98 (t, 1H), 7.08 - 7.15 (m, 3H), 7.21 (t, 1H), 7.55 (s, 1H), 7.90 (dd, 1H), 8.19 (d, 1H), 8.41 (m, 1H), 8.95 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I17	1-Methyl-piperazine	60°C/16hr/NaI	205	m/e 555 $(M+H)^+$	(d-6-DMSO, δ values) 2.26 - 2.38 (m, 2H), 2.80 (s, 3H), 3.20 - 3.66 (m underH2O, 10H), 3.70 (s, 3H), 4.01 (s, 3H), 4.31 (t, 2H), 6.98 (t, 1H), 7.09 - 7.16 (m, 3H), 7.21 (m, 1H), 7.52 (s, 1H), 7.92 (dd, 1H), 8.19 (d, 1H), 8.25 (s, 1H), 8.92 (s, 1H), 9.62 (bs, 1H).
I16	Dimethyl amine	60°C/16hr/NaI/ MeOH	206	m/e 500 $(M+H)^+$	(d-6-DMSO, δ values) 2.19 - 2.30 (m, 2H), 2.79 (s, 3H), 2.80 (s, 3H), 3.16 - 3.28 (m, 2H), 3.68 (s, 3H), 3.99 (s, 3H), 4.32 (t, 2H), 6.98 (t, 1H), 7.08 - 7.16 (m, 3H), 7.21 (m, 1H), 7.48 (s, 1H), 7.89 (d, 1H), 8.17 (d, 1H), 8.34 (s, 1H), 8.88 (s, 1H).
I17	Dimethyl amine	60°C/16hr/NaI/ MeOH	207	m/e 500 $(M+H)^+$	(d-6-DMSO, δ values) 2.18 - 2.28 (m, 2H), 2.76 (s, 6H), 3.16 - 3.22 (m, 2H), 3.68 (s, 3H), 3.95 (s, 3H), 4.26 (t, 2H), 6.96 (t, 1H), 7.00 (d, 1H), 7.11 (d, 2H), 7.19 (m, 1H), 7.32 (s, 1H), 7.76 (dd, 1H), 7.92 (s, 1H), 8.06 (d, 1H), 8.38 (s, 1H), 9.73 (s, 1H).
220	N-(3-chloro-propyl) morpholine	RT/15min/ KOtBu/DMA then RT/18hr/ nBu_4NI/18-crown-6	208		(d-6-DMSO, δ values) 2.24 - 2.35 (m, 2H), 3.04 - 3.16 (m, 2H), 3.24 - 3.33 (m, 2H), 3.43 - 3.51 (m, 2H), 3.68 (s, 3H), 3.72 - 3.83 (m, 2H), 3.91 - 3.98 (m, 2H), 3.99 (s, 3H), 4.34 (t, 2H), 6.98 (t, 1H), 7.08 - 7.14 (m, 3H), 7.21 (m, 1H), 7.47 (s, 1H), 7.90 (dd, 1H), 8.19 (d, 1H), 8.31 (m, 1H), 8.92 (s, 1H).

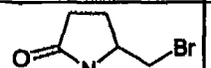
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
221	N-(3-chloro-propyl) morpholine	i) RT/15min/KOt Bu/DMA then ii) RT/18hr/(2)/ nBu_4NI/18-crown-6	209		(d-6-DMSO, δ values) 2.27 - 2.36 (m, 2H), 3.04 - 3.19 (m, 2H), 3.24 - 3.31 (m, 2H), 3.44 - 3.54 (m, 2H), 3.68 (s, 3H), 3.74 - 3.86 (m, 2H), 3.93 - 3.98 (m, 2H), 3.99 (s, 3H), 4.31 (t, 2H), 6.98 (t, 1H), 7.08 - 7.15 (m, 3H), 7.21 (t, 1H), 7.50 (s, 1H), 7.91 (dd, 1H), 8.19 (m, 2H), 8.92 (s, 1H).
203	N-(3-chloropropyl) morpholine	i) RT/15min/KOt Bu/DMA then ii) RT/16hr/(2)/ nBu_4NI/18-crown-6	210	m/e 543 $(M+H)^+$	(d-6-DMSO D4 Acetic, δ values) 2.23 - 2.37 (m, 2H), 3.04 - 3.17 (m, 2H),3.29 (t, 2H), 3.44 - 3.54 (m, 2H), 3.67 (s, 3H), 3.73 - 3.84 (m, 2H), 3.92 - 3.99 (m, 2H), 4.00 (s, 3H), 4.31 (t, 2H), 6.99 (t, 1H), 7.11 - 7.28 (m, 3H), 7.49 (s, 1H), 8.18 (s, 1H), 8.75 (s, 2H), 8.90 (s, 1H).
222		75°C/1.5hr/ TFA/ Thioanisole	211	m/e 429.4 $(M+H)^+$	(d-6-DMSO, δ values) 2.20 (s, 3H), 3.67 (s, 3H), 3.93 (s, 3H), 6.93 - 7.00 (m, 2H), 7.08 - 7.12 (m, 2H), 7.16 - 7.20 (m, 2H), 7.79 (s, 1H), 7.98 (s, 1H), 8.25 (s, 1H), 9.20 (s, 1H), 10.31 (bs, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I20	pyrrolidine	RT/48hr/NaI	214	m/e 623.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.20 (m, 2H), 0.41 (m, 2H), 0.96 (m, 1H), 1.86 - 2.09 (m, 4H), 2.25 - 2.36 (m, 2H), 3.00 - 3.12 (m, 4H), 3.34 (t, 2H), 3.61 (m, 2H), 4.04 (s, 3H), 4.34 (t, 2H), 4.48 (s, 2H), 6.72 - 6.81 (m, 2H), 6.85 (dd, 1H), 7.22 (d, 1H), 7.35 (t, 1H), 7.53 (s, 1H), 7.99 (dd, 1H), 8.24 (s, 1H), 8.35 (d, 1H), 8.95 (s, 1H).
I6	Morpholine	RT/48hr/NaI	215	m/e 542.5 $(M+H)^+$	(d-6-DMSO, δ values) 1.99 (t, 2H), 2.34 - 2.45 (m, 4H), 3.52 - 3.61 (m, 4H), 3.79 (s, 3H), 3.96 (s, 3H), 4.20 (t, 2H), 7.03 (t, 1H), 7.20 - 7.32 (m, 3H), 7.40 (s, 1H), 7.55 (d, 1H), 7.78 (m, 1H), 8.06 (s, 1H), 8.61 (d, 1H), 9.38 (s, 1H), 9.47 (bs, 1H).
I33	Morpholine	RT/48hr/NaI	216	m/e 599.5 $(M+H)^+$	(d-6-DMSO, δ values) 2.21 (m, 2H), 2.61 (d, 3H), 4.00 (s, 3H), 4.27 (t, 2H), 4.52 (s, 2H), 7.09 (t, 1H), 7.18 (d, 1H), 7.27 (t, 2H), 7.49 (s, 1H), 7.64 (m, 1H), 7.75 (m, 1H), 7.87 (dd, 1H), 8.15 (s, 1H), 8.77 (d, 1H), 9.49 (s, 1H), 9.70 (bs, 1H). HPLC time 6.99, 93.5%

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I24	dimethyl morpholine	RT/72hr/NaI	223	m/e 653.6 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.48 (m, 2H), 0.61 (m, 2H), 1.14 (s, 3H), 1.16 (s, 3H), 2.29 - 2.37 (m, 2H), 2.59 - 2.71 (m, 3H), 3.26 (m, 2H), 3.50 (d, 2H), 3.89 - 3.96 (m, 2H), 4.00 (s, 3H), 4.30 (t, 2H), 4.41 (s, 2H), 6.68 - 6.74 (m, 2H), 6.77 (d, 1H), 7.19 (d, 1H), 7.31 (t, 1H), 7.48 (s, 1H), 7.97 (dd, 1H), 8.19 (s, 1H), 8.31 (d, 1H), 8.93 (s, 1H).
I24	pyrollidine	RT/48hr/NaI	224	m/e 609.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.47 (m, 2H), 0.61 (m, 2H), 1.84 - 2.06 (m, 4H), 2.21 - 2.31 (m, 2H), 2.68 (m, 1H), 2.98 - 3.10 (m, 2H), 3.31 (t, 2H), 3.59 (m, 2H), 4.00 (s, 3H), 4.30 (t, 2H), 4.41 (s, 2H), 6.68 - 6.72 (m, 2H), 6.76 (dd, 1H), 7.18 (d, 1H), 7.31 (t, 1H), 7.48 (s, 1H), 7.95 (dd, 1H), 8.15 (s, 1H), 8.29 (d, 1H), 8.89 (s, 1H).
I20	dimethylmorpholine	RT/72hr/NaI	225	m/e 677.6 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.20 (m, 2H), 0.31 (m, 2H), 0.96 (m, 1H), 1.15 (s, 3H), 1.19 (s, 3H), 2.36 (m, 2H), 2.70 (m, 2H), 3.04 (d, 2H), 3.20 (t, 2H), 3.55 (d, 2H), 3.94 - 4.02 (m, 2H), 4.04 (s, 3H), 4.34 (m, 2H), 4.50 (s, 2H), 6.73 - 6.80 (m, 2H), 6.85 (dd, 1H), 7.23 (d, 1H), 7.36 (t, 1H), 7.51 (s, 1H), 8.00 (dd, 1H), 8.20 (s, 1H), 8.33 (d, 1H), 8.95 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
272		75°C/2hrs/thio anisole/TFA	273	m/e 391 $(M+H)^+$	(d-6-DMSO, d values) 3.93 (s, 3H), 8.00 (d, 1H), 8.02 (d, 1H), 8.33 (d, 2H), 8.42 (s, 1H), 8.45 (s, 1H), 8.61 (m, 2H), 8.76 (m, 2H).
I1	Morpholine	RT/18hrs/NaI	274	m/e 518 $(M+H)^+$	(d-6-DMSO, d values) 2.31 (m, 2H), 3.28 (m, 2H), 3.4-3.6 (m, 4H (under H_2O peak)), 3.83 (m, 2H), 3.92 (m, 2H), 3.99 (s, 3H), 4.36 (m, 2H), 7.26 (d, 1H), 7.32 (d, 1H), 7.46 (m, 2H), 7.55 (m, 3H), 8.41 (s, 1H), 8.95 (s, 1H).
I1	N-methylpiperidine	RT/18hrs/NaI	275	m/e 531 (M^+H)	(d-6-DMSO, d values) 2.25 (m, 2H), 2.83 (s, 3H), 3.2-3.7 (m, 10H (under H_2O peak)), 3.99 (s, 3H), 4.32 (m, 2H), 7.25 (d, 1H), 7.33 (d, 1H), 7.50 (m, 5H), 8.26 (bs, 1H), 8.92 (s, 1H).
I1	pyrrolidine	RT/18hrs/NaI	276	m/e 531 (M^+H)	(d-6-DMSO, d values) 1.86 (m, 2H), 2.02 (m, 2H), 2.25 (m, 2H), 3.26 (m, 2H), 3.58 (m, 2H), 3.75 (m, 2H), 3.97 (s, 3H), 4.31 (m, 2H), 7.26 (d, 1H), 7.33 (d, 1H), 7.47 (m, 3H), 7.55 (m, 2H), 8.28 (s, 1H), 9.0 (s, 1H).
I1	piperidine	RT/18hrs/NaI	277	m/e 516 (M^+H)	(d-6-DMSO, d values) 1.53 (m, 1H), 1.61 (m, 4H), 1.80 (m, 1H), 2.23 (m, 2H), 2.97 (m, 4H), 3.21 (m, 2H), 3.99 (s, 3H), 4.28 (m, 2H), 7.28 (d, 1H), 7.33 (d, 1H), 7.40 (s, 1H), 7.47 (m, 4H), 8.11 (s, 1H), 8.88 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I2	morpholine	RT/18hrs/NaI	278	m/e 504 (M^++H)	(d-6-DMSO, d values) 3.26 (m, 2H), 3.42-3.7 (m, 4H (under H_2O peak)), 3.83 (m, 2H), 3.95 (m, 2H), 4.01 (s, 3H), 4.73 (m, 2H), 7.28 (d, 1H), 7.33 (d, 1H), 7.47 (m, 2H), 7.54 (m, 3H), 8.47 (s, 1H), 8.97 (s, 1H).
I2	N-methyl piperidine	RT/36hrs/NaI	279	m/e 531 (M^++H)	(d-6-DMSO, d values) 3.26 (m, 2H), 3.42-3.7 (m, 4H (under H_2O peak)), 3.83 (m, 2H), 3.95 (m, 2H), 4.01 (s, 3H), 4.73 (m, 2H), 7.28 (d, 1H), 7.33 (d, 1H), 7.47 (m, 2H), 7.54 (m, 3H), 8.47 (s, 1H), 8.97 (s, 1H).
I2	piperidine	RT/36hrs/NaI	280	m/e 502 (M^++H)	(d-6-DMSO, d values) 1.53 (m, 1H), 1.64 (m, 4H), 1.80 (m, 1H), 3.01 (m, 4H), 3.4-3.6 (m, 2H (under H_2O peak)), 4.02 (s, 3H), 4.61 (m, 2H), 7.26 (d, 1H), 7.32 (d, 1H), 7.44 (m, 2H), 7.50 (m, 3H), 8.26 (s, 1H), 8.92 (s, 1H).
I2	dimethyl amine	RT/36hrs/NaI/ ethanol	281	m/e 462 (M^++H)	(d-6-DMSO, d values) 2.91 (d, 6H), 3.5-3.7 (m, 2H (under H_2O peak)), 4.00 (s, 3H), 4.68 (m, 2H), 7.28 (d, 1H), 7.33 (d, 1H), 7.46 (m, 2H), 7.54 (m, 3H), 8.53 (s, 1H), 8.95 (s, 1H).
300		75°C/2hrs/ thioanisole/ TFA	282	m/e 391 (M^++H)	(d-6-DMSO, d values) 3.90 (s, 3H), 7.21 (d, 2H), 7.30 (m, 3H), 7.37 (m, 2H), 7.69 (s, 1H), 8.40 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I3	morpholine	RT/18hrs/NaI	283	m/e 488 (M^++H)	(d-6-DMSO, d values) 2.31 (m, 2H), 3.08 (m, 2H), 3.29 (m, 2H), 3.35 (m, 2H), 3.81 (m, 2H), 3.95 (m, 2H), 4.01 (s, 3H), 4.31 (m, 2H), 7.26 (d, 1H), 7.33 (d, 1H), 7.47 (m, 2H), 7.54 (m, 3H), 8.22 (s, 1H), 8.94 (s, 1H).
I3	N-methyl piperazine	RT/18hrs/NaI	284	m/e 531 (M^++H)	(d-6-DMSO, d values) 2.34 (m, 2H), 2.84 (bs, 3H), 3.25-3.8 (m, 10H (under H_2O peak)), 4.02 (s, 3H), 4.31 (m, 2H), 7.26 (d, 1H), 7.33 (d, 1H), 7.47 (m, 2H), 7.55 (m, 3H), 8.26 (s, 1H), 8.96 (s, 1H).
282		RT/18hr/DMA KOtBu/18-crown-6	285	m/e 488 (M^++H)	(d-6-DMSO, d values) 1.95 (m, 2H), 2.10-2.4 (m, 3H), 3.99 (s, 3H), 4.15 (m, 2H), 7.27 (m, 1H), 7.35 (d, 1H), 7.52 (m, 4H), 7.80 (s, 1H), 8.08 (s, 1H), 8.98 (s, 1H).
I3	dimethyl amine	50°C/18hrs/ NaI/ ethanol	286	m/e 476 (M^++H)	(d-6-DMSO, d values) 2.28 (m, 2H), 2.82 (m, 6H), 3.24 (m, 2H), 3.97 (s, 3H), 4.28 (m, 2H), 7.28 (d, 1H), 7.34 (d, 1H), 7.45 (s, 1H), 7.50 (m, 4H), 8.09 (s, 1H), 8.88 (s, 1H), 9.95 (bs, 1H).
288		RT/18hrs/NaOH/MeOH/ water	289	m/e 449 $(M+H)^+$	(d-6-DMSO, d values) 3.92 (s, 3H), 4.90 (s, 2H), 7.21 (m, 2H), 7.30 (d, 1H), 7.34 (m, 4H), 7.74 (s, 1H), 8.45 (s, 1H), 9.51 (bs, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
289	methylamine	RT/18hrs/ THF/EDC/DMAP/DCM	291	m/e 462 $(M+H)^+$	(d-6-DMSO, d values) 2.66 (d, 3H), 3.99 (s, 3H), 4.74 (s, 2H), 7.26 (m, 2H), 7.31 (d, 1H), 7.45 (m, 4H), 7.97 (s, 1H), 8.06 (bs, 1H), 8.76 (s, 1H).
301		75°C/2hrs/ Et_3SiH/ TFA	293	m/e 476 (M^+H)	(d-6-DMSO, d values) 4.03 (s, 3H), 7.26 (m, 2H), 7.32 (d, 1H), 7.45 (m, 4H), 7.50 (m, 1H), 8.81 (s, 1H).
289	cyclopropyl-amine	RT/1 week/EDC/ DMAP/DMA	302	m/e 488 (M^+H)	d-6-DMSO, d values) 0.47 (m, 2H), 0.64 (m, 2H), 2.70 (m, 1H), 3.97 (s, 3H), 4.68 (s, 2H), 7.26 (m, 2H), 7.32 (m, 1H), 7.46 (m, 4H), 8.03 (s, 1H), 8.29 (m, 1H), 8.84 (s, 1H).
I3	cyclopropyl-amine	RT/18hr/NaI	319	m/e 488 (M^+H)	(d-6-DMSO, d values) 1.13 (d, 6H), 2.34 (m, 2H), 2.56 (d, 3H), 2.61 (m, 2H), 3.24 (m, 2H), 3.50 (m, 2H), 3.58 (s, 2H), 3.98 (m, 5H), 4.29 (2H, m), 6.20 (m, 1H), 6.26 (m, 1H), 6.33 (m, 1H), 7.05 (m, 3H), 7.45 (d, 2H), 7.54 (s, 1H), 7.81 (m, 1H), 8.26 (s, 1H), 8.93 (s, 1H).
I3	dimethyl-morpholine	RT/18hr/NaI	260	m/e 546 (M^+H)	(d-6-DMSO, d values) 1.13 (d, 6H), 2.31 (m, 2H), 2.66 (m, 2H), 3.24 (m, 2H), 3.97 (bs, 5H), 4.28 (m, 2H), 7.26 (d, 1H), 7.32 (d, 1H), 7.49 (m, 5H), 8.13 (s, 1H), 8.89 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I19	2,6-dimethylmopholine	5 days	448		(d-6-DMSO, d values) 1.02 (d, 6H), 1.58 (t, 2H), 1.94 (t, 3H), 2.42(m, 2H), 2.56 (d, 3H), 2.75 (d, 2H), 3.53 (m, 2H), 3.69 (d, 2H), 3.91 (s, 3H), 4.17 (t, 2H), 4.53(s, 2H), 7.0 (m, 4H), 7.11 (m, 2H), 7.22 (s, 1H), 7.28 (d, 2H), 7.74 (m, 2H), 7.88 (t, 1H), 8.35 (s, 1H), 9.4 (s, 1H).
I22	dimethylmorpholine	RT/72hr/NaI	449	m/e 666.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.20 (m, 2H), 0.43 (m, 2H), 0.96 (m, 1H), 1.17 (s, 3H), 1.19 (s, 3H), 2.32 - 2.42 (m, 2H), 2.60 (m, 2H), 3.04 (d, 2H), 3.20 (t, 2H), 3.55 (d, 2H), 3.93 - 4.15 (m, 5H), 4.34 (t, 2H), 4.48 (s, 2H), 6.62 - 6.70 (m, 2H), 7.19 (d, 2H), 7.32 (t, 1H), 7.47 - 7.53 (m, 3H), 8.14 (s, 1H), 8.88 (s, 1H).
I21	dimethylmorpholine	RT/72hr/NaI	450	m/e 666.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 1.14 (s, 3H), 1.16 (s, 3H), 1.62 (m, 2H), 1.96 (m, 2H), 2.12 (m, 2H), 2.34 (m, 2H), 2.67 (t, 2H), 3.27 (t, 2H), 3.50 (d, 2H), 3.89 - 4.01 (m, 5H), 4.18 - 4.26 (m, 1H), 4.30 (t, 2H), 4.39 (s, 2H), 6.59 - 6.65 (m, 2H), 6.72 (dd, 1H), 7.16 (d, 2H), 7.27 (t, 1H), 7.45 - 7.52 (m, 3H), 8.14 (s, 1H), 8.89 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I22	pyrrolidine	RT/48hr/NaI	451	m/e 622.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.19 (m, 2H), 0.41 (m, 2H), 0.95 (m, 1H), 1.88 - 2.10 (m, 2H), 2.15 - 2.36 (m, 2H), 3.02 (d, 2H), 3.07 - 3.14 (m, 2H), 3.34 (t, 2H), 3.61 (m, 2H), 4.02 (s, 3H), 4.33 (t, 2H), 4.47 (s, 2H), 6.62 - 6.70 (dd, 1H), 7.18 (d, 2H), 7.31 (t, 1H), 7.46 - 7.56 (m, 3H), 8.24 (s, 1H), 8.89 (s, 1H).
I21	pyrrolidine	RT/48hr/NaI	452	m/e 622.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 1.60 (m, 2H), 1.84 - 2.03 (m, 6H), 2.13 (m, 2H), 2.29 (m, 2H), 3.05 (m, 2H), 3.30(t, 2H), 3.56 (m, 2H), 4.00 (s, 3H), 4.19 - 4.26 (m, 1H), 4.30 (t, 2H), 4.39 (s, 2H), 6.59 - 6.63 (m, 2H), 6.71 (d, 1H), 7.14 (d, 2H), 7.28 (t, 1H), 7.46 (d, 2H), 7.52 (s, 1H), 8.18 (s, 1H), 8.81 (s, 1H).
I23	pyrrolidine	RT/48hr/NaI	453	m/e 608.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.46 (m, 2H), 0.60 (m, 2H), 1.83 - 2.06 (m, 4H), 2.28 (m, 2H), 2.66 (m, 1H), 2.95 - 3.05 (m, 2H), 3.30 (t, 2H), 3.56 (m, 2H), 3.99 (s, 3H), 4.28 (t, 2H), 4.39 (s, 2H), 6.58 - 6.62 (m, 2H), 6.68 (dd, 1H), 7.13 (d, 2H), 7.26 (t, 1H), 7.47 (d, 2H), 7.54 (s, 1H), 8.22 (s, 1H), 8.87 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I23	dimethylmorpholine	RT/72hr/NaI	454	m/e 652.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 0.46 (m, 2H), 0.61 (m, 2H), 1.11 (s, 3H), 1.14 (s, 3H), 2.34 (m, 2H), 2.59 - 2.72 (m, 3H), 3.26 (t, 2H), 3.50 (d, 2H), 3.89 - 4.01 (m, 5H), 4.30 (t, 2H), 4.39 (s, 2H), 6.58 - 6.62 (m, 2H), 6.769(d, 1H), 7.15 (d, 2H), 7.27 (t, 1H), 7.44 - 7.50 (m, 3H), 8.14 (s, 1H), 8.90 (s, 1H).
I25	dimethylmorpholine	RT/72hr/NaI	455	m/e 596.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 1.13 (s, 3H), 1.15 (s, 3H), 2.32 (m, 2H), 2.65 (t, 2H), 2.75 (s, 3H), 3.26 (m, 2H), 3.50 (d, 2H), 3.89 - 3.95 (m, 2H), 3.96 (s, 3H), 4.28 (t, 2H), 7.15 (d, 3H), 7.40 - 7.49 (m, 5H), 7.59 (d, 1H), 8.08 (s, 1H), 8.80 (s, 1H).
I25	pyrrolidine	RT/48hr/NaI	456	m/e 552.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 1.81 - 2.05 (m, 4H), 2.28 (m, 2H), 2.76 (s, 3H), 3.04 (m, 2H), 3.31 (t, 2H), 3.57 (m, 2H), 3.99 (s, 3H), 4.30 (t, 2H), 7.12 - 7.20 (m, 3H), 7.42 - 7.52 (m, 5H), 7.59 (d, 1H), 8.16 (s, 1H), 8.94 (s, 1H).
I26	dimethylmorpholine	RT/72hr/NaI	457	m/e 570.5 (M^++H)	(d-6-DMSO d-4-Acetic, δ values) 1.12 (s, 3H), 1.15 (s, 3H), 2.34 (m, 2H), 2.66 (t, 2H), 3.25 (t, 2H), 3.51 (d, 2H), 3.72 (s, 3H), 3.91 - 3.99 (m, 2H), 4.00 (s, 3H), 4.30 (t, 2H), 6.69 (m, 2H), 6.77 (dd, 1H), 7.19 (d, 1H), 7.30 (t, 1H), 7.50 (s, 1H), 7.97 (dd, 1H), 8.21 (s, 1H), 8.32 (d, 1H), 8.92 (s, 1H).

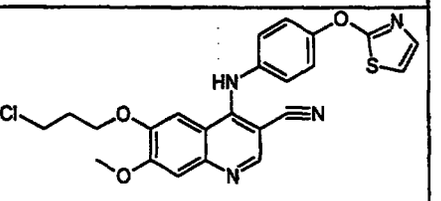
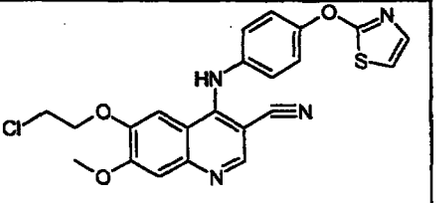
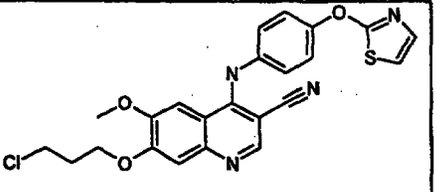
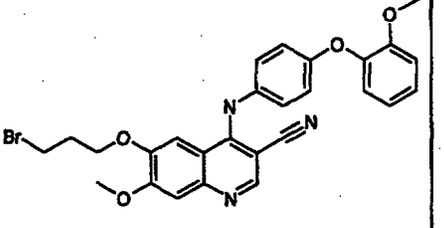
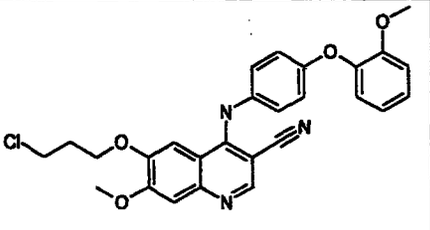
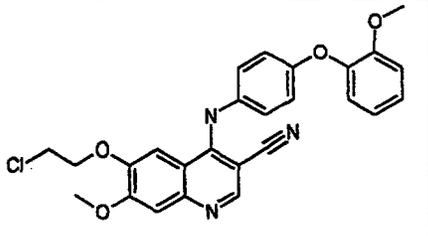
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I27	morpholine	RT/18hr/NaI	458	m/e 623 (M^++H)	(d-6-DMSO, d values) 0.39 (m, 2H), 0.59 (m, 2H), 2.33 (m, 2H), 2.63 (m, 1H), 3.28 (m, 2H), 3.49 (m, 2H), 3.56 (s, 2H), 3.82 (2H, m), 3.94 (m, 2H), 3.99 (s, 3H), 4.30 (2H, m), 6.20 (m, 1H), 6.26 (m, 1H), 6.34 (m, 1H), 7.07 (m, 4H), 7.44 (d, 2H), 7.52 (s, 1H), 8.20 (m, 1H), 8.92 (s, 1H).
I27	dimethylmorpholine	RT/18hr/NaI	459	m/e 651 (M^++H)	(d-6-DMSO, d values) 0.39 (m, 2H), 0.59 (m, 2H), 1.13 (d, 6H), 2.36 (m, 2H), 2.65 (m, 3H), 3.26 (m, 2H), 3.53 (m, 4H), 3.99 (5H, m), 4.31 (m, 2H), 6.20 (m, 1H), 6.27 (m, 1H), 6.35 (m, 1H), 7.07 (m, 3H), 7.45 (d, 2H), 7.52 (s, 1H), 8.18 (m, 1H), 8.97 (s, 1H).
I27	pyrrolidine	RT/18hr/NaI	460	m/e 607 (M^++H)	(d-6-DMSO, d values) 0.38 (m, 2H), 0.60 (m, 2H), 1.89 (m, 2H), 2.01 (m, 2H), 2.37 (m, 2H), 2.64 (m, 1H), 3.03 (m, 2H), 3.31 (m, 2H), 3.57 (m, 4H), 4.00 (s, 3H), 4.30 (m, 2H), 6.21 (m, 1H), 6.27 (m, 1H), 6.34 (m, 1H), 7.08 (m, 3H), 7.46 (d, 2H), 7.52 (s, 1H), 7.96 (m, 1H), 8.21 (s, 1H), 8.94 (s, 1H).

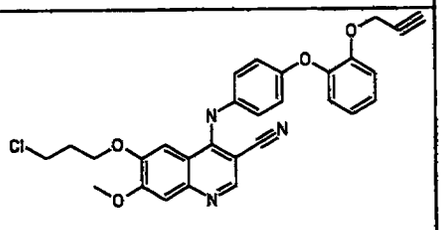
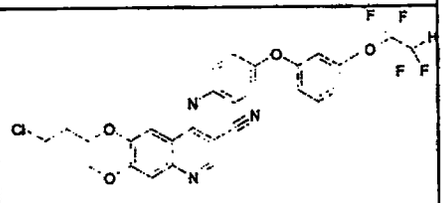
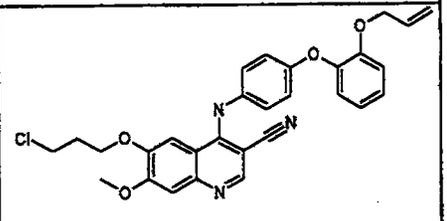
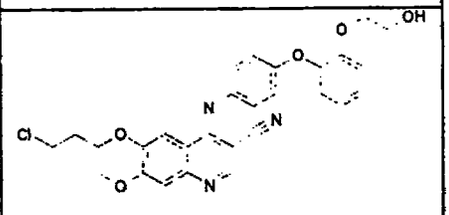
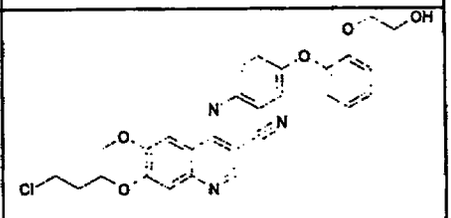
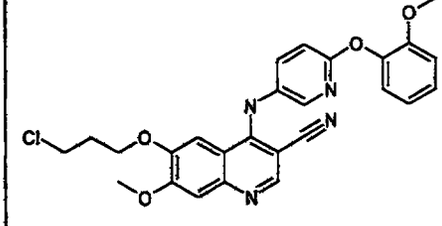
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I28	morpholine	RT/18hr/NaI	461	m/e 637 (M^++H)	(d-6-DMSO, d values) 0.20 (m, 2H), 0.45 (m, 2H), 0.96 (m, 1H), 2.42 (m, 2H), 3.17 (m, 2H), 3.37 (m, 2H), 3.57 (m, 2H), 3.70 (s, 2H), 3.91 (m, 2H), 4.07 (m, 5H), 4.40 (2H, m), 6.30 (m, 1H), 6.38 (m, 1H), 6.46 (m, 1H), 7.14 (m, 3H), 7.53 (d, 2H), 7.61 (s, 1H), 8.01 (m, 1H), 8.30 (s, 1H), 9.01 (s, 1H).
I28	dimethylmorpholine	RT/18hr/NaI	462	m/e 665 (M^++H)	(d-6-DMSO, d values) 0.17 (m, 2H), 0.41 (m, 2H), 0.93 (m, 1H), 1.20 (d, 6H), 2.42 (m, 2H), 2.71 (m, 2H), 3.30 (m, 2H), 3.56 (m, 2H), 3.66 (s, 2H), 3.80 (m, 2H), 4.05 (m, 5H), 4.37 (2H, m), 6.27 (m, 1H), 6.34 (m, 1H), 6.42 (m, 1H), 7.15 (m, 3H), 7.51 (d, 2H), 7.58 (s, 1H), 7.97 (m, 1H), 8.27 (s, 1H), 8.98 (s, 1H).
I28	pyrrolidine	RT/18hr/NaI	463	m/e 621 (M^++H)	(d-6-DMSO, d values) 0.11 (m, 2H), 0.36 (m, 2H), 0.87 (m, 1H), 1.87 (m, 2H), 2.00 (m, 2H), 2.29 (m, 2H), 2.96 (m, 2H), 3.02 (m, 2H), 3.31 (m, 2H), 3.56 (m, 2H), 3.61 (s, 2H), 4.00 (s, 3H), 4.29 (2H, m), 6.23 (m, 1H), 6.30 (m, 1H), 6.38 (m, 1H), 7.11 (m, 3H), 7.45 (d, 2H), 7.56 (s, 1H), 7.95 (m, 1H), 8.28 (s, 1H), 8.96 (s, 1H).

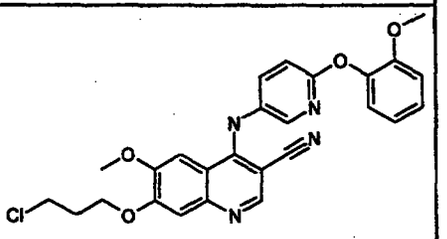
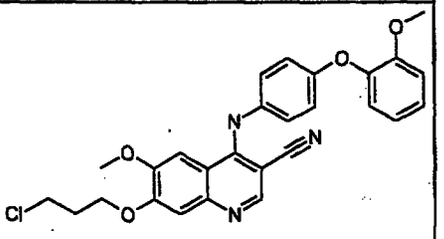
Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I29	morpholine	RT/18hr/NaI	464	m/e 597 (M^++H)	(d-6-DMSO, d values) 2.31 (m, 2H), 3.26 (m, 2H), 3.46 (m, 2H), 3.58 (s, 2H), 3.85 (m, 2H), 3.95 (m, 2H), 4.00 (s, 3H), 4.26 (2H, m), 6.21 (m, 1H), 6.26 (m, 1H), 6.34 (m, 1H), 7.08 (m, 3H), 7.45 (d, 2H), 7.58 (s, 1H), 7.81 (m, 1H), 8.30 (s, 1H), 8.93 (s, 1H).
I29	dimethylmorpholine	RT/18hr/NaI	465	m/e 625 (M^++H)	(d-6-DMSO, d values) 1.13 (d, 6H), 2.34 (m, 2H), 2.56 (d, 3H), 2.61 (m, 2H), 3.24 (m, 2H), 3.50 (m, 2H), 3.58 (s, 2H), 3.98 (m, 5H), 4.29 (2H, m), 6.20 (m, 1H), 6.26 (m, 1H), 6.33 (m, 1H), 7.05 (m, 3H), 7.45 (d, 2H), 7.54 (s, 1H), 7.81 (m, 1H), 8.26 (s, 1H), 8.93 (s, 1H).
I30	dimethylmorpholine	RT/4 days/NaI	466	m/e 651.6 (M^++H)	(d-6-DMSO, (d-4Acetic) d values) 0.45 (m, 2H), 0.64 (m, 2H), 1.17 (d, 6H), 2.37 (m, 2H), 2.68 (m, 3H), 3.29 (t, 2H), 3.54 (d, 2H), 4.01 (m, 5H), 4.33 (t, 3H), 4.46 (s, 2H), 7.05 (m, 5H), 7.18 (m, 1H), 7.45 (d, 2H), 7.51 (s, 1H), 8.17 (m, 1H), 8.95 (s, 1H).
I31	morpholine	RT/18hr/NaI	467	m/e 626.4 (M^++H)	(d-6-DMSO, d values) 1.05 (d, 6H), 2.33 (m, 2H), 3.09 (m, 2H), 3.29 (m, 2H), 3.47 (m, 2H), 3.84 (m, 3H), 3.97 (m, 5H), 4.28 (t, 2H), 4.42 (s, 2H), 7.07 (m, 6H), 7.42 (m, 4H), 8.10 (s, 1H), 8.84 (s, 1H).

Start Comp	Reagent	Conditions	Prod	Mass spec.	Nmr
I30	pyrrolidine	RT/18hr/NaI	468	m/e 608.6 (M^++H)	(d-6-DMSO, d values) 0.47 (m, 2H), 0.67 (m, 2H), 1.92 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.67 (m, 1H), 3.06 (m, 2H), 3.34 (m, 2H), 3.59 (m, 2H), 4.03 (s, 3H), 4.32 (t, 2H), 4.47 (s, 2H), 7.06 (m, 5H), 7.19 (m, 1H), 7.46 (d, 2H), 7.55 (s, 1H), 7.83 (m, 1H), 8.19 (s, 1H), 8.92 (s, 1H).
I32	dimethylmorpholine	RT/96hr/NaI	469	m/e 626.5 (M^++H)	(d-6-DMSO(d4-Acetic), d values) 1.16 (d, 6H), 2.37 (m, 2H), 2.63 (s, 3H), 2.70 (m, 2H), 3.29 (m, 2H), 3.56 (d, 2H), 3.99 (m, 5H), 4.30 (t, 2H), 4.47 (s, 2H), 7.09 (m, 6H), 7.44 (m, 3H), 8.16 (s, 1H), 8.98 (s, 1H).
I32	pyrrolidine	RT/96hr/NaI	470	m/e 582.5 (M^++H)	(d-6-DMSO(d4-Acetic), d values) 1.16 (d, 6H), 2.37 (m, 2H), 2.63 (s, 3H), 2.70 (m, 2H), 3.29 (m, 2H), 3.56 (d, 2H), 3.99 (m, 5H), 4.30 (t, 2H), 4.47 (s, 2H), 7.09 (m, 6H), 7.44 (m, 3H), 8.16 (s, 1H), 8.98 (s, 1H).
I34	Dimethyl morpholine	RT/48hr/NaI	481	m/e 626.6 $(M+H)^+$	(d-6-DMSO, δ values) 1.00 (s, 3H), 1.04 (s, 3H), 1.56 (t, 2H), 1.95 (m, 2H), 2.42 (t, 2H), 2.64 (d, 3H), 2.76 (d, 2H), 3.55 (m, 2H), 3.90 (s, 3H), 4.19 (t, 2H), 4.41 (s, 2H), 6.56 - 6.62 (m, 2H), 6.70 (d, 1H), 7.09 (d, 2H), 7.22 - 7.37 (m, 4H), 7.28 (s, 1H), 8.00 (bs, 1H), 8.40 (s, 1H), 9.50 (s, 1H).

Intermediate Table 9

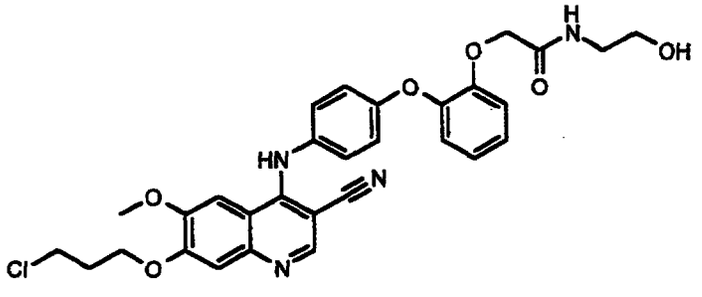
Start No.	Reagent	Conditions	Int.	Mass spec	structure
273	dichloro propane	70°C/2hr//KOtBu/DMA	I1	m/e 467, 469 $(M+H)^+$.	
273	dichloro -ethane	70°C/2hr//KOtBu/DMA	I2	m/e 453,455 (M^+H)	
282	bromo chloro propane	RT/18hrs/ /KOtBu/18-C-6/DMA	I3	m/e 467, 469 $(M+H)^+$.	
26	3-bromo-1-propanol	RT/18hr/ PPh_3/ DEAD/THF	I8	m/e 533,535 $(M+H)^+$.	
26	1,3-dichloro -propane	70°C/4hr/ KOtBu/DMA	I9	m/e 490, 492 $(M+H)^+$.	
26	dichloro -ethane	85°C/4hr/ KOtBu/DMA	I10	m/e 476,478 $(M+H)^+$.	

Start No.	Reagent	Conditions	Int.	Mass spec	structure
109	1-Bromo-3-chloro-propane	RT/ nBu_4NI/ 18crown6	I11	nmr obtained	
108	1-Bromo-3-chloro-propane	RT/ nBu_4NI/ 18crown6	I12	nmr obtained	
126	1-Bromo-3-chloro-propane	RT/ nBu_4NI/ 18crown6	I13	nmr obtained	
123	1-Bromo-3-chloro propane	RT/ nBu_4NI/ DMA 18crown6/18h	I14	m/e 520 $(M+H)^+$	
125	1-Bromo-3-chloro-propane	RT/ nBu_4NI/ DMA 18crown6/ 8hr	I15	m/e 520 $(M+H)^+$	
220	1-Bromo-3-chloro-propane	RT/15min/ KOtBu/DMA then RT/16hr/ /nBu_4NI/18-Crown-6	I16	nmr available	

Start No.	Reagent	Conditions	Int.	Mass spec	structure
221	1-Bromo-3-chloro-propane	RT/15min/ KOtBu/DMA then RT/16hr /nBu_4NI 18-Crown-6	I17	nmr available	
27	1-chloro-3-bromo-propane	RT/18hr/ KO^{t}Bu(1.0M in THF) / DMSO	I18	m/e 490 (M^++H)	

Example 7

In the above Table I4 is a compound of structure



which had been prepared by a method analogous to that described in Example 1, but using reaction conditions of 100°C/2hr/1-PrOH.

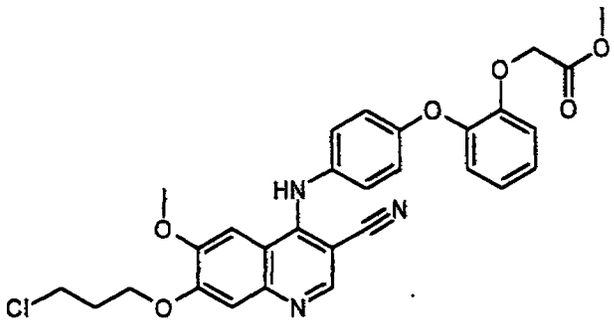
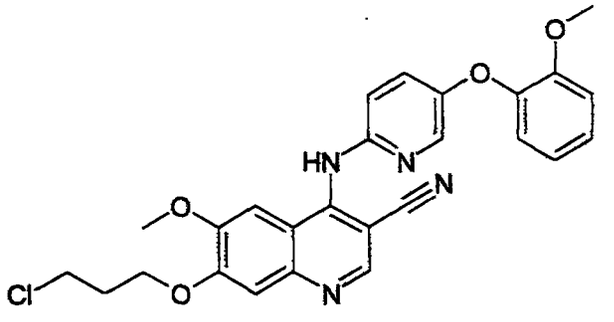
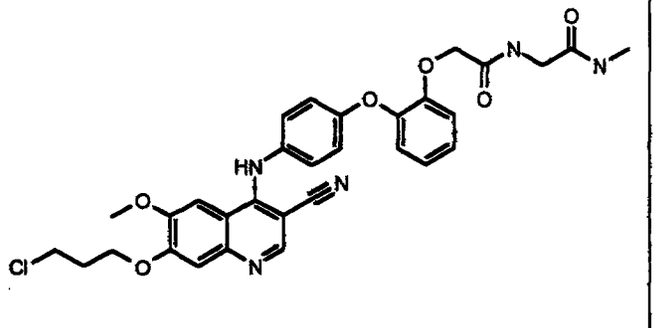
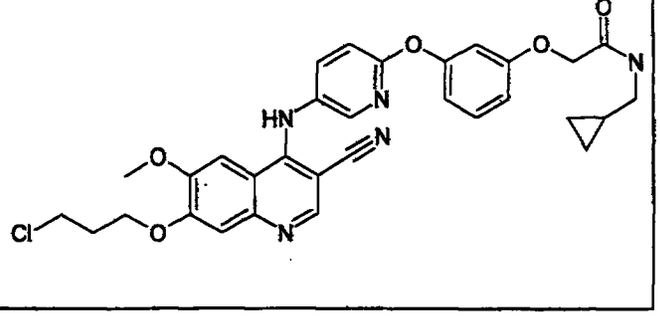
Mass Spectrum m/e 577.45,579.46 (M^++H).

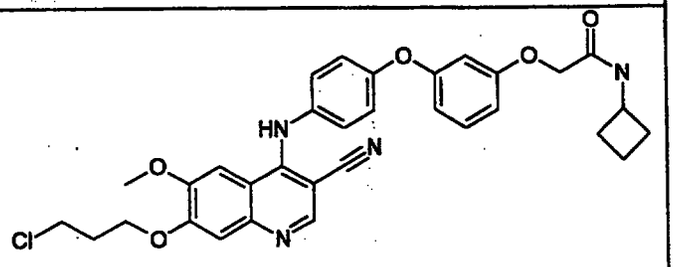
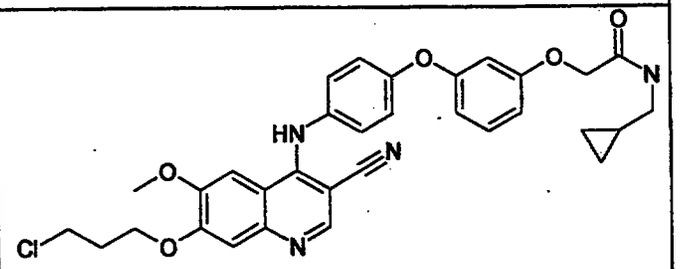
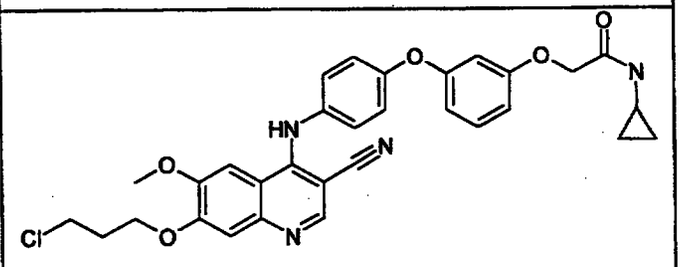
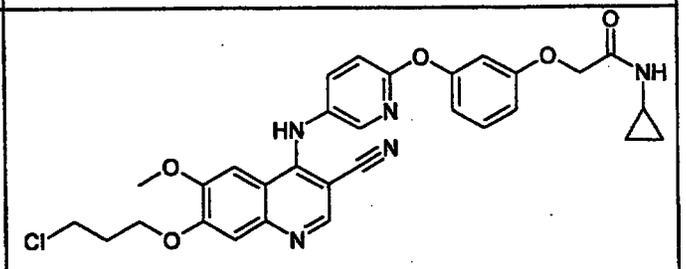
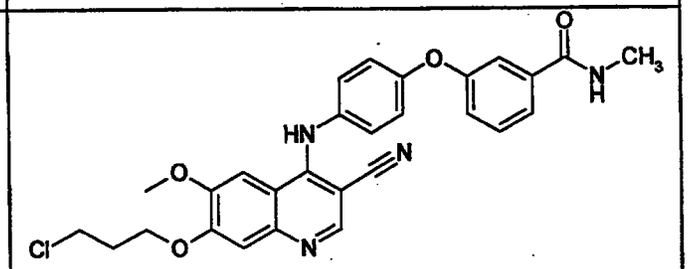
NMR Spectrum (d-6-DMSO, d values) 2.28 (m, 2H), 3.16 (q, 2H), 3.4 (t, 2H), 3.82 (t, 2H), 3.98 (s, 3H), 4.3 (t, 2H), 4.48(s, 2H), 6.95-7.22 (m, 6H), 7.4 (d, 2H), 7.46 (s, 1H), 7.6 (t, 1H), 8.09 (s, 1H), 8.9 (s, 1H), 11.07 (br.s, 1H).

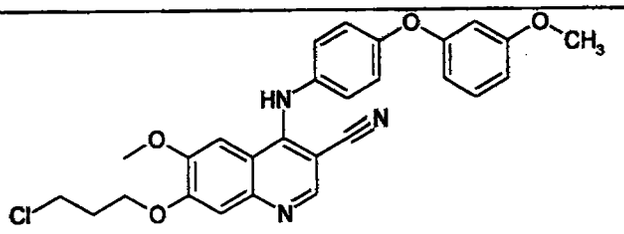
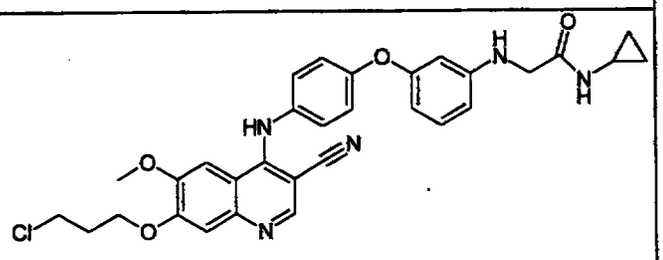
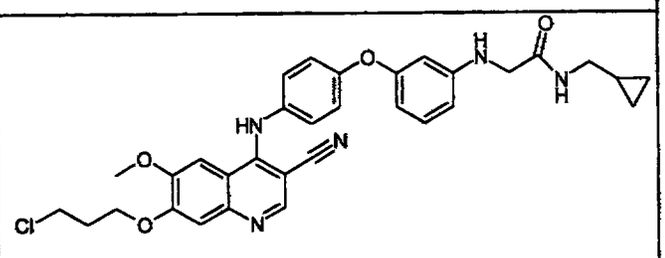
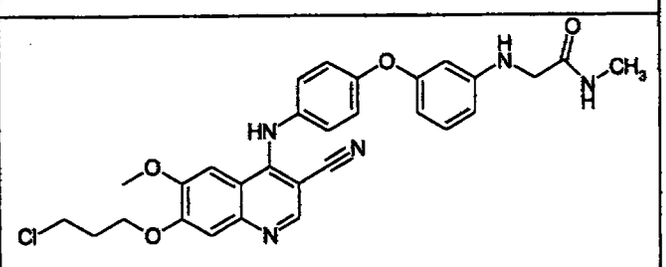
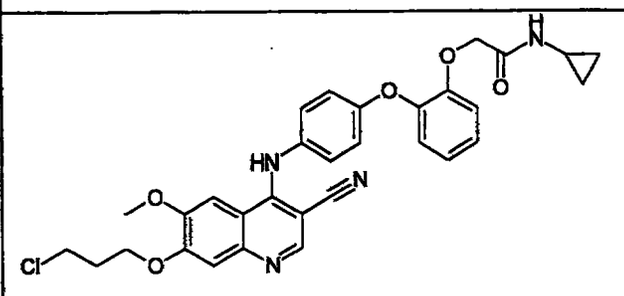
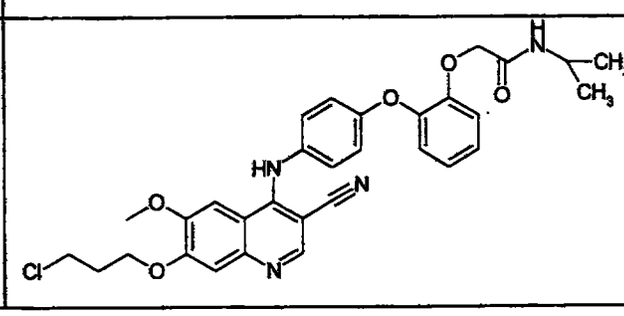
The chloropropoxyquinoline intermediate (Mass Spectrum m/e 311.2 $(M+H)^+$) was prepared by reacting the corresponding hydroxy quinoline with 1-bromo-3-chloropropane at room temperature for 16hr in the presence of nBu4NI/18-crown-6

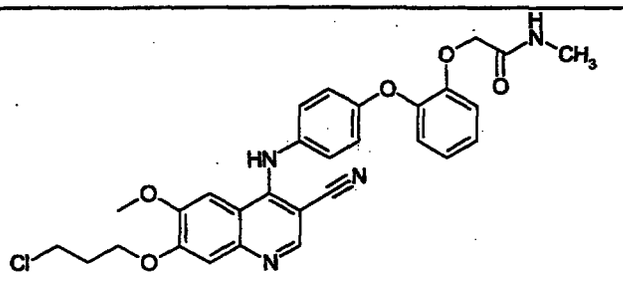
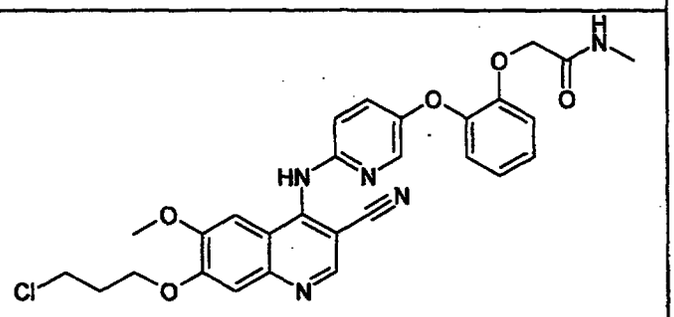
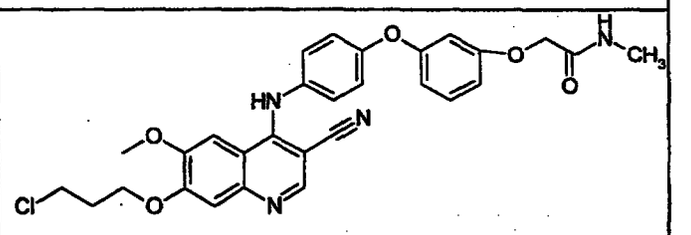
The following haloalkoxy quinolines were prepared by analogous routes:

Table 10

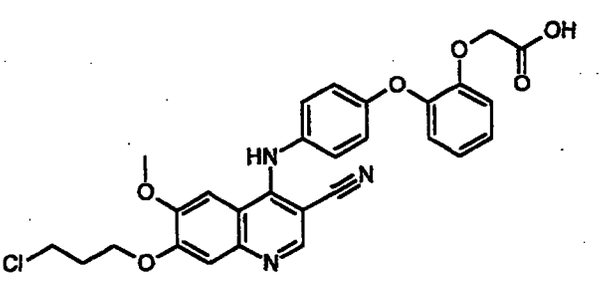
I No.	reaction conditions	mass spec.	structure
I5	100°C/18hr s/n-PrOH	m/e 548.5 $(M+H)^+$	
I6			
I19	100°C/2hr/1-PrOH	m/e 604.44 (M^+H).	
I20	100°C/3.5hr /1-PrOH	m/e 604.44 (M^+H)	

I No.	reaction conditions	mass spec.	structure
I21	100°C/3.5hr /1-PrOH	m/e 587.5 (M^++H)	
I22	100°C/2hr/1 -PrOH	m/e 587.5 (M^++H)	
I23	100°C/2hr/1 -PrOH	m/e 573.4 (M^++H)	
I24	100°C/3.5hr /1-PrOH	m/e 574.4 (M^++H)	
I25	100°C/3.5hr /1-PrOH	m/e 517.3 (M^++H)	

I No.	reaction conditions	mass spec.	structure
I26	100°C/2hr/1-PrOH	m/e 570.5 (M^++H)	
I27	100°C/4hr/1-PrOH	m/e 572, 574 (M^++H)	
I28	100°C/4hr/1-PrOH	m/e 586, 588 (M^++H)	
I29	100°C/4hr/1-PrOH	m/e 546, 548 (M^++H)	
I30	100°C/18hr/1-PrOH	m/e 573.5 (M^++H)	
I31	100°C/18hr/1-PrOH	m/e 575.5 (M^++H)	

I No.	reaction conditions	mass spec.	structure
I32	100°C/18hr/ 1-PrOH	m/e 547.5 (M^++H)	
I33	RT/15min/ NaH/DMA then RT/2hr/(2)		
I34	100°C/2hr/ n-PrOH		

In addition I5 was converted to I7



(I7)

using the following reaction conditions: RT/3hrs/LiOH.H_2O/MeOH/H_2O

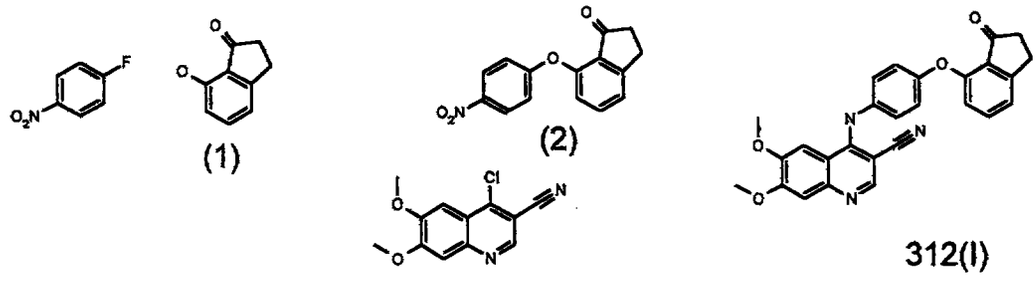
Mass Spectrum m/e 534.5 $(M+H)^+$

NMR Spectrum (d-6-DMSO, d values) 2.26 (m, 2H), 3.82 (m, 2H), 3.93 (s, 3H), 4.26 (t, 2H), 4.68 (s, 2H), 7.04 (m, 6H), 7.29 (m, 2H), 7.39 (s, 1H), 7.93 (s, 1H), 8.55 (s, 1H).

Example 8

Preparation of Compound No. 312

In this example, an intermediate nitro compound of formula (2) was reacted in situ with a chloroquinoline intermediate to produce compound 312, (a compound of formula (I)) directly in accordance with the following scheme:



The reaction conditions were: Cyclohexene, 1-propanol, Pd/C, filter then add quinoline to obtain the desired product

Mass Spectrum m/e 452 (M^++H)

NMR Spectrum ($CDCl_3$, d values) 2.70 (m 2H), 3.15 (m 2H), 3.75 (s, 3H), 4.00 (s, 3H), 6.70 (d, 1H), 6.80 (broad s, 1H), 6.95 (s, 1H), 7.05 (d, 2H), 7.15 (d, 2H), 7.15 (m, 1H), 7.35 (s, 1H), 7.45 (t, 1H), 8.60 (s, 1H).

Quinoline SM: WO 9843960

The reaction conditions used to obtain Intermediate labelled (2) was KOtBu, DMA.

Mass Spectrum m/e 270 (M^++H)

Using an analogous method, the following compounds were also produced

Table 11

No.	Mass spec	N.M.R
313	m/e 429 (M^++H)	($CDCl_3$, d values) 3.70 (s, 3H), 4.00 (s, 3H), 6.85 (broad s, 1H), 6.90 (m, 2H), 7.10 (d, 2H), 7.15 (d, 2H), 7.35 (m, 3H), 8.00 (s, 1H), 8.60 (s, 1H).
314	m/e 453 (M^++H)	(d-6-DMSO@373K, d values) 3.60 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 6.90 (d, 1H), 7.15 (d, 2H), 7.25 (t, 1H), 7.40 (m, 3H), 7.45 (s, 1H), 8.00 (s, 1H), 8.70 (s, 1H).
315	m/e 438 (M^++H)	(d-6-DMSO, d values) 4.00 (s, 3H), 4.00 (s, 3H), 6.75 (d, 1H), 6.85 (d, 1H), 7.20 (d, 2H), 7.30 (t, 1H), 7.40 (d, 1H), 7.50 (d, 2H), 7.50 (s, 1H), 7.95 (d, 1H), 8.20 (s, 1H), 8.95 (s, 1H), 11.30 (broad s, 1H).

Example 9

Preparation of Compounds 136 and 140 in Table 1

Compound 85 prepared as described above, was dissolved in trichloromethane and reacted with oxone in the presence of wet alumina to yield the title compounds.

Compound 136

Mass Spectrum m/e 460 (M^++H)

NMR Spectrum (d-6-DMSO, d values) 2.80 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 6.85 (d, 1H), 7.20 (d, 2H), 7.35 (m, 4H), 7.45 (m, 1H), 7.75 (m, 2H), 8.40 (s, 1H), 9.55 (broad s, 1H).

Compound 140

Mass spec m/e 476 (M^++H)

NMR Spectrum (d-6-DMSO, d values) 3.40 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 6.95 (d, 1H), 7.20 (d, 2H), 7.35 (m, 2H), 7.40 (d, 2H), 7.65 (m, 1H), 7.80 (s, 1H), 7.90 (dd, 1H), 8.45 (s, 1H), 9.65 (broad s, 1H).

Example 10

Preparation of Compound 168 in Table 1

Compound 173 in Table 1 was reacted with methylamine for 18 hours at room temperature in the presence of HCl, EDC, NMM and DCM to yield the desired amide.

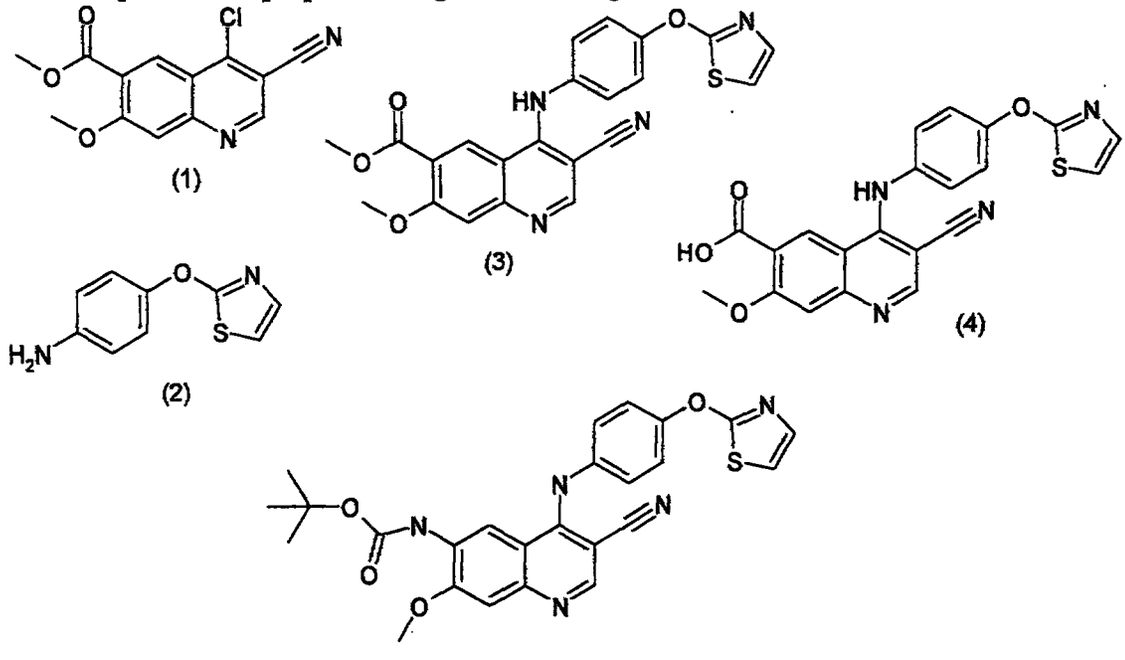
Mass spec. m/e 582 $(M+H)^+$.

NMR Spectrum (d-6-DMSO, d values) 2.33 (m, 2H), 2.55 (d, 3H), 3.12 (m, 2H), 3.22-3.45 (m, 4H (under H_2O signal)), 3.43 (s, 2H), 3.78 (m, 2H), 3.97 (m, 5H), 4.28 (m, 2H), 6.83 (d, 1H), 7.05 (d, 2H), 7.10 (m, 1H), 7.21 (m, 1H), 7.33 (m, 1H), 7.41 (d, 2H), 7.47 (s, 1H), 7.75 (m, 1H), 8.12 (s, 1H), 8.81 (s, 1H).

Example 11

Preparation of Compound 301 in Table 3

This compound was prepared using the following scheme:



Reaction conditions: 100°C/4hrs/NEt_3/Diphenylphosphorylazide/t-BuOH

Chromatography: yes

Mass Spectrum m/e 490 $(M+H)^+$.

NMR Spectrum (d-6-DMSO, d values) 1.48 (s, 9H), 4.01 (s, 3H), 7.26 (d, 1H), 7.33 (d, 1H), 7.45 (m, 1H), 7.49 (m, 2H), 7.53 (d, 2H), 8.70 (s, 1H), 8.82 (s, 1H), 8.97 (s, 1H).

Intermediate (3)

Reaction conditions: 100°C/18hrs/n-PrOH

Mass Spectrum m/e 433 $(M+H)^+$.

Intermediate (4)

Reaction conditions: RT/36hrs/LiOH/MeOH/water

Mass Spectrum m/e 418 $(M+H)^+$.

Example 12

Preparation of Compound 183 in Table 1

Intermediate I7 in Table 1 was reacted with cyclopropylamine and N-methylmorpholine at room temperature for 48hours in the presence of DMAP, EDC and DCM to yield the desired product.

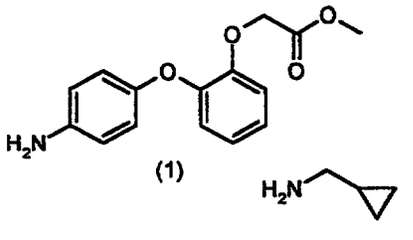
Mass Spectrum m/e 624.5 $(M+H)^+$

NMR Spectrum (d-6-DMSO, d values) 0.42 (m, 2H), 0.61 (m, 2H), 2.30 (m, 2H), 2.63 (m, 1H), 3.11 (m, 2H), 3.35 (2H under H_2O peak), 3.49 (m, 2H), 3.79 (m, 2H), 3.97 (m, 5H), 4.30 (m, 2H), 7.08 (m, 7H), 7.40 (d, 2H), 7.45 (s, 1H), 7.78 (s, 1H), 8.08 (s, 1H), 8.84 (s, 1H).

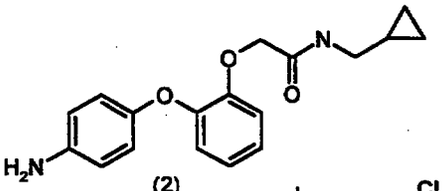
Example 13

Preparation of Compound No 430 in Table 1

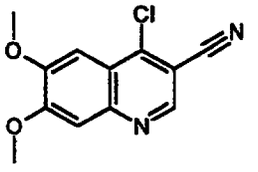
This compound was prepared using the following scheme:

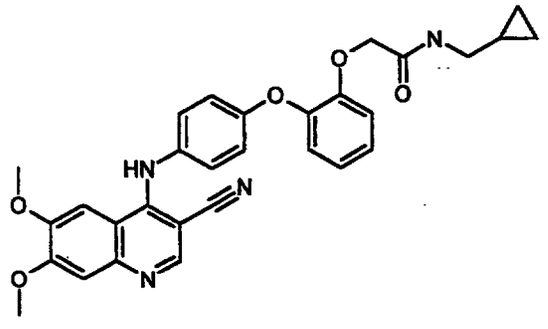


(1)



(2)





100°C/18hrs/n-PrOH

Chromatography: yes

Mass Spectrum m/e 525 $(M+H)^+$

NMR Spectrum (d-6-DMSO, d values) 0.182 (m, 2H), 0.41 (m, 2H), 0.94 (m, 1H), 3.02 (t, 2H), 4.00 (m, 6H), 4.52 (s, 2H), 7.14 (m, 6H), 7.47 (m, 3H), 7.70 (t, 1H), 8.16 (s, 1H), 8.94 (s, 1H).

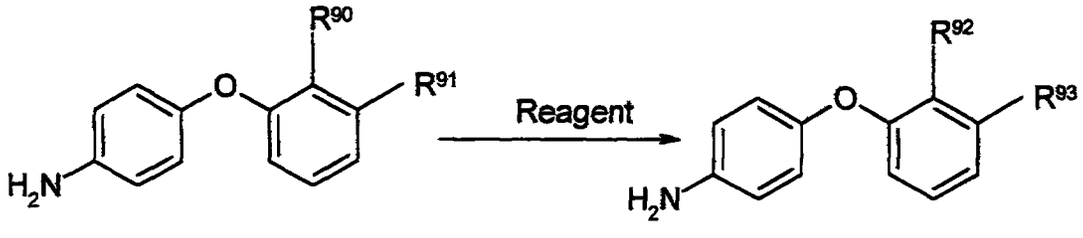
The aniline starting material (1) was prepared as described above in relation to Intermediate I5.

This was converted to Intermediate (2) above by reaction with cyclopropanemethylamine in methanol at room temperature for 18hrs.

Mass Spectrum m/e 313.5 $(M+H)^+$

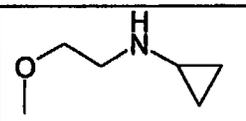
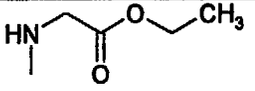
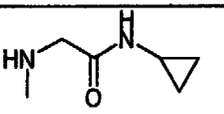
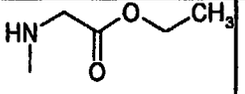
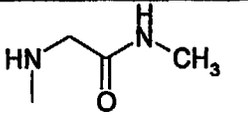
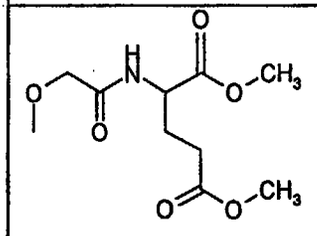
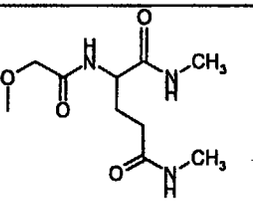
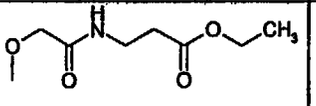
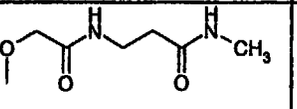
Example 14

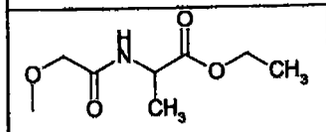
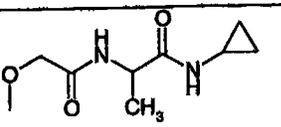
Using a method analogous to that of Example 13, the R^7 group was modified to form a different group R^7 in the anilines used as starting materials in accordance with the following general scheme:



prior to conversion to the corresponding compound of formula (I) as summarised in the following Table 12.

Table 12

Starting aniline R^{90}	R^{91}	Reagent/conditions	Final aniline R^{92}	R^{93}	Final Product
$O(CH_2)_2Br$	H	RT/5days/cyclopropyl amine/NaI/MeOH		H	437
	H	RT/5days/cyclopropyl amine/NaI/MeOH		H	438
H		RT/5days/Me-amine/NaI/MeOH	H		439
	H	methylamine/ethanol		H	444
	H	methylamine/ethanol		H	445

Starting aniline		Reagent/conditions	Final aniline		Final Product
R^{90}	R^{91}		R^{92}	R^{93}	
	H	cyclopropylamine/ ethanol		H	447

Example 15

In the preparation of other compounds of formula (I) the $R^{7'}$ group was modified to form a different group R^{7} in the nitrobenzyl compounds of formula (VII) used as starting materials in accordance with the following general scheme:

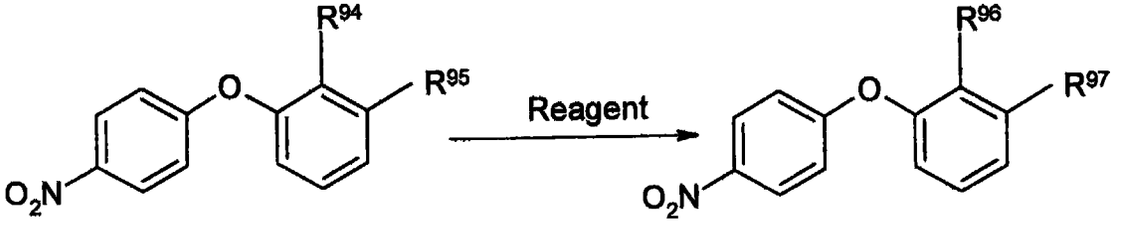
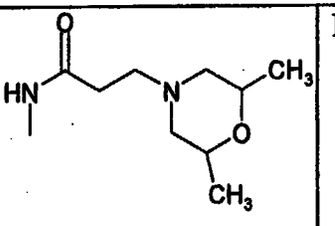
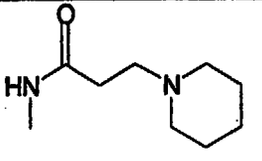
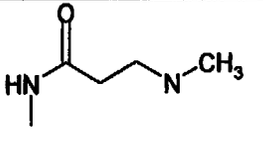
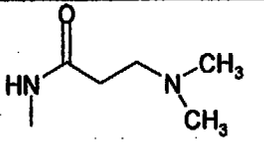
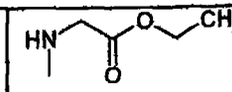
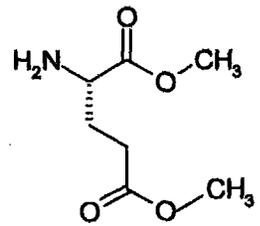
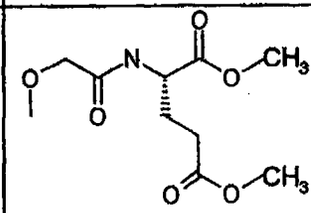
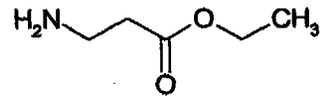
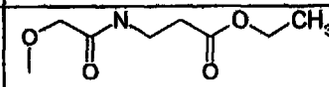
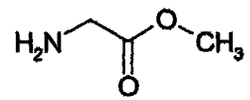
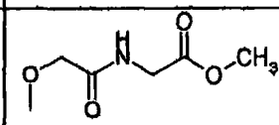
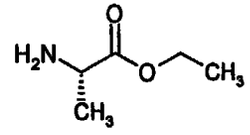
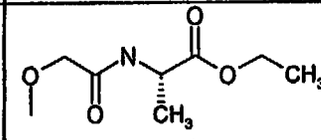
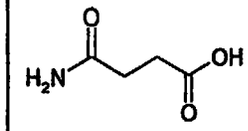


Table 13

Starting 4-phenoxynitrobenzene R^{94}	R^{95}	Reagent/conditions	Final 4-phenoxynitrobenzene R^{96}	R^{97}	Final Product
NH_2	H	3-bromopropionyl chloride, triethylamine, DMA; then dimethyl morpholine		H	433
NH_2	H	3-bromopropionyl chloride, triethylamine, DMA; then piperidine		H	434
NH_2	H	3-bromopropionyl chloride, triethylamine, DMA; then methylamine in methanol		H	435
NH_2	H	3-bromopropionyl chloride, triethylamine, DMA; then dimethylamine in methanol		H	435

Starting 4-phenoxynitrobenzene R^{94}	R^{95}	Reagent/conditions	Final 4-phenoxynitrobenzene R^{96}	R^{97}	Final Product
H	NH_2	80°C/6hrs/ethylbromoacetate/NaOAc/EtOH	H		439
OCH_2COOH	H	EDC/DMAP/HOBT/DMA 		H	441
OCH_2COOH	H	EDC/DMAP/HOBT/DMA 		H	442
OCH_2COOH	H	EDC/DMAP/HOBT/DMA 		H	443

Starting 4-phenoxynitrobenzene R^{94}	R^{95}	Reagent/conditions	Final 4-phenoxynitrobenzene R^{96}	R^{97}	Final Product
OCH_2COOH	H	EDC/DMAP/HOBT/DMA 		H	447* intermediate(see also Ex 15)
$O(CH_2)_2NH_2$	H	RT/48hrs/Succinamic acid/EDC/DEAD/*NMM*/ DCM 	$O(CH_2)_2NHC(O)(CH_2)_2$-CN	H	472
$O(CH_2)_2NH_2$	H	RT/18hrs/acetylchloride/ DCM $iPr_2N(CH_2CH_3)_2$	$O(CH_2)_2NHC(O)CH_3$	H	474
$O(CH_2)_2NH_2$	H	RT/18hrs/ $iPr_2N(CH_2CH_3)_2$/DCM allylchloroformate	$O(CH_2)_2NHC(O)OCH_2$-$CH=CH_2$	H	475
H	$OCH_2C(O)OCH_2CH_3$	RT/2hrs/ methylamine/ MeOH	H	$OCH_2C(O)NH$-CH_3	477

Starting 4-phenoxynitrobenzene R^{94}	R^{95}	Reagent/conditions	Final 4-phenoxynitrobenzene R^{96}	R^{97}	Final Product
H	OH	65°C/1.5hr/K_2CO_3/Ethylbromoacetate/Acetone	H	$OCH_2C(O)O$-CH_2CH_3	477
H	OCH_3	195°C/2hr/Pyridine.HCl	H	OH	477
$OCH_2C(O)OH$	H	RT/18hrs/isopropylamine/EDC/DEAD/NMM/DCM	$OCH_2C(O)NHCH(CH_3)_2$	H	482

Biological Data

Assay for inhibitors of the MAP kinase pathway

To evaluate inhibitors of the MAPK pathway a coupled assay was carried out which measures phosphorylation of serine/threonine residues present in the substrate in the presence or absence of inhibitor. Recombinant glutathione S-transferase fusion protein containing human p45MEK1 (GST-MEK) was activated by c-raf (Sf9 insect cell lysate from triple baculoviral infection with c-raf/ras/lck) and used for the assay. Active GST-MEK was first used to activate a recombinant glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) in the presence of ATP and Mg^{2+} for 60min at room temperature in the presence or absence of potential inhibitors. The activated GST-MAPK was then incubated with myelin basic protein (MBP) as substrate for 10min at room temperature in the presence of ATP, Mg^{2+} and ^{33}P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid. Incorporation of ^{33}P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods. The extent of inhibition was determined by comparison with untreated controls.

The final assay solution contained 10mM Tris, pH 7.5, 0.05mM EGTA, 8.33μM [$\gamma^{33}P$]ATP, 8.33mM $Mg(OAc)_2$, 0.5mM sodium orthovanadate, 0.05%w/v BSA, 6.5ng GST-MEK, 1μg GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

Compounds tested of the present invention had IC_{50} results typically less than 0.5μM. For example, Compound No 252 gave an IC_{50} of 0.15μM.

In vitro MAP kinase assay

To determine whether compounds were inhibiting GST-MEK or GST-MAPK, a direct assay of MAPK activity was employed. GST-MAPK was activated by a constitutively active GST-MEK fusion protein containing two point mutations (S217E, S221E) and used for the assay in the presence and absence of potential inhibitors. The activated GST-MAPK was incubated with substrate (MBP) for 60min at room temperature in the presence of ATP, Mg^{2+} and ^{33}P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid. Incorporation of ^{33}P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods.

The final assay solution contained 12mM Tris, pH 7.5, 0.06mM EGTA, 30μM [γ^{33}P]ATP, 10mM $Mg(OAc)_2$, 0.6mM sodium orthovanadate, 0.06%w/v BSA, 28ng GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

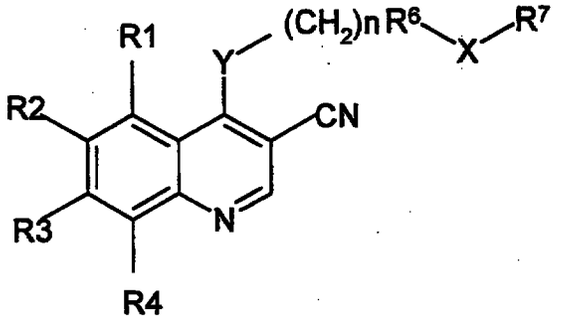
Compounds of the invention showed activity in this screen.

Cell proliferation assays

Cells were seeded into multi-well plates at 20 000 - 40 000 cells/ml in growth medium containing 5% FCS and incubated overnight at 37°C. The compounds were prepared in fresh medium at an appropriate concentration and added to the wells containing the cells. These were then incubated for a further 72 hours. Cells were then either removed from the wells by incubating with trypsin/EDTA and counted using a Coulter counter, or treated with XTT/PMS in PBSA and optical densities read at 450nm. Compounds tested of the present invention had IC_{50} results typically less than 30μM. For example, Compound No 250 gave an IC50 of 7.76 mM in HT29 human colon tumour cells; Compound No 32 gave an IC50 of 1.5μM in HT29 cells and an IC50 of 0.6μM in MC26 mouse colon tumour cells.

Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

wherein:

n is 0-1;

X and Y are independently selected from –NH-, -O-, -S-, or –NR^8- where R^8 is alkyl of 1-6 carbon atoms and X may additionally comprise a CH_2 group;

R^7 is a group $(CH_2)_mR^9$ where m is 0,or an integer of from 1-3 and R^9 is a substituted aryl group, an optionally substituted cycloalkyl ring of up to 10 carbon atoms, or an optionally substituted heterocyclic ring or an N-oxide of any nitrogen containing ring;

R^6 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl,

amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

R_1, R_2, R_3 and R_4 are each independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or a group R^{13}-X^1-$(CH_2)_x$ wherein x is 0 to 3, X^1 represents -O-, $-CH_2-$, -OCO-, carbonyl, -S-, -SO-, $-SO_2-$, $-NR^{14}CO-$, $-CONR^{15}-$, $-SO_2NR^{16}-$, $-NR^{17}SO_2-$ or $-NR^{18}-$ (wherein R^{14}, R^{15}, R^{16}, R^{17} and R^{18} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{13} is selected from one of the following sixteen groups:

1) C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^2COR^{19} (wherein X^2 represents -O- or $-NR^{20}-$ (wherein R^{20} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{19} represents $-NR^{21}R^{22}-$ or $-OR^{23}-$ (wherein R^{21}, R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{24} (wherein X^3 represents -O-, -S-, -SO-, $-SO_2-$, -OCO-, $-NR^{25}CO-$, $-CONR^{26}-$, $-SO_2NR^{27}-$, $-NR^{28}SO_2-$ or $-NR^{29}-$ (wherein R^{25}, R^{26}, R^{27}, R^{28} and R^{29} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{24} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C$_{1-5}$alkylX^5R^{30} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{31}CO-$, $-CONR^{32}-$, $-SO_2NR^{33}-$, $-NR^{34}SO_2-$ or $-NR^{35}-$ (wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{30} represents hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{36} (wherein R^{36} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group

may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) $(CH_2)_qX^6R^{37}$ (wherein q is an integer from 0 to 5, X^6 represents a direct bond, -O-, -S-, -SO-, $-SO_2-$, $-NR^{38}CO-$, $-CONR^{39}-$, $-SO_2NR^{40}-$, $-NR^{41}SO_2-$ or $-NR^{42}-$ (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is a phenyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl, pyridone or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}hydroxyalkoxy, C_{1-4}aminoalkyl, C_{1-4}alkylamino, carboxy, cyano, $-CONR^{43}R^{44}$ and $-NR^{45}COR^{46}$ (wherein R^{43}, R^{44}, R^{45} and R^{46}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

7) C_{2-6}alkenylR^{36} (wherein R^{36} is as defined hereinbefore);

8) C_{2-6}alkynylR^{36} (wherein R^{36} is as defined hereinbefore);

9) X^7R^{47} (wherein X^7 is $-SO_2-$, -O- or $-CONR^{48}R^{49}-$ (wherein R^{48} and R^{49}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{47} represents C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X^7 is $-SO_2-$, X^1 is -O-, when X^7 is -O-, X^1 is carbonyl, when X^7 is $-CONR^{48}R^{49}-$, X^1 is -O- or NR^{18} (wherein R^{48}, R^{49} and R^{18} are as defined hereinbefore);

10) C_{2-6}alkenylR^{37} (wherein R^{37} is as defined hereinbefore);

11) C_{2-6}alkynylR^{37} (wherein R^{37} is as defined hereinbefore);

12) C_{2-6}alkenylX^8R^{37} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{50}CO-$, $-CONR^{51}-$, $-SO_2NR^{52}-$, $-NR^{53}SO_2-$ or $-NR^{54}-$ (wherein R^{50}, R^{51}, R^{52}, R^{53} and R^{54} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

13) C_{2-6}alkynylX^9R^{37} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{55}CO-$, $-CONR^{56}-$, $-SO_2NR^{57}-$, $-NR^{58}SO_2-$ or $-NR^{59}-$ (wherein R^{55}, R^{56}, R^{57}, R^{58} and R^{59} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

14) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{37} (wherein X^{10} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{60}CO-$, $-CONR^{61}-$, $-SO_2NR^{62}-$, $-NR^{63}SO_2-$ or $-NR^{64}-$ (wherein R^{60}, R^{61}, R^{62}, R^{63} and R^{64} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

15) R^{36} (wherein R^{36} is as defined hereinbefore); and

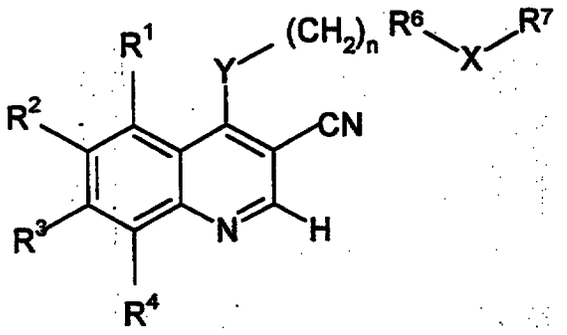
16) $C_{1-3}alkylX^{10}C_{1-3}alkylR^{36}$ (wherein X^{10} and R^{36} are as defined hereinbefore).

2. A compound according to claim 1 wherein R^9 is substituted by one or more groups selected from hydroxy; halo; nitro; cyano; carboxy; C_{1-6}alkoxy; C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{2-6}alkenyloxy; C_{2-6}alkynyloxy; C_{3-6}cycloalkyl; amino; mono- or di-C_{1-6}alkyl amino; heterocyclyl optionally substituted with C_{1-6}alkyl or oxo; $C(O)R^a$, $C(O)OR^a$, $S(O)_dR^a$; $NR^aC(O)R^b$; $C(O)NR^aS(O)_dR^b$, $C(O)NR^aR^b$; $NR^aC(O)NR^bR^c$; $NR^aS(O)_dR^b$ or $N(S(O)_dR^b)S(O)_dR^c$ where d is 0, 1 or 2 and R^a, R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, aryl, C_{3-6}cycloalkyl or heterocylcyl, and wherein any alkyl, alkenyl or alkynyl group or moiety contained within the substituent one R^9 may themselves be optionally substituted with one or more groups selected from hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms, C_{3-6}cycloalkyl, heterocyclyl optionally substituted with C_{1-6}alkyl or oxo; $C(O)R^d$, $C(O)OR^d$ NR^dR^e, $S(O)_e$ R^d, $NR^dC(O)R^e$; $C(O)NR^dR^e$; $NR^dC(O)NR^eR^f$; $NR^dS(O)_eR^e$ where e is 0, 1 or 2 and R^d, R^e and R^f are independently selected from hydrogen or C_{1-6}alkyl optionally substituted with one or more groups selected from hydroxy; cyano; nitro; halo; carboxy; carboalkoxy of 2-7 carbon atoms, C_{3-6}cycloalkyl, heterocyclyl optionally substituted with C_{1-6}alkyl or oxo; $C(O)R^g$, $C(O)OR^g$ NR^gR^h, $S(O)_eR^g$, $NR^hC(O)R^g$; $C(O)NR^gR^h$; $NR^gC(O)NR^hR^i$; $NR^gS(O)_eR^h$ where e is as defined above and R^g, R^h and R^i are independently selected from hydrogen or C_{1-6}alkyl: or two substituents on adjacent atoms may be joined to form the second ring of a bicyclic ring system wherein the said second ring is optionally substituted with one or more of the groups listed above for R^9 and optionally contains one or more heteroatoms.

3. A compound according to claim 1 where R^9 is phenyl substituted with an optionally substituted alkoxy group.

4. A compound according to claim 1 which is a compound of formula (IA)

This Sheet Has Been Replaced



(IA)

or a pharmaceutically acceptable salt thereof.

wherein:

n is 0-1;

X and Y are independently selected from –NH-, -O-, -S-, or –NR^8- where R^8 is alkyl of 1-6 carbon atoms and X may additionally comprise a CH_2 group;

R^7 is a group $(CH_2)_mR^9$ where m is 0,or an integer of from 1-3 and R^9 is a substituted aryl or substituted cycloalkyl ring of up to 10 carbon atoms, wherein the substituents comprise at least one alkoxy group of 1-6 carbon atoms and optionally one or more further substitutents, or R^9 is a heterocyclic ring containing 1 or 2 oxygen atoms and optionally one or more substitutents;

R^6 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally further substituted with one or more groups selected from halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

R_1, R_2, R_3 and R_4 are each independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, -$NR^{11}R^{12}$ (wherein R^{11} and R^{12}, which may be the

same or different, each represents hydrogen or C_{1-3}alkyl), or a group R^{13}-X^1-$(CH_2)_x$ wherein x is 0 to 3, X^1 represents -O-, -CH_2-, -OCO-, carbonyl, -S-, -SO-, -SO_2-, -NR^{14}CO-, -SO_2NR^{16}-, -$NR^{17}SO_2$- or -NR^{18}- (wherein R^{14}, R^{15}, R^{16}, R^{17} and R^{18} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{13} is selected from one of the following sixteen groups:

1) C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^2COR^{19} (wherein X^2 represents -O- or -NR^{20}- (wherein R^{20} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{19} represents -$NR^{21}R^{22}$- or -OR^{23}- (wherein R^{21}, R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{24} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OCO-, -NR^{25}CO-, -$CONR^{26}$-, -SO_2NR^{27}-, -$NR^{28}SO_2$- or -NR^{29}- (wherein R^{25}, R^{26}, R^{27}, R^{28} and R^{29} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{24} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C$_{1-5}$alkylX^5R^{30} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO_2-, -NR^{31}CO-, -$CONR^{32}$-, -SO_2NR^{33}-, -$NR^{34}SO_2$- or -NR^{35}- (wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{30} represents hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{36} (wherein R^{36} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) $(CH_2)_q$$X^6R^{37}$ (wherein q is an integer from 0 to 5, X^6 represents a direct bond, -O-, -S-, -SO-, -SO_2-, -NR^{38}CO-, -$CONR^{39}$-, -SO_2NR^{40}-, -$NR^{41}SO_2$- or -NR^{42}- (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is a phenyl group, a pyridone group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl, pyridone or

aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}hydroxyalkoxy, C_{1-4}aminoalkyl, C_{1-4}alkylamino, carboxy, cyano, $-CONR^{43}R^{44}$ and $-NR^{45}COR^{46}$ (wherein R^{43}, R^{44}, R^{45} and R^{46}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

7) C_{2-6}alkenylR^{36} (wherein R^{36} is as defined hereinbefore);

8) C_{2-6}alkynylR^{36} (wherein R^{36} is as defined hereinbefore);

9) X^7R^{47} (wherein X^7 is $-SO_2-$, -O- or $-CONR^{48}R^{49}-$ (wherein R^{48} and R^{49}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{47} represents C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino) with the provisos that when X^7 is $-SO_2-$, X^1 is -O-, when X^7 is -O-, X^1 is carbonyl, when X^7 is $-CONR^{48}R^{49}-$, X^1 is -O- or NR^{18} (wherein R^{48}, R^{49} and R^{18} are as defined hereinbefore);

10) C_{2-6}alkenylR^{37} (wherein R^{37} is as defined hereinbefore);

11) C_{2-6}alkynylR^{37} (wherein R^{37} is as defined hereinbefore);

12) C_{2-6}alkenylX^8R^{37} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{50}CO-$, $-CONR^{51}-$, $-SO_2NR^{52}-$, $-NR^{53}SO_2-$ or $-NR^{54}-$ (wherein R^{50}, R^{51}, R^{52}, R^{53} and R^{54} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

13) C_{2-6}alkynylX^9R^{37} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{55}CO-$, $-CONR^{56}-$, $-SO_2NR^{57}-$, $-NR^{58}SO_2-$ or $-NR^{59}-$ (wherein R^{55}, R^{56}, R^{57}, R^{58} and R^{59} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

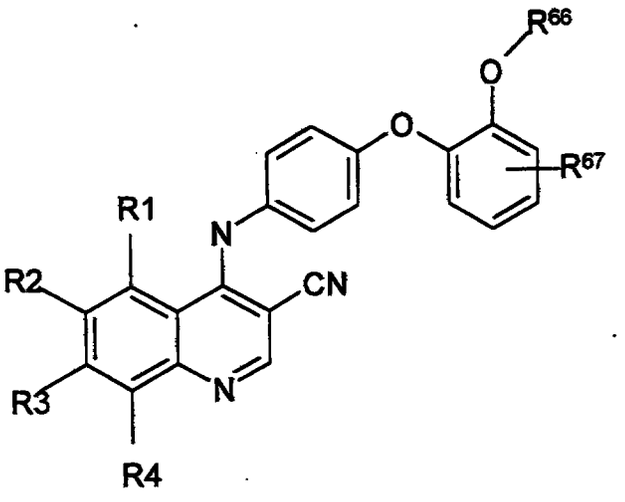
14) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{37} (wherein X^{10} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{60}CO-$, $-CONR^{61}-$, $-SO_2NR^{62}-$, $-NR^{63}SO_2-$ or $-NR^{64}-$ (wherein R^{60}, R^{61}, R^{62}, R^{63} and R^{64} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{37} is as defined hereinbefore);

15) R^{36} (wherein R^{36} is as defined hereinbefore); and

16) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{36} (wherein X^{10} and R^{36} are as defined hereinbefore).



5. A compound according to claim 1 of formula (II)

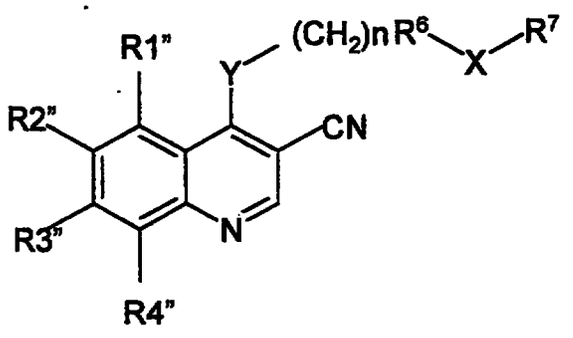


(II)

where R^1, R^2, R^3 and R^4 are as defined in claim 1, R^{66} is an optionally substituted C_{1-6} alkyl and R^{67} is selected from hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino.

* C L M S *

6. A compound of formula (IB)

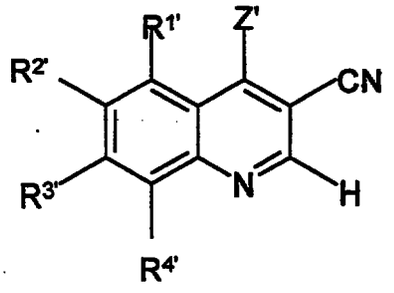


(IB)

where Y, n, R^6, X and R^7 are as defined in claim 1 and at least one of $R^{1"}$, $R^{2"}$, $R^{3"}$ or $R^{4"}$ is a group $R^{13'}$-X^1-$(CH_2)_x$ wherein X^1 and x are as defined in claim 1 and $R^{13'}$ is alkyl substituted by chloro or bromo; and the remainder are groups R^1, R^2, R^3 and R^4 respectively.

7. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in combination with a pharmaceutically acceptable carrier or excipient.

8. A method of preparing a compound of formula (I) as defined in claim 1 which method comprises either (a) reacting a compound of formula (III)



(III)

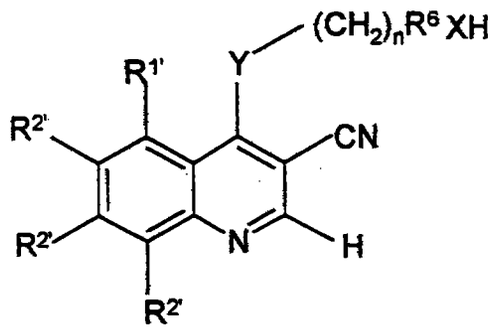
where $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ represent R^1, R^2, R^3 and R^4 respectively as defined in relation to formula (I) or a precursor thereof, and Z' is a leaving group, with a compound of formula (IV)

H- $Y(CH_2)_nR^6XR^{7'}$

(IV)

where R^6, Y, X, and n are as defined in relation to formula (I), and $R^{7'}$ is a group R^7 or a precursor thereof; or

(b) reacting a compound of formula (V)



(V)

where $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are as defined in relation to fomula (III) R^6, X, Y and n are as defined in relation to formula (I), with a compound of formula (VI)

$$R^{7'}\text{-}Z'' \qquad \text{(VI)}$$

where R^7 is as defined in relation to formula (IV) and Z" is a leaving group;

and thereafter if necessary or desired converting precursor groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $R^{7'}$ to groups of formula R^1, R^2, R^3, R^4 and R^7 respectively, or converting a group R^1, R^2, R^3, R^4 and R^7 to a different such group.

9. A compound for use in therapy comprising a compound of formula (I) as defined in claim 1.

10. The use of a compound of formula (I) as defined in claim 1 in the preparation of a medicament for use in the inhibition of MEK enzymes.