(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3, 5-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-5 3-chloro-1-aza-inden-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

Still yet more preferred compounds are selected from
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one and
4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,
or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

Preferred intermediates according to this invention have formula II wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

Other preferred intermediates according to this invention have formula II wherein Z is absent.

Other preferred intermediates according to this invention have formula II wherein R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

More preferred intermediates according to this invention are selected from
(2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,

4-(2-Oxopiperazin-1-ylmethyl)benzamidine,

1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one,

1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one,

2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester,

2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one,

1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one,

4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) l-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one,

(3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one,

1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one,

1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one trifluroacetate,

1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one,

1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one,

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester,

4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,

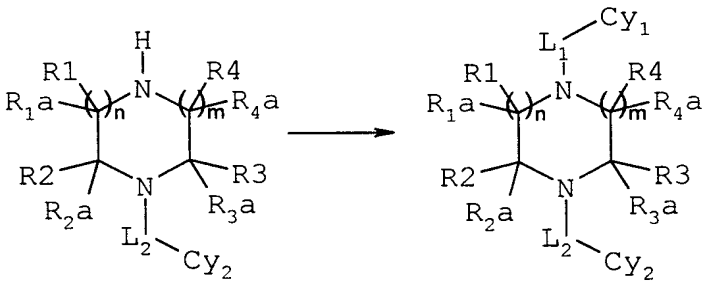
(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester and

(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Preparation of the Compounds of the Invention

A general route to the compounds of this invention wherein A is N and R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, L_1, L_2, Cy_1, Cy_2, m and n are defined herein is outlined in Scheme 1.

Scheme 1



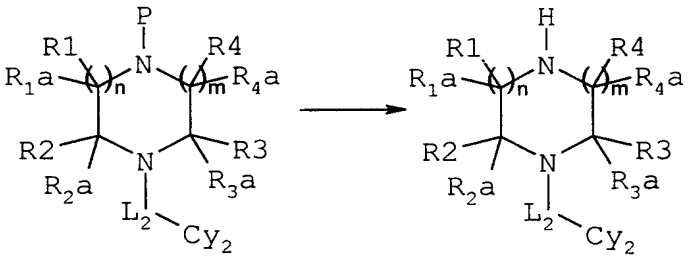
II I

As shown in Scheme 1, coupling of a compound of formula II with a sulfonyl chloride, an alkyl halide, an acid or an activated derivative thereof such as an anhydride or acid chloride, an isocyanate, chloroformate or activated sulfamyl ester in an appropriate solvent generates the compound of formula I

in which the L_1-Cy_1 portion is a sulfonamide, alkyl amine, amide, urea, carbamate or sulfamyl urea respectively. Sulfonamide formation is accomplished with a base such as a trialkylamine in an inert solvent such as dichloromethane, THF or acetonitrile at about 0 °C to about 100 °C in the presence or absence of an activating agent such as dimethylaminopyridine (DMAP). Alkyl amine formation can be achieved with a suitable base such as K_2CO_3 or trialkylamine in an appropriate solvent such as DMF or acetonitrile at about 0 °C to about 100 °C. Amide, urea, carbamate and sulfamyl urea formation can be conducted with acids and coupling reagents such as EDC or TBTU or with any variant of reactive acid derivatives and the use of an appropriate base additive such as triethylamine, N-methylmorpholine or diisopropylethylamine.

The preparation of the compound of formula II wherein R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, L_2, Cy_2, m and n are defined herein is outlined in Scheme 2.

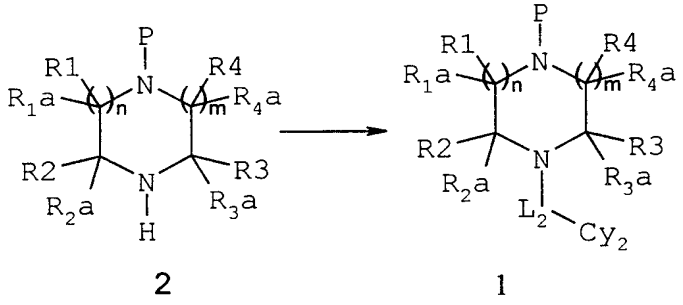
Scheme 2



As shown in Scheme 2, the compound of formula II is prepared by removing a nitrogen protecting group P from the compound of formula 1. In a preferred aspect, P is an alkyl, aralkyl or aryl carbamate moiety which is removed using strong acid, strong base or catalytic hydrogenation in an appropriate solvent such as methanol or ethanol.

The preparation of the compound of formula 1 wherein R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, L_1, L_2, Cy_1, Cy_2, m and n and P are defined herein is outlined in Scheme 3.

Scheme 3

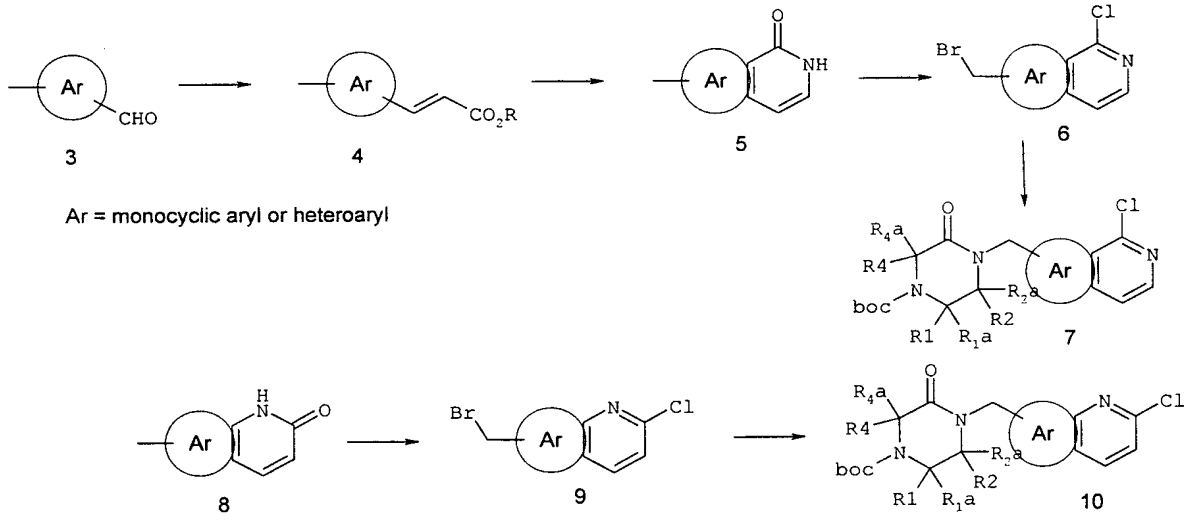


2 1

As shown in Scheme 3, the compound of formula 1 is obtained by coupling a compound of formula 2 with an appropriate Cy_2-L_2-LG group wherein LG is a leaving group such as chloro, bromo, iodo, or optionally substituted lower alkylsulfonyloxy or arylsulfonyloxy in an inert organic solvent such as THF, Et_2O or DMF in the presence of a strong base such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine. In a preferred aspect, P is an alkyl, aralkyl or aryl carbamate group.

The preparation of intermediate compounds of formula 7 and 10 are outlined in Scheme 4.

Scheme 4



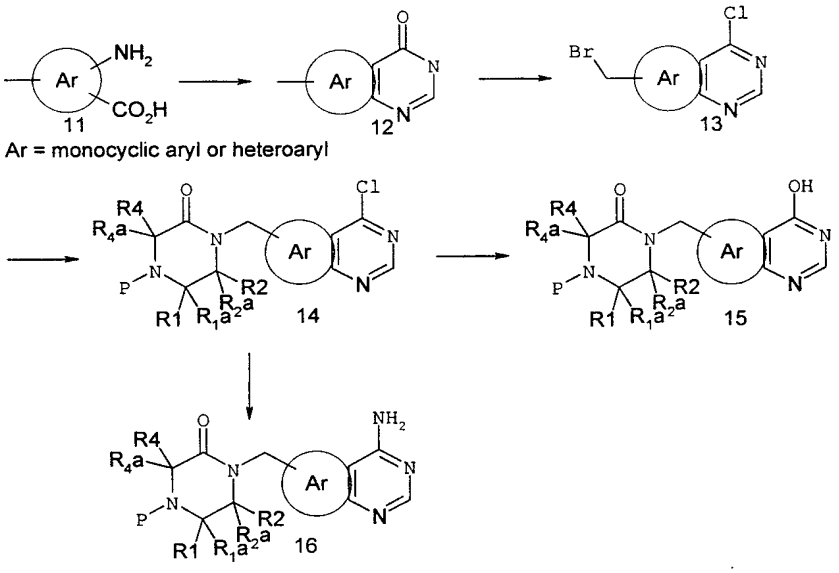
As shown in Scheme 4, reacting a compound of formula 3 with an appropriate malonic acid in a polar solvent such as pyridine or ethanol and a base such as piperidine or pyridine at reflux provides a compound of formula 4 wherein R is H. Alternatively, a compound of formula 3 may be reacted with a suitable Wittig or Horner-Emmons reagent in an inert solvent such as THF to give a compound of formula 4 wherein R is lower alkyl. When R is lower alkyl, the ester is hydrolyzed to the corresponding carboxylic acid (R is H) by an appropriate strong acid or alkali base. The corresponding acid is

converted to the acid chloride using standard methods such as thionyl chloride or is converted to the mixed anhydride in a polar solvent such as acetone or THF to form an activated acyl compound. The activated acyl compound is then treated with a solution of NaN_3 in water at about -10 °C to about 25 °C to yield the corresponding acyl azide. The acyl azide compound is then heated slowly in an inert solvent such as benzene or toluene at about 60 °C to about 110 °C then concentrated in vacuo and heated in a higher boiling inert solvent such as 1,2-dichlorobenzene or phenyl ether at about 180 °C to about 240 °C with a catalyst such as iodine or tributylamine to obtain a compound of formula 5. Alternatively the acyl azide compound can be added directly to a high boiling inert solvent such as phenyl ether at about 190 °C to about 240 °C with a catalyst such as iodine or tributylamine to obtain the compound of formula 5.

A compound of formula 8, prepared as described in Syn., 739 (1975), which is incorporated herein by reference, or formula 5 above may be chlorinated using standard methods such as $POCl_3$ or $POCl_3/PCl_5$ and halogenated using standard conditions such as N-halosuccinimide and benzoyl peroxide in an inert solvent such as carbon tetrachloride to give the corresponding chloro-halomethyl compounds 6 and 9, respectively.

The preparation of aminoquinazoline, quinazolinone or amino-thienopyrimidine intermediates is outlined in Scheme 5.

Scheme 5

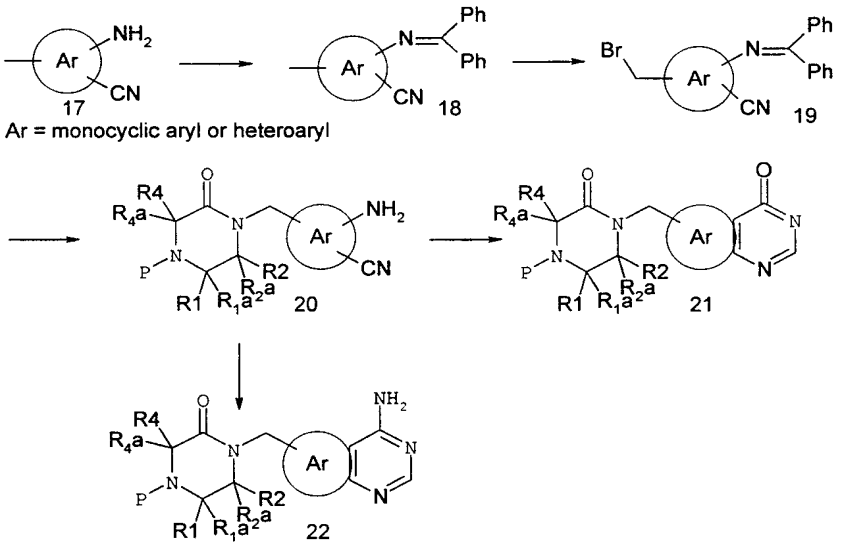


As shown in Scheme 5, an aminoheteroaryl carboxylic acid or an aminoarylcarboxylic acid 11 in which the amino and carboxylic acid are adjacent is treated with formamidine under heat to form the corresponding quinazolinone or thienopyrimidinone 12. The quinazolinone or thienopyrimidinone 12 is

then converted to the chloroquinazoline or chlorothienopyrimidine using a chlorinating reagent such as $P(O)Cl_3$ and heat. The chloroquinazoline or chlorothienopyrimidine is brominated at the benzylic carbon using radical bromination conditions. Alternatively, a chloroquinazoline or chlorothienopyrimidine, containing a hydroxy-methylene group is converted to the corresponding bromide using CBr_4/PPh_3; or PBr_3 conditions. The bromide 13 is then reacted with the anion of the ring nitrogen of compounds of formula 2, formed using NaH, $LiN(SiMe_3)_3$, $NaN(SiMe_3)_3$, LDA, lithium alkoxides, sodium alkoxides or an appropriate base, in an inert solvent such as THF, DMF, ether, or DME. This yields compounds of formula 14 in which Cy_2 is a chloro-quinazoline or a chloro-thienopyrimidine. The chloro group is converted to an amino group using NH_3 in ethanol in the presence of a catalytic acid source. Alternatively, the chloro group is converted to a substituted amino using a primary or secondary amine in a solvent. Alternatively, the chloro group is converted to a hydroxy group using acetic acid in water with heating or using a hydroxide source. Alternatively, the chloro is converted to an alkoxy group using an alcoholic solvent with heated in the presence of a base.

An alternative synthesis of quinazolines and thienoquinazolines is outlined in Scheme 6.

Scheme 6.

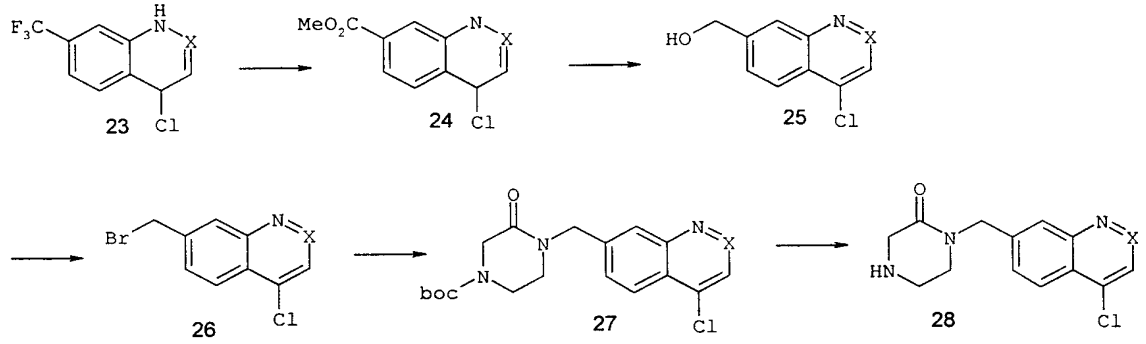


As shown in Scheme 6, an amino-aryl nitrile or an amino heteroaryl nitrile 17 is treated with an aldehyde or ketone under imine forming conditions. The corresponding aryl or heteroaryl imine is brominated using radical bomination with NBS. The bromide is then reacted with the anion of the ring nitrogen of compounds of formula 2, formed using NaH, $LiN(SiMe_3)_3$, $NaN(SiMe_3)_3$, LDA, lithium alkoxides, sodium alkoxides or an appropriate base, in an inert solvent such as THF, DMF, ether, or DME. This yields compounds of formula 20 in which Cy_2 is an imino-aryl nitrile or an imino heteroaryl

nitrile. The imine is deprotected using an acid such as HCl to give the corresponding aniline. The aniline-aryl-nitrile or the aniline-heteroaryl nitrile is converted to the amino-quinazoline or thienopyrimidine using triazine or formamidine. The quinazolinone or thienopyrimidinone 21 is formed using formamide.

The preparation of cinnoline (X = N) and quinoline (X = CH) intermediates is outlined in Scheme 7.

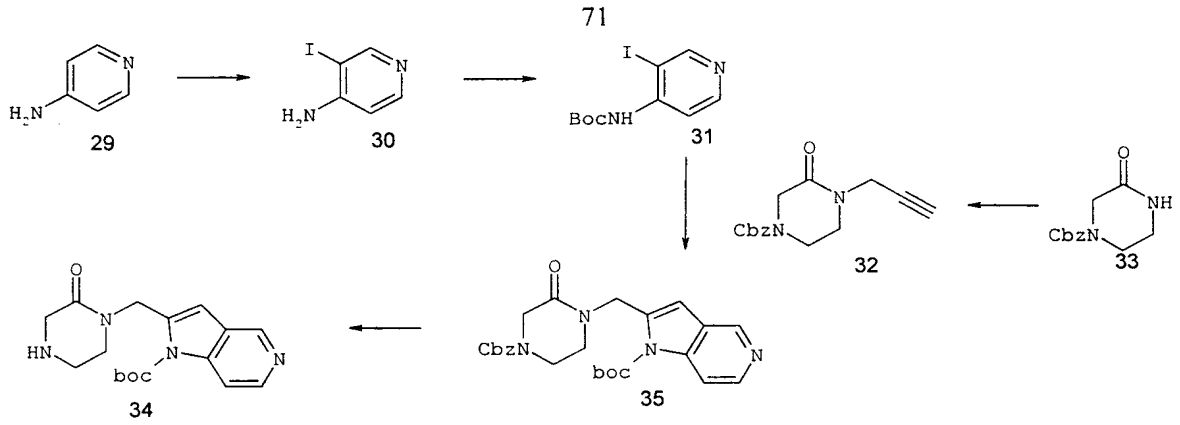
Scheme 7



As shown in Scheme 7, halogenated azaarenes exemplified by 4-chloro-7-trifluoromethylquinoline or cinnoline are treated with H_2SO_4 (70 -95 %) at 180-220 °C for about 16 to 48 hours in a sealed reaction vessel. The solution is cooled, poured into water and neutralized with base to pH ~ 3-4. The product is dissolved in aqueous base and precipitated by acidification to yield 7-carboxy-4-chloroquinoline or cinnoline. This material is converted to the alkyl ester (such as methyl or ethyl) by standard methods. 7-Alkyloxycarbonyl-4-chloroquinoline or cinnoline is dissolved in an anhydrous, aprotic solvent (THF or ether). The solution is cooled (-60 to -95 °C) and treated with a reducing agent such as lithium aluminum hydride. The solution is warmed (approximately -40 to -50 °C) for about 15 to 30 minutes and quenched with a solvent such as ethyl acetate. Standard workup gives the product 7-hydroxymethyl-4-chloroquinoline or cinnoline. This material is treated with 45-50 % HBr and heated to about 100-140 °C for about 45 to 90 minutes. After cooling and standard workup 7-bromomethyl-4-chloroquinoline or cinnoline is obtained.

The preparation of pyrrolopyridine derivatives is outlined in Scheme 8.

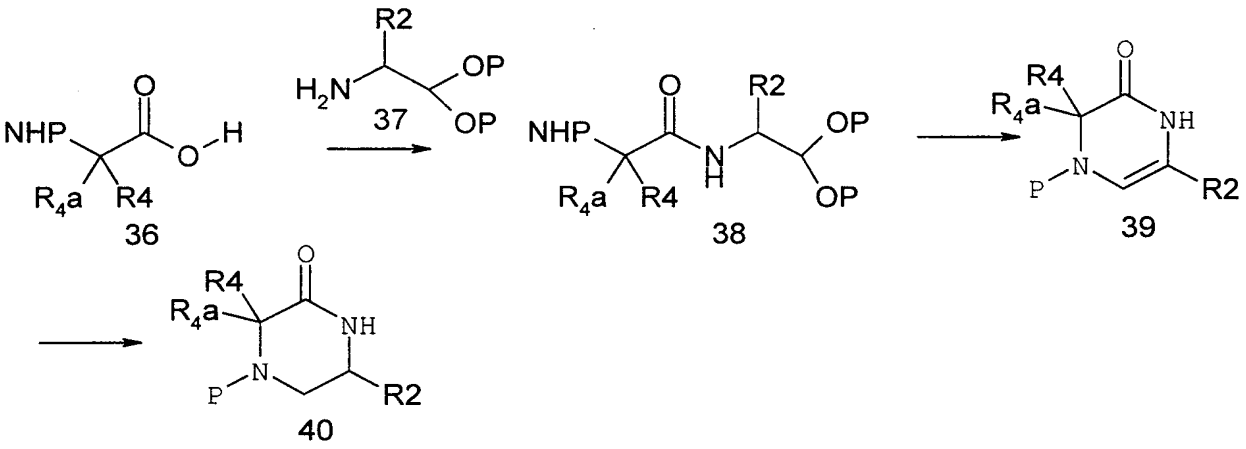
Scheme 8



As shown in Scheme 8 pyrrolopyridine derivatives are prepared by alkylation of a suitably protected oxopiperazine with propargyl bromide in the presence of a base such as sodium hydride. The resulting alkyne is heated (100-120 °C) with a halopyridine optionally substituted with hydroxy, alkoxycarbonylamino, or sulfhydryl, a catalyst such as $Pd(PPh_3)_2Cl_2$, copper iodide and triethylamine in a suitable solvent such as acetonitrile in a sealed vessel or in DMF for 2-20 hours. When the pyridine is substituted with a hydroxyl moiety furopyridines are isolated directly. If the pyridine is substituted with an alkoxycarbonylamino moiety, additional treatment with DBU at about 60 °C in DMF yields pyrrolopyridines. Subsequent carbamate deprotection using transfer hydrogenation conditions such as Pd black in formic acid yields the desired oxopiperazine furopyridines or pyrrolopyridine-1-carboxylic acid alkyl ester derivatives. After further reaction with the L_1-Cy_1 group, an additional deprotection step such as Boc removal using, for example, TFA, HCl is required for generating the oxopiperazine pyrrolopyridines.

The preparation of the compound of formula 40 are shown in Scheme 9.

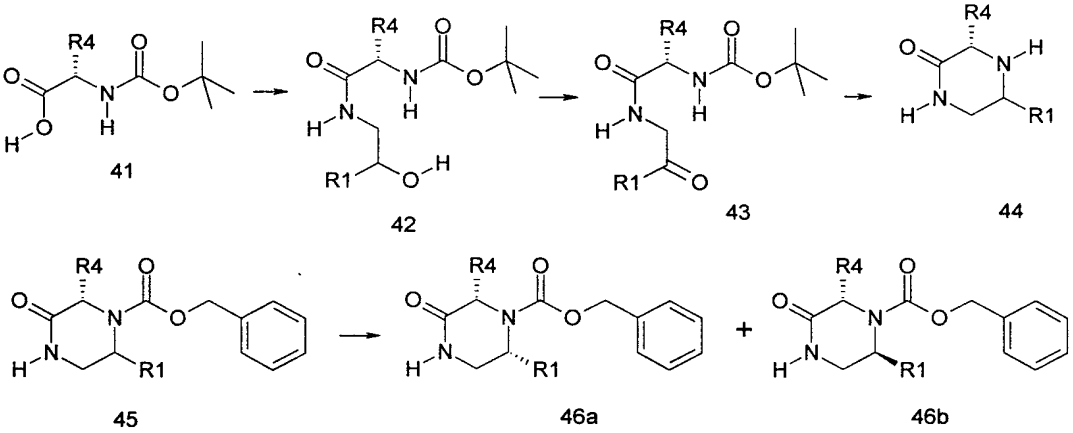
Scheme 9



As shown in Scheme 9, compounds of formula 40 are prepared from an appropriately protected mono- or di- substituted amino-acid. To this is added an amino-acetaldehyde, protected as an acetal derivative, under standard peptide coupling procedures, employing activating reagents such as EDC, TBTU, or BOP. The resulting dipeptidyl moiety is subjected to conditions which remove the acetal, such as acidic conditions (TsOH). The resulting cyclic material is reduced using hydrogenating conditions to yield compounds of formula 40. This reduction, alternatively can be carried out using a reagent which acts as a hydride source.

The preparation of compounds of formula 46a and b is shown scheme 10.

Scheme 10.

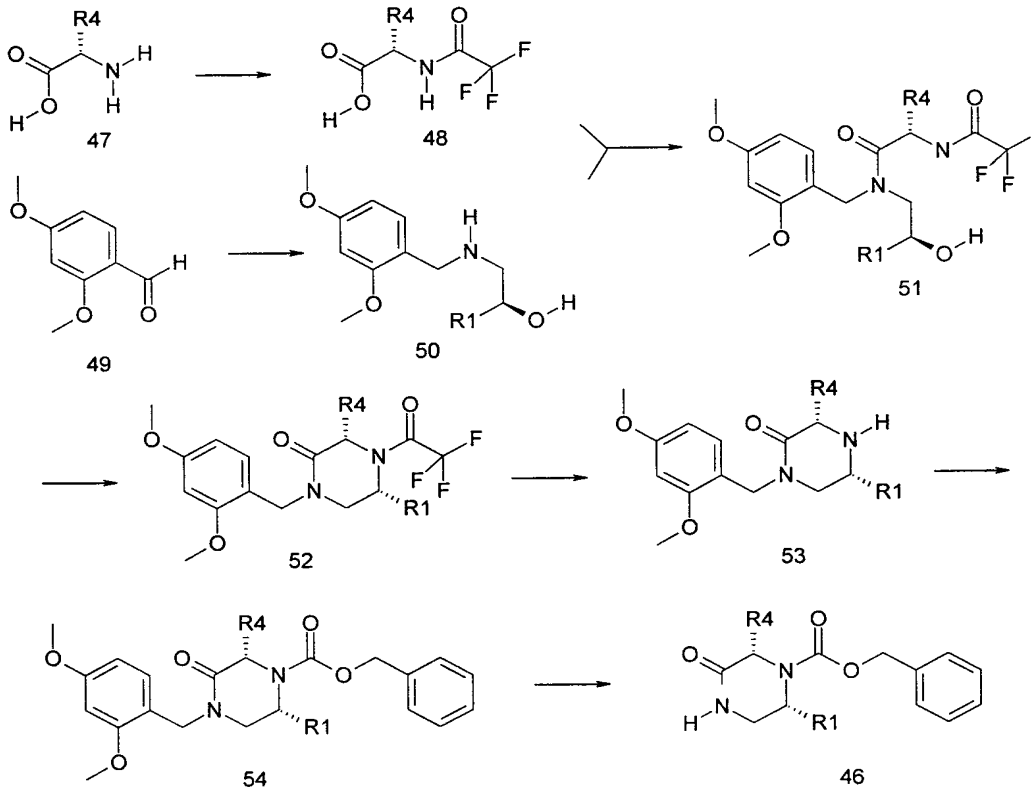


As shown in Scheme 10, a protected amino acid is coupled to a beta-aminoalcohol using standard peptide coupling procedures as describe above. The alcohol is then oxidized to a ketone using, for example, Swern oxidation conditions. The protecting group is removed and the resulting compound

is reduced under hydrogenation conditions to give the 2-piperidinone. The free amine can be reprotected and diastereomers are separated by chromatographic methods, or in some cases by recrystallization.

A chiral synthesis of compounds of formula 46 is shown in Scheme 11.

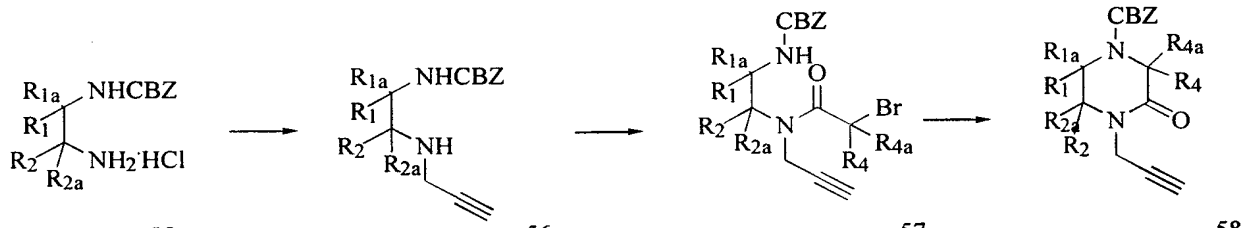
Scheme 11



As shown in Scheme 11, an amino acid is protected as its trifluoroacetate derivative using trifluoroacetic anhydride and a base. An amino-alcohol is derivatized via reductive amination conditions using a benzaldehyde derivative, such as 2,4-dimethoxybenzaldehyde. The resulting secondary amine is then coupled to an amino-acid protected as a trifluoroacetate using standard peptide coupling procedures. Ring closure is then accomplished by utilizing Mitsinobu conditions. The trifluoroacetate group is removed under basic conditions, and the amide of the ring is deproteced using an aqueous solution of potassium persulfate and sodium phosphate and heat. All possible enantiomers of piperazin-2-one can be made from the corresponding amino-alcohol and amino acid as shown in scheme 2c.

The preparation of the compound of formula 58 wherein R_1, R_2, R_{2a} ,R_4 and R_{4a} are hydrogen and R_{1a} is carbomethoxy, methoxymethyl, or a protected hydroxymethyl group is shown in Scheme 12.

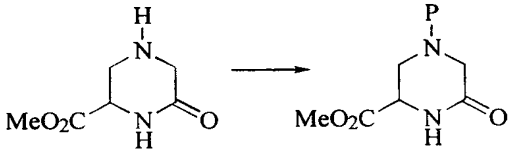
Scheme 12



As shown in Scheme 12, alkylating a compound of formula 55 with propargyl bromide in the presence of an amine base such as triethylamine provides the compound of formula 56. Coupling with bromoacetic acid using a standard reagent such as DCC gives the compound of formula 57 which can be cyclized using a non-nucleophilic strong base such as NaH in a solvent such as THF to yield the desired compound of formula 58.

The preparation of a compound of formula 59 is outlined in Scheme 13.

Scheme 13



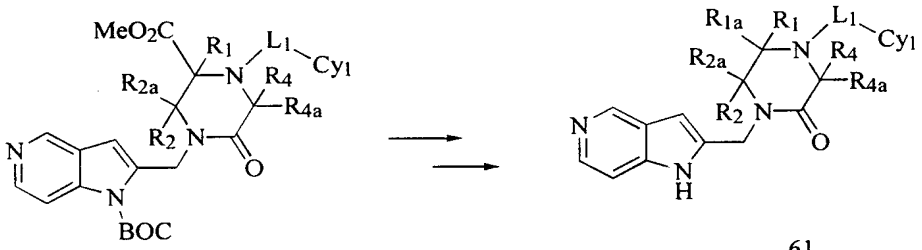
59

As shown in Scheme 13, protection of methyl 6-oxopiperazine-2-carboxylate (Aebischer, B., Helv. Chim. Acta 1989, 72, 1043-1051) using, for example, benzyl chloroformate or allyl chloroformate under standard conditions provides compound 59. Alkylation of 59 with propargyl bromide using a strong base such as NaH in polar solvents as THF or DMF provides the compound of formula 58.

The preparation of a compound of formula 61 wherein R_1, R_2, R_4, R_{4a}, L_1 and Cy_1 are defined as above and R_{1a} or R_{2a} are independently carboxy, acetamido or hydroxymethyl is outlined in Scheme 14.

Scheme 14

75

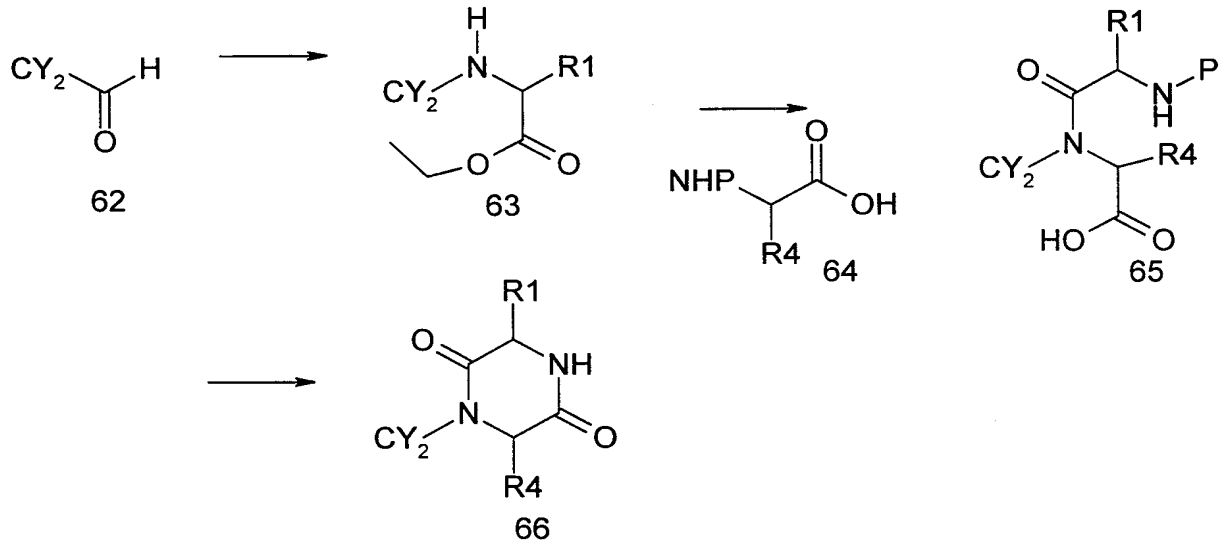


60 61

As shown in Scheme 14, the compound of formula 61 is prepared by hydrolysis of the ester using a base such as NaOH or LiOH to yield the acid, coupling the corresponding acid with a primary or secondary amine or ammonia using standard coupling reagents such as TBTU or EDC and reduction of the ester using a reducing agent such as $NaBH_4$ to yield hydroxymethyl.

The preparation of diketopiperazine compounds formula 66 in which R_1 and R_{1a} together and R_3 and R_{3a} together are oxygen are prepared as outlined in Scheme 15.

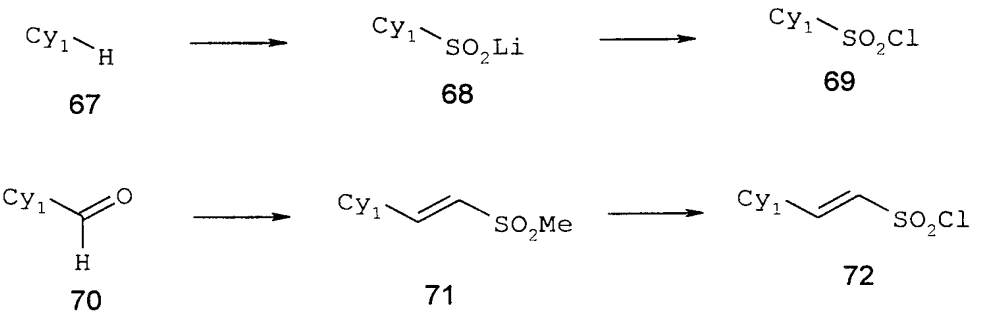
Scheme 15



As shown in Scheme 15, an aldehyde containing the Cy_2 group is condensed with an amino acid ester under reductive amination conditions. The resulting secondary amine is then coupled to an N-protected amino acid. The resulting dipeptide is deprotected which in general results in cyclization to the Cy_2 diketopiperazine. Alternatively for cases which do not cyclize, diketopiperazine formation can be achieved using a peptide coupling reagent such as EDC, TBTU, or BOP.

The preparation of sulfonyl chloride intermediates is outlined in Scheme 16.

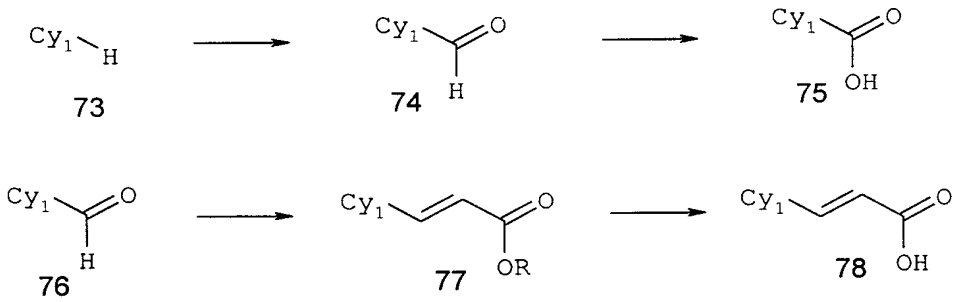
Scheme 17



As shown in Scheme 16, Cy_1 substituted sulfonyl chlorides are prepared by treatment of the appropriate aryl and heteroaryl compounds with a strong base such as n-BuLi at -78 °C followed by the addition of SO_2 gas and treatment of the lithium heteroaryl sulfonate with a chlorinating agent such as NCS or SO_2Cl_2 or, alternately, by homologation of the appropriate aryl and heteroaryl aldehydes using, for example, ethylmethanesulfonate and ethylchlorophosphonate.

The preparation of intermediate compounds of formula Cy_1-CO_2H is outlined in Scheme 17.

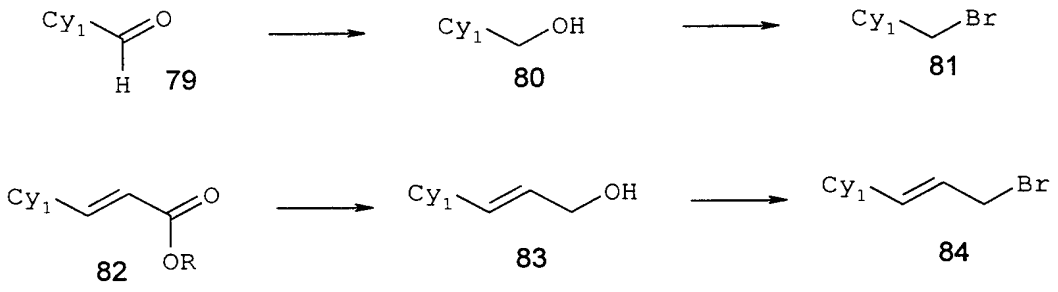
Scheme 17



As shown in Scheme 17, the requisite Cy_1 acids as defined above can be obtained by oxidation of the corresponding alcohols or the aldehydes using, for example, MnO_2, PDC or $AgNO_3$ in an appropriate solvent such as CH_2Cl_2 or H_2O/EtOH. The Cy_1 substituted aryl and heteroaryl groups can be functionalized by deprotonation methods using an appropriate non-nucleophilic base such as n-BuLi in an appropriate solvent such as Et_2O or THF and quenching with an appropriate carbonyl electrophile such as DMF, CO_2 or alkyl chloroformate. Alternatively, the acids can also be generated by hydrolysis of the corresponding esters using, for example, NaOH or LiOH. For example, in the acrylic esters, the Cy_1-(alkenylene)- groups as defined above are generated by homologation of the Cy_1 aldehydes using the usual Wittig type or Horner-Emmons type reagents in an appropriate solvent such as CH_2Cl_2 or THF.

The preparation of Cy_1 alkyl and alkenyl halides is outlined in Scheme 18.

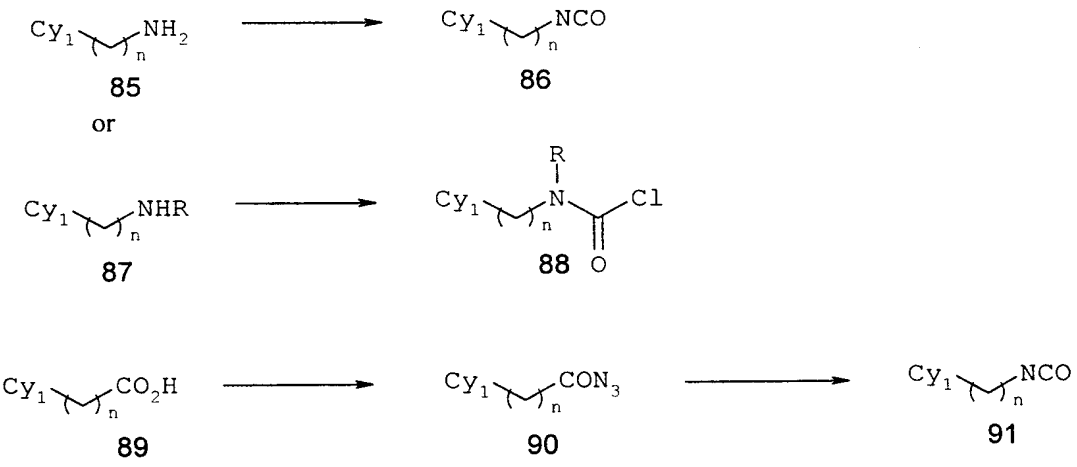
Scheme 18



As shown in Scheme 18, Cy_1 alkyl and alkenyl halides as defined above can be prepared by halogenation of the corresponding alcohols using either NBS, CBr_4 or PBr_3 under standard solvent conditions. The alcohols are generated by reduction of the corresponding aldehydes or esters using $NaBH_4$ or DIBAL in an appropriate solvent.

The preparation of Cy_1 isocyanate intermediates is outlined in Scheme 19.

Scheme 19

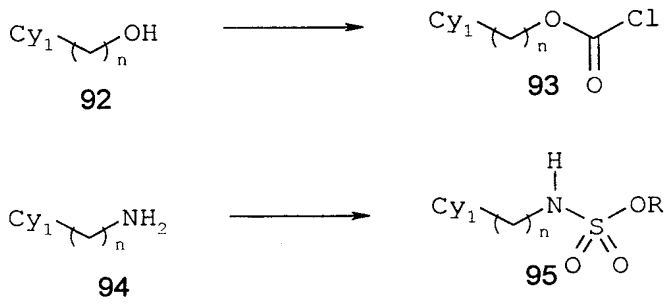


As shown in Scheme 19, Cy_1 isocyanates are obtained by chlorocarbonylation methods using phosgene or triphosgene in an appropriate solvent such as CH_2Cl_2 with an appropriate base additive such as triethylamine or pyridine on the corresponding primary or secondary amines. Alternatively, the isocyanates can also be generated by Curtius rearrangement in an appropriate solvent such as toluene, p-dioxane or DMF of the corresponding Cy_1 carbonyl azides. The carbonyl azides, in turn, are derived

from the corresponding carboxylic acids using either DPPA reagent or by proceeding through the mixed anhydride via an alkyl chloroformate reagent in an appropriate solvent such as DMF or acetone and using an appropriate base additive such as treithylamine.

The preparation of Cy_1 chloroformate intermediates is outlined in Scheme 20.

Scheme 20



As shown in Scheme 20, Cy_1 chloroformates are obtained by chlorocarbonylation methods using reagents such as phosgene, triphosgene or 1,1'-carbonyldiimidazole in an appropriate solvent such as CH_2Cl_2 on the corresponding alcohols. Activated sulfamyl esters are prepared from the corresponding amines using catechol sulfate in an appropriate solvent.

The preparation of acetamido compounds of this invention is outlined in Scheme 21.

Scheme 21

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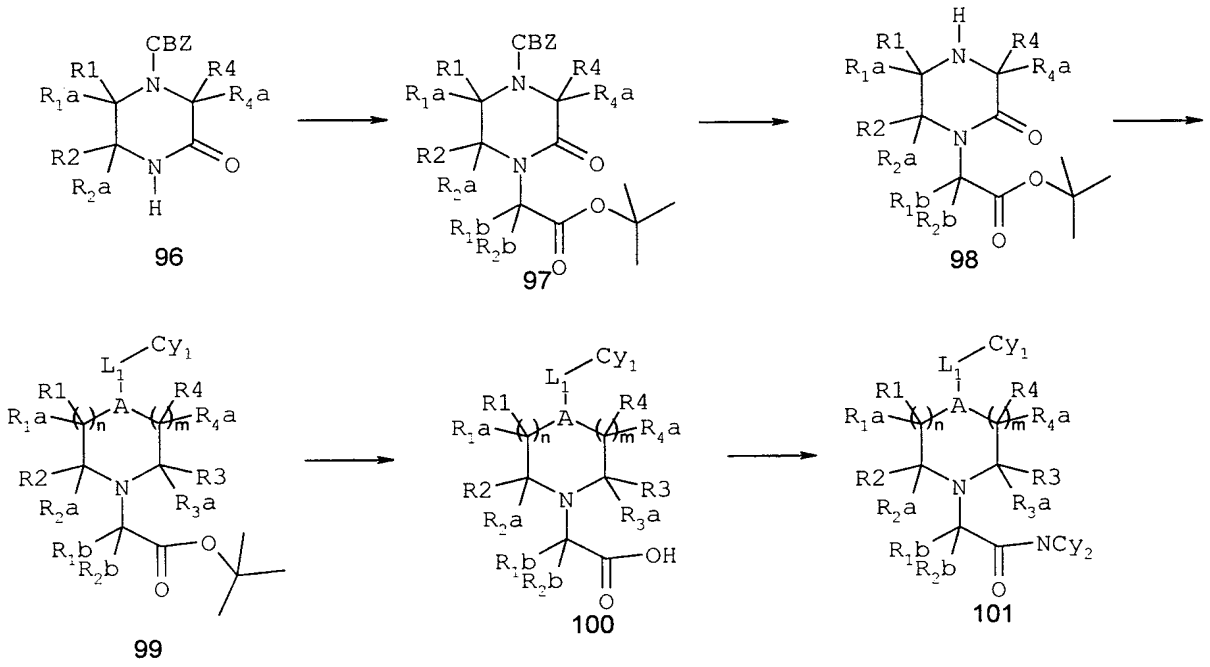
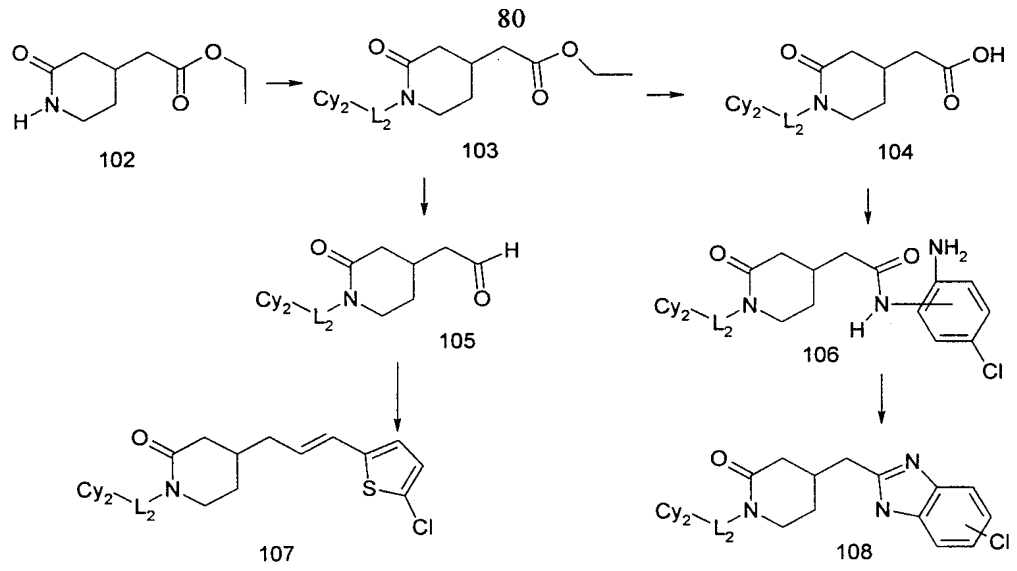


As shown in Scheme 21, alkylation of piperazin-2-one 96 is achieved with a strong base such as NaH and a t-butyl ester of haloacetic acid to give the acetate 97. Pd-catalyzed hydrogenation effectes removal of the CBZ group from the acetate 97 to give amine 98 which is converted to the compound 99 as described in Scheme 1 above. Hydrolysis of t-butyl ester 99 is accomplished using, for example, TFA/CH_2Cl_2. The resulting acid 100 is coupled with the optionally protected amine $HNCy_2$ under typical amide bond formation conditions to give the acetamide 101.

The preparation of compounds of this invention wherein Cy_1 is benzimidazol-2-yl is outlined in Scheme 22.

Scheme 22



Piperidin-2-one 102 is alkylated as described above to give the ester 103 which is hydrolyzed to give the acid 104 or reduced to give aldehyde 105. Coupling of the acid 104 and amines affords amide 106 which is cyclized with acetic anhydride to give the compound 108. Wittig-coupling of aldehyde 105 produces compound 107.

This invention is further exemplified but not limited by the following examples which further illustrate the preparation of the compounds of this invention. The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods described herein or their obvious equivalents.

EXAMPLE 1. 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

A. 1-Chloro-3-(2,2-dimethoxyethylsulfanyl)benzene.

To a solution of 3-chlorothiophenol (2.4 g, 16.6 mmol) in THF (200 mL) at 0°C is added bromoacetaldehyde dimethyl acetal (2.8 g, 16.6 mmol). To the solution is added sodium hydride (60% mineral oil dispersion, 0.70 g, 17.4 mmol). The reaction is stirred for 16 hours, and then is quenched by the addition of saturated NH_4Cl (aq.). The solution is diluted with EtOAc. The organic layer is washed with a saturated NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with hexanes. The title compound (3.7 g, 15.9 mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 1H), 7.25 (m, 1H), 7.12 (m, 1H), 4.47 (m, 1H), 3.07 (s, 3H), 3.02 (s, 3H).

B. 4-Chlorobenzo[b]thiophene and 6-Chlorobenzo[b]thiophene.

A solution containing polyphosphoric acid (8 g) and chlorobenzene (50 mL) is heated at reflux. A solution containing 1-chloro-3-(2,2-dimethoxyethylsulfanyl)benzene (2.7 g, 11.6 mmol) in chlorobenzene (5 mL) is added dropwise to the refluxing polyphosphoric acid solution. After 6 hours, the solution is cooled to ambient temperature. The solution is diluted with CH_2Cl_2 and washed with water and saturated NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with hexanes to yield the title compounds (2.4 g, 9.0 mmol) as a 1:1 isomeric mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (m, 1H), 7.75 (m, 2H), 7.42 (m, 2H). MS (EI): m/z 168, 170 (M+), Cl pattern.

C. 4-Chlorobenzo[b]thiophene-2-sulfonyl chloride and 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

To a solution of 4-chloro-benzo[b]thiophene and 6-chlorobenzo[b]thiophene (11.8 g, 88.1 mmol), in 400 mL of THF at -78°C is added n-BuLi (55 mL of a 1.6M solution in hexanes, 88.1 mmol). After 15 minutes, the solution is added by cannula to a precooled (-78°C) solution of SO_2 (200 g) in 100 mL of THF. After addition, the solution is allowed to warm to ambient temperature. After 0.5 hour, the solution is concentrated. The residue is suspended in hexanes (400 mL) and is cooled to 0°C. To the solution is added SO_2Cl_2 (12.5 g, 92.5 mmol). After stirring for 15 minutes, the solution is concentrated. The residue is dissolved in EtOAc. The organic solution is washed with saturated NH_4Cl (aq.), H_2O and saturated NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is dissolved in CH_2Cl_2 and filtered through a plug of silica gel. The crude product is purified by column chromatography eluting with hexanes to yield the title compound as well as 4-chlorobenzo[b]thiophene-2-sulfonyl chloride as white solids.

4-Chlorobenzo[b]thiophene-2-sulfonyl chloride: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.32 (m, 1H), 7.81 (m, 1H), 7.53 (m, 2H).

6-Chlorobenzo[b]thiophene-2-sulfonyl chloride: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.11 (s, 1H), 7.88 (m, 2H), 7.50 (m, 1H).

EXAMPLE 2. 5'-Chloro-[2,2']bithiophenyl-5-sulfonyl chloride.

A. 5-Chloro-[2,2']bithiophene.

The title compound is prepared from 2-chloro-thiophene according to the procedure described in Bull. Chem. Soc. Japan, 1979, 1126. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to afford a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.24 (m, 1H), 7.11 (d, 1H), 7.03 (dd, 1H), 6.94 (d, 1H), 6.83 (d, 1H). MS (EI) [M+]= 200, 202, Cl pattern.

B. 5'-Chloro-[2,2']bithiophenyl-5-sulfonyl chloride.

The title compound is prepared as described in Example 1, Part C using 5-chloro-[2,2']bithiophene in place of 6-chloro-benzo[b]thiophene. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to give a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.76 (d, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.92 (d, 1H). MS (EI): m/z 298, 300 (M+), Cl pattern.

EXAMPLE 3. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride.

A. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonic acid ethyl ester.

n-Butyllithium (53.1 mL, 2.5M solution in hexanes) is added dropwise to a solution of ethylmethanesulfonate (12.9 mL, 0.12 mol) in THF (300 mL) at -78°C. The reaction mixture is stirred for 15 min then ethylchlorophosphonate (9.9 mL, 0.07 mol) is added dropwise. The solution is stirred at -78°C for 30 minutes and then heated to 50°C for 1 hour. The reaction mixture is then cooled to -78°C and stirred for 1 h then 5-chlorothiophenecarboxaldehyde (7.1 mL, 0.07 mol) is added dropwise. The reaction mixture is allowed to slowly warm to RT overnight. Water (30 mL) is added to the mixture and stirred for 15 min then concentrated in vacuo. The residue is taken up in CH_2Cl_2 and washed with water, brine, dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is purified by column chromatography eluting with 5% EtOAc/hexanes to give title product (11.3 g, 0.04 mol) as an oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.51 (d, 1H), 7.10 (d, 1H), 6.91 (d, 1H), 6.42 (d, 1H), 4.20 (q, 2H), 1.40 (t, 3H).

B. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride.

Tetrabutylammonium iodide (16.3 g, (44.2 mmol) is added to a solution of 2-(5-chloro-thiophen-2-yl)-ethenesulfonic acid ethyl ester (11.3 g, 40.2 mmol) in acetone (100 mL) at room temperature. The mixture is heated to reflux and stirred overnight then cooled to RT and conconcentrated in vacuo. The residue is taken up in CH_2Cl_2 then washed with water and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness to give an oil (18.74 g, 40.2 mmol) which is taken on to the next step without further purification. Sulfuryl chloride (7.1 mL, 88.5 mmol) is added to a solution of triphenylphosphine (21.0 g, 86.42 mmol) in CH_2Cl_2 at 0°C . The ice bath is then removed and the product (18.74 g, 40.2 mmol) from the above reaction is added. After 2 h, the reaction mixture is concentrated in vacuo and the product purified by column chromatography eluting with 10% EtOAc/Hexanes to give the title compound (6.4 g, 26.3 mmol) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, 1H), 7.23 (d, 1H), 7.00 (d, 1H), 6.91 (d, 1H).

EXAMPLE 4. 3-Chlorobenzyl sulfamyl catechol.

To a solution of 3-chlorobenzylamine (0.14 g, 1.0 mmol) in 3 mL of DMF is added Et_3N (0.10 g, 1.5 mmol). The solution is cooled to 0°C. Catechol sulfate (0.172 g, 1.0 mmol) is added. The solution is warmed to ambient temperatures. After 2.5 h, 30 mL of EtOAc is added. The solution is washed with 5% HCl, H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the title compound (0.30 g, 0.97 mmol). ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.94 (s, 1H), 8.82 (m, 1H), 7.41 (m, 4H), 7.19 (d, 1H), 7.10 (m, 1H), 6.95 (d, 1H), 6.79 (m, 1H), 4.32 (AB, 2H).

EXAMPLE 5. 2-Bromomethyl-6-chlorobenzo[b]thiophene.

A. 6-Chlorobenzo[b]thiophene-2-carboxaldehyde.

To a solution of 6-chlorobenzo[b]thiophene (1.0 g, 5.93 mmol) in THF (60 mL) at -78°C is added a 1.6 M solution of n-BuLi in THF (3.9 mL, 6.23 mmol). After 10 minutes, 0.5 mL of DMF is added. The solution is stirred for 0.5 hours, then allowed to warm to ambient temperature. The solution is poured into a solution of saturated NH_4Cl. The solution is diluted with ether and the layers are separated. The organic layer is washed with H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The title compound is obtained as a white solid. MS (EI): m/z 196 (M+).

B. 6-Chlorobenzo[b]thiophen-2-yl)methanol.

To a solution of 6-chlorobenzo[b]thiophene-2-carboxaldehyde in THF at 0°C is added $NaBH_4$. After 1 hour, the solution is diluted with saturated NH_4Cl and ether. The organic layer is washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1H), 7.60 (d, 1H), 7.40 (m, 2H), 4.91 (AB, 2H).

C. 2-Bromomethyl-6-chlorobenzo[b]thiophene.

To a solution of 6-chlorobenzo[b]thiophen-2-yl)-methanol (0.2 g, 1.01 mmol) in THF (10 mL) is added triphenyl phosphine (0.34 g, 1.31 mmol) followed by CBr_4 (0.42g, 1.26 mmol). After 3 hours, the solution is concentrated. The product is purified by column chromatography eluting in a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes. The product is obtained as a white solid (0.25 g, 0.53 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1H), 7.62 (d, 1H), 7.40 (m, 2H), 4.76 (s, 2H).

EXAMPLE 6. 5-Bromomethyl-5'-chloro-[2,2']bithiophenyl.

A. (5'-Chloro-[2,2']bithiophenyl-5-yl)-methanol.

To a solution of 5-chloro-[2,2']bithiophenyl (3.00 g, 14.9 mmol) in 30 mL of THF at 0°C is added n-BuLi (9.8 mL of a 1.6M solution in hexanes, 15.7 mmol) dropwise. DMF (2.30 mL, 30 mmol) is added dropwise and the resulting solution is heated at reflux for 1 hour. The solution is diluted with H_2O and extracted with Et_2O. The organic layer is washed with H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude aldehyde is dissolved in 40 mL of anhydrous MeOH and sodium borohydride (0.85 g, 22.5 mmol) is added portionwise. The mixture is stirred at room temperature for 10 min, then quenched with water. The mixture is diluted with Et_2O and the layers separated. The organic layer is washed with H_2O, then dried over $MgSO_4$, filtered and concentrated to yield the title compound (2.23 g, 9.66 mmol) which is used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300MHz) δ 6.95 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 4.82 (s, 2H), 1.88 (bs, 1H).

B. 5-Bromomethyl-5'-chloro-[2,2']bithiophenyl.

To a solution of (5'-chloro-[2,2']bithiophenyl-5-yl)-methanol (2.23 g, 9.66 mmol) in 65 mL of CH_2Cl_2 is added bromotrimethylsilane (3.82 mL, 29.0 mmol). After 4 h, the solution is concentrated in vacuo. The crude product is stirred in hot hexanes and filtered. The filtrate is concentrated and the title compound (1.67 g, 5.69 mmol) is obtained as a green solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.00 (d, 1H), 6.94 (m, 2H), 6.85 (d, 2H), 4.71 (s, 2H).

EXAMPLE 7. 7-Bromomethyl-4-chloroquinazoline.

A. 7-Methyl-3H-quinazolin-4-one.

A solution of 2-amino-4-methylbenzoic acid (31.6 g, 206 mmol) in formamide (60mL) is heated to 130°C for 1 hour, then at 175°C for 3 hours. The solution is poured into 500 mL of ice water. The resulting solid is collected by filtration and further dried under reduced pressure. The title compound (26.2 g, 170 mmol) is obtained as a white solid. MS (EI): m/z 159 (M+).

B. 4-Chloro-7-methyl-quinazoline.

To a solution of 7-methyl-3H-quinazolin-4-one (10.6 g, 69 mmol) in toluene (350mL) is added triethylamine (17.5 g, 173 mmol) followed by phosphorous oxychloride (12.3 g, 80 mmol). The resulting solution is heated to 80°C. After 4 hours, the solution is cooled to ambient temperature. The reaction mixture is poured into 500 mL of water. The layers are separated and the organic layer is washed with H_2O, saturated $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The resulting crude product is purified by recrystallization from EtOAc. The title compound is obtained

as a white solid (10g, 56 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.02 (s, 1H), 8.16 (d, 1H), 7.87 (s, 1H), 7.55 (d, 1H), 2.62 (s, 3H).

C. 7-Bromomethyl-4-chloroquinazoline.

To a solution of 4-chloro-7-methylquinazoline (7.0 g, 39 mmol) in carbon tetrachloride (140 mL) is added N-bromosuccinimide (8.0 g, 45 mmol), and benzoyl peroxide (0.8 g, 3.3 mmol). The solution is refluxed for 8 hours. After this time, the solution is filtered. The filtrate is concentrated and the residue is stirred with ether to give the title compound as an off-white solid (5.1 g, 20 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.10 (s, 1H), 8.30 (d, 1H), 8.10 (s, 1H), 7.82 (d, 1H), 4.68 (s, 2H). MS (EI): m/z 237 (M+).

EXAMPLE 8. 3-Bromomethyl-7-chloro-1H-quinolin-2-one.

A. N-(3-Chlorophenyl)-2-methyl-3-phenylacrylamide.

To a solution of 3-chloroaniline (0.98 mL, 9.3 mmol) in CH_2Cl_2 (25 mL) at 0°C is added pyridine (0.78mL, 9.5 mmol). To the resulting solution is added dropwise a solution of α-methyl cinnamic acid chloride (1.6 g, 9.3 mmol) in CH_2Cl_2 (8 mL). After 3 hours, the solution is concentrated. The crude product is purified by column chromatography eluting with 5%EtOAc/hexanes to 10%EtOAc/hexanes. The title compound is obtained as a solid (2.5 g, 9.2 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 1H), 7.73 (s, 1H), 7.46 (m, 1H), 7.33 (m, 6H), 7.22 (m, 1H), 7.03 (m, 1H), 2.13 (s, 3H).

B. 7-Chloro-3-methyl-1H-quinolin-2-one.

To a solution of N-(3-chlorophenyl)-2-methyl-3-phenylacrylamide (2.5 g, 9.2 mmol) in chlorobenzene (50 mL) is added $AlCl_3$ (6.2 g, 46 mmol). The solution is heated to 120°C. After 4 hours, the solution is poured onto ice. The solution is filtered. The organic layer is washed with 1N HCl, H_2O and saturated NaCl. The crude product is purified by column chromatography eluting with 2% MeOH/CH_2Cl_2. The title compound is obtained as a white solid (1.5 g, 7.74 mmol). ^{1}H NMR (d6-DMSO, 300 MHz) δ 11.82 (bs, 1H), 7.73 (s, 1H), 7.52 (m, 1H), 7.21 (m, 2H), 2.08 (s, 3H).

C. 3-Bromomethyl-7-chloro-1H-quinolin-2-one.

The title compound is prepared as described in Example 7, Part C, substituting 7-chloro-3-methyl-1H-quinoline-2-one for 7-methyl-4-chloroquinazoline. The title compound is obtained as a white solid. ^{1}H NMR (d6-DMSO, 300 MHz) δ 12.00 (bs, 1H), 8.17 (s, 1H), 7.72 (d, 1H), 7.29 (m, 2H), 4.58 (s, 2H).

EXAMPLE 4. 6-Bromomethyl-2-chloro-quinoline.

A. 6-Methyl-1H-quinolin-2-one.

The title compound is prepared from p-toluidine and cinnamoyl chloride according to the procedure described in Synthesis 1975, 739. The crude product obtained is triturated in Et_2O/hexanes and filtered to give the title compound as a beige solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.60 (bs, 1H), 7.82 (d, 1H), 7.41 (s, 1H), 7.30 (d, 1H), 7.18 (d, 1H), 6.45 (d, 1H), 2.30 (s, 3H).

B. 2-Chloro-6-methylquinoline.

6-Methyl-1H-isoquinolin-2-one (14.6 g, 91.7 mmol) in phosphorus oxychloride (160 mL) is heated at 60°C for 17 hours. The mixture is cooled to room temperature, then concentrated to a beige residue. The residue is diluted with ice water and the pH is adjusted to about 8 by slow addition of 10 N NaOH. The crude product is precipitated out during neutralization of the aqueous solution and the solid is filtered, washed with water and dried. The solid is recrystallize from MeOH to afford the title compound (12.0 g, 67.5 mmol) as a beige solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, 1H), 7.92 (d, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.33 (d, 1H), 2.53 (s, 3H).

C. 6-Bromomethyl-2-chloro-quinoline.

N-Bromosuccinimide (12.9 g, 72.5 mmol) and benzoyl peroxide (0.33 g, 1.30 mmol) are added to a solution of 2-chloro-6-methyl-quinoline (12.0 g, 67.5 mmol) in carbon tetrachloride (300 mL). The mixture is heated at reflux for 6 hours. At this time, the resulting mixture is cooled to room temperature, filtered, washed with CH_2Cl_2 and concentrated in vacuo. The crude residue is recrystallized from 50% EtOAc/hexanes to yield the title compound (8.80 g, 34.3 mmol) as a beige crystalline solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 8.02 (d, 1H), 7.83 (s, 1H), 7.77 (dd, 1H), 7.40 (d, 1H), 4.65 (s, 2H). MS (EI): m/z 256, 258 (M+), Cl pattern.

EXAMPLE 10. 3-Bromomethyl-1,7-dichloro-2H-isoquinoline.

A. 3-(4-Chlorophenyl)-2-methyl-acryloyl azide.

To a solution of 3-(4-chlorophenyl)-2-methyl-acrylic acid (11.2 g, 57 mmol) in 500 mL of acetone at 0°C is added triethyl amine (9.6 mL, 68 mmol) followed by ethyl chloroformate (6.2 mL, 63 mmol). The solution is allowed to warm to ambient temperatures. After 2 h, sodium azide (5.6 g, 86 mmol) in 35 mL of H_2O is added. After addition, the solution is stirred for 2 hours. The solution is diluted with H_2O (100 mL). The resulting solid is collected by filtration giving the title compound as a white solid (11.1 g, 50mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (s, 1H), 3.38 (m, 4H), 2.10 9s, 3H).

B. 7-Chloro-3-methyl-2H-isoquinoline-1-one.

3-(4-Chlorophenyl)-2-methyl-acryloyl azide (11.0 g, 50 mmol) is dissolved in 80 mL of diphenyl ether. The solution is added dropwise to a solution of tributyl amine (11.8 mL, 50mmol) in 170 mL of diphenyl ether at 210°C. After 4 hours., the solution is cooled 50°C and diluted with 1.5 L of hexanes. The resulting solid is collected by filtration giving the title compound as a white solid (7.2 g, 37 mmol). ^{1}H NMR (d6-DMSO, 300 MHz) δ 11.4 (bs, 1H), 8.02 (s, 1H), 7.67 (d, 1H), 7.55 (d, 1H), 6.34 (s, 1H), 2.18 (s, 3H).

C. 1,7-Dichloro-3-methyl-isoquinoline.

A solution of 7-chloro-3-methyl-2H-isoquinoline-1-one (7.1 g, 36.7 mmol) in 100 mL of phosporous oxychloride is heated to 100°C. After 5 h, the solution is concentrated to dryness. The residue is dissolved in CH_2Cl_2. The solution is washed with H_2O. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with a gradient of 3%EtOAc/hexanes to 5% EtOAc/hexanes. The title compound is obtained as a white solid (6.0g, 28 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (s, 1H), 7.68 (m, 1H), 7.63 (m, 1H), 7.40 (s, 1H), 2.64 (s, 3H).

D. 3-Bromomethyl-1,7-dichloro-2H-isoquinoline.

The title compound is prepared as described in Example 7, part C, substituting 1,7-dichloro-3-methyl-isoquinoline for 4-chloro-7-methylquinazoline. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.82 (m, 1H), 7.76 (m, 2H), 4.68 (s, 2H).

EXAMPLE 11. 3-Bromomethyl-7-chloroisoquinoline.

A. 7-Chloro-3-methyl-isoquinoline.

To a solution of 1,7-dichloro-3-methyl-isoquinoline (0.50 g, 2.36 mmol), Example 10, part C, in 5.5 mL of 9:1 acetic acid:H_2O at 75°C is added zinc (0.23 g, 3.54 mmol) After 75 minutes, the solution is cooled to ambient temperatures. The solution is diluted with a 4:1 EtOAc:CH_2Cl_2 solution. To the solution is added 100mL of a 1N NaOH solution. The aqueous solution is extracted with 4:1 EtOAc:CH_2Cl_2. The combined organic layers are washed with a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with a gradient of 5%EtOAc/hexanes to 15% EtOAc/hexanes. The title compound is obtained as a white solid (0.36 g, 1.97 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H), 7.89 (s, 1H), 7.61 (d, 1H), 7.55 (d, 1H), 7.44 (s, 1H) 2.68 (s, 3H). MS (EI): m/z 177, 179 (M+), Cl pattern.

B. 3-Bromomethyl-7-chloroisoquinoline.

The title compound is prepared as described in Example 7, part C, substituting 7-chloro-3-methyl-isoquinoline for 4-chloro-7-methylquinazoline. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.18 (s, 1H), 7.97 (s, 1H), 7.75 (m, 2H), 7.67 (m, 1H), 4.71 (s, 2H).

EXAMPLE 12. 2-Bromomethyl-6-chloronaphthalene.

A. 6-Chloro-3,4-dihydro-1H-naphthalene-2-one.

To a solution of (4-chlorophenyl)-acetyl chloride (17.3 g, 92 mmol) in 50 mL of CH_2Cl_2 at -20°C is added a solution of $AlCl_3$ (24.4 g, 184 mmol) in 200 mL CH_2Cl_2 dropwise. After 20 minutes, ethylene (g) is bubbled through the solution for 30 minutes. The solution is stirred at -10°C for 15 minutes. The reaction mixture is poured into 300 g of ice. The layers are separated. The organic layer is washed with H_2O, saturated $NaHCO_3$ and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting solid is triturated with pentane (2x20mL). The solid is then dried to give the title compound as a solid (15.2 g, 84.2 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 2H), 7.06 (m, 1H), 3.52 (s, 2H), 3.04 (m, 2H), 2.56 (m, 2H).

B. 6-Chloro-2-methyl-1,2,3,4-tetrahydronaphthalene-2-ol.

To a solution of $TiCl_4$ (95 mL, 1M in toluene) at -45°C is added a solution of CH_3MgBr (4.2 mL 3M in THF). The solution is stirred for 20 minutes. After this time, 6-chloro-3,4-dihydro-1H-naphthalene-2-one (11.3 g, 63 mmol) in 80 mL of CH_2Cl_2 is added dropwise over 15 minutes. The reaction is stirred for an additional 15 min at -45°C. The solution is warmed to 0°C. After 2 h, the solution is diluted with H_2O and CH_2Cl_2. The organic layer is dried over $MgSO_4$, filtered and concentrated. The title compound is obtained as an oil (11.3 g, 57.5 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (m, 2H), 6.97 (m, 1H), 3.02 (m, 2H), 2.80 (s, 3H), 1.85 (m, 2H), 1.80 (m, 2H).

C. 2-Chloro-6-methyl naphthalene.

A solution of 6-chloro-2-methyl-1,2,3,4-tetrahydronaphthalene-2-ol (11.3 g, 57.5 mmol) and Ph_3COH (16.5 g, 63 mmol) in 80 mL of TFA is stirred for 2.5 days. After this time, the solution is concentrated to dryness. The residue is dissolved in CH_2Cl_2. The organic layer is washed with H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with hexanes. The title compound is obtained as a white solid (4.05 g, 22.9 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (s, 1H), 7.69 (m, 2H), 7.58 (s, 1H), 7.50 (m, 2H), 2.49 (s, 3H).

D. 2-Bromomethyl-6-chloronaphthalene.

The title compound is prepared as described in Example 7, part C, substituting 2-chloro-6-methyl naphthalene for 4-chloro-7-methylquinazoline. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (m, 2H), 7.78 (s, 1H), 7.76 (m, 2H), 7.52 (d, 1H), 7.42 (d, 1H), 4.62 (s, 2H).

EXAMPLE 13. 2-(Benzhydrylidene-amino)-4-bromomethyl-benzonitrile.

A. 2-(Benzhydrylidene-amino)-4-methyl-benzonitrile.

To a solution of 2-amino-4-methyl benzonitrile (20 g, 151 mmol) in 1000mL of dichloroethane is added benzophenone imine (30g, 166mmol). The solution is refluxed for 48 hours After this time, the solution is cooled to ambient temperatures. The solution is washed with sat. $NaHCO_3$, water and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The product is further purified by recrystallization from t-butyl ether. The title compound (25.5g, 118mmol) is obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (m, 2H), 7.42 (m, 3H), 7.32 (m, 7H), 6.79 (d, 1H), 6.58 (s, 1H), 2.23 (s, 3H).

B. 2-(Benzhydrylidene-amino)-4-bromomethyl-benzonitrile.

To a solution of 2-(benzhydrylidene-amino)-4-methyl-benzonitrile (11.2g, 37.8mmol) in 500mL of CCl_4 is added N-bromosuccinimide (7.06g, 39.7mmol), and benzoyl peroxide (0.92g, 3.8mmol). The solution is heated to reflux for 16 hours. After this time, the solution is filtered and the organic solution is concentrated under vacuum. The residue is purified by column chromatography eluting with a gradient of 20%t-butyl ether/hexanes to 25% t-butyl ether/hexanes. The product is obtained as an oil containing a mixture of the desired monobromide, dibromide and unreacted starting material. The mixture is assayed by proton NMR and is found to have a purity between 60-75%. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (m, 2H), 7.42 (m, 9H), 6.92 (d, 1H), 6.81 (s, 1H), 4.29 (s, 2H).

EXAMPLE 14. 7-Bromomethyl-4-chloroquinoline.

A. 7-Methyloxycarbonyl-4-chloroquinoline.

4-Chloro-7-trifluoromethylquinoline (5.0 g, 21.6 mmol) in 100 mL 80% H_2SO_4 is heated to 200°C for 24 hours in a sealed tube. The solution is cooled, poured into water and neutralized with sodium hydroxide to pH ~ 3-4. The precipitated solid is collected, washed with water and dissolved in 2 N sodium hydroxide. The aqueous solution is washed with ethyl acetate then acidified to pH~3-4. The precipitate is collected, washed with water and dried in a vacuum oven overnight to yield 7-carboxy-4-

chloroquinoline as a solid (5.1 g, 24.6 mmol). A portion of this material (2.0 g, 9.6 mmol) is treated with anhydrous THF (200 mL) and DMF (2 mL) and 2 M oxalyl chloride in methylene chloride (14.5 mL, 29 mmol). The resulting suspension is stirred at room temperature for 2 h then treated with methanol (10 mL). After stirring 30 minutes the solution is concentrated and the residue is taken up in methylene chloride. The solution is washed with saturated sodium bicarbonate and dried (sodium sulfate) and concentrated to yield the title compound as a solid (2.1 g, 9.5 mmol). MS m/z: $M^+ = 221$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.6 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.65 (d, 1H), 7.45 (s, 1H), 3.95 (s. 3H).

B. 7-Hydroxymethyl-4-chloroquinoline.

7-Methyloxycarbonyl-4-chloroquinoline (2.1 g, 9.5 mmol) is dissolved in anhydrous THF (25 mL) and anhydrous ether (200 mL). The solution is cooled in a dry ice/acetone bath and treated 1M lithium aluminum hydride in THF (11.0 mL, 11 mmol). The solution is warmed (approximately -45°C) for 20 minutes and quenched with ethyl acetate. The solution is diluted with ether (100 mL) and treated with water (36 mL), 15% NaOH (36 mL) and water (36 mL) in succession. The mixture is filtered and evaporated to yield the title compound as a residue (2.0 g, 9.7 mmol) which is dried under vacuum and used without further purification. MS m/z: $M^+ = 193$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 7.6 (d, 1H), 7.45 (d, 1H), 4.8 (s, 2H).

C. 7-Bromomethyl-4-chloroquinoline.

7-Hydroxymethyl-4-chloroquinoline (0.2 g, 0.97 mmol) is treated with 48 % HBr and heated to 120°C for 1 hours. The resulting solution is cooled with ice, diluted with water and treated with ethyl acetate and sodium bicarbonate until basic to pH paper. The layers are separated and the organic layer is washed with water, dried (Na_2SO_4) and concentrated to give 7-bromomethyl-4-chloroquinoline (0.23 g, 0.9 mmol). MS m/z: $M^+ = 255$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, 1H), 8.25 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.5 (d, 1H), 4.7 (s. 2H).

EXAMPLE 15. 7-Bromomethyl-4-chlorocinnoline.

A. 4-methyl-2-nitrophenylethanone.

4-Fluro-3-nitrotoluene (7.5 g, 48.4 mmol) is treated with a solution of nitroethane (15.2 mL, 200 mmol) in ethyl acetate (100 mL) and DBU (21 mL, 145 mmol) and stirred overnight at ambient temperature. The solution is concentrated under vacuum, diluted with methanol, treated with 30% H_2O_2 (25 mL) and 10% sodium bicarbonate (25 ml) and stirred overnight at ambient temperature. The reaction mixture is concentrated in vacuo, acidified with 5% HCl and extracted with methylene chloride. The organic layer is dried (sodium sulfate) and chromatographed (35% ethyl acetate/hexane) to give the

title compound (7.2 g, 40.2 mmol). MS m/z: $M^+ = 279$; ^1H NMR ($CDCl_3$, 300MHz) δ 7.8 (s, 1H), 7.48 (d, 1H), 7.32 (d, 1H), 2.5 (s, 3H), 2.4 (s, 3H).

B. 2-Amino-4-methylphenylethanone.

A solution of 4-methyl-2-nitrophenylethanone (5.0 g, 28 mmol) in methanol (100 mL) is treated with ammonium formate (9.6 g, 140 mmol) and 5% palladium on carbon (1.5 g). The mixture is heated to 60°C for 6 h then stirred at ambient temperature for 16 hours. The reaction mixture is filtered through Celite and the filtrate is concentrated in vacuo. The concentrate is treated with sodium bicarbonate and partitioned between water and ethyl acetate. The organic layer is separated, dried with sodium sulfate and concentrated to give crude title compound (4.5 g, 30.2 mmol) which is used without further purification. MS m/z:$M^+ = 149$; ^1H NMR ($CDCl_3$, 300MHz) δ 8.05 (d, 1H), 7.4 (d, 1H), 7.25 (s, 1H), 2.8 (s, 3H), 2.45 (s, 3H).

C. 7-Methyl-1-H-cinnolin-4-one.

A solution of 2-amino-4-methylphenylethanone (5.0 g, 33.6 mmol) in concentrated HCl (100 mL) is treated, in portions, with a solution of sodium nitrite (5.7 g, 82.6 mmol) in water (~ 10 mL). The resulting solution is stirred at 60°C for 2 hr, cooled to ambient temperature and diluted with a saturated solution of sodium acetate (~ 200 mL). Solid sodium acetate is added portionwise until the solution tested basic to pH paper. Upon stirring, the title compound precipitated as a white solid which is collected and air dried (2.3 g, 14.3 mmol). MS m/z: $[M+H]^+ = 161$; ^1H NMR ($CDCl_3$, 300MHz) δ 8.1 (d, 1H), 7.85 (s, 1H), 7.45 (s, 1H) 7.3 (d, 1H), 2.55 (s, 3H).

D. 4-Chloro-7-methylcinnoline.

7-Methyl-1-H-cinnolin-4-one (1.3 g, 8.1 mmol) is treated with about 80 mL of chlorobenzene and heated until the solid dissolves. The resulting solution is cooled and treated with pyridine (0.16 mL, 2 mmol) and $POCl_3$ (1.13 mL, 12.2 mmol). The solution is heated to reflux for 1 h then concentrated to dryness. The residue is chromatographed (20 % ethyl acetate/hexane) to yield the title compound as a tan solid (~ 1 g, 5.6 mmol). MS m/z (M+=178); ^1H NMR ($CDCl_3$, 300MHz) δ 9.3 (s, 1H), 8.35 (s, 1H), 8.1 (d, 1H), 7.7 (d, 1H), 2.68 (s, 3H).

E. 7-Bromomethyl-4-chlorocinnoline.

A solution of 4-chloro-7-methylcinnoline (0.6 g, 3.37 mmol) in carbon tetrachloride (30 mL) is treated with N-bromosuccinimide (0.64 g, 3.4 mmol) and a catalytic amount of 70 % benzoyl peroxide (0.22 g, 0.63 mmol). The solution is heated to 80 °C overnight, then filtered. The filtrate is concentrated in vacuo and the resulting residue is chromatographed (20 % ethyl acetate/ methyl chloride) to give the

title compound (0.3 g, 1.2 mmol) and some unreacted starting material (0.1 g, 0.56 mmol). MS m/z: $[M+H]^+ = 257$; ^1H NMR ($CDCl_3$, 300MHz) δ 9.35 (s, 1H), 8.55 (s, 1H), 8.2 (d, 1H), 8.85 (d, 1H), 4.75 (s, 2H).

EXAMPLE 16. 6-Bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole.

A. 1H-Indole-6-carboxylic acid methyl ester.

To a solution of 6-indole carboxylic acid (0.91 g, 5.67 mmol) in 33 mL of 2:1 THF/MeOH is added (trimethylsilyl)diazomethane (5.0 mL of a 2.0M solution in hexanes, 10.0 mmol). The mixture is stirred for 3 h and concentrated in vacuo to give the title compound (0.87 g, 4.97 mmol). The crude product is used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (bs, 1H), 8.20 (s, 1H), 7.82 (dd, 1H), 7.67 (d, 1H), 7.45 (m, 1H), 6.60 (m, 1H), 3.95 (s, 3H).

B. 3-Chloro-1H-indole-6-carboxylic acid methyl ester.

To a solution of 1H-indole-6-carboxylic acid methyl ester (5.86 g, 33.5 mmol) in 30 mL of CH_2Cl_2 is added N-chlorosuccinimide (0.58, 4.33 mmol) portionwise over 1.5 hours. The mixture is stirred for 2 h, then diluted with water. The layers are separated and the organic phase is washed with water and saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound (5.74 g, 27.3 mmol). The crude product is used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (bs, 1H), 8.19 (s, 1H), 7.90 (dd, 1H), 7.69 (d, 1H), 7.36 (d, 1H), 3.97 (s, 3H).

C. 3-Chloro-1-(toluene-4-sulfonyl)-1H-Indole-6-carboxylic acid methyl ester.

To a solution of 3-chloro-1H-indole-6-carboxylic acid methyl ester (3.00 g, 17.1 mmol) in 40 mL of THF at -78°C is added LDA(8.55 mL of a 2.0M solution in hexanes, 17.1 mmol) dropwise. The solution is stirred at -78°C for 30 minutes p-Toluenesulfonyl chloride (3.43 g, 18.0 mmol) in 15 mL of THF is added dropwise and the resulting solution is stirred at -78°C for 3 hours. The mixture is warmed to 0°C , quenched with saturated $NaHCO_3$ solution and diluted with H_2O and Et_2O. The layers are separated. The organic phase is washed with saturated $NaHCO_3$ solution, H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes to provide the title compound (3.64 g, 10.0 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 8.70 (s, 1H), 8.01 (dd, 1H), 7.80 (d, 2H), 7.70 (s, 1H), 7.60 (d, 1H), 7.38 (m, 2H), 4.00 (s, 3H), 2.49 (s, 3H).

D. [3-Chloro-1-(toluene-1-sulfonyl)-1H-indol-6-yl]-methanol.

To a solution of 3-chloro-1-(toluene-4-sulfonyl)-1H-Indole-6-carboxylic acid methyl ester (3.10 g, 8.53 mmol) in 50 mL of toluene at -78°C is added DIBAL (13.8 mL of a 1.5M solution in toluene, 20.8 mmol) dropwise. The mixture is stirred at -78°C for 2 h, then warmed to room temperature and stirred for 2 hours. The reaction mixture is quenched by the addition of MeOH and washed with saturated disodium tartrate solution. The aqueuos layer is extracted with Et_2O. The combined organics are washed with saturated disodium tartrate solution, water and saturated NaCl solution. The organic phase is then dried over anhydrous $MgSO_4$, filtered and concentrated to give the title compound (2.88 g). The crude product is used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.79 (d, 2H), 7.56 (s, 1H), 7.53 (d, 1H), 7.31 (d, 1H), 7.25 (d, 2H), 4.84 (s, 2H), 2.37 (s, 3H), 1.88 (bs, 1H).

E. 6-Bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole.

To a solution of [3-chloro-1-(toluene-1-sulfonyl)-1H-indol-6-yl]-methanol (0.45 g, 1.34 mmol) in 13 mL of Et_2O at 0°C is added phosphorous tribromide (0.04 mL, 0.40 mmol). The mixture is stirred at 0°C for 15 min, then at room temperature for 2 hours. The mixture is quenched by the addition of water/ice and diluted with Et_2O. The layers are separated and the organic phase is washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution. The organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated to provide the title compound (0.47 g, 1.18 mmol) as an oil. The crude product is used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.50 (d, 1H), 7.35 (d, 1H), 7.27 (m, 2H), 4.66 (s, 2H), 2.39 (s, 3H).

EXAMPLE 17. 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene.

A. 3-(5-Chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester.

To a solution of 5-chloro-2-thiophene-carboxaldehyde (5.10 g, 34.8 mmol) in 100 mL of dry CH_2Cl_2 is added methyl (triphenylphosphoranylidene)acetate (11.8 g, 35.3 mmol). The resulting brown-green mixture is stirred for 19 h at room temperature. The mixture is filtered through a Celite pad, concentrated in vacuo and triturated with hexane. The white precipitate (triphenylphosphine oxide) is filtered off and the filtrate is concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to provide the title compound (6.20 g, 30.6 mmol) as a yellow solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.89 (d, 1H), 6.10 (d, 1H), 3.80 (s, 3H).

B. 3-(5-Chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol.

To a solution of 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester (5.00 g, 24.7 mmol) in 80 mL of CH_2Cl_2 at 0°C is added slowly a solution of DIBAL (36.2 mL of a 1.5M solution in toluene, 54.3 mmol). The mixture is stirred at 0°C for 15 min, then quenched by the addition of 6 mL of MeOH. The mixture is allowed to warm to room temperature, diluted with water/ice and stirred for 15 minutes. The mixture is filtered through a pad of Celite and washed with CH_2Cl_2. The layers are separated and the aqueous layer is extracted with CH_2Cl_2. The combined organics are washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue is purified via flash column chromatography eluting with a gradient of 15% EtOAc/hexanes to 25% EtOAc/hexanes to afford the title compound (4.18 g, 23.9 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77 (d, 1H), 6.71 (d, 1H), 6.60 (d, 1H), 6.10 (m, 1H), 4.30 (d, 2H), 1.79 (bs, 1H).

C. 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene.

To a solution of 3-(5-chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol (4.18 g, 23.9 mmol) in 140 mL of Et_2O at 0°C is added phosphorous tribromide (1.34 mL, 14.3 mmol) in 10 mL of Et_2O. The mixture is stirred at 0°C for 45 min, then at room temperature for 1.5 hours. The mixture is quenched by the addition of water/ice and diluted with Et_2O. The layers are separated and the organic phase is washed with water until neutral (3x) and once with saturated NaCl solution. The organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated to provide the title compound (5.46 g, 23.0 mmol) as an oil. The crude material solidified upon storage in the freezer and can be used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80 (m, 2H), 6.65 (d, 1H), 6.10 (m, 1H), 4.10 (d, 2H).

EXAMPLE 18. 3-(4-Bromo-furan-2-yl)-(E)-propenal.

To a solution of 4-bromo-2-furfuraldehyde (0.5 g, 2.86 mmol) in 30 mL of dry CH_2Cl_2 is added (triphenylphosphoranylidene)acetaldehyde (0.87 g, 2.86 mmol). The resulting mixture is stirred for 16 h at room temperature. The crude mixture is concentrated in vacuo and the residue is purified via flash column chromatography eluting with CH_2Cl_2 to provide the title compound (0.15 g, 0.75 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.62(d, 1H), 7.59 (s, 1H), 7.18 (d, 1H), 6.81 (s, 1H), 6.60 (m, 1H).

EXAMPLE 19. Acetic acid 3-(6-methoxy-pyridin-3-yl)-(E)-allyl ester.

To a solution of 3-(6-methoxy-pyridin-3-yl)-prop-2-(E)-en-1-ol (0.39 g, 2.36 mmol, prepared as described in PREPARATION MB from 6-methoxy-pyridine-3-carbaldehyde (J. Org. Chem. 1990, 72)) in 8 mL of CH_2Cl_2 at 0°C is added triethylamine (0.66 mL, 4.72 mmol), DMAP (0.05 g, 0.40 mmol) and Ac_2O (0.33 mL, 3.54 mmol). The mixture is stirred at 0°C for 45 min, then at room temperature for 16

hours. The mixture is diluted with Et_2O and washed with 1N HCl, water, saturated $NaHCO_3$ solution and saturated NaCl solution. The organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated. The residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to afford the title compound (0.25 g, 1.21 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, 1H), 7.68 (dd, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.18 (dt, 1H), 4.73 (d, 2H), 3.95 (s, 3H), 2.10 (s, 3H).

EXAMPLE 20. 2-(3-Bromo-prop-1-ynyl)-5-chloro-thiophene.

A. 3-(5-Chloro-thiophen-2-yl)-prop-2-yn-1-ol.

Nitrogen (g) is bubbled through a solution of 5-bromo-2-chloro-thiophene (1.00 g, 5.06 mmol) in 8 mL of piperidine. After 5 min, propargyl alcohol (0.32 mL, 5.56 mmol), tetrakis(triphenylphosphine) palladium(0) (0.06 g) and CuI (catalytic amount) are added to the solution. The mixture is heated at 80°C for 1 h in a sealed glass vessel. At this time, the mixture is cooled and diluted with EtOAc/Et_2O. The organic layer is washed 3N HCl, water, saturated $NaHCO_3$ solution and saturated NaCl solution. The organic layer is dried, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to give the title compound (0.8 g, 0.46 mmol) as an oil. ^1H NMR (DMSO-d_6, 300 MHz) δ 6.99 (d, 1H), 6.80 (d, 1H), 4.49 (s, 2H), 1.90 (bs, 1H). EI MS, $[M]^+$=172, 174 (Cl pattern).

B. 2-(3-Bromo-prop-1-ynyl)-5-chloro-thiophene.

The title compound is prepared as described in EXAMPLE 17, Part C, using 3-(5-chloro-thiophen-2-yl)-prop-2-yn-1-ol in place of 3-(5-chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol. The crude product is used in the subsequent step without further purification.

^1H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, 1H), 6.80 (d, 1H), 4.98 (d, 2H).

EXAMPLE 21. 2-Bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A. 5-Chloro-2-methyl-indole-1-carboxylic acid tert-butyl ester.

A solution containing 5-chloro-2-methylindole (4.0 g, 24.1 mmol) and DMAP (295 mg, 2.42 mmol) in anhydrous THF (100 mL) is cooled to 0°C. A solution containing $(Boc)_2O$ (5.27 g, 24.1 mmol) in anhydrous THF (100 mL) is then added over a 20 min period. The reaction mixture is stirred for 2 h at 0°C and then at ambient temperature for 16 hours. The reaction mixture is concentrated and the crude residue is purified by flash silica gel chromatography (2% EtOAc/hexane to 5% EtOAc/hexane) to provide 5.2 g (81%) of title compound as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (s,

9H), 2.57 (s, 3H), 6.24 (t, J = 0.9 Hz, 1H), 7.16 (dd, J = 8.8, 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H) ppm; MS (EI): m/z 265 (M+).

B. 2-Bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A solution containing 5-chloro-2-methyl-indole-1-carboxylic acid tert-butyl ester (3.0 g, 11.3 mmol), NBS (1.33 g, 11.3 mmol), and benzoyl peroxide (0.4 g, 1.13 mmol) in CCl_4 (100 mL) is heated at 80°C for 3 hours. An additional portion of NBS (0.65 g, 5.65 mmol), and benzoyl peroxide (0.2 g, 0.56 mmol) is then added and the reaction mixture is heated for an additional 3 hours. After cooling to ambient temperature, the reaction mixture is filtered. The filtrate is concentrated to a brown oil which is triturated with hexane to remove residual succinimide, filtered, and concentrated. The resultant oil (4.5 g, >100%) is used directly in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 9H), 4.88 (s, 2H), 6.63 (s, 1H), 7.27 (dd, J = 9.0, 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H) ppm; MS (EI): m/z 343 (M+).

EXAMPLE 22. 3-Bromomethyl-5-iodo-2-methoxy-pyridine

A. 5-Iodo-3-methyl-2-methoxy-pyridine.

To a solution containing 2-bromo-5-iodo-3-methyl-pyridine (4.80 g, 16.0 mmol) in DMSO (15 mL) is added methanolic NaOMe (3.33 M, 5.3 mL, 17.7 mmol) at 0 °C. The solution is allowed to warm to ambient temperature and then heated at 70°C for 1 hour. The reaction mixture is diluted with diethyl ether (300 mL) and water (200 mL) and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 2.86 g (71%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.90 (s, 3H), 7.60 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H) ppm; MS (EI): m/z 249 (M+).

B. 3-Bromomethyl-5-iodo-2-methoxy-pyridine.

A solution containing 5-iodo-3-methyl-2-methoxy-pyridine (1.00 g, 4.00 mmol) and NBS (0.78 g, 4.40 mmol) in CCl_4 (20 mL) is warmed to reflux. AIBN is added in 5 mg portions (0.03 mmol) every hour. After 3 h, the reaction mixture is cooled and then concentrated in vacuo. The residue is dissolved in EtOAc (150 mL) and washed successively with aqueous $Na_2S_2O_3$ (100 mL), water (100 mL), brine then dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product ispurified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 0.72 g (55%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.38 (s, 2H), 7.83 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H) ppm; MS (EI): m/z 327 (M+).

EXAMPLE 23. 5-Bromomethyl-6-methoxy -nicotinic acid methyl ester.

A. 6-Methoxy-5-methyl-nicotinic acid methyl ester.

A solution containing 5-iodo-3-methyl-2-methoxy-pyridine (10.0 g, 40.0 mmol), Et_3N (8.0 g, 80.0 mmol), and $(Ph_3P)_4PdCl_2$ (2.80 g, 4.00 mmol) in 1:1 DMF/MeOH (100 mL) is cooled to 0°C. Carbon monoxide is bubbled into the cooled solution for approx. 5 min at which time the reaction mixture is sealed under a balloon of CO. The reaction mixture is allowed to warm to ambient temperature and then stirred for 16 hours. The reaction mixture is concentrated in vacuo and the residue is partitioned between water (300 mL) and EtOAc (300 mL) and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 4.10 g (57%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.88 (s, 3H), 4.00 (s, 2H), 7.96 (d, J = 2.2 Hz, 1H), 8.65 (d, J = 2.2 Hz, 1H) ppm; MS (ISP loop): m/z 182 (M+H).

B. 5-Bromomethyl-6-methoxy -nicotinic acid methyl ester.

A solution containing 6-methoxy-5-methyl-nicotinic acid methyl ester (4.00 g, 22.1 mmol), NBS (5.11 g, 28.7 mmol), and AIBN (0.90 g, 5.5 mmol) in CCl_4 (100 mL) is warmed to reflux. After 5 h, the reaction mixture is cooled and then concentrated in vacuo. The residue is dissolved in EtOAc (500 mL) and washed successively with aqueous $Na_2S_2O_3$ (300 mL), water (100 mL), brine then dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 9:1) to provide 3.10 g (54%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.07 (s, 3H), 4.46 (s, 2H), 8.19 (d, J = 2.2 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H) ppm; MS (EI): m/z 259 (M+).

EXAMPLE 24. 5-Chloro-2-thienyloxyacetic acid.

A. 2-Hydroxy-thiophene.

Thiophene (42g, 500mmol) is dissolved in ether (250mL). To the solution is added n-BuLi (200mL of a 2.5N solution in hexanes, 500mmol) at a rate which maintains a gentle reflux. After addition, the solution is stirred for 0.5 hour. The solution is then cooled to -78°C and triethyl borate (102 g, 700mL) is added dropwise. The solution is stirred for 3 hours. The cold bath is removed and 130mL of a 30% H_2O_2 is added dropwise with rapid stirring. After addition, the solution is allowed to refluxed for an additional 20 minutes. The solution is then cooled to 0°C and acidified to pH=3 with 6N HCl. The resulting solution is extracted with ether. The organic solution is washed with 10% ferric

ammonium sulfate, water and saturated NaCl. The solution is dried over $MgSO_4$, filtered and concentrated under vacuum. The title compound (32g, 320mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 7.60 (m, 1H),6.35 (m, 1H), 4.12 (d, 2H).

B. Ethyl 2-thienyloxyacetate.

To a solution of 2-hydroxy-thiophene (32g, 320 mmol) in $CHCl_3$ (500mL) is added ethyl bromoacetate (53.4 g, 320 mmol). To the resulting solution is added a solution containing n-Bu_4NHSO_4 (25g, 74mmol) and NaOH (15.8g, 394 mmol) in water (500mL). After addition, the solution is stirred vigorously using mechanical stirring. The reaction is stirred for 12 hours. After this time, the layers are separated. The aqueous layer is extracted with $CHCl_3$. The combined organic layers are washed with water and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 30%CH_2Cl_2:hexanes to 60%CH_2Cl_2:hexanes. The title compound (11.5g, 62mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 6.68 (dd, 1H), 6.60 (d, 1H), 6.22 (d, 1H), 4.62 (s, 2H), 4.30 (q, 2H), 1.31 (t, 3H).

C. Ethyl 5-chloro-2-thienyloxyacetate.

To a solution of ethyl 2-thienyloxyacetate (1.1g, 5.9mmol) in acetic acid (15mL) is added N-chlorosuccinimide (0.78g, 5.9mmol). The solution is stirred for 1.5 hour. After this time the solution is concentrated. The resulting oil is dissolved in ether and washed with 1N NaOH, water and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The title compound (1.26g, 5.7mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 6.52 (d, 1H), 6.06 (d, 1H), 4.60 (s, 2H), 4.24 (q, 2H), 1.31 (t, 3H).

D. 5-Chloro-2-thienyloxyacetic acid.

To a solution of ethyl 5-chloro-2-thienyloxyacetate (0.39g, 1.77mmol) in 9mL of a 1:1:1 mixture of CH_3OH:THF:water is added LiOH (0.38g, 9.0 mmol). The solution is stirred for 16 hours. After this time, the solution is concentrated to 1/3 its volume. The resulting solution is acidified to pH=3 with 1N HCl. The aqueous solution is extracted with CH_2Cl_2. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The title compound (0.32g, 1.66mmol) is obtained as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 6.50 (d, 1H), 6.07 (d, 1H), 4.66 (s, 2H).

EXAMPLE 25. 3-(5-Chloro-thiophen-2-yl)-(E)-acrylic acid.

To a mixture of 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester (0.60 g, 2.96 mmol) in 15 mL of 1:1:1 THF/MeOH/H_2O at 0°C is added lithium hydroxide monohydrate (0.62 g, 14.7 mmol).

The mixture is stirred at 0°C for 1 h, then at room temperature for 1 h and concentrated in vacuo. The residue is diluted with EtOAc and washed with 1N HCl. The aqueous layer is extracted with EtOAc and the combined organics are washed with water (2x), dried, filtered and concentrated to provide the title compound (0.54 g, 2.86 mmol) as a white solid. The crude material can be used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.90 (d, 1H), 6.10 (d, 1H).

EXAMPLE 26. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid.

A. 4-Chloro-2-thiophene-carboxaldehyde.

To a solution of 2-thiophene-carboxaldehyde (6.33 g, 56.4 mmol) in 100 mL of $CHCl_3$ at 0°C is added aluminum trichloride (16.8 g, 126 mmol) portionwise over a few minutes. In a separate vessel, chlorine gas (4.00 g) is bubbled for about 2 min into 100 mL of CCl_4 at 0°C and then added to the former mixture slowly at 0°C . The resulting mixture is stirred at 0°C for 45 min, then allowed to warm to room temperature and stirred overnight. After 16 h, the reaction mixture is poured slowly into 6N HCl at 0°C , then stirred at room temperature for 2 hours. The layers are separated. The aqueous layer is extracted with $CHCl_3$. The combined organic layers are washed with H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with 10% EtOAc/hexanes to yield the title compound (6.70 g, 45.9 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H).

B. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester.

The title compound is prepared as described in EXAMPLE 1, Part A from 4-chloro-2-thiophene-carboxaldehyde. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 6.25 (d, 1H), 3.82 (s, 3H).

C. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid.

The title compound is prepared as described in EXAMPLE 1, Part B from 3-(4-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, 1H), 7.19 (d, 2H), 6.25 (d, 1H).

EXAMPLE 27. (5-Chloro-thiophen-2-yl)-acetic acid.

A. [2-(5-Chloro-thiophen-2-yl)-1-dimethylaminovinyl]phosphonic acid diethyl ester.

To a suspension of sodium hydride (0.25 g, 6.25 mmol, 60% mineral oil dispersion) in 10 mL of THF is added slowly a solution of tetraethyl dimethylaminomethylenediphosphonate (2.03 g, 6.14 mmol, prepared according to the procedure described in Psaume, Montury, and Cosmetic Comm. 1982, 12, 415) in 10 mL of THF. After stirring 1 h, a solution of 5-chloro-2-thiophene carboxaldehyde (0.90 g, 6.14 mmol) in 10 mL of THF is added. The resulting mixture is heated at reflux for 1 h, then cooled to room temperature. The reaction mixture is partitioned between Et_2O and water. The organic layer is washed sequentially with 1N HCl, water and saturated NaCl, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified via flash column chromatography eluting with a gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to afford the title compound (1.52 g, 4.69 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 1H), 6.95 (d, 1H), 6.82 (d, 1H), 4.15 (m, 4H), 2.62 (s, 6H), 1.60 (t, 6H).

B. (5-Chloro-thiophen-2-yl)-acetic acid.

A mixture of [2-(5-chloro-thiophen-2-yl)-1-dimethylaminovinyl]phosphonic acid diethyl ester (1.52 g, 4.69 mmol) and 30 mL of 6N HCl is heated at reflux for 2 hours. After cooling to room temperature, ice water is added and the mixture is partitioned between Et_2O and water. The organic layer is washed with water (2x), dried over $MgSO_4$, filtered and concentrated to give the title compound (0.62 g, 3.51 mmol) as a brown solid. The crude material can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (bs, 1H), 7.79 (d, 1H), 6.71 (d, 1H), 3.81 (s, 2H).

EXAMPLE 28. 3-(5-Chloro-thiophen-2-yl)-propionic acid.

A. 3-(5-Chloro-thiophen-2-yl)-propionaldehyde.

To a mixture of $Pd(OAc)_2$ (0.12 g, 0.53 mmol), $NaHCO_3$ (0.52 g, 6.19 mmol) and NaI (0.28 g, 1.87 mmol) in 5 mL of HMPA is added 5-bromo-2-chloro-thiophene (1.00 g, 5.06 mmol) and allyl alcohol (1.03 mL, 15.2 mmol). The mixture is heated to 90°C and stirred for 16 hours. The reaction mixture is cooled to room temperature, diluted with Et_2O and washed with water. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue is purified by flash column chromatography eluting with a gradient of 10% Et_2O/hexanes to 20% Et_2O/hexanes to provide the product (0.18 g, 1.03 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, 1H), 6.71 (d, 1H), 6.58 (d, 1H), 3.07 (t, 2H), 2.81 (t, 2H).

B. 3-(5-Chloro-thiophen-2-yl)-propionic acid.

Silver nitrate (117 mg, 0.69 mmol) in 1 mL of H_2O is added to 1.36 mL of 1N NaOH at 0°C and stirred for 5 minutes. To the brown suspension is added 3-(5-chloro-thiophen-2-yl)-propionaldehyde (60

mg, 0.34 mmol) and the resulting mixture is allowed to warm to room temperature over 2 hours. The precipitate is filtered and washed with hot water (2x). The combined aqueous layers are acidified with 6 N HCl and extracted with EtOAc (2x). The combined organic layers are washed with water (2x), then dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound (50 mg, 0.26 mmol) as a beige solid. The crude material can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.72 (d, 1H), 6.60 (d, 1H), 3.07 (t, 2H), 2.71 (t, 2H).

EXAMPLE 29. 3-Fluorophenoxy-acetic acid.

A. 3-Fluorophenoxy-acetic acid ethyl ester.

To a solution of 3-fluorophenol (1.2g, 11.8mmol) in 20mL of DMF at 0°C is added sodium hydride (0.47g, 10.7mmol). After stirring for 10 minutes Ethyl bromoacetate (1.2g, 10.7 mmol) is added dropwise. The reaction is allowed to warm to ambient temperatures and is stirred for 16 hours. To the reaction is added a saturated solution NH_4Cl (aq.). The resulting mixture is diluted with EtOAc and H_2O. The layers are separted. The organic layer is washed with H_2O and a saturated solution NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product (2g, 10mmol) as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 7.22 (m, 1H), 6.65 (m, 3H), 4.61 (s, 2H), 4.27 (q, 2H), 1.24 (t, 3H).

B. 3-Fluorophenoxy-acetic acid.

To a solution of ethyl 3-fluorophenoxy-acetate (2g, 10mmol) in 24mL of a 1:1:1 solution of MeOH:H_2O:THF is added lithium hydroxide monohydrate (2.25g, 54mmol). The solution is stirred for 16 hours. After this time, the solution is concentrated under reduced pressure to 1/3 of its volume. The remaining solution is acidified to pH=3 with 1N HCl (aq.). The aqueous solution is extracted with EtOAc. The organic layer is washed with a saturated solution NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product (1.65g, 9.7mmol) as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 9.8 (bs, 1H), 7.28 (m, 1H), 6.69 (m, 3H), 4.70 (s, 2H).

EXAMPLE 30. 2-Chloropyrdin-3-ylamino-acetic acid.

To a solution of 3-amino-2-chloropyridine (1.0g, 7.8mmol) in 20mL of MeOH is added glyoxylic acid (0.86mL of a 50% by weight solution in H_2O, 7.8mmol). After stirring for 10 minutes, $NaCNBH_3$ (1.54 g, 23mmol) is added. The reaction is stirred for 16 hours., then is concentrated under reduced pressure. The resulting residue is dissolved in H_2O. The solution is acidified to pH=3 with 1N HCl (aq.). The solution is extracted with EtOAc/CH_2Cl_2 (2:1). The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting product is obtained as a white solid (0.95g, 5.1mmol). ^1H NMR

(d6-DMSO, 300MHz) δ 12.7 (bs, 1H), 7.62 (m, 1H), 7.44 (m, 1H), 6.90 (m, 1H), 5.8 (bs, 1H), 3.95 (AB, 2H).4.70 (s, 2H).

EXAMPLE 31. 5-Chlorothiophen-2-yl-sulfanyl acetic acid.

A. Thiophen-2-yl-sulfanyl acetic acid ethyl ester.

To a solution of thiophene-2-thiol (1.49g, 116mmol) in 40mL of CH_3CN is added ethyl bromoacetate (2.14g, 167mmol) followed by K_2CO_3 (3.54g, 138mmol). The solution is stirred for 16 hours. After this time, the solution is filtered. The solvent is evaporate to give the product as an oil (2.4g, 118mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 7.37 (m, 1H), 7.21 (m, 1H), 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H). MS (EI): m/z 202 (M+).

B. 5-Chlorothiophen-2-yl sulfanyl acetic acid.

To a solution of thiophen-2-yl-sulfanyl acetic acid ethy (0.52g, 2.6mmol) in 25 mL of CH_2Cl_2 is added N-chlorosuccinimide (0.35g, 2.6mmol). The solution is stirred for 10 minutes. After this time, 1 drop of TFA is added. The solution is stirred for 16 hours. The reaction mixture is then diluted with 25 mL of CH_2Cl_2. The resulting solution is washed with 1N NaOH and a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting product is obtained as an oil which is determined to contain 45% of the desired product. The oil is then dissolved in 60 mL of 1:1:1 THF:MeOH:H_2O. To the solution is added lithium hydroxide monohydrate (1.26g, 30mmol). The solution is stirred for 16 hours. After this time, the solution is acidified to pH=3 with 1N HCl. The aqueous solution is washed with H_2O and saturated NaCl solution. The solution is extracted with EtOAc/CH_2Cl_2 (2:1). The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting crude product is purified by column chromatography eluting with 20% MeOH:Et_2O to give the product as a white solid (0.4g, 1.9mmol). MS (EI): m/z 208, 210 (M+), Cl pattern.

EXAMPLE 32. 5'-Chloro-[2,2']bithiophenyl-5-carboxylic acid.

A. 5'-Chloro-[2,2']bithiophenyl-5-carbaldehyde.

To a solution of 5-chloro-[2,2']bithiophene (1.06 g, 5.28 mmol) in 12 mL of THF at -78°C is added n-BuLi (4.4 mL of a 1.6M solution in hexanes, 6.99 mmol). After 15 minutes, DMF (0.97 mL, 14 mmol) is added and the resulting solution is allowed to warm to 0°C. After 15 min, the solution diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. The organic solution is washed with H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by flash column chromatography eluting with a gradient of 10% Et_2O/hexanes to 20%

Et_2O/hexanes to yield the title compound (0.89 g, 3.89 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.70 (d, 1H), 7.20 (d, 1H), 7.15 (d, 1H), 6.91 (d, 1H).

B. 5'-Chloro-[2,2']bithiophenyl-5-carboxylic acid.

The title compound is prepared as described in EXAMPLE 28, Part B using 5'-chloro-[2,2']bithiophenyl-5-carbaldehyde. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H), 7.09 (d, 1H), 7.06 (d, 1H), 6.89 (d, 1H). EI MS, $[M]^+$=243,245 (Cl pattern).

EXAMPLE 33. 7-Chloro-isoquinoline-3-carboxylic acid.

A. 7-Chloro-isoquinoline-3-carbaldehyde.

A 20mL of 80% H_2SO_4 is added 7-chloro-3,3-dibromomethyl isoquinoline (0.69g, 2.06mmol) is heated to 150°C for 16 hours. The solution is then cooled to ambient temperatures and diluted with 40 mL of H_2O. The resulting solution is basified to pH=11 with 1N NaOH. The aqueous solution is extracted with CH_2Cl_2. The organic solution is washed with H_2O and a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product as an oil (0.25g, 1.3 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 10.0 (s, 1H), 9.30 (s, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.95 (d, 1H), 7.78 (d, 1H). MS (EI): m/z 191, 193 (M+), Cl pattern.

B. 7-Chloro-isoquinoline-3-carboxylic acid.

To 4.5 mL of a 1N NaOH solution at 0°C is added a solution of $AgNO_3$ (0.31g, 1.8mmol) in 3 mL of H_2O, followed by a solution of of 7-chloro-isoquinoline-3-carbaldehyde (0.25g, 1.3mmol) in 3 mL of EtOH. The solution is stirred at 0°C for 10 minutes, then at room temp. For 3 hours. The solution is acidified to pH=3 with 1H HCl. The resulting solution is extracted with $CHCl_3$. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product as a white solid (0.2g, 0.96mmol). ^1H NMR (CD_3OD, 300MHz) δ 9.18 (s, 1H), 8..63 (s, 1H), 8.18 (m, 1H), 7.80 (m, 2H). 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H). MS (EI): m/z 208, 210 (M+), Cl pattern.

EXAMPLE 34. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid.

A. 4-(5-Chloro-thiophen-2-ylmethylene)-2-methyl-4H-oxazol-5-one.

A mixture consisting of 5-chlorothiophene-2-carboxaldehyde (1.00 g, 6.82 mmol), N-acetylglycine (0.96 g, 8.18 mmol), NaOAc (0.67 g, 8.18 mmol) in Ac_2O (5 mL) is warmed at reflux for 16 hours. The reaction mixture is cooled to ambient temperature and diluted with dilute aqueous NaOH (0.5 M, 100 mL) and CH_2Cl_2 (100 mL). The layers are separated and the organic phase is washed with

aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 1.5 g (100%) of the title compound as a colorless oil which is used without further purification in the next reaction. ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.94 (d, J = 4.0 Hz, 1H), 7.21 (s, 1H), 7.26 (d, J = 4.0 Hz, 1H) ppm.

B. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid.

To a solution containing 4-(5-chloro-thiophen-2-ylmethylene)-2-methyl-4H-oxazol-5-one (1.5 g, 6.82 mmol) in MeOH (18 mL) is added 1.0 M NaOH (12.0 mL, 12 mmol) at ambient temperature. After 3 h, the reaction mixture is diluted with water (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The basic, aqueous layer is washed with CH_2Cl_2 and then acidified using 1.0 M HCl (20 mL) to provide a crude solid which is collected on a Buchner funnel. Drying in vacuo provided 1.2 g (75%) of the title compound as a pale brown solid which is used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H), 7.14 (d, J = 4.01 Hz, 1H), 7.38 (d, J = 4.01 Hz, 1H), 7.63 (s, 1H), 9.28 (s, 1H), 12.73 (br s, 1H) ppm; MS (EI): m/z 245 (M+).

EXAMPLE 35. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-propionic acid.

To a solution containing 2-acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid (1.00 g, 4.08 mmol) and K_2CO_3 (1.70 g, 12.1 mmol) in DMF (20 mL) is added MeI (0.87 g, 6.12 mmol) at ambient temperature. After 2 h, the reaction mixture is diluted with water (100 mL) and EtOAc (100 mL) and the layers are separated. The aqueous layer is extracted with EtOAc (50 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 0.92 g (83%) of the methyl ester which is used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.77 (s, 3H), 6.86 (d, J = 4.02 Hz, 1H), 6.99 (m, 1H), 7.05 (d, J = 4.02 Hz, 1H), 7.64 (s, 1H) ppm.

A small Parr® vessel is charged with the crude ester (0.85 g, 3.13 mmol) and $(Ph_3P)_3RhCl$ (0.10 g, 0.10 mmol) in MeOH (50 mL). The vessel is pressurized to 50 PSI H_2 pressure and agitated for 7 h at ambient temperature. The reaction mixture is then filtered and concentrated to provide the desired compound, which is used without further purification. MS (EI): m/z 261 (M+).

The above-prepared saturated ester is dissolved in a 1:1:1 solution of water/THF/MeOH (15 mL). LiOH monohydrate (0.14 g, 3.23 mmol) is added and the heterogeneous mixture is stirred for 16 hours. The reaction mixture is diluted with water (100 mL) and EtOAc (100 mL) and the layers are separated. The aqueous layer is extracted with EtOAc (50 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 0.62 g (81%) of the title compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.30 (m, 2H), 4.81 (m, 1H), 6.45 (br d, J = 6.45 Hz, 1H), 6.58 (d, J = 3.68 Hz, 1H), 6.71(d, J = 3.68 Hz, 1H), 9.79 (br s, 1H) ppm; MS (EI): m/z 247 (M+).

EXAMPLE 36. 3-(6-Amino-pyridin-3-yl)-acrylic acid.

A. N-(5-Bromo-pyridin-2-yl)-acetamide.

Triethylamine(17.7mL, 75 mmol) is added to a mixture of 2-amino-5-bromopyridine (5.0 g, 29 mmol) and acetic acid (7.1 mL, 75 mmol). The solution is heated to reflux for 48 hours. After this time, the solution is concentrated. The reside is dissolved in water and the pH is adjusted to 10 with 1N NaOH. The solids are collected by filtration. The crude product is recrystallized from boiling water to give the title compound (2.6 g 12.0 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (1H, bs), 8.42 (s, 1H), 8.01 (m, 2H), 2.05 (s, 3H).

B. 3-(6-Acetylamino-pyridin-3-yl)-acrylic acid

To a mixture of N-(5-bromo-pyridin-2-yl)-acetamide (1.26 g, 5.86 mmol) and tri-n-butylamine in xylenes (10 mL)is added $Pd(OAc)_2$ (1.4 mg, 0.006 mmol) and triphenyl phosphine (15.4mg, 0.06 mmol). Acrylic acid (0.48 mL, 7.03 mmol) is then added dropwise over 5 minutes. The mixture is heated to reflux for 5 hours. The solution is cooled to ambient temperatures. The mixture is diluted with water and the pH is adjusted to 4 with 1N HCl. The solution is extracted with EtOAc/CH_2Cl_2 (2:1). The resulting suspension is filtred to give the title compound (0.80 g, 3.88 mmol) as a white solid. MS (ion spray) 207, (M+H).

C. 3-(6-Amino-pyridin-3-yl)-acrylic acid

To 3-(6-acetylamino-pyridin-3-yl)-acrylic acid (0.80 g, 3.88 mmol) in ethanol (10 mL) is added 1N NaOH (20mL). The solution is heated to reflux. After 16 h, the solution is concentrated to 1/3 its volume. The aqueous solution is diluted with water and acidified to pH=2 with 6N HCl. The solution is concentrated to dryness. The residue is dissolved in methanol. The solution is filtered. The organic solution is concentrated. The crude product is purified by RP-HPLC eluting with a gradient of 5%CH3CN/H2O (0.1% TFA) to 30% CH3CN/H2O (0.1%TFA) to give the product as a white solid (0.54 g, 1.93 mmol). ^{1}H NMR (300 MHz, CD_3OD) δ 8.34 (d, 1H), 8.07 (s, 1H), 7.54 (d, 2H), 7.06 (d, 1H), 6.47 (d, 1H). MS (ion spray) 165, (M+H).

EXAMPLE 37. 4-Chloro-benzyl isocyanate.

To a solution of triphosgene (0.54 g, 1.85 mmol) in 10 mL of dry CH_2Cl_2 at 0°C is added 4-chloro-benzylamine (0.61 mL, 5.00 mmol) dropwise as a white precipitate forms. Et_3N (1.39 mL, 10.0 mmol) in 5 mL of CH_2Cl_2 is added immediately and the resulting mixture is stirred at 0°C for 5 min, then at room temperature for 3 hours. The mixture is concentrated in vacuo and triturated with EtOAc.

The white precipitate (triethylamine hydrochloride) is filtered off and the filtrate is concentrated. The title compound (6.20 g, 30.6 mmol) is isolated as a crude yellow residue and used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, 2H), 7.25 (d, 2H), 4.50 (s, 2H).

EXAMPLE 38. 5-Chloro-thiophene-2-carbonyl azide.

To a solution of 5-chloro-2-thiophene-carboxylic acid (5.00 g, 30.7 mmol) in 130 mL of acetone is added Et_3N (4.29 mL, 30.7 mmol). The mixture is cooled to 0°C and ethyl chloroformate (3.23 mL, 33.8 mmol) is added. The mixture is stirred at 0°C for 1h and sodium azide (3.40 g, 52.3 mmol) is added. The mixture is stirred at 0°C for 2 h, then poured into 300 mL of ice water and the aqueous layer is extracted with CH_2Cl_2 (2x). The combined organics are washed with water (2x) and brine, then dried, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with 10% EtOAc/hexanes to provide the title compound (3.00 g, 16.0 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, 1H), 6.99 (d, 1H).

EXAMPLE 39. 4-Nitro-2,3,5,6-tetrachloropyridine.

Pentachloropyridine (80 g, 320 mmol) is treated with benzyl amine (104 mL, 96 mmol), dissolved in dioxane (1 L) and refluxed for 16 hours. The reaction mixture is cooled to ambient temperature and the precipitated white solid is removed by filtration. The filtrate is concentrated to a brown residue and triturated with 4 % ethyl acetate in hexane (3 X 250 mL) to give 4-benzylamino-2,3,5,6-tetrachloropyridine as an off-white solid (40 g, 124 mmol). This material is dissolved in chloroform (400 mL), cooled in an ice bath and treated with trifluoroacetic acid (500 mL) and 30% hydrogen peroxide (100 mL). The reaction mixture is warmed to room temperature overnight and treated with additional trifluoroacetic acid (500 mL) and 30% hydrogen peroxide (100 mL). After stirring 24 hours the reaction is treated with water (1L). The lower organic layer is separated and the aqueous layer is extracted with chloroform. The combined organic layers are concentrated to a solid residue and redissolved in ethyl acetate/hexane (30 mL). The suspended orange solid is removed and the filtrate is loaded on a silica flash column. The column is eluted with hexane and the title compound is collected as a white solid (15.6 g, 60 mmol). EI MS m/z 260, 262, 264 [M+].

EXAMPLE 40. 4-(tert-Butyloxycarbonyl)-piperazin-2-one

4-(Benzyloxycarbonyl)-piperazin-2-one (2.2 g, 9.4 mmol) and Boc anhydride (2.5 g, 11.3 mmol) are dissolved in methanol (100 mL), treated with 5% Pd /C and shaken 16 h under hydrogen gas (30 PSI). The reaction vessel contents are filtered through Celite and the filtrate is concentrated to yield 4-(tert-Butyloxycarbonyl)-2-oxopiperazine (1.9 g, 9.4 mmol) which is used without further purification. EI

MS m/z 200, M^+; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.17 (br, 1H), 4.20 (s, 2H), 3.55 (t, 2H), 3.38 (m, 2H), 1.48 (s, 9H).

EXAMPLE 41. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. N-Cbz-O-methylserine-aminoacetaldehyde dimethyl acetal.

To a solution of N-Cbz-O-methylserine (10.8g, 41.8mmol) in 500mL of CH_2Cl_2 is added Et_3N (12.7 g, 125mmol). The solution is cooled to 0°C and TBTU (13.5g, 42mmol) and aminoacetaldehyde dimethyl acetal (4.83g, 46mmol) are added. The solution is stirred for 16 hours. The solution is diluted with 500mL of ether. The resulting solution is washed with water, 1N $KHSO_4$, and sat. NaCl. The title compound (13.7g, 41.8mmol) is obtained as a white foam. ^1H NMR ($CDCl_3$, 300MHz) δ 7.40 (m, 5H),6.55 (bs, 1H), 5.66 (bs, 1H), 5.32 (m, 1H), 5.13 (s, 2H), 4.32 (m, 2H), 3.79 (dd, 1H), 3.44 (m, 2H), 3.40 (m, 9H).

B. N-Cbz-2-Oxo-3-(S)-methoxymethyl-(4,5-dihydro)piperazine.

To a solution of N-Cbz-O-methylserine-aminoacetaldehyde dimethyl acetal (13.7g, 41.8mmol) in 300mL of toluene is added TsOH.H2O (0.80g, 4.2mmol). The solution is heated to 60°C. After 5h, the solution is diluted with ether. The resulting organic solution is washed with water, sat. NaHCO3, and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 10%EtOAc:CH_2Cl_2 to 20%EtOAc:CH_2Cl_2. The title compound (10.7g, 38mmol) is obtained as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H), 6.45 and 6.30 (d, 1H rotational isomers), 5.61 and 5.50 (d, 1H rotational isomers), 5.20 (s, 2H), 4.92 and 4.83 (bs, 1H rotational isomers), 3.63 (m, 3H), 3.32 and 3.20 (s, 1H rotational isomers).

C. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of N-Cbz-2-oxo-3-(S)-methoxymethyl-(4,5-dihydro)piperidine (10.7g, 38mmol) in 50mL of methanol is added Pt/C (1gm, 10% by weight). The atmosphere above the reaction is replaced by hydrogen. After 24h, the solution is filtered and the filtrate is washed with methanol. The collected organic solutions are concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH/CH_2Cl_2 to 5%MeOH/CH_2Cl_2. The title compound (6.0g, 22mmol) is obtained as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.35 (m, 5H),6.42 (bs, 1H), 5.20 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 3.50 (m, 4H), 3.27 (s, 3H).

EXAMPLE 42. 2-Butyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-norleucine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300mHz) δ 7.32 (m, 5H), 5.13 (AB, 2H), 4.60 (m, 1H), 4.13 (m, 1H), 3.38 (m, 2H), 3.23 (m, 2H), 1.90 (m, 1H), 1.66 (m, 1H), 1.29 (m, 4H), 0.89 (m, 3H). MS (ion spray) m/z 291, (M+H).

EXAMPLE 43. 2-Ethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-2-amino-butric acid for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300mHz) δ 7.37 (m, 5H), 6.55 (bs, 1H), 5.10 (AB, 2H), 4.57 (m, 1H), 4.24 (m, 1H), 3.42 (m, 1H), 3.26 (m, 2H), 2.20 (m, 1H), 1.81 (m, 1H), 0.96 (m, 3H).

EXAMPLE 44. 2-Propyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-norvaline for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300mHz) δ 7.32 (m, 5H), 7.00 (bs, 1H), 5.12 (AB, 2H), 4.58 (m, 1H), 4.21 (m, 1H), 3.40 (m, 1H), 3.19 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.37 (m, 2H), 0.91 (m, 3H). MS (ion spray) m/z 277, (M+H).

EXAMPLE 45. 2-Ethoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-ethyl-serine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 5H),6.96 (bs, 1H), 5.17 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 4.03 (m, 1H), 3.66 (m, 2H), 3.44 (m, 3H), 3.27 (s, 1H), 1.06 (m, 3H). MS (ion spray) m/z 293, (M+H).

EXAMPLE 46. 2-Methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-alanine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.34 (m, 5H),7.02 (bs, 1H), 5.17 (AB, 2H), 4.65 (m, 1H), 4.17 (m, 1H), 3.42 (m, 1H), 3.23 (m, 2H), 1.41 (d, 3H). MS (EI) m/z 248, (M+).

EXAMPLE 47. 2-Benzyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

The title compound is prepared as in EXAMPLE 41, substituting Cbz-phenylalanine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.22 (m, 10H), 7.00 (bs, 1H), 5.10 (AB, 2H), 4.10 (m, 1H), 3.27 (m, 2H), 3.10 (m, 2H), 2.55 (m, 2H). MS (EI) m/z 324, (M+).

EXAMPLE 48. 2-(1-Methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-methyl-threonine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.52 (bs, 1H), 7.22 (m, 5H), 5.12 (AB, 2H), 4.33

(m, 1H), 4.05 (m, 2H), 3.60 (m, 1H), 3.14 (s, 3H), 3.10 (m, 1H), 2.82 (m, 1H), 1.10 (d, 3H). MS (ion spray) m/z 293, (M+H).

EXAMPLE 49. 2,2-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-2-amino-isobutryic acid for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H),6.52 (bs, 1H), 5.12 (s, 2H), 3.72 (m, 2H), 3.33 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H). MS (EI) m/z 262, (M+).

EXAMPLE 50. 2-Isopropyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-valine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H),5.88 (bs, 1H), 5.10 (s, 2H), 4.35 (m, 1H), 3.44 (m, 1H), 3.27 (m, 2H), 2.31 (m, 1H), 1.00 (d, 3H), 0.94 (d, 2H).

EXAMPLE 51. 2-Isobutyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-leucine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.35 (m, 5H), 6.50 (m, 1H), 5.15 (s, @H), 4.18 (m, 1H), 3.42 (m, 2H), 3.21 (m, 2H), 1.50 (m, 3H), 0.90 (m, 6H).

EXAMPLE 52. 2-(2-Methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-methyl-homo-serine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 5H), 6.85 (bs, 1H), 5.14 (s, 2H), 4.75 (m, 2H), 4.20 (m, 2H), 3.42 (m, 1H), 3.21 (m, 3H), 2.12 (m, 4H).

EXAMPLE 53. 2-Methoxymethyl-5-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting 2-amino-propionaldehyde dimethyl acetal for aminoacetaldehyde dimethyl acetal. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.42 (m, 5H), 6.96 (bs, 1H), 5.12 (AB, 2H), 4.52 (m, 1H), 4.21 (m, 1H), 3.92 (m, 1H), 3.58 (m, 2H), 3.22 (s, 3H), 3.10 (m, 1H), 0.95 (m, 3H).

EXAMPLE 54. 3-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester.

A. 2-tert-Butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propionic acid.

tert-Butyldimethylchlorosilane (32.3 g, 0.214 mol) in THF (50 mL) is added dropwise via cannula to a solution of BOC serine (20.0g, 0.098 mol) and imidazole (15.3 g, 0.224 mol) in THF (360

mL) at RT. The resulting slurry is stirred for 2.5 h then the solvent is removed in vacuo. The crude product is dissolved in MeOH (180 mL) and 5N NaOH (58 mL) is slowly added at RT. The mixture is stirred for 3 h then diluted with water (180 mL) after which time the aqueous layer is washed with ether (180 mLx2). The aqueous layer is acidified to pH 4-5 with 2N HCl and extracted with diethyl ether. The organic layer is washed with saturated $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated to dryness. The crude product (12.67g, 0.040 mol) is used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.35 (bs, 1H), 4.30 (bs, 1H), 4.13 (dd, 1H), 3.80 (dd, 1H), 1.45 (s, 9H), 0.98 (s, 9H), 0.10 (s, 6H). EI MS, $[M+H]^+$=320.

B. [2-(tert-Butyl-dimethyl-silanyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester.

N,N-Dimethylaminopyridine (2.60 g, 21.3 mmol) and BOP reagent (18.15 g, 41.0 mmol) are added to a solution of 2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propionic acid (12.37 g, 38.7 mmol), diisopropylethylamine (8.1 mL, 46.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (4.53 g, 46.4 mmol) in THF (260 mL) at RT. The resulting suspension is stirred at RT overnight then concentrated to dryness. The residue is diluted with EtOAc and washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product which is purified by flash chromatography eluting with 10-30% EtOAc/Hexanes to yield the title compound (11.86 g, 30.37 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.35 (bd, 1H), 4.71 (bs, 1H), 3.78-3.85 (m, 2H), 3.72 (s, 3H), 3.20 (s, 3H), 1.42 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H).

C. [1-(tert-Butyl-dimethyl-silanyloxymethyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester.

A solution of [2-(tert-butyl-dimethyl-silanyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester (11.86, 30.37 mmol) in Et_2O (100 mL) is added dropwise to a 1.0M solution of LAH in ether (35.5 mL) at -5°C-0°C . The resulting mixture is stirred for 2.5 h then an aqueous solution of $KHSO_4$ is slowly added. The reaction mixture is stirred for 30 minutes and then washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product which is purified by flash chromatography eluting with 30% EtOAc/Hexanes to yield the title compound (6.04 g, 19.9 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.65 (s, 1H), 5.30 (bs, 1H), 4.20 (m, 1H), 3.65 (4.90 (m, 2H), 1.48 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). Ion spray MS, $[M+H]^+$=304.

D. [2-tert-Butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propylamino]-acetic acid methyl ester.

Sodium cyanoborohydride (2.63 g, 41.9 mmol) is added to a solution of [1-(tert-butyl-dimethyl-silanyloxymethyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (6.04 g, 19.9 mmol) and glycine methyl ester hydrochloride (2.75 g, 32.9 mmol) in MeOH (500 mL). The mixture is stirred for 2 days at RT then concentrated to dryness. The crude product is purifed by flash chromatography eluting with 1-5% MeOH/CH_2Cl_2 to yield the title compound (3.06, 8.12 mmol) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (bs, 1H), 3.75 (s, 3H), 3.60-3.70 (m, 4H), 3.40 (d, 1H), 2.80 (dd, 1H), 2.68 (dd, 1H), 1.40 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). Ion spray MS, $[M+H]^+$=377.

E. (Benzyloxycarbonyl-[2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propyl]-amino)-acetic acid methyl ester.

Benzylchloroformate (1.4 mL, 9.81 mmol) is added dropwise to a solution of N,N-dimethylaminopyridine (1.09 g, 8.93 mmol) and [2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propylamino]-acetic acid methyl ester (3.06 g, 8.12 mmol) in CH_2Cl_2 at RT. The resulting mixture is stirred overnight then concentrated to dryness. The crude product is purifed by flash chromatography eluting with 1% MeOH/CH_2Cl_2 to yield the title compound (3.52 g, 6.89 mmol) as a colorless oil. Ion spray MS, $[M+H]^+$=511.

F. 3-(tert-Butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester

(Benzyloxycarbonyl-[2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propyl]-amino)-acetic acid methyl ester (3.52 g, 6.89 mmol) is stirred in 50% TFA/CH_2Cl_2 (40 mL) at RT for 40 minutes. The reaction mixture is concentrated in vacuo and the crude product is purifed by flash chromatography eluting with 1% MeOH/CH_2Cl_2 to yield the title compound (1.1 g, 2.9 mmol) as a colorless oil. Ion spray MS, $[M+H]^+$=379.

EXAMPLE 55. 5-Oxo-piperazine-1,3(R or S)-dicarboxylic acid 1-benzyl ester 3-methyl ester.

N,N-Dimethylaminopyridine (0.43 g, 3.5 mmol) and benzylchloroformate (0.55 g, 3.8 mmol) are added to a solution of methyl 6-oxopiperazine-2-carboxylate (0.50 g, 3.2 mmol) (Aebischer, B., Helv. Chim. Acta 1989, 72, 1043-1051) in CH_2Cl_2 at RT. After 1 h, the reaction mixture is poured into EtOAc and washed with saturated $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated to dryness to give a solid (0.90 g, 3.1 mmol) which is used in subsequent reactions without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (bs, 5 H), 6.32 (bs, 1H), 5.15 (s, 2H), 4.00-4.30 (m, 3H), 4.23 (s, 3H), 3.70-3.80 (m, 2H). MS (EI) m/z 292 (M+).

EXAMPLE 56. (S)-5-Oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing methyl (S)-6-oxopiperazine-2-carboxylate (1.32 g, 8.35 mmol), prepared by the method of Aebischer, in anhydrous dichloromethane (30 mL) at 0 °C is added triethylamine (1.26 g, 12.5 mmol) followed by allylchloroformate (1.20 g, 10.0 mmol). After 1 h, the reaction mixture is poured onto a 1:1 mixture of CH_2Cl_2/water (200 mL), acidified using 1 N HCl and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 1% MeOH/CH_2Cl_2) to provide 1.22 g (60%) of EXAMPLE 35 as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (bs, 1H), 5.90 (m, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H); MS (ISP loop): m/z 243 (M+H).

EXAMPLE 57. (2S, 6R)-4-(2,6-dimethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

and

EXAMPLE 58. (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester

N-(tert-Butoxycarbonyl)-L-alanine (10.0 g, 52.8 mmol) is dissolved in 150 mL of THF. Once the triethylamine (11.0 ml, 79.2 mmol) is added, the solution is cooled to 0°C . Isopropyl chloroformate in toluene (1M) (52.8 ml, 52.8 mmol) is added slowly followed by the addition of (2RS) 1-amino-2-propanol (6.1 ml, 79.2 mmol). After stirring overnight, the mixture is washed with 1N sodium hydroxide and 1N hydrochloric acid. Concentration of the organic solvent afforded (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester (9.92 g, 76% yield) as a clear oil.

B. (1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester

Dimethylsulfoxide (7.16 ml, 100.8 mmol) is added to a solution of oxalyl chloride (4.41 ml, 50.4 mmol) in 126 mL of methylene chloride at -78 °C . The mixture is left to stir for fifteen minutes, and a solution of (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester (9.92 g, 40.32 mmol) in 100 mL of CH_2Cl_2 is added dropwise. After stirring for 15 minutes at -78 °C , the reaction is quenched with triethylamine (28 mL, 381 mmol), and the temperature is allowed to rise to room temperature. The volatile solvents are removed, and the residue is purified by flash column (SiO_2, 60% EtOAc/Hexane). The product (1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester (5.93 g, 60 %) is isolated as a white solid. MS $C_{11}H_{20}N_2O_4$ MS m/z: 245.

C: (3S, 5RS)-3,5-dimethyl-piperazin-2-one.

(1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester (5.93 g, 24.3 mmol) is stirred in a solution of 30 % trifluoroacetic acid in methylene chloride (100 mL) for three hours. The

solvents are removed in vacuo. The residue is dissolved in 50 mL of MeOH and transferred to a par bottle. Palladium on carbon (10 % , 1.0 g) is added, and the mixture is hydrogenated under pressure for 24 hours. The catalyst is filtered off ; the MeOH is removed in vacuo to afford (3S, 5RS)-3,5-dimethyl-piperazin-2-one which is directly protected with a benzyl carbamate without further purification.

D: (2S, 6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of (3S, 5RS)-3,5-dimethyl-piperazin-2-one (24.3 mmol) in 100 mL of methylenechloride is added triethylamine (8.45 mL, 60.75 mmol) and N-(benzyloxycarbonyloxy)succinimide (12.1 g, 48.6 mmol). After stirring overnight, the CH_2Cl_2 is removed, and the crude mixture is chromatographed (50 % EtOAc/Hexane). (2S, 6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (3.3 g, 52 % yield over three steps) is isolated as a white powder. MS $C_{14}H_{18}N_2O_3$ MS m/z: 263.

E. (2S, 6R)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

The two single enantiomers [(2S, 6R)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester] can be seperated by column chromatography from (2S, 6RS)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, which can also be used directly in combination or separation of its derivatives as shown below.

EXAMPLE 59. (2S, 6R)-4-(2,4-Dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. (2S, 2S)-N-(2, 4-dimethoxy-benzyl)-N-(2-hydroxy-propyl)-2-(2,2,2-trifluoroacetylamino)-propionamide.

To a slurry of (2S)-2-(2,2,2-trifluoroacetylamino)-propionic acid (15.3 g, 53.4 mmol) in 120 mL of methylene chloride is added triethylamine (5.6 mL, 40.0 mmol). The heterogeneous mixture is cooled to 0°C and isopropyl chloroformate (27 mL, 27.0 mmol) is added slowly. After stirring for 20 minutes at room temperature, a solution of the (2S)-1-(2,4-dimethoxy-benzylamino)-propan-2-ol (6.0 g, 26.7 mmol, obtained from the reductive amination of the corresponding aldehyde and aminoalcohol) in 5mL of methylene chloride is added. The resulting mixture is left to stir overnight. Ethyl acetate (500 mL) is added, and the organic solution is washed with 1N hydrochloric acid (50 mL) and 1N sodium hydroxide (50 mL). The ethyl acetate is dried with magnesium sulfate, filtered and condensed. The resulting residue is chromatographed on silica gel (25% ethyl acetate/hexane) to give (2S, 2S)-N-(2,4-dimethoxy-benzyl)-N-(2-hydroxy-propyl)-2-(2,2,2-trifluoroacetylamino)-propionamide (6.29g, 60% yield) as a clear oil. MS $C_{17}H_{23}F_3N_2O_5$ MS m/z: 393.

B. (3S, 5R)-1-(2,4-dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one.

(2S, 2S)-N-(2,4-Dimethoxy-benzyl)-N-(2-hydroxypropyl)-2-(2,2,2-trifluoroacetylamino)-propionamide (3.64 g, 9.29 mmol) is dissolved in 25 mL of tetrahydrofuran. Triphenylphosphate (3.65 g, 14.0 mmol) is added, and the resulting mixture is cooled to 0 °C before diethyl azodicarboxylate (2.2 mL, 14 mmol) is added slowly. The resulting mixture is left to stir overnight. The reaction mixture is condensed, and the residue is purified by column chromatography (SiO_2, 25% ethyl acetate/hexane). The desired product, (3S, 5R)-1-(2,4-dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one (1.5 g, 43% yield), is isolated as a clear oil.

C. (3S, 5R)-1-(2,4-Dimethoxy-benzyl)-3,5-dimethyl-piperazin-2-one.

(3S, 5R)-1-(2,4-Dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one (575 mg, 1.54 mmol) is dissolved in 30 mL of methanol and 3 mL of H_2O. Potassium carbonate (883 mg, 6.4 mmol) is added to the solution, and the reaction is refluxed for one and half hours before concentration. Ethyl acetate (3x 50 mL) is used to extract the aqueous layer. Removal of Ethyl acetate afforded the crude amine (387 mg, 91% yield) as a clear oil. $C_{15}H_{22}N_2O_3$ MS m/z: 279.

D. (2S, 6R)-4-(2,4-dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Triethylamine (0.4 mL, 2.8 mmol) and N-(benzyloxycarbonyloxy)-succinimide (1.04 g, 4.2 mmol) is added to a solution of the above crude amine (387 mg, 1.4 mmol) in 15 mL of methylene chloride. The reaction mixture is left to stir overnight. The residue after concentration is chromatographed on silica gel (30% ethyl acetate/hexane) to give (2S, 6R)-4-(2,4-dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (450 mg, 78 % yield) as a clear oil.

E. (2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6R)-4-(2,4-Dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.13 g, 2.74 mmol) is dissolved in 20 mL of acetonitrile. An aqueous solution of potassium persulfate (2.2 g, 8.23 mmol) and sodium phosphate (2.3 g, 16.5 mmol) in 12 mL of H_2O is added, and the resulting mixture is heated to 95-100 °C for two hours. After cooling to room temperature, ethyl acetate (200 mL) is used to extract the aqueous layer and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed (SiO_2, 60% ethyl acetate/hexane) to give (2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (480 mg, 67 % yield) as a yellow oil.

EXAMPLE 60. (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (380 mg, 1.45 mmol) is dissolved in 10 mL of THF and 1mL of DMF. Sodium hydride (60%, 72 mg, 3.14 mmol) is added at 0 °C and left to stir at room temperature for thirty minutes before 7-bromomethyl-4-chloro-quinoline (257 mg, 1.0 mmol) is added. The reaction is stirred for four hours. Ethyl acetate is added to the mixture, and the reaction is quenched with 3 mL of H_2O. The two layers are separated and ethyl acetate (2x 30 ml) is used to extract before dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (60% EtOAc/Hexane) to give (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (417 mg, 95 % yield).$C_{22}H_{20}ClN_3O_3$ MS m/z: 438, 440.

EXAMPLE 61. (3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

and

EXAMPLE 62. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

and

EXAMPLE 63 (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

(2S, 6RS)-4-(4-Chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (417 mg, 1.0 mmol) is taken up in 7 mL of acetonitrile, and iodotrimethyl- silane (0.43 mL, 3.0 mmol) is added. The resulting mixture is stirred for one hour at room temperature before quenched with methanol (1 mL). The residue after concentration is taken up in 2N hydrochloric acid (3 mL) and is extracted with ether (2x 30 mL). The aqueous layer is condensed to dryness and the residue is recrystalized from isopropanol and ether to give a mixture (1:4 ratio) of (3S, 5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one as a yellow solid (290 mg). The two epimers are separated using a flash column (SiO_2, 1% triethylamine/3% methanol/methylene chloride). $C_{16}H_{18}ClN_3O$ MS m/z: 304, 306. The minor isomer (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.is (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one while the major isomer is (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one. Alternatively, (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one can be made via the same chemistry shown below from pure (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, respectively.

Alternative synthesis of (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A. (2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (750 mg, 2.86 mmol) is dissolved in 20 mL of THF and 2 mL of DMF. Sodium hydride (60%, 142.6 mg, 6.20 mmol) is added at 0 °C , and the reaction is left to stir at room temperature for thirty minutes at which time the 7-bromomethyl-4-chloro-quinoline (952 mg, 3.72 mmol) is added. The reaction is complete after stirring for four hours. Ethyl acetate (200 mL) is added to the mixture, and the reaction is quenched with 3 mL of H_2O . The two layers are separated, and ethyl acetate (2x 30 mL) is used to extract and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (60% EtOAc/Hexane) to give (2S,6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.04 g, 83 %).

B. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A 33 % solution of hydrogen bromide in acetic acid (10 mL) is added to (2S,6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.04 g, 2.38 mmol). The reaction is left to stir at room temperature for one hour. The reaction mixture is diluted with ethyl acetate and stirred vigorously to force the product to precipitate out of solution. The ethyl acetate is decanted off and the precipitate is purified on a silica gel column (1 % triethylamine/3 % methanol/methylene chloride) to 582 mg (81% yield) of (3S,5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one as a white solid.

EXAMPLE 64. (3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one.

and

EXAMPLE 65. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one.

The crude (3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (69 mg, 0.20 mmol) obtained from above is dissolved in 1 mL of DMF. Potassium carbonate (76 mg, 0.60 mmol) is added followed by the addition of 2-(3-bromopropenyl)-5-chloro-thiophene (56 mg, 0.24 mmol). The reaction is left to stir overnight. The potassium carbonate is filtered off, and the crude material is purified. The two epimers are separated at this stage by preparative thin layer chromatography (80 % EtOAc/hexane) to give a major epimer (3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one (25 mg, 26% yield) and a minor epimer (3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one (7 mg, 7.5% yield).

EXAMPLE 66. 4-(2-Oxopiperazin-1-ylmethyl)benzamidine.

A. 4-(4-Cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxo-piperazine-1-carboxylic acid benzyl ester (3.0 g, 12.8 mmol) and 4-bromomethyl tolylnitrile (2.76 g, 14.1 mmol) in 135 mL of THF and 15 mL of DMF at 0°C is added a 60% dispersion in mineral oil of NaH (0.49 g, 12.8 mmol). After 5 hours, the solution is diluted with saturated NH_4Cl and EtOAc. The organic layer is washed with H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography over silcia gel eluting with 20% EtOAc/CH_2Cl_2. The title compound is obtained as a white solid (4.01 g, 11.4 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.62 (d, 2H), 7.39 (m, 7H), 5.14 (s, 2H), 4.68 (s, 2H), 4.27 (s, 2H), 3.73 (m, 2H), 3.30 (m, 2H).

B. 4-(4-Carbamimidoylbenzyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A solution of 4-(4-cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (2.4 g, 6.87 mmol) in 30mL of pyridine and 3 ml of Et_3N is saturated with H_2S. The resulting mixture is sealed and stirred for 16 hours. After this time, the solution is concentrated. The residue is dissolved in 30 mL of acetone and methyl iodide (19.4 g, 137 mmol) is added. The solution is refluxed for 2 hours. After this time, the solution is concentrated. The residue is dissolved in MeOH (40 mL) and NH_4OAc (5.0 g, 65 mol) is added. The solution is reluxed for 3 hours. After this time, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of CH_3CN to 60% CH_3CN/H_2O(0.1%TFA). The appropriate collected fractions are lyophilized to give the product as a white foam. MS (FAB) m/z 367, (M+H).

C. 4-(2-Oxopiperazin-1-ylmethyl)benzamidine.

To a solution of 4-(4-carbamimidoylbenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (2.0 g, 5.0 mmol) in 40 mL of MeOH and 4 mL of AcOH is added 10% Pd/C (0.4 g). The atmosphere above the reaction is replaced by hydrogen. After 4hours, the solution is filtered through a pad of Celite. The organic layer is concentrated. The resulting crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1%TFA) to 40% CH_3CN/H_2O (0.1% TFA). The title compound is obtained as a white foam. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.3 (bs, 4H), 9.1 (bs, 2H), 7.83 (d, 2H), 7.42 (d, 2H), 4.78 (s, 2H), 3.80 (s, 2H), 3.44 (m, 2H), 3.32 (m, 2H).

EXAMPLE 67. 1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one.

A. 4-(2-Chloro-quinolin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid benzyl ester (4.65 g, 19.8 mmol) and 6-bromomethyl-2-chloroquinoline (5.40 g, 21.0 mmol) in 80 mL of a 3:1 mixture of THF:DMF at 0°C is added sodium hydride (0.81 g, 20.2 mmol, 60% mineral oil dispersion). The resulting mixture is stirred for 1 hour at 0°C then at room temperature for 18 hours. The reaction mixture is quenched with saturated NH_4Cl solution, then diluted with EtOAc. The organic layer is washed sequentially with 1N HCl, water, saturated $NaHCO_3$ and saturated NaCl, then dried over $MgSO_4$, filtered and concentrated. The crude product is triturated in Et_2O/hexanes/EtOAc and filtered to afford the title compound (6.96 g, 17.0 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 8.00 (d, 1H), 7.69 (s, 1H), 7.63 (dd, 1H), 7.41 (d, 1H), 7.35 (s, 5H), 5.15 (s, 2H), 4.78 (s, 2H), 4.28 (s, 2H), 3.70 (m, 2H), 3.32 (bs, 2H).

B. 4-(2-Phenoxyquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester.

A mixture of phenol (15.1 g, 160 mmol) and 4-(2-chloroquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (6.60 g, 16.1 mmol) is melted together at 70°C until a homogeneous mixture is obtained. Potassium hydroxide (3.15 g, 56.1 mmol) is added and the resulting mixture is heated overnight at 120°C. After 24 hours, the brown/black residue is cooled to room temperature, diluted with CH_2Cl_2 and stirred with 1N NaOH (100 mL) for 30 minutes. The two layers are separated and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with 1N NaOH, saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The crude title compound (6.92 g, 14.8 mmol) is obtained as a beige foam and used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 1H), 7.76 (d, 1H), 7.63 (s, 1H), 7.50 (dd, 1H), 7.42 (m, 2H), 7.34 (m, 6H), 7.25 (m, 2), 7.09 (d, 1H), 5.14 (s, 2), 4.75 (s, 2H), 4.27 (s, 2H), 3.66 (m, 2H), 3.30 (bs, 2H).

C. 4-(2-Aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester

A mixture of ammonium acetate (18.7 g, 242 mmol) and 4-(2-phenoxyquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (6.92 g, 14.8 mmol) is heated overnight at 150°C. After 21 hours, an additional 3 g of ammonium acetate is added and the heating is continued. After 5 hours, the mixture is cooled to room temperature, diluted with CH_2Cl_2 and stirred with 1N NaOH (100 mL) for 30 minutes. The two layers are separated and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with 1N NaOH, saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The crude mixture of the title compounds (5.50 g, 14.1 mmol) is obtained as a beige foam and used in the subsequent step without further purification.

Major component (4-(2-aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.45 (d, 1H), 7.35 (s, 5H), 6.74 (d, 1H), 5.14 (s, 2H), 4.79 (bs, 2H), 4.71 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H).

Minor component (3-oxo-4-(2-oxo-1,2-dihydroquinolin-6-ylmethyl)piperazine-1-carboxylic acid benzyl ester): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, 1H), 7.48 (m, 2H), 7.37 (m, 6H), 6.70 (d, 1H), 5.14 (s, 2H), 4.66 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H).

D. 1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one.

To a solution of a mixture of 4-(2-aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester and 3-oxo-4-(2-oxo-1,2-dihydro-quinolin-6-ylmethyl)piperazine-1-carboxylic acid benzyl ester (5.50 g, 14.1 mmol) in 100 mL of 10:1 MeOH/HOAc is added a catalytic amount of 10% palladium on activated carbon. The heterogenous mixture is hydrogenated at room temperature under a balloon of H_2 for 18 hours. The reaction mixture is filtered through a pad of Celite, washed with MeOH, and the filtrate is concentrated in vacuo. The crude mixture of products is purified by RP-HPLC eluting in a gradient of 2% CH_3CN/H_2O (0.1% TFA) to 20% CH_3CN/H_2O(0.1% TFA) and the appropriate product fractions are concentrated in vacuo to provide 1-(2-aminoquinolin-6-ylmethyl)-piperazin-2-one ditrifluoroacetate (2.64 g, 5.45 mmol) as the major product in the form of a white solid. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.78 (bs, 2H), 8.31 (d, 1H), 7.80 (s, 1H), 7.66 (m, 2H), 7.08 (d, 1H), 4.70 (s, 2H), 3.84 (s, 2H), 3.46 (bs, 4H). MS m/z 256, [M+]. Elemental analysis calculated with 0.25 mol of H_2O cal. C=44.25%, H=3.82%, N=11.47%, found C=44.23%, H=3.76%, N=11.23%.
The minor by-product 6-(2-oxo-piperazin-1-ylmethyl)-1H-quinolin-2-one(0.62 g, 1.28 mmol) is also isolated from the RP-HPLC separation as a white solid ^{1}H NMR (d^6-DMSO, 300 MHz) δ 11.76 (bs, 1H), 9.30 (bs, 2H), 7.85 (d, 1H), 7.55 (s, 1H), 7.42 (d, 1H), 7.28 (d, 1H), 6.50 (d, 1H), 4.60 (s, 2H), 3.80 (s, 2H), 3.38 (bs, 4H). MS m/z 257, [M+]. Elemental analysis calculated with 0.5 mol of H_2O cal. C=43.72%, H=3.68%, N=8.50%, found C=43.70%, H=3.62%, N=8.61%.

EXAMPLE 68. 1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one.

The title compound is prepared as described in EXAMPLE 67 substituting 6-bromomethyl-1-chloroisoquinoline for bromomethyl-2-chloroquinoline. ^{1}H NMR (d6-DMSO, 300 MHz) δ (9.18 (bs, 2H), 8.53 (d, 1H), 7.81 (s, 1H), 7.63 (m, 2H), 7.14 (d, 1H), 4.77 (s, 2H), 3.88 (s, 2H), 3.50 (m, 4H).

EXAMPLE 69. 2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

A. 3-Iodopyridin-4ylamine.

A solution of potassium iodide (19.48 g, 117.4 mmol) and iodine (18.37 g, 72.3 mmol) in water (77 mL) is added dropwise via an addition funnel to a refluxing solution of 4-aminopyridine (9.21 g, 97.8 mmol) and sodium carbonate (6.12 g, 57.7 mmol) in water (35 mL). Upon complete addition the mixture is stirred for 2 hours at reflux then cooled to room temperature and extracted with ethyl acetate. The combined organic layers are washed with saturated sodium thiosulfate solution (3x) and brine then dried

over $MgSO_4$, filtered and concentrated to give the title product (8.37 g, 38.0 mmol) and a trace of the di-iodo compound as an yellow/orange solid. This material is used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.10 (d, 1H), 6.55 (d, 1H), 4.60 (bs, 2H).

B. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (20.7 g, 94.8 mmol) is added to a solution of 3-iodopyridin-4-ylamine (19.0 g, 86.4 mmol) in THF (86 mL). The resulting solution is stirred for 2 hours at room temperature then concentrated. The residue is diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated. The residue is purified by column chromatography eluting with 1% EtOAc/CH_2Cl_2 to give the title product and a small amount of the BOC-protected di-iodo compound. Trituration of the mixture with ether/hexane removes the undesired compound leaving the title product in the solution. Filtration of the solid and concentration of the filtrate yields the title product (18.95 g, 59.2 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.0 (bs, 1H), 1.55 (s, 9H).

C. 3-Oxo-4-prop-2-ynylpiperazine-1-carboxylic acid benzyl ester.

Sodium hydride (0.82 g, 23.0 mmol, 60% mineral oil dispersion) is added to a solution of 4-benzyloxycarbonylpiperazin-2-one (5.13 g, 21.9 mmol) in THF/DMF (75 mL, 3/1 v/v) at 0°C . The mixture is stirred for 5 minutes, then propargyl bromide (3.7 mL, 41.5 mmol) is added dropwise. The resulting solution is stirred for 1 hour then brought to room temperature and stirred for 2 hours. The reaction is quenched with saturated ammonium chloride solution then diluted with ethyl acetate and washed with water (4x) and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The residue is purified by column chromatography eluting with 5% MeOH/CH_2Cl_2 to give the product (5.96 g, 21.9 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 5.12 (s, 2H), 4.25 (s,2H), 4.16 (s, 2H), 3.75 (m, 2H), 3.47 (m, 2H), 2.22 (s, 1H).

D. 2-(4-Benzyloxycarbonyl-2-oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

$Pd(PPh_3)_2Cl_2$ (0.29 g, 0.41 mmol), CuI (0.05 g, 0.25 mmol) and triethylamine (4.6 mL, 32.9 mmol) is added to a solution of 3-oxo-4-prop-2-ynylpiperazine-1-carboxylic acid benzyl ester (2.24 g, 8.23 mmol) and (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester (2.63 g, 8.23 mmol) in DMF (30 mL) at room temperature. The mixture is heated to 100°C and stirred for 1.5 hours. The reaction mixture is then cooled to 50°C and DBU (2.5 mL, 16.5 mmol) is added. After 30 minutes the solution is cooled to room temperature, diluted with ethyl acetate and washed with saturated ammonium chloride, water and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting solid is

purified by column chromatography eluting with a gradient of 2% MeOH/$CH_2Cl_2$to 5% MeOH/ $CH_2Cl_2$to give the product (2.93 g, 6.31 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.4 (d, 1H), 7.85 (d, 1H), 7.35 (m, 5H), 6.38 (s, 1H), 5.2 (s, 2H), 5.00 (s, 2H), 4.29 (s, 2H), 3.85 (m, 2H), 3.52 (m, 2H), 1.7 (s, 9H). Ion spray MS, $[M+H]^+$= 465.

E. 2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

Palladium black (1.1 g, 10.3 mmol) is added to a solution of 2-(4-benzyloxycarbonyl-2-oxo-piperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (1.7 g, 3.7 mmol) in HCO_2H/MeOH (45 mL, 4.4% solution). After 40 minutes the catalyst is filtered through Celite and washed with MeOH. The filtrate is concentrated in vacuo to remove methanol then the resulting solution is diluted with methylene chloride and washed with saturated sodium bicarbonate, and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The resulting solid is purified by column chromatography eluting with a gradient of 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the product (0.8 g, 2.5 mmol) as a pale yellow foamy solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.40 (d, 1H), 7.9 (d, 1H), 6.48 (s, 1H), 4.98 (s, 2H), 3.7 (s, 2H), 3.51 (t, 2H), 3.40 (t, 2H), 1.91 (bs, 1H), 1.70 (s, 9H).

EXAMPLE 70. 2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A. 2-Benzyloxycarbonylamino-3-(prop-2-ynylamino)-propionic acid methyl ester.

Propargyl bromide (1.6 mL, 14.4 mmol) is added to a solution of 3-amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride (4.0 g, 13.9 mmol) and triethylamine (4.1 mL, 29.4 mmol) in THF (46 mL). The resulting mixture is heated to 50°C and stirred overnight then cooled to RT and concentrated in vacuo. The crude residue is diluted with methylene chloride, washed with saturated $NaHCO_3$ and brine then the organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material (4.0 g) is taken on to the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.30 (m, 5H), 5.75 (bs, 1H), 5.20 (s, 2H), 4.45 (bs, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.31 (s, 2H), 3.08 (dd, 1H), 2.98 (dd, 1H), 2.20 (t, 1H). EI MS, $[M+H]^+$=291.

B. 2-Benzyloxycarbonylamino-3-(bromoactyl-prop-2-ynyl-amino)-propionic acid methyl ester.

DCC (2.27 g, 11.0 mmol) and bromoacetic acid (1.48 g, 10.7 mmol) is added to a solution of 2-benzyloxycarbonylamino-3-(prop-2-ynylamino)-propionic acid methyl ester (3.10 g, 10.7 mmol) in CH_2Cl_2 at RT. The mixture is stirred overnight then diluted with ether. The white solid which precipitates out is filtered and the filtrate is concentrated to give a yellow oil. The crude product is

purified by chromatography eluting with a gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to yield the title product (2.1g, 5.12 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.70 (d, 1H), 5.10 (s, 2H), 4.63 (m, 1H), 4.15 (d, 2H), 4.00 (m, 1H), 3.80 (s, 3H), 3.75 (s, 2H), 3.70 (dd, 1H), 2.27 (bs, 1H). Ion spray MS, $[M+H]^+$=411, 413, Br pattern.

C. 5-Oxo-4-prop-2-ynyl-piperazine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester.

Sodium hydride (0.20 mg, 4.9 mmol) is added to a solution of 2-benzyloxycarbonylamino-3-(bromoactyl-prop-2-ynyl-amino)-propionic acid methyl ester (2.0 g, 4.8 mmol) in THF (50 mL) at 0°C. The solution is stirred for 40 minutes then quenched with saturated NH_4Cl solution. The reaction mixture is concentrated in vacuo then diluted with CH_2Cl_2 and washed with brine. The organic layer is dried over , filtered and concentrated in vacuo. The crude product is purified by chromatography eluting with 50% EtOAc/hexanes to give the title product (1.4 g, 4.1 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.20 (s, 2H), 5.10 (m, 1H), 4.30 (dd, 1H), 4.25 (d, 2H), 4.08 (m, 1H), 4.00 (dd, 1H), 3.78 (dd, 1H), 3.78 (s, 3H), 2.25 (t, 1H).

D. 2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.41 (d, 1H), 7.90 (d, 1H), 6.42 (s, 1H), 5.00 (AB, 2H), 3.85-3.93 (m, 2H), 3.78 (s, 3H), 3.70-3.81 (m, 3H), 1.65 (s, 9H). Ion spray MS, $[M+H]^+$=389.

EXAMPLE 71. 2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (s, 1H), 8.43 (d, 1H), 7.90 (d, 1H), 6.48 (s, 1H), 5.63 (d, 1H), 4.40 (d, 1H), 4.20 (m, 1H), 3.78 (s, 3H), 3.70 (d, 1H), 3.52 (d, 1H), 3.33 (dd, 1H), 2.92 (s, 1H), 1.55 (s, 9H). Ion spray MS, $[M+H]^+$=389.

EXAMPLE 72. 1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one.

A. 4-(4-Chloroquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid tert-butyl ester (3.93 g, 19.6 mmol) and 7-bromomethyl-4-chloroquinazoline, EXAMPLE 7, (5.0 g, 19.6 mmol) in 150 mL of THF and 15 mL of DMF at 0°C is added a 60% dispersion in mineral oil of NaH (0.79 g, 19.6 mmol). The solution is stirred at 0°C for 0.5 hours and then is allowed to warm to ambient temperature. After 4 hours, the solution is poured into a saturated solution of NH_4Cl. The layers are separated and the organic layer is washed with

H_2O, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The title compound is obtained as a white solid (5.1 g, 13.4 mmol). MS (FAB) m/z 377, 379, (M+H), chlorine pattern.

B. 4-(4-Aminoquinazoline-7-ylmethyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester.

A solution of 4-(4-chloroquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester (1.84 g, 4.9 mmol) in 120 mL of ethanol is saturated with NH_3 gas. To the resulting solution is added acetic acid (0.03 mL). The solution is heated to reflux. After 16 hours, the solution is concentrated. The resulting solid is dissolved in CH_2Cl_2 and the inorganic salts are filtered off. The organic solution is concentrated. The resulting solid is triturated with EtOAc. The title compound is obtained a a white solid (1.59 g, 4.5 mmol). MS (FAB) m/z 356, (M+H).

C. 1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one.

A solution of 4-(4-aminoquinazoline-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.92 g, 5.4 mmol) in EtOAc (200 mL) at 0 °C is saturated with HCl gas. The solution is stirred at 0°C for 4 hours. After this time, the solution is concentrated. The title compound is obtained as a white solid (1.79 g, 5.4 mmol). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.9 (bs, 3H), 9.7 (bs, 2H), 8.8 (s, 1H), 8.46 (d, 1H), 7.72 (s, 1H), 7.61 (d, 1H), 4.78 (s, 2H), 3.83 (s, 2H), 3.4 (m, 4H).

Example 73. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one.

A. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 72, Part A, substituting 6-bromomethyl-4-chlorothieno[2,3-d]pyrimidine. for 7-bromomethyl-4-chloroquinazoline. Followed by treatment as described in EXAMPLE 72, Part B, the title compound is obtained. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.22 (s, 1H), 7.35 (s, 1H), 5.48 (s, 2H), 4.10 (s, 2H), 3.60 (m, 2H), 3.40 (m, 2H), 1.45 (s, 9H). MS (ion spray), 364, (M+H).

B. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one.

The title compound is obtained by treatment of 1-(4-amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester as described in EXAMPLE 72, Part C. MS (EI), 2634, (M+).

EXAMPLE 72. 4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester.

A. 4-[3-(1-tert-butoxycarbonyl-piperidin-4-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as described in EXAMPLE 72, Part A, substituting 3-oxopiperazine-1-carboxylic acid benzyl ester for 3-oxopiperazine-1-carboxylic acid tert-butyl ester and 4-(3-bromopropyl)-piperidine-1-carboxylic acid tert-butyl ester for 7-bromomethyl-4-chloroquinazoline. The title compound is obtained as a white foam. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.38 (m, 5H), 5.12 (s, 2H), 4.18 (m, 4H), 3.73 (m, 2H), 3.33 (m, 4H), 2.66 (m, 2H), 1.58 (m, 6H), 1.42 (s, 9H), 1.38 (m, 3H).

B. 4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester.

4-[3-(1-tert-butoxycarbonyl-piperidin-4-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester is treated as described in EXAMPLE 67, Part D, to give the title compound as an oil.

EXAMPLE 75. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one.

A. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 2-oxo-3-(S)-methoxymethylpiperidine (5.36g, 19.3mmol), EXAMPLE 41, in 200mL of 10:1 THF:DMF is added 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (12.6g, 60%purity, 19.3mmol), prepared as in EXAMPLE 13. The solution is cooled to 0°C. To the solution is added NaH (0.77g of a 60% dispersion in mineral oil, 19.3mmol). The solution is stirred for 16 hours. After this time, 1N HCl is added until the pH=1. The solution is stirred for 1 hour. After this time, the solution is diluted with EtOAc. The organic layer is washed with water and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 20%EtOAc/CH_2Cl_2 to 40%EtOAc/CH_2Cl_2. The title compound (6.8g, 16.7mmol) is obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.34 (m, 5H), 6.61 (m, 2H),5.13 (AB, 2H), 4.76 (m, 1H), 4.40 (AB, 2H), 4.08 (m, 5H), 3.74 (m, 2H), 3.32 (m, 1H), 3.30 (s, 3H), 3.10 (m, 1H).

B. 4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (6.8g, 16.7mmol) in 100mL of ethanol is added triazine (2.2g, 26.4mmol) and acetic acid (1.6g,26.4mmol). The solution is heated to a reflux. After 36h, the solution is concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2. The title compound (5.8g, 13.3mmol) is obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.55 (s, 1H), 7.72 (m, 2H), 7.48 (m, 1H), 7.35 (m, 5H), 6.40 (bs, 2H), 5.16 (AB, 2H), 5.06 (m, 1H),4.72 (m, 1H), 4.59 (m, 1H), 4.09 (m, 2H), 3.74 (m, 2H), 3.44 (m, 1H), 3.30 (s, 3H), 3.12 (m, 1H). MS (ion spray) m/z 436, (M+H).

C. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one.

To a solution of 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (5.8g, 13.3mmol) in 50mL of acetic acid is added dropwise, 20mL of a 30%HBr in AcOH solution. The solution is stirred for 1 hour. After this time, the solution is concentrated. The resulting crude product is purified by column chromatography eluting with CH_2Cl_2:MeOH:NH_4OH (20:5:1). The title compound (2.0g, 6.6mmol) is obtained as a white solid. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.60 (s, 1H), 7.72 (m, 2H),7.48 (d, 1H), 5.60 (bs, 2H), 4.72 (AB, 2H), 3.87 (m, 2H), 3.71 (m, 1H), 3,42 (m, 1H), 3.40 (s, 3H), 3.19 (m, 2H), 3.02 (m, 1H). MS (ion spray) m/z 302, (M+H).

EXAMPLE 76. 1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-butyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 42, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d, 1H), 7.54 (s, 1H), 7.41 (d, 1H), 4.74 (s, 2H), 3.43 (m, 2H), 3.28 (m, 1H), 3.09 (m, 1H), 2.95 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.39 (m, 4H), 0.93 (m, 3H). MS (ion spray) m/z 314, (M+H).

EXAMPLE 77. 1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-ethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester r, Example 43, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.42 (d, 1H), 4.78 (s, 2H), 3.40 (m, 2H), 3.29 (m, 1H), 3.11 (m, 1H), 2.98 (m, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.20 (m, 3H). MS (ion spray) m/z 286, (M+H).

EXAMPLE 78. 1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-propyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 44, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.13 (d, 1H), 7.60 (s, 1H), 7.47 (d, 1H), 4.78 (s, 2H), 3.44 (m, 2H), 3.30 (m, 1H), 3.11 (m, 1H), 2.97 (m, 1H), 1.98 (m, 1H), 1.72 (m, 1H), 1.50 (m, 2H), 0.97 (m, 3H). MS (ion spray) m/z 300, (M+H).

EXAMPLE 79. 1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-ethoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 45, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.34 (s, 1H), 8.07 (d, 1H), 7.53 (s, 1H),

7.40 (d, 1H), 4.79 (AB, 2H), 3.90 (m, 1H), 3.72 (m, 1H), 3.68 (m, 1H), 3.52 (m, 2H), 3.36 (m, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 1.92 (m, 3H). MS (ion spray) m/z 316, (M+H).

EXAMPLE 80. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 46, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.44 (d, 1H), 4.79 (AB, 2H), 3.58 (m, 1H), 3.47 (m, 1H), 3.31 (m, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 1.41 (d, 3H). MS (ion spray) m/z 272, (M+H).

EXAMPLE 81. 1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-benzyl-3-oxo-piperazine-1-carboxylic acid benzyl, Example 47, ester for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d, 1H), 7.57 (s, 1H), 7.38 (d, 1H), 7.27 (m, 5H), 4.74 (AB, 2H), 3.76 (m, 1H), 3.47 (m, 1H), 3.30 (m, 3H), 3.08 (m, 1H), 2.96 (m, 1H). MS (ion spray) m/z 348, (M+H).

EXAMPLE 82. 1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-(1-methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 48, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. This compound is isolated as the bis hydrobromide salt. ^{1}H NMR (CD_3OD, 300MHz) δ 8.70 (s, 1H), 8.40 (d, 1H), 7.88 (s, 1H), 7.71 (d, 1H), 4.94 (AB, 2H), 4.30 (m, 2H), 3.76 (m, 1H), 3.68 (m, 3H), 3.36 (s, 3H), 1.42 (d, 3H). MS (ion spray) m/z 316, (M+H).

EXAMPLE 83. 1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2,2-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 49, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.34 (s, 1H), 8.12 (d, 1H), 7.72 (bs, 2H), 7.41 (s, 1H), 7.26 (d, 1H), 4.60 (s, 2H), 3.33 (m, 2H), 2.98 (m, 2H), 1.27 (s, 6H).

EXAMPLE 84. 1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-isopropyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 50, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.32 (s, 1H), 8.12 (d, 1H), 7.66 (bs, 2H),

7.42 (s, 1H), 7.27 (d, 1H), 4.60 (AB, 2H), 3.23 (m, 2H), 3.05(m, 1H), 2.79 (m, 1H), 2.34 (m, 1H), 0.92 (s, 3H), 0.80 (s, 3H).

EXAMPLE 85. 1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-isobutyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 51, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.65 (s, 1H), 7.70 (m, 2H), 7.48 (m, 1H), 5.61 (m, 2H), 4.82 (m, 1H), 4.65 (m, 1H), 3.52 (dd, 1H), 3.37 (m, 1H), 3.18 (m, 2H), 2.98 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.59 (m, 2H), 0.95 (m, 6H).

EXAMPLE 86. 1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) l-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-(2-methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 52, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.32 (s, 1H), 8.13 (d, 1H), 7.70 (bs, 2H), 7.42 (s, 1H), 7.28 (m, 1H), 4.60 (m, 2H), 3.32 (m, 8H), 3.11 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H).

EXAMPLE 87. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-methoxymethyl-5-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 53, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.72 (s, 1H), 8.32 (d, 1H), 7.78 (m, 2H), 5.11 (m, 1H), 4.81 (m, 1H), 4.42 (m, 1H), 4.13 (m, 1H), 4.04 (m, 1H), 3.74 (m, 2H), 3.52 (m, 1H), 3.43 (s, 3H), 1.34 (d, 3H).

EXAMPLE 88. (3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A. (2S,6RS)-4-[3-(benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of the (2S,6RS)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.98 g, 7.56 mmol in 20 mL of tetrahydrofuran and 2 mL of DMF is added sodium hydride (60%, 289 mg, 12.6 mmol) at 0°C. The reaction is stirred for one hour at room temperature and the 2-benzhydrylidene-amino)-4-bromomethyl-benonitrile (4.24 mg, 11.34 mmol), Example 13, is added. After stirring at room temperature overnight, the tetrahydrofuran is removed. The residue is taken up in ethyl acetate. Excess sodium hydride is quenched with 5 mL of water, and normal aqueous work-up followed. The crude product is chromatographed on silica gel (50% EtOAc/Hexane) to give (2S,6RS)-

4-[3-(benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.6 g, 65%). $C_{35}H_{32}N_4O_3$ MS m/z: 557.

B. (2S,6RS)-4-(3-amino)-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6RS)-4-[3-(Benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.6 g, 5.21 mmol) is dissolved in 100 mL of ethyl acetate and cooled to 0°C. A 12N solution of hydrochloric acid (0.5 ml, 6.0 mmol) is added dropwise. The deprotection is complete in thirty minutes. The reaction mixture is washed with 10 % sodium bicarbonate. The ethyl acetate layer is dried with magnesium sulfate, filtered and condensed. The resulting residue is purified by flash colunm (SiO_2, 60 % ethyl acetate/hexane) to give the product (2S,6RS)-4-(3-amino)-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.03 g, 99 %).

C. (2S,6RS)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Glacial acetic acid (0.9 ml, 15.54 mmol) and 1,3,5-triazine (840 mg, 10.36 mmol) is added to a solution of (2S,6RS)-4-(3-amino-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.03 g, 5.18 mmol) in ethanol. The resulting mixture is heated to reflux overnight. Replaced the ethanol with ethyl acetate and washed with saturated sodium bicarbonate (5 mL). The ethyl acetate layer is dried with magnesium sulfate, filtered and condensed. The resulting residue is purified by flash colunm (SiO_2, 20% methanol/methylene chloride) to give the product (2S,6RS)-4-(4-amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.85 g, 85%) as a yellow solid. $C_{23}H_{25}N_5O_3$ MS m/z: 420.

D. (3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

Palladium on carbon (10 %, 700 mg) is added to a solution of (2S,6RS)-4-(4-amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.62 g, 3.87 mmol) in 20 mL of methanol and 2 mL of acetic acid. The reaction mixture is left to stir in an atmosphere of hydrogen for eight hours. The palladium is filtered off, and the volitale solvents are removed on the rotovap. The crude product (1.7 g, 95 %) is isolated as a white solid. The two epimers are separated on silica gel (1% triethylamine/15% methanol/methylene chloride). The minor epimer is assigned as (3S,5R)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and the major epimer is assigned as (3S,5S)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

EXAMPLE 89. 1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one.

4-(Benzyloxycarbonyl)-piperazin-2-one (1.1 g, 4.6 mmol) is dissolved in THF (50 mL), cooled in an ice bath and treated with tretrabutylammonium iodide (0.18 g, mmol) and 60% sodium hydride (0.24 g, 6.0 mmol). The reaction mixture is stirred at 0 C for 30 minutes then treated dropwise with a solution of 7-bromomethyl-4-chloroquinoline (1.2 g, 4.6 mmol), Example 14, in THF (50 mL). The resulting solution is stirred at 0 C for 2 h then quenched with ammonium chloride solution and concentrated. Dilution with ethyl acetate is followed by a water wash; the organic layer is dried (sodium sulfate) and concentrated. The residue is chromatographed (4% methanol/methylene chloride) to yield solid

4-(benzyloxycarbonyl)-1-(4-chloroquinolin-7-ylmethyl)-piperazin-2-one (1.2 g, 2.9 mmol). A portion of this material (0.75 g, 1.8 mmol) is dissolved in acetonitrile (20 mL) and treated with iodo trimethylsilane (0.78 mL, 5.4 mmol) at room temperature for 3 hours. The reaction is quenched with methanol and concentrated to dryness. Methanol addition and concentration is repeated four times. The final residue is taken up is 2M aqueous HCl; the solution is washed with ether and concentrated. The residue is recrystallized from isopropanol and ether to yield the title compound (0.63 g, 2.3 mmol) MS m/z: M^+ = 275; ^{1}HNMR (CD_3OD, 300 MHz) δ 9.1 (d, 1H), 8.5 (d, 1H), 8.2-8.3 (m, 2H), 8.0 (d, 1H), 5.2 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H).

EXAMPLE 90. 1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one.

4-(t-Butyloxycarbonyl)-piperazin-2-one (0.6 g, 3.0 mmol), EXAMPLE 40, is dissolved in THF (80 mL), cooled in an ice bath and treated with tretrabutylammonium iodide (0.23 g, 0.62 mmol) and 60% sodium hydride (0.12 g, 3.0 mmol). The reaction mixture is stirred at °C for 40 minutes then treated dropwise with a solution of 7-bromomethyl-4-chlorocinnoline (10.7g, 2.7 mmol), Example 15, in THF (20 mL). The resulting solution is warmed to ambient temperature over 2 hours. The solution is evaporated to dryness and the residue is taken up in ethyl acetate and 10 % aqueous sodium bicarbonate solution. The organic layer is separated, washed with water, dried (sodium sulfate) and concentrated. The residue is chromatographed (ethyl acetate) to yield the title compound (0.6 g, 1.6 mmol). A portion of this material (0.21 g, 1.26 mmol) is dissolved in THF (~ 4 mL) and treated with a saturated solution of HCl in ethyl acetate (50 mL) at room temperature for 2 hours. The solution is filtered and concentrated to a residue (0.14 g, 0.4 mmol). MS m/z: M^+ = 275; ^{1}H NMR (CD_3OD, 300 MHz) δ 9.15 (d, 1H), 8.5 (d, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 5.0 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H).

EXAMPLE 91. 1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one.

4-(Benzyloxycarbonyl)-3-(S)-methylpiperazin-2-one (1.0 g, 4.0 mmol), EXAMPLE 46, is dissolved in THF (60 mL), cooled in an ice bath and treated with tretrabutylammonium iodide (0.10 g, 0.27 mmol) and 60% sodium hydride (0.18 g, 4.4 mmol). The reaction mixture is stirred at 0°C for 30

minutes then treated dropwise with a solution of 7-bromomethyl-4-chloroquinoline (1.12 g, 4.4 mmol), EXAMPLE 14, in THF (5 mL). The resulting solution warmed to room temperature over approximately 1 h then quenched with sodium bicarbonate solution and concentrated. The residue is partitioned between ethyl acetate and water; the organic layer is dried (sodium sulfate) and concentrated. The residue is chromatographed (5 % methanol/methylene chloride) to yield solid 4-(Benzyloxycarbonyl)-1-(4-chloroquinolin-7-ylmethyl)-3-(S)-methyl-piperazin-2-one (1.32 g, 3.1 mmol). A portion of this material (0.10 g, 0.23 mmol) is dissolved in acetonitrile (6 mL) and treated with iodotrimethyl-silane (0.1 mL, 0.75 mmol) at room temperature for 2 hours. The reaction is quenched with methanol and concentrated to dryness. Methanol addition and concentration is repeated six times. The final residue is taken up is 2M aqueous HCl; the solution is washed with ether and concentrated to yield the title compound. MS m/z: $M^+ = 289$; ^{1}H NMR (CD_3OD, 300 MHz) δ 9.2 (d, 1H), 8.6 (d, 1H), 8.2-8.3 (m,2H), 8.0 (d, 1H), 5.1 (q, 1H), 4.3-4.4 (m, 1H), 3.8-4.0 (m, 2H), 3.6-3.8 (m, 3H), 1.75 (d, 3H).

EXAMPLE 92. 1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one.

A. 4-(tert-Butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-piperazin-2-one (8.0 g, 40 mmol), EXAMPLE 40, is dissolved in THF (160 mL), cooled in an ice bath and treated with 60 % sodium hydride (1.9 g, 48 mmol). The reaction mixture is stirred 40 minutes, then treated with tetra-butylammonium iodide (0.35 g, 0.95 mmol) and bromoacetonitrile (3.4 mL, 48 mmol). After 2 h the reaction is quenched with water, concentrated to a small volume and extracted with methylene chloride (3 X). The combined organic extracts are concentrated and the residue is chromatographed (50 % ethyl acetate/hexane) to give 4-(tert-butyloxycarbonyl)-1-cyanomethyl-piperazin-2-one (5.2 g, 21.7 mmol). This material is dissolved in ethanol (140 mL) and treated with platinum oxide (0.83 g) at 50 PSI of hydrogen gas for 24 hours. The catalyst is removed by filtration and the solution is concentrated to yield 4-(tert-butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one (5.2 g, 21.6 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.08 (s, 2H), 3.62 (m, 2H), 3.44 (t, 2H), 3.38 (t, 2H), 2.89 (t, 2H).

B. 4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]- piperazin-2-one.

4-(tert-Butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one (4.0 g, 16 mmol) is dissolved in methylene chloride (150 mL) and treated with 4-nitro-2,3,5,6-tetrachloro-pyridine (4.8 g, 18 mmol) and N-methylmorpholine (4.0 mL, 36 mmol). The reaction mixture is stirred for 5 h, concentrated and the residue is purified by chromatography (50% ethyl acetate/hexane) to give the title compound (4.8 g, 10.5 mmol). Fab MS m/z: 457, 469, 461, $[M+1]^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.00 (t, 1H), 4.10 (s, 2H), 3.97 (m, 2H), 3.66 (m, 2H), 3.38 (m, 2H).

C. 1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl-piperazin-2-one (3.5 g, 7.6 mmol) is dissolved in methanol (20 mL) and 0.5 M sodium methoxide in methanol (150 mL, 75 mmol). The solution is treated with Pd/C (0.5 g) and agitated under 50 PSI of hydrogen gas for 16 hours. The solvent is removed and the residue is extracted with methylene chloride which is filtered. The filtrate is concentrated and loaded onto a silica flash column. The column is eluted with 5% MeOH/CH_2Cl_2 followed by NH_4OH/MeOH/CH_2Cl_2 (1:5:95) and NH_4OH/MeOH/ CH_2Cl_2 (1:10:70) to yield 4-(tert-Butyloxycarbonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one as a white foam (1.5 g, 4.7 mmol). This material (1.5 g, 4.7 mmol) is treated with 20% trifluoroacetic acid in methylene chloride (110mL) at ambient temperature for 2 hours. The solution is concentrated and the residue is treated with saturated bicarbonate solution and ammonium hydroxide until a basic solution is obtained. The solution is applied to a silica column and eluted with NH_4OH/MeOH/CH_2Cl_2 (1:10:60) and 1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one is isolated as a mixture of desired product and inorganic salts (estimate 25 % by weight) EI MS m/z: 220, M^+; ^1H NMR (CD_3OD, 300 MHz) δ 8.07 (d, 2H), 6.96 (d, 2H), 3.77 (s, 2H), 3,65 (m, 6H), 3.44 (t, 2H).

EXAMPLE 93. 1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one trifluroacetate.

4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]-piperazin-2-one (0.19 g, 0.41 mmol), Example 92, Part B, is dissolved in DMF (3 ml) and treated with 60 % NaH (20 mg, 0.5 mmol). After 10 minutes methyl iodide (0.025 ml, 0.40 mmol) is added and the yellow solution is stirred at r.t. overnight. The solution is diluted with EtOAc and washed with H_2O (6 X). The organic layer is dried (MgSO4) and concentrated to a residue (0.19 g, 0.40 mmol). The residue is dissolved in methanol (2 ml) and treated with 0.5 M NaOMe in MeOH (8 ml, 4.0 mmol)). The solution is treated with Pd/C and agitated under 60 PSI of hydrogen gas overnight and filtered. The filtrate is concentrated and extracted several times with CH_2Cl_2; removal of solvent in vacuo gives 4-(tert-Butyloxycarbonyl)-1-[2-{(methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one as an amorphous residue (0.16 g). EI MS m/z: 335, $[M+1]^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, 2H), 6.56 (d, 2H), 3.99 (s, 2H), 3.60 (t, 2H), 3.53 (t, 2H), 3.47 (t, 2H), 3.28 (t, 2H), 2.98 (s, 3H), 1.46 (s, 9H). Treatment of the above product with 20% TFA/CH_2Cl_2 (10 mL) at r.t. for 1 h gives, after concentration, the title compound as a residue which is used without further purification. ^1H NMR (CD_3OD, 300 MHz) δ 8.14 (d, 2H), 7.30 (br, 1H), 7.00 (br, 1H), 3.88-3.67 (m, 8H), 3.53 (t, 2H), 2.26 (s, 3H).

EXAMPLE 94. 1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one.

A. 4-[2-(3-Methylpyridin-4-ylimino)-ethyl]-3-oxo-piperazine-1-carboxlic acid benzyl ester.

4-(Benzyloxycarbonyl)-piperazin-2-one (4.7 g, 20 mmol) is dissolved in THF (50 mL) and treated with 1.5M LDA (20 mL, 30 mmol) at 0°C. The reaction mixture is treated with condensed ethylene oxide (3 mL, 40 mmol) and stirred at r.t. overnight. The mixture is neutralized with 2N HCl, concentrated, and extracted with EtOAc. The EtOAc layer is washed with H_2O and concentrated to a crude residue. Further extraction of the crude with Et_2O and concentration of the ethereal layer gives an oil (1.5 g). The above oil is dissolved in CH_2Cl_2 (25 mL) and added to the solution of 2M oxalyl chloride (7.5 mL, 15 mmol) and DMSO (2.3 mL, 29.7 mmol) in CH_2Cl_2 (25 mL) at -60°C. After 15 minutes, Et_3N (2.1 ml, 15 mmol) is added. The mixture is stirred at -50 °C for 10 minutes then warmed to r.t for 10 minutes. The reaction is quenched with 0.5 N HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer is washed with 0.5 N HCl, brine (2 X), H_2O, and concentrated to a residue. The residue is purified by chromatography (2% MeOH/CH_2Cl_2) to give 4-amino-3-methyl pyridine as an oil (0.5 g, 1.6 mmol). A solution of the oil (0.2 g, 2 mmol), and (1R)-(-)-10-camphorsulfonic acid (15 mg) in toluene (100 ml) is refluxed with a Dean Stark set up overnight. The mixture is concentrated and the residue is purified by chromatography (2-4% MeOH/CH2Cl2) to give the title imine as a white foam (0.20 g, 0.54 mmol). Ion spray MS m/z: 367, $[M+1]^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 8.14 (s, 1H), 7.35 (s, 5H), 6.60 (d, 1H), 6.18 (dd, 1H), 5.15 (s, 2H), 4.97 (d, 1H), 4.30 (s, 2H), 3.78 (t, 2H), 3.50 (bm, 2H), 2.15 (s, 3H).

B. 1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one.

4-[2-(3-Methylpyridin-4-ylimino)-ethyl]-3-oxo-piperazine-1-carboxlic acid benzyl ester (0.20 g, 0.54 mmol) is dissolved in anhydrous ethanol (20 mL) and hydrogenated at 50 PSI with 10% Pd/C overnight. After filtration, the filtrate is concentrated. The residue is treated with Pd black in 5% HCO_2H/CH_2Cl_2 (10 ml) for 10 minutes. Filtration and concentration gives crude residue, which is purified by chromatography using NH_4OH/MeOH/CH_2Cl_2 (1:5:95) to give the title compound as a clear syrup (0.078 g, 0.33 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, 1H), 8.03 (s, 1H), 7.35 (s, 5H), 6.36 (d, 1H), 5.30 (b, 1H), 3.74 (t, 2H), 3.53 (s, 2H), 3.38 (m, 4H), 3.08 (t, 2H), 2.02 (s, 3H).

EXAMPLE 95. 1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one.

1-(2-Aminoethyl)-4-(tert-butyloxycarbonyl)-piperazin-2-one from EXAMPLE 92, Part A (1.0 g, 4.1 mmol) is treated with 3,4,5-trichloropyridazine (0.81 g, 4.1 mmol), triethylamine (0.57 mL, 4.1 mmol), THF (25 mL) and heated to 120°C in a sealed tube for 3 hours. Upon cooling, the solution is diluted with ethyl acetate and washed with aqueous sodium bicarbonate (25 mL), water and dried over sodium sulfate. The organic layer is concentrated and chromatographed (5% methanol/methylene chloride) to give a mixture of isomers (0.8 g, 20 mmol). The mixture is dissolved in 0.5 M sodium methoxide in methanol (200 mL), treated with 10% Pd/C (0.5 g) and agitated under 50 PSI of hydrogen

for 20 hours. The reaction mixture is filtered; the filtrate is concentrated to a residue which is chromatographed (NH_4OH/H_2O/MeOH/EtOAc, 1:1:2:90) to give crude 4-(tert-butyloxycarbonyl)-1-[2-(pyridazin-4-ylamino)-ethyl]-piperazin-2-one. This material is dissolved in a minimal amount of THF and treated with a saturated solution of HCl in ethyl acetate (50 mL). The solution is stirred at ambient temperature for 2 h and diluted with diethyl ether (50 mL). The precipitated title compound is collected and air dried (0.5 g, 1.7 mmol). MS m/z: 367, $[M+1]^+$; ^1H NMR (CD_3OD, 300 MHz) δ 8.8 (d, 1H), 8.5 (s, 1H), 7.4 (d, 1H), 4.1 (s, 2H), 3.5-3.8 (m, 8H).

EXAMPLE 96. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

A. 1-Allyl-4-(tert-butyloxycarbonyl)-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-piperazin-2-one (1.0 g, 5.0 mmol), EXAMPLE 40, is alkylated with allyl bromide (0.48 ml, 5.5 mmol) in THF (20 ml) using the procedure described in Example 92, PartA. The title compound (0.92 g, 3.8 mmol) is obtained as a colorless liquid after chromatographed (50 % ethyl acetate/hexane). EI MS m/z 240 (M+); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80-5.68 (m, 1H), 5.23-5.15 (m, 2H), 4.09 (s, 2H), 4.03 (d, 2H), 3.63 (t, 2H), 3,30 (t, 2H), 1.45 (s, 9H).

B. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

1-Allyl-4-(tert-butyloxycarbonyl)-piperazin-2-one (0.49 g, 2.0 mmol) is treated with (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (0.64 g, 2.0 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), $P(o\text{-}tol)_3$ (37 mg, 0.12 mmol), and Et_3N (0.56 mmol) in a seal tube. The mixture is stirred at 100 °C overnight, then diluted with CH_2Cl_2 and washed H_2O (2 X). The CH_2Cl_2 layer is concentrated and the residue is chromatographed (5% MeOH/CH_2Cl_2) to give a mixture of two isomers (0.40 g, 0.92 mmol). The mixture is separated into its constituent isomers upon further chromatography (EtOAc) to give 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (90 mg, 0.21 mmol, higher R_f value) and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (0.24 g, 0.56 mmol, lower R_f value). For the former: MS m/z 433 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.38 (d, 1H), 8.28 (s, 1H), 7.93 (d, 1H), 7.48 (d, 1H), 6.67 (s, 1H), 5.10 (m, 1H), 4.15 (s, 2H), 3.70 (t, 2H), 3,46 (t, 2H), 3.39 (d, 2H), 1.48 (s, 9H), 1.45 (s, 9H). For the latter: MS m/z 433 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (s, 1H), 8.37 (d, 1H), 7.98 (d, 1H), 6.77 (s,

1H), 6.52 (d, 1H), 6.07 (m, 1H), 4.23 (d, 2H), 4.12 (s, 2H), 3,69 (t, 2H), 3.40 (t, 2H), 1.52 (s, 9H), 1.45 (s, 9H).

EXAMPLE 97. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

A mixture of the two isomers from EXAMPLE 96, Part B. (0.11 g, 0.25 mmol) is dissolved in MeOH (7 ml), treated with with 10% Pd/C and is stirred under a balloon of hydrogen for 4 hours. Filtration and concentration gives a white foam (80 mg, 0.18 mmol). EI MS m/z 434 (M+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (d, 1H), 8.30 (s, 1H), 8.05 (d, 1H), 4.08 (s, 2H), 3.64 (t, 2H), 3.50 (t, 2H), 3.35 (t, 2H), 2.58 (t, 2H), 1.90 (m, 2H), 1.57 (s, 9H), 1.48 (s, 9H).

EXAMPLE 98. 4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one

4-(Benzyloxycarbonyl)-1-(2-hydroxyethyl)-piperazin-2-one, prepared as described in EXAMPLE 94, part A. (0.26 g, 0.94 mmol) in methylene chloride (6 mL) is treated with triphenyl phosphine (0.60 g, 2.3 mmol), imidazole (0.16 g, 2.3 mmol), and iodine (0.47 g, 1.9 mmol) for 0.5 h at 0 °C. The reactin mixture is partitioned between water and methylene chloride; the organic layer is concentrated and the residue is chromatographed (15 % EtOAc/ methylene chloride) to give 4-(benzyloxycarbonyl)-1-(2-iodoethyl)-piperazin-2-one (0.24 g, 0.62 mmol). Pyrrolo[3,2-c]pyridine (0.073 g, g, 0.62 mmol) is dissolved in DMF (3 mL) and treated with 60 % sodium hydride (0.03 g, 0.74 mmol) and all of the 4-(benzyloxycarbonyl)-1-(2-iodoethyl)-piperazin-2-one from the previous step; the reaction mixture is stirred at r.t. for 16 g. The reaction mixture is concentrated to dryness and the residue is partitioned between water and methylene chloride. The organic layer is concentrated and subjected to chromatography (2-5 % MeOH/methylene chloride) to yield the title compound (0.028 g, 0.074 mmol) Ion Spray MS m/z: 379, $[M+1]^+$.

EXAMPLE 99. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester

A solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (55 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) is cooled to 0°C. DIPEA (24 mg, 0.18 mmol) is then added followed by the addition of 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (32 mg, 0.12 mmol), EXAMPLE 1. The reaction mixture is warmed to ambient temperature. After 16 h, the reaction mixture is absorbed directly onto silica gel and chromatographed (CH_2Cl_2 to 2% MeOH/

CH_2Cl_2) to provide 60 mg (73%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (dd, J = 12.3, 3.4 Hz, 1H), 3.50-3.72 (m, 3H), 3.79 (s, 3H), 4.15 (dd, J = 12.3, 1.4 Hz, 1H), 4.24 (d, J = 16.9 Hz, 1H), 5.41 (d, J = 15.3 Hz, 1H), 6.50 (s, 1H), 6.76 (dd, J = 7.9, 1.4 Hz, 1H), 7.11-7.86 (m, 15H) ppm; MS (ISP loop): m/z 683 (M+H).

B. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester

Concentrated HCl (12M, one drop) is added at 0°C to a mixture containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (60 mg, 0.08 mmol) in MeOH (5 mL). Added THF (2 mL) followed by a second drop of 12M HCl and warmed reaction mixture to ambient temperature. The reaction is quenched by pouring the reaction mixture onto a 1:1 mixture of CH_2Cl_2/aqueous $NaHCO_3$ and the layers are separated. The aqueous phase is washed with CH_2Cl_2 and then the combined organic phase is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 4% MeOH/ CH_2Cl_2) to provide 42 mg (93%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (dd, J = 12.5, 3.5 Hz, 1H), 3.60 (d, J = 16.8 Hz, 1H), 3.69 (d, J = 15.3 Hz, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.21-4.31 (m, 2H), 4.44 (br s, 2H), 5.36 (d, J = 15.3 Hz, 1H), 6.47 (dd, J = 8.0, 1.4 Hz, 1H), 6.54 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.5, 1.8 Hz, 1H), 7.80-7.86 (m, 3H) ppm; MS (ISP loop): m/z 519 (M+H).

EXAMPLE 100. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Water (5 drops) is added to a solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (30 mg, 0.05 mmol), EXAMPLE 99, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (7 mg, 1.66 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 10 mg (34%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.18 (dd, J = 12.1, 3.5 Hz, 1H), 3.61 (d, J = 16.0 Hz, 1H), 3.77 (d, J = 16.0 Hz, 1H), 3.95 (d, J = 16.0 Hz, 1H), 4.06 (d, J = 12.1 Hz, 1H), 4.14 (m, 1H), 6.40 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.57 (dd, J = 8.6, 1.9 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 8.18 (s, 1H), 8.33 (s, 1H) ppm; MS (ISP loop): m/z 505 (M+H).

EXAMPLE 101. 4-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxo-piperazine-1-ylmethyl]benzamidine.

To a solution of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (0.38 g, 0.83mmol), EXAMPLE 66, in CH_2Cl_2 (5 mL) is added Et_3N (0.35 mL, 2.6 mmol) and 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.23 g, 0.85 mmol, EXAMPLE 1. After 6 hours, the solution is concentrated. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 70% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (0.37 g, 0.65 mmol). ^1H NMR (d^6-DMSO, 300MHz) δ 9.33 (bs, 2H), 8.96 (bs, 2H), 8.30 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.70 (m, 2H), 7.50 (m, 1H), 7.28 (m, 2H), 4.55 (s, 2H), 3.86 (s, 2H), 3.44 (m, 2H), 3.22 (m, 2H).

The following compounds are prepared from 1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, Example 77, and the appropriate sulfonyl chloride using the method of Example 101.

Example #	Name	m/z (M+H)
102	4-[4-(4-Methoxy-benzenesulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	403
103	4-[4-(5-Chloro-thieno[3,2-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465
104	4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
105	4-[2-Oxo-4-(thieno[2,3-c]pyridine-2-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	430
106	4-[4-(7-Chloro-thieno[2,3-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
107	4-[4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	495, 497 Cl pattern
108	4-[4-(4-Chloro-thieno[3,2-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
109	4-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	387
110	4-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	429
111	4-Amino-3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	478, 480 Cl pattern
112	3-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-	387

	benzamidine	
113	3-[4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	447
114	3-[4-(4-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
115	3-[4-(5-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
116	3-[4-(6-Methoxy-naphthalene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	453
117	3-{4-[5-(5-Nitro-pyridine-2-sulfonyl)-thiophene-2-sulfonyl]-2-oxo-piperazin- 1-ylmethyl}-benzamidine	565
118	3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]- benzamidine	463, 465 Cl pattern
119	3-{4-[2-(3-Chloro-phenyl)-ethenesulfonyl]-2-oxo-piperazin-1-ylmethyl}- benzamidine	433, 435 Cl pattern
120	3-[2-Oxo-4-(4-phenylazo-benzenesulfonyl)-piperazin-1-ylmethyl]-benzamidine	477
121	3-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	429

EXAMPLE 122. 4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine.

Hydrogen chloride gas is bubbled into an ice-cooled solution of 4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile (100 mg, 0.264 mmol), (prepared by deprotecting 4-(4-cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester, EXAMPLE 66, Part A, followed by alkylation with 6-chloro-2-chloromethylbenzimidazole) in 15 mL of methanol. The solution contained 3Å molecular sieves. The reaction mixture is stored at -30°C. The methanol is removed on the rotovap. Fresh methanol (20 ml) is added folowed by a stream of ammonia gas. The resulting mixture is heated to reflux for three hours. The reaction mixture is filtered at room temperature. The mother liquor is condensed and the resulting residue is purified by reverse phase HPLC (0-50 % ACN/H_2O). The product is isolated as a white solid with a melting point of 91-95°C . MS $C_{20}H_{21}ClN_6O$ m/z: 397, 399. Anal. cald. for $C_{20}H_{21}ClN_6O \cdot 3C_2HF_3O_2$: C, 42.26; H, 3.27; N, 11.37. Found C, 42.20; H, 3.44; N, 11.36.

EXAMPLE 123. 4-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl}benzamidine.

To a solution of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (75 mg, 0.16 mmol), EXAMPLE 66, in 1.5 mL of DMF is added N,N-diisopropylethylamine (0.14 mL, 0.80 mmol). After stirring 10 min at room temperature, 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid (32 mg, 0.17 mmol), EXAMPLE 25, is added, followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (55 mg, 0.17 mmol). The resulting mixture is stirred at room temperature for 16 h and the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (77 mg, 0.15 mmol) as a white solid. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.27 (bs, 2H), 9.10 (bs, 2H), 7.77 (d, 2H), 7.65 (d, 1H), 7.49 (dd, 2H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.65 (s, 2H), 4.45, 4.21 (m, 2H, rotamers), 3.80 (m, 2H), 3.35 (m, 2H). ESI MS, $[M+H]^+$=403,405 (Cl pattern).

EXAMPLE 124. 3-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl}benzamidine.

The title compound is prepared as described in EXAMPLE 123 using 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid (EXAMPLE 25) and 3-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (prepared from 3-bromomethyl toluylnitrile as described in EXAMPLE 66). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.32 (bs, 2H), 9.16 (bs, 2H), 7.65 (m, 5H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.64 (s, 2H), 4.44, 4.21 (m, 2H, rotamers), 3.93, 3.79 (m, 2H, rotamers), 3.36 (m, 2H). ESI MS, $[M+H]^+$=403,405 (Cl pattern).

EXAMPLE 125. 3-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine.

A white solid (13.0 mg, 13%). $C_{20}H_{21}ClN_6O$ MS m/z: 397, 399 Anal. cald. for $C_{20}H_{21}ClN_6O \cdot 3C_2HF_3O_2$: C, 42.26; H, 3.27; N, 11.37. Found C, 43.70; H, 3.71; N, 11.95.

EXAMPLE 126. 1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)piperazin-2-one.

The title compound is prepared as described in Example 101 using 1-(2-aminoquinolin-6-ylmethyl)piperazin-2-one, EXAMPLE 67, and 5'-chloro-[2,2']bithiophenyl-5-sulfonyl chloride, EXAMPLE 2. The crude product is triturated in CH_2Cl_2 and filtered to provide the title compound as a white solid. ^{1}H NMR (d_6-DMSO, 300 MHz) δ 7.82 (d, 1H), 7.68 (d, 1H), 7.42 (m, 3H), 7.36 (d,1H),

7.25 (d, 1H), 7.20 (d, 1H), 6.70 (d, 1H), 6.43 (bs, 2H), 4.53 (s, 2H), 3.78 (s, 2H), 3.31 (m, 4H). MS (ion spray) m/z 519, 521, (M+H), Cl pattern.

EXAMPLE 127. 6-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]-1H-quinolin-2-one.

The title compound is prepared as described in EXAMPLE 101,using 6-(2-oxopiperazin-1-ylmethyl)-1H-quinolin-2-one, minor product from EXAMPLE 67, Part D, and 6-chlorobenzo[b]thiophene-2-sulfonyl chloride, EXAMPLE 1. The crude product is triturated in CH_2Cl_2 and filtered to provide the title compound as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 11.72 (bs, 1H), 8.33 (s, 1H), 8.18 (s, 1H), 8.07 (d,1H), 7.78 (d,1H), 7.58 (dd, 1H), 7.45 (s, 1H), 7.30 (dd, 1H), 7.18 (d, 1H), 6.46 (d, 1H), 4.52 (s, 2H), 3.86 (s, 2H), 3.43 (m, 2H), 3.31 (m, 2H). MS (ion spray) m/z 488, 490, (M+H), Cl pattern.

The following compounds are prepared using starting materials prepared as described in Examples 67, 68 and 73 and the appropriate carboxylic acid according to the method of Example 123.

Example #	Name	m/z (M+H)
128	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-3-ylmethyl-piperazin-2-one	478, 480 Cl pattern
129	1-(2-Amino-quinoxalin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	
130	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-one	478, 480 Cl pattern
131	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	478, 480 Cl pattern
132	1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	488, 490 Cl pattern
133	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-hydroxy-isoquinolin-6-ylmethyl)-piperazin-2-one	488, 490 Cl pattern
134	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-6-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
135	7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one	488, 490 Cl pattern
136	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-	506, 508

	isoquinolin-7-ylmethyl)-piperazin-2-one	Cl pattern
137	1-(7-Amino-thieno[2,3-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
138	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
139	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-quinolin-6-ylmethyl-piperazin-2-one	472, 474 Cl pattern
140	7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-1H-quinolin-2-one	488, 490 Cl pattern
141	1-(2-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
142	1-(4-Amino-thieno[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
143	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1,2,3,4-tetrahydro-isoquinolin-6-ylmethyl)-piperazin-2-one	475, 477 Cl pattern
144	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-isoquinolin-6-ylmethyl-piperazin-2-one	472, 474 Cl pattern
145	1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
146	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-6-ylmethyl)-piperazin-2-one	482, 484 Cl pattern
147	1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
148	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-7-ylmethyl)-piperazin-2-one	482, 484 Cl pattern
149	1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
150	1-(4-Amino-thieno[3,2-c]pyridin-3-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
151	(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid	536, 538 Cl pattern
152	(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid	536, 538 Cl pattern
153	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-	471, 473

	(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	Cl pattern
154	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	475, 477 Cl pattern
155	(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-piperazin-2-one	494, 496, 498, Cl_2 pattern
156	(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-piperazin-2-one	490, 492, 494, Cl_2 pattern
157	(S)-4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
158	1-(2-Amino-quinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	427, 429 Cl pattern

The following compounds are prepared from starting materials prepared as described in Example 67 and the appropriate aryl-methyl bromide or allyl-methyl bromide using a K_2CO_3-mediated alkylation reaction.

Example #	Name	m/z (M+H)
159	1-(2-Aminoquinolin-6-ylmethyl)-4-(4-methoxybenzyl)piperazin-2-one	377
160	1-(2-Aminoquinolin-6-ylmethyl)-4-6-chlorobenzo[b]thiophen-2-ylmethyl)piperazin-2-one	436, 438 Cl pattern
161	1-(2-Aminoquinolin-6-ylmethyl)-4-(5-methoxy-1H-benzoimidazol-2-ylmethyl)piperazin-2-one	417
162	1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)piperazin-2-one	469, 471 Cl pattern
163	1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	413, 415 Cl pattern
164	1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]piperazin-2-one	601, 603, 605 Br_2 pattern
165	3-[4-(2-Aminoquinolin-6-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one	431

166	1-(2-Aminoquinolin-6-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	430

The following compounds are prepared from starting materials prepared as described in Examples 66, 67, 68 and 73 and the appropriate aryl-methyl bromide or allyl-methyl bromide using a K_2CO_3-mediated alkylation reaction.

Example #	Name	m/z (M+H)
167	3-(4-Biphenyl-3-ylmethyl-3-oxo-piperazin-1-ylmethyl)-benzamidine	399
168	4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
169	1,4-Bis-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	427
170	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
171	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	444, 446 Cl pattern
172	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	420, 422 Cl pattern
173	1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	401
174	1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	426
175	1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	443
176	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	413, 415 Cl pattern
177	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-benzamidine	413, 415 Cl pattern
178	4-(4-Cyclohexylmethyl-2-oxo-piperazin-1-ylmethyl)-benzamidine	329
179	1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	437, 439 Cl pattern
180	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-	457, 459

	yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one	Cl pattern
181	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	468
182	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	454
183	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one	483
184	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one	453

EXAMPLE 185. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one.

The title compound is prepared as described in EXAMPLE 101, substituting 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, for 4-(2-oxopiperazin-1-ylmethyl)-benzamidine. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA). The appropriate collected fractions are lyopholized to afford the title compound as a white solid. MS (ion spray) m/z 488, 490, (M+H). ^1H NMR (d_6-DMSO, 300 MHz) δ 9.65 (s, 2H), 8.80 (s, 1H), 8.30 (m, 2H), 8.20 (s, 1H), 8.05 (d, 1H), 7.60 (m, 3H), 4.70 (s, 2H), 3.85 (s, 2H), 3.50-3.20 (m, 4H).

EXAMPLE 186. 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 3-chloro-benzylamide.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, (0.10g, 0.30mmol) is 9 mL of DMF is added 3-chlorobenzyl sulfamyl catechol (0.09g, 0.30mmol), EXAMPLE 4, Et_3N (0.08g, 0.75 mmol) and DMAP (0.001 g, 0.12 mmol). The solution is heated to 60°C. After 16 h, the solution is concentrated. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_20 (0.1%TFA) to 100% CH_3CN. The product fractions are lyophilized to give the title compound (0.077g, 0.17 mmol) as the TFA salt. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.82 (bs, 2H), 8.98 (s, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 7.60 (m, 2H), 7.35 (m, 4H), 4.69 (AB, 2H), 4.11 (m, 2H), 3.77 (s, 2H), 3.38 (m, 2H), 3.27 (m, 2H). MS (ion spray) m/z 461, 463, (M+H), Cl pattern.

The following compounds are prepared from the compound of Example 72 and the appropriate sulfonyl choride using the method of Example 101.

Example #	Name	m/z (M+H)
187	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	489, 491 Cl pattern
188	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one	520, 522 Cl pattern
189	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 4-chloro-benzylamide	460
190	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-isoxazol-3-yl-thiophene-2-sulfonyl)-piperazin-2-one	471
191	1-(4-Amino-quinazolin-7-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one	455
192	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(3-chloro-phenyl)-ethyl]-amide	474
193	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(4-chloro-phenyl)-ethyl]-amide	474
194	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-piperazin-2-one	472
195	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	464, 466 Cl pattern
196	4-(3-Amino-benzenesulfonyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	413

The following compounds are prepared from starting materials obtained as described in Examples 75-88 and the appropriate sulfonyl chloride using the method of Example 101.

Example #	Name	m/z (M+H)
197	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-ethyl-piperazin-2-one	492, 494 Cl pattern
198	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-ethyl-piperazin-2-one	516, 518 Cl pattern
199	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-ethyl-piperazin-2-one	548, 550 Cl pattern
200	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methyl-piperazin-2-one	534, 536 Cl pattern

201	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methyl-piperazin-2-one	502, 504 Cl pattern
202	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one	502, 504 Cl pattern
203	(+/-)-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-piperazin-2-yl]-acetic acid	546, 548 Cl pattern

The following compounds are prepared from starting materials obtained as described in Examples 72 and 73 and the appropriate sulfonyl chloride according to the method of Example 101 or the appropriate carboxylic acid according to the method of Example 123.

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Example #	Name	m/z (M+H)
204	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	470, 472 Cl pattern
205	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
206	1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	494, 496 Cl pattern
207	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-6-ylmethyl)-piperazin-2-one	489, 491 Cl pattern
208	1-(4-Amino-thieno[3,2-d]pyrimidin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	494, 496 Cl pattern
209	1-(4-Amino-quinazolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	488, 490 Cl pattern
210	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-7-ylmethyl)-piperazin-2-one	489, 491 Cl pattern
211	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one	478, 480 Br pattern
212	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	434, 436 Cl pattern

EXAMPLE 213. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-{4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-2-oxopiperazin-1-ylmethyl}pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

To a solution of 2-(2-oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (0.71 g, 2.1 mmol), EXAMPLE 69, in CH_3CN (7 mL) is added triethylamine (0.60 mL, 4.3 mmol) followed by 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride, EXAMPLE 3, (0.57 g, 2.1 mmol). The mixture is stirred overnight, then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound (1.2 g, 2.1 mmol) as a light yellow solid. The crude material can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.80 (s, 1H), 8.42 (d, 1H), 7.88 (d, 1H), 7.55 (d, 1H), 7.14 (d, 1H), 6.98 (d, 1H), 6.41 (s, 1H), 6.36 (d, 1H), 5.00 (s, 2H), 3.98 (s, 2H), 3.61 (m, 4H), 1.71 (s, 9H). Ion spray MS, $[M+H]^+$= 537, 539, Cl pattern.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

Trifluoroacetic acid (2.2 mL, 28.6 mmol) is added dropwise to a slurry of 2-[4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.32 g, 2.4 mmol) in CH_2Cl_2 (25 mL) at 0°C. After 1.5 hours, the ice bath is removed and the solution stirred at room temperature for 4 hours. The reaction mixture is diluted with methylene choride and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound as the free base. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are lyophilized to provide the title compound (1.29 g, 2.2 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 14.90 (bs, 1H), 12.81 (s, 2H), 9.12 (s, 1H), 8.41 (d, 1H), 7.89 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 6.95 (s, 1H), 4.80 (s, 2H), 3.98 (s, 2H), 3.48 (s, 4H). Ion spray MS, $[M+H]^+$= 437, 439, Cl pattern.

EXAMPLE 214. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.7 (s, 1H), 8.41 (d, 1H), 7.9-7.8 (m, 3H), 7.45 (d, 1H), 7.25 (d, 1H), 6.31 (s, 1H), 4.95 (s, 2H), 3.98 (s, 2H), 3.65 (m, 2H), 3.55 (m, 2H), 1.68 (s, 9H). Ion spray MS, $[M+H]^+$= 561, 563, Cl pattern.

B. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one trifluoroacetate.

^{1}H NMR (d6-DMSO, 300 MHz) δ 14.68 (bs, 1H), 12.6 (s, 1H), 9.1 (s, 1H), 8.36 (d, 1H), 8.29 (d, 1H), 8.17 (s, 1H), 8.05 (d, 1H), 7.82 (d, 1H), 7.56 (m, 2H), 6.83 (s, 1H), 4.1 (s, 2H), 3.84 (s, 2H), 3.38 (m, 4H). Ion spray MS, $[M+H]^+$= 461,463, Cl pattern.

EXAMPLE 215. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(5-oxy-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one (0.06 g, 0.13 mmol) is dissolved in anhydrous methylene chloride (20 ml), treated with m-chloroperbenzoic acid (0.03 g, mmol) and stirred at room temperature for 4 hours. The solution is diluted with methylene chloride, washed with $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (5-10 % MeOH/CH_2Cl_2) and converted to the TFA salt to provide the title compound (0.015 g, 0.032 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.14 (bs, 1H), 8.95 (d, 1H), 7.8- 7.87 (m, 3H), 7.57 (d, 1H), 7.48 (dd, 1H), 6.87 (s, 1H), 4.90 (s, 2H), 3.95 (s, 2H), 3.86 (s, 3H), 3.49 (s, 3H). EI MS, $[M^+]$ = 474, 476, Cl pattern.

EXAMPLE 216. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one (0.59 g, 1.28 mmol), EXAMPLE 214, is dissolved in anhydrous DMF (30 ml), cooled in an ice bath, treated with 60 % sodium hydride (0.061 g, 1.53 mmol) and stirred at room temperature for 30 minutes. The solution is treated with methyl iodide (83 mL, 1.33 mmol) and warmed to room temperature over 4 hours. The reaction is quenched with ammonium chloride solution, diluted with ethyl acetate and separated. The organic layer is washed with brine (3x), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (5-10 % MeOH/CH_2Cl_2) to provide the title compound (0.31 g, 0.65 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.55 (d, 1H), 7.99 (dd, 1H), 7.82 (m, 3H), 7.49 (dd, 1H), 7.43 (d, 1H), 6.55 (s, 1H), 4.75 (s, 2H), 3.96 (s, 2H), 3.52 (m, 4H), 3.86 (s, 3H), 3.49 (s, 3H). Ion Spray MS, $[M+H]^+$=477.

The following compounds are prepared from starting materials obtained as described in Example 69 and the appropriate sulfonyl chlorides according to the method of Example 101.

Example #	Name	m/z (M+H)

217	4-(3-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	460
218	4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.	462, 464 Cl pattern
219	4-(6-Bromobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	505
220	2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]-benzo[b]thiophene-6-carbonitrile	452
221	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	493
222	4-[2-(4-Chlorophenyl)ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	431
223	{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid	519, 521 Cl pattern
224	4-(5-Pyridin-4-ylthiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	454
225	{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid ethyl ester	547, 549 Cl pattern
226	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-methoxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one	519, 520
227	4-(6-Chlorothieno[3,2-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	462, 464
228	{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[2,3-c]pyridin-1-yl} acetic acid methyl ester	533, 535
229	2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]benzo[b]thiophene-5-carbonitrile	452
230	4-(5-Aminomethylbenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	456
231	2-{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl}acetamide	518, 520
232	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one	505
233	4-(6-Chloro-1H-benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	445, 447

234	4-(1H-Benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	411
235	4-(6-Aminomethyl-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	456
236	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	428
237	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one	428
238	4-[2-(5-Chloro-thiophen-2-yl)-ethanesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
239	4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453
240	4-[2-(5-Chloro-4-methoxy-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	467, 469
241	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	462, 464
242	4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	446
243	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one	460, 462 Cl pattern
244	4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one	462, 464 Cl pattern
245	{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[2,3-c]pyridin-1-yl}-acetic acid methyl ester	533, 535 Cl pattern
246	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one	461, 463 Cl pattern

EXAMPLE 247. 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)piperazin-2-one.

A. (2-Chloro-pyridin-4-yl)-carbamic acid tert-butyl ester.

NaHMDS (61.7 mL, 1.0M solution in THF) is rapidly added to a solution of 2-chloro-pyridin-ylamine (4.0 g, 30.9 mmol) amd BOC anhydride (6.74 g, 30.9 mmol) in THF (28 mL) at RT. The reaction mixture is cooled in an ice water bath (0°C) for 1h then stirred for 3 hr at RT. The gelatinous mixture is concentrated in vacuo and diluted with ethyl acetate and saturated NH_4Cl solution. The

organic layer is washed with 0.1N HCl, saturated $NaHCO_3$ and brine. The organic layer is then dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1% MeOH/CH_2Cl_2 to yield the title product (5.57 g, 24.4 mmol) as a yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, 1H), 7.48 (d, 1H), 7.12 (dd, 1H), 1.60 (s, 9H). EI MS $[M]^+$=228.

B. (2-Chloro-3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester.

tert-Butyllithium (36.3 mL, 1.7M in pentane) is added dropwise to a solution of (2-chloro-pyridin-4-yl)-carbamic acid tert-butyl ester (6.00 g, 26.2 mmol) in THF (46 mL) at -78 °C under Ar. The yellow/orange mixture is stirred for 2 h at -78°C then warmed to -40 °C for 1 h then cooled to -78°C before dropwise addition of I_2 (15.65 g, 61.7 mmol) in THF (49 mL). The reaction mixture is stirred for 1.5 h at -78°C then at -10°C for 30 minutes. The reaction is quenched with saturated NH_4Cl solution then diluted with CH_2Cl_2 and washed with saturated NH_4Cl, saturated sodium thiosulfate, water then brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-2% MeOH/CH_2Cl_2 to yield the title product (7.96 g, 22.5 mmol) as a bright yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, 1H), 8.02 (d, 1H), 7.32 (bs, 1H), 1.60 (s, 9H). EI MS $[M]^+$=354, 356, Cl pattern.

C. 4-(4-Chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Trifluoroacetic acid (10 mL) is added to a solution of 2-(4-benzyloxycarbonyl-2-oxo-piperazin-1-ylmtheyl)-4-chloro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (5.66 g, 11.3 mmol, prepared in the same manner as described previously) in CH_2Cl_2 (10 mL). The solution is stirred overnight then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH_2Cl_2 to yield the title product (3.81 g, 9.56 mmol) as a foamy yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.43 (bs, 1H), 8.08 (d, 1H), 7.38 (s, 5H), 7.18 (d, 1H), 6.51 (s, 1H), 5.15 (s, 2H), 4.58 (s, 2H), 4.20 (s, 2H), 3.71 (m, 2H), 3.50 (m, 2H). Ion spray $[M+H]^+$= 399, 401, Cl pattern.

D. 4-(1-Benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Powdered NaOH (0.96 g, 23.9 mmol) followed by nBu_4NHSO_4 (0.32 g, 0.96 mmol) and benzene sulfonyl chloride (1.8 mL, 14.1 mmol) is added to a solution of 4-(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (3.81 g, 9.56 mmol) in CH_2Cl_2 (32 mL) at RT. The resulting slurry is stirred for 3.5 h then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH_2Cl_2 to yield the title product (5.06 g, 9.38 mmol). ^1H

NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, 1H), 7.97 (d, 1H), 7.84 (d, 2H), 7.61 (d, 1H), 7.51 (m, 2H), 7.38 (s, 5H), 6.50 (s, 1H), 5.18 (s, 2H), 5.03 (s, 2H), 4.29 (s, 2H), 4.29 (s, 2H), 3.80 (m, 2H), 3.51 (m, 2H). Ion spray $[M+H]^+$= 539, 541, Cl pattern.

E. 1-(1-Benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

TMSI (2.7 mL, 19.0 mmol) is added to a solution of 4-(1-benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (5.06 g, 9.38 mmol) in CH_3CN (134 mL) at 0°C. The reaction mixture is warmed to RT and stirred for 5 hours. The reaction mixture is concentrated to dryness and the red residue is diluted with MeOH and concentrated to dryness (this is repeated twice). The mixture is diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH_2Cl_2 to yield the title product (0.70 g, 1.74 mmol) and unreacted starting material (3.58 g, 6.64 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 7.93 (d, 1H), 7.85 (d, 2H), 7.60 (d, 1H), 7.51 (m, 2H), 6.50 (s, 1H), 5.01 (s, 2H), 3.45 (m, 2H), 3.18 (m, 2H). Ion spray $[M+H]^+$= 405, 407, Cl pattern.

F. 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one.

Anhydrous ammonium acetate (0.56 g, 7.2 mmol), phenol (0.45 g, 4.8 mmol) and 1-(1-benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one (0.31 g, 0.48 mmol, prepared as described previously) are heated to 100°C for 3.5 days. The mixture is cooled to RT then the crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN then the appropriate product fractions are lyophilized to provide the title compound (1.29 g, 2.2 mmol) as a white solid (22.4 mg, 0.038 mmol). ^1H NMR (DMSO-d_6, 300 MHz) δ 12.40 (bs, 1H), 12.00 (bs, 1H), 8.31 (d, 1H), 8.20 (s, 1H), 8.06 (d, 1H), 8.02 (bs, 2H), 7.57 (dd, 1H), 7.48 (m, 1H), 6.89 (d, 1H), 6.81 (s, 1H), 4.60 (s, 2H), 3.81 (s, 2H), 3.40 (m, 4H). LR-FAB MS, $[M+H]^+$=476, 478.

EXAMPLE 248. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

Sodium borohydride (0.005 g, 0.13 mmol) is added to a solution of 2-{4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-methoxycarbonyl-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-

carboxylic acid tert-butyl ester (0.04 g, 0.07 mmol), (prepared from 2-(2-(±)-methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester, EXAMPLE 71, and 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride, EXAMPLE 3, using the procedure described in EXAMPLE 214, Part A) in MeOH (3 mL) at RT. The reaction mixture is stirred for 6 h then quenched with water and concentrated in vacuo. The crude product (0.04 g) is taken onto the next step without further purification.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Trifluoroacetic acid (1.8 mL) is added to a solution of 2-{4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.04 g) in CH_2Cl_2 (4.2 mL) at RT. The reaction mixture is stirred for 4 h then concentrated in vacuo. The title compound is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and lyophilizing the appropriate product fractions. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.10 (s, 1H), 8.46 (d, 1H), 7.82 (d, 1H),7.50 (d, 1H) 7.43 (d, 1H), 7.14 (d, 1H), 7.01 (d, 1H), 6.94 (s, 1H), 5.12 (bs, 1H), 4.80 (AB, 2H), 3.98 (d, 2H0, 3.90 (m, 1H), 3.40-3.50 (m, 4H). APCI MS, $[M+H]^+$=467, 469.

The following compounds are prepared from starting materials obtained using the methods of Examples 69, 70 and 71 and the appropriate sulfonyl chorides according to the method of Example 101.

Example #	Name	m/z
249	1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	519, 521 Cl pattern
250	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	495, 497 Cl pattern
251	1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	505, 507 Cl pattern
252	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493 Cl pattern

The following enantiomerically pure compounds are obtained by chiral resolution on a CHIRACEL OD prep column.

Example #	Name	%ee	m/z
253	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid methyl ester	99% (-)	495, 497 Cl pattern
254	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester	95% (+)	495, 497 Cl pattern

EXAMPLE 255. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 6-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Trifluoroacetic acid (0.25 mL) is added to a solution of 2-{2-(R)-(tert-butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.025 g, 0.037 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture is stirred for 2 h then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product (0.019 g, 0.033 mmol) is used in the subsequent step without further purification.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Glacial acetic acid (3 mL, 0.046 mmol) and tetrabutylammonium fluoride (92 mL, 0.092 mmol) is added to a solution of 6-(R)-(tert-butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one (0.019 g, 0.033 mmol) in THF (0.5 mL). The resulting solution is stirred for 4 h then concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are lyophilized to provide the title compound (0.009 g, 0.016 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 14.50 (bs, 1H), 12.60 (bs, 1H), 9.18 (s, 1H), 8.38 (d, 1H), 7.89 (d, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.21 (d, 1H), 7.08 (d, 1H), 6.90 (s, 1H), 5.03 (s, 2H), 4.63 (d, 2H), 3.70-3.90 (AB, 2H), 3.75 (m, 1H), 3.21 (m, 2H). Ion spray MS, $[M+H]^+$=467, 469, Cl pattern.

The following compounds are prepared from starting materials obtained as described in Examples 69, 70 and 71 and the appropriate sulfonyl chloride according to the method of Example 101.

Example #	Name	m/z
256	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493
257	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	495, 497 Cl pattern
258	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	519, 521 Cl pattern
259	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	481, 483 Cl pattern
260	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	505, 507 Cl pattern
261	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493 Cl pattern
262	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	467, 469 Cl pattern
263	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid amide	504, 506 Cl pattern
264	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483
265	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507
266	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	537, 539
267	4-[2-(4-Chloro-phenyl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	475, 477

EXAMPLE 268. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-ylmethyl)piperazin-2-one.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride (1.84 g, 5.73 mmol), EXAMPLE 72, in DMF (20 mL) is added 2-bromomethyl-6-chloro-benzo[b]thiophene, EXAMPLE 5, (1.5 g, 5.73 mmol) and K_2CO_3 (4.0 g, 28.7 mmol). The solution is stirred for 16 hours. After this time, the solution is diluted with water. The solution is acidified with trifluoroacetic acid. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 50% CH_3CN/H_2O (0.1% TFA). The appropriate collected fractions are lyopholized to afford the title compound as a white solid. ^1H NMR (d^6-DMSO, 300MHz) δ 9.78 (bs, 3H), 8.82 (s, 1H), 8.34 (d, 1H), 8.07 (s, 1H), 7.81 (d, 1H), 7.63 (d, 1H), 7.51 (s, 1H), 7.32 (m, 2H), 4.71 (s, 2H), 3.95 (s, 2H), 3.28 (m, 4H), 2.80 (m, 2H).

EXAMPLE 269. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one.

A mixture of 1-(4-aminoquinazolin-7-ylmethyl)piperazin-2-one (50 mg, 0.15 mmol), EXAMPLE 72, 6-chloro-2-chloromethylbenzimidazole (30.5 mg, 0.15 mmol) and potassium carbonate (83 mg, 0.6 mmol) in 2 mL of DMF is stirred at ambient temperature overnight. The mixture is purified on reverse phase HPLC (CH_3CN/H_2O/TFA) to give the trifluoroacetic acid salt of 1-(4-aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one (25 mg) as a solid. ^1H NMR (CD_3OD, 300 MHz) δ 8.69 (s, 1H), 8.33 (d, 1H), 7.79 (s, 1H), 7.75-7.69 (m, 3H), 7.57-7.54 (m, 1H), 4.86 (s, 2H), 4.22 (s, 2H), 3.31 (m, 4H), 2.99 (m, 2H). MS m/z 422 (M+H).

EXAMPLE 270. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (76 mg, 0.23 mmol), EXAMPLE 72, in 2 mLof DMF is added potassium carbonate (127 mg, 0.92 mmol) followed by 6-chloro-2-chloromethyl-benzothiazole (prepared according to the procedure of B.L.Mylari, Synthesis Comm. 1989, 16, 2921) (50 mg, 0.23 mmol). The resulting mixture is stirred overnight at room temperature. The undissolved potassium carbonate is removed by filtration and the mother liquor is purified by reverse phase HPLC (10-100% CH_3CN/H_2O). The desired is product is obtained as a white solid with a melting point of 123-126°C. $C_{21}H_{19}ClN_6OS$ MS m/z: 439, 441. Anal. cald. for $C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60. Found C, 44.15; H, 3.19; N, 11.79.

EXAMPLE 271. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one.

The desired product (10.0 mg, 7 %) is isolated as a white solid. $C_{21}H_{19}ClN_6O_2$ MS m/z: 423, 425.

EXAMPLE 272. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one.

The desired product (19.0 mg, 22%) is obtained as a white solid. $C_{21}H_{19}ClN_6OS$ MS m/z: 438,440. Anal. cald. for $C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60. Found C, 43.35; H, 3.26; N, 12.65.

EXAMPLE 273. 3-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxopiperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one.

The title compound is prepared as described in EXAMPLE 268, substituting 3-bromomethyl-7-chloro-1H-quinoline-2-one, EXAMPLE 8, for 2-bromomethyl-6-chlorobenzo[b]thiophene. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 50% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyopholized to afford the title compound as a white solid. ^1H NMR (d^6-DMSO, 300MHz) δ 12.18 (bs, 1H), 9.75 (m, 1H), 8.86 (s, 1H), 8.40 (m, 1H), 8.11 (d, 1H), 8.10 (s, 1H), 7.78 (m, 1H), 7.69 (m, 2H), 7.37 (m, 1H), 4.80 (s, 2H), 4.10 (m, 2H), 3.47 (m, 4H), 3.30 (m, 2H). MS (ion spray) m/z 449, (M+H).

EXAMPLE 274. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one.

A. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1-(toluene-4-sulfonyl)-1H-indol-6-ylmethyl)-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 268 using 6-bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole, EXAMPLE 16, in place of 2-bromomethyl-6-chloro-benzo[b]thiophene. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.75 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.64 (m, 2H), 7.60 (m, 2H), 7.40 (d, 1H), 7.23 (m, 1H), 7.19 (m, 2H), 6.99 (d, 2H), 5.09 (s, 2H), 4.78 (s, 2H), 4.10 (m, 2H), 3.40 (m, 4H), 2.49 (s, 3H).

B. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-(3-chloro-1-(toluene-4-sulfonyl)-1H-indol-6-ylmethyl)-piperazin-2-one ditrifluoroacetate (31 mg, 0.04 mmol) in 2 mL of MeOH is added 0.3 mL of 1N NaOH solution. The solution is heated at 100°C for 3 hours. After this time, the solution is diluted with water/acetonitrile and neutralized with trifluoroacetic acid. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and

the appropriate product fractions are combined and lyopholized to give the title compound (21 mg, 0.03 mmol) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.71 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.63 (m, 3H), 7.53 (d, 1H), 7.50 (s, 1H), 7.20 (d, 1H), 4.78 (s, 2H), 4.30-3.10 (m, 8H). ESI MS, $[M+H]^+$=421, 423 (Cl pattern).

EXAMPLE 275. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one bishydrochloride (100 mg, 0.31 mmol), EXAMPLE 72, in 3 mL of DMF is added 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene (73 mg, 0.31 mmol), prepared as described in EXAMPLE 17., and K_2CO_3 (0.21 g, 1.54 mmol). The solution is stirred at room temperature for 16 hours. After this time, the solution is diluted with water/acetonitrile and neutralized with trifluoroacetic acid. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (80 mg, 0.12 mmol) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.76 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.70 (s, 1H), 7.62 (dd, 1H), 7.10 (m, 2H), 6.90 (d, 1H), 6.05 (dt, 1H), 4.80 (s, 2H), 3.77 (m, 4H), 3.50 (m, 2H), 3.37 (m, 2H). ESI MS, $[M+H]^+$=414,416 (Cl pattern). Anal. ($C_{20}H_{20}ClN_5OS \cdot 2.0TFA \cdot 1.1H_2O$) C, H, N.

EXAMPLE 276. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-(E)-enyl]-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.70 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.68 (s, 1H), 7.61 (d, 1H), 7.10 (m, 2H), 5.88 (t, 1H), 4.79 (s, 2H), 3.75 (m, 4H), 3.49 (m, 2H), 3.29 (m, 2H), 2.09 (s, 3H). EI MS, $[M+H]^+$=427, 429 (Cl pattern).

EXAMPLE 277. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-2-methyl-(E)-allyl]-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.80 (bs, 2H), 8.85 (s, 1H), 8.41 (d, 1H), 7.70 (s, 1H), 7.68 (d, 1H), 7.06 (d, 1H), 7.05 (d, 1H), 6.70 (bs, 1H), 4.80 (s, 2H), 4.30 (bs, 2H), 3.45 (m, 4H), 3.10 (m, 2H), 1.99 (s, 3H). ESI MS, $[M+H]^+$=428, 430 (Cl pattern).

EXAMPLE 278. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-furan-2-yl)-(E)-allyl]-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (50 mg, 0.20 mmol), EXAMPLE 72.in 3 mL of acetonitrile is added 3-(4-bromo-furan-2-yl)-(E)-propenal (43 mg, 0.22 mmol), prepared as described in EXAMPLE 18, 2 drops of HOAc and sodium triacetoxyborohydride (62

mg, 0.29 mmol). The solution is stirred at room temperature for 16 hours. After this time, the solution is diluted with water/acetonitrile. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (48 mg, 0.07 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.75 (bs, 2H), 8.85 (s, 1H), 8.60 (d, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H), 6.80 (s, 1H), 6.65 (d, 1H), 6.19 (dt, 1H), 4.80 (s, 2H), 3.70 (m, 4H), 3.50 (m, 2H), 3.28 (m, 2H). ESI MS, $[M+H]^+$=441,443 (Br pattern).

EXAMPLE 279. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-methoxy-pyridin-3-yl)-(E)-allyl]-piperazin-2-one.

Nitrogen (g) is bubbled through a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (100 mg, 0.39 mmol), EXAMPLE 72, in 2 mL of CH_3CN. After 5 min, acetic acid 3-(6-methoxy-pyridin-3-yl)-(E)-allyl ester (75 mg, 0.36 mmol, prepared as described in EXAMPLE 19 in 2 mL of CH_3CN, palladium(II) acetate (catalytic amount), triphenylphosphine (catalytic amount), 2 mL of H_2O and 0.5 mL of triethylamine are added to the solution. The mixture is heated at 80°C for 1 hours. At this time, the mixture is cooled, filtered and concentrated in vacuo. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (44 mg, 0.07 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.86 (s, 1H), 9.79 (s, 1H), 8.83 (s, 1H), 8.40 (d, 1H), 8.25 (s, 1H), 7.95 (d, 1H), 7.75 (s, 1H), 7.63 (d, 1H), 6.86 (d, 1H), 6.82 (d, 1H), 6.32 (dt, 1H), 4.78 (s, 2H), 3.98 (s, 2H), 3.93 (m, 2H), 3.85 (s, 3H), 3.53 (m, 4H). ESI MS, $[M+H]^+$=405.

EXAMPLE 280. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-4-oxy-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one ditrifluoroacetate (0.60 g, 0.94 mmol), prepared as described in EXAMPLE 275, in 25 mL of CH_2Cl_2 is added m-chloroperoxybenzoic acid (0.30 g, 0.96 mmol, 55% pure grade). The mixture is stirred at room temperature for 3 h and then concentrated in vacuo. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (0.5 mg, 0.76 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.68 (bs, 2H), 8.79 (s, 1H), 8.39 (d, 1H), 7.68 (s, 1H), 7.60 (d, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 7.06 (d, 1H), 6.17 (dt, 1H), 4.84 (s, 2H), 4.53 (m, 2H), 4.50 (AB, 2H), 4.04 (m, 2H), 3.78 (m, 1H), 3.60 (m, 1H). ESI MS, $[M+H]^+$=430,432 (Cl pattern). Anal. ($C_{20}H_{20}ClN_5O_2S \cdot 2.0TFA \cdot 1.4H_2O$) C, H, N.

EXAMPLE 281. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-prop-2-ynyl]-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 275 using 2-(3-bromo-prop-1-ynyl)-5-chloro-thiophene (prepared as described in EXAMPLE 20) in place of 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.63 (d, 1H), 7.58 (s, 1H), 7.25 (d, 1H), 7.13 (d, 1H), 4.74 (s, 2H), 3.74 (s, 2H), 3.32 (m, 4H), 2.85 (m, 2H). ESI MS, $[M+H]^+$=412, 414 (Cl pattern).

EXAMPLE 282. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one

The title compound is prepared as described in EXAMPLE 278 using 3-(5-chloro-thiophen-2-yl)-propionaldehyde (EXAMPLE 28, Part A) in place of 3-(4-bromo-furan-2-yl)-(E)-propenal. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.39 (d, 1H), 7.71 (s, 1H), 7.60 (d, 1H), 6.95 (d, 1H), 6.77 (d, 1H), 4.78 (s, 2H), 3.88 (m, 2H), 3.50 (m, 2H), 3.42 (m, 2H), 3.05 (m, 2H), 2.80 (t, 2H), 1.96 (m, 2H). ESI MS, $[M+H]^+$=416,418 (Cl pattern).

EXAMPLE 283. 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one.

A. 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one.

Propargyl bromide (0.29 g, 1.95 mmol) is added to a solution containing 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (0.5 g, 1.95 mmol), EXAMPLE 72, and K_2CO_3 (0.40 g, 2.93 mmol) in DMSO (10 mL) at ambient temperature. After 15 min, the reaction mixture is partitioned between aqueous $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The aqueous phase is subsequently saturated with NaCl and extracted three times with $CHCl_3$ (50 mL). The combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 390 mg (68%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (m, 1H), 3.13-3.37 (m, 6H), 4.07 (app q, J = 5.2 Hz, 1H), 4.63 (s, 2H), 7.28 (dd, J = 8.4, 1.4 Hz, 1H), 7.42 (s, 1H), 7.72 (br s, 2H), 8.14 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H) ppm; MS (ISP loop): m/z 296 (M+H).

EXAMPLE 284. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-2-yl-prop-2-ynyl)-piperazin-2-one.

A solution containing 1-(4-amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one (50 mg, 0.17 mmol), EXAMPLE 283, 2-bromobiphenyl (44 mg, 0.19 mmol), Et_3N (69 mg, 0.68 mmol), $(Ph_3P)_4PdCl_2$ (6 mg, 0.008 mmol), and CuI (1 mg, 0.005 mmol) in anhydrous DMF (2 mL) is warmed at 80°C for 1 hours. The reaction mixture is cooled to 50 °C and the solvent is removed over 16 h under a stream of nitrogen. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to afford a colorless gum which is triturated with ethyl alcohol to provide 4 mg (5%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.03 (s, 2H), 3.14 (m, 2H), 3.31 (m, 2H), 3.50 (s, 2H), 7.21-7.55 (m, 11H), 7.76 (br s, 2H), 8.18 (d, J = 8.6 Hz, 1H), 8.36 (s, 1H) ppm; MS (ion spray): m/z 448 (M+H).

EXAMPLE 285. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. (3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-prop-1-ynyl}-pyridin-4-yl)-carbamic acid tert-butyl ester.

A solution containing 1-(4-amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one (100 mg, 0.34 mmol), EXAMPLE 283, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester, EXAMPLE 69, Part B, (108 mg, 0.34 mmol), Et_3N (140 mg, 1.36 mmol), $(Ph_3P)_4PdCl_2$ (12 mg, 0.017 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 59 mg (36%) of SC34 as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.84 (m, 2H), 3.35 (m, 2H), 3.44 (s, 2H), 3.71 (s, 2H), 4.75 (s, 2H), 6.19 (br s, 2H), 7.24 (d, J = 5.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 8.37 (s, 1H), 8.49 (s, 1H), 8.58 (s, 1H) ppm; MS (ISP loop): m/z 488 (M+H).

B. 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (37 mg, 0.24 mmol) is added to a suspension containing (3-{3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-prop-1-ynyl}-pyridin-4-yl)-carbamic acid tert-butyl ester (59 mg, 0.12 mmol) in anhydrous CH_3CN (5 mL) and the mixture is warmed to 50 °C. Dimethylformamide (1 mL) is added to solubilize and the homogeneous solution is maintained for 5 h at 50°C. The reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are

separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 50 mg of the product as a crude solid which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 9H), 2.78 (m, 2H), 3.30 (m, 2H), 3.37 (s, 2H), 3.95 (s, 2H), 4.74 (s, 2H), 6.24 (br s, 2H), 6.63 (s, 1H), 7.40 (dd, J = 8.5, 1.6 Hz, 1H), 7.64 (s, 1H), 7.81 (d, J = 5.8 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 8.58 (s, 1H), 8.77 (s, 1H) ppm.

C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (50 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 34 mg (73%, two steps) of the title compound as a white, lyophilized solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (s, 3H), 3.23 (s, 2H), 3.31 (m, 2H), 3.89 (s, 2H), 4.00 (br s, 3H), 4.71 (s, 2H), 6.94 (s, 1H), 7.60 (m, 2H), 7.84 (d, J = 6.5 Hz, 1H), 8.36 (m, 2H), 8.81 (s, 1H), 9.18 (s, 1H), 9.73 (br s, 2H), 12.87 (s, 1H) ppm; MS (ion spray): m/z 388 (M+H).

The following compounds are prepared from the compound of Example 72 using the procedures described above.

Example #	Name	m/z (M+H)
286	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-piperazin-2-one	418, 420 Cl pattern
287	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-indol-2-ylmethyl)-piperazin-2-one	435, 437 Cl pattern
288	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	414, 416 Cl pattern
289	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-piperazin-2-one	464, 466 Cl pattern
290	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-4-methyl-thiophen-2-yl)-allyl]-piperazin-2-one	428, 430 Cl pattern
291	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-ylmethyl)-piperazin-2-one	422, 424 Cl pattern

292	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-5-ylmethyl)-piperazin-2-one	421, 423 Cl pattern
293	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	421, 423 Cl pattern
294	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,7-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one	455, 457 Cl pattern
295	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	421, 423 Cl pattern
296	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-p-tolyl-prop-2-ynyl)-piperazin-2-one	386
297	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-m-tolyl-prop-2-ynyl)-piperazin-2-one	386
298	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406, 408 Cl pattern
299	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406, 408 Cl pattern
300	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406
301	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-4-yl-prop-2-ynyl)-piperazin-2-one	448
302	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4,5-dibromo-thiophen-2-yl)-allyl]-piperazin-2-one	536, 538, 540 Br_2 pattern
303	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-3-yl-prop-2-ynyl)-piperazin-2-one	448
304	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-thiophen-3-yl)-prop-2-ynyl]-piperazin-2-one	446, 448 Cl pattern
305	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-propyl]-piperazin-2-one	410, 412 Cl pattern
306	1,4-Bis-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	415
307	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one	388
308	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-nitro-thiophen-2-yl)-allyl]-piperazin-2-one	425
309	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-pyridin-3-	409, 411

	yl)-allyl]-piperazin-2-one	Cl pattern
310	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	388
311	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-allyl]-piperazin-2-one	414, 416 Cl pattern
312	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-allyl]-piperazin-2-one	442, 444 Br pattern
313	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-methyl-thiophen-2-yl)-penta-2,4-dienyl]-piperazin-2-one	420
314	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-5-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
315	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methyl-thiophen-2-yl)-allyl]-piperazin-2-one	394
316	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methoxy-thiophen-2-yl)-allyl]-piperazin-2-one	410
317	4-(1-Amino-7-chloro-isoquinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	448, 450 Cl pattern
318	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-acetamide	431
319	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one	433, 435 Cl pattern
320	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenyl)-2-(S)-hydroxy-ethyl]-piperazin-2-one	412, 414 Cl pattern
321	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one	428, 430 Cl pattern
322	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-methylene-1,1-dioxo-2,3-dihydro-1H-11 6-benzo[b]thiophen-3-yl)-piperazin-2-one	470
323	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-nitro-phenyl)-allyl]-piperazin-2-one	419
324	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-6-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
325	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(4-chloro-phenyl)-acetamide	425, 427 Cl pattern
326	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-	437, 439

	pyrrolidin-3-yl]-piperazin-2-one	Cl pattern
327	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethyl]-piperazin-2-one	402, 404 Cl patten
328	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propyl]-piperazin-2-one	410, 412 Cl pattern
329	2-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chlorophenyl)-acrylic acid	452, 454 Cl pattern
330	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-1-hydroxy-isoquinolin-3-ylmethyl)-piperazin-2-one	449, 451 Cl pattern
331	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	432, 434 Cl pattern
332	1-(4-Amino-quinazolin-7-ylmethyl)-4-isoquinolin-3-ylmethyl-piperazin-2-one	399
333	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(3-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one	437, 439 Cl pattern
334	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1,7-dichloro-isoquinolin-3-ylmethyl)-piperazin-2-one	467, 469 Cl pattern
335	4-(2-Amino-7-chloro-quinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	448, 450 Cl pattern
336	1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one.	438, 440 Cl pattern
337	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one	428, 430 Cl pattern
338	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(6-chloro-benzo[b]thiophen-2-yl)-ethyl]-piperazin-2-one	452, 454 Cl pattern
339	1-(4-Aminoquinazolin-7-ylmethyl)-4-[2-(4-chloro-phenoxy)-ethyl]-piperazine-2-one	412, 414 Cl pattern
340	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-4H-benzo[1,4]thiazin-3-one	469, 471 Cl pattern
341	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,7-dichloro-quinolin-3-ylmethyl)-piperazin-2-on	467, 469 Cl_2 pattern
342	2-[[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-(4-chloro-phenyl)-methyl]-acrylic acid ethyl ester	480, 482 Cl pattern
343	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-	480, 482

	ylmethyl]-3-(4-chloro-phenyl)-acrylic acid ethyl ester	Cl pattern
344	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazin-2-one	408, 410 Cl pattern
345	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazin-2-one	408, 410 Cl pattern
346	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-allyl]-piperazin-2-one	458, 460 Br pattern
347	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-allyl]-piperazin-2-one	458, 460 Br pattern
348	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one	433
349	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinoxalin-2-one	450, 452 Cl pattern
350	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	436, 438 Cl pattern
351	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-3H-quinazolin-4-one	492, 494 Cl pattern
352	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-thiophen-2-yl-propyl)-piperazin-2-one	382
353	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-quinolin-3-ylmethyl)-piperazin-2-one	432, 434 Cl pattern
354	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5,7-dichloro-1H-quinolin-2-one	483, 485 Cl pattern
355	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6,7-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	472, 474 Cl_2 pattern
356	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-1H-quinolin-2-one	449, 451 Cl pattern
357	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-[2,3']bithiophenyl-5'-ylmethyl)-piperazin-2-one	470, 472 Cl pattern
358	4-(6-Amino-benzo[b]thiophen-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	419
359	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one	433, 435 Cl pattern
360	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-1H-	466, 468

	benzoimidazol-2-ylmethyl)-piperazin-2-one	Br pattern
361	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-nitro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	449
362	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	464, 466
363	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	468, 470 Cl pattern
364	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinolin-2-one	449, 451 Cl pattern
3653	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-trifluoromethyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	456
366	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	450
367	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
368	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3,3'-dimethyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	498, 500 Cl pattern
369	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-2-one	602, 604, 606 Br_2 pattern
370	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
371	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
372	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
373	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	484, 486 Cl pattern
374	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	388
375	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-bromo-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	514, 516 Br pattern
376	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-oxazol-2-ylmethyl]-piperazin-2-one	473
377	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-	472, 474

	benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	Cl pattern
378	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4,5-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	472, 474 Cl pattern
379	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one	423, 425 Cl pattern
380	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
381	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
382	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	484, 486 Cl pattern
383	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
384	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	456
385	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-benzooxazol-2-yl-benzyl)-piperazin-2-one	464
386	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	464, 466 Cl pattern
387	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	402
388	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2,2']bithiophenyl-5-ylmethyl-piperazin-2-one	435
389	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	422
390	1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-fluoro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one.	422
391	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(1-methyl-5-trifluoro-methyl-1H-pyrazol-3-yl)-thiophen-2-ylmethyl]-piperazin-2-one	501
392	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)-piperazin-2-one	438
393	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	452, 454 Cl pattern
394	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methyl-	452, 454

	benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	Cl pattern
395	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophen-2-ylmethyl] piperazin-2-one	502
396	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-nitro-phenyl)-furan-2-ylmethyl]-piperazin-2-one	459
397	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-6-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
398	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-methoxy-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	460
399	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-hydroxy-2-pyridin-2-yl-pyrimidin-5-ylmethyl)-piperazin-2-one	443
400	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-fluoro-phenoxy)-benzyl]-piperazin-2-one	458
401	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one	465, 467 Cl pattern
402	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	482, 484 Br pattern
403	1-(4-Amino-quinazolin-7-ylmethyl)-4-benzo[b]thiophen-2-ylmethyl-piperazin-2-one	404
404	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	470, 472 Cl pattern
405	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-bis-trifluoromethyl-benzyl)-piperazin-2-one	488
406	1-(4-Amino-quinazolin-7-ylmethyl)-4-biphenyl-4-ylmethyl-piperazin-2-one	423 (M+)
407	1-(4-Amino-quinazolin-7-ylmethyl)-4-naphthalen-2-ylmethyl-piperazin-2-one	397 (M+)
408	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-3-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
409	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-piperazin-2-one	438, 440 (M+), Cl pattern

EXAMPLE 410. 1-(4-Aminoquinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, in place of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.40 (dd, 1H), 7.68 (d, 1H), 7.65 (s, 1H), 7.58 (d, 2H), 7.15 (d, 2H), 4.80 (s, 2H), 4.33, 4.15 (m, 2H, rotamers), 3.70 (m, 2H), 3.49 (m, 2H). ESI MS, $[M+H]^+$=456, 458 (Br pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example #	Name	m/z [M+H]
411	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-thiophene-2-carbonyl)-piperazin-2-one	402, 404 Cl pattern
412	4-[3-(3-Amino-4-chloro-phenyl)-(E)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	437, 439 Cl pattern
413	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-piperazin-2-one	435, 437 Cl pattern
414	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]piperazin-2-one	432, 434 Cl pattern
415	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	472, 474 Br pattern
416	5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-amide	459, 461 Cl pattern
417	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	428, 430 Cl pattern
418	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-piperazin-2-one	435, 437 Cl pattern
419	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	478, 480 Cl pattern
420	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	472, 474 Br pattern
421	5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-methyl-2-oxo-ethyl}-amide	473, 475 Cl pattern

422	5-Chloro-thiophene-2-carboxylic acid {3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-amide	473, 475 Cl pattern
423	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one	426, 428 Cl pattern
424	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-piperazin-2-one	440, 442 Cl pattern
425	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-piperazin-2-one	484, 486 Cl pattern
426	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-piperazin-2-one	430, 432 Cl pattern
427	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one	422, 424 Cl pattern
428	N-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-(5-chloro-thiophen-2-ylmethyl)-2-oxo-ethyl]-benzamide	428, 430 Cl pattern
429	N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-benzamide	549, 550 Cl pattern
430	N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-acetamide	485, 487 Cl pattern
431	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one	422, 424 Cl pattern
432	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yl)-acetyl]-piperazin-2-one	415, 417 Cl pattern
433	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one	451, 453 Cl pattern
434	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-6-chloro-4H-benzo[1,4]thiazin-3-one	483, 485 Cl pattern
435	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-benzo[b]thiophen-2-yl)-acetyl]-piperazin-2-one	466, 468 Cl pattern

EXAMPLE 436. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid 4-chloro-benzylamide.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (25 mg, 0.097 mmol), EXAMPLE 72, in 1 mL of DMF is added 4-chloro-benzyl isocyanate (22 mg, 0.13 mmol, prepared as described in EXAMPLE 37). After stirring 1 h at room temperature, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80%

CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (36 mg, 0.067 mmol) as a white solid. ^1H NMR (d6-DMSO, 300 MHz) δ 9.76 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.64 (d, 1H), 7.60 (s, 1H), 7.34 (d, 2H), 7.31 (m, 1H), 7.26 (d, 2H), 4.75 (s, 2H), 4.22 (d, 2H), 4.08 (s, 2H), 3.60 (m, 2H), 3.35 (m, 2H). ESI MS, $[M+H]^+$=425,427 (Cl pattern).

EXAMPLE 437. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-ylmethyl)amide.

To a solution of (5-chloro-thiophen-2-yl)-acetic acid (0.18 g, 1.04 mmol), prepared as described in EXAMPLE 27 in 6 mL of dry CH_2Cl_2 is added Et_3N (0.15 mL g, 1.04 mmol) and diphenylphosphoryl azide (0.24 mL, 1.04 mmol). The mixture is stirred at room temperature for 2.5 h, then heated at 50°C for 2 hours. To the solution is added 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (0.10 g, 0.41 mmol), EXAMPLE 72, and Et_3N (0.15 mL g, 1.04 mmol) and the mixture is heated at 50°C for 2 h, then stirred at room temperature for 16 hours. The resulting mixture is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (10 mg, 0.02 mmol) as a white solid. ^1H NMR (d6-DMSO, 300 MHz) δ 9.69 (bs, 2H), 8.80 (s, 1H), 8.48 (d, 1H), 7.61 (d, 1H), 7.60 (s, 1H), 7.41 (t, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 4.77 (d, 2H), 4.30 (d, 2H), 4.10 (s, 2H), 3.61 (m, 2H), 3.38 (m, 2H). ESI MS, $[M+H]^+$=431,433 (Cl pattern).

EXAMPLE 438. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide.

A mixture of 5-chloro-thiophene-2-carbonyl azide (55 mg, 0.29 mmol, prepared as described in EXAMPLE 38) and 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (50 mg, 0.20 mmol), EXAMPLE 72, in 3 mL of dry toluene is heated at 105°C for 1 hours. The resulting mixture is concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (35 mg, 0.02 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 10.04 (s, 1H), 9.71 (bs, 2H), 8.81 (s, 1H), 8.38 (dd, 1H), 7.64 (d, 1H), 7.61 (s, 1H), 6.77 (d, 1H), 6.42 (d, 1H), 4.76 (s, 2H), 4.21 (s, 2H), 3.73 (m, 2H), 3.40 (m, 2H). ESI MS, $[M+H]^+$=417,419 (Cl pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example #	Name	m/z [M+H]
439	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	417, 419 Cl pattern
440	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide	461, 463 Br pattern
441	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3-amino-4-chloro-phenyl)-amide	426, 428 Cl pattern
442	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	455, 457 Br pattern
443	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	411, 413 Cl pattern
444	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide	407
445	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	445, 447 Cl_2 pattern

EXAMPLE 446. 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester.

To a solution of 5-chloro-2-thiophene-methanol (0.10 g, 0.67 mmol, prepared by $NaBH_4$ reduction of 5-chloro-2-thiophene-carboxaldehyde) in 6 mL of CH_2Cl_2 is added 1,1'-carbonyldiimidazole (0.11 g, 0.67 mmol). The mixture is stirred at room temperature for 3 hours. Then 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (0.17 g, 0.67 mmol, EXAMPLE 72) and a catalytic amount of DMAP is added to the solution and the resulting mixture is heated at 35°C for 18 hours. The mixture is dissolved in water/MeOH and the crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN. The appropriate fractions are combined and lyopholized to provide the title compound as a white solid. ESI MS, $[M+H]^+$=432,434 (Cl pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example #	Name	m/z [M+H]
447	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-carboxylic acid 6-chloro-benzooxazol -2-ylmethyl ester	467, 469 Cl pattern
448	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic	481, 483

	acid 1-(3-chloro-phenyl)-pyrrolidin-3-yl ester	Cl pattern

EXAMPLE 449. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one.

To a solution of 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80, (0.06g, 0.2mmol) in 2 mL of DMF is added 3-bromomethyl-7-chloroisoquinoline, EXAMPLE 11, 0.052g, 0.20mmol), and K_2CO_3 (0.08 g, 0.06 mmol). After 16 h, the reaction mixture is concentrated to dryness. The crude product is purified by RP-HPLC eluting with a gradient of 5%CH_3CN/H_2O (0.1% TFA) to 50%CH_3CN/H_2O (0.1% TFA). The product fractions are lyophilized to give the title compound as a tristrisfluoroacetic acid salt (0.06g, 0.08 mmol) as a white solid. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.79 (bs, 2H), 9.40 (s, 1H), 8.73 (s, 1H), 8.33 (d, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H), 7.79 (d, 1H), 7.60 (m, 2H), 4.80 (AB, 2H), 4.72 (AB, 2H), 4.28 (m, 1H), 3.54 (m, 4H), 1.96 (d, 3H). MS (ion spray) 447, 449, (Cl pattern). Elemental analysis $C_{28}H_{25}ClF_6N_6O_6 \cdot 3CF_3CO_2H \cdot 0.28H_2O$, cal C=45.38%, H=3.35%, N=10.58%; found C=45.38, H=3.35%, N=10.63%.

EXAMPLE 450. 4-(4-Amino-quinazolin-7-ylmethyl)- 4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 274 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.79 (bs, 2H), 8.82 (s, 1H), 8.39 (d, 1H), 7.61 (m, 3H), 7.57 (d, 1H), 7.52 (d, 1H), 7.49 (d, 1H), 7.20 (d, 1H), 7.10 (d, 1H), 4.75 (AB, 2H), 4.57 (m, 1H), 4.23 (m, 1H), 3.97 (m, 1H), 3.50 (m, 3H), 1.65 (d, 3H). ESI MS, $[M+H]^+$= 435,437 (Cl pattern). Anal. ($C_{23}H_{23}ClN_6O \cdot 2.15TFA \cdot 0.25H_2O$) C, H, N.

The following compounds are prepared from the compound of Example 80 using the methods described above.

Example #	Name	m/z [M+H]
451	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	428, 430 Cl pattern
452	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	478, 480 Cl pattern
453	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-methyl-piperazin-2-one	429, 431 Cl pattern
454	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-	435, 437

	ylmethyl)-3-(S)-methyl-piperazin-2-one	Cl pattern
455	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-methyl-piperazin-2-one	442, 444 Cl pattern
456	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methyl-piperazin-2-one	483 (M+) (EI)
457	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-benzoimidazol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	536, 538 Cl pattern
458	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	428, 430 Cl pattern
459	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
460	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	453, 455 Cl pattern
461	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	452, 454 Cl pattern
462	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	452, 454 Cl pattern
463	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one	452, 454 Cl pattern
464	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one	452, 454 Cl pattern

EXAMPLE 465 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80, and 3-(4-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 26. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.62 (m, 5H), 7.05 (d, 1H), 4.92 (m, 1H), 4.80 (m, 2H), 4.73 (m, 1H), 4.50 (m, 1H), 3.40 (m, 2H), 1.42 (m, 3H). ESI MS, $[M+H]^+$= 442, 444 (Cl pattern).

The following compounds are prepared from the compound of Example 80 using the methods described above.

Example #	Name	m/z [M+H]

466	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
467	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
468	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	486, 488 Br pattern
469	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-3-(S)-methyl-piperazin-2-one	449, 451 Cl pattern
470	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methyl-piperazin-2-one	461, 463 Cl pattern
471	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
472	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	486, 488 Br pattern
473	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methyl-piperazin-2-one	440, 442 Cl pattern
474	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-3-(S)-methyl-piperazin-2-one	498, 500 Cl pattern
475	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-methyl-piperazin-2-one	456, 458 Cl pattern
476	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methyl-piperazin-2-one	466, 468 Cl pattern
477	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	442, 444 Cl pattern

EXAMPLE 478. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 278 using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, EXAMPLE 77 and 3-(5-chloro-thiophen-2-yl)-propionaldehyde, EXAMPLE 28. ^{1}H NMR (d6-DMSO + 1 drop TFA, 300 MHz) δ 9.80 (bs, 2H), 8.79 (s, 1H), 8.32 (d, 1H), 7.58 (m, 2H), 6.88 (d, 1H), 6.70 (d, 1H), 4.72 (AB, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.48 (m, 2H), 3.23 (m, 3H), 2.72 (m, 2H), 1.96 (m, 4H), 0.98 (m, 3H). MS (ion spray), m/z, (M+H) = 444, 446 (Cl pattern).

The following compounds are prepared from the compound of Example 77 using the methods described above.

Example #	Name	m/z [M+H]
479	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one	442, 444 Cl pattern
480	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-ethyl-piperazin-2-one	456, 458 Cl pattern
481	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-ethyl-piperazin-2-one	461, 463 Cl pattern
482	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one	442, 444 Cl pattern
483	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	460, 462 Cl pattern
484	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	466, 468 Cl pattern
485	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	467, 469 Cl pattern

EXAMPLE 486. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, EXAMPLE 77 and 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 25. ^{1}H NMR (d6-DMSO + 1 drop TFA, 300 MHz) δ 9.78 (bs, 2H), 8.79 (s, 1H), 8.37 (d, 1H), 7.65 (m, 2H), 7.50 (s, 1H), 7.41 (m, 1H), 7.11 (d, 1H), 6.98 (d, 1H), 4.88 (m, 2H), 4.60 (m, 1H), 4.31 (m, 1H), 3.52 (m, 1H), 3.30 (m, 2H), 1.96 (m, 2H), 0.88 (m, 3H). MS (ion spray), m/z, (M+H) = 456, 458 (Cl pattern). Elemental analysis, cal $C_{22}H_{22}ClN_5O_2S \cdot 1.5C_2HF_3O_2$ %C=47.89, %H=3.78, %N=11.17; found %C=47.34, %H=4.00, %N=11.12.

The following compounds are prepared from the compound of Example 77 using the methods described above.

Example #	Name	m/z [M+H]
487	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-	460, 462

	yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one	Cl pattern
488	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one	460, 462 Cl pattern
489	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(S)-3-ethyl-piperazin-2-one	456, 458 Cl pattern
490	2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetamide	517, 519 Cl pattern
491	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid	518, 520 Cl pattern
492	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one	514, 516, 518 Cl_2 pattern
493	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one	480, 482 Cl pattern
494	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	546, 548 Cl pattern
495	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one	494, 496 Cl pattern
496	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester	532, 534 Cl pattern
497	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-(3S)-ethyl-piperazin-2-one	463, 465
498	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-ethyl-piperazin-2-one	475, 477 Cl pattern
499	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one	460, 462 Cl pattern
500	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	500, 502 Br pattern
501	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	456, 458 Cl pattern
502	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	500, 502 Br pattern

503	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3-(S)-ethyl-piperazin-2-one	458, 460 Cl pattern
504	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-1H-pyrrole-2-carbonyl]-3-(S)-ethyl-piperazin-2-one	489, 491 Cl pattern
505	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-3-(S)-ethyl-piperazin-2-one	470, 472 Cl pattern
506	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-ethyl-piperazin-2-one	470, 472 Cl pattern
507	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-ethyl-piperazin-2-one	454, 456 Cl pattern
508	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	450, 452 Cl pattern
509	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-3-(S)-ethyl-piperazin-2-one	463, 465 Cl pattern
510	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propionyl]-3-(S)-ethyl-piperazin-2-one	452, 454 Cl pattern
511	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethyl-4-[3-(4-methoxy-phenyl)-propionyl]-piperazin-2-one	448
512	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-ethyl-piperazin-2-one	480, 482 Cl pattern

EXAMPLE 513. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one, EXAMPLE 78 and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.81 (s, 1H), 8.35 (d, 1H), 7.60 (m, 2H), 7.51 (s, 1H), 6.69 (m, 1H), 6.21 (d, 1H), 4.91 (AB, 2H), 4.72 (m, 2H), 3.84 (m, 1H), 3.52 (m, 2H), 3.23 (m, 1H), 1.80 (m, 2H), 1.24 (m, 2H), 0.82 (m, 3H). MS (ion spray), m/z, 474, 476, (M+H) (Cl pattern). Elemental analysis, cal $C_{22}H_{22}ClN_5O_2S \cdot C_2HF_3O_2 \cdot 1.15H_2O$ %C=47.31, %H=4.52, %N=11.50; found %C=47.39, %H=4.140, %N=11.19.

EXAMPLE 514. 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one, EXAMPLE 78 and 3-(6-amino-pyridin-3-yl)-acrylic acid,

EXAMPLE 36. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.36 (m, 2H), 8.22 (m, 3H), 7.62 (d, 1H), 7.52 (m, 1H), 7.39 (m, 1H), 7.21 (m, 1H), 6.91 (d, 1H), 5.00 (m, 1H), 4.78 (m, 1H), 4.60 (m, 2H), 4.34 (m, 1H), 3.30 (m, 2H), 1.87 (m, 2H), 1.24 (m, 2H), 0.90 (m, 3H). MS (ion spray), m/z, 446, 448 (M+H), (Cl pattern).

The following compounds are prepared from the compound of Example 78 using the methods described above.

Example #	Name	m/z [M+H]
515	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	508, 509, 511, Cl_2 pattern
516	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	474, 476 Cl pattern
517	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	514, 516 Br pattern
518	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern
519	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one	468, 470 Cl pattern
520	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	474, 476 Cl pattern
521	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one	498, 500 Cl pattern
522	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern
523	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern

EXAMPLE 524. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 278 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one, EXAMPLE 75 and 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene EXAMPLE 17. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.80 (s, 1H), 8.38 (d, 1H), 7.69 (m, 2H), 7.02 (dd, 1H), 6.84 (d, 1H), 6.02 (m, 1H), 4.76 (AB, 2H), 3.86 (m, 4H), 3.30 (s, 3H), 3.23 (m, 2H), 3.02 (m, 2H). MS (ion spray), m/z, 458, 460, (M+H) (Cl pattern). Elemental analysis, cal

$C_{22}H_{24}ClN_5O_2S \cdot 2C_2HF_3O_2 \cdot 1.45H_2O$ %C=43.85, %H=4.09, %N=9.83; found %C=43.92, %H=3.61, %N=9.63.

The following compounds are prepared from the compound of Example 75 using the methods described above.

Example #	Name	m/z [M+H]
525	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	465, 467
526	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
527	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
528	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(R)-methoxymethyl-piperazin-2-one	477, 479 Cl pattern
529	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	477, 479 Cl pattern
530	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	476, 478 Cl pattern
531	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	482, 484 Cl pattern

EXAMPLE 532. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one.

To a solution of 4-(4-amino-quinazoline-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, EXAMPLE 75, (0.69g, 2.29mmol) in 9mL of DMF is added N,N-diisopropylethyl amine (0.89g, 6.87mmol), TBTU (0.76g, 2.36mmol), and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24, (0.40g, 2.08mmol). The solution is stirred for 16 hours. After this time the solution is concentrated. The crude material is purified by RP-HPLC eluting with a gradient of 10%CH_3CN/H_2O (0.1%TFA) to 80%CH_3CN/H_2O (0.1%TFA). The product fractions are lyophilized to give the product as a white solid (1.0g, 1.57mmol). ^{1}H NMR (d6-DMSO, 300MHz) δ 9.70 (bs, 2H), 8.78 (s, 1H), 8.29 (m, 1H), 7.55 (m, 2H), 6.72 (m, 1H), 6.22 (m, 1H), 4.80 (m, 4H),3.78 (m, 4H), 3.59 (m, 3H), 3.31and 3.2 (s, 3H rotational isomers).MS (ion spray) M+H=476.Elemental Analysis: C21H22ClN5O4S·1.4CF3CO2H cal: C=45.03%, H=3.68%, N=11.04%; found C=44.98%, H=3.71%, N=11.02%.

EXAMPLE 533. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one.

To a solution of 4-(4-amino-quinazoline-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, EXAMPLE 75, (20 mg, 0.066 mml) in 1.5 mL of DMF is added TBTU (923.4 mg, 0.073 mmol), diisopropylethylamine (0.013 ml, 0.073 mmol) and 6-chloro-1H-benzoimidazole-2-carboxylic acid (prepared from literature in Eur.J.med.Chem. 1993, 28, 71) (14.3 mg, 0.073 mmol). The resulting mixture is left to stir at room temperature overnight. The crude mixture is directly purified by reverse phase HPLC (10-70% ACN/H_2O). The product (30.1 mg, 55%) is isolated as a white powder. $C_{23}H_{22}ClN_7O_3$ MS m/z: 480, 481. Anal. cald. for $C_{23}H_{22}ClN_7O_3 \cdot 2C_2HF_3O_2$: C, 45.81; H, 3.42; N, 13.85. Found C, 45.19; H, 3.59; N, 13.76.

The following compounds are prepared from the compound of Example 75 using the methods described above.

Example #	Name	m/z [M+H]
534	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)- methoxymethyl-piperazin-2-one	476, 478 Cl pattern
535	4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	447
536	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-3H-imidazol-4-yl-acryloyl)-3-(S)-methoxymethyl-piperazin-2-one	
537	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512, Cl_2 pattern
538	(1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	480, 482 Cl pattern
539	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
540	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	500, 502 Br pattern
541	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512 Br pattern
542	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	466, 468 Cl pattern

543	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	576, 578 Br pattern
544	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	466, 468 Cl pattern
545	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	576, 578 Br pattern
546	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)--methoxymethyl-piperazin-2-one	476, 478 Cl pattern
547	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
548	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
549	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	448
550	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	500, 502 Cl pattern
551	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
552	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl_2 pattern
553	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-fluoro-thiophen-2-yloxy)-acetyl]-3-(S)- methoxymethyl-piperazin-2-one	460
554	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	453
555	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenoxy)-propionyl]-3-(S)-methoxymethyl-piperazin-2-one	484, 486 Cl pattern
556	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
557	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-[(4-trifluoromethylsulfanyl-phenoxy)-acetyl]-piperazin-2-one	536
558	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	469, 471 Cl pattern
559	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	469, 471 Cl pattern

560	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
561	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid	534, 536 Cl pattern
562	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-ylsulfanyl)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	492, 494 Cl pattern
563	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern
564	2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-	533, 535 Cl pattern
565	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	496, 498 Cl pattern
566	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	530, 532, 534 Cl_2 pattern
567	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512, 514 Cl_2 pattern
568	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester	548, 550 Cl pattern
569	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	562, 564 Cl pattern
570	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern
571	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,3-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl_2 pattern
572	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	454
573	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	484, 486 Cl pattern

574	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,4-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl_2 pattern
575	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	491, 493 Cl pattern
576	(1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	516, 518 Br pattern
577	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
578	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(R)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
579	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
580	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	496, 498 Cl pattern
581	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern

EXAMPLE 582. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one, EXAMPLE 79 and, (6-chloro-pyridin-3-yloxy)-acetic acid, prepared similary to the procedure descibed in EXAMPLE 29. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.37 (m, 1H), 8.10 (m, 1H), 7.61 (m, 2H), 7.40 (m, 2H), 4.98 (m, 2H), 4.65 (m, 2H), 4.50 (m, 1H), 3.91 (m, 1H), 3.75 (m, 1H), 3.59 (m, 2H), 3.31 (m, 2H), 1.07 (m, 3H). MS (ion spray), m/z, 485, 487 (M+H), (Cl pattern).

The following compounds are prepared from the compound of Example 79 using the methods described above.

Example #	Name	m/z [M+H]
583	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethoxymethyl-4-[(3-fluoro-phenoxy)-acetyl]-piperazin-2-one	454
584	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-	486, 488

	acryloyl]-3-(S)-ethoxymethyl-piperazin-2-one	Cl pattern
585	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	484, 486 Cl pattern
586	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	484, 486 Cl pattern
587	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	490, 492 Cl pattern

The following compounds are prepared from the compounds of Examples 81-85 using the methods described above.

Example #	Name	m/z [M+H]
588	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	518, 520 Cl pattern
589	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one	542, 544 Cl pattern
590	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	504, 506 Cl pattern
591	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	528, 530 Cl pattern
592	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one	516, 518 Cl pattern
593	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	522, 524 Cl pattern
594	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one	506, 508 Cl pattern
595	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
596	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	472, 474 Cl pattetn
597	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern
598	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	530, 532 Br pattern

599	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	491, 493 Cl pattern
600	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-isopropyl-piperazin-2-one	480, 482 Cl, pattern
601	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,3-dimethyl-piperazin-2-one	466. 468 Cl pattern
602	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,3-dimethyl-piperazin-2-one	442, 444 Cl pattern
603	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,3-dimethyl-piperazin-2-one	456, 458 Cl pattern
604	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3,3-dimethyl-piperazin-2-one	480, 482 Cl pattern
605	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
606	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469, 471 Cl pattern
607	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
608	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	510, 512 Cl pattern

EXAMPLE 609. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 268, using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one, EXAMPLE 87, and 2-bromomethyl-6-chloronaphthalene, EXAMPLE 12. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 7.79 (d, 1H), 7.70-7.12 (m, 3H), 7.68-7.67 (m, 2H), 7.55 (d, 1H), 7.39 (d, 1H), 4.78 (d, 2H), 3.98 (d, 2H), 3.44 (s, 3H), 3.38 (t, 1H), 2.64 (m, 2H), 1.26 (d, 3H). MS (ISP) 490, 492, (M+H), Cl pattern.

The following materials are prepared from starting materials obtained as described in Example 87 using the methods described above.

Example #	Name	m/z [M+H]
610	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-	458, 460

	propyl]-3-(S)-ethyl-6-methyl-piperazin-2-one	Cl pattern
611	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(R)-methyl-piperazin-2-one	490, 492 Cl pattern
612	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	472, 474 Cl pattern
613	(1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl pattern
614	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-6-dimethyl-piperazin-2-one	491, 493 Cl pattern
615	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-6-methyl-piperazin-2-one	442, 446 Cl pattern
616	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methyl-piperazin-2-one	428, 430 Cl pattern

EXAMPLE 617. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one, EXAMPLE 87, and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24. ^{1}H NMR (CD_3OD300 MHz) δ 8.68 (s, 1H), 8.27 (d, 1H), 7.62 (m, 2H), 6.54 (d, 1H), 6.18 (m, 1H), 7.39 (d, 1H), 4.94 (m, 4H), 4.15 (m, 2H), 3.76 (m, 2H), 3.44 (s, 3H), 3.10 (m, 2H), 1.28 (d, 3H).

The following compounds are prepared from compounds obtained as described Examples 75-87 using the methods described above.

Example #	Name	m/z [M+H]
618	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl pattern
619	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl_2 pattern
620	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-4-fluoro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	502, 504 Cl_2 pattern
621	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	502, 504 Cl pattern

622	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-phenyl)-acryloyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	514
623	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-2-methyl-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	498, 500 Cl_2 pattern
624	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	518
625	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	484
626	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3(S)-ethyl-6-methyl-piperazin-2-one	472, 474 Cl pattern
627	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-ethyl-6-methyl-piperazin-2-one	474
628	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	514, 516 Br pattern
629	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	470, 472 Cl pattern
630	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one	486, 488 Cl pattern
631	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one	530, 532 Br pattern
632	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3(S)-6-dimethyl-piperazin-2-one	480 Cl pattern
633	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one	500, 502 Br pattern
634	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one	456, 458 Cl pattern
635	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-6-methyl-piperazin-2-one	442, 444 Cl pattern

EXAMPLE 636. 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

The title compound is prepared as described in EXAMPLE 436 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one, EXAMPLE 75, and 4-chlorophenyl isocyanate. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.70 (s, 1H), 8.40 (d, 1H), 7.64 (d, 1H), 7.61 (s, 1H),

7.49 (d, 2H), 7.28 (d, 2H), 4.88 (m, 1H), 4.80 (AB, 2H), 4.19 (m, 1H), 3.96 (m, 1H), 3.74-3.42 (m, 4H), 3.28 (s, 3H). ESI MS, $[M+H]^+$=455,457 (Cl pattern). Anal. ($C_{22}H_{23}ClN_6O_3 \cdot TFA \cdot 1.5H_2O$) C, H, N.

EXAMPLE 637. 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide.

The title compound is prepared as described in EXAMPLE 438 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one (EXAMPLE 80) and 5-chloro-thiophene-2-carbonyl azide (EXAMPLE 38). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.01 (s, 1H), 9.73 (bs, 2H), 8.83 (s, 1H), 8.39 (d, 1H), 7.65 (d, 1H), 7.58 (s, 1H), 6.79 (d, 1H), 6.44 (d, 1H), 4.85 (d, 1H), 4.71 (m, 1H), 4.69 (d, 1H), 4.17 (d, 1H), 3.50 (m, 3H), 1.45 (d, 3H). ESI MS, $[M+H]^+$=431,433 (Cl pattern). Anal. ($C_{19}H_{19}ClN_6O_2S \cdot TFA \cdot 1.9H_2O$) C, H, N.

EXAMPLE 638. 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide.

The title compound is prepared as described in EXAMPLE 439 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one (EXAMPLE 75) and 5-chloro-thiophene-2-carbonyl azide (EXAMPLE 38). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.00 (s, 1H), 9.73 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.65 (d, 1H), 7.60 (s, 1H), 6.80 (d, 1H), 6.42 (d, 1H), 4.86 (d, 1H), 4.80 (m, 1H), 4.70 (d, 1H), 4.18 (d, 1H), 3.96 (dd, 1H), 3.60 (m, 4H), 3.30 (s, 3H). ESI MS, $[M+H]^+$=461,463 (Cl pattern). Anal. ($C_{20}H_{21}ClN_6O_3S \cdot TFA \cdot 1.1H_2O$) C, H, N.

The following compounds are prepared using the methods described above.

Example #	Name	m/z [M+H]
639	4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469
640	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	467, 469 Cl pattern
641	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide	505, 507
642	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-3-yl)-amide	461, 463
643	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	461

644	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	453, 455 Cl pattern
645	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-bromo-phenyl)-amide	499
646	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	459, 461
647	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-2-methoxy-phenyl)-amide	483, 485 Cl pattern
648	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-2-chloro-phenyl)-amide	533, 535
649	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-trifluoromethoxy-phenyl)-amide	505
650	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide	439
651	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-dichloro-phenyl)-amide	489, 491
652	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-difluoro-phenyl)-amide	457
653	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide	455
654	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide	459, 460 Cl pattern
655	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide	426, 428
656	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	499, 501
657	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	486, 488
658	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-5-(R,S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469, 471
659	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	483, 485
660	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	425, 427

661	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	439, 441
662	4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-4-methoxy-thiophen-2-yl)-amide	491, 493 Cl pattern

EXAMPLE 663. (3S, 5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one.

(3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (260 mg, 0.56 mmol), EXAMPLE 88, is dissolved in 5 mL of DMF. Potassium carbonate (193.4 mg, 1.4 mmol) is added followed by the addition of 2-bromomethyl-6-chloro-benzo[b]thiophene (218 mg, 0.84 mmol), EXAMPLE 5. Reaction is left to stir overnight. The crude mixture is purified by reverse phase HPLC (10 -70% ACN/H_2O) to afford the product (27 mg, 6%) as a clear wax with a melting point of 130-131 °C . $C_{24}H_{24}ClN_5OS$ MS m/z: 466, 468.

EXAMPLE 664. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one.

and

EXAMPLE 665. (3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one.

(3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (60 mg, 0.13 mmol) is dissolved in 1 mL of DMF. Potassium carbonate (53 mg, 0.39 mmol) is added followed by the addition of 3-bromoallyl-5-chloro-thiophene (75 mg, 0.32 mmol). Reaction is left to stir overnight. The two epimers are separated by reverse phase HPLC (10 -70% ACN) in 43% yield.

The major epimer is assigned as (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5 -dimethyl-piperazin-2-one trifluoroacetic acid salt (30.8 mg) and is isolated as a yellow solid with a melting point of 69-72 °C . $C_{22}H_{24}ClN_5OS$ MS m/z: 442, 444.

The minor epimer is assigned as (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one trifluoroacetic acid salt (13.1 mg) with a melting point of 67-70 °C . $C_{22}H_{24}ClN_5OS$ MS m/z: 442, 444. 1H NMR (CD_3OD) δ: 8.67 (s, 1H); 8.31 (d, 1H, J = 8.56 Hz); 7.83 (s, 1H); 7.74 (d, 2H, J = 8.56 Hz); 7.14 (d, 1H, J = 15.6 Hz); 6.92 (d, 1H, J = 3.74 Hz); 6.10-6.03 (m, 1H); 5.0-4.74 (m, 2H); 4.25-3.63 (m, 6 H); 1.78 (d, 3H, J = 7.03 Hz); 1.50 (d, 3H, J = 6.47 Hz).

EXAMPLE 666. (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one.

(3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (43 mg, 0.123 mmol), minor epimer fromEXAMPLE 88, Part D, is taken up in methylene chloride to this is added triethylamine (0.034 ml, 0.25 mmol) followed by 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride (40 mg, 0.16 mmol), EXAMPLE 3. The reaction is stirred overnight, and the crude material is purified by preparative thin layer chromatography (15 % methanol/CH_2Cl_2). The product (1.4 mg, 2.3%) is isolated as a yellow wax. $C_{21}H_{22}ClN_5O_3S_2$ MS m/z: 492, 494. 1H NMR (CD_3OD) δ 8.36 (s, 1H); 8.03 (d, 1H, J = 7.5 Hz); 7.61 (s, 1H); 7.49-7.44 (m, 2H); 7.19 (d, 1H, J = 3.83 Hz); 6.98 (d, 1H, J = 3.75 Hz); 6.76 (d, 1H, J = 15.1 Hz); 4.86-4.71 (m, 2H); 4.45-4.39 (m, 1H); 4.13-4.09 (m, 1H); 3.64-3.7 (m, 2H); 1.63 (d, 3H, J = 7.09 Hz); 1.33 (d, 3H, J = 6.80 Hz).

EXAMPLE 667. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one.

The product (7 mg, 9.4 %) is isolated as a yellow solid with a melting point of 218-221 °C . $C_{21}H_{22}ClN_5O_3S_2$ MS m/z: 492, 494. 1H NMR (CD_3OD) δ 8.37 (s, 1H); 8.10 (d, 1H, J = 8.57 Hz); 7.61-7.45 (m, 3H); 7.24 (d, 1H, J = 3.94 Hz); 6.98 (d, 1H, J = 3.85 Hz); 6.71 (d, 1H, J = 15.1 Hz); 4.76 (s, 2H); 4.32 (m, 1H); 3.71 (m, 1H); 3.36 (m, 2H); 1.62 (d, 3H, J = 7.06 Hz); 1.20 (d, 3H, J = 6.63 Hz).

EXAMPLE 668. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-sulfonyl)-3,5-dimethyl-piperazin-2-one.

The desired product (5.4 mg, 8.5 %) is isolated as yellow solid with a melting point of 224-226° C. $C_{23}H_{22}ClN_5O_3S_2$ MS m/z: 516, 518.

EXAMPLE 669. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-piperazin-2-one.

To a solution of (3S,5S)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (42 mg, 0.147 mmol), major epimer from EXAMPLE 88, Part D, in 2 mL of DMF is added TBTU (52 mg, 0.162 mmol), triethylamine (0.02 mL, 0.162 mmol) and 3-(5-chloro-thiophen-2-yl)-acrylic acid (28 mg, 0.15 mmol), EXAMPLE 25. After stirring for two hours, the reaction mixture is directly purified by reverse phase HPLC (10-70 % ACN/H_2O). The product (35.5 mg, 36%) is isolated as a yellow solid with a melting point of 116-120°C. $C_{22}H_{22}ClN_5O_2S$: MS m/z: 456, 458. Anal. calcd. for $C_{22}H_{22}ClN_5O_2S \bullet C_2HF_3O_2$: C, 50.57; H, 4.07; N, 12.29. Found: C, 46.48; H, 3.64; N, 11.04.

EXAMPLE 670. (3S, 5R)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide.

4-Bromo-phenyl isocyanate (20.8 mg, 0.105 mmol) is added to solution of (3S,5R)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (30 mg, 0.105 mmol), minor epimer from EXAMPLE 88, Part D, in 1 mL of DMF. The reaction is stirred for two hours at room temperature. The product (21.4 mg, 33%) is isolated from reverse phase HPLC (10 -70% ACN/H_2O) as white solid. The melting of the compound is 142-144 °C . $C_{22}H_{23}BrN_6O_2$ MS m/z: 483, 485. Anal. cald.for $C_{22}H_{23}BrN_6O_2$ •$2C_2HF_3O_2$: C, 43.90; H, 3.54; N, 11.81. Found: C, 44.52; H, 3.86; N, 12.44.

EXAMPLE 671. (3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide.

The desired product (35 mg, 47%) is isolated as a white solid with a melting point of 142-144°C . $C_{22}H_{23}BrN_6O_2$ MS m/z: 483, 485. Anal. cald.for $C_{22}H_{23}BrN_6O_2$•$2C_2HF_3O_2$: C, 43.90; H, 3.54; N, 11.81. Found: C, 44.73; H, 3.59; N, 12.38.

EXAMPLE 672. (3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

The product (24.7 mg, 50%) is obtained as a white solid with a melting point of 123-125 °C . $C_{22}H_{23}ClN_6O_2$ MS m/z: 439, 441. Anal. cald.for $C_{22}H_{23}ClN_6O_2$•$2C_2HF_3O_2$: C, 46.82; H, 3.78; N, 12.60. Found: C, 47.69; H, 4.33; N, 13.32.

EXAMPLE 673. 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

A. 1-(4-Chloroquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

1-(4-chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one hydrochloride (0.49 g, 1.4 mmol), EXAMPLE 89, is treated with acetonitrile (20 mL), triethyl amine (1.2 ml, 8.4 mmol) and a solution of 6-chlorobenzo[b]thiophen-2-sulfonyl chloride (0.41 g, 1.54 mmol), EXAMPLE 1, in acetonitrile (10 mL) at 0°C. After 2 h the solution is poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried over sodium sulfate and concentrated to yielded the title compound (0.45 g, 0.95 mmol). MS m/z: 506, $[M+1]^+$; ^1H NMR (CD_3OD, 300 MHz) δ 8.8 (d, 1H), 8.15 (d, 1H), 7.9 (d, 2H), 7.85 (s, 1H), 7.4-7.5 (m, 2H), 6.8 (s, 1H), 4.8 (s, 2H), 4.0 (s, 2H), 3.4-3.45 (m, 4H).

B. 1-(4-Azidoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one

1-(4-Chloroquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one (0.52 g, 1.03 mmol) is dissolved in DMF (15 mL), treated with sodium azide (0.52 g, 8.0 mmol), tetrabutyl ammonium chloride (0.1 g, 0.36 mmol) and heated to 65 °C overnight. The reaction mixture is cooled,

poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried (sodium sulfate) and concentrated to give the title compound (0.5 g, 1.04 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.0 (d, 1H), 8.2 (d, 1H),8.0 (s, 1H), 7.9 (d, 2H), 7.8 (d,1H), 7.6 (d,1H), 7.5 (d,1H),6.9 (s, 1H), 4.85 (s, 2H), 4.0 (s, 2H), 3.5-3.7 (m, 4H).

C. 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

A suspension of 1-(4-azidoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one (0.50 g, 1.04 mmol) in 100 mL of acetic acid/methanol (~ 1:10) is treated with 10% Pd/C (0.15 g) and stirred under hydrogen for 1.5 hours. The resulting solution is filtered through Celite and the filtrate is evaporated in vacuo. The organic layer is concentrated and the residue is purified by reverse phase HPLC (gradient elution of 30 % of 0.1 % aqueous TFA/acetonitrile to 100 % acetonitrile) and lyopholized to give the title compound (0.39 g, 0.86 mmol). MS (ISP) m/z 487, 489, (M+H), Cl pattern.

The following compounds are prepared from the compound of Example 89 or 91 using the methods described above.

Example #	Name	m/z [M+H]
674	1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	463, 465
675	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-methyl-piperazin-2-one	501, 503
676	(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one	491, 493
677	(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one	491, 493
678	(S,R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid	531, 533
679	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide	544
680	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	558
681	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	558

682	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	600

EXAMPLE 683. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

A. (S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

(S)-1-(4-chloroquinolin-7-ylmethyl)-3-methylpiperazin-2-one hydrochloride (0.25 g, 1.0 mmol), EXAMPLE 91, is treated with 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene (0.35 g 1.2 mmol), EXAMPLE 17, and potassium carbonate (0.5 g, 3 mmol). The resulting suspension is sonicated for 10 minutes then stirred vigorously for 16 h at ambient temperature. The reaction mixture is poured into water and extracted with ethyl acetate (2 X 150 mL). The organic layer is washed with water (4 X 200 mL), dried over sodium sulfate and concentrated. The residue is chromatographed (3 % methanol/methylene chloride) to give the title compound (0.31 g, 0.73 mmol).

B. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

(S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one (0.35 g, 0.82 mmol) is treated with phenol (2 g) and ammonium acetate (0.7 g, 9.1 mmol) and heated to 120 °C in a sealed vessel for 1 hour. Upon cooling, the solution is partitioned between 2 N NaOH and ethyl acetate. The organic layer is separated and washed with fresh 2 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC to give the title compound as a white solid (0.15 g, 0.35 mmol). MS (ISP) m/z 427, 429, (M+H), Cl pattern.

The following compounds are prepared from starting materials prepared as described in Examples 61-64, 89 or 91 using the methods described above.

Example #	Name	m/z [M+H]
684	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	413, 415
685	(3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one	465, 467
686	(3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one	464
687	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-	446,448

	ylmethyl)-3-methyl-piperazin-2-one	
688	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-methyl-piperazin-2-one	444
689	(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one	441, 443
690	(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one	441, 443
691	1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	420, 422
692	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-ethyl-piperazin-2-one	458
693	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one	470
694	1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-(S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one	489
695	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one	464, 466
696	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methyl-piperazin-2-one	434, 436
697	4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(2-hydroxy-ethylamino)-quinolin-7-ylmethyl]-piperazin-2-one	464
698	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one	462
699	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one	492
700	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one	448
701	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one	478
702	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-4-oxy-piperazin-2-one	443

EXAMPLE 703. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one.

A. (S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl piperazin-2-one.

(S)-1-(4-chloroquinolin-7-ylmethyl)-3-methylpiperazin-2-one hydrochloride (0.35 g, 1.4 mmol), EXAMPLE 91, is treated with DMF (20 mL), 3-(4-bromothiophen-2-yl)-(E)-acrylic acid (0.32 g, 1.4 mmol), prepared according to EXAMPLE 26, using 4-bromothiophene-2-carboxaldehyde, triethyl amine (0.21 ml, 1.4 mmol) and 2-(1H-benzotriazol-1-yl)1,1,3,3-tertamethyluronium tetrafluoroborate (0.45 g, 1.4 mmol) and heated to 50 °C for 5 minutes. The reaction mixture is stirred at ambient temperature for 16 h then partitioned between ethyl acetate and water. The organic layer is concentrated and the residue is chromatographed (5% methanol/methylene chloride) to give crude title compound (0.5 g , 0.9 mmol). MS m/z: $[M+H]^+ = 504$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.9 (d, 1H), 8.2-8.3(m, 2H), 8.0 (s, 1H), 7.7-7.8 (m, 1H), 7.4 (s, 1H), 7.3-7.4 (m, 1H), 6.7-6.8 (m, 1H), 6.6 (d, 1H), 5.1-5.2 (m, 1H), 4.6-4.7 (m, 2H), 3.4-3.6 (m, 2H), 3.0-3.3 (m, 2H), 1.5 (d, 3H).

B. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one.

(S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl piperazin-2-one (0.50 g, 0.9 mmol) is treated with phenol (~ 2 g) and ammonium acetate (0.5 g, 6.4 mmol) and heated to 120 °C in a sealed vessel for 1 hour. Upon cooling, the solution is partitioned between 2 N NaOH and ethyl acetate. The organic layer is separated and washed with fresh 2 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC (gradient elution of 10 % of 0.1 % aqueous TFA/acetonitrile to 100 % acetonitrile) to give the title compound (0.22 g, 0.56 mmol). MS m/z: $[M+H]^+ = 485, 487$, Cl pattern. ^1H NMR (CD_3OD, 300 MHz) δ 8.2-8.4 (m, 2H), 7.7-7.8 (m, 2H), 7.6 (d, 1H), 7.5 (s, 1H), 7.3 (s, 1H), 6.9-7.0 (m, 1H), 6.7 (d, 1H), 5.0-5.1 (m, 1H), 4.9 (q, 2H), 4.3-4.4 (m, 1H), 3.5-3.7 (m, 2H), 3.3-3.4 (m, 2H), 1.5 (d, 3H).

The following compounds are prepared from starting materials prepared as described in Examples 75-87 using the methods described above.

Example #	Name	m/z [M+H]
704	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	469 Cl pattern
705	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-(S)-3-ethyl-1-(4-hydroxyamino-quinolin-7-ylmethyl)-piperazin-2-one	471, 473
706	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-	427, 429

	acryloyl]-piperazin-2-one	
707	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	454
708	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one	441, 443
709	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one	471, 473
710	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-piperazin-2-one	470
711	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	498
712	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one	458
713	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-6-methyl-piperazin-2-one	488
714	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-3-(1-(R)-methoxy-ethyl)-piperazin-2-one	484
715	1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)-acryl-oyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate	528
716	1-(4-Aminoquinolin-7-ylmethyl)-4-[(5-chlorothiophen-2-yloxy-acetyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate	488
717	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	454

EXAMPLE 718. 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one.

A. 1-(4-Chlorocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one

1-(4-chlorocinnolin-7-ylmethyl)-piperazin-2-one hydrochloride (0.14 g, 0.4 mmol), EXAMPLE 90, is treated with acetonitrile (20 mL), triethylamine (2 mL, 14 mmol) and 2-(5-chlorothiophen-2-yl)ethene-sulfonyl chloride (0.097 g, 0.4 mmol), EXAMPLE 3, at 0°C. The solution is warmed to ambient temperature over 1.5 h and diluted with ethyl acetate. The solution is washed with 10 % sodium bicarbonate solution and water, dried (sodium sulfate) and concentrated to yield the title compound (0.17 g, 0.35 mmol). MS m/z: $[M+H]^+ = 483$; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.4 (s, 1H), 8.4 (s, 1H), 8.3 (d,

1H) 7.85 (d, 1H), 7.7 (d, 1H), 7.1 (d, 1H), 6.95 (d, 1H), 6.35 (d, 1H), 4.9 (s, 2H), 4.0 (s, 2H), 3.4-3.5 (m, 4H).

B. 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one

1-(4-Chlorocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one (0.06 g, 0.12 mmol) is treated with phenol (0.20 g) and ammonium acetate (0.2 g, 2.6 mmol) and heated to 120 °C for 45 minutes. The reaction mixture is cooled, diluted with ethyl acetate and washed with 1 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC (20 % aqueous TFA (0.1 %)/acetonitrile to 100 % acetonitrile). Fractions containing the desired product are lyophilized to obtain the title compound (0.02 g, 0.043 mmol). MS m/z: $[M+H]^+$ = 464; ^1H NMR (CD_3OD, 300 MHz) δ 8.6 (s, 1H), 8.4 (d, 1H), 7.75 (d, 1H), 7.65 (d, 1H), 7.35 (d, 1H), 7.1 (d,1H), 6.8 (d, 1H), 4.9 (s, 2H), 4.05 (s, 2H), 3.6 (m, 4H).

EXAMPLE 719. 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one.

1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one (0.20 mmol), EXAMPLE 90, is dissolved in MeCN (5 mL) and treated with 4-methylmorphorline (0.055 ml, 0.50 mmol). 6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl chloride (54 mg, 0.20 mmol) in MeCN (2 mL) is added dropwise. The reaction mixture is stirred at r.t. for 1.5 h, then subjected to HPLC purification, to give the title compound as white solid (0.021 g, 0.037 mmol). MS m/z 452, 454 (M+1); ^1H NMR (CD_3OD, 300 MHz) δ 8.37 (d, 1H), 8.30 (b, 1H), 8.12 (d, 1H), 8.02 (s, 1H), 7.97 (d, 1H), 7.57 (d. 1H), 6.98 (d, 1H), 6.88 (d, 2H), 3.73 (s, 2H), 3.60-3.48 (m, 8H).

EXAMPLE 720. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(methyl-pyridin-4-yl-amino)-ethyl]-piperazin-2-one.

A portion (~50%) of the crude 1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one, EXAMPLE 93 is reacted with 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (54 mg, 0.20 mmol), EXAMPLE 1, using same procedure as described in EXAMPLE 719. The residue obtained after HPLC purification is subjected to silica gel chromatography using $NH_4OH/MeOH/CH_2Cl_2$ (1:4:95) as eluant to give title compound (30 mg, 0.064 mmol) as a white solid. MS m/z 465, 457 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, 2H), 7.88 (s, 1H), 7.85 (d, 1H), 7.79 (s, 1H), 7.47 (d, 1H), 6.47 (d. 2H), 3.80 (s, 2H), 3.50 (m, 4H), 3.43 (d, 2H), 3.30 (d, 2H), 2.98 (s, 3H).

EXAMPLE 721. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one.

1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one (38 mg, 0.16 mmol), EXAMPLE 94, is reacted with 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride (40 mg, 0.16 mmol), EXAMPLE 3, using the same procedure as described in EXAMPLE 719. Reverse phase HPLC purification gives the title compound (29 mg, 0.052 mmol) as a white solid. MS m/z 441, 443 (M+H); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (d, 1H), 7.98 (s, 1H), 7.56 (d, 1H), 7.30 (d, 1H), 7.02 (s, 1H), 7.00 (d. 1H), 6.78 (d, 1H), 3.87 (s, 2H), 3.70-3.50 (m, 8H), 2.15 (s, 3H).

The following compounds are prepared from starting materials obtained as described in Examples 92-97 using the methods described above.

Example #	Name	m/z [M+H]
722	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	520 (M+)
723	1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	417
724	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	483,485
725	1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one	418
726	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	427,429
727	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(methylpyridin-4-ylamino)-ethyl]-piperazin-2-one	441
728	4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	443
729	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one	465, 467
730	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-yl-ethyl)-piperazin-2-one	450, 452
731	1-[2-(2-Amino-3-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	476, 478
732	1-[2-(2-Amino-5-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	476, 478
733	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(2,3,5,6-	563, 565,

	tetrachloro-pyridin-4-ylamino)-ethyl]-piperazin-2-one	567, 569
734	1-[2-(2-Amino-3,5,6-trichloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	544, 546, 548
735	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	391, 393

EXAMPLE 736. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridazin-4-yl-amino)-ethyl]-piperazin-2-one.

1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one hydrochloride (0.5 g, 1.7 mmol), EXAMPLE 95, is reacted with 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.40 g, 1.5 mmol), EXAMPLE 1, using essentially the same procedure as described in EXAMPLE 719. Reverse phase HPLC purification gives the title compound (0.34 g, 0.75 mmol) as a white solid. MS m/z (M+H= 452); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.6 (d, 1H), 8.4 (d, 1H), 8.05 (s, 1H), 8.05 (s, 1H), 7.9 (d, 1H), 7.5 (d, 1H), 7.2 (d, 1H), 3.8 (s,2H), 3.4-3.7 (m, 8H).

EXAMPLE 737. 1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one.

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester from EXAMPLE 96, Part B (45 mg, 0.10 mmol) is dissolved in 20% TFA/ CH_2Cl_2 and stirred at r.t. for 2 hours. The solution is concentrated to residue. The residue is dissolved in MeCN (2.5 ml) and treated with 4-methylmorphorline (0.027 ml, 0.25 mmol). 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride (24 mg, 0.10 mmol), EXAMPLE 3, in MeCN (1 mL) is then added dropwise. The reaction mixture is stirred at r.t. for 1 h, then subjected to reverse phase HPLC purification, to give the title compound as white solid (0.040 g, 0.037 mmol). MS m/z 439, 441 (M+H); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.20 (br, 1H), 8.10 (s, 1H), 8.08 (d, 1H), 7.60 (d, 1H), 7.53 (d. 1H), 7.35 (d, 1H), 7.21 (d, 1H), 7.07 (d,1H), 6.82 (d, 1H), 5.27 (m, 1H), 3.88 (s, 2H), 3.60-3.50 (m, 4H), 3.30 (d, 2H).

The following compounds are prepared from starting materials obtained as described in Examples 92-97 using the methods described above.

Example #	Name	m/z [M+H]
738	1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	463, 465
739	1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-(6-chloro-benzo[b]thiophene-2-	463, 465

	sulfonyl)-piperazin-2-one	
740	1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	439, 441
741	1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	465, 467
742	1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	441, 443

EXAMPLE 743. 4-[2-(5-Chlorothiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one.

4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one (0.028 g, 0.074 mmol), EXAMPLE 98, is treated with 4 % HCO_2H/MeOH (5 mL) and a catalytic amount of Pd black for 5 minutes. The reaction mixture is filtered washed with methanol and the filtrate is concentrated to a residue. The residue is treated with acetonitrile (3 mL) excess N-methylmorpholine (0.04 mL) and 2-(5-chlorothiophen-2-yl)ethene-sulfonyl chloride (0.018 g, 0.074 mmol), EXAMPLE 3, and processed as usual (EXAMPLE 719). Further chromatographic purification (NH_4OH/MeOH/CH_2Cl_2:1/4/95) yields the title compound: MS m/z 451, 453 (M+H); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 (bs, 1H), 8.24 (bs, 1H), 7.41 (d, 1H), 7.23 (d, 1H), 7.14 (m, 2H), 6.94 (d, 1H), 6.68 (d. 1H), 6.18 (d, 1H), 4.43 (t, 2H), 3.67 (t, 2H), 2.88 (t, 2H), 2.66 (t, 2H).

EXAMPLE 744. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.3 g, 13.0 mmol), EXAMPLE 69, in CH_3CN (250 mL) is cooled to 0°C. Potassium carbonate (1.98 g, 14.3 mmol) is added to the reaction mixture followed by propargyl bromide (1.55g, 13.0 mmol). The mixture is slowly warmed to ambient temperature and maintained until complete consumption of starting material is observed by TLC (approx. 8 h). The mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to provide 3.38 g (70%) of the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.34 (t, J = 2.4 Hz, 1H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J = 2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J = 1.4 Hz, 2H), 6.42

(br s, 1H), 7.88 (dd, J = 5.8, 0.8 Hz, 1H), 8.41 (d, J = 5.8 Hz, 1H), 8.78 (d, J = 0.8 Hz, 1H) ppm; MS (EI): m/z 368 (M+).

B. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.3 g, 3.53 mmol) in CH_2Cl_2 (100 mL) is added TFA (20 mL) at 0 °C. After 6 h, the reaction mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (500 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 616 mg (65%) of the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (app t, J = 2.4 Hz, 1H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J = 2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 8.85 (d, J = 0.9 Hz, 1H), 9.34 (br s, 1H) ppm; MS (EI): m/z 268 (M+).

EXAMPLE 745. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.27 mmol), EXAMPLE 743, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.27 mmol), EXAMPLE 69, Part B, Et_3N (110 mg, 1.08 mmol), $(Ph_3P)_4PdCl_2$ (10 mg, 0.013 mmol), and CuI (1 mg, 0.008 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 77 mg (51%) of SC41 as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ~2:1mixture of rotamers) major rotamer: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1H), 8.09 (m, 2H), 8.34 (m, 1H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; MS (ISP loop): m/z 561 (M+H).

B. 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (42 mg, 0.27 mmol) is added to a suspension containing 2-{4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (SC41, 77 mg, 0.14 mmol) in anhydrous CH_3CN (10 mL) and the mixture is warmed to 50 °C. After 4 h, the reaction mixture is concentrated to dryness and the residue is partitioned between CH_2Cl_2 (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 85 mg of the title compound as a crude solid which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J = 1.1 Hz, 2H), 6.39 (d, J = 0.7 Hz, 1H), 6.68 (d, J = 0.7 Hz, 1H), 7.86 (m, 1H), 8.41 (m, 1H), 8.76 (br s, 1H), 8.82 (br s, 1H) ppm; MS (EI): m/z 561 (M+H).

C. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (85 mg, 0.14mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at 0°C and the solution is allowed to slowly warm to ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 35 mg (36%, two steps) of SC43 as a pale yellow, lyophilized solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 8.37 (d, J = 6.7 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1H), 14.91 (br s, 2H) ppm; MS (ion spray): m/z 361 (M+H). $C_{23}H_{25}ClN_4OS$ MS m/z: 441,443.

The following compounds are prepared from starting materials obtained as described in Examples 69-71 using the methods described above.

Example #	Name	m/z [M+H]
746	4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	395, 397
747	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	443, 445
748	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	386, 388
749	4-(5-Chloro-1H-indol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-	394, 396

	ylmethyl)-piperazin-2-one	
750	4-(6-Chloro-naphthalen-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	405, 407
751	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	406, 408
752	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	501, 503
753	1-(5-Chloro-1H-indol-2-ylmethyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazıne-2-(±)-carboxylic acid methyl ester	452, 454
754	1-[(5-Chloro-thiophen-2-yloxy)-acetyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	463, 465
755	1-(6-Chloro-benzo[b]thiophene-2-carbonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	483, 485
756	1-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	554, 556
757	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one	361
758	4-(3-Phenyl-prop-2-ynyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	345
759	4-[3-(5-Chloro-thiophen-2-yl)-prop-2-ynyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	384

The following compounds are prepared from 3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one using the procedures described above.

Example #	Name	m/z [M+H]
760	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	431, 433
761	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438, 440
762	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-	487, 489

	1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	
763	4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	469, 471
764	4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	540, 542
765	4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	439, 441
766	(S)-2-Methoxymethyl-3-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	428, 430
767	(S)-4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	445, 447

EXAMPLE 768. 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-[4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-2-oxopiperazin-1-ylmethyl]-(pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 123 using 6-chloro-benzo[b]thiophene-2-carboxylic acid, EXAMPLE 1 and 2-(2-oxopiperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester EXAMPLE 69. The mixture is stirred overnight, then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound as a solid. The crude material can be used in the subsequent step without further purification.

B. 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

Trifluoroacetic acid (0.5 mL) is added dropwise to a solution of 2-[4-(6-chloro-benzo[b]thiophene-2-carbonyl)-2-oxopiperazin-1-ylmethyl]-(pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (0.14 g, 0.27 mmol) in 6 mL CH_2Cl_2 at 0°C. After 1 h, the ice bath is removed and the solution stirred at room temperature for 2 hours. The reaction mixture is concentrated in vacuo. The crude residue is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are combined and lyophilized to provide the title compound (0.07 g, 0.13 mmol) as a white solid. ESI MS, $[M+H]^+$=425, 427 (Cl pattern).

The following compounds are prepared using starting materials obtained as described in Example 69 using the methods described above.

Example #	Name	m/z [M+H]
769	4-[3-(6-Chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451, 453
770	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	405, 407
771	4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	497, 499
772	4-(5'-Chloro-[2,2']bithiophenyl-5-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	457, 459
773	4-(5-Chloro-1H-indole-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	364, 366
774	4-[4-(6-Methoxy-pyridin-3-yl)-benzoyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	442
775	4-(4-Pyridin-3-yl-benzoyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	412
776	4-[3-(4-Bromo-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	446
777	4-[3-(5-Chloro-thiophen-2-yl)-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	403, 405
778	4-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453, 455
779	4-[2-(4-Chloro-phenyl)-2-methyl-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	411, 413
780	4-[3-(3,4-Dichloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	431, 433
781	4-[(4-Chloro-phenyl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	383, 385
782	4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	395, 397
783	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-	400, 402

	c]pyridin-2-ylmethyl)-piperazin-2-one	

EXAMPLE 784. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing (S)-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester (0.43 g, 1.77 mmol), EXAMPLE 56, and 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (0.66 g, 1.77 mmol), EXAMPLE 13, in anhydrous DMF (5 mL) at 0°C is added 60% NaH (78 mg, 1.95 mmol). After 30 min, the reaction mixture is warmed to ambient temperature and maintained for 6 hours. The reaction mixture is carefully quenched with water and then diluted with water and diethyl ether. The layers are separated and the organic phase is washed twice with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (2:1 hexane/ethyl acetate to 1:1 hexane/ethyl acetate) to provide 0.37 g (39%) of the title compound as a glassy solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01-3.22 (m, 2H), 3.58 (m, 2H), 3.73 (s, 3H), 3.86-3.92 (m, 1H), 4.42-4.58 (m, 4H), 5.25 (m, 2H), 5.93 (m, 1H), 6.57 (br s, 1H), 6.85 (d, J = 8.2 Hz, 1 H), 7.17-7.51 (m, 9H), 7.76 (m, 2H) ppm; MS (ion spray): m/z 537 (M+H).

B. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

Tetrakis(triphenylphosphine)palladium(0) (237 mg, 0.2 mmol) is added to a solution containing (±)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester (1.10 g, 2.05 mmol) and morpholine (894 mg, 10.2 mmol) in CH_2Cl_2 (30 mL). After ~5 min, the reaction mixture is absorbed onto silica gel and chromatographed (CH_2Cl_2 to 10% MeOH/ CH_2Cl_2) to provide 900 mg (97%) of the title compound as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (br s, 1H), 2.95 (dd, J = 13.5, 4.3 Hz, 1H), 3.27 (br d, J = 13.5 Hz, 1H), 3.46-3.72 (m, 4H), 3.73 (s, 3H), 5.40 (d, J = 15.3 Hz, 1H), 6.57 (br s, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 7.17-7.50 (m, 9H), 7.75-7.77 (m, 2H) ppm; MS (ion spray): m/z 453 (M+H).

C. (±)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester.

To a mixture of (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (630 mg, 1.39 mmol) and K_2CO_3 (380 mg, 2.78 mmol) in anhydrous CH_3CN (5 mL) at 0 °C is added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (720 mg, 2.09

mmol), EXAMPLE 21, in CH_3CN (4 mL). The reaction mixture is allowed to warm to ambient temperature then maintained for 16 hours. The reaction mixture is diluted with diethyl ether/water and the layers are separated. The organic phase is washed twice with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 550 mg (55%) of the title compound which is used directly in the next reaction without further characterization.

D. (±)-2-[4-(3-Amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

Partially-purified (±)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (550 mg, 0.76 mmol) is suspended in reagent grade MeOH (20 mL). To the heterogeneous mixture is added 12M HCl (5 drops) and the reaction mixture is maintained at ambient temperature until homogeneous (~30 min). The reaction mixture is partitioned between diethyl ether and water containing excess $NaHCO_3$ (500 mL). The layers are separated and the organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 400 mg (94%) of the title compound which is used directly in the next reaction. MS (ISP loop): 532 (M+H).

E. (±)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A solution containing (±)-2-[4-(3-amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (100 mg, 0.18 mmol), 1,3,5-triazine (146 mg, 1.81 mmol), and glacial HOAc (99 mg, 1.81 mmol) in absolute EtOH (10 mL) is maintained at reflux for 16 hours. A second portion of 1,3,5-triazine (146 mg, 1.81 mmol) and glacial HOAc (99 mg, 1.81 mmol) is added and the reaction mixture is maintained at reflux for an additional 16 hours. The reaction mixture is concentrated in vacuo and the crude product is diluted with water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 26 mg (20%) of the title compound as a white solid which is used directly in the next reaction without further characterization.

F. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

To a solution containing (±)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (26 mg, 0.03 mmol) in CH_2Cl_2

(4 mL) is added trifluoroacetic acid (1mL) at ambient temperature. After 4 h, the reaction mixture is concentrated in vacuo and then dissolved in water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 10 mg (47%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 2.62 (m, 1H), 3.05-3.51 (m, 4H), 3.59 (s, 3H), 3.81 (d, J = 14.0 Hz, 1H), 4.26 (m, 1H), 4.69 (ABq, Δ_{AB} = 310 Hz, J_{AB} = 16.4 Hz, 2H), 6.26 (s, 1H), 7.02 (dd, J = 8.6, 2.0 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.47 (s, 1H), 8.77 (s, 1H), 9.69 (br s, 2H), 11.17 (s, 1H) ppm; MS (ion spray): m/z 479 (M+H).

EXAMPLE 785. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

A. (±)-1-(3-Amino-4-cyano-benzyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

LiOH monohydrate (380 mg, 9.06 mmol) is added at ambient temperature to a solution containing (±)-2-[4-(3-amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (1.0 g, 1.81 mmol), EXAMPLE 784, Part E, in 1:1:1 THF/MeOH/water (30 mL). After 16 h, HOAc (0.5 mL) is added and the reaction mixture is concentrated in vacuo. The residue is dissolved in CH_3CN/water and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 378 mg (48%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.03 (m, 1H), 3.48 (m, 1H), 3.51 (ABq, Δ_{AB} = 69.2 Hz, J_{AB} = 16.4 Hz, 2H), 3.78 (d, J = 15.9 Hz, 1H), 4.05-4.09 (m, 2H), 5.04 (d, J = 15.9 Hz, 1H), 6.41 (m, 2H), 6.58 (s, 1H), 7.04 (dd, J = 8.6, 2.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.51, d, J = 2.0 Hz, 1H) ppm; MS (ISP loop): m/z 438 (M+H).

B. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (200 mg, 0.30 mmol), 1,3,5-triazine (244 mg, 3.00 mmol), and glacial HOAc (180 mg, 3.00 mmol) in absolute EtOH (20 mL) is maintained at reflux for 16 hours. The reaction mixture is cooled to ambient temperature and the solid is collected on a Buchner funnel and washed with EtOH followed by diethyl ether. Oven-drying in vacuo provided 13 mg (76%) of the title compound as an off-white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 2.63 (m, 1H), 3.06 (d, J = 16.4 Hz, 1H), 3.24-3.42 (m, 4H), 3.68 (ABq, Δ_{AB} = 34.5 Hz, J_{AB} = 14.1 Hz, 2H), 3.96 (m, 1H), 4.63 (ABq, Δ_{AB} = 400 Hz, J_{AB} =

15.8 Hz, 2H), 6.27 (s, 1H), 6.99 (dd, J = 8.6, 2.0 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.40 (s, 1H), 7.46 (s, 1H), 7.69 (br s, 2H), 8.10 (d, J = 8.5 Hz, 1H), 8.32 (s, 1H), 11.20 (s, 1H) ppm; MS (ion spray): m/z 465 (M+H).

EXAMPLE 786. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide

To a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (25 mg, 0.03 mmol), EXAMPLE 785, and N-methylmorpholine (36 mg, 0.36 mmol) in anhydrous DMF (1 mL) is added methylamine hydrochloride (10 mg, 0.14 mmol) followed by HATU (40 mg, 0.10 mmol) at ambient temperature. After 3 h, the solvent is removed under high vacuum and the residue is dissolved in CH_3CN/water and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 22 mg (88%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 2.57 (d, J = 4.4 Hz, 3H), 2.70 (m, 1H), 3.0 (m, 1H), 3.66 (d, J = 14.2 Hz, 1H), 3.77 (d, J = 14.2 Hz, 1H), 3.85 (m, 1H), 4.03 (d, J = 16.3 Hz, 1H), 5.18 (d, J = 16.3 Hz, 1H), 6.28 (s, 1H), 7.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.51 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.97 (m, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.79 (s, 1H), 9.72 (br s, 2H), 11.18 (s, 1H) ppm; MS (ISP loop): m/z 478 (M+H).

Table 1: Amide Analogs Derived From C-6 Carboxylic Acid.

Example #	Name	m/z [M+H]
787	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	492
788	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	492
789	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid benzylamide	554
790	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide	508
791	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid bis-(2-hydroxy-ethyl)-amide	552

792	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	534
793	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylcarbamoylmethyl-amide	535

The following compounds are prepared using the procedures described above.

Example #	Name	m/z [M+H]
794	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid	458
795	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester	472
796	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid amide	457
797	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid ethylamide	458
798	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-(4-methyl-piperazine-1-carbonyl)-piperazin-2-one	540

EXAMPLE 799. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (42 mg, 0.08 mmol), EXAMPLE 99, 1,3,5-triazine (40 mg, 0.48 mmol), and glacial HOAc (30 mg, 0.48 mmol) in absolute EtOH (1 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated and then dissolved in water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 17 mg (32%) of the title compound as a white solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 3.47 (m, 1H), 3.67 (s, 3H), 3.71 (d, J = 16.1 Hz, 1H), 4.00 (d, J = 16.5 Hz, 1H), 4.05 (m, 1H), 4.52 (m, 1H), 4.72 (ABq, Δ_{AB} = 248 Hz, J_{AB} = 16.5 Hz, 2H), 7.57 (m, 2H), 8.05 (d, J = 8.6 Hz, 1H), 8.20 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.49 (s, 1H), 8.72 (s, 1H), 9.57 (br s, 2H) ppm; MS (ion spray): m/z 546 (M+H).

EXAMPLE 800. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Water (1 mL) is added to a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (20 mg, 0.03 mmol), EXAMPLE 799, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (15 mg, 0.35 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 12 mg (63%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.69 (d, J = 16.0 Hz, 1H), 3.97 (d, J = 16.0 Hz, 1H), 4.08 (d, J = 11.7 Hz, 1H), 4.18 (d, J =16.2 Hz, 1H), 4.31 (d, J = 2.7 Hz, 1H), 5.20 (d, J =16.2 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.52 (s, 1H), 7.58 (dd, J = 8.6, 1.9 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.54 (s, 1H), 8.77 (br s, 1H) ppm; MS (ion spray): m/z 532 (M+H).

EXAMPLE 801. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide

To a mixture containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (45 mg, 0.08 mmol), EXAMPLE 800, N-methylmorpholine (18 mg, 0.18 mmol), and HATU (35 mg, 0.09 mmol) in anhydrous DMF (1 mL) is added NH_3 (7N in MeOH, 2 drops, approx. 0.5 mmol). The heterogeneous mixture is stirred 16 h at ambient temprature and then concentrated to dryness. The residue is dissolved in water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 25 mg (46%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.63 (d, J = 16.0 Hz, 1H), 4.01 (m, 4H), 5.17 (d, J = 16.6 Hz, 1H), 7.58 (m, 3H), 8.08 (d, J = 8.6 Hz, 1H), 8.17 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.74 (s, 1H), 9.63 (br s, 2H) ppm; MS (ISP loop): m/z 531 (M+H).

The following compounds are prepared using the procedures described above.

Example #	Name	m/z [M+H]
802	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester	560
803	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid	531
804	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-	544

	benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide	
805	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	558
806	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	558
807	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	600

EXAMPLE 808. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

To a solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (1.17 g, 2.6 mmol), EXAMPLE 784, Part B, 5-chlorothiophen-2-yloxyacetic acid (0.5 g, 2.6 mmol), EXAMPLE 24,and N-methylmorpholine (0.58 g, 5.72 mmol) in anhydrous DMF (10 mL) is added HATU (1.09 g, 2.86 mmol) at ambient temperature. After 1.5 h, the reaction mixture is diluted with CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ (100 mL) and the layers are separated. The aqueous phase is washed four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed once with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude amide is purified by flash silica gel chromatography (hexane/EtOAc, 4:1 to 1:2) to afford 1.5 g of the title compound which is used directly in the next reaction. ^1H NMR (300 MHz, $CDCl_3$, ~2:1 mixture of rotomers) major rotomer: δ 3.55 (d, J = 15.2 Hz, 1H), 3.60 (m, 1H), 3.69 (m, 5H), 4.37 (d, J = 17.7 Hz, 1H), 4.62 (m, 2H), 4.79 (d, J = 13.3 Hz, 1H), 5.35 (d, J = 15.2 Hz, 1H), 6.05 (d, J = 3.9 Hz, 1H), 6.52 (m. 2H), 6.84 (d, J = 8.1 Hz, 1H), 7.18-7.49 (m, 11H), 7.76 (m, 1H) ppm; MS (ISP loop): m/z 627 (M+H).

B. (±)-1-(3-Amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

Concentrated HCl (12M, 0.5 mL) is added at 0 °C to a solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (1.5 g, 2.39 mmol) in 4:1 MeOH/THF (25 mL). After 1.5 h, the reaction

mixture is concentrated to dryness and then partitioned between a 1:1 mixture of EtOAc/aqueous $NaHCO_3$ (200 mL) and the layers are separated. The aqueous phase is extracted with EtOAc and then the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (hexane/EtOAc, 4:1 to 1:2) to provide 934 mg (84%, two steps) of the title compound. ^1H NMR (300 MHz, $CDCl_3$, ~2:1 mixture of rotomers) selected peaks: δ 3.16 (app. dd, J 14.0, 3.8 Hz, 1H), 3.68 (s, 3H), 3.96 (app. dd, J = 3.8, 2.0 Hz, 1H), 4.17 (d, J = 17.7 Hz, 1H), 4.45 (br s, 2H), 4.62 (m, 2H), 4.87 (d, J = 14.1 Hz, 1H), 5.21 (d, J = 15.1 Hz, 1H), 6.07 (m, 1H), 6.51 (d, J = 3.8 Hz, 1H), 6.57 (d, J = 7.9 Hz, 1H), 6.62 (br s, 1H), 7.35 (d, J = 7.9 Hz, 1H) ppm; MS (ISP loop): m/z 463 (M+H).

C. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (110 mg, 0.25 mmol), 1,3,5-triazine (207 mg, 2.55 mmol), and glacial HOAc (157 mg, 2.55 mmol) in absolute EtOH (5 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated to dryness and then purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 50 mg (32%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.34-3.89 (m, 2H), 3.60 (s, 3H), 4.14-4.54 (m, 3H), 4.64 (br d, J = 14.4 Hz, 1H), 4.78-5.11 (m, 3H), 6.19 (d, J = 4.1 Hz, 1H), 6.73 (d, J = 4.1 Hz, 1H), 7.64 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.79 (s, 1H), 9.71 (br s, 2H) ppm; MS (ion spray): m/z 490 (M+H).

EXAMPLE 809. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methylamide.

Water (1 mL) is added to a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (20 mg, 0.03 mmol), EXAMPLE 808, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (3 mg, 0.07 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 25 mg (>100 %) of the associated acid as a white solid after lyophilization which is used directly in the next reaction. To a mixture containing (+/-)-1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid (12 mg, 0.02 mmol), N-methylmorpholine (19 mg, 0.19 mmol), and HATU (22 mg, 0.05 mmol) in anhydrous DMF (1 mL) is added $MeNH_2$ hydrochloride (5 mg, 0.19 mmol). The reaction mixture is stirred 1 h at ambient temperature and then concentrated to dryness. The residue is dissolved in water

and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 7 mg (58%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) mixture of rotamers: δ 2.51 (m, 3H), 4.07-4.54 (m, 6H), 4.87 (m, 2H), 5.10 (m, 1H), 6.18 (m, 1H), 6.74 (m, 1H), 7.62 (m, 2H), 8.06 (br s, 1H), 8.32 (br d, J = 8.8 Hz, 1H), 8.78 (s, 1H), 9.61 (br s, 2H) ppm; MS (ISP loop): 489 (M+H).

The following compound is prepared using the procedures described above.

Example #	Name	m/z [M+H]
810	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethylamide	503

EXAMPLE 811. (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid.

Water (0.5 mL) is added to a solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (35 mg, 0.08 mmol), EXAMPLE 808, Part B, in a 1:1 mixture of THF/MeOH (1 mL). At ambient temperature, LiOH monohydrate (4 mg, 0.10 mmol) is then added. After 16 h, an additional portion of LiOH monohydrate (4 mg, 0.10 mmol) is added and the reaction mixture is stirred for another 2 h then diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 40 mg (95%) of the associated acid as a white solid after lyophilization which is used directly in the next reaction. MS (ISP loop): m/z 449 (M+H).

A solution containing (+/-)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid (20 mg, 0.03 mmol), 1,3,5-triazine (28 mg, 0.34 mmol), and glacial HOAc (20 mg, 0.34 mmol) in absolute EtOH (6 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated to dryness and then purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 15 mg (75%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.75-4.38 (m, 5H), 4.67 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 15.3 Hz, 1H), 4.95 (m, 1H), 5.09 (br d, J = 16.0 Hz, 1H), 6.18 (m, 1H), 6.71 (m, 1H), 7.64 (m, 2H), 8.31 (d, J = 8.5 Hz, 1H), 8.75 (s, 1H), 9.64 (br s, 2H) ppm; MS (ISP loop): m/z 476 (M+H).

EXAMPLE 812. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.3 g, 13.0 mmol), EXAMPLE 69, in CH_3CN (250 mL) is cooled to 0°C. Potassium carbonate (1.98 g, 14.3 mmol) is added to the reaction mixture followed by propargyl bromide (1.55g, 13.0 mmol). The mixture is slowly warmed to ambient temperature and maintained until complete consumption of starting material is observed by TLC (approx. 8 h). The mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to provide 3.38 g (70%) of the title compound as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.34 (t, J = 2.4 Hz, 1H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J = 2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J = 1.4 Hz, 2H), 6.42 (br s, 1H), 7.88 (dd, J = 5.8, 0.8 Hz, 1H), 8.41 (d, J = 5.8 Hz, 1H), 8.78 (d, J = 0.8 Hz, 1H) ppm; MS (EI): m/z 368 (M+).

B. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.3 g, 3.53 mmol) in CH_2Cl_2 (100 mL) is added TFA (20 mL) at 0 °C. After 6 h, the reaction mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (500 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 616 mg (65%) of the title compound as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (app t, J = 2.4 Hz, 1H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J = 2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 8.85 (d, J = 0.9 Hz, 1H), 9.34 (br s, 1H) ppm; MS (EI): m/z 268 (M+).

EXAMPLE 813. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.27 mmol), EXAMPLE 812, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.27 mmol), EXAMPLE 69, Part B, Et_3N (110 mg, 1.08 mmol),

$(Ph_3P)_4PdCl_2$ (10 mg, 0.013 mmol), and CuI (1 mg, 0.008 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 77 mg (51%) of SC41 as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$, ~2:1mixture of rotamers) major rotamer: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1H), 8.09 (m, 2H), 8.34 (m, 1H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; MS (ISP loop): m/z 561 (M+H).

B. 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (42 mg, 0.27 mmol) is added to a suspension containing 2-{4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (SC41, 77 mg, 0.14 mmol) in anhydrous CH_3CN (10 mL) and the mixture is warmed to 50 °C. After 4 h, the reaction mixture is concentrated to dryness and the residue is partitioned between CH_2Cl_2 (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 85 mg of SC42 as a crude solid which is used directly without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J = 1.1 Hz, 2H), 6.39 (d, J = 0.7 Hz, 1H), 6.68 (d, J = 0.7 Hz, 1H), 7.86 (m, 1H), 8.41 (m, 1H), 8.76 (br s, 1H), 8.82 (br s, 1H) ppm; MS (EI): m/z 561 (M+H).

C. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (85 mg, 0.14mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at 0 °C and the solution is allowed to slowly warm to ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 35 mg (36%, two steps) of SC43 as a pale yellow, lyophilized solid. ^1H NMR (300 MHz, d_6-DMSO) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 8.37 (d, J = 6.7 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1H), 14.91 (br s, 2H) ppm; MS (ion spray): m/z 361 (M+H). $C_{23}H_{25}ClN_4OS$ MS m/z: 441,443.

EXAMPLE 814. 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile.

A. {1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester:

Sodium hydride (140 mg, 3.51 mmol) is added to a cooled solution of (2-oxo-piperidin-4-yl)-acetic acid ethyl ester (500 mg, 2.70 mmol) in 10 mL of THF. After stirring for forty five minutes, 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (1.43 g, 3.82 mmol), EXAMPLE 13, is added, and the reaction is left to stir overnight. THF is removed, and the residue is taken up in 250 mL of ethyl acetate. Excess sodium hydride is quenched with 5 mL of water, and normal aqueous work-up followed. The crude product is chromatographed on silica gel (50% EtOAc/Hexane) to give{1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester (732 mg, 57%)as a light yellow solid. $C_{30}H_{29}N_3O_3$ MS m/z: 480, 482. Anal cald. for $C_{30}H_{29}N_3O_3$: C,75.13; H, 6.09; N, 8.76. Found C, 73.01; H, 6.02; N, 8.46.

B. {1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid

To a solution of {1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester (732 mg, 1.53 mmol) in 5 mL of THF is added 1N sodium hydroxide (1.53 ml, 1.53 mmol). After stirring for four hours, the THF is removed and EtOAc (500 mL) is added. The reaction mixture is acidified to a pH of 6 and normal aqueous work-up followed. The desired carboxylic acid (571 mg, 83% yield) is isolated as a white solid.

C. N-(2-amino-5-chloro-phenyl)-2-{1-[3-(benzhydrylidene-amino)-4-cyano-benyl]-2-oxo-piperidin-4-yl}-acetamide

To a slurry of the {1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid (190 mg, 0.422 mmol) in THF (5 mL) and methylene chloride (3 mL) is added triethylamine (0.09 ml, 0.633 mmol). The solution is cooled to 0 °C , and 1M isopropyl chloroformate in toluene (0.422 mL, 0.422 mmol) is added. The homogenous mixture is allowed to warm to room temperature, and 4-chloro-1,2-phenylene-diamine (150 mg, 1.06 mmol) is added. The reaction is stirred at room temperature overnight. The volatile solvents are removed, and the resulting residue is chromatographed (SiO_2, 5%MeOH/EtOAc) to give N-(2-amino-5-chloro-phenyl)-2-{1-[3-(benzhydrylidene-amino)-4-cyano-benyl]-2-oxo-piperidin-4-yl}-acetamide (200 mg, 82% yield). $C_{34}H_{30}ClN_5O_2$ MS m/z: 576, 578.

D. 2-(Benzhydrylidene-amino)-4-[4-(6-cloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl}-benzonitrile

The acetamide (200 mg, 0.35 mmol) is dissolved in 2 mL of acetic acid and refluxed for three hours. The acetic acid is removed, and the residue taken up in ethyl acetate and washed with saturated sodium bicarbonate. Concentration of the solvent afforded 2-(benzhydrylidene-amino)-4-[4-(6-cloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl}-benzonitrile (200 mg, 100% yield) which is used without further purification. $C_{34}H_{28}ClN_5O_5$ MS m/z:+ 558, 560.

E. 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt

The above benzonitrile (220 mg, 0.36 mmol) is dissolved in 5 ml of methanol. Hydrochloric acid is bubbled into the ice-cooled methanol solution followed by three drops of water. After stirring at room temperature for one hour, the MeOH is removed. The resulting white solid is titurated with EtOAc. After drying under high vacuum, 2-amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (145.6 mg, 87% yield) is obtained as a white solid. $C_{21}H_{20}ClN_5O$: MS m/z: 394,396.

EXAMPLE 815. 4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzamidine

Hydrochloric acid is bubbled into an ice cooled solution of 4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile (127 mg, 0.336 mmol) in 10 mL of methanol. The solution also contained 3Å molecular sieves. The reaction is stored at -30 for forty-eight hours. The methanol is condensed on the rotovap. Fresh methanol (15 mL) is added followed by a stream of ammonia gas. The reaction is heated to reflux for two and half hours. The reaction mixture is filtered at room temperature. Methanol is removed from the mother liquor. The resulting residue is purified by reverse phase HPLC (0-50 % ACN/H_2O). The product is isolated as a white solid with a melting point of 105-110 °C . $C_{21}H_{22}ClN_5O$ MS m/z: 396,398. Anal. cald. for $C_{21}H_{22}ClN_5O \cdot 2C_2HF_3O_2$: C, 48.13; H, 3.88; N,11.22. Found: C, 45.05; H, 3.52; N, 9.89.

EXAMPLE 816. 1-(4-Amino-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one.

To a solution of 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (143 mg, 0.308 mmol), EXAMPLE 814, Part E, in 2 mL of ethanol is added triethylamine (0.05 mL, 0.366 mmol), glacial acetic acid (0.02mL, 0.366 mmol) and triazine (15 mg, 0.183 mmol). The resulting mixture is refluxed overnight. The volatile solvents are removed on the rotovap, and the residue is purified by reverse phase HPLC (0 - 50% Acetonitrile/H_2O). The desired product (110 mg, 55% yield) is isolated as a white powder with a melting point of 128-132

°C . $C_{22}H_{21}ClN_6O$ MS m/z: 421, 423. Anal. calcd. for $C_{22}H_{21}ClN_6O$: C, 48.12; H, 3.57; N, 12.95. Found: C, 45.79; H, 3.68; N, 11.94. H NMR (CD_3OD) δ: 8.67 (s, 1H); 8.31 (d, 1H, J = 4.0 Hz); 7.83-7.55 (m, 5H); 4.93-4.73 (m, 2H); 3.48-3.42 (m, 2H); 3.31-3.21 (m, 2H); 2.71-2.58 (m, 2H); 2.43-2.33 (m, 1H); 2.07- 2.01 (m, 1H); 1.82 - 1.69 (m, 1H).

EXAMPLE 817. 4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(2,4-diamino-quinazolin-7-ylmethyl)-piperidin-2-one

2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (70 mg, 0.15 mmol), EXAMPLE 814, Part E, pyridine (1.0 mL) and freshly made chloroformamide hydrochloride (150 mg, 1.33 mmol) are placed in a sealed tube and heated to 200 °C . The resulting mixture is heated for twenty four hours. The crude reaction mixture is directly purified by reverse phase HPLC (0-50% ACN/H_2O). The product (53 mg, 45% yield) is isolated as a tanish solid. $C_{22}H_{22}ClN_7O$ MS m/z: 436,438. Anal. calcd. for $C_{22}H_{22}ClN_7O$: C, 43.23; H, 3.24; N, 12.60. Found: C, 43.16; H, 3.44; N, 13.40.

EXAMPLE 818. 1-(4-Amino-2-methyl-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one.

A stream of hydrogen chloride gas is bubbled intermittently through an ice-cold mixture of 2-amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (57 mg, 0.123 mmol), EXAMPLE 814, Part E, and acetonitrile (0.03 mL, 0.93 mmol) in 1.5 mL of dioxane for six hours. The dioxane is removed; the residue is purified by reverse phase HPLC (0-40 % ACN/H_2O). The desired product (9.5 mg, 12% yield) is isolated as a clear wax. $C_{23}H_{23}ClN_6O$ MS m/z : 435, 437.

The following compounds are prepared using the methods described above.

Example #	Name	m/z [M+H]
819	(3S, 5R)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443
820	(3S,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443
821	4-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl}-benzamidine	431, 433
822	(3R,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443

EXAMPLE 823. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide.

A. 4-tert-Butoxycarbonylmethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid benzyl ester (4.68g, 20mmol) in 20 mL of DMF at) 0°C is added sodium hydride (60%, 880 mg, 22 mmol). The suspension is stirred at ambient temperature for one t-butyl bromoacetate (4.68 g, 24 mmol) is added. The resulting mixture is stirred at ambient temperature overnight. After dilution with ethyl acetate (200 mL), the mixture is washed with brine (3 x 50 mL). The crude residue obtained from concentration of the organic phase is chromatographied on silica gel (30% ethyl acetate/Hexane) to give 5.57 g (80%) of 4-tert-butoxycarbonylmethyl-3-oxopiperazine-1-carboxylic acid benzyl ester as a white solid.

B. (2-Oxo-piperazin-1-yl)acetic acid tert-butyl ester.

4-tert-Butoxycarbonylmethyl-3-oxopiperazine-1-carboxylic acid benzyl ester (2.0g, 5.75 mmol) is dissolved in 20 mL of methanol and 2 mL of acetic acid. Palladium (5%) on carbon (100 mg) is added, and the reaction mixture is stirred in an atmosphere of hydrogen overnight. The mixture is filtered and concentrated. Ethyl acetate is added, and the mixture is neutralized to pH 7 using 1N NaOH. The organic layer is concentrated to give (2-oxo-piperazin-1-yl)acetic acid tert-butyl ester (1.22g).

C. [4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester.

To a solution of (2-oxo-piperazin-1-yl)acetic acid tert-butyl ester (1.22 g, 5.7 mmol) in 10 ml of methylene chloride is added triethylamine (1.2 mL, 8.55 mmol) and 6-chlorobenzothiophenesulfonyl chloride (1.52 g, 5.7 mmol). The reaction mixture is stirred overnight at ambient temperature. Flash column chromatography (50 % ethyl acetate / hexane) affords 2.3 g (92%) of [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester.

D. [4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]-acetic acid.

[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester (500 mg, 1.13 mmol) is dissolved in 1 mL of trifluoroacetic acid and 3 mL of CH_2Cl_2. The solvents are azeotropically removed with toluene. [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid (438 mg) is isolated as a white solid.\

E. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide.

To a slurry of [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid (47 mg, 0.12 mmol) in 2 mL of tetrahydrofuran is added Et_3N (0.025 mL, 0.18 mmol). The mixture is cooled to 0°C, and 1M solution of isopropyl chloroformate in toluene (0.12 mL, 0.12mmol) is added. The mixture is stirred for fifteen minutes and histamine (13.3 mg, 0.12 mmol) is added. The mixture is stirred overnight at room temperature. Reverse phase HPLC ($AcCN/H_2O$/TFA) affords 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide trifluoroacetic acid salt (17 mg, 25%) as a solid. mp 77-82°C; MS m/z 482 (M+H).

The followin compounds are prepared from the appropriate starting materials using the method of EXAMPLE 823.

Example #	Name	m/z [M+H]
824	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-4-yl-acetamide	465, 467
825	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-3-ylmethyl-acetamide	479, 481
826	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-piperidin-4-yl-acetamide	471, 473
827	N-(1-Carbamimidoyl-piperidin-4-yl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	513, 515
828	5-(2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetylamino}-ethyl)-imidazole-1-carboxylic acid ethyl ester	554, 556
829	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyrimidin-4-yl-acetamide	466, 468
830	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-phenyl-acetamide	464, 466
831	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(9H-purin-6-yl)-acetamide	506, 508
832	N-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	509, 511
833	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-imidazol-1-yl-propyl)-acetamide	496, 498
834	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-	496, 498

	N-[2-(1-methyl-1H-imidazol-4-yl)-ethyl]-acetamide	
835	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-4-yl-ethyl)-acetamide	493, 495
836	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(3-methyl-3H-imidazol-4-yl)-ethyl]-acetamide	496, 498
837	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-2-yl-ethyl)-acetamide	493, 495
838	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-3-yl-ethyl)-acetamide	493, 495
839	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-imidazol-1-yl-ethyl)-acetamide	482, 484
840	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]-acetamide	495, 497
841	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-acetamide	496, 498
842	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(4-dimethylamino-[1,3,5]triazin-2-yl)-acetamide	510, 512
843	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-pyridin-4-yl-acetamide	479, 481
844	N-[2-(2-Amino-pyridin-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	508, 510
845	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(4-methyl-thiazol-5-yl)-ethyl]-acetamide	513, 515
846	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-thiazol-4-yl-ethyl)-acetamide	499, 501
847	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-guanidino-propyl)-acetamide trifluoroacetic acid salt	487, 489
848	N-(3-Amino-propyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	445, 447
849	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-mercapto-1H-imidazol-4-yl)-ethyl]-acetamide	514, 516
850	N-[2-(2-Amino-thiazol-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	514, 516

851	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-(2-pyridin-4-yl-ethyl)-acetamide	507, 509
852	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-methylsulfanyl-1H-imidazol-4-yl)-ethyl]-acetamide	528, 530

EXAMPLE 853. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one.

A. 3-Oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester.

3-Oxo-piperazin-1-carboxylic acid benzyl ester (702 mg, 3.0 mmol) is dissolved in dimethylformamide (10 mL) and cooled to 0°C . Sodium hydride (60%, 148 mg, 3.7 mmol) is added, followed by the addition of 5-(3-chloro-propenyl)-1-trityl-1H-imidazole (473 mg, 1.2 mmol). The resulting mixture is left to stir at room temperature overnight. Most of the dimethylformamide is removed on the high vacuum. The reaction mixture is diluted with ethyl acetate (250 mL) and quenched with water. The two layers are separated and ethyl acetate (2x 100 mL) is used to extract and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (50% EtOAc/hexane) to give 3-oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester (360 mg) as the desired product.

B. 4-[3-(3-tert-Butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

3-Oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester (360 mg, 0.62 mmol) is stirred vigorously in a 30% solution of trifluoroacetic acid and methylene chloride (10 mL). After stirring for three hours, the trityl group is removed. The volatile solvents are removed in vacuo, and the crude product is taken-up in methylene chloride (10 mL). Pyridine (0.5 ml) and Di-tert-butyl dicarbonate (176 mg, 0.81 mmol) is added to the solution, and the resulting mixture is left to stir overnight. The reaction mixture is condensed and purified by flash column (SiO_2, 20% EtOAc/Hexane) to give 4-[3-(3-tert-butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (100 mg).

C. 5-{3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester.

Palladium on carbon (10 %, 15 mg) is added to a solution of 4-[3-(3-tert-butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (50 mg, 0.114 mmol) in 5 mL of methanol. The reaction mixture is left to stir in an atmosphere of hydrogen overnight. The palladium is

filtered off, and the volatile solvents are removed on the rotovap. The crude product (50 mg, 0.114 mmol) is redissolved in methylene chloride (5 mL). Triethylamine (0.06 ml, 0.43 mmol) 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (39 mg, 0.15 mmol) is added, and the resulting mixture is stirred overnight. The crude product is directly purified by flash column (SiO_2, 30% EtOAc/Hexane) to afford 5-{3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester (30 mg).

D. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one:

5-{3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester (30 mg, 0.055 mmol) is stirred vigorously in a 30 % solution of trifluoroacetic acid and methylene chloride (2 mL). The reaction is complete after stirring for three hours. The volatile solvents are removed on the rotovap, and the gummy solid is titurated with ether several times to afford 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one trifluoroacetic acid salt (30 mg) as a yellow solid. $C_{18}H_{19}ClN_4O_3S_2$ (m/z)+: 439, 441. Anal cald. for $C_{18}H_{19}ClN_4O_3S_2 \cdot C_2HF_3O_2$: C, 43.44; H, 3.65; N, 10.13. Found C, 42.03; H, 3.55; N, 8.26.

The following compounds are prepared using the methods described above.

Example #	Name	m/z [M+H]
854	4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamidine	470, 472 Cl pattern
855	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperazin-1-yl-propyl)-piperazin-2-one	457, 459 Cl pattern
856	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-pyridin-4-yl-propyl)-piperazin-2-one	450, 452 Cl pattern
857	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-piperidin-4-yl-butyl)-piperazin-2-one	470, 472 Cl pattern
858	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-piperidin-4-yl-ethyl)-piperazin-2-one	442
859	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperidin-4-yl-propyl)-piperazin-2-one	456

EXAMPLE 860. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one.

A. 3-Methoxymethyl-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared by the method in EXAMPLE 66, Part A, substituting 5-(4-bromomethyl-phenyl)-2-methoxy-pyridine for 4-bromomethyl tolynitrile and 2-methoxymethyl-3oxopiperazin-1-carboxylic acid benzyl ester for 3-oxopiperazin-1-carboxylic acid benzyl ester. MS (ISP) m/z 476, (M+H).

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one

The title compound is prepared by deprotecting 3-methoxymethyl-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester as described in EXAMPLE 75, Part C. The crude amine is then coupled as described in EXAMPLE 123 with 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 25. MS (ISP) m/z 516, 518, (M+H), Cl pattern.

The following compounds are prepared according to the method of Example 860.

Example #	Name	m/z [M+H]
861	4'-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile	522, 524 Cl pattern
862	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-3-hydroxy-benzyl)-piperazin-2-one	471, 473 Cl pattern
863	1-Benzyl-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	421,423 Cl pattern
864	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-benzyl)-piperazin-2-one	455, 457 Cl pattern
865	4-[(4-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516, 518 Cl pattern
866	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	502, 504 Cl pattern
867	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516, 518 Cl pattern
868	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	502, 504 Cl pattern
869	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-methoxy-	482

	pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	
870	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	468
871	1-Biphenyl-4-ylmethyl-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	
872	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	498, 500 Cl pattern
873	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	512, 514 Cl pattern

EXAMPLE 874. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one.

A. 2-Amino-4-(2-oxo-piperazin-1-ylmethyl)-benzonitrile.

To a solution of 4-(3-Amino-4-cyano-benzyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester hydrochloride (4.0 g, 10.0mmol) in CH_3OH (45 ml) and CH_2Cl_2 (10 ml) is added 10% Pd on carbon (0.6 g). The mixture is stirred under an atmosphere of H_2 for 2 hours then is filtered through a pad of celite. The filtrate is concentrated and the residue purified by column chromatography eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2 to yield the title compound (1.62 g, 7.0 mmol). ^{1}H NMR (DMSO,300MHz) δ 7.34 (d, 1H), 6.64 (s, 1H), 6.46 (d, 1H), 6.04 (bs, 2H), 4.40 (s, 2H), 3.28 (s, 2H), 3.14 (m, 2H), 2.87 (m, 2H), 2.77 (bs, 1H). MS (ion spray): m/z 231 $(M+H)^+$.

B. 2-Amino-4-[4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile.

To a cooled solution (0° C) of 2-Amino-4-(2-oxo-piperazin-1-ylmethyl)-benzonitrile (0.345 g, 1.5 mmol) in DMF (2 ml) is added finely powdered anhydrous K_2CO_3 (0.311 g, 2.25 mmol) and allowed to stir for 20 minutes. To this mixture is added a solution of 2-bromomethyl-benzo[b]thiophene (0.392 g, 1.5 mmol) in DMF (3 ml), the cold bath removed and allowed to stir for 2 hours. The reaction mixture is concentrated under high vacuum and the residue purified by column chromatography eluting with 55% EtOAc/ 5% CH_3OH/ hexane to yield the title compound (0.477 g, 1.16 mmol) as a white solid. ^{1}H NMR (DMSO,300MHz) δ 8.06 (d, 1H), 7.78 (d, 1H), 7.37 (m, 3H), 6.64 (s, 1H), 6.44 (d, 1H), 6.09 (bs, 2H), 4.42 (s, 2H), 3.88 (s, 2H), 3.21 (m, 4H), 2.72 (m, 2H). MS (ion spray): m/z 411, 413 $(M+H)^+$, Cl pattern.

C. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one.

To a cooled solution (0° C) of 2-Amino-4-[4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile (0.365 g, 0.89 mmol) in concentrated HCl (2.1 ml) is added dropwise a solution of sodium nitrite (0.068 g, 0.98 mmol) in H_2O (0.2 ml). The reaction mixture is added to a cooled solution (0° C) of tin (II) chloride dihydrate (1.61 g, 7.12 mmol) in concentrated HCl (0.62 ml) and H_2O (3 ml). The precipitate is collected by vacuum filtration and dried under high vacuum. The crude solid is purified by column chromatography eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2 to yield the title compound (0.144 g, 0.34 mmol) as a yellow solid. ^{1}H NMR (DMSO,300MHz) δ 11.35 (bs, 1H), 8.05 (d, 1H), 7.78 (d, 1H), 7.64 (d, 1H), 7.37 (m, 2H), 7.08 (s, 1H), 6.78 (d, 1H), 5.75 (s, 1H), 5.40 (bs, 1H), 4.58 (s, 2H), 3.88 (s, 2H), 3.20 (m, 4H), 2.70 (bt, 2H). MS (ion spray): m/z 426 $(M+H)^+$. Anal. cald. for $C_{21}H_{20}N_5OSCl;(H_2O)_{0.25}$: C, 58.6; H, 4.8; N, 16.3. Found C, 58.6; H, 4.7; N, 15.9. M.P.= 246-248°C.

EXAMPLE 875. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one.

A. 2-Amino-4-{4-[3-(5-chloro-thiophen-2-yl)-allyl]-2-oxo-piperazin-1-ylmethyl}-benzonitrile.

Using essentially the same procedure as in EXAMPLE 874, Part B using 2-(3-bromo-propenyl)-5-chloro-thiophene is obtained the title compound. MS (EI): m/z 386, 388 (M^+), Cl pattern.

B. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one.

Using essentially the same procedure as in EXAMPLE 874, Part C there is obtained the title compound. ^{1}H NMR (DMSO, 300MHz) δ 11.32 (bs, 1H), 7.62 (d, 1H), 7.06 (s, 1H), 7.02 (d, 1H), 6.96 (d, 1H), 6.78 (d, 1H), 6.67 (d, 1H), 5.96 (m, 1H), 5.32 (bs, 2H), 4.57 (s, 2H), 3.19 (bt, 2H), 3.12 (m, 4H), 2.64 (bt, 2H). MS (EI): m/z 401, 403 (M^+), Cl pattern. Anal. cald. for $C_{19}H_{20}ClN_5OS$: C, 56.8; H, 5.0; N, 17.4. Found C, 56.6; H, 4.8; N, 17.2. M.P.= 167-169°C

EXAMPLE 876. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

A. 2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperzin-1-ylmethyl]-benzonitrile.

Using essentially the same procedure as in EXAMPLE 874, Part B except using 6-chloro-benzo[b]thiophene-2-sulfonyl chloride, EXAMPLE 1, is obtained the title compound. MS (ion spray): m/z 461, 463 $(M+H)^+$, Cl pattern.

B. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

Using essentially the same procedure as in EXAMPLE 874, Part C there is obtained the title compound. ^{1}H NMR (DMSO, 300MHz) δ 11.29 (s, 1H), 8.35 (s, 1H), 8.18 (s, 1H), 8.08 (d, 1H), 7.58

(m, 2H), 7.05 (s, 1H), 6.70 (d, 1H), 5.30 (bs, 2H), 4.56 (s, 2H), 3.84 (s, 2H), 3.40 (m, 2H), 3.30 (m, 2H). MS (ion spray): m/z 476, 478 $(M+H)^+$, Cl pattern. Anal. cald. for $C_{20}H_{18}ClN_5O_3S_2$: C, 50.5; H, 3.8; N, 14.7. Found C, 50.3; H, 3.6; N, 14.5. M.P.=274-276°C.

The following compounds are prepared using the procedures described above.

Example #	Name	m/z
877	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(S)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine	441, 443 Cl pattern
878	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(R)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine	441, 443 Cl pattern
879	3-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine	427, 429 Cl pattern
880	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine	427, 429 Cl pattern

Inhibition of Factor Xa

The compounds described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, controlling the activity of Factor Xa. Both the activity of free Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula 1. The inhibition of the Factor Xa activity is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective inhibition of the Factor Xa activity is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the activity of Factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that

often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

Accumulated experimental evidence has also reflected that prothrombin activation is only one of the biological activities of Factor Xa. EPR-1 (effector cell protease receptor-1, recognizing Factor Xa), is believed to mediate several of the vascular wall interactions by Factor Xa. It has been shown to be expressed on human umbilical vein endothelial cells, rat smooth muscle cells and platelets(CR McKenzie, et al., Arterioscler Thromb Vasc Biol 16 1285-91 (1996); also F Bono, et al., J Cell Physiol 172 36-43 (1997), AC Nicholson, et al., J Biol Chem 271 28407-13 (1996),J.M. Herbert, et al., J Clin Invest 101 993-1000 (1998)). This protease-receptor interaction could mediate not only prothrombinase-catalyzed thrombin generation, but also diverse cellular functions such as cell proliferation, release of PDGF and DNA syntheses. The mitogenic effect of Factor Xa has been reported to be dependent on Factor Xa enzymatic activity (F Bono, et al., J Cell Physiol 172 36-43 (1997), J.M. Herbert, et al., J Clin Invest 101 993-1000 (1998)). TAP for example inhibited the mitogenesis of human and rat cultured vascular smooth muscle cells (F Bono, et al., J Cell Physiol 172 36-43 (1997)). In a study of the rabbit carotid artery air-drying injury model, increased EPR-1 expression is detected after vascular injury. Animals treated with the specific Factor Xa inhibitor, DX-9065a, exhibited less neointimal proliferation. The important regulatory role of Factor Xa in the coagulation process coupled with its mitogenic effects points to Factor Xa's involvement in the formation of thrombin at the luminal surface of the vessel wall and contribution to the atherothrombotic process and abnormal proliferation of vascular cells resulting in restenosis or angiogenesis.

These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of inhibitors of the activity of Factor Xa with standard heparin, low molecular weight heparin, direct thrombin inhibitors (i.e. hirudin), aspirin, fibrinogen receptor antagonists, streptokinase, urokinase and/or tissue plasminogen activator may result in greater antithrombotic or thrombolytic efficacy or efficiency. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates

including humans. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any inhibitor of Factor Xa activity can be added to or contacted with any medium containing or suspected of containing Factor Xa and in which it is desired that blood coagulation be inhibited.

In addition to their use in anticoagulant therapy, Factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, a physiological condition which can be ameliorated by the administration of an inhibitor of the Factor Xa activity, for example conditions as hereinbefore described, which comprises the administration to the patient of a therapeutically effective amount of compound of formula I or a composition containing a compound of formula I. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting the activity of Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I in association with a pharmaceutically acceptable carrier or coating.

In practice compounds of the present invention may generally be administered parenterally, intravenously, subcutaneously intramuscularly, colonically, nasally, intraperitoneally, rectally or orally.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can

contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100,

preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature which tests results are believed to correlate to pharmacological activity in humans and other mammals. The following pharmacological test results are typical characteristics of compounds of the present invention.

Enzyme Assays:

The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of factor Xa and thrombin are determined by active site titration and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays. The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC50). The apparent Ki values are then determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

An additional in vitro assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated partial thromboplastin time is a plasma-based clotting assay that relies on the in situ generation of factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the ex vivo effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this in vitro assay is considered as a surrogate marker for in vivo anticoagulant activity.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 ml of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 ml of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a 3 minute warming period the instrument automatically adds 100 ml of activated cephaloplastin reagent (Actin, Dade) followed by 100 ml of 0.035 M $CaCl_2$ to initiate the clotting reaction. Clot formation is determined spectrophotometrically and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the compound according to the invention.

A compound according to the invention may also be evaluated for their in vivo antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, respectively.

Experimental Plazma Protein Binding Assay

Compounds are dissolved into DMSO to prepare a 10 mM stock. Serial dilutions of compounds are made in a buffer containing 0.05M Tris, 0.15M NaCl, 0.1% PEG-8000, PH 7.5. Human FXa and the substrate, Spectrozyme FXa, are prepared in the aforementioned buffer containing human Albumin and fibrinogen at 3.45 mg/ml and 2.3 mg/ml, respectively. The FXa assay is carried out at room temperature in the 96-well microtiter plates with a final enzyme concentration and substrate concentration of 1nM and 200 μM, respectively. Compound dilutions are added to the wells containing buffer and FXa and preincubated for 30 minutes. The enzyme reactions are initiated by the addition of substrate, Spectrozyme FXa, and the color

developed from the release of p-nitroanilide from each chromogenic substrate is monitored continuously for 5 minutes at 405 nm on a Thermomax microtiter plate reader(Molecular Devices, Sunnyvale, CA.). In the final reaction mixture, the concentration of albumin and fibeinogen is 3mg/ml and 2 mg/ml, respectively.Under the experimental conditions, less than 10% of the substrate is consumed in all assays. The initial velocities measured are used to determine the amount of inhibitor required to diminish 50% of the control velocity and defined as IC_{50} of the inhibitor. Assuming the kinetic mechanisms are competitive inhibition, the apparent Ki values are then calculated according to the Cheng-Prusoff equation , $Ki = IC_{50}/(1 + [S]/Km)$

Experimental In Vivo Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) in vivo generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of 1 ml/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 ml/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled with 0.5 ml of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The

vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 ml ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental In Vivo Rat Arterial Thrombosis Model:

The antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery $FeCl_2$-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper

previously saturated in 35% $FeCl_2$ is placed on top of the vessel downstream from the probe for ten minutes and then removed. The $FeCl_2$ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the $FeCl_2$-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 ml of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to $FeCl_2$ application. The time between $FeCl_2$ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of $FeCl_2$, a second blood sample is drawn (B2). After 10 minutes of $FeCl_2$ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 ml/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

Experimental Canine intravenous and intragastric dosing experiments.

Beagle dogs (9-13 kg) of either sex are used to evaluate the pharmacodynamic effect of compounds of this invention after intravenous and intragastric dosing. Blood samples for these experiments are obtained via venipuncture of the cephalic vein. After discarding the first 0.5 ml of blood drawn, the control sample of 4.5 ml of blood is drawn into chilled plastic syringes containing 0.5 ml of trisodium citrate. After drug administration, 0.9 ml of blood is obtained at each time point (after discarding the first 0.5 ml of blood) by drawing the sample directly into chilled plastic syringes containing 0.1 ml trisodium citrate.

For the intravenous experiments, compounds are administered in the cephalic vein in the forelimb contralateral to that used for blood sampling. Compounds are dissolved in saline (0.5 ml/kg body weight) and administered as an i.v. bolus. Post-dosing blood samples are obtained at specific time points after dosing.

For the intragastric experiments, Compounds (in 0.5% methyl cellulose and 1 % polysorbate-80, 1 ml/kg dosing volume) are administered via an intragastric feeding tube. A pre-dosing control blood sample is obtained as above and post-dosing samples are obtained at specific time points after dosing.

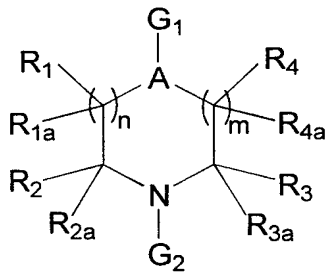
Coagulation times. Platelet-poor plasma is used for determination of activated partial thromboplastin time (APTT) and prothrombin time (PT), which are measured using a Microsample Coagulation Analyzer (MCA210, Bio Data Corp, Horsham, PA) and Dade® reagents (Thromboplastin-C Plus and Actin® FS Activated PTT reagent, Baxter Diagnostics, Inc., Deerfield, IL).

Ex vivo inhibition of Factor Xa. Factor-Xa inhibitory activity is analyzed by chromogenic methods using reagents (bovine factor Xa and spectrozyme Xa) supplied by American Diagnostica (Greenwich, CT). The rate of change of optical density (Vmax, 405 nm) is measured using a SPECTRAmax microtiter plate spectrophotometer and Softmax Pro software (Molecular Devices Corp., Sunnyvale, CA). Inhibition of Xa activity is determined as follows: percent inhibition of Xa activity = 1-(Vmax of sample with inhibitor/Vmax of the pre-drug control sample) X 100.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects of the invention and obtain the ends and advantages mentioned, as well as those inherent therein. The compounds, compositions and methods described herein are presented as representative of the preferred embodiments, or intended to be exemplary and not intended as limitations on the scope of the present invention.

We Claim

1. A compound of formula



or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof

wherein

G_1 and G_2 are L_1-Cy_1 or L_2-Cy_2, provided that when R_1 and R_{1a} or R_4 and R_{4a} taken together form O or S, then G_1 is L_2-Cy_2 and G_2 is L_1-Cy_1, or when R_2 and R_{2a} or R_3 and R_{3a} taken together form O or S, then G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

Cy_1 and Cy_2 are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is O, NR_5, $-S(O)_p-$, $-S(O)_pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$,

L_3 and L_5 are independently absent, optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene;

L_4 is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene;

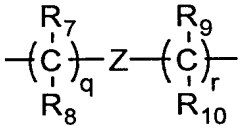
Q and Q' are independently absent, O, S, NR_5, $-S(O)_p-$, $-S(O)_pNR_5-$ or -C(X)Y-;

A is CH or N;

R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, Y^1Y^2NCO, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a}, R_3 and R_{3a}, or R_4 and R_{4a} taken together form O or S;

m and n are independently 0, 1 or 2, provided that m and n are not both 0 and further provided that when R_1 and R_{1a} taken together form O or S, n is 1 and when R_4 and R_{4a} taken together form O or S, m is 1;

L_2 is absent or a group of formula



R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)_v-$, $R_6O_2C(CH_2)_x-$, $Y^1Y^2NC(O)(CH_2)_x-$, or $Y^1Y^2N(CH_2)_v-$;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy

or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α substituted to a N, O or S in Z;

X is O or S;

Y is absent or is selected from O, S and NR_5;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, $S(O)_p$, NR_5, $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4;

v is 2, 3 or 4;

p is 1 or 2; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0;

2. A compound according to claim 1 wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

3. A compound according to claim 1 wherein Z is absent or is selected from O, $S(O)_p$ and NR_5;

4. A compound according to claim 3 wherein m is 1; and n is 1.

5. A compound according to claim 4 wherein A is N.

6. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

7. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2, R_{2a} and R_4 are hydrogen; and R_{4a} is optionally substituted alkyl.

8. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2 and R_4 are hydrogen; and R_{2a} and R_{4a} are optionally substituted alkyl.

9. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a} and R_4 are hydrogen; and R_{1a} and R_{4a} are optionally substituted alkyl.

10. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a}, R_4 and R_{4a} are hydrogen; and R_{1a} is carboxy, alkoxycarbonyl, Y^1Y^2NCO or optionally substituted alkyl.

11. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_4 and R_{4a} are hydrogen; and R_{2a} is carboxy, alkoxycarbonyl, Y^1Y^2NCO or optionally substituted alkyl.

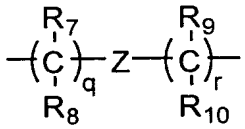
12. A compound according to claim 5 wherein L_1 is $-S(O)_p-$, -C(X)Y- or -L3-Q-L4-Q'-L5-.

13. A compound according to claim 5 wherein Cy_1 is optionally substituted aryl or optionally substituted heteroaryl.

14. A compound according to claim 5 wherein L_2 is alkylene of one to three carbon atoms.

15. A compound according to claim 14 wherein L_2 is $-CH_2-$.

16. A compound according to claim 5 wherein L_2 is a group of formula



wherein Z is NR_5; q is 2; r is 0; R_5 is hydrogen or optionally substituted alkyl; and R_7 and R_8 are hydrogen.

17. A compound according to claim 16 wherein R_5 is hydrogen.

18. A compound according to claim 5 wherein Cy_2 is optionally substituted aryl or optionally substituted heteroaryl.

19. A compound according to claim 5 wherein L_1 is $-S(O)_2-$.

20. A compound according to claim 5 wherein L_1 is -C(X)Y-; X is O; and Y is NH.

21. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; Q is $-S(O)_2-$ or -C(O)-; and L_4 is optionally substituted alkenylene.

22. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; and L_4 is optionally substituted alkylene.

23. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; Q is -C(O)-; Q' is O; and L_4 is optionally substituted alkylene.

24. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; L_3 is optionally substituted alkylene; and L_4 is optionally substituted alkenylene.

25. A compound according to claim 5 wherein Cy_1 is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl, optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

26. A compound according to claim 5 wherein Cy_2 is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

27. A compound according to claim 1 wherein Z is $-NR_5C(O)-$ and $-C(O)NR_5-$.

28. A compound according to claim 27 wherein m is 1; and n is 1.

29. A compound according to claim 28 wherein A is N.

30. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

31. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2, R_{2a} and R_4 are hydrogen; and R_{4a} is optionally substituted alkyl.

32. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2 and R_4 are hydrogen; and R_{2a} and R_{4a} are optionally substituted alkyl.

33. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a} and R_4 are hydrogen; and R_{1a} and R_{4a} are optionally substituted alkyl.

34. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a}, R_4 and R_{4a} are hydrogen; and R_{1a} is carboxy, alkoxycarbonyl or optionally substituted alkyl.

35. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_4 and R_{4a} are hydrogen; and R_{2a} is carboxy, alkoxycarbonyl or optionally substituted alkyl.

36. A compound according to claim 29 wherein L_1 is $-S(O)_p-$, -C(X)Y- or-L3-Q-L4-Q'-L5-.

37. A compound according to claim 29 wherein Cy_1 is optionally substituted aryl or optionally substituted heteroaryl.

38. A compound according to claim 29 wherein R_5, R_7, R_8, R_9 and R_{10} are hydrogen.

39. A compound according to claim 29 wherein Cy_2 is optionally substituted aryl or optionally substituted heteroaryl.

40. A compound according to claim 29 wherein L_1 is $-S(O)_2-$.

41. A compound according to claim 29 wherein L_1 is -C(X)Y-; X is O; and Y is NH.

42. A compound according to claim 29 wherein L_1 is -L3-Q-L4-Q'-L5-; Q is $-S(O)_2-$ or -C(O)-; and L_4 is optionally substituted alkenylene.

43. A compound according to claim 29 wherein L_1 is-L3-Q-L4-Q'-L5-; and L_4 is optionally substituted alkylene.

44. A compound according to claim 29 wherein L_1 is-L3-Q-L4-Q'-L5-; Q is -C(O)-; Q' is O; and L_4 is optionally substituted alkylene.

45. A compound according to claim 29 wherein L_1 is-L3-Q-L4-Q'-L5-; L_3 is optionally substituted alkylene; and L_4 is optionally substituted alkenylene.

46. A compound according to claim 29 wherein Cy_1 is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl, optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

47. A compound according to claim 29 wherein Cy_2 is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

48. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

49. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of the compound according to claim 1.

50. A compound selected from

4-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxo-piperazine-1-ylmethyl]benzamidine,
4-[4-(4-Methoxy-benzenesulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(5-Chloro-thieno[3,2-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[2-Oxo-4-(thieno[2,3-c]pyridine-2-sulfonyl)-piperazin-1-ylmethyl]-benzamidine,
4-[4-(7-Chloro-thieno[2,3-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(4-Chloro-thieno[3,2-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine,
4-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-Amino-3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

3-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine,

3-[4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

3-[4-(4-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

3-[4-(5-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

3-[4-(6-Methoxy-naphthalene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

3-{4-[5-(5-Nitro-pyridine-2-sulfonyl)-thiophene-2-sulfonyl]-2-oxo-piperazin- 1-ylmethyl}-benzamidine,

3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]- benzamidine,

3-{4-[2-(3-Chloro-phenyl)-ethenesulfonyl]-2-oxo-piperazin-1-ylmethyl}- benzamidine,

3-[2-Oxo-4-(4-phenylazo-benzenesulfonyl)-piperazin-1-ylmethyl]-benzamidine,

3-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]- benzamidine,

4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

4-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl}benzamidine,

3-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl}benzamidine,

3-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)piperazin-2-one,

6-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]-1H-quinolin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-3-ylmethyl-piperazin-2-one,

1-(2-Amino-quinoxalin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-one,

1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-hydroxy-isoquinolin-6-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-6-ylmethyl)-piperazin-2-one,

7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-7-ylmethyl)-piperazin-2-one,

1-(7-Amino-thieno[2,3-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-quinolin-6-ylmethyl-piperazin-2-one,

7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-1H-quinolin-2-one,

1-(2-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1,2,3,4-tetrahydro-isoquinolin-6-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-isoquinolin-6-ylmethyl-piperazin-2-one,

1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-6-ylmethyl)-piperazin-2-one,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-7-ylmethyl)-piperazin-2-one,

1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-c]pyridin-3-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid,

(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-piperazin-2-one,

(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-piperazin-2-one,

(S)-4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one,

1-(2-Amino-quinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-(4-methoxybenzyl)piperazin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-6-chlorobenzo[b]thiophen-2-ylmethyl)piperazin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-(5-methoxy-1H-benzoimidazol-2-ylmethyl)piperazin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)piperazin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]piperazin-2-one,

3-[4-(2-Aminoquinolin-6-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one,

1-(2-Aminoquinolin-6-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one,

3-(4-Biphenyl-3-ylmethyl-3-oxo-piperazin-1-ylmethyl)-benzamidine,

4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-piperazin-2-one,

1,4-Bis-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-,

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-benzamidine,

4-(4-Cyclohexylmethyl-2-oxo-piperazin-1-ylmethyl)-benzamidine,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one,

(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 3-chloro-benzylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 4-chloro-benzylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-isoxazol-3-yl-thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(3-chloro-phenyl)-ethyl]-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(4-chloro-phenyl)-ethyl]-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

4-(3-Amino-benzenesulfonyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methyl-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,

(+/-)-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-piperazin-2-yl]-acetic acid,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-6-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(5-oxy-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(3-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(6-Bromobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]-benzo[b]thiophene-6-carbonitrile,

4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-[2-(4-Chlorophenyl)ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid,

4-(5-Pyridin-4-ylthiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid ethyl ester,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-methoxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one,

4-(6-Chlorothieno[3,2-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[2,3-c]pyridin-1-yl} acetic acid methyl ester,

2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]benzo[b]thiophene-5-carbonitrile,

4-(5-Aminomethylbenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

2-{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl}acetamide,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one,

4-(6-Chloro-1H-benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(1H-Benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Aminomethyl-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,

1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethanesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2-(5-Chloro-4-methoxy-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one,

4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one,

4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one,

{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[2,3-c]pyridin-1-yl}-acetic acid methyl ester,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)piperazin-2-one,

(±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(±)-1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

(±)-1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

(±)-1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid,

(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(-)-1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

(+)-1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

(±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid,

(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid,

(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid amide,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2-(4-Chloro-phenyl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-ylmethyl)piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one,

3-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxopiperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-(E)-enyl]-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-2-methyl-(E)-allyl]-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-furan-2-yl)-(E)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-methoxy-pyridin-3-yl)-(E)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-4-oxy-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-prop-2-ynyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-2-yl-prop-2-ynyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-4-methyl-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,7-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-p-tolyl-prop-2-ynyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-m-tolyl-prop-2-ynyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-4-yl-prop-2-ynyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4,5-dibromo-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-3-yl-prop-2-ynyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-thiophen-3-yl)-prop-2-ynyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-propyl]-piperazin-2-one,

1,4-Bis-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-nitro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-pyridin-3-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-methyl-thiophen-2-yl)-penta-2,4-dienyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methyl-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methoxy-thiophen-2-yl)-allyl]-piperazin-2-one,

4-(1-Amino-7-chloro-isoquinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenyl)-2-(S)-hydroxy-ethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-methylene-1,1-dioxo-2,3-dihydro-1H-11 6-benzo[b]thiophen-3-yl)-piperazin-2-one ,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-nitro-phenyl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-6-ylmethyl)-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(4-chloro-phenyl)-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propyl]-piperazin-2-one,

2-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chlorophenyl)-acrylic acid,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-1-hydroxy-isoquinolin-3-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-isoquinolin-3-ylmethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(3-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1,7-dichloro-isoquinolin-3-ylmethyl)-piperazin-2-one,

4-(2-Amino-7-chloro-quinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(6-chloro-benzo[b]thiophen-2-yl)-ethyl]-piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-[2-(4-chloro-phenoxy)-ethyl]-piperazine-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-4H-benzo[1,4]thiazin-3-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,7-dichloro-quinolin-3-ylmethyl)-piperazin-2-one,

2-[[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-(4-chloro-phenyl)-methyl]-acrylic acid ethyl ester,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chloro-phenyl)-acrylic acid ethyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-allyl]-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinoxalin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-3H-quinazolin-4-one,.

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-thiophen-2-yl-propyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-quinolin-3-ylmethyl)-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5,7-dichloro-1H-quinolin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6,7-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-1H-quinolin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-[2,3']bithiophenyl-5'-ylmethyl)-piperazin-2-one,

4-(6-Amino-benzo[b]thiophen-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-nitro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinolin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-trifluoromethyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3,3'-dimethyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-bromo-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-oxazol-2-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4,5-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-benzooxazol-2-yl-benzyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2,2']bithiophenyl-5-ylmethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-fluoro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(1-methyl-5-trifluoro-methyl-1H-pyrazol-3-yl)-thiophen-2-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophen-2-ylmethyl] piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-nitro-phenyl)-furan-2-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-6-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-methoxy-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-hydroxy-2-pyridin-2-yl-pyrimidin-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-fluoro-phenoxy)-benzyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-benzo[b]thiophen-2-ylmethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-bis-trifluoromethyl-benzyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-biphenyl-4-ylmethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-naphthalen-2-ylmethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-3-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Aminoquinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-thiophene-2-carbonyl)-piperazin-2-one,

4-[3-(3-Amino-4-chloro-phenyl)-(E)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,

5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,

5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-methyl-2-oxo-ethyl}-amide,

5-Chloro-thiophene-2-carboxylic acid {3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one,

N-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-(5-chloro-thiophen-2-ylmethyl)-2-oxo-ethyl]-benzamide,

N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-benzamide,

N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yl)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-6-chloro-4H-benzo[1,4]thiazin-3-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-benzo[b]thiophen-2-yl)-acetyl]-piperazin-2-one,

4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid 4-chloro-benzylamide,

4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-ylmethyl)amide,

4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3-amino-4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-carboxylic acid 6-chloro-benzooxazol -2-ylmethyl ester,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 1-(3-chloro-phenyl)-pyrrolidin-3-yl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)- 4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-benzoimidazol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(S)-3-ethyl-piperazin-2-one,

2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetamide,

(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one,

(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one,

(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-(3S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-1H-pyrrole-2-carbonyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propionyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethyl-4-[3-(4-methoxy-phenyl)-propionyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(R)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-3H-imidazol-4-yl-acryloyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

(1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)--methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-fluoro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenoxy)-propionyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-[(4-trifluoromethylsulfanyl-phenoxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-ylsulfanyl)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester,

(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,3-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,4-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

(1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(R)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethoxymethyl-4-[(3-fluoro-phenoxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-isopropyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,3-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,3-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,3-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3,3-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-(2-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(R)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

(1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-6-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-4-fluoro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-phenyl)-acryloyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-2-methyl-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3(S)-6-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-6-methyl-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-3-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-bromo-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-2-methoxy-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-2-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-trifluoromethoxy-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-dichloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-difluoro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-5-(R,S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-4-methoxy-thiophen-2-yl)-amide,

(3S, 5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,

(3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-sulfonyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,

(3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,

(3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-methyl-piperazin-2-one,

(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,

(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,

(S,R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,

(S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

(3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-methyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-methyl-piperazin-2-one,

(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,

(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-ethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-(S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methyl-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(2-hydroxy-ethylamino)-quinolin-7-ylmethyl]-piperazin-2-one,

(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one,

(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one,

(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-4-oxy-piperazin-2-one,

(S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-(S)-3-ethyl-1-(4-hydroxyamino-quinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-3-(1-(R)-methoxy-ethyl)-piperazin-2-one,

1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)-acryloyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate,

1-(4-Aminoquinolin-7-ylmethyl)-4-[(5-chlorothiophen-2-yloxy-acetyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate,

(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one,

1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(methyl-pyridin-4-yl-amino)-ethyl]-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(methylpyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-yl-ethyl)-piperazin-2-one,

1-[2-(2-Amino-3-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

1-[2-(2-Amino-5-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(2,3,5,6-tetrachloro-pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-[2-(2-Amino-3,5,6-trichloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridazin-4-yl-amino)-ethyl]-piperazin-2-one,

1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

4-[2-(5-Chlorothiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,

4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-naphthalen-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester,

1-(5-Chloro-1H-indol-2-ylmethyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester,

1-[(5-Chloro-thiophen-2-yloxy)-acetyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

1-(6-Chloro-benzo[b]thiophene-2-carbonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

1-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(3-Phenyl-prop-2-ynyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-prop-2-ynyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(S)-2-Methoxymethyl-3-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

(S)-4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

4-[3-(6-Chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indole-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(6-Methoxy-pyridin-3-yl)-benzoyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(4-Pyridin-3-yl-benzoyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(4-Bromo-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2-(4-Chloro-phenyl)-2-methyl-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(3,4-Dichloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[(4-Chloro-phenyl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid benzylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid bis-(2-hydroxy-ethyl)-amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylcarbamoylmethyl-amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid ethylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-(4-methyl-piperazine-1-carbonyl)-piperazin-2-one,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester,

(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide,

(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,

(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid,

4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile,

4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzamidine,

1-(4-Amino-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one,

4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(2,4-diamino-quinazolin-7-ylmethyl)-piperidin-2-one,

1-(4-Amino-2-methyl-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one,

(3S, 5R)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine,

(3S,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine,

4-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl}-benzamidine,

(3R,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamidine,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperazin-1-yl-propyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-pyridin-4-yl-propyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-piperidin-4-yl-butyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-piperidin-4-yl-ethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperidin-4-yl-propyl)-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

4'-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-3-hydroxy-benzyl)-piperazin-2-one,

1-Benzyl-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-benzyl)-piperazin-2-one,

4-[(4-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

1-Biphenyl-4-ylmethyl-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one,

1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(S)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine,

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(R)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine,

3-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine,

and

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine,

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

51. A compound selected from

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-4-oxy-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-4-oxy-piperazin-2-one,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-((S)-1-(R)-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(R)-carboxylic acid ethyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-butyl-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

(3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-6-methyl-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-6-dimethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one,

(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-ethyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamidine,

4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-(S)-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxy-ethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]-piperazin-2-one,

4-(6-Bromo-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

(3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3, 5-dimethyl-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(R)-carboxylic acid methyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid methyl ester,

1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-(R)-hydroxymethyl-3-(S)-methoxymethyl-piperazin-2-one,

1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)- propyl-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid amide

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide,

4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)- propyl-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)- propyl-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)- propyl-piperazin-2-one,

1-(4-Amino-cinnolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid ethyl ester,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3, 5-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3, 5-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-5 3-chloro-1-aza-inden-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

52. A compound which is

2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-4-yl-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-3-ylmethyl-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-piperidin-4-yl-acetamide,

N-(1-Carbamimidoyl-piperidin-4-yl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,

5-(2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetylamino}-ethyl)-imidazole-1-carboxylic acid ethyl ester,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyrimidin-4-yl-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-phenyl-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(9H-purin-6-yl)-acetamide,
N-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-imidazol-1-yl-propyl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-imidazol-4-yl)-ethyl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-4-yl-ethyl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(3-methyl-3H-imidazol-4-yl)-ethyl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-2-yl-ethyl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-3-yl-ethyl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-imidazol-1-yl-ethyl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(4-dimethylamino-[1,3,5]triazin-2-yl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-pyridin-4-yl-acetamide,
N-[2-(2-Amino-pyridin-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(4-methyl-thiazol-5-yl)-ethyl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-thiazol-4-yl-ethyl)-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-guanidino-propyl)-acetamide trifluoroacetic acid salt,
N-(3-Amino-propyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-mercapto-1H-imidazol-4-yl)-ethyl]-acetamide,

N-[2-(2-Amino-thiazol-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-(2-pyridin-4-yl-ethyl)-acetamide, or

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-methylsulfanyl-1H-imidazol-4-yl)-ethyl]-acetamide,

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

53. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

54. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

55. A compound which is 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

56. A compound which is 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

57. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

58. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one, or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

59. A compound which is 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one, or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

60. A compound which is 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one, or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

61. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

62. A method of inhibiting Factor Xa comprising contacting a Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

63. A method of inhibiting the formation of thrombin comprising contacting Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

64. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of the compound according to claim 1.

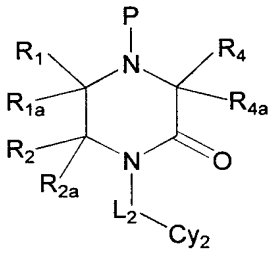
65. The method according to claim 63 wherein the physiological condition is venous vasculature, arterial vasculature, abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip

surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

66. The method according to claim 63 wherein the physiological condition is abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, transient ischemic attacks, intermittent claudication or bypass grafting of the coronary or peripheral arteries, restenosis post coronary or venous angioplasty, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery or a risk of pulmonary thromboembolism.

67. The method according to claim 63 wherein the physiological condition is stroke, vessel luminal narrowing, maintenance of vascular access patency in long-term hemodialysis patients, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

68. A compound of formula

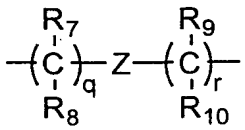


wherein

P is H or a nitrogen protecting group;

R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, Y^1Y^2NCO, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

L_2 is a group of formula



Cy_2 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)_v$-, $R_6O_2C(CH_2)_x$-, $Y^1Y^2NC(O)(CH_2)_x$-, or $Y^1Y^2N(CH_2)_v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α substituted to a N, O or S in Z;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, $S(O)_p$, NR_5, $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4;

v is 2, 3 or 4; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0.

69. A compound according to claim 68 wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

70. A compound according to claim 67 wherein Z is absent.

71. A compound according to claim 68 wherein R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

72. A compound according to claim 67 which is

(2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,

4-(2-Oxopiperazin-1-ylmethyl)benzamidine,

1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one,

1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one,

2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester,

2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one,

1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one,

4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) l-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one,

(3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one,

1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one,

1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one trifluroacetate,

1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one,

1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one,

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester,

4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,

(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester, or

(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/505; C07C 409/14
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According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/253; 544/293

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,612,353 A (EWING et al.) 18 March 1997, whole document.	1-72

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Authorized officer
RICHARD L. RAYMOND
JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX
Telephone No. (703) 308-1235

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(71) Applicant *(for all designated States except US)*: VERSICOR, INC. [US/US]; 34790 Ardentech Court, Fremont, CA 94555 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GORDEEV, Mikhail F. [RU/US]; 15267 Hesperian Boulevard, San Leandro, CA 94578 (US). LUEHR, Gary, W. [US/US]; 33252 Palomino Common, Fremont, CA 94555–1522 (US). PATEL, Dinesh, V. [US/US]; 45109 Cougar Circle, Fremont, CA 94539 (US). NI, Zhi–Jie [CN/US]; 34497 Winslow Terrace, Fremont, CA 94555 (US). GORDON, Eric [US/US]; 955 Channing Avenue, Palo Alto, CA 94301 (US).

(74) Agents: JOHNSTON, Madeline, I. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304–1018 (US).

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(54) Title: OXAZOLIDINONE COMBINATORIAL LIBRARIES, COMPOSITIONS AND METHODS OF PREPARATION

(57) Abstract

Oxazolidinones and methods for their synthesis are provided. Also provided are combinatorial libraries comprising oxazolidinones, and methods to prepare the libraries. Further provided are methods of making biologically active oxazolidinones as well as pharmaceutically acceptable compositions comprising the oxazolidinones. The methods of library preparation include the attachment of oxazolidinones to a solid support. The methods of compound preparation in one embodiment involve the reaction of an iminophosphorane with a carbonyl containing polymeric support.

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OXAZOLIDINONE COMBINATORIAL LIBRARIES, COMPOSITIONS AND METHODS OF PREPARATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of U.S. Patent Application Serial No. 09/012,535, filed January 23, 1998, and a continuation in part of U.S. Patent Application Serial No. 09/086,702, filed May 28, 1998, the disclosures of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention is directed to oxazolidinones; oxazolidinone compositions; oxazolidinone combinational libraries; and methods for their preparation and use.

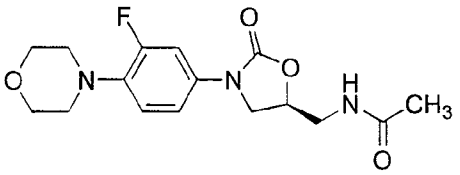
BACKGROUND ART

Oxazolidinones are compounds where an amine group and a hydroxyl group on adjacent carbon atoms have been cyclized to form a 5-membered ring containing a carbonyl group. Certain oxazolidinones have been shown to exhibit a variety of biological activities. For example, some oxazolidinones are inhibitors of monoamine oxidase-B, an enzyme implicated in Parkinson's disease. See, for example, Ding *et al., J. Med. Chem.* 36:3606-3610 (1993).

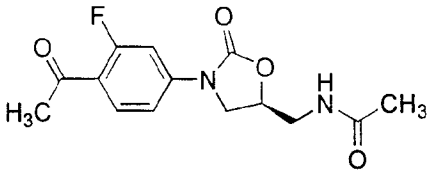
A a ten step synthesis of oxazolidinone antibiotics has been described. U.S. Patent No. 5,547,950. A four step synthesis of the antibacterial compound U-100592 also has been reported. Schauss *et al., Tetrahedron Letters,* 37:7937-7940 (1996). A five step preparation of enantiomerically pure *cis*- and *trans*-N-(propionyl)hexahydrobenzoxazolidin-2-ones further was reported. De Parrodi *et al., Tetrahedron: Asymmetry,* 8:1075-1082 (1997).

Scientists have reported that certain oxazolidinone derivatives exhibit beneficial antibacterial effects. For instance, N-[3-[3-fluoro-4-(morpholin-4-yl)phenyl]2-oxooxazolidin-5(s)-ylmethyl] acetamide (below) has been reported to be useful for the

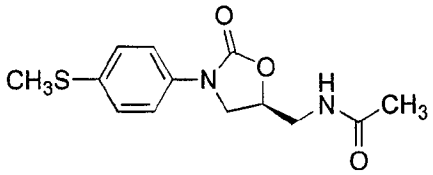
treatment of bacterial infections. Lizondo *et al., Drugs of the Future,* 21:1116-1123 (1996).



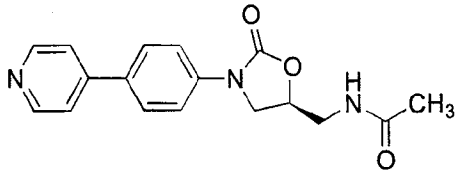
The synthesis of the oxazolidinone antibacterial agent shown below has been reported. Wang *et al., Tetrahedron,* 45:1323-1326 (1989). This oxazolidinone was made using a process that included the reaction of an aniline with glycidol to provide an amino alcohol, and the diethylcarbonate mediated cyclization of the amino alcohol to afford an oxazolidinone.



The synthesis of oxazolidinone antibacterial agents, including the compound shown below has been reported. U.S. Pat. No. 4,705,799. The process used to make the compound shown below included a metal mediated reduction of a sulfonyl chloride to provide a sulfide.



The synthesis of oxazolidinone antibacterial agents, including the pyridyl compound shown below has been reported. U.S. Patent No. 4,948,801. The process used included an organometallic mediated coupling of an organotin compound and an aryl iodide.



Synthetic routes to oxazolidinones often allow a chemist to produce only one compound at a time. These laborious methods can provide a limited number of compounds for evaluation in a biological screen. These methods cannot, however, provide the number of compounds required to supply a high-throughput biological screen, an assay technique whereby the activity of thousands of drug candidates, for example, per week, may be analyzed. This limitation on compound production is of practical importance since high-throughput screens are desirable and efficient for the discovery of new drugs.

SUMMARY OF INVENTION

Provided are oxazolidinones and combinatorial libraries, compositions comprising oxazolidinones, as well as methods of their synthesis and use. Using the methods provided herein, one of skill in the art can rapidly produce the large number of compounds required for high-throughput screening.

In one embodiment, provided are methods for the solid phase synthesis of oxazolidinones.

In one embodiment, the method comprises attaching an olefin to a solid support, oxidizing the olefin to provide an epoxide functionality, opening the epoxide with an amine and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching an allylic amine to a solid support, oxidizing the olefin of the allylic amine to provide an epoxide, opening the epoxide with an amine, and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching allylamine to a solid support, oxidizing the olefin of allylamine to provide an epoxide, opening the epoxide with an amine and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching an olefin to a solid support, oxidizing the olefin to provide an epoxide, opening the epoxide with an amino acid and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching an olefin to a solid support, oxidizing the olefin to provide an epoxide, opening the epoxide with an aromatic amine and cyclizing the resulting amino alcohol using a phosgene equivalent.

Methods also are provided for the synthesis of oxazolidinone combinatorial libraries.

In one embodiment, the method comprises attaching an olefin group to an array of solid supports, oxidizing the individual olefin groups to provide an array of solid support bound epoxides, opening the epoxides with amine units, and cyclizing the resulting array of amino alcohols using a phosgene equivalent.

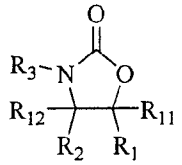
In another embodiment, the method comprises attaching an allylic amine to an array of solid supports, oxidizing the individual olefin groups to provide an array of solid support bound epoxides, opening the epoxides with amine units and cyclizing the resulting array of amino alcohols using a phosgene equivalent.

In another embodiment, the method comprises attaching allyl amine to an array of solid supports, oxidizing the individual olefin groups to provide an array of solid support bound epoxides, opening the epoxides with amine units and cyclizing the resulting array of amino alcohols using a phosgene equivalent.

In another embodiment, the method comprises attaching an olefin to an array of solid supports, oxidizing the individual olefin groups to provide an array of solid support bound epoxides, opening the epoxides with amino acid units and cyclizing the resulting array of amino alcohols using a phosgene equivalent.

In another embodiment, the method comprises attaching an olefin to an array of solid supports, oxidizing the individual olefin groups to provide an array of solid support bound epoxides, opening the epoxides with aromatic amine units and cyclizing the resulting array of amino alcohols using a phosgene equivalent.

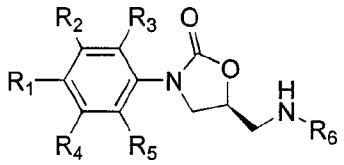
Provided are a variety of oxazolidinones and combinatorial libraries thereof. In one embodiment, the oxazolidinones have the structure:



1a

where R_1 is selected from the group consisting of alkyl, heteroalkyl aryl and heteroaryl; R_2 is selected from the group consisting of hydrogen, alkyl, heteroalkyl; aryl and heteroaryl; R_3 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; R_{11} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; and R_{12} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl.

In another embodiment, oxazolidinones and combinatorial libraries are provided wherein the oxazolidinones are of the structure **1b**, wherein R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl,



1b

heteroalkyl, heteroaryl or an electron withdrawing group; R_6 is acyl or sulfonyl; and, R_1 is one of the following functional groups: $C(O)NR_7R_8$, wherein R_7 and R_8 are, independently, hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $C(O)OR_9$, wherein R_9 is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $C(O)R_{10}$, wherein R_{10} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; SR_{11}, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)_2R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $NR_{12}R_{13}$, wherein R_{12} and R_{13} are, independently, hydrogen, acyl, sulfonyl, alkyl, heteroalkyl, aryl or heteroaryl; 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position of the oxazolyl, and wherein R_{14} and R_{15} are, independently, hydrogen, alkyl, heteroalkyl, aryl,

heteroaryl or an electron withdrawing group; 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position of the thiazole, and wherein R_{16} and R_{17}, are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; and, $CH_2NR_{18}R_{19}$, wherein R_{18} and R_{19} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, acyl or sulfonyl.

All compounds disclosed herein can exist as different isomer forms including stereoisomers and enantiomerically pure forms, and all such isomers and forms are within the scope of the invention. For example, while structure **1b** is shown with the preferred embodiment of a S isomer at the 5 position of the oxazolidinone, the R isomer is within the scope of the invention. Similarly, in all of the other oxazolidinone compounds, in the case where a preferred stereoisomer is shown at the 5 position of the oxazolidinone, both stereoisomers are within the scope of the invention.

In one embodiment of structure **1b**, R_1 is $C(O)R_7R_8$.

In another embodiment of structure **1b**, R_1 is $C(O)OR_9$.

In another embodiment of structure **1b**, R_1 is $C(O)R_{10}$.

In another embodiment of structure **1b**, R_1 is SR_{11}.

In another embodiment of structure **1b**, R_1 is $S(O)_2R_{11}$.

In another embodiment of structure **1b**, R_1 is $S(O)R_{11}$.

In another embodiment of structure **1b**, R_1 is $NR_{12}R_{13}$. In another embodiment, R_1 is $NR_x(C=O)R_y$, wherein R_x and R_y are independently hydrogen, alkyl, heteroalkyl, aryl, or heteroaryl;

or R_1 is $NR_x(SO_2)R_y$, wherein R_x and R_y are independently hydrogen, alkyl, heteroalkyl, aryl, or heteroaryl with the proviso that R_y is not H;

In another embodiment of structure **1b**, R_1 is 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position of the oxazole group.

In another embodiment of structure **1b**, R_1 is 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position of the aminothiazolyl group.

In another embodiment of structure **1b**, R_1 is $CH_2NR_{18}R_{19}$.

In another embodiment of structure **1b**, R_1 is $C(O)NR_7R_8$; and, R_3, R_4 and R_5 are hydrogen.

In another embodiment of structure **1b**, R_1 is $C(O)NR_7R_8$; R_3, R_4 and R_5 are

hydrogen; and, R_2 is fluorine.

In another embodiment of structure **1b**, R_1 is $C(O)NR_7R_8$; R_3, R_4 and R_5 are hydrogen; R_2 is fluorine; and, R_6 is $C(O)CH_3$.

In another embodiment of structure **1b**, R_1 is $C(O)NR_7R_8$; R_3, R_4 and R_5 are hydrogen; R_2 is fluorine; R_6 is $C(O)CH_3$; and, R_7 is hydrogen.

In another embodiment of structure **1b**, R_1 is $C(O)NR_7R_8$; R_3, R_4 and R_5 are hydrogen; R_2 is fluorine; R_6 is $C(O)CH_3$; R_7 is hydrogen; and, R_8 is heteroaryl.

A variety of methods of preparing combinatorial libraries comprising oxazolidinones are provided.

In one embodiment, the method is for the preparation of oxazolidinones, such as those of structure **1b**. The method comprises the steps of: attaching a plurality of aryl oxazolidinones to a plurality of solid supports; functionalizing the 4-position of the aryl groups of the attached oxazolidinones; and, optionally, removing the oxazolidinones from the solid supports.

In another embodiment, the aryl oxazolidinone is attached to a solid support through the reaction of an iminophosphorane with a carbonyl containing resin to form an imine. In another embodiment, the aryl oxazolidinone is attached to a solid support through the reaction of an amine with a carbonyl containing resin to form an imine.

In another embodiment, the aryl oxazolidinone is attached to a solid support through the reaction of an iminophosphorane with a carbonyl containing resin to form an imine, and the imine is reduced to form an amine. In another embodiment, the aryl oxazolidinone is attached to a solid support through the reaction of an amine with a carbonyl containing resin to form an imine, and the imine is reduced to form an amine.

Also provided are biologically active oxazolidinones and compositions comprising biologically active oxazolidinones. For example, the oxazolidinones may have antibiotic activity.

In one embodiment, the biologically active oxazolidinones are of the structure **1b**.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is $C(O)NR_7R_8$.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is 2 oxazolyl containing R_{14} at the 4-position and R_{15}

at the 5-position of the oxazole.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is 2-aminothiazolyl containing R_{16} at the 4-position and R_{17} at the 5-position of the aminothiazole.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is $C(O)NR_7R_8$, and wherein R_3, R_4 and R_5 are hydrogen.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is 2 oxazolyl containing R_{14} at the 4-position and R_{15} at the 5-position of the oxazole, and wherein R_3, R_4 and R_5 are hydrogen.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is 2-aminothiazolyl containing R_{16} at the 4-position and R_{17} at the 5-position of the aminothiazole, and wherein R_3, R_4 and R_5 are hydrogen.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is $C(O)NR_7R_8$, and wherein R_3, R_4 and R_5 are hydrogen, and further wherein R_2 is fluorine.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is 2 oxazolyl containing R_{14} at the 4-position and R_{15} at the 5-position of the oxazole, and wherein R_3, R_4 and R_5 are hydrogen, and further wherein R_2 is fluorine.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is 2-aminothiazolyl containing R_{16} at the 4-position and R_{17} at the 5-position of the aminothiazole, and wherein R_3, R_4 and R_5 are hydrogen, and further wherein R_2 is fluorine.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is 5-chloropyridine-3-yl, thiazole-2-yl, 5'-(5-aminopyridine-2-yl)thiopyridine-3'-yl, or pyridine-3-yl; and wherein R_3, R_4 and R_5 are hydrogen; and further wherein R_2 is fluorine; and further wherein R_6 is $C(O)CH_3$.

In another embodiment, the biologically active oxazolidinones are of the structure **1b**, wherein R_1 of the oxazolidinone is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is 5-

chloropyridine-3-yl; and wherein R_3, R_4 and R_5 are hydrogen; and further wherein R_2 is fluorine; and further wherein R_6 is $C(O)CH_2SMe$.

In another embodiment, the biologically active oxazolidinones are of the structure **1b** wherein R_1 of the oxazolidinone is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is 5-chloropyridine-3-yl; and wherein R_3, R_4 and R_5 are hydrogen; and further wherein R_2 is fluorine; and further wherein R_6 is C(O)CHCH(pyridine-3-yl).

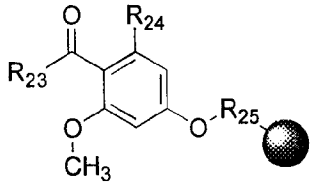
In another embodiment, the biologically active oxazolidinones are of the structure **1b** wherein R_1 of the oxazolidione is 5-amino-4-cyanooxazole-2-yl; and wherein R_2 is fluorine; and further wherein R_3, R_4 and R_5 are hydrogen; and still further wherein R_6 is $C(O)CH_3$.

In another embodiment, the biologically active oxazolidinones are of the structure **1b** wherein R_1 of the oxazolidione is 4-phenylthiazole-2-yl-amino; and wherein R_2 is fluorine; and further wherein R_3, R_4 and R_5 are hydrogen; and still further wherein R_6 is $C(O)CH_3$.

A variety of methods of synthesizing biologically active oxazolidinones are provided.

In one embodiment, methods are provided for the preparation of oxazolidinones, such as those of the structure **1b**, and comprise the steps of: providing an iminophosphorane; mixing the iminophosphorane with a resin that comprises carbonyl groups to form an imine intermediate; and, reducing the imine intermediate to afford a compound attached to the resin through an amine linkage. In another embodiment, the iminophosphorane is provided from an azide that is reacted with a phosphine. In another embodiment, the iminophosphorane is provided from an amine that is reacted with a (trisubstituted)phosphine dihalide.

In another embodiment, the resin comprising carbonyl groups is of the structure



1c

wherein R_{23} is hydrogen, alkyl, aryl, O-alkyl or O-aryl; R_{24} is hydrogen, CH_3O or NO_2; R_{25} is $(CH_2)_nCONH$, wherein n is an integer ranging between 1 and about 5; and, the filled circle is a polymeric support.

In another embodiment of structure **1c**, R_{23} is hydrogen, R_{24} is CH_3O, R_{25} is $(CH_2)_3CONH$ and the filled circle is Tentagel, (cross-linked)polystyrene, (cross-linked)polyethylene glycol or polyethyleneglycol-polystyrene compositions.

Methods also are provided of synthesizing biologically active oxazolidinone compositions from a corresponding amine. In one embodiment, the method is for the preparation of oxazolidinones, for example, of the structure **1b**, and comprises the steps of: reacting an amine with a resin that comprises carbonyl groups to form an imine intermediate; and, reducing the imine intermediate to afford a compound attached to the resin through an amine linkage.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is shows the structure of an oxazolidinone **1b**.

Figure 2 is a scheme showing the synthesis of a combinatorial library comprising oxazolidinones of structure **1b**, wherein R_1 is $C(O)R_7R_8$.

Figure 3 is a scheme showing the synthesis of a set of azido oxazolidinones.

Figure 4 is a scheme showing the synthesis of a combinatorial library comprising oxazolidinones of structure **1b**, wherein R_1 is $C(O)R_7R_8$, and wherein R_3, R_4 and R_5 are hydrogen; and wherein in Figure 4, the N-Ac group of **17**, **18** and **19** also may be $NCOR_1$, wherein R_1 is a substituent, such as H, alkyl, heteroalkyl, aryl, or heteroaryl.

Figure 5 is a scheme showing the synthesis of combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is $C(O)OR_9$ or $C(O)R_{10}$.

Figure 6 is a scheme showing the synthesis of combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is SR_{11}.

Figure 7 is a scheme showing the synthesis of combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is $S(O)R_{11}$ or $S(O)_2R_{11}$.

Figure 8 is a scheme showing the synthesis of a set of thio substituted azido oxazolidinones.

Figure 9 is a scheme showing the synthesis of a combinatorial library comprising

oxazolidinones of structure **1b**, wherein R_1 is $NR_{12}R_{13}$.

Figure 10 is a scheme showing the synthesis of a combinatorial library comprising oxazolidinones of structure **1b**, wherein R_1 is an oxazole.

Figure 11 is a scheme showing the synthesis of combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is an oxazole.

Figure 12 is a scheme showing the synthesis of combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is an aminothiazole.

Figure 13 is a scheme showing the synthesis of combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is $CH_2NR_{18}R_{19}$.

Figure 14 is a scheme showing the synthesis of a set of acetal containing azido oxazolidinones.

Figure 15 is a scheme showing a general synthetic method for the preparation of oxazolidinones.

Figure 16 is a scheme showing a general synthetic method for the preparation of azido oxazolidinones.

Figure 17 is a graphical depiction of a linking portion connecting an oxazolidinone to a solid support.

Figure 18 is a scheme showing the synthesis of an oxazolidinone of structure **1b**, wherein R_1 is $NR_{12}R_{13}$.

Figure 19 is a scheme showing the synthesis of an oxazolidinone of structure **1b** wherein R_1 is an aminothiazole.

Figure 20 is a scheme showing the synthesis of an oxazolidinone of structure **1b**, wherein R_1 is an oxazole.

Figure 21 is a scheme showing the synthesis of oxazolidinones of structure **1b** wherein R_1 is $C(O)R_{10}$.

Figure 22 is a scheme showing the synthesis of oxazolidinones of structure **1b**, wherein R_1 is $NR_{12}R_{13}$.

Figure 23 is a scheme showing a general synthetic method for the preparation of oxazolidinones.

Figure 24 is a scheme showing a method of preparation of N-[(3-phenyl-2-oxo-5-oxazolidinyl)methyl]acetamide.

Figure 25 is a scheme showing a method of preparation of N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide.

Figure 26 is a scheme showing a method of preparation for solid support bound (S)-N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]-methyl]acetamide.

Figure 27 is a scheme showing a method of preparation for sulfonyl, amidyl and ureayl derivatives of (S)-N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]-methyl]acetamide.

Figure 28 is a scheme showing the preparation of α-thio acetamide, α, β-unsaturated acetamide and α-amino acetamide derivatives of (S)-N-[[3-(3-fluoro-4-morpholinyl-phenyl)-2-oxo-5-oxazolidinyl]-methyl]acetamide.

Figure 29 shows a nonlimiting group of amines that are used in the preparation of sulfonyl, amidyl and ureayl oxazolidinone combinatorial libraries.

Figure 30 shows another nonlimiting group of amines that are used in the preparation of sulfonyl, amidyl and ureayl oxazolidinone combinatorial libraries.

Figure 31 shows another nonlimiting group of amines that are used in the preparation of sulfonyl, amidyl and ureayl oxazolidinone combinatorial libraries.

Figure 32 shows a nonlimiting group of amines that are attached to a solid support in a manner analogous to amine **32a** in Figure 26 and then used to construct sulfonamide, amide and urea oxazolidinone libraries in an manner analogous to solid support bound amine **33a** in Figure 27.

Figure 33 is a group of amines for use in the preparation of oxazolidonones that was for example used to prepare combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is derived from the shown amine, R_2 is fluorine, R_3 is hydrogen, R_4 is hydrogen, R_5 is hydrogen and R_6 is $C(O)CH_3$.

Figure 34 is a group of amines for use in the preparation of oxazolidinones that was for example used to prepare combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is derived from the shown amine, R_2 is fluorine, R_3 is hydrogen, R_4 is hydrogen, R_5 is hydrogen and R_6 is $C(O)CH_3$.

Figure 35 is a group of amines for use in the preparation of oxazolidinones that was for example used to prepare combinatorial libraries comprising oxazolidinones of structure

1b, wherein R_1 is derived from the shown amine, R_2 is fluorine, R_3 is hydrogen, R_4 is hydrogen, R_5 is hydrogen and R_6 is $C(O)CH_3$.

Figure 36 is a group of amines for use in the preparation of oxazolidinones that was used for example to prepare combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is derived from the shown amine, R_2 is fluorine, R_3 is hydrogen, R_4 is hydrogen, R_5 is hydrogen and R_6 is $C(O)CHCHC_6H_4CH(p\text{-}NOCH_3)$ or $C(O)CHCHC_6H_4(p\text{-}OCH_3)$.

Figure 37 is a group of amines for use in the preparation of oxazolidinones that was used for example to prepare combinatorial libraries comprising oxazolidinones of structure **1b**, wherein R_1 is derived from the shown amine, R_2 is fluorine, R_3 is hydrogen, R_4 is hydrogen, R_5 is hydrogen and R_6 is $C(O)CH_2SCH_3$ or $C(O)CHCH(3\text{-}C_5H_4N)$.

Figure 38 shows a group of biologically active oxazolidinone compounds, with an MIC range of about 1.25-20 μg/ml against *E. faecium*.

Figure 39 is a scheme showing the synthesis of acylamino oxazolidinone compounds and libraries, wherein R_1 and R_2 are substituents, for example, H, alkyl, heteroalkyl, aryl, heteroaryl, or alkoxy.

Figure 40 is a scheme showing the synthesis of sulfonamide oxazolidinone compounds and libraries, wherein R_1 is a substituent, for example, H, alkyl, heteroalkyl, aryl, heteroaryl, or alkoxy.

Figure 41 is a scheme showing the synthesis of sulfide oxazolidinone compounds and libraries, wherein R_1 is a substituent, for example, H, alkyl, heteroalkyl, aryl, heteroaryl, or alkoxy.

Figures 42 and 43 illustrate building blocks R_2COOH that may be used for synthesis of acylamino oxazolidinone libraries and compounds as shown in Figure 39, and also may be used in other syntheses such as those shown in Figure 9.

Figures 44 and 45 illustrate building blocks R_2X, where X is halo, which may be used in the synthesis of sulfide oxazolidinone libraries and compounds as shown in Figure 41 and also can be used as $R_{11}X$ in the synthesis shown in Figure 6.

Figure 46 illustrates sulfonyl chloride building blocks R_2SO_2Cl that may be used in the synthesis of sulfonamide oxazolidinone libraries and compounds as shown in Figure 40, and also may be used in the syntheses shown in Figure 18.

Figure 47 illustrates amine building blocks R_7R_8NH that may be used in the synthesis of oxazolidinone libraries and compounds as shown in Figure 4.

Figure 48 shows building blocks R_2R_3NH and R_1COOH that may be used to make compounds of formula **1k** and libraries thereof.

Figure 49 is a general scheme showing routes of synthesis of 3-(heteroaryl)oxazolidinones.

Figure 50 is another general scheme showing routes of synthesis of 3-(heteroaryl)oxazolidinones.

DETAILED DESCRIPTION

Definitions

As used herein, the terms and phrases have the meanings and definitions known in the art. Some of the more commonly used phrases are described in more detail below.

"Combinatorial library" or "array" is an intentionally created collection of differing molecules which can be prepared synthetically and screened for biological activity in a variety of different formats (e.g., libraries of soluble molecules, libraries of molecules bound to a solid support). Typically, combinatorial libraries contain between about 6 and two million compounds. In one embodiment, combinatorial libraries contain between about 48 and 1 million compounds. For example, combinatorial libraries may contain between about 96 and 250,000 compounds. In another embodiment, combinatorial libraries may contain about 40 to 100 compounds.

"Alkyl" refers to a cyclic, branched or straight chain chemical group containing only carbon and hydrogen, such as methyl, pentyl, and adamantyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, *e.g.*, halogen, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, and benzyl. Alkyl groups can be saturated or unsaturated (e.g., containing -C=C- or -C≡C- subunits), at one or several positions. Typically, alkyl groups will comprise about 1 to 12 carbon atoms, for example about 1 to 10, or about 1 to 8 carbon atoms.

"Heteroalkyl" refers to a cyclic, branched or straight chain chemical group containing carbon, hydrogen and at least one heteroatom. The heteroatom will be typically nitrogen, oxygen or sulfur. Heteroalkyl groups can either be unsubstituted or substituted

with one or more substituents, *e.g.*, halogen, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl. Where the heteroalkyl group contains a nitrogen atom, the nitrogen atom can be primary, secondary, tertiary, quaternary or can be in various forms such as an amide or sulfonamide. Heteroalkyl groups can contain one or more unsaturated (e.g., -C=C- or -C≡C-) subunits. Typically, heteroalkyl groups will comprise 1 to 12 atoms, for example 1 to 8, or 1 to 4 carbon atoms.

"Aryl" refers to a monovalent unsaturated aromatic carbocyclic group having a single ring (e.g. phenyl), multiple rings (e.g. biphenyl), or multiple condensed rings (e.g. naphthyl or anthryl). Aryl groups can be optionally unsubstituted or substituted with amino, hydroxyl, alkyl, heteroalkyl, alkoxy, halo, mercapto and other substituents. Typically, the aryl group is a substituted single ring compound. For example, the aryl group is a substituted phenyl ring.

"Heteroaryl" refers to a monovalent unsaturated aromatic carbocyclic group having a single ring (*e.g.*, pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl) and having at least one heteroatom within the ring. The heteroatom in the ring is preferably nitrogen, oxygen or sulfur. Heteroaryl groups can be optionally unsubstituted or substituted with amino, hydroxyl, alkyl, heteroalkyl, alkoxy, halo, mercapto and other substituents. In one embodiment, the heteroaryl group is substituted.

"Electron withdrawing group" refers to a substituent that draws electrons to itself more than a hydrogen atom would if it occupied the same position in a molecule. This definition according to field effect is discussed in March, "Advanced Organic Chemistry," 3d Edition, pp. 16-17, Wiley-Interscience, New York. It should be contrasted with a definition based on resonance effects. Examples of electron withdrawing groups include $-NR_2$, $-COOH$, $-OR$, $-SR$, $-F$, $-COR$, $-Cl$, $-SH$, $-NO_2$, $-Br$, $-NH_2$, $-SO_2R$, $-I$, $-OH$, $-CN$, $-C{=}CR_2$, where R is alkyl, heteroalkyl, aryl or heteroaryl.

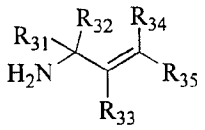
"Chemical module" refers to a general class of molecules that can be incorporated into a combinatorial library at a discrete step in the library synthesis. For example, thiols are chemical modules that can be coupled to a substrate, where the synthetic route employs a nucleophile to displace a solid support bound leaving group; isocyanates are chemical modules that can be coupled to a substrate, where the synthetic route employs an

electrophile to react with a solid support bound amine. Chemical modules can contain tens, hundreds or thousands of different individual members.

"Protecting group" refers to a chemical group that exhibits the following characteristics: (1) reacts selectively with the desired functionality in good yield to give a protected substrate that is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagents compatible with the other functional group(s) generated in such protection reactions. Examples of protecting groups can be found in Greene *et al.* (1991) *Protective Groups in Organic Synthesis*, 2nd Ed. (John Wiley & Sons, Inc., New York).

"Biologically active oxazolidinone compounds" or "bioactive oxazolidinone compounds" refers to an oxazolidinone compound, for example, of structure **1b** that exhibits biological activity. For instance, a biologically active oxazolidinone can inhibit the interaction between an enzyme or receptor and its respective substrate(s) or endogenous ligand(s), or inhibit cell growth of a microorganism, by about at least 15% at a solution concentration of 10^{-3} molar or lower (i.e., it has inhibitory activity). For example, the biologically active oxazolidinone will inhibit such processes at solution concentrations of about 10^{-4} M or lower, or 10^{-5} M or lower, or, *e.g.*, of about 10^{-6} M or lower.

"Allylic amine" refers to a compound of the following structure:



where R_{31}, R_{32}, R_{33}, R_{34} and R_{35} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl. Where R_{31}, R_{32}, R_{33}, R_{34} and R_{35} are all hydrogen, the allylic amine is allylamine.

"Phosgene equivalent" refers to a chemical reagent that can add a C=O group to a molecule in either one or more than one chemical steps. A nonlimiting example of a phosgene equivalent that can add a C=O group in one chemical step is carbonyldiimidazole

(CDI). A nonlimiting example of a phosgene equivalent that can add a C=O group in more than one chemical step is ethyl chloroformate.

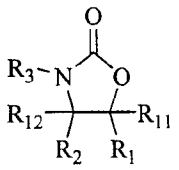
"Acyl" refers to a group -(C=O)-R, where R is a substituent such as H, aryl, heteroaryl, alkyl or heteroalkyl. Exemplary acyl groups include formyl, acetyl, propionyl and butyryl.

"Sulfonyl" refers to a group -(SO_2)-R, where R is a substituent such as alkyl, heteroalkyl, aryl, or heteroaryl. Exemplary sulfonyl groups include methylsulfonyl and trifluoromethylsulfonyl.

Oxazolidinones

Provided are oxazolidinones and combinatorial libraries thereof, as well as methods for their synthesis, for example by solid phase synthesis methods.

In one embodiment, oxazolidinones have the following structure:



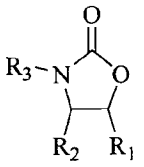
1a

where R_1 is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl; R_2 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; R_3 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; R_{11} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; and R_{12} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl.

In another embodiment, R_3 of the oxazolidinones **1a** is selected from the group consisting of aryl and heteroaryl, where the aryl and heteroaryl groups are the aryl and heteroaryl groups attached to the amines of Table 2 and Figures 29, 30 and 31.

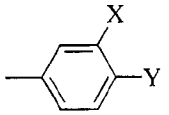
In another embodiment, R_3 of the oxazolidinones **1a** is a heteroaryl group such as a pyridyl group, a thienylphenyl group, an oxazolyl group or a pyrrolyl group, or is a (morpholino)fluorophenyl group.

In another embodiment, the oxazolidinones have the structure



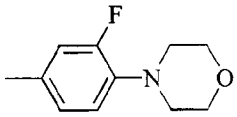
1d

where R_1 is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl, R_2 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, and R_3 has the structure

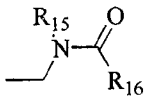


where 'X' is selected from the group consisting of hydrogen, electron withdrawing groups, alkyl, heteroalkyl, aryl and heteroaryl, and 'Y' is selected from the group consisting of hydrogen, electron withdrawing groups, alkyl, heteroalkyl, aryl and heteroaryl.

In another embodiment, R_3 of the oxazolidinones **1d** is the following structure:

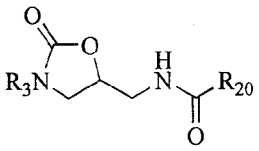


In another embodiment, R_1 of the oxazolidinones **1d** is the following structure:



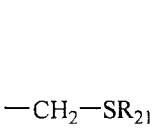
where R_{15} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, and where R_{16} is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl.

In one embodiment, oxazolidinones are provided that are antimicrobial compounds. In one embodiment, the antimicrobial compounds have the structure:

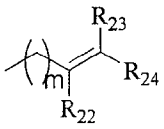


1e

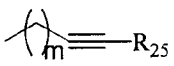
where R_3 is selected from the group consisting of aryl and heteroaryl, and where R_{20} is selected from the group consisting of structures A, B, C, I, J and K:



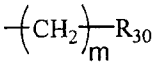
A



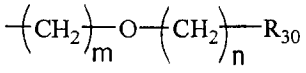
B



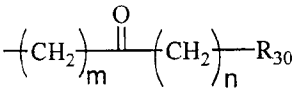
C



I



J

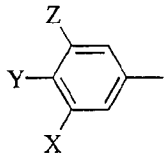


K

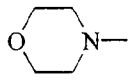
where m is 0, 1, 2 or 3, and where n is 0, 1, 2 or 3. and where R_{21} is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl, and where R_{22}, R_{23} and R_{24} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl and heteroaryl, and where R_{25} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, and where R_{30} is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl.

In another embodiment, R_3 of the antimicrobial compound **1e** is selected from the group consisting of aryl and heteroaryl, where the aryl and heteroaryl groups are the aryl and heteroaryl groups attached to the amines of Table 2 and Figures 29, 30 and 31.

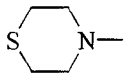
In another embodiment, R_3 of the antimicrobial compound **1e** has the following structure:



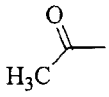
where X and Z are independently selected from the group consisting of hydrogen and fluoride, and where Y is selected from the group consisting of structures D, E, F, G and H:



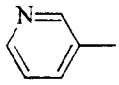
D



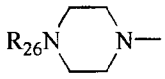
E



F



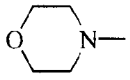
G



H

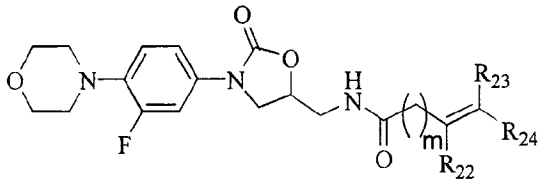
where R_{26} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl.

In another embodiment, Y of the antimicrobial compound **1e** has the structure D:



D

In another embodiment, the antimicrobial compound has the structure:

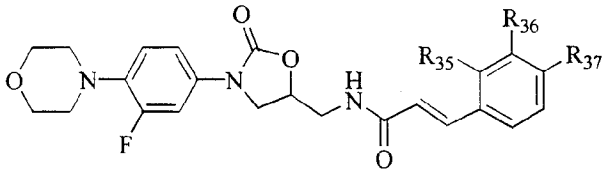


1f

where m is 0, 1, 2 or 3, and where R_{22}, R_{23} and R_{24} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl and heteroaryl.

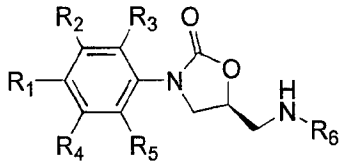
In another embodiment, m in the antimicrobial compound **1f** is 0, R_{22} and R_{23} are hydrogen, and R_{24} is an aryl group.

In another embodiment, the antimicrobial compound is of the structure



where R_{35}, R_{36} and R_{37} are independently selected from the group consisting of hydrogen, an electron withdrawing group, alkyl, heteroalkyl, aryl and heteroaryl.

In another embodiment, oxazolidinones and combinatorial libraries thereof, of the structure **1b** shown in Figure 1 are provided:



1b

In one embodiment, substituent R_1 of compound **1b** is one of the following functional groups: $C(O)NR_7R_8$, wherein R_7 and R_8 are, independently, hydrogen, alkyl, heteroalkyl, aryl or heteroaryl (See Figures 33, 34, 35, 36 and 37 for nonlimiting examples of amines used to construct such libraries); $C(O)OR_9$, wherein R_9 is hydrogen, alkyl, heteroalkyl, aryl

or heteroaryl; $C(O)R_{10}$, wherein R_{10} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; SR_{11}, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)_2R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $NR_{12}R_{13}$, wherein R_{12} and R_{13} are, independently, hydrogen, acyl, sulfonyl, alkyl, heteroalkyl, aryl or heteroaryl; $NR_x(C=O)R_y$, wherein R_x and R_y are independently hydrogen, alkyl, heteroalkyl, aryl, or heteroaryl; $NR_x(SO_2)R_y$, wherein R_x and R_y are independently hydrogen, alkyl, heteroalkyl, aryl, or heteroaryl, provided R_y is not H; 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position, and wherein R_{14} and R_{15} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position, and wherein R_{16} and R_{17} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; and, $CH_2NR_{18}R_{19}$, wherein R_{18} and R_{19} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, acyl or sulfonyl. The substituents R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group; and, R_6 is acyl or sulfonyl.

In one embodiment, the substituents of compound **1b** are defined as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is alkyl, heteroalkyl aryl or heteroaryl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is aryl or heteroaryl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$, and wherein n is an integer ranging from 0 to about 5. In one embodiment, the substituents are as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is heteroaryl; R_2 is fluorine (F); R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is $C(O)OR_9$, wherein R_9 is alkyl, heteroalkyl, aryl or heteroaryl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl. In one embodiment the substituents are as follows: R_1 is $C(O)OR_9$, wherein R_9 is alkyl or heteroalkyl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$, and wherein n is an integer ranging from 0 to about 5. For example, the substituents are as follows: R_1 is $C(O)OR_9$, wherein R_9 is alkyl; R_2 is fluorine;

R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is $C(O)R_{10}$, wherein R_{10} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is $C(O)R_{10}$, wherein R_{10} is alkyl or aryl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$, and wherein n is an integer ranging from 0 to about 5. For example, the substituents are as follows: R_1 is $C(O)R_{10}$, wherein R_{10} is alkyl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is SR_{11}, wherein R_{11} is alkyl, heteroalkyl, aryl or heteroaryl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is SR_{11}, wherein R_{11} is alkyl or heteroalkyl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$. For example, the substituents are as follows: R_1 is SR_{11}, wherein R_{11} is alkyl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is $S(O)_2R_{11}$, wherein R_{11} is alkyl, heteroalkyl, aryl or heteroaryl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is $S(O)_2R_{11}$, wherein R_{11} is alkyl or heteroalkyl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$. For example, the substituents are as follows: R_1 is $S(O)_2R_{11}$, wherein R_{11} is alkyl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is $S(O)R_{11}$, wherein R_{11} is alkyl, heteroalkyl, aryl or heteroaryl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is $S(O)R_{11}$, wherein R_{11} is alkyl or heteroalkyl; R_2 is a

halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$. For example, the substituents are as follows: R_1 is $S(O)R_{11}$, wherein R_{11} is alkyl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is $NR_{12}R_{13}$, wherein R_{12} is hydrogen and R_{13} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, acyl or sulfonyl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is $NR_{12}R_{13}$, wherein R_{12} is hydrogen and R_{13} is acyl or sulfonyl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$, and wherein n is an integer ranging from 0 to about 5. For example, the substituents are as follows: R_1 is $NR_{12}R_{13}$, wherein R_{12} is hydrogen and R_{13} is acyl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position, and wherein R_{14} and R_{15} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position, and wherein R_{14} and R_{15} are, independently, an electron withdrawing group; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$. For example, the substituents are as follows: R_1 is 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position, and wherein R_{14} and R_{15} are, independently, an electron withdrawing group; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position, and wherein R_{16} and R_{17} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position, and wherein

R_{16} and R_{17} are, independently, an electron withdrawing group; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$, and wherein n is an integer ranging from 0 to about 5. For example, the substituents are as follows: R_1 is 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position, and wherein R_{16} and R_{17} are, independently, an electron withdrawing group; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the substituents of compound **1b** are defined as follows: R_1 is $CH_2NR_{18}R_{19}$, wherein R_{18} is hydrogen and R_{19} is alkyl, heteroalkyl, aryl, heteroaryl, acyl or sulfonyl; R_2 is an electron withdrawing group; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In one embodiment, the substituents are as follows: R_1 is $CH_2NR_{18}R_{19}$, where R_{18} is hydrogen and R_{19} is acyl or sulfonyl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)(CH_2)_nCH_3$. For example, the substituents are as follows: R_1 is $CH_2NR_{18}R_{19}$, wherein R_{18} is hydrogen and R_{19} is acyl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

Synthesis of Combinatorial Libraries of Oxazolidinones **1b**

Provided are methods for the preparation of combinatorial libraries comprising oxazolidinones, for example, of the structure **1b**. (For a general discussion of combinatorial library synthesis, see U.S. Pat. No. 5,549,974, which is hereby incorporated by reference for all purposes.) In one embodiment, the methods comprise attaching an aryl oxazolidinone to a solid support; functionalizing the 4-position of the aryl group; and removing the oxazolidinone from the solid support.

Figure 2 shows a method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is $C(O)NR_7R_8$. A plurality of azides **2** are converted to the corresponding iminophosphoranes upon reaction with a phosphine. The ylides are mixed with a plurality of solid supports containing a carbonyl functional group, producing a plurality of imines. The imines are reduced (*e.g.*, $NaBH_3CN$) to provide a plurality of amines **3**. The ester group of **3** is deprotected to afford a plurality of acids **4**. Acylation of the amine and activation of the acid of **4** yields a plurality of activated esters **5**. The activated esters are reacted with an R_7R_8NH amine unit, providing a plurality of

amides **5**. The solid support bound amides **5** are removed from the solid support using a suitable reagent (*e.g.*, TFA) to afford a plurality of amides **7** in solution.

The plurality of azides **2** is produced starting from a set of substituted methylnitrobenzenes (**8**, Figure 3). The methyl group of **8** is oxidized to provide the corresponding carboxylic acids **9**. The acids are esterified, affording a set of nitro esters **10**. The nitro group of **10** is reduced to yield a set of amines **11**. Acylation of **11** provides a set of protected amines **12**. Amines **12** are reacted with a substituted epoxide to afford a set of amino alcohols, which are cyclized to a set of oxazolidinones **13**. Displacement of the primary alcohol of **13** yields the azides **2**.

Figure 4 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein the substituents are defined as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is alkyl, heteroalkyl, aryl or heteroaryl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$. A plurality of azides **14** were converted to the corresponding iminophosphoranes upon reaction with triphenylphosphine. The iminophosphoranes were mixed with a plurality of 5-formyldimethoxyphenoxybutyric acid resin beads (BAL resin beads, Novabiochem), producing a plurality of imines. The imines were reduced with $NaBH_3CN$ to provide a plurality of amines **15**. The ester group of **15** was deprotected using trimethylsilylchloride (TMSCl) to afford a plurality of acids (**16**). Acylation of the amine with Ac_2O and activation of the acid with $PfpOCOCF_3$ yielded a plurality of activated esters **17**. The activated esters were reacted with an R_7R_8NH unit, providing a plurality of amides **18**. The solid support bound amides **18** were removed from the solid support using TFA to afford a plurality of amides **19** in solution. Figure 47 illustrates amine building blocks R_7R_8NH that may be used in the synthesis of oxazolidinone libraries and compounds as shown in Figure 4.

Figure 5 shows exemplary methods for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is either $C(O)OR_9$ or $C(O)R_{10}$. A plurality of solid support bound acids **4** are converted into activated acids **20**. To prepare an oxazolidinone library, wherein R_1 is $C(O)OR_9$, the activated acids **20** are reacted with an R_9OH unit, providing a plurality of esters **21**. The esters are removed from the solid support upon treatment with a suitable reagent, affording a plurality of amides **22** in

solution. To prepare an oxazolidinone library, wherein R_1 is $C(O)R_{10}$, the activated acids **20** are reacted with an amine, providing a plurality of Weinreb amides **23**. The Weinreb amides are reacted with an organometallic unit (e.g., LiAlH4 or MeMgBr), affording a plurality of ketones **24**. The ketones **24** are removed from the solid support upon treatment with a suitable reagent, producing a plurality of ketones **25** in solution.

Figure 6 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is SR_{11}. A plurality of azides **26** are converted to the corresponding iminophosphoranes upon reaction with a phosphine. The iminophosphoranes are mixed with a plurality of solid supports containing a carbonyl functional group, producing a plurality of imines. The imines are reduced to provide a plurality of amines **27**. Acylation of the amine and deprotection of the sulfide of **27** yields a plurality of thiols **28**. Alkylation of **28** with an electrophile provides a plurality of sulfides **29**. The solid support bound sulfides **29** are removed from the solid support using a suitable reagent to afford a plurality of sulfides **30** in solution. Another embodiment is shown in Figure 41. Figures 44 and 45 illustrate building blocks R_2X, where X is halo, which may be used in the synthesis of sulfide oxazolidinone libraries and compounds as shown in Figure 41 and also can be used as $R_{11}X$ in the synthesis shown in Figure 6.

Figure 7 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is $S(O)R_{11}$ or $S(O)_2R_{11}$. To prepare an oxazolidinone library, wherein R1 is $S(O)R_{11}$, a plurality of solid support bound sulfides **29** is converted into a plurality of sulfoxides **31** upon oxidation. The sulfoxides are removed from the solid support upon treatment with a suitable reagent, affording a plurality of sulfoxides **32** in solution. To prepare an oxazolidinone library, wherein R_1 is $S(O)_2R_{11}$, a plurality of solid support bound sulfides **29** is converted into a plurality of sulfones **33** upon oxidation. The sulfones are removed from the solid support upon treatment with a suitable reagent, affording a plurality of sulfones **34** in solution.

The plurality of azides **26** is produced starting from a set of substituted anilines **35**. The aniline is subjected to electrophilic aromatic substitution at the 4-position, providing a set of isothiocyanates **36**. The amine portion of **36** is protected to produce **37**. The isothiocyanate group of **37** is reacted with sodium sulfide and trityl bromide to afford a set of protected sulfides **38**. The protected aniline of **38** is reacted with a substituted epoxide

and cyclized, yielding a set of oxazolidinones **39**. Conversion of the primary alcohol of **39** to an azide produces the set of azides **26**. See Figure 8.

Figure 9 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is $NR_{12}R_{13}$. A plurality of solid support bound azides **5**, which contain an activated ester, are converted into a plurality of acyl azides **40**. The acyl azides are rearranged, providing a plurality of protected anilines **41**. Deprotection of **41** affords a plurality of anilines **42**, which are reacted with electrophilic units $R_{12}X$ and $R_{13}X$ to yield a plurality of substituted anilines **43**. The solid support bound substituted anilines **43** are removed from the solid support using a suitable reagent to afford a plurality of substituted anilines **44** in solution. Another embodiment is shown in Figure 39, which is a scheme showing the synthesis of acylamino oxazolidinone compounds and libraries, wherein R_1 and R_2 are substituents, for example, H, alkyl, heteroalkyl, aryl, heteroaryl, or alkoxy. Figures 42 and 43 illustrate building blocks R_2COOH that may be used for synthesis of acylamino oxazolidinone libraries and compounds as shown in Figure 39, and also may be used in other syntheses such as those shown in Figure 9.

Figure 10 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is 2-oxazolyl with a cyano group at the 4-position and an amino group at the 5-position. A plurality of azides **2** are converted to the corresponding iminophosphoranes upon reaction with a phosphine. The ylides are mixed with a plurality of solid supports containing a carbonyl functional group, producing a plurality of amines **3**. The ester group of **3** is deprotected to provide plurality of carboxylic acids. The amine is acylated and the carboxylic acid activated, yielding a plurality of esters **5**. Reaction of **5** with amino malonitrile affords a plurality of oxazoles **45**. The solid support bound oxazoles are removed from the solid support using a suitable reagent to produce a plurality of oxazoles **46** in solution.

Figure 11 shows exemplary methods for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is either 2-oxazolyl containing R_{14} at the 4-position and R_{15} and the 5-position, or 2-oxazolyl containing cyano at the 4-position and R_{15} at the 5-position. To prepare an oxazolidinone library, wherein R_1 is 2-oxazolyl containing R_{14} at the 4-position and R_{15} at the 5-position, a plurality of solid

support bound oxazoles **45** is reacted with a reagent capable of converting the 4-cyano group to a different functionality (e.g. hydrolysis to acid) to provide a plurality of oxazole compounds **47**. The 5-amino substituent of **47** is alkylated or acylated to produce a plurality of compounds **48**. The solid support bound oxazoles **48** are removed from the solid support using a suitable reagent to afford a plurality of R_{14}, R_{15}-substituted oxazoles **49** in solution. To prepare an oxazolidinone library, wherein R_1 is 2-oxazolyl containing cyano at the 4-position and R_{15} at the 5-position, the 5-amino substituent of **45** is alkylated or acylated to produce a plurality of compounds **50**. The solid support bound oxazoles **50** are removed from the solid support using a suitable reagent to afford a plurality of cyano, R_{15} substituted oxazoles **51** in solution.

Figure 12 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is 2-aminothiazolyl containing R_{16} at the 4-position and R_{17} at the 5-position. A plurality of anilines **42** is reacted with a protected isothiocyanate to provide a plurality of protected thiocarbamates **52**. The thiocarbamates are deprotected, producing a plurality of thiocarbamates **53**. Reaction of **53** with an α-halo ketone yields a plurality of aminothiazoles **54**. The solid support bound amino thiazoles are removed from the solid support using a suitable reagent to afford a plurality of aminothiazoles **55** in solution.

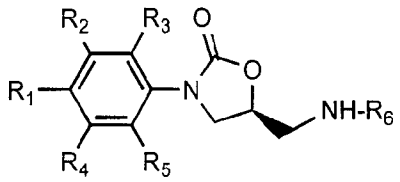
Figure 13 shows an exemplary method for the preparation of combinatorial libraries comprising oxazolidinones of the structure **1b**, wherein R_1 is $CH_2NR_{18}R_{19}$. A plurality of azides **56** is converted to the corresponding iminophosphoranes upon reaction with a phosphine. The iminophosphoranes are mixed with a plurality of solid supports, producing a plurality of imines. The imines are reduced and acylated to provide a plurality of acetals **57**. The acetals are removed, yielding a plurality of aldehydes **58**. Reductive amination of the aldehydes affords a plurality of amines **59**. The solid support bound amines are removed from the solid support using a suitable reagent to afford a plurality of amines **60** in solution.

The plurality of azides **67** is produced starting from a set of substituted methylnitrobenzenes **61** (Figure 14). The methyl group of **61** is oxidized to provide the acetals **62**. Transacetalization of **62** yields a set of dimethyl acetals **63**. The nitro group of **63** is reduced, affording a set of anilines **64**, which are protected **65**. The protected anilines

are reacted with a substituted epoxide, and the resulting amino alcohols are cyclized to yield a set of oxazolidinones **66**. The primary of alcohol of **66** is displaced with azide, producing **67**.

Embodiments of Biologically Active Oxazolidinone Compounds

In one embodiment, biologically active oxazolidinones, for example with antibiotic activity, are provided, for example, of the structure **1b**:



1b

In one embodiment, the substituents on **1b** are as follows:

Substituent R_1 of compound **1b** is one of the following functional groups: $C(O)NR_7R_8$, wherein R_7 and R_8 are, independently, hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $C(O)OR_9$, wherein R_9 is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $C(O)R_{10}$, wherein R_{10} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; SR_{11}, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)_2R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $NR_{12}R_{13}$, wherein R_{12} and R_{13} are, independently, hydrogen, acyl, sulfonyl, alkyl, heteroalkyl, aryl or heteroaryl; 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position, and wherein R_{14} and R_{15} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position, and wherein R_{16} and R_{17} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; and $CH_2NR_{18}R_{19}$, wherein R_{18} and R_{19} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, acyl or sulfonyl. The substituents R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group; and, R_6 is acyl or sulfonyl.

In one embodiment, the biologically active oxazolidinones of structure **1b** are substituted as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is alkyl,

heteroalkyl, aryl or heteroaryl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$. In one embodiment, the oxazolidinone is substituted as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is aryl or heteroaryl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$. In another embodiment, the oxazolidinone is substituted as follows: R_1 is $C(O)NR_7R_8$, wherein R_7 is hydrogen and R_8 is heteroaryl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the biologically active oxazolidinones of structure **1b** are substituted as follows: R_1 is 2-oxazolyl, containing a cyano group at the 4-position and an amino group at the 5-position of the oxazole; R_2 and R_4 are, independently, hydrogen or an electron withdrawing group; R_3 and R_5 are hydrogen; and, R_6 is acyl or sulfonyl. The oxazolidinone is, for example, substituted as follows: R_1 is 2-oxazolyl, containing a cyano group at the 4-position and an amino group at the 5-position of the oxazole; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl. In another embodiment, the oxazolidinone is substituted as follows: R_1 is 2-oxazolyl, containing a cyano group at the 4-position and an amino group at the 5-position of the oxazole; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

In another embodiment, the biologically active oxazolidinones of structure **1b** are substituted as follows: R_1 is 2-aminothiazolyl, wherein the 4-position of the thiazole contains R_{16} and the 5-position contains R_{17}, and wherein R_{16} and R_{17} are, independently, hydrogen, alkyl, aryl or heteroaryl; R_2 and R_4 are, independently, hydrogen or an electron withdrawing group; R_3 and R_5 are hydrogen; and, R_6 is acyl. For example, the oxazolidinone is substituted as follows: R_1 is 2-aminothiazolyl, wherein the 4-position of the thiazole contains R_{16} and the 5-position contains R_{17}, and wherein R_{16} and R_{17} are, independently, hydrogen, alkyl or aryl; R_2 is a halogen; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$. In another embodiment, the oxazolidinone is substituted as follows: R_1 is 2-aminothiazolyl, wherein the 4-position of the thiazole contains R_{16} and the 5-position contains R_{17}, and wherein R_{16} and R_{17} are, independently, hydrogen or aryl; R_2 is fluorine; R_3, R_4 and R_5 are hydrogen; and, R_6 is acyl, wherein the acyl group is of the structure $C(O)CH_3$.

Synthesis of Biologically Active Oxazolidinone Compounds **1b**

Exemplary methods for the solid phase synthesis of biologically active oxazolidinones, for example, of the structure **1b** are provided. The methods comprise: providing an iminophosphorane; mixing the iminophosphorane with a resin that comprises carbonyl groups to form an imine intermediate; and reducing the imine intermediate to afford a compound attached to the resin through an amine linkage.

Figure 15 generally shows the solid phase synthesis of oxazolidinone compounds. Oxazolidinone **68**, wherein R_{20} is (4-R_1)-aryl (1), is converted into imine **71** by 1 of 2 pathways: azide **68** is treated with a phosphine (R_{21} is alkyl or aryl) to provide iminophosphorane **69**, which is reacted with a carbonyl containing resin; or, azide **68** is reduced to amine **70**, which is reacted with a carbonyl containing resin. Imine **71** is reduced using an appropriate reducing agent (e.g., $NaBH_3CN$), affording compound **72**, which is attached to the resin through an amine linkage.

Figure 16 generally shows the synthesis of compound **68**. Epoxide **73** is subjected to nucleophilic attack by $R_{20}NH_2$, producing an amino alcohol. The amino alcohol is cyclized to provide oxazolidinone **74**. Removal of the ester protecting group of **74** affords a primary alcohol **75**. Displacement of the primary alcohol with azide yields **68**.

The carbonyl containing resin is graphically depicted on Figure 15. Substituent R_{23} is hydrogen, alkyl, aryl, O-alkyl or O-aryl. The polymeric support (filled circle) is composed of a variety of materials, including, without limitation, Tentagel, (cross-linked)polystyrene, (cross-linked)polyethyleneglycol, poly-ethyleneglycol-polystyrene compositions, and polyacrylate. Substituent R22 is shown on Figure 17: R24 is hydrogen, CH_3O, NO_2; and, R_{25} is $(CH_2)_nCONH$, wherein n is an integer ranging from 1 to about 5.

Figure 18 shows an embodiment of the solid phase synthesis methods. Azide **14** is converted into an iminophosphorane upon treatment with triphenylphosphine. The iminophosphorane is reacted with BAL resin to provide an imine, which is reduced with $NaBH_3CN$, affording amine **15**. Compound **15** is reacted with TMSCl to remove the ester group (**16**). The amine of **16** is acylated and the carboxylic acid is transformed into an activated ester (**17**). Treatment of the activated ester with Bu_4NN_3 or $TMSN_3$ affords acyl azide **77**. Acyl azide **77** is rearranged, yielding a protected aniline (**78**). The Fmoc protecting group is removed (**79**), and the resulting aniline is sulfonated with p-

$O_2NC_6H_4SO_2Cl$ (**80**). The sulfonated aniline (**80**) is removed from the solid support upon reaction with TFA, providing **81**. Another embodiment is shown in Figure 40. Figure 46 illustrates sulfonyl chloride building blocks R_2SO_2Cl that may be used in the synthesis of sulfonamide oxazolidinone libraries and compounds as shown in Figure 40, and also may be used in the syntheses shown in Figure 18.

Figure 19 shows another embodiment of the solid phase synthesis methods. Aniline **79** is reacted with Fmoc-N=C=S to provide protected thiourea **82**. The protected thiourea is treated with piperidine, affording a deprotected thiocarbamate (**83**). Reaction of **83** with 2-bromoacetophenone yields thiazole **84**. Treatment of **84** with TFA cleaves the thiazole from the solid support, providing **85**.

Figure 20 shows another embodiment of the solid phase synthesis methods. Azide **4** is converted into an iminophosphorane upon treatment with triphenyl phosphine. The iminophosphorane is reacted with BAL resin, providing an imine. The imine is reduced using $NaBH_3CN$ to afford solid support bound amine **15**. The ester of **15** is deprotected using TMSCl, yielding a carboxylic acid; the amine is acylated upon reaction with Ac_2O; and, the acid is activated using PfpOCOCF3, yielding **17**. Reaction of **17** with aminomalonitrile provides oxazole **86**. Treatment of **86** with TFA cleaves the oxazole from the solid support to afford **87**.

Figure 21 shows two embodiments of the solid phase synthesis methods. Compound **17** is treated with $HN(OCH_3)CH_3$ to provide Weinreb amide **88**. Amide **88** is either reduced with $LiAlH_4$ to afford aldehyde **89** or reacted with MeMgI, a Grignard reagent, to yield ketone **91**. Treatment of either aldehyde **89** or ketone **91** with TFA provides, respectively, cleaved products **90** and **92**.

Figure 22 shows two embodiments of the solid phase synthesis methods. Compound **79** is treated with either a dialdehyde to provide morpholine **93** or a diacetal to afford pyrrole **95**. Treatment of either morpholine **93** or pyrrole **95** with TFA provides, respectively, cleaved products **94** and **96**.

Figure 48, shows building blocks R_2R_3NH and R_1COOH that may be used to make exemplary oxazolidinone compounds of formula **1k** and libraries thereof.

Synthesis of Oxazolidinone Compounds **1a**

Oxazolidinone compounds **1a** and precursors thereof may be made by a variety of methods as disclosed herein.

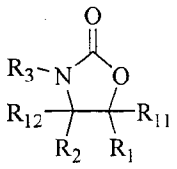
An embodiment of a solid phase synthesis method to make amino alcohols, where R_1 is an alkyl, is shown in Figure 23. An olefin group is attached to the surface of a solid support (**5a**) providing the functionalized resin **6a**. The olefin can have the following functionality: "m" is 0, 1, or 2; "n" is 0, 1, or 2; R_{10}, R_{11} R_{12}, R_2 and R_3 are independently hydrogen, alkyl, heteroalkyl, aryl or heteroaryl. The olefin is chemically modified yielding epoxide **7a**. Addition of a substituted amine to the distal carbon of immobilized epoxide **7a** affords solid support bound amino alcohol **8a**. Solid support bound amino alcohol **8a** is treated with a phosgene equivalent providing oxazolidinone **15a**, which is cleaved under standard conditions to yield free oxazolidinone **16a**. Acylation of **16a** yields oxazolidinone **16b**.

Another embodiment of the solid phase synthesis method to make oxazolidinones is shown in Figure 24. Immobilized epoxide **12a** was treated with aniline in the presence of lithium triflate to provide solid support bound amino alcohol **19a**. Reaction of **19a** with CDI yielded oxazolidinone **20a**. Alternatively, **20a** was prepared directly from epoxide **12a** upon treatment with a lithium salt of aniline benzylcarbamate. Addition of TFA to oxazolidinone **20a** provided free oxazolidinone **21a**, which was acetylated to yield acetamide **22a**.

Another embodiment of the solid phase synthesis method to make oxazolidinones is shown in Figure 25. PNP Wang Resin (**23a**) was reacted with allyl amine to provide carbamate **24a**. The terminal olefin of carbamate **24a** was oxidized with *m*CPBA to yield immobilized epoxide **12a**. Addition of 3-fluoro-4-morpholino aniline to **12a** produced amino alcohol **25a**, which was cyclized to oxazolidinone **26a** upon treatment with CDI. Reaction of **26a** with TFA provided free amine **27a**. Addition of acetyl chloride to **27a** produced acetamide **28a**.

Synthesis of Combinatorial Libraries Comprising Oxazolidinones **1a**

In one embodiment, provided are methods for the synthesis of combinatorial libraries comprising oxazolidinones **1a** and compositions formed from this method. In one embodiment, oxazolidinones **1a** are compounds of the following structure:



1a

where R_1 is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl; R_2 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; R_3 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; R_{11} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl; and R_{12} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl.

An embodiment of the solid phase method to make oxazolidinone libraries, where R_1 is an alkyl group, is described in reference to Figure 23. Olefin groups are attached to the surface of a plurality of solid supports **5a** providing functionalized resins **6a**. The olefin groups can have the following functionality: "m" is 0, 1, or 2; "n" is 0, 1, or 2; R_2, R_3, R_{10}, R_{11} and R_{12} are independently hydrogen, alkyl, heteroalkyl, aryl or heteroaryl. The individual olefin groups are chemically modified to yield epoxides **7a**. Addition of different amine units to the distal carbon of the epoxides 7a affords a plurality of amino alcohols **8a**.

A plurality of solid support bound amino alcohols **8a** is treated with a phosgene equivalent to provide a plurality of oxazolidinones **15a**, which are cleaved under standard conditions to yield the free oxazolidinones **16a**.

Another embodiment of the solid phase method to make oxazolidinone libraries is shown in Figures 26 and 27. Carboxylic acid **30a** is attached to amine resin **29a** to provide amide **31a**. Reductive amination of **31a** employing amine **32a** yields the functionalized amine **33a**, which is added to an array of individual reaction chambers. Addition of sulfonyl chloride units to a plurality of amines **33a** produces the sulfonamides **34a**. The sulfonamides are cleaved from the solid support using standard conditions providing a plurality of free sulfonamides **35a**. Addition of carboxylic acid or carboxylic acid derivative units to a plurality of amines **33a** produces the amides **36a**. The amides **36a** are

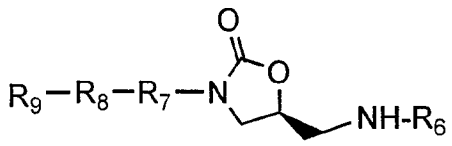
cleaved from the solid support using standard conditions providing a plurality of free amides **37a**. Addition of isocyanate units to a plurality of amines **33a** produces the ureas **38a**. The ureas **38a** are cleaved from the solid support using standard conditions providing a plurality of free ureas **39a**.

Another embodiment of the solid phase method to make oxazolidinone libraries is shown in Figure 28. Coupling of α-bromo acetic acid to amine **33a** provides amide **40a**, which is divided into an array of individual reaction chambers. Nucleophilic addition of thiol units to a plurality of amides **40a** yields the α-thio amides **41a**, which are cleaved from the solid support upon treatment with TFA producing a plurality of free α-thio amides **42a**. Nucleophilic addition of triphenylphospine to a plurality of amides **40a** yields solid support bound Wittig reagents that are coupled with aldehyde units affording a plurality of α, β-unsaturated amides **43a**. The amides were cleaved from the solid support upon treatment with TFA to produce a plurality of free α, β-unsaturated amides **44a**. Nucleophilic addition of amine units to a plurality of amides **40a** yields the α-amino amides **45a**, which are cleaved from the solid support upon treatment with TFA producing a plurality of free α-amino amides **46a**.

3-(Polysubstituted)oxazolidinones

A variety of 3-(polysubstituted)oxazolidinones are provided, which optionally have biological activity, such as antimicrobial activity.

In one embodiment, 3-(polysubstituted)oxazolidinones **2c** as well as combinatorial libraries comprising the compounds are provided:



2c

In **2c**, in one embodiment:

R_6 is acyl or sulfonyl;

R_7 is aryl or heteroaryl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, where n = 0-6, and R and R' are substituents, for example, independently H, or alkyl, such as C_1-C_7 alkyl, or heteroalkyl, aryl or heteroaryl; and

R_9 is hydrogen, OH, alkyl, aryl, heteroalkyl, or heteroaryl.

In another embodiment, 3-[4-(heteroaryl)aminocarbonylaryl]- oxazolidinones and 3-[4-(N-oxide heteroaryl)aminocarbonylaryl]-oxazolidinones are provided.

In one embodiment of **2c**:

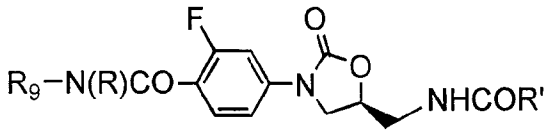
R_6 is C(=O)R, where R is a substituent, for example, H or alkyl, such as C_1-C_7 alkyl, such as methyl or ethyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl;

R_7 is aryl;

R_8 is an amide group, such as NH(C=O) or NR'(C=O), where R' is a substituent, for example, H, heteroalkyl, aryl, heteroaryl, or alkyl, such as C_1-C_7 alkyl, such as methyl; and

R_9 is hydrogen or a heteroaryl group, such as an unsubstituted or substituted heteroaryl group, wherein the heteroaryl group is for example pyridinyl, thiazolyl, benzothiazolyl, isothiazolyl, quinolinyl, 1,3,4-triazolyl, or 1,3,4-thiadiazolyl.

For example, compounds of formula **2d** are provided:



2d

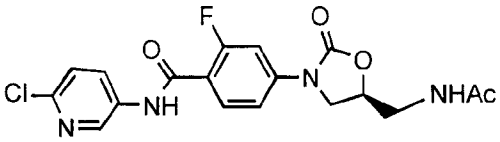
wherein

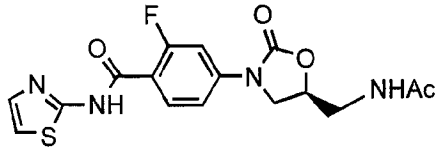
R_9 is hydrogen or an unsubstituted or substituted heteroaryl group, such as pyridinyl, thiazolyl, benzothiazolyl, isothiazolyl, quinolinyl, 1,3,4-triazolyl, or 1,3,4-thiadiazolyl; and

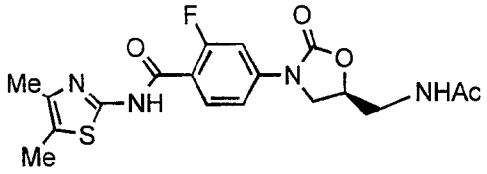
R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, such as methyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

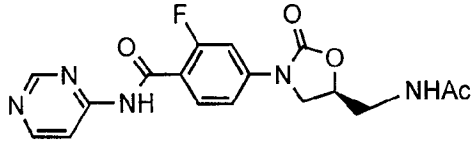
Exemplary compounds are shown below.

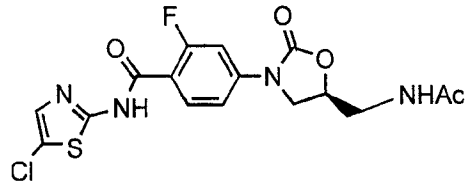
In one embodiment the following nine preferred compounds are provided, which have an MIC against *S. aureus* of about 0.5 to 1 μg/mL using a standard whole cell assay as disclosed herein.

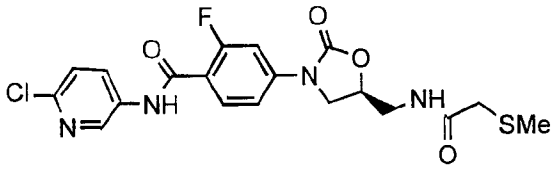


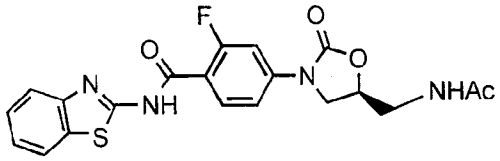


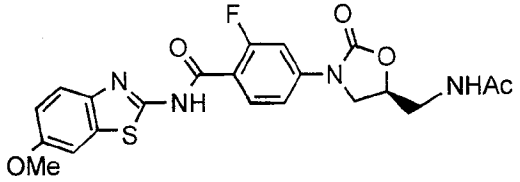


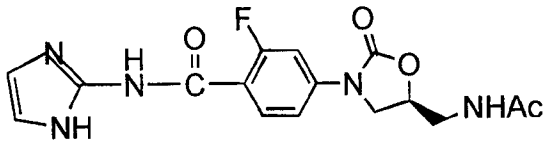




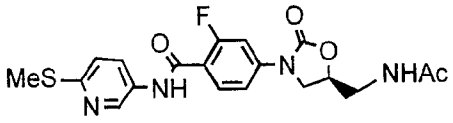


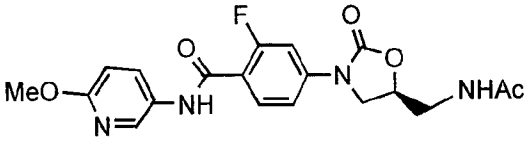


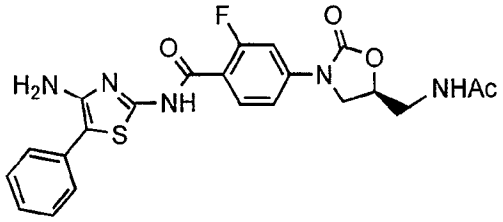


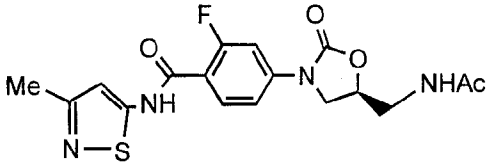


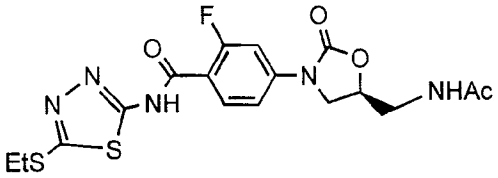
The following nine compounds also are provided that have an MIC against *S. aureus* of about 2 to 4 μg/mL using a standard whole cell assay as disclosed herein.

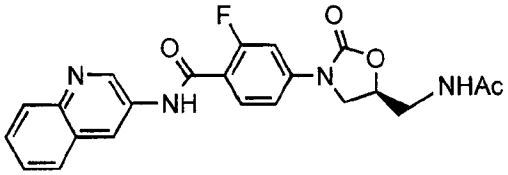


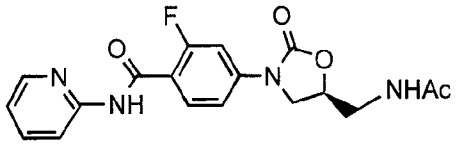


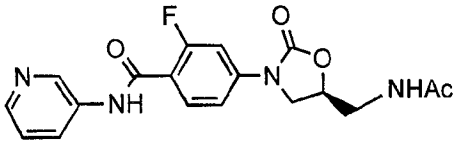


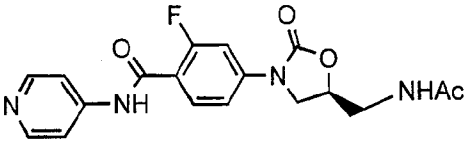




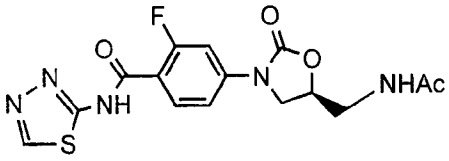


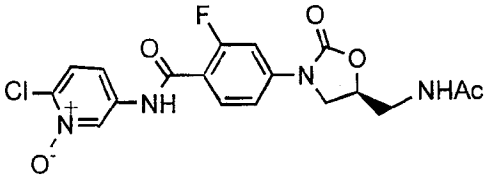


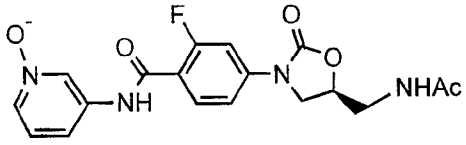


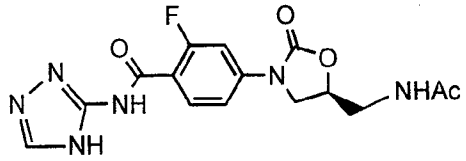


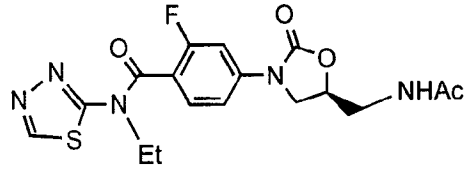
Also provided are the following compounds.



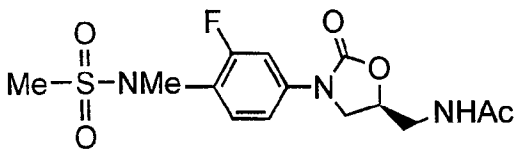


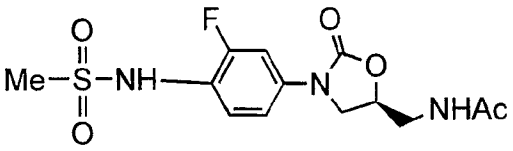


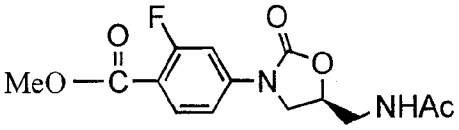


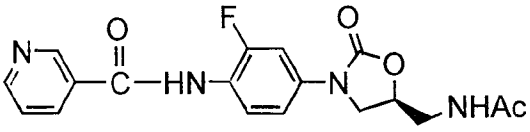


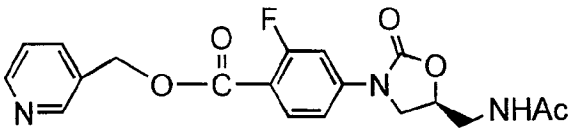
Other exemplary oxazolidinone compounds within the scope of the invention are shown below:











Further provided are 3-(aminocarbonyl)oxazolidinones of formula **2c**, wherein:

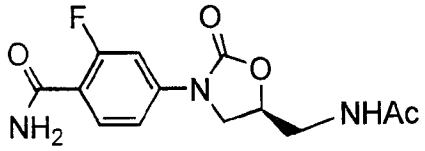
R_6 is an acyl group, such as C(=O)R, where R is a substituent, for example, H or alkyl, such as C_1-C_7 alkyl, including methyl, or *e.g.*, heteroalkyl, aryl or heteroaryl;

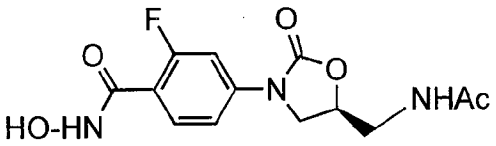
R_7 is aryl;

R_8 is NH(C=O); and

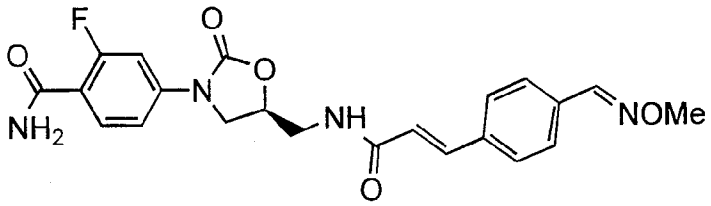
R_9 is hydrogen or OH;

Exemplary compounds are shown below:





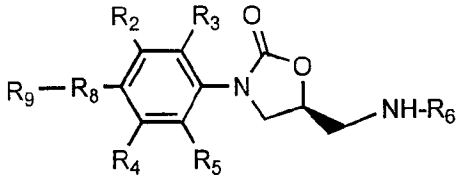
In one embodiment the following compound is provided, which has an MIC against *S. aureus* of about 0.5 μg/mL using a standard whole cell assay as disclosed herein.



3-[(Substituted)aryl] oxazolidinones

A variety of 3-[(substituted)aryl] oxazolidinones are provided, which optionally are biologically active, for example as antimicrobial compounds.

In one embodiment oxazolidinones of formula **3c**, and combinatorial libraries comprising compounds of formula **3c** are provided:



3c

In one embodiment in **3c**:

R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, where n = 0-6, and where R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl; and

R_9 is alkyl, aryl, heteroalkyl, or heteroaryl.

In a further embodiment, 3-[4-(alkylthio)aryl] oxazolidinones are provided. For example, compounds of formula **3c** are provided, wherein:

R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

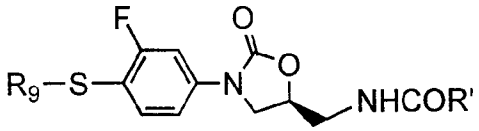
R_6 is acyl, such as $C(=O)CH_3$;

R_7 is an aryl group;

R_8 is thio group, such as S; and

R_9 is a heteroalkyl group.

In another embodiment, compounds of formula **3d** are provided:



3d

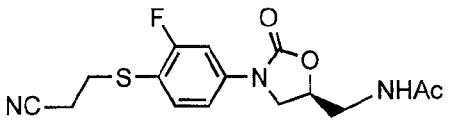
wherein

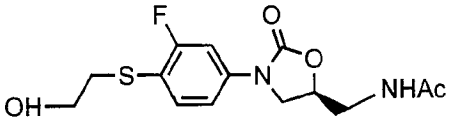
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

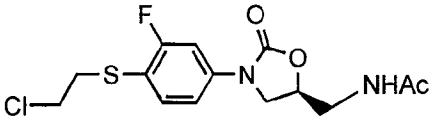
R' is a substituent, for example, H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

Exemplary compounds are shown below.

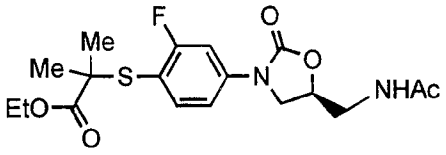
In one preferred embodiment, the following three compounds are provided that have an MIC against *S. aureus* of about 2 μg/mL using a standard whole cell assay as disclosed herein.

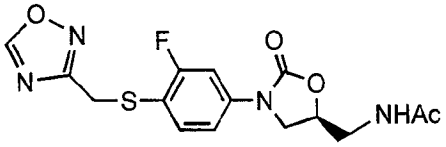


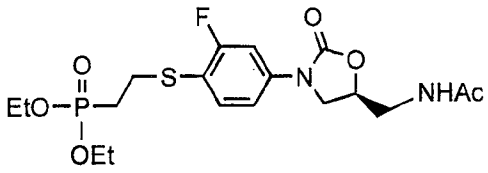


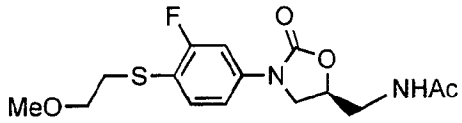


In another embodiment, the following four compounds are provided that have an MIC against *S. aureus* of about 8 μg/mL using a standard whole cell assay as disclosed herein.

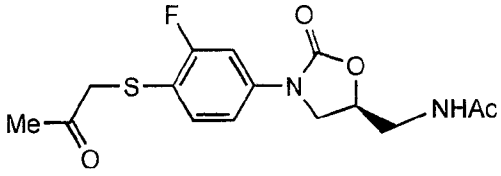


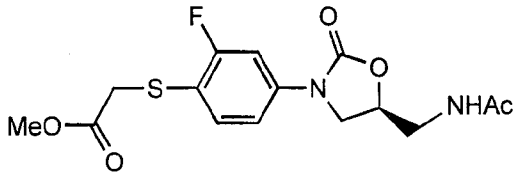


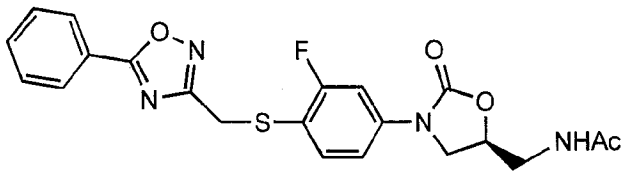




Also provided are the following compounds:







In another embodiment, 3-[4-(ester group)aryl] oxazolidinones useful as antimicrobial agents are provided. For example, compounds of formula **3c** are provided wherein:

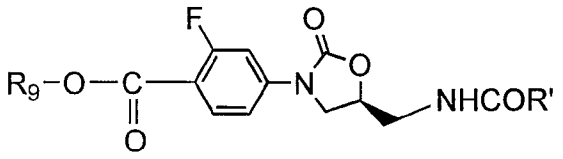
R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

R_6 is an acyl group, such as $C(=O)CH_3$;

R_8 is an ester, such as $OC(=O)$; and

R_9 is an alkyl group, such as a C_1-C_7 alkyl group.

In one embodiment, compounds of structure **3e** are provided:



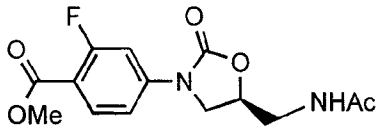
3e

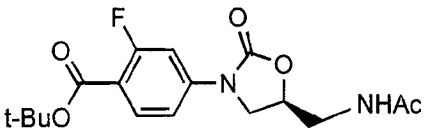
wherein

R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R' is a substituent, for example, H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

Exemplary compounds are shown below:

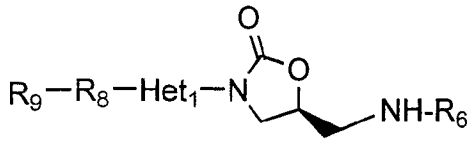




3-[(Substituted)heteroaryl] oxazolidinones

In another embodiment, a variety of 3-[(substituted)heteroaryl] oxazolidinones, which optionally are biologically active, for example, as antimicrobial compounds, are provided.

In one embodiment, compounds of the formula **4c**, and combinatorial libraries thereof are provided:



4c

In one embodiment of **4c**:

R_6 is acyl or sulfonyl;

Het_1 is heterocyclic group such as an unsubstituted or substituted heteroaryl group, such as thienylphenyl, thiazolyl, 1,3,4-thiadiazolyl, pyridinyl, or pyrimidinyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, where n = 0-6, and R and R' are substituents, for example, independently, H, or alkyl, such as C_1-C_7 alkyl, or, e.g., heteroalkyl, aryl or heteroaryl; and

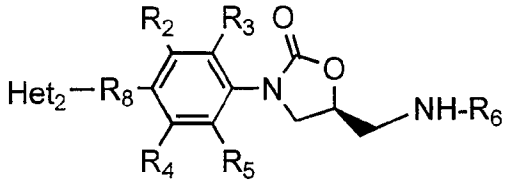
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl.

In **4c**, substituents on the heteroaryl group Het_1 are, for example, independently, hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OH, OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in the Het_1 nuclei, and R'' and R''' are substituents, for example are independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

3-[4-(Linked heteroaryl)aryl] oxazolidinones

In a further embodiment, 3-[4-(linked heteroaryl)aryl] oxazolidinones are provided, which optionally have biological activity, for example, as antimicrobial compounds.

For example, compounds of the formula **5c**, and combinatorial libraries thereof are provided:



5c

In one embodiment of **5c**:

R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O)NOR C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, where n = 0-6, and R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl; and

Het_2 is a heterocyclic group, such as an unsubstituted or substituted heterocyclic group, such as an oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-oxadiazolyl, thienylphenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-triazinyl, 1,2,4-triazinyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, or 1,2,4,5-tetrazinyl;

wherein substituents in heteroaryl group Het_2 are, for example, independently, hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OH, OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in

the Het_2 nuclei, where R'' and R''' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

In another embodiment, 3-[4-(linked heteroaryl)aryl] oxazolidinones are provided, which optionally have antimicrobial activity, of formula **5c** wherein:

R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

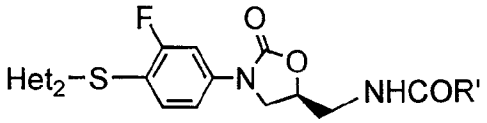
R_6 is acyl, for example, $C(=O)CH_3$;

R_7 is an aryl group;

R_8 is a thio group, such as S; and

Het_2 is a substituted or unsubstituted thienylphenyl or thiazolyl heteroaryl group.

Also provided are compounds of structure **5d**:



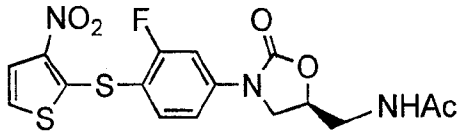
5d

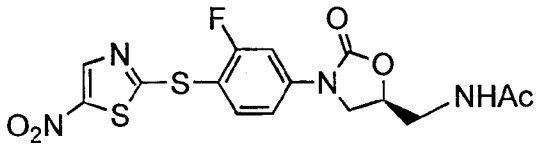
wherein

Het_2 is a substituted or unsubstituted thienylphenyl or thiazolyl heteroaryl group; and

R' is a substituent, for example, H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

Exemplary compounds are shown below:





In another embodiment, 3-[4-(triazinylamino)aryl] oxazolidinones are provided, which are optionally antimicrobial compounds. For example, compounds of formula **5e** are provided wherein:

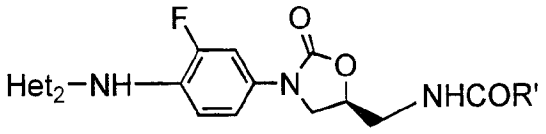
R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

R_6 is acyl, such as $C(=O)CH_3$;

R_8 is amino group, such as NH; and

Het_2 is 1,3,5-triazinyl.

Additionally, compounds of structure **5e** are provided:



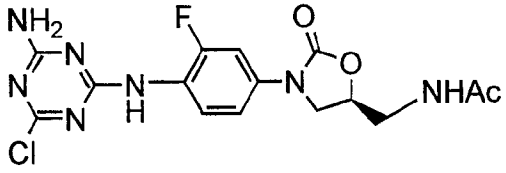
5e

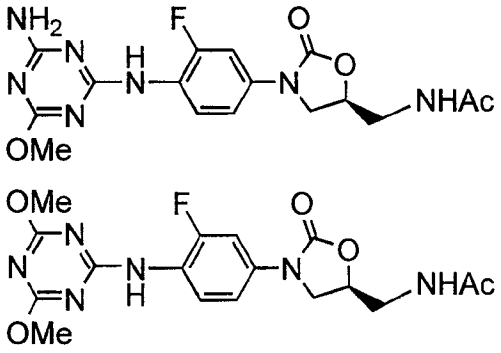
wherein

Het_2 is a unsubstituted or substituted 1,3,5-triazinyl; and

R' is a substituent, for example, H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

Exemplary compounds are shown below:

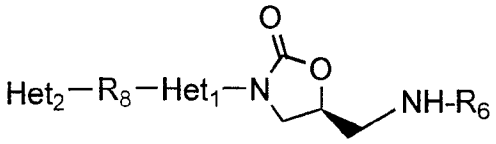




3-[4-(Linked heteroaryl)heteroaryl] oxazolidinones

In another embodiment, 3-[4-(linked heteroaryl)heteroaryl] oxazolidinones are provided, which are optionally biologically active, for example, as antimicrobial compounds.

For example, compounds of formula **6c**, and combinatorial libraries thereof are provided:



6c

In one embodiment of **6c**:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O)NOR C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, where n = 0-6, and R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl;

Het_1 is a heterocyclic group such as an unsubstituted or substituted heterocyclic group, for example, thienylphenyl, thiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyrimidinyl, phenyl or fluorophenyl;

wherein substituents in heteroaryl group Het_1 are independently, for example, hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in the Het_1 nuclei, where R'' and R''' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl; and

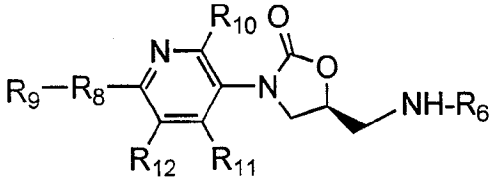
Het_2 is an unsubstituted or substituted heterocyclic preferably heteroaryl group, such as an oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-oxadiazolyl, thienylphenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-triazinyl, 1,2,4-triazinyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, or 1,2,4,5-tetrazinyl;

wherein substituents in heteroaryl group Het_2 are independently, for example, hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR_xR_y, OH, OR_x, SR_x, S(=O)R_x, SO_2R_x, C(=O)R_x, C(=O)OR_x, OC(=O)R_x, C(=O)NR_xR_y, N(R_x)C(=O)R_y, or N-oxide group in the Het_2 nuclei, where R_x and R_y are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

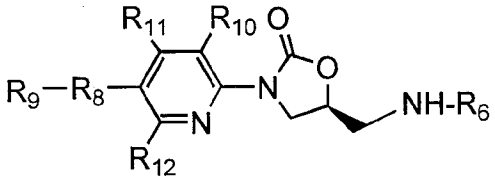
3-(Substituted pyridyl)oxazolidinones

Also provided are 3-(substituted pyridyl)oxazolidinones, which are optionally biologically active, for example as antimicrobial compounds.

In one embodiment, compounds of the formulas **7c** or **8c** and combinatorial libraries thereof are provided:



7c



8c

In one embodiment, in **7c** and **8c**:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl;

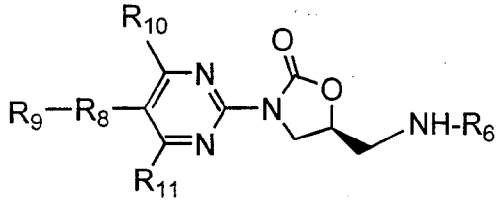
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R_{10}, R_{11} and R_{12} are, for example, independently hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in the pyridine nuclei, where R'' and R''' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

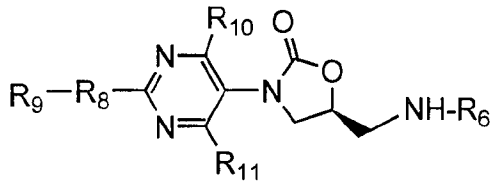
3-(Substituted pyrimidinyl)oxazolidinones

A variety of 3-(substituted pyrimidinyl)oxazolidinones, which optionally have biological activity, such as antimicrobial activity, also are provided.

In one embodiment, compounds of the formulas **9c** and **10c**, as well as combinatorial libraries thereof, are provided:



9c



10c

In one embodiment of **9c** and **10c**:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl group, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, where n = 0-6, and where R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl;

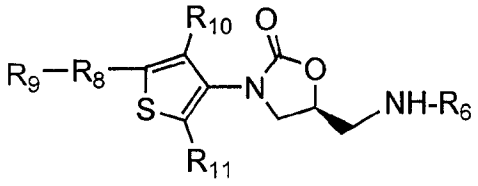
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R_{10} and R_{11} are independently hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in the pyrimidine nuclei, where R'' and R''' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

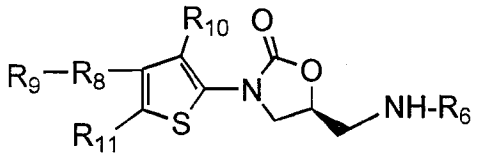
3-(Thienyl)oxazolidinones

A variety of 3-(thienyl)oxazolidinones are provided, which optionally have biological activity, such as antimicrobial activity.

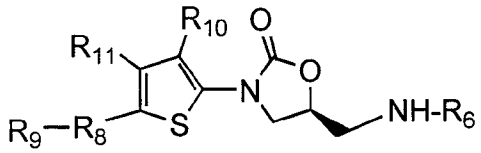
In one embodiment, compounds of formulas **11c, 12c** and **13c**, and combinatorial libraries thereof are provided:



11c



12c



13c

In one embodiment of formulas **11c, 12c** and **13c**:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, where n = 0-6, and where R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl;

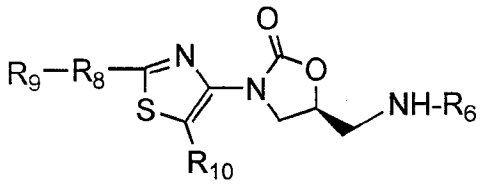
R_9 is an alkyl, aryl, heteroalkyl, or heteroaryl group; and

R_{10} and R_{11} are independently hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', where R'' and R''' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

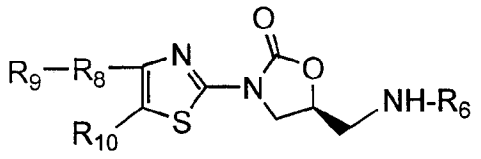
3-(Thiazolyl)oxazolidinones

Also provided are 3-(thiazolyl)oxazolidinones, which optionally have biological activity, such as antimicrobial activity.

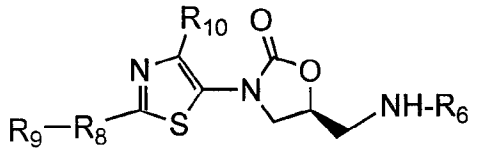
In one embodiment, compounds of formulas **14c, 15c** and **16c**, and combinatorial libraries thereof are provided:



14c



15c



16c

In one embodiment of **14c**, **15c** and **16c**:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are substituents, for example, independently H or alkyl, such as C1-C7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl;

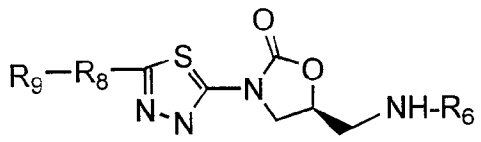
R_9 is an alkyl, aryl, heteroalkyl, or heteroaryl group; and

R_{10} is hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', or N(R'')C(=O)R''', where R'' and R''' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl.

3-(1,3,4-Thiadiazolyl)oxazolidinones

A variety of 3-(1,3,4-thiadiazolyl)oxazolidinones are provided, which optionally have biological activity, such as antimicrobial activity.

In one embodiment, compounds of formula **17c** and combinatorial libraries thereof are provided:



17c

In one embodiment of **17c**:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, where n = 0-6, and where R and R' are substituents, for example, independently H or alkyl, such as C_1-C_7 alkyl, or, *e.g.*, heteroalkyl, aryl or heteroaryl; and

R_9 is alkyl, aryl, heteroalkyl, or heteroaryl.

Synthesis of 3-(Heteroaryl)Oxazolidinones

3-(Heteroaryl)oxazolidinones and other oxazolidinones may be synthesized by a variety of routes as disclosed herein. In one embodiment, the synthesis may be conducted as shown in Figure 49, wherein the synthesis includes: reaction of an appropriate heteroaryl halide with 3-aminopropane-1,2-diol; cyclization of the resulting (heteroaryl)aminodiol with phosgene or equivalent; conversion of 5-(R)-hydroxymethyl-3-

heteroaryloxazolidinone into resin immobilized 5-(S)-aminomethyl-3-heteroaryl oxazolidinone. Further reaction of this reagent produces the desired oxazolidinone.

In another embodiment, which is illustrated in Figure 50, the 5-(S)-azidomethyl-3-heteroaryloxazolidinone reagent is produced from an appropriate heteroarylhalide and 5-(S)-azidomethyloxazolidinone or equivalent thereof in the presence of a base. The resulting azide or amine intermediate is then immobiilzed on a BAL linker resin. Further reaction of the X group and or the amine group attached to the solid phase provides an array of desired 3-heteroaryloxazolidones.

As will be appreciated by those skilled in the art, using these and other methods disclosed herein, based on the teachings of the specification, the oxazolidinones disclosed herein can be readily synthesized.

Combinatorial Library Synthesis

Combinatorial library synthesis is typically performed on a solid support. See, for example, Lam et al. (1991) *Nature* 354:82-84; and Houghten et al. (1991) *Nature* 354:84-86. There are two general technologies for the construction of combinatorial libraries: "mix and split" technology and "multiple parallel synthesis" technology.

For the "mix and split" technology, a large number of beads or particles are suspended in a suitable carrier (such as a solvent) in a parent container. The beads, for example, are provided with a functionalized point of attachment for a chemical module. The beads are then divided and placed in various separate reaction vessels. The first chemical module is attached to the bead, providing a variety of differently substituted solid supports. Where the first chemical module includes 3 different members, the resulting substituted beads can be represented as A_1, A_2 and A_3.

The beads are washed to remove excess reagents and subsequently remixed in the parent container. This bead mixture is again divided and placed into various separate reaction vessels. The second chemical module is coupled to the first chemical module. Where the second chemical module includes 3 different members, B_1, B_2 and B_3, 9 differently substituted beads result: A_1B_1, A_1B_2, A_1B_3,A_2B_1, A_2B_2, A_2B_3, A_3B_1, A_3B_2 and A_3B_3. Each bead will have only a single type of molecule attached to its surface.

The remixing/redivision synthetic process can be repeated until each of the different chemical modules has been incorporated into the molecule attached to the solid

support. Through this method, large numbers of individual compounds can be rapidly and efficiently synthesized. For instance, where there are 4 different chemical modules, and where each chemical module contains 20 members, 160,000 beads of different molecular substitution can be produced.

Combinatorial library synthesis using the "mix and split" technology can be performed either manually or through the use of an automated process. For the manual construction of a combinatorial library, a scientist would perform the various chemical manipulations. For the construction of a combinatorial library through an automated process, the various chemical manipulations will typically be performed robotically. For example, see U.S. Patent No. 5,463,564.

For the "multiple parallel synthesis" technology, beads or particles are suspended in a suitable carrier (such as a solvent) in an array of reaction chambers. The beads or particles are provided with a functionalized point of attachment for a chemical module. Different members of a chemical module are added to each individual reaction chamber, providing an array of differently functionalized beads. Where there are 96 separate reaction chambers and 96 different chemical module members, a combinatorial library of 96 compounds is formed. The compounds can be assayed on the solid support, cleaved from the solid support and then assayed, or subjected to the addition of another chemical module.

Combinatorial library synthesis using the "multiple parallel synthesis" technology can be performed either manually or through the use of an automated process. For the manual construction of a combinatorial library, a scientist would perform the various chemical manipulations. For the construction of a combinatorial library through an automated process, the various chemical manipulations will typically be performed robotically.

Solid Supports

The solid phase synthesis of the compositions provided herein in one embodiment is performed on a solid support. "Solid support" includes an insoluble substrate that has been appropriately derivatized such that a chemical module can be attached to the surface of the substrate through standard chemical methods. Solid supports include, but are not limited to, beads and particles such as peptide synthesis resins. For example, see Merrifield (1963) *J. Am. Chem. Soc.* 85:2149-2154; U.S. Patent No. 4,631,211; and Geysen *et al.* (1984) *Proc. Natl. Acad. Sci. USA* 81:3998-4002.

Solid supports can consist of many materials, limited primarily by the capacity of the material to be functionalized through synthetic methods. Examples of such materials include, but are not limited to, polymers, plastics, resins, polysaccharides, silicon or silica based materials, carbon, metals, inorganic glasses and membranes. Preferred resins include Sasrin resin (a polystyrene resin available from Bachem Bioscience, Switzerland), Wang resin or p-nitrophenylcarbonate Wang resin (PNP resin, Novabiochem), and TentaGel S AC, TentaGel PHB, or TentaGel S NH_2 resin (polystyrene-polyethylene glycol copolymer resins available from Rapp Polymere, Tubingen, Germany or from Perseptive, Boston).

The solid support can be purchased with suitable functionality already present such that a chemical module can be attached to the support surface (e.g., Novabiochem, Bachem Bioscience, Rapp Polymere). Alternatively, the solid support can be chemically modified such that a chemical module can be attached to the support surface. Grant (1992) *Synthetic Peptides. A User's Guide*, W.H. Freeman and Co.; and Hermkens *et al.* (1996) *Tetrahedron* 52:4527-4554. One of ordinary skill in the art will understand that the choice of functionality used for attaching a molecule to the solid support will depend on the nature of the compound to be synthesized and the type of solid support. Examples of functionality present on the solid support that can be used to attach a chemical module include, but are not limited to, alkyl or aryl halides, aldehydes, alcohols, carbonates, ketones, amines, sulfides, carboxyl groups, aldehyde groups and sulfonyl groups.

The functional group on the solid support that permits the attachment of a chemical module is, for example, an alcohol, an amine, an aldehyde, a carbonate, or a diol group.

Gordon *et al.* (1994) *J. Med. Chem.* 37:1385-1401; and Hermkens *et al.* (1996) *Tetrahedron* 52:4527-4554.

For making certain combinatorial libraries, one can purchase a solid support with an existing, protected chemical module already attached. An example of such a support is FmocGly Sasrin, which is commercially available from Bachem. Typically, however, the first step of the combinatorial library synthesis is the attachment of a chemical module to the solid support through the existing functionality on the support surface. Examples of chemical reactions that can be used to attach a chemical module to the support include, but are not limited to, nucleophilic displacement of a halide or other leaving group, etherification of an alcohol, esterification of an alcohol, amidation of an amine, carbamation of an amine, reductive amination of a carbonyl compound, acetalization of an aldehyde and ketalization of a ketone. Hermkens *et al.* (1996) *Tetrahedron* 52:4527-4554.

The reaction used to attach the chemical module to the solid support is, for example, a carbamation of an amine, a reductive amination of a carbonyl compound or a nucleophilic displacement of a halide or other leaving group. For example, see Hermkens *et al.* (1996).

For the attachment of certain chemical modules to the solid support, it may be necessary to mask functionality that is not involved in the attachment process, but that is incompatible with the mode of attachment. A non-limiting example of this type of process is the esterification of an alcohol functionalized solid support, using a hydroxyl-substituted carboxylic acid as the coupling partner. Prior to the esterification reaction, the hydroxyl group of the carboxylic acid would be "protected" through alkylation, silylation, acetylation, or through another method known to one of skill in the art. Strategies for the use of masking or protecting groups have been well-described in the art, such as in Green (1985) *Protecting Groups in Organic Synthesis*, Wiley.

Methods of Compound Cleavage from a Solid Support

The cleavage of oxazolidinones from a solid support to produce the corresponding "free" compounds can be accomplished using a variety of methods. For example, a compound can be photolytically cleaved from a solid support (Wang *et al.* (1976) *J. Org. Chem.* 41:3258; Rich *et al.* (1975) *J. Am. Chem. Soc.* 97:1575-1579), and through nucleophilic attack (U.S. Patent No. 5,549,974), or through hydrolysis (Hutchins *et al.*

(1994) *Tetrahedron Lett.* 35:4055-4058). The cleavage of compounds from a solid support to produce soluble compounds is accomplished, for example, using hydrolytic conditions, such as through the addition of trifluoroacetic acid.

Screening

The libraries of this invention can be used to select one or more bioactive molecules. Preferably, the bioactive molecules possess activity against a cellular target, including but not limited to enzymes and receptors, or a microorganism. A target cellular ligand or microorganism is one that is known or believed to be of importance in the etiology or progression of a disease. Examples of disease states for which amino alcohol, thio alcohol, oxazolidinone and sulfone libraries can be screened include, but are not limited to, inflammation, infection, hypertension, central nervous system disorders, and cardiovascular disorders.

Several methods have been developed in recent years to screen libraries of compounds to identify bioactive molecules. Methods for isolating library compound species that demonstrate desirable affinity for a receptor or enzyme are well-known in the art.

For example, an enzyme solution can be mixed with a solution of the compounds of a particular combinatorial library under conditions favorable to enzyme-ligand binding. See Bush et al. (1993) *Antimicrobial Agents and Chemotherapy* 37:851-858; and Daub et al. (1989) *Biochemistry* 27:3701-3708. Specific binding of library compounds to the enzyme can be detected, for instance, by any of the numerous enzyme inhibition assays which are well known in the art. Compounds which are bound to the enzyme are separated readily from compounds which remain free in solution by applying the solution to a suitable separation material such as Sephadex G-25 gel filtration column. Free enzyme and enzyme-ligand complexes pass through the column quickly, while free library compounds are retarded in their progress through the column. The mixture of enzyme-ligand complex and free enzyme is then treated with a suitable denaturing agent, such as guanidinium hydrochloride or urea, to cause release of the ligand from the enzyme. The solution is then injected onto an HPLC column (for example, a Vydac C-4 reverse-phase column, and eluted with a gradient of water and acetonitrile ranging from 0% acetonitrile to 80% acetonitrile). Diode array detection provides discrimination of the compounds of

the combinatorial library from the enzyme. The compound peaks are then collected and subjected to mass spectrometry for identification.

An alternate manner of identifying compounds that inhibit an enzyme is to divide the library into separate sublibraries where one step in the synthesis is unique to each sublibrary. To generate a combinatorial library, reactants are mixed together during a step to generate a wide mixture of compounds. At a certain step in the synthesis, however, the resin bearing the synthetic intermediates is divided into several portions, with each portion then undergoing a unique transformation. The resin portions are then (separately) subjected to the rest of the synthetic steps in the combinatorial synthetic method. Each individual resin portion thus constitutes a separate sublibrary. When testing the compounds, if a given sublibrary shows more activity than the other sublibraries, the unique step of that sublibrary is then held fixed. The sublibrary then becomes the new library, with that step fixed, and forms the basis for another round of sublibrary synthesis, where a different step in the synthesis is optimized. This procedure is executed at each step until a final compound is arrived at. The aforementioned method is the generalization of the method described in Geysen, WO 86/00991, for determining peptide "mimotopes," to the synthetic method of this invention.

Finding a compound that inhibits an enzyme is performed most readily with free compound in solution. The compounds can also be screened while still bound to the resin used for synthesis; in some applications, this may be the preferable mode of finding compounds with the desired characteristics. For example, if a compound that binds to a specific antibody is desired, the resin-bound library of compounds is contacted with an antibody solution under conditions favoring a stable antibody-compound-resin complex. A fluorescently labeled second antibody that binds to the constant region of the first antibody is then contacted with the antibody-compound-resin complex. This allows identification of a specific bead as carrying the compound recognized by the first antibody binding site. The bead is then physically removed from the resin mixture and subjected to mass spectral analysis. If the synthesis is conducted in a manner such that only one compound is likely to be synthesized on a particular bead, then the binding compound has been identified. If the synthesis is carried out so that many compounds are present on a

single bead, the information derived from analysis can be utilized to narrow the synthetic choices for the next round of synthesis and identification.

The enzyme, antibody, or receptor target need not be in solution. Antibody or enzyme can be immobilized on a column. The library of compounds is then passed over the column, resulting in the retention of strongly binding compounds on the column after weaker-binding and non-binding compounds are washed away. The column is then washed under conditions that dissociate protein-ligand binding, which removes the compounds retained in the initial step. These compounds are then analyzed, and synthesized separately in quantity for further testing. Similarly, cells bearing surface receptors are contacted with a solution of library compounds. The cells bearing bound compounds are readily separated from the solution containing non-binding compounds. The cells are then washed with a solution which dissociates the bound ligand from the cell surface receptor. Again, the cells are separated from the solution, and the solution analyzed.

Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise a bioactive oxazolidinone compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The compositions of the invention include those in a form adapted for oral, topical or parenteral use and can be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds, also referred to herein as antimicrobial compounds, according to the invention can be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics. Such methods are known in the art and are not described in detail herein.

The composition can be formulated for administration by any route known in the art, such as subdermal, by-inhalation, oral, topical or parenteral. The compositions may be in any form known in the art, including but not limited to tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention can be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings

and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present, for example, from about 1% up to about 98% of the formulation. For example, they may form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods will known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle or other suitable solvent. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as a local anesthetic preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is

then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain, for example, from about 0.1% by weight, e.g., from about 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will contain, for example, from about 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will range, for example, from about 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to about 1.5 to 50 mg/kg per day. Suitably the dosage is, for example, from about 5 to 20 mg/kg per day.

Pharmaceutical Applications

The oxazolidinones disclosed herein can be used in a variety of pharmaceutical applications.

The compounds may be used, for example, as pharmaceutically active agents that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autocoid systems, the alimentary and excretory systems, the histamine system and central nervous systems as well as other biological systems. Thus, the compounds may be used as sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, anti-Parkinson agents, analgesics, antiinflammatories, local anesthetics, muscle contractants, antibiotic, antiviral, antiretroviral, antimalarials, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, neoplastics, antineoplastics and chemotherapy agents. These compounds could further be used to treat cardiovascular diseases, central nervous system diseases, cancer, metabolic disorders, infections and dermatological diseases as well as other

biological disorders and infections. The compounds also may be used as monoamine oxidase inhibitors.

In one embodiment, the compounds may be used as antimicrobial agents for the treatment of infectious disorders that are caused by microbial agents, such as bacteria.

In one embodiment, compositions, for treating or preventing infectious disorders are provided, comprising an oxazolidone compound as disclosed herein in combination with a pharmaceutically acceptable carrier.

In another embodiment, there is provided a dosage amount of an oxazolidinone as disclosed herein in an effective amount for the treatment, prevention or alleviation of a disorder, such as an infectious disorder.

Oxazolidinones can be screened for activity against different microbial agents and appropriate dosages may be determined using methods available in the art. Advantageously, the methods of making combinatorial libraries as disclosed herein permit large quantities of oxazolidinones to be made and screened against a wide variety of microbial agents to permit the rapid isolation of an effective oxazolidinone for a particular target microbe. The method also may be used to determine new oxazolidinones for use after and if bacterial resistance occurs.

The compounds may be used to treat a subject to treat, prevent, or reduce the severity of an infection. Subjects include animals, plants, blood products, cultures and surfaces such as those of medical or research equipment, such as glass, needles and tubing.

In one embodiment, methods of treating or preventing an infectious disorder in a subject, such as a human or other animal subject, are provided, by administering an effective amount of an oxazolidinone as disclosed herein to the subject. In one embodiment, the compound is administered in a pharmaceutically acceptable form optionally in a pharmaceutically acceptable carrier. As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection, such as bacterial infections. Such infectious disorders include, for example central nervous system infections, external ear infections, infections of the middle ear, such as acute otitis media, infections of the cranial sinuses, eye infections, infections of the oral cavity, such as infections of the teeth, gums and mucosa, upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections,

gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients. The compounds and compositions comprising the compounds can be administered by routes such as topically, locally or systemically. Systemic application includes any method of introducing the compound into the tissues of the body, *e.g.*, intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The specific dosage of antimicrobial to be administered, as well as the duration of treatment, may be adjusted as needed.

The compounds of the invention may be used for the treatment or prevention of infectious disorders caused by a variety of bacterial organisms. Examples include Gram positive and Gram negative aerobic and anaerobic bacteria, including *Staphylococci*, for example *S. aureus*; *Enterococci*, for example *E. faecalis*; *Streptococci*, for example *S. pneumoniae*; *Haemophilus*, for example *H. influenza*; *Moraxella*, for example *M. catarrhalis*; and *Escherichia*, for example *E. coli*. Other examples include *Mycobacteria*, for example *M. tuberculosis*; intercellular microbes, for example *Chlamydia* and *Rickettsiae*; and *Mycoplasma*, for example *M. pneumoniae*.

The following examples are provided to illustrate but not limit the claimed invention.

EXAMPLES

Abbreviations: ACN, acetonitrile; CDI, carbonyldiimidazole; DIEA, diethylisopropylamine; DCM, dichloromethane; DIC, diisopropyldiimide; DMF, dimethylformamide; HATU, O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)-uronium hexafluorophosphate; NMM, N-methyl morpholine; *m*CPBA, *m*-chloro-peroxybenzoic acid; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMOF, trimethylorthoformate.

General. Reagents were obtained from Aldrich (St. Louis, MO), Sigma (St. Louis, MO), Bachem Biosciences, Rapp Polymere, Perseptive, and Novabiochem, and used without further purification. The resin Tentagel S NTi was purchased from Rapp Polymere. Concentration of solutions after workup was performed by reduced pressure rotary evaporation, or using the Savant's SpeedVac instrument. Reactions with moisture-sensitive reagents were performed under nitrogen atmosphere.

Mass-spectra were obtained using ESI technique. HTLC analysis and purification were performed using Beckman System Gold R®; detection at 220 nm. Analytical EPLC was performed on YMC 5 micron C18 (4.6 mm x 50 mm) reverse phase column (gradient from 100% of the aq. 0.1% TFA to 100% of 0.1% TFA in MECN over 6 min', flow rate 2.0 mL/min). Preparative TLC was performed using EM silica gel 60 F_{254} plates (20 x 20 cm, thickness 2 min).

NMR spectra were obtained on a Varian Gemini 300 MHz instrument with $CDCl_3$ as solvent, unless otherwise noted. 1H NMR spectra were reported as follows: chemical shift relative to tetramethylsilane (0.00 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling, and integration.

2-Fluoro-4-Nitrobenzoic Acid

Concentrated sulfuric acid (32 ml) was added carefully with stirring to a solution of 2-fluoro-4-nitrotoluene (16.5 g, 0.106 mol) in acetic acid (200 ml). The mixture was warmed up to 95 °C, and solution of chromium trioxide (37.1 g, 0.371 mol) in water (32 ml) was added dropwise with stirring over 2 h. The mixture was heated with stirring for another 30 minutes, allowed to cool down to r.t., and poured into water (1000 ml). The product was extracted with diethyl ether (3 x 200 ml). Combined ether layers were washed

with water and evaporated to dryness. The residue was dissolved in 10% aqueous potassium carbonate and washed with ether. The aqueous layer was acidified with con. HCl, and the resulting white precipitate filtered and dried (16.3 g, 83%), m.p. 174-177 °C. ^{1}H NMR.

Tert-Butyl 2-Fluoro-4-Nitrobenzoate

Thionyl chloride (45 ml, 0.62 mol) was added to 2-fluoro-4-nitrobenzoic acid (23.0 g, 0.124 mol), and the mixture was stirred under reflux for 2 h. Solvent was removed under vacuum, and the residue thoroughly dried under vacuum to give crystalline acid chloride (25.2 g, 99%). The acid chloride was dissolved in tetrahydrofuran (150 ml) under nitrogen, and 1M lithium tert-butoxide in tetrahydrofuran (136 ml, 0.136 mol) was added dropwise with stirring at room temperature. The mixture was stirred overnight, diluted with water (300 ml) and extracted with ether. The ether layer was washed with saturated aqueous sodium bicarbonate, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to gave the product as a white crystalline solid (24.2 g, 81%); mp 81-82 °C. ^{1}H NMR.

tert-Butyl-2-Fluoro-4-Aminobenzoate

Tert-butyl 2-fluoro-4-nitrobenzoate (24.2 g, 0.100 mol) was added to a warm (95 °C) solution of ammonium chloride (53.5 g, 1.00 mol), dissolved in ethanol (300 ml) and water (150 ml). Iron powder (325 mesh, 16.8 g, 0.300 mol) was added with stirring in small portions over ca. 1 h. The reaction mixture was stirred and heated at 95 °C for another 30 minutes and then filtered while still warm. The filter cake was washed thoroughly with excess ethanol. The filtrate and washings were diluted with water (1 L) and extracted with ether (3 X 150 ml).

Combined ether extracts were washed with water and brine, dried ($MgSO_4$), and evaporated to give the product as an off-white solid (21.1 g, 98%); mp 100-101 °C. ^{1}H NMR.

O-Benzyl-N-(3-fluoro-4-butoxycarbonylphenyl)carbamate

Benzyl chloroformate (15.9 ml, 0.112 mol) was added dropwise with stirring to a mixture of *tert*-butyl-2-fluoro-4-aminobenzoate (21.5 g, 0.102 mol) and pyridine (16.5 ml, 0.204 mol) in dichloromethane (200 ml) at O °C. The reaction mixture was stirred for 30 minutes at 0 °C, allowed to warm up to room temperature, and then poured into water (ca.

300 ml). The organic layer was separated, washed with water, brine and dried ($MgSO_4$). Evaporation gave a white solid, which was washed with hexane and dried under vacuum to afford the product (32.8 g, 93%); mp 117-118 °C. ^{1}H NMR.

5-(R)-Hydroxymethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one

1M Lithium bis(trimethylsilyl)amide in tetrahydrofuran (104 ml, 0.104 mol) was added dropwise with stirring at -78 °C to a solution of O-benzyl-N-(3-fluoro-4-butoxycarbonylphenyl)-carbamate (32.8 g, 0.0948 mol) in tetrahydrofuran (150 ml). The mixture was stirred at -78 °C for 1 hour, and then (R)-glycidyl butyrate (15.0 g, 0.104 mol) was added dropwise with stirring. The mixture was allowed to warm to room temperature overnight, and was then quenched with saturated aqueous ammonium chloride (100 ml). The mixture was extracted with ethyl acetate, and the combined organic layers washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum, and the crude product purified by silica gel column chromatography (eluent: 30% ethyl acetate in hexanes) to afford the product as a white solid (20.0 g, 68%); mp 148-149 °C. ^{1}H NMR.

5-(S)-Azidomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one

Methanesulfonyl chloride (2.61 ml, 0.0337 mol) was added dropwise with stirring to a solution of 5-(R)-hydroxymethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (10.0 g, 0.0321 mol) and triethylamine (6.71 ml, 0.0482 mol) in dichloromethane (150 ml) at 0 °C over ca. 15 minutes. The reaction mixture was allowed to warm up to room temperature and then poured into water. The organic layer was separated, washed with water, saturated aq. $NaHCO_3$, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the mesylate intermediate as an oil (11.6 g, 99%). A mixture of the mesylate (13.4 g, 0.0370 mol) and sodium azide (12.0 g, 0.185 mol) in DMF (130 ml) was heated with stirring at 75 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with water (300 ml), and extracted with ethyl acetate (3 x 100 ml). Combined organic layers were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was washed with diethyl ether to give the pure azide as a white solid (9.76 g, 90.5%); mp 91-92 °C. ^{1}H NMR.

S-(S)-Azidomethyl-3-[4'-N-methyl-N-methoxyamido-3'-fluorophenyl]oxazolidine-2-one

5-(S)-Azidomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one

(3.36 g, 0.01 mol) is dissolved in dichloromethane (ca. 100 ml), and trifluoroacetic acid (50 ml) added with stirring. The mixture is kept at room temperature for 3-4 h, solvent removed under vacuum, and residue washed with diethyl ether-hexanes (1: 3, ca. 20 ml) to afford an intermediate acid. The acid (1.40 g, 0.005 mol) is dissolved in dichloromethane (100 ml) and dimethylformamide (50 ml), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.96 g, 0.005 mol) added. The mixture is stirred for ca. 2 h, and N-methyl-N-methoxyamine hydrochloride (0.48 g, 0.005 mmol) added, followed by triethylamine (1.5 ml, 0.015 mmol). The mixture is stirred at room temperature for 3-4 h, poured into water (ca. 200 ml), and extracted with ethyl acetate (3 x 150 ml). Combined organic layers are washed with water (4 x 250 ml), brine, and dried ($MgSO_4$). Solvent is removed under vacuum to afford the Weinreb amide.

2-Fluoro-4-nitrobenzylidene diacetate

2-Fluoro-4-nitrotoluene (21.65 g, 0.140 mol) was dissolved in acetic anhydride (145 ml) and concentrated sulfuric acid (30 ml) was added slowly with stirring. The mixture was cooled to 0 °C, and a solution of chromium trioxide (42.0 g, 0.420 mol) in acetic anhydride (200 ml) added at such a rate that the temperature did not exceed 10 °C. The reaction mixture was stirred at 0 °C for another 2 h, and then poured into ice water (1000 ml). The resulting precipitate was filtered, washed with water and then dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated aq. sodium bicarbonate, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the product as a white crystalline solid (37.9 g, 70 %); mp 116-117 °C. ^{1}H NMR.

2-Fluoro-4-nitrobenzaldehyde Dimethyl Acetal

2-Fluoro-4-nitrobenzylidene diacetate (9.30 g, 0.0343 mol) was dissolved in methanol (200 ml), and potassium carbonate (4.74 g, 0.0343 mol) was added in one portion. The mixture was stirred at room temperature for 2 h and then evaporated to dryness. The residue was dissolved in diethyl ether, washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford an aldehyde intermediate (5.68 g, 98 %) The aldehyde (6.00 g, 0.0355 mol) was dissolved in a mixture of methanol (4.5 ml) and trimethyl orthoformate (4.27 ml,. 0.0390 mol). Ammonium chloride (0.10 g, 0.00178 mol) was added, and the mixture was refluxed for 2 h. Solvent was removed under vacuum, and the residue was washed with diethyl ether. The resulting ether solution was

washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the product as a colorless oil. Yield 7.60 g (99 %). ^{1}H NMR.

4-Amino-3-fluorobenzaldehyde Dimethyl Acetal

2-Fluoro-4-nitrobenzaldehyde dimethyl acetal (0.59 g, 2.74 mmol) was dissolved in methanol: (20 ml), and 5% palladium on carbon (0.059 g) was added. The flask was charged with hydrogen gas, and the mixture was stirred at room temperature for 20 h. The catalyst was filtered through Celite, and solvent was removed under vacuum to afford the product. Yield 0.40 g (78 %). ^{1}H NMR.

O-Benzyl-N-[3-fluoro-4-(dimethoxymethyl)phenyl]carbamate

Benzyl chloroformate (0.34 ml, 2.38 mmol) was added dropwise with stirring to a solution of 4-amino-3-fluorobenzaldehyde dimethyl acetal (0.40 g, 2.16 mmol) and pyridine (0.26 ml, 3.24 mmol) in dichloromethane (10 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature, and was washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to give the desired product as a white solid. Yield 0.56 g (81%). ^{1}H NMR.

S-(R)-Hydroxymethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]oxazolidine-2-one

1 M Lithium bis(trimethylsflyl)amide in tetrahydrofuran (0.86 ml, 0.941 mmol) was added dropwise with stirring at -78 °C to O-benzyl-N-[3-fluoro-4-(dimethoxymethyl)-phenyl]carbamate (0.273 g, 0.855 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at -78 °C for 1 h, and then (R)-glycidyl butyrate (0.145 ml, 1.03 mmol) was added dropwise with stirring. The mixture was allowed to warm to room temperature overnight, and was then quenched with saturated aq. ammonium chloride (5 ml). The mixture was extracted with ethyl acetate, and the product was washed with water, brine, and dried ($MgSO_4$). Solvent was removed in vacuum, and the crude product purified by silica gel column chromatography (eluent: 30 % ethyl acetate in hexanes) to give the alcohol as an oil. Yield 0.24 g, 99%. ^{1}H NMR.

5-(S)-Azidomethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]oxazolidine-2-one

Methanesulfonyl chloride (0.0664 ml, 0.858 mmol) was added with stirring to a solution of S-(R)-hydroxymethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]oxazolidine-2-one (0.233 g, 0.817 mmol) and triethylamine (0.228 ml, 1.63 mmol) in dichloromethane (10 ml) at 0 °C. The reaction was allowed to warm to room temperature, and was then

poured into water. The organic layer was separated and washed with water, saturated aq. $NaHCO_3$, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to give a mesylate intermediate as an oil (0.246 g, 83%). A mixture of the mesylate (0.189 g, 0.520 mmol) and sodium azide (0.170 g, 2.60 mmol) in DMF (5 ml) was heated at 75 °C for 12 h. The reaction was cooled to room temperature, diluted with water (50 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with water, brine, and then dried ($MgSO_4$). Solvent was removed in vacuum, and the crude product was purified by silica gel column chromatography (eluent: 50% ethyl acetate in hexanes) to give the desired product as a colorless oil (0.154 g, 95%). MS (m/z): 311 $[M + H]^+$. ^1H NMR.

3-Fluoro-4-thiocyanoaniline

N-Bromosuccinimide (1.76 g, 9.89 mmol) and potassium thiocyanate (1.75 g, 18.0 mmol) in methanol (30 ml) were stirred for 15 minutes at room temperature. The reaction mixture was cooled to 0 °C, and 3-fluoroaniline (1.00 g, 9.0 mmol) was added dropwise. The mixture was stirred at 0 °C for 2 h. Solvent was removed under vacuum, and the residue was washed with dichloromethane. The mixture was filtered to remove succinimide by-product, and the solution was washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the desired product as a colorless oil. Yield 1.45 g (96%). ^1H NMR.

O-Benzyl-N-[3-fluoro-4-(thiocyano)phenyl]carbamate

Benzyl chloroformate (1.87 ml, 13.1 mmol) was added to a mixture of 3-fluoro-4-thiocyanoaniline (2.00 g, 11.9 mmol) and pyridine (2.12 ml, 26.2 mmol) in dichloromethane (30 ml) at 0 °C. The mixture was stirred for 30 minutes at O °C, allowed to warm to room temperature, and then poured into water. The organic layer was separated, washed with brine, and dried ($MgSO_4$). Solvent was removed under vacuum. The crude product was washed with ether-hexanes and dried under vacuum to afford the desired product. Yield 3.64 g (92%); m.p. 74-75 °C. ^1H NMR.

O-Benzyl-N-[3-fluoro-4-(triphenylmethylthio)phenyl]carbamate

Sodium sulfide nonahydrate (0.794 g, 3.31 mmol) in water (3 ml) was added dropwise at room temperature to a solution of O-benzyl-N-[3-fluoro-4-(thiocyano)phenyl]carbamate (1.00 g, 3.31 mrnol) in ethanol (10 ml). The reaction

mixture was stirred at room temperature for 30 minutes, and then triphenylmethyl bromide (1.07 g, 3.31 mol) in 1,4-dioxane (5 ml) was added dropwise. The reaction was stirred overnight. Organic solvent was removed under vacuum, and the residue taken up in ethyl acetate. The solution was washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum, and the crude product purified by silica gel column chromatography (eluent: 10% ethyl acetate in hexanes) to give the desired compound as a white solid. Yield 1.10 g, (64%); mp 152-153 °C. ^{1}H NMR.

5-(R)-Hydroxymethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]oxazolidine-2-one

1M Lithium bis(trimethylsilyl)amide in tetrahydrofuran (54 mL, 69.9 mmol) was added dropwise with stirring at -78 °C to a solution of O-benzyl-N-[3-fluoro-4-(triphenylmethylthio)phenyl]carbamate (33.0 g, 63.5 mmol) in tetrahydrofuran (250 ml). The mixture was stirred at -78 °C for 1 hour, and then (R)-glycidyl butyrate (11.0 g, 76.2 mmol) was added dropwise with stirring. The mixture was allowed to warm up to room temperature overnight, and then quenched with saturated aqueous ammonium chloride (125 ml). The mixture was extracted with ethyl acetate, and combined organic layers washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum, and the crude product purified by silica gel column chromatography (gradient from 30% to 75% of ethyl acetate in hexane) to afford the product. TLC: R_f 0.2 (ethyl acetate-hexanes 1:1). MS 486 $[M+H]^+$. ^{1}H NMR.

5-(S)-Azidomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]oxazolidine-2-one

Methanesulfonyl chloride (3.91 mL, 50.6 mmol) was added dropwise with stirring to a solution of 5-(R)-hydroxymethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]oxazolidine-2-one (23.4 g, 48.2 mmol) and triethylamine (10.1 mL, 73.8 mmol) in dichloromethane (200 mL) at 0 °C over ca. 10 minutes. The reaction mixture was allowed to warm up to room temperature and then poured into water. The organic layer was separated, washed with water, saturated aq. $NaHCO_3$, brine, and dried ($MgSO_4$). Solvent is removed under vacuum to afford the mesylate intermediate as an oil (27.2 g, 99%). The mesylate (27.2 g, 48.2 mmol) and sodium azide (15.7 g, 241.0 mmol) in DMF (150 ml) was heated with stirring at 70 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with water (750 mL), and extracted with ethyl acetate. Combined organic layers were washed with water, brine, and dried ($MgSO_4$). Solvent was

removed under vacuum and the crude product purified by silica gel column chromatography (eluent: 30% ethyl acetate in hexanes) to afford the azide product as a white solid. Yield 18.1 g (73%). M.p. 77-79 °C. $[\alpha]^D$ = -114 ° (c = 1, methanol). ^{1}H NMR.

5-Benzyloxycarbonylaminoindazole

Benzyl chloroformate (9.9 ml, ca. 66 mmol) in tetrahydrofuran (66 ml) was added dropwise with stirring to 5-aminoindazole (4.44 g, 33 mmol) in tetrahydrofuran (150 ml) and pyridine (12.0 ml, 150 mmol) at -5 °C. The mixture was allowed to warm to room temperature, stirred for 4 h, and concentrated under vacuum. Ethyl acetate (100 ml) and water (150 ml) were added, and the aqueous layer was extracted with ethyl acetate (2 x 100 ml). The combined organic laters were washed with 0.3 N aq. HCI (2 x 100 ml), water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the crude product as a mixture of two regioisomers. MS (m/z): 402.1 $[M+H]^+$. 0.3 M lithium hydroxide monohydrate in methanol (250 ml, ca. 75 mmol) was added. The mixture was stirred at room temperature for 45 min and then carefully acidified with 6 N aq. HCl until the pH of the solution was 2. The resulting product was filtered off, washed with water and dried under vacuum to afford the desired compound. R_t 4.2 min. MS (m/z): 268.1 $[M+H]^+$. ^{1}H NMR.

5-Benzyloxycarbonylamino-l-triphenylmethylindazole

5-Benzyloxycarbonylaminoindazole (0.534 g, 2 mmol) was stirred with trityl chloride (0.556 g, 2 mmol) and tetrabutylammonium iodide (0.074 g, 0.2 mmol) in tetrahydrofuran (5 ml) and triethylamine (0.42 ml, 3 mmol) for 3 days at room temperature. Solvent was removed under vacuum, and the solid residue was triturated with methanol (3 ml). The solid was washed with a mixture of methanol-water (5:1, ca. 15 ml) and dried under vacuum to afford the desired product. Yield 0.73 g (72%). ^{1}H NMR.

5-[5-(R)-Hydroxymethyloxazolidine-2-one-3-yl]-l-triphenylmethylindazole

1 M Lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.1 mL, 1.1 mmol) was added dropwise with stirring at -78 °C to 5-benzyloxycarbonylamino-l-tritylindazole (0.510 g, 1 mmol) in tetrahydrofuran (10 mL) under nitrogen atmosphere. The mixture was stirred at -78 °C for 1.5 h. (R)-Glycidyl butyrate (0.160 mL, 1.2 mmol) was added dropwise with stirring. The mixture was allowed to warm to r.t. overnight. Saturated aq.

NH_4Cl (10 mL) was added, and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried ($MgSO_4$). Solvent was evaporated to 3 mL, and the residue was triturated with hexanes (50 mL). White crystalline product was filtered off, washed with hexanes, and dried in vacuo. Yield 0.440 g (93%). MS (m/z): 232.1 $[M-Trt]^+$. ^1H NMR.

5-[5-(S)-Azidomethyloxazolidine-2-one-3-yl]-1-triphenylmethylindazole

Methanesulfonyl chloride (0.066 ml, 0.85 mmol) was added dropwise with stirring to a solution of 5-[5-(R)-hydroxymethyloxazolidine-2-one-3-yl]-1-triphenylmethylindazole (0.300 g, 0.63 mmol) and triethylamine (0.18 ml, 1.3 mmol) in dichloromethane (7.0 ml) at - 30 °C over 5 minutes. The reaction mixture was stirred at 5 °C for 2 h and quenched with water (15 ml). Ethyl acetate (20 ml) was added, and the organic layer was washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford a mesylate intermediate. The mesylate and sodium azide (0.205 g, 3.15 mmol) in DMF (4 ml) was heated with stirring at 75 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with water (ca. 10 ml), and extracted with ethyl acetate (2 x 15 ml). The combined organic layers were washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the desired product as off-white crystals. Yield 0.31 g (95%). MS (m/z): 257.1 $[M-Trt]^+$. ^1H NMR.

BAL Aldehyde Resin

4-(4-Formyl-3,5-dimethoxyphenoxy)butyric acid (9.33 g, 34.8 mmol), pyridine (15 ml), and diisopropylcarbodiimide (3.00 ml, 19.1 mmol) in dichloromethane (135 ml) were stirred at room temperature for 1 h. Tentagel S-NH, resin (Rapp Polymere, 0.29 mmol/g, 8.7 mmol) was added, and the mixture was agitated at room temperature overnight. The resin was filtered, washed liberally with MeOH and dichloromethane and dried under vacuum.

5-[5-(S)-Acetamidomethyloxazolidine-2-one-3-yl]-1-indazole

Tetrahydrofuran (1.0 mL) was added to the mixture of 5-[5-(S)-azidomethyloxazolidine-2-one-3-yl]-1-triphenylmethylindazole (0.065 g, 0.13 mmol, ca. 3 eq. with respect to the resin reagent), triphenylphosphine (0.034 g, 0.13 mmol), and BAL aldehyde resin (150 mg, ca. 0.044 mmol). The mixture was stirred at r.t. for 2 h. A rubber septum was replaced with a teflon-coated cap, and the mixture was agitated at 75 °C for ca.

10 h. A tetrahydrofuran-triethylorthoformate mixture (1:1, 1 mL) was added to the resulting imine resin, followed by 0.5 M $NaBH_3CN$ (0.5 mL, 0.25 mmol). The mixture was agitated at room temperature for 3 h. The resulting amine resin was washed liberally with MeOH and dichloromethane, and dried under vacuum. An acetic anhydride-pyridine-dichloromethane solution (1 to 1.5 to 3, 4 mL) was added, and the mixture was agitated for 2 h (until negative ninhydrine test indicated completion of the acylation). The trityl protection was removed by treatment with 1% TFA in DCM (2 x 4 mL, 15 min), and the product was cleaved with 60% TFA in DCM (2 mL) over 2 h. HPLC purity for the cleaved product was 90% (Rt 2.95 min). Solvent was removed under vacuum, and the product was purified by preparative silica gel TLC (eluent: dichloromethane-MeOH 5:1). Yield 7.0 mg (58%). R_t 2.9 min. (given below). MS (m/z): 275.1 $[M+H]^+$. ^1H NMR.

BAL Resin Immobilized 5-(S)-Aminomethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]-oxazolidine-2-one

Triphenylphosphine (0.130 g, 0.496 mmol) was added to a mixture of BAL aldehyde resin (0.57 g, 0.165 mmol) and 5-(S)-azidomethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]-oxazolidine-2-one (0.154 g, 0.496 mmol) in THF (3 ml) at room temperature. The mixture was stirred at room temperature for 2 h, and then at 75°C for 16 h. The mixture was cooled to room temperature, and 1M sodium cyanoborohydride in THF (0.99 ml, 0.992 mmol) was added in one portion. The reaction mixture was agitated for 8 h. The resulting amine resin was washed liberally with methanol and dichloromethane and dried under vacuum.

BAL Resin Immobilized 5-(S)-Acetamidomethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]-oxazolidine-2-one

Acetic anhydride-pyridine-dichloromethane solution (1 to 1.5 to 3, 4 mL) was added to BAL resin immobilized 5-(S)-aminomethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]-oxazolidine-2-one, and the mixture was agitated for ca. 2 h (until negative ninhydrine test indicated completion of the acylation). The resin was filtered, washed liberally with methanol and dichloromethane and dried under vacuum.

5-(S)-Acetamidomethyl-3-[4'-formyl-3'-fluorophenyl]oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-dimethoxymethyl-3'-fluorophenyl]-oxazolidine-2-one (0.100 g, 0.029 mmol) was suspended in 60%

trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. The mixture was filtered, and supernatant was evaporated under vacuum to give the crude product. The crude product was purified by preparative HPLC to afford the desired product as an oil. Yield 4.9 mg, (60%). R_t 3.0 min. MS (m/z): 281.1 $[M + H]^+$. ^1H NMR.

BAL Resin Immobilized 5-(S)-Aminomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Triphenylphosphine (7.61 g, 29.0 mmol) was added to a mixture of BAL aldehyde resin (33.3 g, 9.67 mmol) and 5-(S)-azidomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one (9.76 g, 29.0 mmol) in tetrahydrofuran (170 ml) under nitrogen at room temperature. The mixture was agitated at room temperature for 2 h and then at 75 °C for 16 h. The mixture was cooled to room temperature, and 1 M sodium cyanoborohydride in THF (58.0 ml, 58.0 mmol) was added in one portion. The reaction mixture was agitated for 8 h. The resulting amine resin was filtered, washed liberally with methanol and dichloromethane, and dried under vacuum.

BAL Resin Immobilized 5-(S)-Aminomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one

A mixture of 1 M chlorotrimethylsilane in dichloromethane (290 ml, 0.29 mol) and 1M phenol in dichloromethane (290 ml, 0.29 mol) was added to BAL resin immobilized 5-(S)-aminomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one, and the reaction mixture was agitated at room temperature for 36 h. The resulting acid resin was filtered, washed liberally with methanol and dichloromethane, and dried under vacuum.

General Procedure for the Synthesis of Immobilized 5-(S)-Acylaminomethyl-3-[4'-carboxy-3'-fluorophenyl]-oxazolidine-2-ones

A selected carboxylic acid (18.0 mmol), pyridine (1.46 ml,18.0 n-tmol) and diisopropylcarbodiimide (1.35 ml, 9.90 mmol) in a mixture of dimethylformamide-dichloromethane (4:1, 8 ml) were stirred at room temperature for 1 h. An appropriate BAL resin immobilized 5-(S)-aminomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (1.80 mmol) was added and the mixture was agitated at room temperature for 16 h (or until ninhydrine test indicated a completion of the acylation). The resin was filtered, washed liberally with dimethylformamide, MeOH, dichloromethane, and dried under vacuum.

5-(S)-Acetamidomethyl-3-[4'-carboxy-3'-fluorophenyll-oxazolidine-2-one

Acetic anhydride-pyridine-dichloromethane solution (1:1.5:3, 200 mL). was added to an immobilized 5-(S)-acylaminomethyl-3-[4'-carboxy-3'-fluorophenyl]-oxazolidine-2-one (33.3 g, 9.67 mmol), and the mixture was agitated overnight. The resin was filtered, washed liberally with methanol and dichloromethane and dried under vacuum. The acylated resin (0.100 g, 0.029 mmol) was suspended in 60% trifluoroacetic acid in dichloromethane for 2 h at room temperature. The mixture was filtered, and the supernatant was evaporated under vacuum to give a white solid which was washed with ether and dried under vacuum. Yield 7.6 mg (88%); mp 252-253 °C. ^{1}H NMR.

BAL Resin Immobilized 5-(S)-Acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Pentafluorophenyl trifluoroacetate (7.10 ml, 41.3 mmol) was added to a mixture of BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (20.4 g, 5.90 mmol) and pyridine (8 ml) in N-methylpyrrolidine-2-one (35 ml). The reaction mixture was agitated at room temperature for 16 h. The resin was filtered, washed with N-methylpyrrolidine-2-one and dichloromethane, and dried under vacuum. The resin was analyzed by cleavage with 60% trifluoroacetic acid in dichloromethane (2 ml per 0.100 g. 0.029 mmol of the resin, 2 h). The resulting supernatant was evaporated under vacuum to give the released pentafluorophenyl ester as a white solid. The solid was purified by preparative TLC (eluent 10% MEOH in dichloromethane). Yield 8.0 mg (60%); m.p. 172-173 °C. ^{1}H NMR.

5-(S)-Acetamidomethyl-3-[4'-(4''-morpholinophenylamino)carbonyl-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.100g, 0.029 mmol) was agitated with 4-morpholinoaniline (0.155 mg, 0.87 mmol) in 10% pyridine in dimethylformamide (2 ml) for 24 h. The resin was filtered and washed liberally with dimethylformamide, MeOH, DCM, and dried under vacuum. The dry resin was cleaved in 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. The supernatant was evaporated under vacuum, and the crude product was purified by

preparative TLC (eluent: 10% methanol in dichloromethane to give product as a white solid. Yield 6.6 mg (50%). MS (m/z): 457.2 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(3''-pyridylamino)carbonyl-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.100g, 0.029 mmol) was agitated with 3-aminopyridine (0.082 mg, 0.87 mmol) in 10% pyridine in dimethylformamide (2 ml) for 24 h. The resin was filtered and washed liberally with dimethylformamide, MeOH, DCM, and dried under vacuum. The dry resin was cleaved in 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. The supernatant was evaporated under vacuum, and the crude product was purified by preparative TLC (eluent: 10% methanol in dichloromethane) to give the product as a white solid. Yield 4.3 mg (40%). MS(m/z): 373.1 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(4''-morpholino)carbonyl-3'-fluorophenyl]oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.100g, 0.029 mmol) was agitated with morpholine (0.10 ml, 0.116 mmol) in N-methylpyrrolidine-2-one (2 ml) for 16 h. The resin was filtered and washed liberally with N-methylpyrrolidine-2-one, MeOH, dichloromethane, and dried under vacuum. The dry resin was cleaved in 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. The resin was filtered, the filtrate evaporated under vacuum, and the crude product was purified by preparative TLC (eluent: 10% MeOH in dichloromethane) to give the product as a white solid. Yield 5.6 mg (53%); m.p. 210-211 °C. ^1H NMR.

BAL Resin Immobilized Weinreb Amide: 5-(S)-Acetamidomethyl-3-[4'-N-methoxy-N-methylaminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (1.00 g, 0.29 mmol) was agitated with N-methoxy-N-methylamine hydrochloride (0.59 g, 6.0 mmol) and triethylamine (0.84 ml, 6.0 mmol) in N-methylpyrrolidine-2-one for 16 h at room temperature. The resin was filtered, washed liberally with N-methylpyrrolidine-2-one,

MeOH, dichloromethane, and dried under vacuum. A small portion of the resin (ca. 10 mg) was cleaved in 60% trifluoroacetic acid in dichloromethane (0.20 ml) for 2 h at room temperature. The supernatant was concentrated under vacuum to afford the cleaved Weinreb amide as an oil. R_t 2.8 min. MS (m/z): 340.1 $[M + H]^+$. ^1H NMR.

BAL Resin Immobilized Aldehyde 5-(S)-Acetamidomethyl-3-[4'-formyl-3'-fluorophenyl]-oxazolidine-2-one

0.1 M Lithium aluminum hydride in tetrahydrofuran (0.52 ml) was added dropwise with stirring to BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-N-methoxy-N-methylaminocarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.150 g, 0.044 mmol) in tetrahydrofuran (2 ml) at -78 °C. The mixture was agitated at -78 °C for 4-6 h. It was then allowed to warm to room temperature overnight. The resin was filtered, washed liberally with tetrahydrofuran, MeOH, dichloromethane, and dried under vacuum. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-formyl-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-formyl-3'-fluorophenyl]-oxazolidine-2-one (0.150 g, 0.0435 mol) was cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. Supernatant was evaporated under vacuum to give the crude product as an oil. MS (m/z): 281.1 [M + H]+. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-acetyl-3'-fluorophenyl]oxazolidine-2-one

3.0 M Methylmagnesium iodide in diethyl ether (0.022 ml, 0.066 mmol) is added dropwise with stirring to BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-N-methoxy-N-methylaminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one (0.150 g, 0.044 mmol) in tetrahydrofuran (2 ml) at -78 °C. The mixture is agitated at 78 °C for 5-10 h, and then allowed to warm to room temperature overnight. The resin is filtered, washed liberally with tetrahydrofuran, MeOH, dichloromethane, and dried under vacuum. The resulting ketone resin is cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. The supernatant is evaporated under vacuum to afford the desired product.

BAL Resin Immobilized Acyl Azide 5-(S)-Acetamidomethyl-3-[4'-azidocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Method A: with azidotrimethylsilane and tetrabutylammonium fluoride. 1 M Tetrabutylammonium fluoride in tetrahydrofuran (0.609 ml, 0.609 mmol) was added to azidotrimethylsilane (0.34 ml, 2.6 mmol) in tetrahydrofuran (3.5 ml), and the mixture was kept at room temperature for 0.5 h. The resulting solution was added to BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one, and the mixture was agitated at room temperature for 4-5 h. The acyl azide resin was filtered, washed with dichloromethane and acetone. IR (cm-'): 2136 (N_3). The resin was further analyzed by cleavage with 60% trifluoroacetic acid in dichloromethane (2 ml per 0.100 g, 0.029 mmol of the resin, 2 h). The resulting supernatant was evaporated under vacuum to give the released acyl azide product. R_t 3.3 min. IR (cm^{-1}): 2138 (N_3). MS (m/z): 278.1 $[M-N_2+H]^+$. ^1H NMR.

Method B: with tetrabutylammonium azide. BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (Tentagel HL NH_2 resin, 1.00 g, ca. 0.40 mmol/g) was agitated with tetrabutylammonium azide (0.797 g, 2.8 mmol) in tetrahydrofuran (10 ml) for 5 h at room temperature. The resin was filtered, washed liberally with dichloromethane and acetone, and dried under vacuum.

BAL Resin Immobilized Protected Amine 5-(S)-Acetamidomethyl-3-[4'-(9''-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized acyl azide 5-(S)-acetamidomethyl-3-[4'-azidocarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.75 g, 0.22 mmol) and (9-fluorenyl)methanol (1.18 g, 6.0 mmol) in tetrahydrofuran (7.0 ml) were agitated at 80 °C for 4 h. The resulting Fmoc-protected amine resin was washed with tetrahydrofuran, MeOH, dichloromethane, and dried under vacuum.

5-(S)-Acetamidomethyl-3-[4'-(9''-fluorenylmethoxycarbonyl)amino-3'-fluoro-phenyl]-oxazolidine-2-one

Method A. BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9''-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]oxazolidine-2-one (0.200 g) was cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h. The resulting

supernatant was evaporated under vacuum to give the released Fmoc carbamate product. R_t 4.3 min. MS (m/z): 490.2 $[M+H]^+$. ^1H NMR.

Method B. 9-Fluorenylmethyl chloroformate (0-039 g, 0.15 mmol) in dichloromethane (0.300 ml) and pyridine (0.05 ml, 0.62 mmol) was added to BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-amino-3'-fluorophenyl]oxazolidine-2-one, and the mixture was agitated at room temperature for 2 h. The resulting resin was worked up and cleaved as described above for Method A. R_t 4.3 min. MS (m/z): 490.2 $[M+H]^+$. ^1H NMR.

BAL Resin Immobilized Amine 5-(S)-Acetamidomethyl-3-[4'-amino-3'-fluorophenyl]-oxazolidine-2-one

Method A. BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9''-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]oxazolidine-2-one (ca. 0.200 g) was deprotected with 20% piperidine in dimethylformamide (2 ml) for 20 min. The resulting amine resin was washed liberally with MeOH, dichloromethane, and dried under vacuum. The resin was analyzed by cleavage with 60% trifluoroacetic acid in dichloromethane (2 ml, 2 h). The resulting supernatant was evaporated under vacuum to give the released amine product. MS (m/z): 268.1 $[M+H]^+$. ^1H NMR.

Method B. BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)-oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.200 mg), azidotrimethylsilane (0.240 ml, 1.74 mmol) and catalytic tetrabutylammonium fluoride (0.05 ml, 0.05 mmol) in tetrahydrofuran (5 ml) were agitated at 80 °C for 4 h. The resulting amine resin was washed liberally with MeOH and dichloromethane. It was dried under vacuum and analyzed as described above for Method A. MS (m/z): 268.1 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(*para*-nitrobenzene)sulfonamido-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-amino-3'-fluorophenyl]-oxazolidine-2-one (0.200 g) was agitated with para-nitrobenzenesulfonyl chloride (0.108 g, 0.50 mmol) in dichloromethane (2.0 ml) with N-methylmorpholine (0.200 ml) for 14 h at room temperature. The resulting sulfonamide resin was filtered, washed liberally with dimethylformamide, MeOH, dichloromethane, and dried under vacuum. The dry resin was

cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml, 2 h). The resulting supernatant was evaporated under vacuum to give the sulfonamide product. MS (m/z): 453.1 $[M+H]^+$. ^1H NMR.

N^1-(9-Fluorenylmethoxycarbonyl)-N^2-[4'-(5''-(S)-acetamidomethyloxazolidine-2-one-3''-yl)-3'-fluorophenyl]thiourea

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-amino-3'-fluorophenyl]-oxazolidine-2-one (0.200 g) was agitated with 9-fluorenylmethoxycarbonylisocyanate (0.140 g, 0.50 mmol) in dichloromethane (2.0 ml) for 14 h at room temperature. The resulting thiourea resin was filtered, washed liberally with dimethylformamide, MeOH, dichloromethane, and dried under vacuum. The dry resin was cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml, 2 h). The resulting supernatant was evaporated under vacuum to give the sulfonamide product. R_t 4.5 min. MS (m/z): 549.1 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(4''-phenylthiazole-2''-yl)amino-3'-fluoro-phenyl]oxazolidine-2-one

BAL resin immobilized N^1-(9-Fluorenylmethoxycarbonyl)-N^2-[4'-(5''-(S)-acetamidomethyloxazolidine-2-one-3''-yl)-3'-fluorophenyl]thiourea was deprotected with 20% piperidine in dimethylformamide (2 ml) for 40 min, filtered, washed liberally with MeOH, dichloromethane, and dried under vacuum. 2-Bromoacetophenone (0.100 g, 0.50 mnol) in tetrahydrofuran (2.0 ml) was added, and the mixture was agitated at room temperature for 2 h. The resulting thiazole resin was washed liberally with MeOH, dichloromethane, and dried under vacuum. The dry resin was cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml, 2 h). The resulting supernatant was evaporated under vacuum to give the thiazole product. R_t 3.9 min. MS (m/z): 427.1 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(5''-amino-4''-cyanooxazole-2''-yl)-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)-oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.100 g) was agitated with aminomalonitrile tosylate (0.253 g, 1 mmol) in a mixture of dry pyridine and N-methylpyrrolidine-2-one (1:1, 2.0 ml) at 60 °C for 8-10 h. The resulting aminooxazole

resin was washed liberally with MeOH, dichloromethane, and dried under vacuum. The dry resin was cleaved with 60% trifluoroacetic acid in dichloromethane (2 ml, 2 h). The resulting supernatant was evaporated under vacuum to give the oxazole product. R_t 3.2 min. MS (m/z): 360.1 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]oxazolidine-2-one

Triphenylphosphine (2.82 g, 10.8 mmol) was added portionwise to a solution of 5-(S)-azidomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]- oxazolidine-2-one (5.00 g, 9.79 mmol) in THF (40 mL), and the mixture stirred for 2 h at room temperature. Water (1.41 mL, 78.3 mmol) was added, and the mixture heated at 40 °C overnight. Solvent was removed under vacuum, and the oily residue dissolved in dichloromethane (50 mL). Acetic anhydride (4.62 ml, 49.0 mmol) and pyridine (7.92 ml, 97.9 mmol) were added, and the mixture stirred for 8 h at r.t. Solvent was removed under vacuum and the crude product purified by silica gel flash column chromatography (eluent: 30% ethyl acetate in hexanes) to give the product as a foam (4.98 g, 97 %); MS: 527 $[M+H]^+$. ^1H NMR.

BAL Resin Immobilized 5-(S)-Aminomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]-oxazolidine-2-one

Diisopropylcarbodiiimide (4.24 ml, 27.0 mmol) aws added to 4-(4-formyl-3,5-dimethoxyphenoxy)butyric acid (13.19 g, 49.2 mmol) and pyridine (20 mL) in dichloromethane (190 mL), and the mixture was stirred at room temperature for 1 h. Tentagel S-NH_2 resin (Rapp Polymere, 30.0 g, 12.3 mmol) was added, and the mixture agitated at room temperature overnight. Resulted BAL resin was filtered, washed liberally with methanol and dichloromethane and dried under vacuum. Triphenylphosphine (7.97 g, 0.0304 mol) was added to a mixture of above BAL aldehyde resin (50.9 g, 0.0209 mol) and 5-(S)-azidomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]oxazolidine-2-one (15.5g, 30.4 mmol) in THF (200 ml) under nitrogen at r.t. (room temperature). The mixture was agitated at r.t. for 2 h and then heated at 75 °C for 16 h. The mixture was cooled to r.t., and 1M sodium cyanoborohydride in THF (62.7 ml, 62.7 mmol) was added. The mixture was agitated for 8 h at r.t. The resin was filtered, washed liberally with methanol and dichloromethane and dried under vacuum.

BAL Resin Immobilized 5-(S)-Acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one

BAL resin immobilized 5-(S)-Aminomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]-oxazolidine-2-one (5.00 g, 2.05 mmol) was suspended in 5% trifluoroacetic acid and 2.5% triisopropylsilane in dichloromethane (50 mL), and the mixture was agitated for 1 h. The resin was filtered and the procedure repeated with fresh 5% trifluoroacetic acid and 2.5% triisopropylsilane in dichloromethane (50 mL) for another 30 minutes. The resin was filtered and washed liberally with dichloromethane. Resulted thiol resin was immediately suspended in a mixture of acetic anhydride (20 mL) and pyridine (30 mL) in DCM (50 mL), and the mixture was agitated overnight at r.t. The resin was filtered, washed liberally with dichloromethane and dried under vacuum.

5-(S)-Acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one. (0.15 g, 0.041 mmol) was suspended in 60% trifluoroacetic acid in dichloromethane for 2 at r.t. Supernatant was evaporated under vacuum and the crude product was purified by TLC (10% methanol in dichloromethane). Yield 8.7 mg (67 %). MS: 327 $[M+H]^+$. ^1H NMR.

Ester Oxazolidinone Derivatives

General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones

Method A. 4.37 M Sodium methoxide in methanol (0.0927 ml, 0.405 mmol) was added to an appropriate BAL resin immobilized 5-(S)-amidomethyl-3-[4'-acylthio-3'-fluorophenyl]oxazolidine-2-one (prepared as described above; 0.15 g, 0.041 mmol) in a polar aprotic solvent (preferably, N-methylpyrrolidine-2-one, 1.5 mL), and the mixture was agitated for 5-25 min (typically completed within 5 min for acetylated compounds). Optionally, an organic base was used instead of sodium methoxide (e.g., tetramethylguanidine or alkylamine). An appropriate alkylating or (hetero)arylating reagent (0.8-1.6 mmol) was added, and the mixture agitated at r.t. for 12-36 h (typically, complete overnight). The resin wash washed thoroughly with N-methylpyrrolidine-2-one, dichloromethane, and methanol. The resin was suspended in 60% trifluoroacetic acid in dichloromethane and agitated at room temperature for 2 h. Supernatant was evaporated

under vacuum and the crude product purified by TLC (methanol-dichloromethane mixtures).

Method B. 5% Trifluoroacetic acid and 2.5% triisopropylsilane in dichloromethane (2.0 mL) was added to 5-(S)-acetamidomethyl-3-[4'-triphenylmethylthio-3'-fluorophenyl]oxazolidine-2-one (0.10, 0.19 mmol), and the mixture was stirred at r.t. for 1 h. and the mixture stirred for 1 h at room temperature. Solvent was removed under vacuum, and the residue dissolved in methanol (3 mL). An appropriate alkylating or (hetero)arylating reagent (19-0.38 mmol) was added, followed by dropwise addition of 4.37 M sodium methoxide in methanol (0.087 ml, 0.380 mmol). Optionally, an organic base was used instead of sodium methoxide (e.g., tetramethylguanidine or alkylamine). The mixture was stirred at 20-70 °C for 2-24 h (typically, 2 h at r.t.). Solvent was removed under vacuum and the crude product purified by TLC (methanol-dichloromethane mixtures).

5-(S)-Acetamidomethyl-3-[4'-(6"-chloropyridazine-3"-yl)thio-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one with 3,6-dichloropyridazine (0.12 g, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 3.9 mg (24%). MS: 397 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(4",6"-dimethoxy-1",3",5"-triazine-2"-yl)thio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one with 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.1 g, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 6.1 mg (36%). MS: 424 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(5"-nitropyridine-2"-yl)thio-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one with 2-chloro-5-nitropyridine (0.13 g, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 7.0 mg (44%). MS: 407 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-(4'-[2"-(4"'-morpholino)ethyl]thio-3'-fluorophenyl)-oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one with 4-(2-chloroethyl)morpholine hydrochloride (0.28 g, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 2.4 mg (15%). MS: 398 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(pyridine-3"-yl)methylthio-3'-fluorophenyl)-oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one with 3-(chloromethyl)pyridine hydrochloride (0.13 g, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 3.6 mg (24%). MS: 376 $[M+H]^+$.

5-(S)-Acetamidomethyl-3-(4'-methylthio-3'-fluorophenyl)oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazoli- dine-2-one with methyl iodide (0.05 mL, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 6.3 mg (52%). MS: 299 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-methylthiazole-4"-yl)methylthio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-acetylthio-3'-fluorophenyl]oxazolidine-2-one with 4-chloromethyl-2-methylthiazole hydrochloride (0.15 g, 0.81 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. overnight, and the crude cleaved product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 6.9 mg (43%). MS: 396 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(1",2",4"-oxadiazole-3"-yl)methylthiazole-4"-yl)methylthio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]- oxazolidine-2-one with 3-chloromethyl-1,2,4-oxadiazole (0.045 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.043 g (62%). MS: 367 $[M+H]^+$.

5-(S)-Acetamidomethyl-3-[4'-(methoxycarbonyl)methylthio-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with methyl bromoacetate (0.058 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.056 g (83%). M.p. 119-120 °C. MS: 357 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-methoxyethyl)thio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 2-chloroethyl methyl ether (0.036 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.034 g (52%). MS (m/z): 343 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(3"-nitrothien-2"-yl)thio-3'-fluorophenyl]oxazo-lidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones

from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 2-chloro-3-nitrothiophene (0.062 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.066 g (85%). M.p. 194-195 °C. MS (m/z): 412 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(acetylmethyl)thio-3'-fluorophenyl]oxazo-lidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with chloroacetone (0.062 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.039 g (61%). MS (m/z): 341 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-hydroxyethyl)thio-3'-fluorophenyl]oxazo-lidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 2-bromoethanol (0.048 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.045 g (72%). MS (m/z): 329 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(5"-carboxypyridine-3"-yl)thio-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with t-butyl 2-chloronicotinate (0.081 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The intermediate t-butyl ester of the product was deprotected with 20% trifluoroacetic acid in dichloromethane (1 mL, 2 h at

r.t.). Solvent was evaporated under vacuum, and the crude product washed with diethyl ether. Yield 0.050 g (65%). MS (m/z): 406 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-(4'-cyclopropylmethylthio-3'-fluorophenyl)oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with chloromethyl cyclopropane (0.051 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.053 g (82%). MS (m/z): 339 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(3"-cyanoethyl)thio-3'-fluorophenyl]oxazo-lidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 3-bromopropionitrile (0.051 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.032 g (50%). MS (m/z): 338 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(5"-nitrothiazole-2"-yl)thio-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 2-bromo-5-nitrothiazole (0.079 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.061 g (78%). MS (m/z): 413 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(5"-phenyl-1",2",4"-oxadiazole-3"-yl)methylthio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamido- methyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 3-chloromethyl-5-phenyl-1,2,4-oxadiazole (0.074 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.040 g (47%). MS (m/z): 443 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(3"-methoxycarbonylpropane-2"-one-1"-yl)thio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamido-methyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with methyl 4-chloroacetoacetate (0.057 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.027 g (35%). MS (m/z): 399 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-chloroethyl)thio-3'-fluorophenyl]oxazolidi-ne-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 1-bromo-2-chloroethane (0.055 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.047 g (72%). MS (m/z): 347 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(1"-ethoxycarbonyl-1",1"-dimethyl)methylthio-3'-fluorophenyl]oxazo-lidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones

from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with ethyl 2-bromoisobutyrate (0.074 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.061 g (80%). MS (m/z): 399 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-diethoxyphosphinoyl)ethylthio-3'-fluorophenyl]oxazo-lidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with diethyl (2-bromoethyl)phosphonate (0.093 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.043 g (50%). MS (m/z): 449 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(thiocyano)methylthio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with chloromethyl thiocyanate (0.041 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.022 g (35%). MS (m/z): 324 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(3"-methyltetrahydrofuran-2"-one-3"-yl)thio-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazoli-dine-2-ones from 5-(S)-acetamido- methyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with α-bromo-α-methyl-γ-butyrolactone (0.068 g, 0.38 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified

by TLC (eluent: 10% methanol in dichloromethane). Yield 0.035 g (48%). MS (m/z): 383 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-diethylamino)ethylthio-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(substituted)thio-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamido- methyl-3-[4'-(triphenylmethyl)lthio-3'-fluorophenyl]oxazolidine-2-one with 2-(diethylamino)ethyl chloride hydrochloride (0.065 g, 0.38 mmol) and 4.37 M sodium methoxide (0.174 mL, 0.760 mmol) in N-methylpyrrolidine-2-one (1 mL). The synthesis was performed at r.t. for 2 h. The crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.011 g (15%). MS (m/z): 383 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-hydroxyethyl)sulfinyl-3'-fluorophenyl]oxazolidine-2-one

Sodium periodate (0.014 g, 0.065 mmol) in water (0.5 mL) was added to 5-(S)-acetamidomethyl-3-[4'-(2"-hydroxyethyl)thio-3'-fluorophenyl]-oxazo-lidine-2-one (0.020 g, 0.061 mmol) in methanol (1 mL), and the mixture was stirred at r.t. overnight. Solvent was removed under vacuum, and the residue dissolved in ethyl acetate (ca. 5 mL). Resulting solution was washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum, and the crude product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.018 g (86%). MS (m/z): 345 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(2"-hydroxyethyl)sulfonyl-3'-fluorophenyl]-oxazolidine-2-one

30% Hydrogen peroxide (0.023 mL, 0.244 mmol) was added to 5-(S)-acetamidomethyl-3-[4'-(2"-hydroxyethyl)thio-3'-fluorophenyl]oxazoli-dine-2-one (0.020 g, 0.061 mmol) in acetic acid (1 mL), and the mixture was stirred at 60 °C overnight. Solvent was removed under vacuum, and the residue dissolved in ethyl acetate (ca. 5 mL). Resulting solution was washed with water, brine, and dried ($MgSO_4$). Solvent was removed under vacuum, and the crude product purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.017 g (77%). M.p. 162-163 °C. MS (m/z): 361 $[M+H]^+$. ^1H NMR.

Ester Oxazolidinone Derivatives

5-(S)-(N-Acetylaminomethyl)-3-[4'-(*tert*-butoxy)carbonyl-3'-fluorophenyl] -oxazolidine-2-one.

Triphenylphosphine (0.521 g, 1.99 mmol) was added portionwise to a solution of 5-(S)-(N-azidomethyl)-3-[4'-(*tert*-butoxy)carbonyl-3'-fluorophenyl]oxazolidine-2-one (0.607 g, 1.80 mmol) in THF (10 ml), and the mixture was stirred at r.t. for 2 h. Water (0.259 ml, 14.4 mmol) was added, and the mixture heated at 40 °C overnight. Solvent was removed under vacuum. The oily residue was dissolved in a mixture of acetic anhydride (0.849 ml, 9.00 mmol) and pyridine (0.146 ml, 18.0 mmol) in dichloromethane (10 ml) and stirred for 4 h. Solvent was removed under vacuum, and the crude product was purified by TLC (eluent: 10 % methanol in dichloromethane). Yield 0.62 g (98 %). MS (m/z): 353 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetylaminomethyl)-3-[4'-carboxy-3'-fluorophenyl]-oxazolidine-2-one

5-(S)-(N-Acetylaminomethyl)-3-[4'-(4"-(*tert*-butoxy)carbonyl-3'-fluorophenyl]oxazolidine-2-one (6.20 g, 17.5 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane, and the mixture stirred at r.t. overnight. Solvent was removed under vacuum, and the residue triturated with ether to give product as a white solid. Yield 5.20 g (99 %). M.p. 252-253 °C; MS: 297 $[M+H]^+$. ^1H NMR.

General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[alkyl[or (hetero)aryl]oxy]carbonyl-3'-fluorophenyl]-oxazolidine-2-ones

Method A. An appropriate 5-(S)-(N-acylaminomethyl)-3-[4'-(4"-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one resin of the type **5** (0.1 mmol; prepared from resin **4** *via* two step acylation with an appropriate N-acylating reagent, and subsequent Pfp-activation as described above) was mixed with a selected alcohol reagent (1-3 mmol, typically, 1-2 mmol) and 4-dimethylaminopyridine (0.2-1 mmol; typically, 1 mmol) in aprotic solvent (N,N-dimethylformamide, dichloromethane, or dimethylsulfoxide; preferably, N,N-dimethylformamide, 4-6 mL). The mixture was agitated at 20-70 °C for 6-48 h (typically, at r.t. overnight). The resin was filtered, washed liberally with N,N-dimethylformamide, dichloromethane, methanol, dried *in vacuo*, and cleaved with 60% trifluoroacetic acid in dichloromethane (5 ml, 2 h). Resulting supernatant was evaporated *in vacuo*, and the crude product purified by HPLC or TLC.

Method B. An appropriate alkylating reagent (0.35-1.2 mmol; preferably, 1 mmol) was added to 5-(S)-(N-acetamidomethyl)-3-[4'-(pentafluoro-phenyloxy)carbonyl-3'-fluorophenyl]oxazolidine-2-one (0.100 g, 0.34 mmol) and potassium carbonate (0.187 g, 1.35 mmol) in N,N-dimethylformamide (2 mL), and the mixture agitated at 20-80 °C for 6-24 h (typically, at r.t. overnight). Water (ca. 10-15 mL) was added, and the mixture was extracted with ethyl acetate (ca. 3 x 20 mL). Combined organic solvents were washed with water, brine, and dried ($MgSO_4$). Solvent was evaporated *in vacuo*, and the crude product purified by HPLC or TLC.

5-(S)-(N-Acetylaminomethyl)-3-[4'-cyclopropylmethoxycarbonyl-3'-fluoro-phenyl]oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[alkyl[or (hetero)aryl]oxy]carbonyl-3'-fluorophenyl]oxazolidine-2-ones from BAL resin 5-(S)-(N-acylaminomethyl)-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluo- rophenyl]oxazolidine-2-one (0.1 mmol) and hydroxymethylcyclopropane (0.144 g, 2 mmol) with 4-dimethylaminopyridine (1 mmol) in N,N-dimethylformamide (4 mL). Reaction performed at r.t. overnight. Crude cleaved product was purified by TLC (eluent: 10% methanol in dichloromethane). MS (m/z): 350 $[M+H]^+$. Aternatively, the compound was made according to Method B of aforementioned General Procedure from 5-(S)-(N-acetamidomethyl)-3-[4'-carboxy-3'-fluorophenyl]-oxazolidine-2-one (0.100 g, 0.34 mmol) and (bromomethyl)cyclopropane (0.098 mL, 1 mmol). Reaction was performed at 70 °C overnight. Crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.100 g (85%). MS (m/z): 350 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-methoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[alkyl[or (hetero)aryl]oxy]- carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-(N-acetamido-methyl)-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (0.100 g, 0.34 mmol) and methyl iodide (0.063 mL, 1 mmol). Reaction was performed at r.t. overnight. Crude product was purified by TLC

(eluent: 10% methanol in dichloromethane). Yield 104 mg (99%). MS (m/z): 311 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-isopropoxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[alkyl[or (hetero)aryl]oxy]- carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-(N-acetamido-methyl)-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (0.100 g, 0.34 mmol) and 2-bromopropane (0.095 mL, 1 mmol). Reaction was performed at 70 °C overnight. Crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 105 mg (92%). MS (m/z): 339 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-ethoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[alkyl[or (hetero)aryl]oxy]- carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-(N-acetamido-methyl)-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (0.100 g, 0.34 mmol) and ethyl iodide (0.081 mL, 1 mmol). Reaction was performed at r.t. overnight. Crude product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 107 mg (98%). MS (m/z): 325 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-[(N-isopropylidene)imino]oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one

A mixture of 5-(S)-(N-acetamidomethyl)-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (0.100 g, 0.34 mmol), 4-(dimethylamino)-pyridine (0.041 g, 0.34 mmol), diisopropylcarbodiimide (0.053 ml, 0.34 mmol) and acetone oxime (0.025 g, 0.34 mmol) in N, N-dimethyformamide (2 ml) was stirred at r.t. overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. Organic layers were washed with brine, and dried ($MgSO_4$). Solvent was remove under vacuum, and the residue was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.098 g (83 %). MS (m/z): 352 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-(pyridine-3"-yl)methoxycarbonyl-3'-fluoro-phenyl]oxazolidine-2-one

A mixture of 5-(S)-(N-acetamidomethyl)-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (0.100 g, 0.34 mmol), 4-(dimethylamino)pyridine (0.041 g, 0.34 mmol), diisopropylcarbodiimide (0.053 ml, 0.34 mmol) and 3-pyridylcarbinol (0.033 g, 0.34 mmol) in N, N-dimethyformamide (2 ml) was stirred at r.t. overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. Organic layers were washed with brine, and dried ($MgSO_4$). Solvent was remove under vacuum, and the residue was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.094 g (72 %). MS (m/z): 388 $[M+H]^+$. ^1H NMR.

Amide Oxazolidinone Derivatives

General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[(un)substituted amino]carbonyl-3'-fluorophenyl]-oxazolidine-2-ones 7

Method A. An appropriate 5-(S)-(N-acylaminomethyl)-3-[4'-(4"-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one resin of the type **5** (prepared from BAL resin immobilized 5-(S)-aminomethyl-3-[4'-carboxy-3'-fluorophenyl]-oxazolidine-2-one **4** *via* two step acylation with an appropriate N-acylating reagent, and subsequent Pfp-activation as described above (0.029 mmol) was agitated with a selected amine compound (0.1-0.2 mmol; preferably 0.116 mmol) in a polar non-protic solvent such as N-methylpyrrolidine-2-one, N,N-dimethylformamide (2-4 ml) for 16-48 h at 25-70 °C (preferably, at 60 °C overnight) containing 10-20% v/v of an organic base (pyridine, 2,6-lutidine, or diisopropylethylamine). Optionally, dimethylsulfoxide (0.5-1 mL) was added for less soluble amine reagents. Also optionally, functionalized amines (such as amino acids or amino alcohols) were pre-dissolved with addition of a silylating reagent (such as bis-trimethylsilylacetamide, 0.2-0.6 mmol) prior to addition to the resin, and the reaction was performed under inert gas atmosphere (nitrogen). Resulted resin was filtered and washed liberally with N-methylpyrrolidine-2-one, MeOH, dichloromethane, and dried under vacuum. The dry resin was cleaved in 60% trifluoroacetic acid in dichloromethane (2 ml) for 2 h at room temperature. The resin was filtered, the filtrate evaporated under vacuum, and crude product purified by preparative TLC (MeOH - dichloromethane) or reverse phase HPLC.

Method B. 60% Trifluoroacetic acid in dichloromethane (5 mL) was added to 5-(S)-azidomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.336 g, 1 mmol), and the solution kept at r.t. for 1 h. Solvents were removed *in vacuo* to afford 5-(S)-azidomethyl-3-[4'-carboxy-3'-fluorophenyl-]oxazolidine-2-one dried (0.280 g, 99%). N-Trimethylsilyl-N,N-diethylamine (0.23 mL, 1.2 mmol) was added to above product in dry dichloromethane (3 mL) under nitrogen atmosphere, and the solution stirred for 15 min. Solvents and excess reagent were removed *in vacuo*, and residue dissolved in dichloromethane (4 mL). The solution was cooled to ca. 0 °C, and oxalyl chloride (1.5 mmol, 0.13 mL) was added dropwise, followed by catalytic N,N-dimethylformamide (ca. 0.01 mL). The mixture was alllowed to warm up to r.t., and stirred at r.t. for another 2 h. Solvents were removed *in vacuo*, and the resulting 5-(S)-azidomethyl-3-[4'-chlorocarbonyl-3'-fluorophenyl]- oxazolidine-2-one redissolved in dry aprotic solvent (preferably, tetrahydrofuran, pyridine, or acetonitrile, 3-10 mL). Resulted solution (0.8 mL, ca. 0.2 mmol) was added to an appropriate amine reagent (1 mmol) in aprotic solvent (preferably, acetonitrile, or pyridine, 1-5 mL) optionally containing an organic base (preferably, pyridine, 0.5-2 mL). The mixture was stirred at r.t. for 1-5 h. Solvent was removed *in vacuo*, and resulting 5-(S)-azidomethyl-3-[4'-(substituted)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one was typically washed with water, and dried *in vacuo*. Triphenylphosphine (0.262 g, 1.0 mmol) in tetrahydrofuran (10 mL) was added to above azide intermediate, and the mixture stirred at 45-55 °C °C for 2 h. Water (0.5 mL) was added, and the mixture stirred overnight at 50-60 °C. Solvents were removed *in vacuo*, and resulting crude amine intermediates typically washed with excess diethyl ether. Aprotic solvent was added (preferably, tetrahydrofuran, 5-15 mL) was added, followed by pyridine (0.25-0.5 mL) and acetic anhydride (0.2-0.5 mL), and the mixture stirred at r.t. for 0.5-2 h (typically, 1 h). Solvents were removed *in vacuo*, and resulting product typically washed with excess diethyl ether and dried *in vacuo*.

Method C. N,N-Diisopropyl-N-ethylamine (0.34 mL, 2 mmol) was added to 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (0.296 g, 1 mmol) and a coupling reagents, [preferably, O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)] in a polar aprotic solvent such as N,N-dimethylformamide (3 mL) and tetrahydrofuran (2 mL), and the solution was kept at r.t.

for 20 min. An appropriate amine (1 mmol) was added, followed by an organic base (preferably, N,N-diisopropyl-N-ethylamine, 0.17 mL, 1 mmol), and the mixture stirred at 20-60 °C for 1-24 h (typically, at r.t. for 1-2 h). Additional base (typically, 1 mmol) was added when amine salts were employed. Optionally, catalytic 4-dimethylaminopyridine (0.05-0.2 mmol) was added for acylation of less reactive amines. Volatile organic solvents were removed *in vacuo*. The product was typically isolated by precipitation with excess of water (5-60 mL), or by extraction from aqueous solutions with ethyl acetate (20-40 mL). In the latter case, organic layers were washed with saturated aqueous sodium bicarbonate, water, 3% aqueous citric acid, water, brine, and dried ($MgSO_4$). Organic solvent was removed *in vacuo*, and the product further purified by washing with excess of diethyl ether, or by crystallization from an appropriate solvent (typically, methanol or ethanol).

Method D. N-Ethyl-N'-(3-diethylaminopropyl)carbodiimide (0.92 g, 4.8 mmol) was added to 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one (1.18 g, 4.0 mmol) and pentafluorophenol (0.81 g, 4.4 mmol) in N,N-dimethylfomamide (50 mL) and the soliution stirred at r.t. for 24 h. Most of solvent was removed *in* vacuo, the residue dissolved in acetonitrile (ca. 40 mL), and this solution added dropwise with stirring into 3% aqueous citric acid (ca. 150 mL). Precipitated 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxa-zolidine-2-one was filtered off, washed with water, and dried *in vacuo* (yield 1.30 g, 70%; M.p. 172-173 °C; Rt 5.2 min). The resulting ester (1 mmol) was dissolved in a polar solvent (preferably, tetrahydrofuran or acetonitrile 10 mL), and an appropriate amine (1-5 mmol) added. The mixture was stirred at r.t. for 1-10 h (typically, 1-2 h). Solvent and excess reagent were removed *in vacuo*, and the product purified by chromatography or crystallization from an appropriate solvent.

5-(S)-Acetamidomethyl-3-[4'-(6"-chloropyridine-3"-yl)aminocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Method A. Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one and 2-chloro-5-amino-pyridine in 10% pyridine in N-methylpyrrolidine-2-one (70 °C, 48 h). MS: 407

$[M+H]^+$. To obtain the hydrochloride form of this compound, above material (41 mg, ca. 0.1 mmol) was dissolved in methanol (10 mL) with 2M HCl in 1,4-dioxane (5 mL). Resulted solution was filtered, solvents removed *in vacuo*, and the crude salt washed with excess of diethyl ether.

Method B. Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)- carbonyl-3'-fluoro-phenyl]-oxazolidine-2-ones by amide coupling of 5-(S)-azidomethyl-3-[4'-chlorocarbonyl-3'-fluorophenyl]oxazolidine-2-one and 2-chloro-5-aminopyridine in pyridine (3 mL, r.t., 1 h). Solvent was removed *in vacuo*, and resulting 5-(S)-azidomethyl-3-[4'-(6"-chloropyridine-3"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one was washed with water (5 x 3 mL mL), and dried *in vacuo*. Triphenylphosphine (0.262 g, 1.0 mmol) in tetrahydrofuran (10 mL) was added to above azide intermediate, and the mixture stirred at 45 °C for 2 h. Water (0.5 mL) was added, and the mixture stirred overnight at 50 °C. Solvents were removed *in vacuo*, and resulting crude amine intermediate washed with excess diethyl ether. Tetrahydrofuran (15 mL) was added, followed by pyridine (0.25 mL) and acetic anhydride (0.2 mL), and the mixture stirred at r.t. for 1 h. Solvents were removed *in vacuo*, and resulting product washed with excess diethyl ether. MS: 407 $[M+H]^+$. ^1H NMR.

<u>5-(S)-Acetamidomethyl-3-[4'-(thiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one</u>

Method A. Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]-oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one and 2-aminothiazole in 10% pyridine in N-methylpyrrolidine-2-one (r.t., 24 h). MS: 379 $[M+H]^+$. Rt 3.8 min. To obtain the hydrochloride form of this compound, above material (38 mg, ca. 0.1 mmol) was dissolved in methanol (10 mL) with 2M HCl in 1,4-dioxane (5 mL), filtered, solvents removed *in vacuo*, and the residue washed with excess of diethyl ether.

Method B. Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)-carbonyl-3'-

fluorophenyl]-oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 2-aminothiazole (0.10 g, 1 mmol). The synthesis was performed at r.t. overnight. Tetrahydrofuran was removed *in vacuo*, and the residue added to water (60 mL). Resulted suspension was kept at r.t. for 1 h, filtered, and the product washed with excess water and dried *in vacuo*.

5-(S)-Acetamidomethyl-3-[4'-(4,5-dimethylthiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Method A. Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)-carbonyl-3'-fluorophenyl]-oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one and 2-amino-4,5-dimethylthiazole in 10% pyridine in N-methylpyrrolidine-2-one (r.t., 24 h). MS: 407 $[M+H]^+$. Rt 4.1 min. ^{1}H NMR.

Method B. Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)-carbonyl-3'-fluorophenyl]-oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 2-amino-4,5-dimethyl-thiazole. The synthesis was performed at r.t. for 3 h. MS: 407 $[M+H]^+$. Rt 4.1 min. ^{1}H NMR.

5-(S)-Acetamidomethyl-3-[4'-(pyrimidine-4"-yl)aminocarbonyl-3'-fluorophe- nyl]-oxazolidine-2-one

Method A. Prepared according to Method A of the the General Procedurse for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]-oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one and 4-aminopyrimidine in 10% pyridine in N-methylpyrrolidine-2-one (70 °C, 48 h). MS: 374 $[M+H]^+$. Rt 3.4 min. ^{1}H NMR.

Method B. Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)-carbonyl-3'-fluorophenyl]-oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 4-aminopyrimidine. The synthesis was performed at

r.t. for 24 h. Water (15 mL) was, and the mixture kept at r.t. for 3 days to allow for product crystallization. MS: 374 $[M+H]^+$. Rt 3.4 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(thiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Method A. Prepared according to the General Procedure for preparation of 5-(S)-(N-acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluoro-phenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)-oxycarbonyl-3'-fluorophenyl]oxa-zolidine-2-one and 5-chloro-2-aminothiazole in 10% pyridine in N-methylpyrrolidine-2-one (70 °C, 48 h). MS: 413 $[M+H]^+$. ^1H NMR.

Method B. Prepared according to Method B of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)- carbonyl-3'-fluoro-phenyl]-oxazolidine-2-ones by amide coupling of 5-(S)-azidomethyl-3-[4'-chlorocarbonyl-3'-fluorophenyl]oxazolidine-2-one and 5-chloro-2-aminothiazole hydrochloride in tetrahydrofuran (ca. 4 mL) and acetonitrile (2.5 mL) with pyridine (0.5 mL). The mixture was stirred for 2 h at r.t., and methanol (ca. 7 mL) was added. Resulted precipitate of 5-(S)-azidomethyl-3-[4'-(thiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidi-ne- 2-one was filtered, washed with methanol (8 mL), diethyl ether, and dried *in vacuo*. Triphenylphosphine (0.31 g, 1.2 mmol) in N-methylpyrrolidine-2-one (1.25 mL) and tetrahydrofuran (1.25 mL) was added to above azide intermediate, and the mixture stirred at r.t. for 2 h. Water (0.1 mL) was added, and the mixture stirred overnight at 50 °C. Solvents were removed *in vacuo*, and resulting crude amine intermediate washed with excess diethyl ether. Tetrahydrofuran (8 mL) was added, followed by pyridine (0.5 mL) and acetic anhydride (0.5 mL), and the mixture stirred at r.t. for 30 min. Solvents were removed *in vacuo*, and resulting product washed with excess diethyl ether, water (2 x 3 mL), diethyl ether, and dried *in vacuo*.. MS: 413 $[M+H]^+$. ^1H NMR.

5-(S)-(Methylthio)acetamidomethyl-3-[4'-(6"-chloropyridine-3"-yl)amino-carbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)-carbonyl-3'-fluorophen-yl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-(methylthio)acetamidomethyl-3-

[4'-(pentafluorophenyl)-oxycarbonyl-3'-fluo-rophenyl]-oxazolidine-2-one and 2-chloro-5-aminopyridine. MS: 453 $[M+H]^+$. To obtain the hydrochloride form of this compound, above material (45 mg, ca. 0.1 mmol) was dissolved in methanol (10 mL) with 2M HCl in 1,4-dioxane (5 mL), filtered, solvents removed *in vacuo*, and the residue washed with excess of diethyl ether.

5-(S)-Acetamidomethyl-3-[4'-(benzothiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 2-aminobenzothiazole. The synthesis was performed at r.t. over 3 h. MS: 429 $[M+H]^+$. Rt 4.6 min. ^{1}H NMR.

5-(S)-Acetamidomethyl-3-[4'-(6"-methoxybenzothiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 6-methoxy-2-aminobenzothiazole. The synthesis was performed at r.t. over 3 h. MS: 459 $[M+H]^+$. Rt 4.7 min. ^{1}H NMR.

5-(S)-Acetamidomethyl-3-[4'-(6"-methoxybenzothiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)-carbonyl-3'-fluorophenyl]-oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 5-methylthio-3-aminopyridine. The synthesis was performed at r.t. overnight. MS: 419 $[M+H]^+$. Rt 3.8 min. ^{1}H NMR.

5-(S)-Acetamidomethyl-3-[4'-(4"-amino-5"-phenylthiazole-2"-yl)aminocarbo-nyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-

fluorophenyl]oxazolidine-2-one and 2,4-diamino-5-phenylthiazole hydrobromide. The synthesis was performed at r.t. overnight. MS: 470 $[M+H]^+$. Rt 4.5 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(5"-ethylthio-1,3,4-thiadiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 5-ethylthio-2-amino-1,3,4-thiadiazole. MS: 440 $[M+H]^+$. R_t 4.4 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(1,3,4-thiadiazole-2"-yl)aminocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method C of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one and 2-amino-1,3,4-thiadiazole. MS: 380 $[M+H]^+$. R_t 3.6 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(imidazole-2"-yl)aminocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-(methylthio)acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.400 g, ca. 0.1 mmol) and 2-aminoimidazole sulfate (0.234 g, 2 mmol). The amine reagent was pre-dissolved in a mixture of 10% pyridine in N-methylpyrrolidine-2one (4 mL), bis-(trimethylsilyl)acetamide (0.5 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 1 mmol) at 70 ^0C over 2 h. Coupling with the resin reagent was performed at r.t. over 48 h. The crude product after cleavage from resin was purified by reverse-phase HPLC. MS: 362 $[M+H]^+$. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(1,3,4-triazole-2"-yl)aminocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-(methylthio)acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.400 g, ca. 0.1 mmol) and 2-amino-1,3,4-triazole (0.168 g, 2 mmol). The amine reagent was pre-dissolved in a mixture of 10% pyridine in N-methylpyrrolidine-2-one (4 mL), bis-(trimethylsilyl)acetamide (0.5 mL) at 70 °C over 2 h. Coupling with the resin reagent was performed at 60 °C over 48 h. The crude product after cleavage from resin was purified by reverse phase HPLC. MS: 363 $[M+H]^+$. R_t 3.1 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(pyridine-3"-yl-1"-oxide)aminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

30% Aqueous hydrogen peroxide (0.05 mL) was added to 5-(S)-acetamidomethyl-3-[4'-(3"-pyridylamino)carbonyl-3'-fluoro- phenyl]-oxazolidine-2-one (7 mg, ca. 0.02 mmol) and methylrhenium trioxide (MTO, 0.9 mg) in N-methylpyrrolidine-2-one (0.15 mL). The mixture was stirred for 30 min at r.t., and solvents removed *in vacuo* (0.1 Torr, r.t.). The crude product was washed with methanol (0.5 mL) and diethyl ether. MS: 389 $[M+H]^+$. R_t 3.3 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-hydroxyaminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method D of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamidomethyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one (0.046 g, 0.1 mmol) and O-trimethylsilylhydroxylamine (0.052 mL, ca. 0.5 mmol) in tetrahydrofuran (1 mL). The synthesis was performed for 2 h at r.t. Diethyl ether (4 mL) was added, the precipitated product washed with diethyl ether, tetrahydrofuran (2 x 0.5 mL), excess ether, and dried *in vacuo*. MS: 312 $[M+H]^+$. R_t 2.8 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-methylaminocarbonyl-3'-fluorophenyl]-oxazolidine-2-one

Prepared according to Method D of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acetamido-methyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one (0.046 g, 0.1 mmol) and 2 M methylamine in tetrahydrofuran (1 mL, 2 mmol). The synthesis was performed at r.t. for 45 min. Diethyl ether (4 mL) was added, the precipitated product washed with diethyl ether, tetrahydrofuran (2 x 0.5 mL), excess ether, and dried *in vacuo*. MS: 310 $[M+H]^+$. R_t 3.2 min. ^1H NMR.

5-(S)-*trans*--[4"-Methoxyimino)cinnamoyl]methyl-3-[4'-aminocarbonyl-3'-fluorophenyl]oxazolidine-2-one

Prepared according to Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-(4"-(un)substituted amino)carbonyl-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-[*trans*--(4"-methoxyimino)cinnamoyl)methyl-3-[4'-(pentafluorophenyl)oxycarbonyl-3'-fluorophenyl]oxazolidine-2-one (0.400 g, ca. 0.1 mmol) and 2 M ammonia in 1,4-dioxane (5 mL, ca. 10 mmol). The synthesis was performed at r.t. overnight. The crude product after cleavage from resin was purified by reverse phase HPLC. MS: 441 $[M+H]^+$. ^1H NMR.

General Procedure for Preparation of 5-(S)-Amidomethyl-3-[4'-[(un)substituted 1",3",5"-triazine-2"-yl]amino-3'-fluorophenyl]oxazolidine-2-one

An appropriate BAL resin immobilized 5-(S)-acylaminomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]oxazolidine-2-one (0.06-0.1 mmol) was deprotected by agitation with 20% piperidine in DMF (4 mL) for 45 min. Resulted aniline resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, and dried *in vacuo*. A solution of an appropriate halogen-substituted triazine reagent (preferably, a chlorotriazine derivative, 1-3 mmol) and organic base (preferably N,N-diisopropyl-N-ethylamine or 2,6-di-t-butylpyridine, 3-6 mmol) in aprotic solvent (preferably, N-methylpyrrolidine-2-one, dichloromethane, 1,4-dioxane, or acetonitrile) was added, and the mixture agitated at 0-80 °C for 12-36 h (typically, at 0-40 °C overnight). Resulted aniline resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, and dried *in vacuo*. When the triazine oxazolidinone contained

more than one halogen substituent, the reaction was optionally repeated using amine, thiol, or alcohol reagents as described above (40-80°C, 12-36 h). Washed and dry resin was cleaved with 60% trifluoroacetic acid in dichloromethane (5 ml, 2 h). Resulted supernatant was evaporated *in vacuo*, and the crude product purified by HPLC or TLC.

5-(S)-Acetamidomethyl-3-[4'-(4"-chloro-6"-1",2",3"-triazine-2"-yl)amino-3'-fluorophenyl]oxazolidine-2-one

BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophen-yl]oxazolidine-2-one (0.06 mmol) was deprotected by agitation with 20% piperidine in DMF (4 mL) for 45 min. Resulted aniline resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, and dried *in vacuo*. A solution of cyanuric trichloride (0.194 g, 1.0 mmol) and 2,6-di-t-butylpyridine (0.36 mL, 1.5 mmol) in dichloromethane (4 mL) was added, and the mixture agitated at r.t. for 24 h. Resulted aniline resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, and dried *in vacuo*. 0.5 M Ammonia in 1,4-dioxane (5 mL, 2.5 mmol) was added, and the mixture agitated at r.t. for 24 h. The resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, dried *in vacuo*, and cleaved with 60% trifluoroacetic acid in dichloromethane (5 ml, 2 h). Resulting supernatant was evaporated *in vacuo*, and the crude product purified by preparative TLC (eluent methanol - dichloromethane 1:10). MS: 396 $[M+H]^+$. R_t 3.6 min. ^1H NMR.

5-(S)-Acetamidomethyl-3-[4'-(4",6"-dimethoxy-1",3",5"-triazine-2"-yl)amino-3'-fluoro-phenyl]oxazolidine-2-one

Prepared according to the General Procedure for Preparation of 5-(S)-Amidomethyl-3-[4'-[(un)substituted triazinyl]-3'-fluorophenyl]oxazolidine-2-one from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophe-nyl]oxazolidine-2-one (0.06 mmol) and 2-chloro-4,6-dimethoxytriazine (0.275 g, 1.5 mmol). Reaction of the immobilized aniline and the triazine reagent was repeated twice in a mixture of N-methylpyrrolidine-2-one and dichloromethane (1:1, 4 mL) at r.t. overnight. The crude cleaved product was purified by preparative TLC (eluent methanol - dichloromethane 1:10). MS: 407 $[M+H]^+$. ^1H NMR.

Acylamino Oxazolidinone Derivatives

General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-acylamino-3'-fluorophenyl]oxazolidine-2-ones

An appropriate BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)ami-no-3'-fluorophen-yl]oxazolidine-2-one (0.1 mmol) was deprotected by agitation with 20% piperidine in DMF (4 mL) for 45 min. Resulting aniline resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, and dried *in vacuo*. Separately, N,N-diisopropyl-N-ethylamine (3-6 mmol; typically, 3 mmol) was added to selected carboxylic acid (1-2 mmol; typically, 1 mmol) and a coupling reagent [preferably, O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate or diisopro-pylcarbodiimide; 3-6 mmol; typically, 3 mmol) in a polar aprotic solvent such as N,N-dimethylformamide (7-10 mL, and the mixture agitated at r.t. for 20-30 min. Resulted solution of the pre-activated acid reagent was added to above aniline resin, and the mixture agitated at 20-60 °C for 6-24 h (typically, at r.t. overnight). The resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, dried *in vacuo*, and cleaved with 60% trifluoroacetic acid in dichloromethane (5 ml, 2 h). Resulting supernatant was evaporated *in vacuo*, and the crude product purified by HPLC or TLC.

5-(S)-(N-Acetamidomethyl)-3-[4'-acetamido-3'-fluorophenyl]oxazolidine-2-ones

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-acylamino-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]oxazolidine-2-one (0.1 mmol). The intermediate aniline was acylated with the mixture of acetic anhydride - pyridine - dichloromethane (1:1.5:3, 2 mL). Crude cleaved product was purified by TLC (eluent: 10 % methanol in dichloromethane). Yield 0.014 g (46 %). MS: 310 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-(2",4"-thiazole-5"-yl)carbonylamino-3'-fluorophenyl]oxazolidine-2-ones

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-acylamino-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-

fluorophen-yl]oxazolidine-2-one (0.1 mmol). Acylation was performed with 2,4-dimethylthiazole-5-carboxylic acid (0.157 g, 1 mmol) pre-activated with diisopropylcarbodiimide (0.086 mL, 0.55 mmol) and pyridine (0.081 mL, 1 mmol) in a mixture of N,N-dimethylformamide - dichloromethane 4:1 (2 mL) at r.t. overnight. Crude cleaved product was purified by TLC (eluent: 10 % methanol in dichloromethane). Yield 0.028 g (68 %). MS: 407 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acetamidomethyl)-3-[4'-(pyridine-3"-yl)carbonylamino-3'-fluoro-phenyl]oxazolidine-2-ones

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-acylamino-3'-fluorophenyl]oxazolidine-2-ones from BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophen-yl]oxazolidine-2-one (0.02 mmol). Acylation was performed with nicotinic acid (0.049 g, 0.40 mmol) pre-activated with O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.160 g, 0.20 mmol) and N,N-diisopropyl-N-ethylamine (0.21 mL, 1.20 mmol) in N,N-dimethylformamide (1 mL) at r.t. overnight. Crude cleaved product was purified by TLC (eluent: 10 % methanol in dichloromethane). Yield 0.023 g (62 %). MS: 373 $[M+H]^+$. ^1H NMR.

Sulfonamido Oxazolidinone Derivatives

General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluorophenyl]oxazolidine-2-ones

An appropriate BAL resin immobilized 5-(S)-acylaminomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)ami-no-3'-fluorophenyl]oxazolidine-2-one (0.1 mmol) was deprotected by agitation with 20% piperidine in DMF (4 mL) for 45 min. Resulted aniline resin was washed liberally with N,N-dimethylformamide, dichloromethane, methanol, and dried *in vacuo*. The resin was suspended in 20% pyridine in dichloromethane (2 mL), and a solution of selected sulfonyl chloride reagent (1-2 mmol; preferably, 1.25 mmol) in dichloromethane was added. The mixture was agitated at 20-40 °C for 12-36 h (typically, at r.t. overnight). Resin was filtered, washed with methanol, and suspended in 0.1M lithium hydroxide monohydrate in methanol (4 mL). The mixture was agitated at r.t. for 30-90 min (typically, for 90 min). The resin was filtered, washed liberally with N,N-dimethylformamide, dichloromethane, methanol, dried *in vacuo*, and cleaved with 60%

trifluoroacetic acid in dichloromethane (5 ml, 2 h). Resulted supernatant was evaporated *in vacuo*, and the crude product purified by HPLC or TLC.

5-(S)-(N-Acylaminomethyl)-3-[4'-methylsulfonamido-3'-fluorophenyl]-oxazolidine-2-ones

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acylaminomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]oxazolidine-2-one (0.1 mmol) and methanesulfonyl chloride (0.2 mL, 1.25 mmol). The crude cleaved product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.022 g (65%). MS (m/z): 346 $[M+H]^+$. ^1H NMR.

5-(S)-(N-Acylaminomethyl)-3-[4'-(benzo-2",1",3"thiadiazole-4"-yl)sulfon-amido-3'-fluorophenyl]oxazolidine-2-ones

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluorophenyl]oxazolidine-2-ones from 5-(S)-acylaminomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl] oxazolidine-2-one (0.1 mmol) and benzo-2,1,3-thiadiazole-4-sulfonyl chloride (0.295 g, 1.25 mmol). The crude cleaved product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.024 g (52%). MS (m/z): 466 $[M+H]^+$.

5-(S)-(N-Acetamidomethyl)-3-[4'-(4",5"-dibromothiophene-2"-yl)sulfonami-do-3'-fluorophenyl]oxazolidine-2-one.

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluorophenyl]oxazolidine-2-ones from from BAL resin immobilized 5-(S)-acylaminomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophen-yl]oxazolidine-2-one (0.1 mmol) and 2,3-dibromothiophene-5-sulfonyl chloride (0.43 g, 1.25 mmol). The crude cleaved product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.044 g (77%). ^1H NMR. MS (m/z): 572 $[M+H]^+$.

5-(S)-(N-Acetamidomethyl)-3-[4'-(6"-chloroimidazo[2,1-b]thiazole-5"-yl)sulfonamido-3'-fluorophenyl]oxazolidine-2-one.

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluorophenyl]oxazolidine-2-ones from from BAL resin immobilized 5-(S)-acylamino-methyl-3-[4'-(9"-fluorenylmethoxycarbonyl)-amino-3'-fluorophenyl]oxazolidi-ne-2-one (0.1 mmol) and 6-chloro-imidazo[2,1-b]thiazole-5-sulfonyl chloride (0.32 g, 1.25 mmol). The crude cleaved product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.019 g (39%). ^{1}H NMR. MS (m/z): 572 $[M+H]^+$.

5-(S)-(N-Acetamidomethyl)-3-[4'-(2"-acetamido-4"-methylthiazole-5"-yl)-sulfonamido-3'-fluorophenyl]oxazolidine-2-one.

Prepared according to the General Procedure for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluorophenyl]oxazolidine-2-ones from from BAL resin immobilized 5-(S)-acylamino-methyl-3-[4'-(9"-fluorenylmethoxycarbonyl)-amino-3'-fluorophenyl]oxazolidine-2-one (0.1 mmol) and 2-acetamido-4-methyl-5-thiazolesulphonyl chloride (0.32 g, 1.25 mmol). The crude cleaved product was purified by TLC (eluent: 10% methanol in dichloromethane). Yield 0.025 g (52%). ^{1}H NMR. MS (m/z): 486 $[M+H]^+$.

5-(S)-(N-Acetamidomethyl)-3-[4'-(N-methyl)methylsulfonamido-3'-fluorophenyl]-oxazolidine-2-one

BAL resin immobilized 5-(S)-(N-acetamidomethyl)-3-[4'-methylsulfonamido-3'-fluorophenyl]oxazolidine-2-one was prepared from from BAL resin immobilized 5-(S)-acylaminomethyl-3-[4'-(9"-fluorenylmethoxycarbonyl)amino-3'-fluorophenyl]oxazolidine-2-one (0.1 mmol) and methanesulfonyl chloride (0.2 mL, 1.25 mmol) as described above in the synthesis of 5-(S)-(N-acetamidomethyl)-3-[4'-methylsulfonamido-3'-fluorophenyl]oxazolidine-2-one. N-Methylpyrrolidi-ne-2-one (2 ml) was added, followed by methyl iodide (0.16 ml, 2.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.37 ml, 2.5 mmol). The mixture was agitated overnight at r.t. The resin was filtered, washed thoroughly with dichloromethane and methanol, and dried under vacuum. Oroduct was cleaved with 60% trifluoroacetic acid in dichloromethane (5 mL, 2 h), solvent

removed under vacuum, and the crude product purified by TLC (eluent: 10 % methanol in dichloromethane). Yield 0.017 g (48 %). ^{1}H NMR. MS (m/z): 360 $[M+H]^+$.

Procedures for Preparation of 3-(Heteroaryl)oxazolidine-2-one Derivatives.

5-(S)-Azidomethyloxazolidine-2-one

5-(R)-Chloromethyloxazolidine-2-one (prepared according to [Danielmeier et al. Efficient Pathways to (R)- and (S)-hydroxymethyl-2-oxazolidinone and some derivatives. Tetrahedron: Asymmetry. 1995, vol. 6, pp. 1181-1190] (5 mmol) is reacted with sodium azide (7-10 mmol) in acetone (ca. 40-50 mL) at r.t. for ca. 24 h (until the reaction is completed). Solids are filtered off, and supernatant evaporated under vacuum to afford the product which is immediately used for the next step. Optionally, the synthesis is performed in dry N,N-dimethylformamide under inert atmosphere with sodium azide (5-10 mmol) or tetrabutylammonium azide (5-10 mmol), and the resulting solution of the crude 5-(S)-azidomethyloxazolidine-2-one is employed for the next step without solvent removal.

5-(S)-Azidomethyl-3-(heteroaryl)oxazolidine-2-ones and Application Thereof for Preparation of 3-(Heteroaryl)oxazolidine-2-ones

An appropriate heteroarylchloride or heteroarylbromide (e.g. pyridyl, pyrimidyl, thienyl, thiazolyl, or thiadiazolyl halide; 5 mmol) is added to the solution of 5-(S)-azidomethyloxazolidine-2-one (ca. 5 mmol) in dry N,N-dimethylformamide (ca. 30-50 mL) at 0-20 °C (typically, at 10 -15 °C), followed by addition of a strong base (typically, sodium hydride, 5-15 mmol). The mixture is stirred at 20-120 °C for 2-24 h (typically, for 6 h at r.t.). Excess base is carefully quenched with acetic acid (to pH ca. 5-7), and most of the solvent is removed under vacuum. Water is added, and the mixture extracted with ethyl acetate. Combined organic layers are washed with water, 3% aq. citric acid, water, and the crude product purified by crystallization from appropriate solvents or by silica gel chromatography. Resulted 5-(S)-azidomethyl-3-(hetero-aryl)oxazolidine-2-ones are immobilized on BAL resin just as described above for the synthesis of BAL resin immobilized 5-(S)-aminomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]oxazolidine-2-one, and the polymeric reagents thus obtained are used for synthesis of 3-

(heteroaryl)oxazolidine-2-ones analogously to described above procedures for the synthesis of respective 3-(fluorophenyl)oxazolidinones.

5-(S)-Azidomethyl-3-[5'-methoxycarbonyl-6'-trifluoromethylpyrimidine-2'-yl]oxazolidine-2-one

The compound is prepared according to above protocol for the synthesis of 5-(S)-azidomethyl-3-heteroaryloxazolidine-2-ones from 2-chloro-5-methoxycarbonyl-6-trifluoromethylpyrimidine (1 mmol) and 5-(S)-azidomethyloxazolidine-2-one (1.2 mmol) in N,N-dimethylformamide (5 mL). The reaction is performed with 60% sodium hydride in oil (3 mmol) at 15-20 °C for ca. 2 h. The crude product is purified by silica gel chromatography.

5-(S)-Azidomethyl-3-[5'-carboxy-6'-trifluoromethylpyrimidine-2'-yl]oxazoli-dine-2-one

0.2 M Lithium or sodium hydroxide in a mixture of tetrahydrofuran - water (ca. 10 mL, 2 mmol) is added to 5-(S)-azidomethyl-3-[5'-methoxycarbonyl-6'-trifluoromethylpyrimidine-2'-yl]oxazolidine-2-one (1 mmol), and the mixture stirred at r.t. until the reaction is completed (by TLC analysis). Tetrahydrofuran is removed under vacuum, 3% aq. citric acid is added (to pH ca. 2-4), and the acid product is extracted with ethyl acetate. Organic layers are washed with water, brine, and dried ($MgSO_4$). Solvent removed under vacuum and the crude product is purified by silica gel chromatography.

BAL Resin Immmobilized 5-(S)-Aminomethyl-3-[5'-carboxy-6'-trifluoromethylpyrimidine-2'-yl]oxazolidine-2-one and Its Application Its Preparation of 3-(Pyrimidyl)oxazolidine-2-ones.

Triphenylphosphine (3 mmol) is added to a mixture of BAL aldehyde resin (0.3 mmol) and 5-(S)-azidomethyl-3-[5'-hydroxy-6'-trifluoromethylpyrimidine-2'-yl]oxazolidine-2-one (3 mmol) in tetrahydrofuran (10 mL) with bis(trimethylsilyl)acetamide (ca. 6 mmol) under nitrogen at r.t.. The mixture is agitated at room temperature for 2 h and then at 75 °C for 16 h. The mixture is cooled to room temperature, and 1M sodium cyanoborohydride in THF (6 mL, 6 mmol) is added in one portion. The reaction mixture is agitated for 6-8 h, resulted amine resin filtered, washed liberally with methanol and dichloromethane, and dried under vacuum. BAL resin immmobilized 5-(S)-aminomethyl-3-[5'-carboxy-6'-trifluoromethylpyrimidine-2'-

yl]oxazolidine-2-one thus obtained is further used for synthesis of 3-(pyrimidyl)oxazolidine-2-ones just as described above for the synthesis of respective 3-(fluorophenyl)oxazolidinones from BAL resin immobilized 5-(S)-aminomethyl-3-[4'-carboxy-3'-fluorophenyl]-oxazolidine-2-one.

3-(Pyridine-2-yl)oxazolidinone Derivatives

t-Butyl 6-chloronicotinate.

Thionyl chloride (25 mL) was added to 6-chloronicotinic acid (5.00 g, 0.0317 mol) containing 1 drop of N,N-dimethylformamide, and the mixture heated under reflux for 2 h. The solution was evaporated under vacuum, and residue thoroughly dried under vacuum. The acid chloride thus obtained was dissolved in tetrahydrofuran (50 mL), and 1 M lithium t-butoxide in tetrahydrofuran (66.6 mL, 0.0666 mol) added dropwise at r.t. The mixture was stirred overnight, diluted with water (100 mL) and extracted with ethyl acetate. The extract was washed with sat. aqueous $NaHCO_3$, brine and dried ($MgSO_4$). Solvent was removed under vacuum to afford the pure ester as an off white solid. Yield 6.23 g (92%). ^1H NMR. MS (m/z): 214 $[M+H]^+$.

3-(t-Butoxycarbonyl)-6-[(R)-propane-1,2-diol-3-yl]aminopyridine

A mixture of t-butyl 6-chloronicotinate (4.69 g, 0.0220 mol) and (R)-3-amino-1,2-propanediol (5.00g, 0.0549 mol) in isopropanol (20 ml) was heated at 100 °C overnight. Solvent was removed under vacuum, and the residue taken up in ethyl acetate, washed with water, brine, dried ($MgSO_4$), and evaporated to give nearly pure product as a yellow oil. Yield 5.90 g (99%). ^1H NMR. MS: 269 $[M+H]^+$.

5-(R)-Hydroxymethyl-3-[3"-(t-butoxycarbonyl)pyridine-6"-yl]oxazolidine-2-one

Triethylamine (0.0518 mL, 0.558 mmol) was added to a solution of 3-(t-butoxy-carbonyl)-6-[(R)-propane-1,2-diol-3-yl]aminopyridine (0.100 g, 0.372 mmol) in dichloromethane (3 mL). The mixture was cooled in an ice bath, and 20% phosgene in toluene (0.236 mL, 0.446 mmol) was added dropwise with stirring. The reaction was allowed to warm to r.t. and stirred for at r.t. for 2 h. Water (3 mL) was added, and the organic layer separated, washed with brine and dried ($MgSO_4$). Evaporation under vacuum afforded a white solid residue which was purified by flash column chromatography (eluent: ethyl acetate - hexanes 1:1). Yield 0.093 g (85%). ^1H NMR. MS (m/z): 295 $[M+H]^+$.

5-(S)-Azidomethyl-3-[3"-(t-butoxycarbonyl)pyridine-6"-yl]oxazolidine-2-one

Methanesulfonyl chloride (1.38 mL, 0.0179 mol) was added dropwise with stirring to a solution of 5-(R)-hydroxymethyl-3-[3'-(t-butoxycarbonyl)pyridine-6"-yl]oxazolidine-2-one (5.00 g, 0.0170 mol) and triethylamine (3.55 mL, 0.0255 mol) in dichloromethane (50 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and then poured into water. The organic layer was separated, washed with water, sat. aq. $NaHCO_3$, brine, and dried ($MgSO_4$). Solvent was removed under vacuum to afford the mesylate intermediate. The intermediate thus obtained was heated with sodium azide (5.53 g, 0.085 mol) in N,N-dimethylformamide (ca. 40 mL) at 65 °C for 12 h. The reaction mixture was diluted with water (ca. 100 mL) and extracted with ethyl acetate. Organic layers was washed with water and brine, and dried ($MgSO_4$). The solvent was removed under vacuum and the residue purified by column chromatography (ethyl acetate - hexanes) to afford the pure product. Rt 5.0 min. ^{1}H NMR. MS (m/z): 320 [M+H]+.

5-(S)-(N-Acylaminomethyl)-3-[3"-[(un)substituted amino]carbonylpyridine-6"-yl]oxazolidine-2-ones

5-(S)-Azidomethyl-3-[3'-(t-butoxycarbonyl)pyridine-6"-yl]oxazolidine-2-one is immobilized on BAL-type resin with triphenylphosphine and soodium cyanoborohydride as described above for preparation of BAL resin immobilized 5-(S)-aminomethyl-3-[4'-*tert*-butoxycarbonyl-3'-fluorophenyl]-oxazolidine-2-one. The polymeric reagent thus obtained is deprotected as described for the preparation of BAL resin immobilized 5-(S)-aminomethyl-3-[4'-carboxy-3'-fluorophenyl]oxazolidine-2-one, and resulting BAL resin immobilized 5-(S)-(N-acylaminomethyl)-3-(3"-carboxypyridine-6"-yl)oxazolidine-2-one employed for the synthesis of 5-(S)-(N-acylaminomethyl)-3-[3"-[(un)substituted amino]carbonylpyridine-6"-yl]-oxazolidine-2-ones analogously to the Method A of the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-[(un)substituted amino]-carbonyl-3'-fluorophenyl]oxazolidine-2-ones 7.

BAL Resin Immobilized 5-(S)-(N-Acylaminomethyl)-3-[3"-(9"'-fluorenylmethoxycarbonyl)amino]pyridine-6"-yl]oxazolidine-2-ones and Application Thereof for Preparation of 3-(Pyridyl)oxazolidinones

The compound prepared from BAL resin immobilized 5-(S)-(N-acylaminomethyl)-3-(3"-carboxypyridine-6"-yl)oxazolidine-2-on as described above in the procedure for preparation of BAL resin immobilized 5-(S)-acetamidomethyl-3-[4'-(9"-

fluorenylmethoxycarbonyl)amino-3'-fluorophe-nyl]oxazolidine-2-one. The polymeric reagent thus obtained is further employed, e.g., for synthesis of respective 3"-acylated and 3"-sulfonylated 3-(pyridyl)oxazolidinones just as described above in the General Procedures for Preparation of 5-(S)-(N-Acylaminomethyl)-3-[4'-acylamino-3'-fluorophenyl]-oxazolidine-2-ones 5-(S)-(N-Acylaminomethyl)-3-[4'-sulfonamido-3'-fluoro-phenyl]oxazolidine-2-ones [except that resulting products incorporate 3-(pyridyl)oxazolidinone group instead of 3-(fluorophenyl)oxazolidinone group].

Preparation of immobilized epoxide (**12a**). To PNP resin (**23a**) (0.5 g, 0.77 mmol/g loading) at room temperature was added allylamine (125 μL, 1.67 mmol) in 2mL of DMF. The resin was shaken overnight and then filtered. It was sequentially washed with DMF and DCM. After being dried *in vacuo*, the olefin resin (**24a**, 100 mg) was treated with *m*CPBA (80%, 72 mg, 0.355 mmol) in DCM for 16 hrs. The reaction mixture was filtered, and the resin was washed with DCM. Epoxide resin **12a** was provided upon drying *in vacuo*. See Figure 25.

General method for the reaction of immobilized epoxide 5 with an amine. To epoxide resin **12a** at room temperature was added lithium triflate (LiOTf, 5 equivalents) and the amine (1 M in ACN, 10 equivalents). The mixture was shaken at room temperature for 15 hours, providing resin bound amino alcohol. The resin was filtered and sequentially washed with ACN and DMF. Treatment of the resin with TFA in DCM cleaved the amino alcohol. The reaction mixture was filtered and the resin washed with DCM. Concentration of the filtrate *in vacuo* provided the free amino alcohol.

Amino Alcohol Library. To an array of individual reaction chambers each containing particles or beads of epoxide resin **12a** (25 mg) in ACN was added lithium triflate and an amine unit (0.5 mmol). The amine units of Table 2 were used. The array was shaken at room temperature for 15 hours, filtered and sequentially washed with ACN and DMF. The amino alcohol resin was cleaved upon treatment with TFA. The resin was filtered and washed with DCM. A plurality of amino alcohols was provided upon concentration of the filtrate array *in vacuo*.

General method for the preparation of oxazolidinones. To the resin bound amino alcohol **8a** in DMF at room temperature was added N-methylmorpholine (NMM, 10 equivalents) and carbonyldiimidazole (CDI, 5 equivalents). The resin was shaken for 10

hrs, filtered and sequentially washed with DMF and DCM. Treatment of the resin with TFA in DCM for 0.5 hr cleaved the oxazolidinone. The resin was filtered and washed with DCM. The filtrate was concentrated *in vacuo* to yield an oxazolidinone amine residue **16a**. Semi-preparative HPLC provided pure oxazolidinone amine.

Acetylation of Oxazolidinone Amine. To the crude oxazolidinone amine residue **16a** in DCM at room temperature was added pyridine (30 equivalents) and acetic anhydride (20 equivalents). The solution was stirred for 2 hrs and concentrated *in vacuo*. The oxazolidinone acetamide residue was purified by HPLC to provide pure oxazolidinone acetamide.

Oxazolidinone Library. To an array of individual reaction chambers each containing particles or beads of epoxide resin **12a** (25 mg) in CAN was added lithium triflate and an amine unit (0.5 mmol). The amine units of Table 2 were used. The array was shaken at room temperature for 15 hours, filtered and sequentially washed with CAN and DMF. To the array of amino alcohol resin was added NMM (10 equivalents) and CDI (5 equivalents). The array was shaken at room temperature for 10 hours, filtered and sequentially washed with DMF and DCM. The oxazolidinone resin was cleaved upon treatment with TFA. The resin was filtered and washed with DCM. The filtrate array was concentrated *in vacuo* and dissolved in DCM, and treated with pyridine (20 equivalents) and acetic anhydride (10 equivalents) for 30 min. A plurality of oxazolidinones was provided upon concentration of the solution array *in vacuo*.

Preparation of N-[(3-phenyl-2-oxo-5-oxazolidinyl)methyl]acetamide (**22a**).

To epoxide resin **12a** (100 mg) in ACN at room temperature was added LiOTf (50 mg, 0.32 mmol) followed by aniline (61 μL, 0.66 mmol). After 16 hrs, the mixture was filtered and the resin sequentially washed with ACN and DMF. The resin (50 mg) in DMF (0.5 mL) was treated with CDI (27 mg, 0.17 mmol) and NMM (50 μL) to provide resin bound oxazolidinone **20a**. The mixure was allowed to stand for 2 hours, after which the resin was filtered and sequentially washed with DMF and DCM. The resin was treated with TFA (90% in DCM, 1 mL) for 1h, filtered and washed with DCM. The filtrate was concentrated *in vacuo* to provide a residue (**21a**). The residue was treated for 1 h at 0 °C with triethylamine (18 μL, 0.13 mmol) and acetyl chloride (10 μL, 0.13 mmol). *In vacuo*

concentration of the reaction mixture provided crude product, which was purified by semi-preparative HPLC to give oxazolidinone **22a** (3.6 mg).

Direct preparation of oxazolidinone **20a**.

To a solution of N-phenyl O-benzyl carbamate (152 mg, 0.67 mmol) in THF (2 mL) at -78 °C was added n-butyl lithium (1.5 M, 0.6 mL, 0.9 mmol). After stirring for 10 min, epoxide resin **12a** (100 mg) was added to the reaction mixture. The mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution was added to the reaction mixture. The resin was filtered and sequentially washed with water, DMF and DCM. A portion of the resin was treated with TFA (90% in DCM, 1 mL) to cleave the oxazolidinone, which was isolated upon *in vacuo* concentration.

Preparation of N-[(3-(4-bromophenyl)-2-oxo-5-oxazolidinyl)methyl]-acetamide.

To epoxide resin **12a** (300 mg) in ACN (2 mL) at room temperature was added LiOTf (219 mg, 1.41 mmol) followed by 4-bromoaniline (0.5 g, 2.9 mmol). The reaction mixture allowed to stand overnight. The resin was then filtered, washed sequentially with ACN, DMF and DCM and dried *in vacuo*. The resin (230 mg) was suspended in DMF (2 mL) at room temperature and treated with CDI (125 mg, 0.77 mmol) and NMM (84 μL, 0.77 mmol). After shaking overnight, the resin was filtered and sequentially washed with DMF and DCM. To a portion of the resin (20 mg) was added TFA (50% in DCM, 1 mL) at room temperature and the resulting mixture was stirred for 30 min. The resin was filtered and washed with DCM. The filtrate was concentrated *in vacuo* to provide a residue. Acetic anhydride (0.1 mL) and pyridine (0.1 mL) were added to the residue in DCM (2 mL). The mixture was concentrated and purified by semi-preparative HPLC to give N-[(3-(4-bromophenyl)-2-oxo-5-oxazolidinyl)methyl]-acetamide (2 mg, 41% theoretical yield). ^{1}H NMR.

Preparation of N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]-methyl]acetamide (**28a**).

To epoxide resin **5a** (100 mg) in ACN (1.0 mL) at room temperature was added LiOTf (78 mg, 0.5 mmol) followed by 3-fluoro-4-morpholinylaniline (197 mg, 1.0 mmol). The reaction mixture was allowed to stir overnight. The resin was then filtered, sequentially washed with ACN, DMF and DCM and dried *in vacuo*. A portion of the resin (**25a**) was suspended in DMF (0.8 mL) and treated with CDI (60 mg, 0.38 mmol) and

NMM (100 μL, 0.91 mmol). After shaking overnight, the resin was filtered and washed sequentially with DMF and DCM. To a portion of the resin (**26a,** 48 mg) was added TFA (90% in DCM, 1 mL) and the resulting mixture was allowed to stand for 1 h. The resin was filtered and washed with DCM. The filtrate was concentrated *in vacuo* to provide a residue. Acetyl chloride (12 μL, 0.17 mmol) and triethylamine (37 μL, 0.268 mmol) were added to the residue in DCM (2 mL) at 0 °C. The mixture was concentrated and purified by semi-preparative HPLC to give N-[[(3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide **28a** (1.8 mg, 15% theoretical yield). ^{1}H NMR.

Preparation of N-[[3-(4-fluoro-2-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide. To epoxide resin **12a** (50 mg) in methanol (0.5 mL) was added 4-fluoro-2-morpholinylaniline (50 mg, 0.255 mmol). The reaction mixture was heated to 60 °C overnight and then allowed to cool to room temperature. The resin was filtered, sequentially washed with methanol and DCM and dried *in vacuo*. To the resin in DMF (0.5 mL) was added CDI (25 mg, 0.15 mmol) and NMM (50 μL, 0.45 mmol). The reaction mixture was shaken for 4 hrs. The mixture was filtered, and the resin was sequentially washed with DMF and DCM. A portion of the resin (19 mg) was treated with TFA (90% in DCM, 1 mL) for 1h. The reaction mixture was filtered, and the resin was washed with DCM. The filtrate was concentrated to provide a residue. The residue was dissolved in DCM (2 mL) and treated with pyridine (100 μL) and acetic anhydride (100 μL) at room temperature for 1 h. The mixture was concentrated in vacuo and purified by semi-preparative HPLC to give N-[[3-(4-fluoro-2-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (1.8 mg, 36% theoretical yield). ^{1}H NMR.

Attachment of Amine **32a** to a solid support. To dry Peg HS HCl resin (30 g, Perseptive Inc.) was added DIEA (30% in DCM, 150 mL). The mixture was stirred at room temperature for 30 min. The resin was filtered, sequentially washed with DCM, methanol and DCM and dried *in vacuo*. To 30 g. (18 mmol) of the resin in DMF (80 mL) were added Bal Linker **30a** (8.04 g, 1.7 eq., Perseptive Inc.), HATU (11.3 g, 1.6 eq.) and DIEA (18 mL, 3.5 eq.). The reaction mixture was allowed to stand overnight at room temperature. The mixture was filtered and the resin was sequentially washed with DMF, MeOH, DCM and TMOF. To the resin was added amine **32a** (18.2 g, 3 eq.) in 100 mL of TMOF. The mixture was stirred for 1 h, after which 50 mL of a $NaBH_3(CN)$-THF solution

(1 M) was added. The reaction mixture was stirred for 30 min., filtered and sequentially washed with methanol and DCM. *In vacuo* concentration of the filtrate afforded amine resin **33a**. Cleavage of a portion of the resin with TFA provided a 70% theoretical loading yield (0.6 mmol/g) of amine **32a**. ^{1}H NMR.

Preparation of amides derived from amine **33a**. To amine resin **33a** (25 mg) in DMF (1 mL) at room temperature was added a solution of carboxylic acid (0.5 mmol) and diisopropylcarbodiimide (0.25 mmol). After 16 hrs, the reaction mixture was filtered, and the resin **36a** was sequentially washed with DMF and DCM. The resin was treated with TFA (90% in DCM) to provide the free amide **37a**, which was obtained upon filtration and *in vacuo* concentration. HPLC and MS analysis of the amide residue showed that it was of greater than 80% purity.

Preparation of sulfonamides derived from amine **33a**.

To amine resin **33a** (25 mg) was added a solution of sulfonyl chloride (0.5 mmol) in DCM at room temperature. After standing for 16 hrs, the reaction mixture was filtered, and the resin was sequentially washed with DMF and DCM. The resin was treated with TFA (90% in DCM) to provide the free sulfonamide **35a**, which was obtained upon filtration and *in vacuo* concentration. HPLC and MS analysis of the amide residue showed that it was of greater than 80% purity.

Preparation of ureas derived from amine **33a**.

To amine resin **33a** (25 mg) was added a solution of isocyanate (0.5 mmol) in DCM at room temperature. After standing for 16 hrs, the reaction mixture was filtered, and the resin was sequentially washed with DMF and DCM. The resin was treated with TFA (90% in DCM) to provide the free urea **39a**, which was obtained upon filtration and *in vacuo* concentration. HPLC and MS analysis of the amide residue showed that it was of greater than 80% purity.

Preparation of phenylsulfide derivatives from amine **33a**.

To amine resin **33a** was added a solution of bromoacetic acid (3 eq.) and DIC (1.5 eq.) in DMF at room temperature. After 16 hrs, the reaction mixture was filtered to provide the bromoacetyl derivative **40a**. The resin was sequentially washed with DMF and DCM and dried *in vacuo*. To the resin (50 mg) in DMF was added potassium carbonate (50 mg) and thiophenol (0.5 mmol). The mixture was shaken overnight, filtered and

sequentially washed with DMF, water, DMF and DCM. The resin was treated with TFA (90% in DCM) to afford the sulfide (5.0 mg, 40% theoretical yield).

Method of Wittig Reaction from Acetyl Bromide **40a.**

To the bromoacetyl resin (40, 50 mg) in DMF (1mL) was added triphenylphosphine (10 equivalents). After 16 hrs at room temperature, the resin was washed with DMF, and treated with potassium carbonate (20 equivalents) and benzaldehyde (10 equivalents) for 16 hrs at room temperature. The resin was washed with DMF, water, DMF and DCM, and cleaved with TFA (50% in DCM) to give (S)-N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl] cinnamamide (44): ^{1}H NMR (300 MHz) 7.62 (d, J=15.6 Hz, 1H) , 7.54-7.33 (m, 6H), 7.09 (d, J= 8.8 Hz, 1H), 6.94 (t, J = 9.2 Hz, 1H,), 6.53 (d, J =15.6 Hz, 1H,), 4.87-4.82 (m, 1H), 4.08 (t, J=9.0 Hz, 1 H), 3.86 (t, J=4.2 Hz, 4 H), 3.84-3.63 (m, 3H), 3.05 (t, J=4.2 Hz, 4H); MS (m/z) 426 (M^++1).

Arylsulfide Library.

To an array of individual reaction chambers each containing particles or beads of bromoacetyl resin **40a** in DMF is added potassium carbonate and a thiol unit at room temperature. The thiol units designated in Table 1 are used. The array is shaken for 10 hrs, filtered and sequentially washed with DMF, water, DMF and DCM. The thio alcohol resin is cleaved upon treament with TFA. The resin is filtered and washed with DCM. A plurality of sulfides is provided upon concentration of the filtrate array *in vacuo*.

Preparation of an amide library derived from amine **33a.**

To an array of individual reaction chambers each containing particles or beads of amine resin **33a** in DMF was added a solution of a carboxylic acid unit and diisopropylcarbodiimide. The carboxylic acid units designated in Table 4 were used. The array was shaken at room temperature for 16 hrs, filtered and sequentially washed with DMF and DCM. The amide resin was cleaved upon treament with TFA. The resin was filtered and washed with DCM. A plurality of amides was provided upon concentration of the filtrate array *in vacuo*.

Preparation of a sulfonamide library derived from amine **33a.**

To an array of individual reaction chambers each containing particles or beads of amine resin 33 in DCM was added a solution of a sulfonyl chloride unit. The sulfonyl chloride units designated in Table 3 were used. The array was allowed to stand for 16 hrs.

It was then filtered and sequentially washed with DMF and DCM. The sulfonamide resin was cleaved upon treatment with TFA. The resin was filtered and washed with DCM. A plurality of sulfonamides was provided upon concentration of the filtrate array *in vacuo*.

Preparation of a urea library derived from amine **33a**.

To an array of individual reaction chambers each containing particles or beads of amine resin **33a** in DCM was added a solution of an isocyanate unit. The isocyanates of Table 3 were used. The array was allowed to stand for 16 hrs. It was then filtered and sequentially washed with DMF and DCM. The urea resin was cleaved upon treatment with TFA. The resin was filtered and washed with DCM. A plurality of ureas was provided upon concentration of the filtrate array *in vacuo*.

Preparation of an amide library using the amine units in Figure 30

To an array of individual reaction chambers each containing particles or beads of aldehyde functionalized resin **31a** is added an amine subunit in TMOF. The subunits listed in Figure 30 are used. The mixture is stirred for 1 h, after which a $NaBH_3(CN)$-THF solution is added. The reaction is stirred for 30 min., filtered and sequentially washed with methanol and DCM. *In vacuo* concentration of the filtrate affords the respective amine resins. The respective amine resin is placed in an array of individual reaction chambers. To the individual reaction chambers is added a solution of a carboxylic acid unit and diisopropylcarbo-diimide. The carboxylic acid units designated in Table 4 are used. The array is shaken at room temperature for 16 hrs, filtered and sequentially washed with DMF and DCM. The amide resin is cleaved upon treatment with TFA. The resin is filtered and washed with DCM. A plurality of amides is provided upon concentration of the filtrate array *in vacuo*.

Preparation of an amide library using the amine units in Figures 29, 30, and 31

To epoxide resin **7a** (X = NH) in DMF is added a solution of a carboxylic acid unit and diisopropylcarbodiimide. The carboxylic acid units designated in Table 4 are used. After 3 hours, the resin is filtered, sequentially washed with DMF and DCM, and dried *in vacuo*. The respective resin is placed in an array of individual reaction chambers. To the resin in CAN in the individual reaction chambers is added LiOTf followed by an amine unit. The amine units shown in Figures 29, 30, and 31 are used. The array is shaken at room temperature for 15 hours, filtered and sequentially washed with CAN and DMF. To

the array of amino alcohol resins is added NMM (10 equivalents) and CDI (5 equivalents). The array is shaken at room temperature for 10 hours, filtered and sequentially washed with DMF and DCM. The oxazolidinone resin is cleaved upon treatment with TFA. The resin is filtered and washed with DCM. A plurality of oxazolidinones is provided upon concentration of the solution array *in vacuo*. (The amines of Figures 29, 30, and 31 can be made according to procedures described in the following publications: U.S. Pat. No. 4,948,801; U.S. Pat. No. 4,705,799; U.S. Pat. No. 5,164,510; U.S. Pat. No. 4,975,538; U.S. Pat. No. 5,225,565; U.S. Pat. No. 5,182,403; U.S. Pat. No. 5,247,090; U.S. Pat. No. 5,231,188; U.S. Pat. No. 4,461,773; EP 0 785 201 A1; WO 97/19089; DE 196 01 265 A1; WO 97/27188; EP 0 789 026 A1; DE 196 01 264 A1; DE 196 04 223 A1; WO 97/30995; WO 97/09328; Van Delft *et al.* (1997) *Synthesis* 450-454; Wang *et al.* (1989) *Tetrahedron* 45:1323-1326; and Denis *et al.* (1994) Bioorg. & Med. Chem. Lett. 4:1925-1930; which are hereby incorporated by reference.)

Assay Protocol for β-Lactamase Inhibition. The lactamase (20-120 ng/mL) was incubated with a potential inhibitor with 1% DMSO in 50 mM potassium phosphate buffer, pH 7.0, with 0.005% Brij-35 for 30 min at room temperature. 100 μM of nitrocefin was then added to the reaction mixture and the hydrolysis of the nitrocefin was monitored by measuring the absorption increase at 490 nm. Inhibition of the potential compounds was calculated by comparing the rate of absorption increase with the control sample which containing the identical mixture except inhibitors. The IC_{50}, was obtained by fitting the inhibition data into a standard 2-parameter IC_{50} equation with a non-linear least-square fitting program (DeltaGraph).

Assay Protocol for Antimicrobial Activity. Minimum inhibitory concentrations (MICs) were determined using the microdilution method in 96-well format plates. Compounds were suspended in DMSO at 5 or 10 mg/ml and stored at 4°C until used. They were diluted in Mueller-Hinton Broth (MHB) or Trypticase Soy Broth (TSB) and used for MIC determination. The range of concentrations tested was 64-0.0625 μg/ml final concentration using a two-fold dilution system.

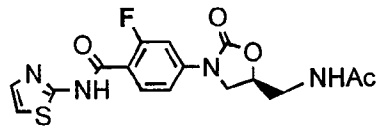
The inoculum was prepared from cells grown on Trypticase Soy Agar (TSA) and incubated overnight at 35 °C, 5 to 10 colonies were used to inoculate MHB or TSB broths,

and the culture was incubated overnight at 35°C. The overnight culture was diluted 1:10, incubated for one hour at 35°C, diluted to the appropriate inoculum size and applied to the wells containing broth and test compound. Inoculum sizes were $1x10^5$ to $5x10^5$ CFU/ml. Strains used included *P. aeruginosa* VPAE1001, E. *faecium V* VEFA1001, *E. faecium* VanA VEFA1002, *S. aureus* VSAU1003, *S. aureus* MRSA VSAU1004, *E. coli* VEC05, and *E. coli* (arc-) VEC05.

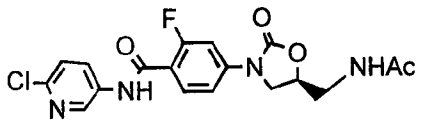
Plates were incubated at 35°C for 48 hours and MIC were recorded after 18 hours of incubation, for bacteria, and 48 for yeasts. MIC was defined as the lowest concentration of compound that does not produce visible growth after incubation.

Antimicrobial Activity for Representative Compounds in Animals

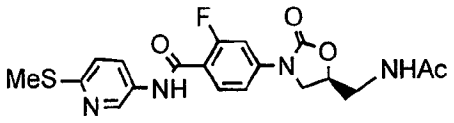
In vivo data was obtained for representative compounds **i**, **ii**, and **iii** to demonstrate the practical utility of the oxazolidinone compounds for treatment of a bacterial infection in animals.



i



ii



iii

CD1 female mice (Charles River Laboratories) weighing 18-22 grams were injected intraperitoneally with 0.2 ml of a suspension containing 3 * 10^7 cfu of *S. aureus* (Smith strain) in 7% hog gastric mucosa (mucin). The mice were treated, either intravenously (i.v.) or orally (p.o.), 1 h and 5 h after infection. Five groups of six mice each were given different dosage levels representing two-fold dilutions of each compound (range of 25 mg/kg - 1.56 mg/kg). The compounds were all formulated in 40% aqueous hydroxypropyl-beta-cyclodextrin in PBS and untreated controls were dosed with vehicle alone.

Mortality in each group was monitored daily for 6 days and cumulative mortality was used to determine the 50% protective doses (PD_{50}) which were calculated using the method of Reed and Muench [(a) Lorian, V. Antibiotics in laboratory medicine. Baltimore: Williams & Wilkins. 1996, p. 635-636; (b) Reed, L. J.; Muench H. A simple method of estimating fifty percent endpoints. Am. J. Hyg. 1938, 27, pp. 493-497] (Table 1). For animals receiving vehicle alone, there was a 79% mortality rate (19/24) in the p.o. dosing group and an 88% mortality rate (15/17) in the i.v. group; giving a total mortality rate for untreated controls of 83%.

PD_{50} for above compounds was in a range 2.3-7.2 mg/kg for i.v. administration and 7.5-14.9 mg/kg for p.o. administration, with compound iii being the most preferred.

Table 1: Thiols

2-mercaptobenzothiazole
2-mercapto-4-methylpyrimidine HCl
2-mercaptothiazoline
2-mercaptopyridine
2-mercapto-(3H)-quinazoline
2-mercapto-1-methyl imidazole
5-(methylthio)-1,3,4-thiodiazole-2-thiol
2-mercapto-6-thien-2-yl-4-(trifluoromethyl)pyridine-3-carbonitrile
thiazolo[4,5-b]pyridine-2-thiol
4-(4-methoxyphenyl)pyrimidine-2-thiol
2-mercapto-3-(trifluoromethyl)pyridine
4,6-dimethyl-2-mercaptopyridine-3-carbonitrile
4-trifluoromethylpyrimidine-2-thiol
ethyl 3-cyano-2-mercapto-6-methylpyridine-4-carboxylate
2-mercapto-5-(trifluoromethyl)pyridine
5-chloro-2-mercaptobenzothiazole
4-methyl-4H-1,2,4-triazole-3-thiol
2,4,6-trimethylbenzylmercaptan
2-quinolinethiol
8-quinolinethiol HCl
3-chloro-5-(trifluoromethyl)pyridine-2-thiol
7-trifluoromethyl-4-quindine-thiol
2,4,6,-trichlorobenzenethiol
5-[3-(trifluoromethyl)benzylthio]-1,3,4-thiadiazole-2-thiol
4-(4-chlorophenyl)pyrimidine
thiomalic acid

2,6-dichlorobenzenethiol
4-hydroxythiophenol
5-(4,5-dichloroimidazole)
3-mercaptopropionic acid
3,4-dichlorobenzenethiol
2,6,-dichlorobenzenethiol
2-methoxybenzenethiol
2-bromothiophenol
4-fluorothiophenol
4-bromo-2-(trifluoromethoxy)benzenethiol
3-(trifluoromethyl)benzenethiol
thiolactic acid
3,4-dimethoxybenzenethiol
4-methoxybenezenethiol
2-(trifluoromethyl)benzenethiol
4-(trifluoromethoxy)benzylthiol

Table 2: Amines

4-iodoaniline
2-iodoaniline
4-phenoxyaniline
3-trifluoromethylamine
m-anisidine
o-anisidine
2-trifluoromethylaniline
3-chloroaniline
1,4-benzodioxane-6-amine
5-aminoindan
3,4-(methylenedioxy)-aniline
3-phenoxyaniline
4-morpholinoaniline
4-amino-1-benzyl-piperidine
2-Bromoanaline
3-fluoroanaline
4-trifluoromethoxyaniline
4-methylymercaptoaniline
3-bromoaniline
2-fluoroaniline
4-fluoroaniline
2,4-difluoroaniline
3,4-difluoroaniline
2,5-difluoroaniline
1-amino-5,6,7,8,-tetrahydronapthalene
3,5-difluoroaniline
3-fluorobenzylamine

4-fluorobenzylamine
4-aminoacetophenone
4-aminobenzophenone
3-benzyloxyaniline
1-(3-aminopropyl)imidazole
4-(2-aminoethyl)-morpholine
m-phenetidine
3-chloro-4-fluoroaniline
2-bromo-5-(trifluoromethyl)aniline
2-amino-3-benzyloxypyridine
2'-aminoacetophenone
4-aminobenzoic acid
4-aminobiphenyl
3'-aminocetophenone
4-(3'-aminopropyl)morpholine
aminopyrazine
2-aminopyridine
3-aminopyridine
4-aminopyridine
6-aminoquinoline
8-aminoquinoline
4-aminoveratrole
4-bromo-2,6-difluoroaniline
4-bromo-2-fluoroaniline
4-bromo-3-(trifluoromethyl)aniline
4-bromo-3-methylaniline
2-bromo-4-fluoroaniline
2-bromo-4-methylaniline
3-bromo-4-methylaniline
4-butoxyaniline
3-fluoro-4-methylaniline
4-aminoquinaldine
2-chloro-4,6-dimethylaniline
2-chloro-4-aminotoluene
2-chloro-4-fluoroaniline
4-chloroaniline
2,4-dibromo-6-fluoroaniline
2,4-dibromoaniline
2,5-dibromoaniline
2,4-dichloroaniline
2,5-dichloroaniline
3,4-dichloroaniline
3,5-dichloroaniline
2,3-difluoroaniline
N,N-dimethy-1,4-phenylenediamine
5-fluoro-2-methylaniline

2-fluoro-4-iodoaniline
5-amino-2-methoxpyridine
2-methylmercapto)-aniline
sulfanilamide
sulfisomidine
p-bromoaniline
2-(4-aminophenyl)-6-methylbenzothiazole
4-amino-4'-nitrodiphenyl sulfide
3-aminophenol
4-aminophenol
4'-aminoacetanilide
3-aminobenzyl alcohol
4-aminophenethyl alcohol
2-aminoanthraquinone
6-aminonicotinamide
2-amino--6-fluorobenzothiazole
2-amino-5-(4-nitrophenylsulfone)thiazole
2-amino-4-methoxybenzothiazole
2-amino-4-chlorobenzothiazole
2-amino-5-bromothiazole HBr
2-aminothiazole
2-aminobenzothiazole
2-amino-6-methoxybenzothiazole
2-amino-6-nitrobenzothiazole
2-amino-4-methylbenzothiazole
2-amino-4-(4-chlorophenyl)thiazole
2-amino-5,6-dimethylbenzothiazole
2-amino-6-methylbenzothiazole
2-amino-6-chlorobenzothiazole
2-amino-6-ethoxybenzothiazole
2-amino-5-nitrothiazole
2-amino-5-(ethylthio)-1,3,4-thiadiazole
methyl 3-amino-2-thiophene carboxylate
N-[4-(4-aminobenzyl)phenyl)]-5-norbornene-2,3-dicarboximide
2-amino-4-pheylthiazole HBr
2-amino-3,5-dichloropyridine
2-amino-5-bromo-pyridine
2-amino-4-picoline
5-amino-2-chloropyridine
2-amino-4,6-dimethylpyridine
2-amino-5-chloropyridine
2-amino-2-chloropyridine
2-amino-5-picoline
2-amino-6-picoline
9-aminoacridine
5-aminoisoquinoline

3-aminoquinoline
2-amino-4,6-dimethylpyrimidine
1-aminoisoquinoline
5-aminoquinoline
2-amino-4,6-dichloropyrimididine
3-amino-5,6-dimethyl-1,2,4-triazine
2-amino-4-chloro-6-methylpyrimidine
2-amino-4-methylpyrimidine
5-amino-3-methylisothiazole
2-amino-5-bromopyrimidine
2-amino-4,6-dimethoxypyrimidine
2-amino-4-methoxy-6-pyrimidine
4-amino-6-chloro-2-(methylthio)pyrimidine
2-amino-5-chlorobenzoxazole
2-amino-5-trifluoromethyl-1,3,4-thiadizole
3-amino-5-methylisoxazole
4-amino-2,1,3-benzothiadiazole
2-amino-1,3,4-thiadiazole
3-amino-1-phenyl-2-pyrazolin-5-one
6-amino-1,3-dimethyluracil
4-amino-1,2-naphthoquinone hemihydrate
3-amino-1-(2,4,6-trichlorophenyl)-2-pyrazolin-5-one
1-(2-aminophenyl)pyrrole
N-(4-amino-2-methylphenyl)-4-chlorophthalimide
2-amino-3-chloro-5-(trifluoromethyl)pyridine
2-amino-3-picoline
2-amino-4-methyl-5-nitropyridine
2-amino-4-methylthiazole
2-amino-5-ethyl-1,3,4-thiadiazole
2-aminopyrimidine
3-aminocrotononitrile
3-amino-1,2,4-trizole
3-aminopyrazole
4-amino-2,3,5,6-tetrafluoropyridine
4-aminopyrimidine
5-amino-1-ethylpyrazole
5-amino-1-phenyl-4-pyrazolecarboxamide
5-amino-3-methylisoxazole
5-aminouracile

Table 3: Sulfonyl chlorides and Isocyanates

p-toluenesulfonyl chloride
2,4-dichlorobenzenesulfonyl chloride
2-thiophenesulfonyl chloride
styrenesulfonyl chloride

2-methoxycarbonylphenyl isocyanate
4-acetylphenyl isocyanate
cyclohexyl isocyanate
p-tolyl isocyanate

Table 4: Carboxylic acids

pyruvic acid
p-toluic acid
o-tolylacetic acid
phenylacetic acid
trans-2-pentenoic acid
methylthio acetic acid
4-methoxycinnamic acid
nonanoic acid
3-methoxypropionic acid
4-methoxycyclohexanecarboxylic acid
phenylpropiolic acid
1-naphthylacetic acid
pentafluoropropionic acid
piperonylic acid
N-(2-furoyl)glycine
propionic acid
2,3,4,5,6-pentafluorophenylacetic acid
4-pentenoic acid
octanoic acid
3-methoxyphenylacetic acid
4-methylcinnamic acid
methacrylic acid
p-(dimethylamino)cinnamic acid
phenylpyruvic acid
nicotinic acid
2-methylcinnamic acid
methoxyacetic acid
phenoxybenzoic acid
phenoxyacetic acid
cyclopropanecarboxylic acid
glycolic acid
trans-3-hexenoic acid
4- (trifluoromethyl)mandelic acid
2-(2-methoxyethoxy)acetic acid
diphenylacetic acid
2-bromo-4,5-dimethoxycinnamic acid
3,4-dihydroxyhydrocinnamic acid
3-methoxycinnamic acid
4-chlorophenoxyacetic acid

4-(4-nitrophenyl)butyric acid
3-(4-chlorobenzoyl)propionic acid
2- (4-hydroxyphenoxy)propionic acid
2-chlorocinnamic acid
2-biphenylcarboxylic acid
2-(4-chlorophenoxy)-2-methylpropionic acid
benzoylpropionic acid
3-(phenylthio)acrylic acid
3,5-di-tert-butyl-4-hydroxycinnamic acid
4-bromobutyric acid
4-bromomandelic acid
decanoic acid
4-hydroxycinnamic acid
2-nitrocinnamic acid
2,3,4-trifluorocinnamic acid
homovanillic acid
3-methoxycyclohexanecarboxylic acid
2-ethoxycinnamic acid
2,5-difluorophenylacetic acid
4-fluorocinnamic acid
2,6-difluorophenylacetic acid
3,3-diphenylpropionic acid
cis-pinonic acid
2-fluorobenzoic acid
cyanoacetic acid
1,2,3,4-tetrahydro-2-naphthoic acid
trans-2-phenyl-1-cyclopropanecarboxylic acid
4- (4-methoxyphenyl)butyric acid
2-formylphenoxyacetic acid
3- (4-fluorobenzoyl)propionic acid
difluoroacetic acid
3-chlorobenzo[b]thiophene-2-carboxylic acid
4-methoxybenzylidenecyanoacetic acid
1-adamantaneacetic acid
1-adamantanecarboxylic acid
1-fluorencarboxylic acid
(2-naphthoxy)acetic acid
1H-benzimidazole-5-carboxylic acid
2- (2,4,5-trichlorophenoxypropionic acid)
3-hydroxycinnamic acid
abietic acid
isoxazole-5-carboxylic acid
(4-chloro-o-tolyloxy)-butyric acid
3-pyridylacetic acid
alpha-methyl-2,4,5-trimethoxycinnamic acid
2-chlorophenylacetic acid

3-fluorophenylacetic acid
(S)-(+)-mandelic acid
2,4-difluorophenylacetic acid
butyric acid
4-methoxyphenylacetic acid
4-ethoxyphenylacetic acid
trans-2-hexenoic acid
3,4-dihydroxycinnamic acid
2,3-dichlorophenoxyacetic acid
S-benzylthioglycolic acid
3,4-(methylenedioxy)phenylacetic acid
(alpha, alpha,alpha-trifluoro-m-tolyl) acetic acid
3,4-difluorophenylacetic acid
2-furioic acid
4-acetylphenoxyacetic acid
4-(3,4-dimethoxyphenyl)butyric acid
cyclohexanepropionic acid
7-methoxy-2-bezofuran carboxylic acid
2- (triflouromethyl)cinnamic acid
2,4-dinitrophenylacetic acid
2,4-dichlorophenylacetic acid
2-nitrophenylpyruvic acid
iodoacetic acid
acetic acid
4- (2,4-dichlorophenoxy)-butyric acid
3-(3,4,5-trimethoxyphenyl)propionic acid
6-chloro-2H-1-benzopyran-3-carboxylic acid
4-acetamidocinnamic acid
3-hydroxyphenylacetic acid
2-chloro-6-fluorocinnamic acid
3-fluoro-4-hydroxyphenylacetic acid
4-fluorophenylacetic acid
trans-3-fluorocinnamic acid
3-bromocinnamic acid
2-pyridylacetic acid
alpha-fluorocinnamic acid
4-(2-cyclohexenyloxy)benzoic acid
1-naphthoic acid
2-bromophenylacetic acid
4-nitrocinnamic acid
2-propylpentanoic acid
3,4-dihydro-2,2-dimethyl-4-oxo-2h-pyran-6-carboxylic acid
3-(2-methoxyphenyl)propionic acid
2-fluorocinnamic acid
tiglic acid
(4-pyridylthio)acetic acid

4-hydroxyphenylacetic acid
4-bromophenylacetic acid
chloroacetic acid
chromone-2-carboxylic acid
4-bromocinnamic acid
alpha-phenyl-cinnamic acid
benzoylformic acid
dichloroacetic acid
3,5-dimethoxy-4-hydroxycinnamic acid
trans-4-(trifluoromethyl) cinnamic acid
cyclohexylacetic acid
cyclopentylpropionic acid
(-)-mentoxyacetic acid
alpha-fluorophenylacetic acid
3-(3,4-dimethoxyphenyl)propionic acid
3,4-dichlorocinnamic acid
4-fluorophenoxyacetic acid
thiophenoxyacetic acid
3,5-bis(trifluoromethyl)phenylacetic acid
(4-methylphenoxy)acetic acid
6-methylchromone-2-carboxylic acid
(3,4-dimethoxyphenyl)acetic acid
3-chlorophenylacetic acid
2,3,4,5,6-pentafluorocinnamic acid
3-indolepropionic acid
2-thiopheneacetic acid
6-bromocoumarin-3-carboxylic acid
4-pyridylacetic acid
alpha-methylhydrocinnamic acid
alpha-phenylcinnamic acid
cis-2-methoxycinnamic acid
4-phenylcinnamic acid
4-chloro-o-anisic acid
4-ethoxycinnamic acid
2-phenylpropionic acid
3,4-(methylenedioxy)cinnamic acid
1-phenyl-1-cyclopropanecarboxylic acid
3-cyanobenzoic acid
3,4,5-trimethoxyphenylacetic acid
(2-amino-thiazole-4-yl)acetic acid
2,3-dimethoxybenzoic acid
4-chorophenylacetic acid
bis(4-chlorophenoxy)acetic acid
tetrahydro-2-furoic acid
trans-styrylacetic acid
4-chlorocinnamic acid

alpha-methylcinnamic acid
alpha-cyanocinnamic acid
4-methylvaleric acid
4-pyrazolecarboxylic acid
2-fluorophenylacetic acid
3-(1-naphthyl)acrylic acid
3-bromophenylacetic acid
alpha-cyano-3-hydroxycinnamic acid
2-(3-chlorophenoxy)propionic acid
2,5-dimethylcinnamic acid
2,6-dichlorophenylacetic acid
3-phenoxypropionic acid
2,6-dichlorocinnamic acid
(2,5-dimethoxyphenyl)acetic acid
2,3,4-trimethoxycinnamic acid
2,3,4-trimethoxybenzoic acid
2-chlorobenzoic acid
3,4,5-trimethoxycinnamic acid
cyclobutanecarboxylic acid
cyclohexene-1-carboxylic acid
4-nitrophenylacetic acid
benzoylbutyric acid
3,5-dimethoxybenzoic acid
alpha-cyano-4-hydroxycinnamic acid
cyclopentanecarboxylic acid
5-(pyrid-2-yl)thiophene-2-carboxylic acid
bromoacetic acid
trans-4-hydroxy-3-methoxycinnamic acid
4-chloro-2-fluorocinnamic acid
2-octynoic acid
3-(p-tolyl)propionic acid
4-chlorobenzoic acid
2-methoxyphenylacetic acid
4-biphenylcarboxylic acid
2-chloro-4-fluorocinnamic acid
2-norbornameacetic acid
2-naphthylacetic acid
2-methyl-1-cyclohexanecarboxylic acid
(1-naphthoxy)acetic acid
2,5-dimethoxybenzoic acid
cyclopentylacetic acid
ethoxyacetic acid
cyclohexanebutyric acid
2-methylcyclopropane-carboxylic acid
4-methylcyclohexaneacetic acid
4-hydroxymandelic acid monhydrate

4-bromo-2-fluorocinnamic acid
lauric acid
2-bromovaleric acid
2,6-dimethoxybenzoic acid
trans-2,3-dimethoxycinnamic acid
3-(4-hydroxyphenyl)propionic acid
3-(4-methoxybenzoyl)-propionic acid
(alpha, alpha,alpha-tri-fluoro-p-tolyl)acetic acid
hydrocinnamic acid
3,4-difluorocinnamic acid
3,5-bis(trifluoromethyl)benzoic acid
(3,5-dimethoxyphenyl)acetic acid
9-anthracenecarboxylic acid
3-(trifluoromethyl)cinnamic acid
m-tolylacetic acid
4-formylcinnamic acid
3-furic acid
crotonic acid
alpha-acetamidocinnamic acid
alpha-phenylcyclopentaneacetic acid
diphenylacetic acid
4,5-dimethoxy-2-nitrocinnamic acid
4-(methylthio)phenylacetic acid
3,5-dimethoxycinnamic acid
3-nitrocinnamic acid
5-chlorobenzo[b]thiophene-3-acetic acid
3-methyl-2-phenylvaleric acid
3-(trifluorometoxy)cinnamic acid
4-biphenylacetic acid
3-bromo-4-fluorocinnamic acid
3-(2-hydroxyphenyl)propionic acid
2,4-difluorocinnamic acid
5-methoxy-1-indanone-3-acetic acid
alpha-methoxyphenylacetic acid
2-thiophenecarboxylic acid
3-(4-methoxyphenyl)propionic acid
4-acetoxy-3-methoxycinnamic acid
2-methoxycinnamic acid
3-benzoylbenzoic acid
levulinic acid
3,4-dichlorophenylacetic acid
3-methylindene-2-carboxylic acid
4-phenoxybutyric acid
2-hydroxycinnamic acid
2-ethoxy-1-naphthoic acid
2-chloro-5-nitrocinnamic acid

3,3-dimethylacrytic acid
4-pentynoic acid
4-acetoxycinnamic acid
2-(p-toluoyl)-benzoic acid
3,5-difluorocinnamic acid
2-ethoxybenzoic acid
trans-2-methyl-2-pentenoic acid
cycloheptanecarboxylic acid
tetrahydro-3-furoic acid
3,5-difluorophenylacetic acid
trans-2,6-difluorocinnamic acid
thioctic acid
5-bromo-2-fluorocinnamic acid
11-phenoxyundecanoic acid 2,4 -dichlorophenoxyacetic acid
2- (2,4-dichlorophenoxy)-propionic acid
2,2-dimethylbutyric acid
o-tolulic acid
2-bromo(4,5-(methylenedioxy)cinnamic acid
alpha-bromophenylacetic acid
trans-N-(2-furfurylideneacetyl)-glycine 3-chlorobenzoic acid
D-3-phenyllactic acid
2-phenoxybutyric acid
2- (4-chlorophenoxy)propionic acid
2-acetoxycinnamic acid
(R)-(-)-mandelic acid
(+-)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid
(+-)-2-(2-chlorophenoxyy)propionic acid
(+/-) 2-phenyoxypropionic acid
1-methyl-1-cyclohexanecarboxylic acid
2,5-dimethoxycinnamic acid
2-(2-aminothiazole-4-yl-2-methoxyiminoacetic acid
2-acetamidoacrylic acid

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those skilled in the art that certain changes and modifications may be practical. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

What is claimed is:

1. A method for the solid phase synthesis of oxazolidinones, comprising the steps of:

a) attaching an olefin to a solid support;

b) oxidizing the olefin to provide an epoxide functionality;

c) opening the epoxide with an amine to form an amino alcohol; and

d) cyclizing the amino alcohol using a phosgene equivalent.

2. The method according to claim 1, where the olefin is an allylic amine or allylamine.

3. The method according to claim 1, where the amine is an amino acid, or an aromatic amine.

4. A method for the synthesis of oxazolidinone combinatorial libraries, comprising the steps of:

a) attaching an olefin group to an array of solid supports;

b) oxidizing the individual olefin groups to provide an array of solid support bound epoxides; and

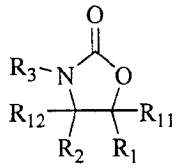
c) opening the epoxide with an amine to form an amino alcohol; and

d) cyclizing the amino alcohol using a phosgene equivalent.

5. The method according to claim 4, where the olefin is an allylic amine, or allylamine.

6. The method according to claim 4, where the amine units are amino acids or aromatic amines.

7. An oxazolidinone combinatorial library, where the oxazolidinones comprising the library are of the following structure:



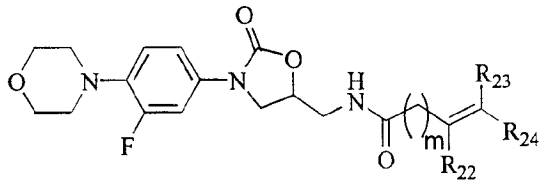
1a

where R_1 is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl, R_2 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, R_3 is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, R_{11} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, and R_{12} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl.

8. The combinatorial library according to claim 7, where R_3 is selected from the group consisting of aryl and heteroaryl, and further where the aryl and heteroaryl groups are the aryl and heteroaryl groups attached to the amines of Table 2 and Figures 29, 30, and 31.

9. The combinatorial library according to claim 7, where R_3 is a heteroaryl group selected from the group consisting of a pyridyl group, a thienylphenyl group, an oxazolyl group, a pyrrolyl group, and a morpholinofluorophenyl group.

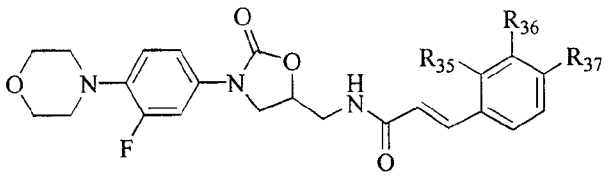
10. An antimicrobial compound where the compound is of the structure:



where m is 0, 1, 2 or 3, and where R_{22}, R_{23} and R_{24} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl.

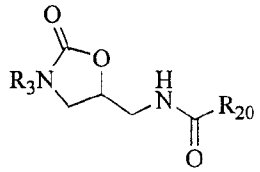
11. The antimicrobial compound according to claim 10, where m is 0, and where R_{22} and R_{23} are hydrogen, and where R_{24} is an aryl group.

12. The antimicrobial compound according to claim 11, where the compound is of the structure:

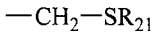


where R_{35}, R_{36} and R_{37} are independently selected from the group consisting of hydrogen, electron withdrawing group, alkyl, heteroalkyl, aryl and heteroaryl.

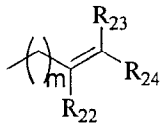
13. An antimicrobial compound, where the compound has the following structure:



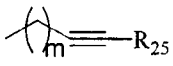
where R_3 is selected from the group consisting of aryl and heteroaryl, and where R_{20} is selected from the group consisting of structures A, B, C, I, J and K



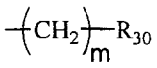
A



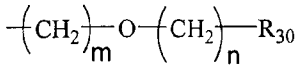
B



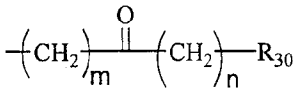
C



I



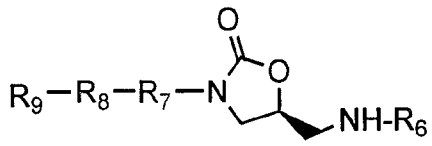
J



K

wherein m is 0, 1, 2 or 3, and where n is 0, 1, 2 or 3, and wherein R_{21} is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl, and where R_{22}, R_{23} and R_{24} are independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, and where R_{25} is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl and heteroaryl, and where R_{30} is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl.

14. A compound of formula **2c**:



2c

wherein:

R_6 is acyl or sulfonyl;

R_7 is aryl or heteroaryl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl; and

R_9 is hydrogen, OH, alkyl, aryl, heteroalkyl, or heteroaryl.

15. The compound of claim 14 wherein:

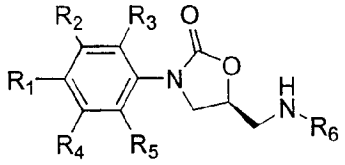
R_6 is C(=O)R, wherein R is H, alkyl, or aryl;

R_7 is aryl;

R_8 is NH(C=O) or NR'(C=O), where R' is H, alkyl, or aryl; and

R_9 is hydrogen, pyridinyl, thiazolyl, benzothiazolyl, isothiazolyl, quinolinyl, 1,3,4-triazolyl, or 1,3,4-thiadiazolyl.

16. A compound of the structure **1b**:



1b

wherein R_2, R_3, R_4 and R_5 are, independently, hydrogen alkyl, heteroalkyl, heteroaryl or an electron withdrawing group; R_6 is acyl or sulfonyl; and, R_1 is one of the following functional groups: C(O)NR_7R_8, wherein R_7 and R_8 are, independently, hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; C(O)OR_9, wherein R_9 is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; C(O)R_{10}, wherein R_{10} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; SR_{11}, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $S(O)_2R_{11}$, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; S(O)R_{11}, wherein R_{11} is hydrogen, alkyl, heteroalkyl, aryl or heteroaryl; $NR_{12}R_{13}$, wherein R_{12} and R_{13} are, independently, hydrogen, acyl, sulfonyl, alkyl, heteroalkyl, aryl or heteroaryl; 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position of the oxazolyl, and wherein R_{14}

and R_{15} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position of the thiazole, and wherein R_{16} and R_{17}, are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or an electron withdrawing group; and, $CH_2NR_{18}R_{19}$, wherein R_{18} and R_{19} are, independently, hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, acyl or sulfonyl.

17. A combinatorial library of compounds according to claim 16.

18. A compound of claim 16, wherein R_1 is $C(O)NR_7R_8$, $C(O)OR_9$, $C(O)R_{10}$, SR_{11}, $S(O)_2R_{11}$, $S(O)R_{11}$ or $NR_{12}R_{13}$.

19. A compound according to claim 16, wherein R_1 is $C(O)NR_7R_8$.

20. A compound according to claim 16, wherein R_1 is $C(O)OR_9$.

21. A compound according to claim 16, wherein R_1 is $C(O)R_{10}$.

22. A compound according to claim 16, wherein R_1 is SR_{11}.

23. A compound according to claim 16, wherein R_1 is $NR_x(C=O)R_y$, wherein R_x and R_y are independently hydrogen, alkyl, heteroalkyl, aryl, or heteroaryl.

24. A compound according to claim 16, wherein R_1 is $NR_x(SO_2)R_y$, wherein R_x and R_y are independently hydrogen, alkyl, heteroalkyl, aryl, or heteroaryl with the proviso that R_y is not H.

25. A compound according to claim 16, wherein R_1 is $NR_{12}R_{13}$.

26. A compound according to claim 16, wherein R_1 is 2-oxazolyl, wherein R_{14} is at the 4-position and R_{15} is at the 5-position of the oxazole group.

27. A compound according to claim 16, wherein R_1 is 2-aminothiazolyl, wherein R_{16} is at the 4-position and R_{17} is at the 5-position of the aminothiazolyl group.

28. A compound according to claim 16, wherein R_1 is $CH_2NR_{18}R_{19}$.

29. A compound according to claim 18, wherein R_3, R_4 and R_5 are hydrogen.

30. A compound according to claim 29, wherein R_2 is fluorine.

31. A compound according to claim 30, wherein, R_6 is $C(O)CH_3$.

32. A compound according to claim 31, wherein R_1 is $C(O)NR_7R_8$ and R_7 is hydrogen.

33. A compound according to claim 32, wherein R_8 is heteroaryl.

34. A biologically active oxazolidinone derived from a combinatorial library

according to claim 17.

35. A compound according to claim 19, wherein R_3, R_4 and R_5 are hydrogen.

36. A compound according to claim 26, wherein R_3, R_4 and R_5 are hydrogen.

37. A compound according to claim 27, wherein R_3, R_4 and R_5 are hydrogen.

38. A compound according to claim 35, wherein R_2 is fluorine.

39. A compound according to claim 36, wherein R_2 is fluorine.

40. A compound according to claim 37, wherein R_2 is fluorine.

41. A compound according to claim 38, wherein R_6 is $C(O)CH_3$, and NR_7R_8 is NH(5'-(5-aminopyridine-2-yl)thiopyridine-3'-yl) or NH(pyridine-3-yl).

42. A compound according to claim 38, wherein R_6 is $C(O)CH_2SMe$, and NR_7R_8 is NH(5-chloropyridine-3-yl).

43. A compound according to claim 38, wherein R_6 is C(O)CHCH(pyridine-3-yl), and R_7R_8 is NH(5-chloropyridine-3-yl).

44. A method of preparing the combinatorial libraries according to claim 17, comprising the steps of:

a) attaching a plurality of aryl oxazolidinones to a plurality of solid supports;

b) functionalizing the 4-position of the aryl groups of the attached oxazolidinones; and, optionally,

c) removing the oxazolidinones from the solid supports.

45. The method according to claim 44, wherein the aryl oxazolidinone is attached to a solid support through the reaction of an iminophosphorane with a carbonyl containing resin to form an imine.

46. The method according to claim 44, wherein the aryl oxazolidinone is attached to a solid support through the reaction of an amine with a carbonyl containing resin to form an imine.

47. The method according to claim 45, wherein the attachment further comprises the step of reducing the imine.

48. The method according to claim 46, wherein the attachment further comprises the step of reducing the imine.

49. A method of synthesizing the compounds according to claim 16, wherein

the method comprises the steps of:

a) providing an iminophosphorane;

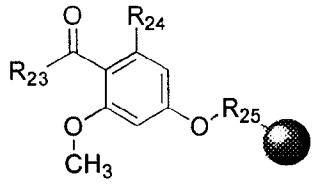
b) mixing the iminophosphorane with a resin that comprises carbonyl groups to form an imine intermediate; and,

c) reducing the imine intermediate to afford a compound attached to the resin through an amine linkage.

50. A method according to claim 49, wherein the iminophosphorane is provided from an azide that is reacted with a phosphine.

51. A method according to claim 49, wherein the iminophosphorane is provided from an amine that is reacted with a (trisubstituted)phosphine dihalide.

52. A method according to claim 49, wherein the resin comprising carbonyl groups is of the structure



1c

wherein R_{23} is hydrogen, alkyl, aryl, O-alkyl or O-aryl; R_{24} is hydrogen, CH_3O or NO_2; R_{25} is $(CH_2)_nCONH$, wherein n is an integer between 1 and about 5; and, the filled circle is a polymeric support.

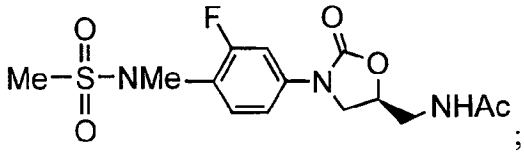
53. A method according to claim 52, wherein R_{23} is hydrogen, R_{24} is CH_3O, R_{25} is $(CH_2)_3CONH$, and the filled circle is Tentagel, (cross-linked)polystyrene, (cross-linked)polyethyleneglycol or polyethyleneglycol-polystyrene compositions.

54. A method of synthesizing a compound according to claim 16, wherein the method comprises the steps of:

a) reacting an amine with a resin that comprises carbonyl groups to form an imine intermediate; and

b) reducing the imine intermediate to afford a compound attached to the resin through an amine linkage.

55. The compound of claim 14 selected from the group consisting of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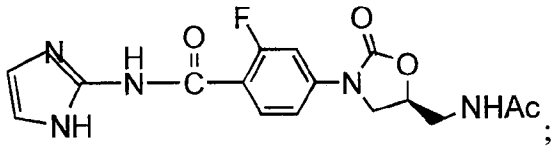
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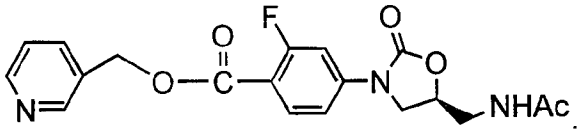
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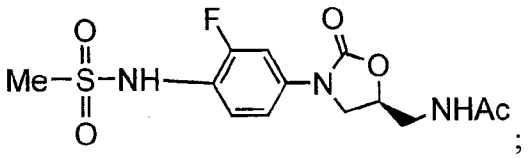
56. The compound of claim 14 selected from the group consisting of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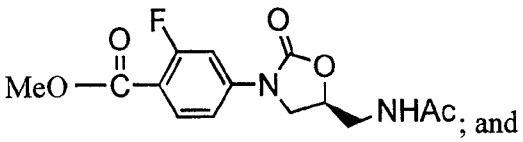
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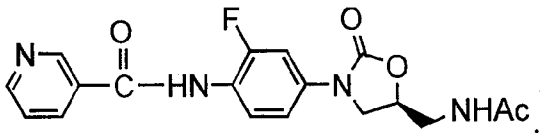
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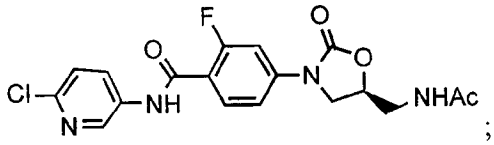
57. The compound of claim 14 selected from the group consisting of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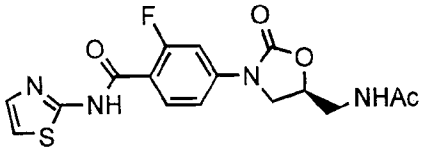
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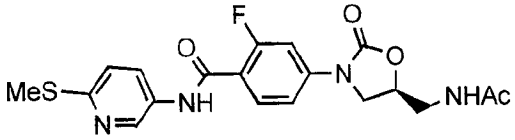
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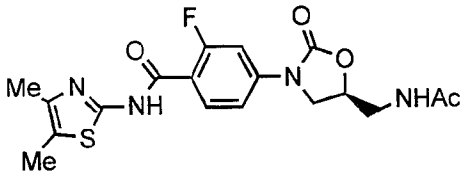
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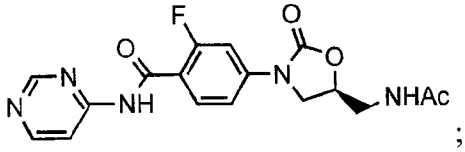
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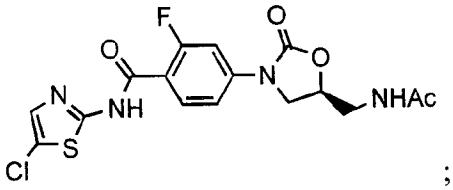
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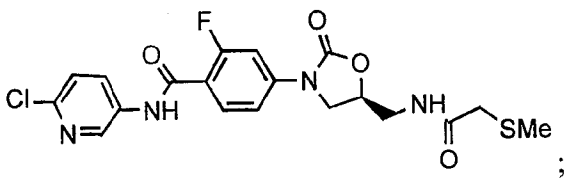
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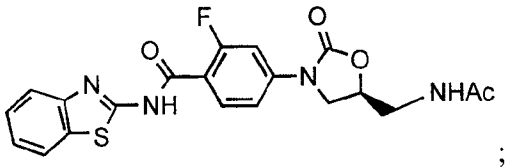

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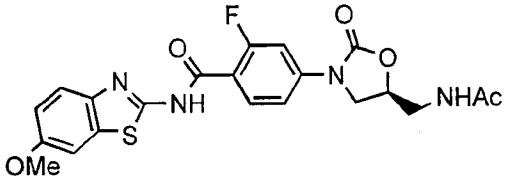

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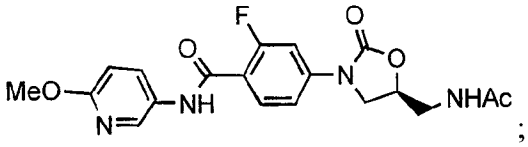
58. The compound of claim 14 selected from the group consisting of



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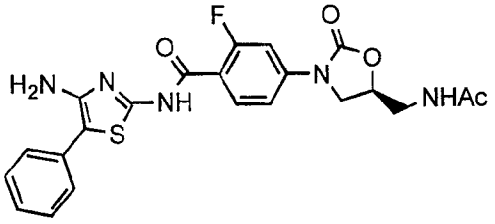

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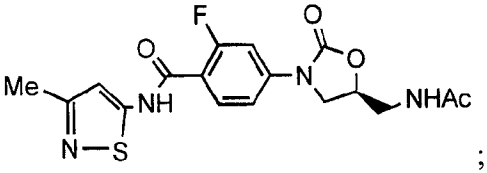

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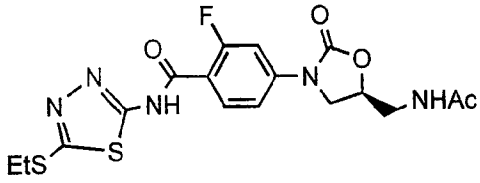

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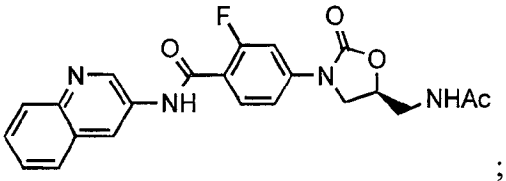

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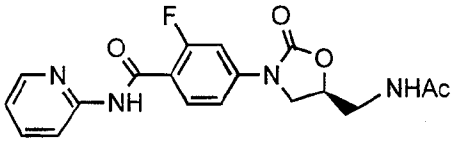

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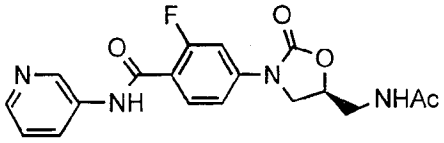

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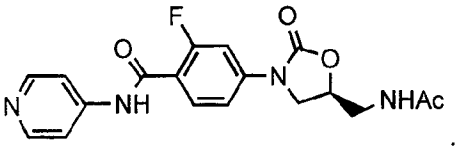

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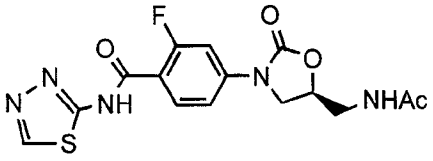
59. The compound of claim 14 selected from the group consisting of



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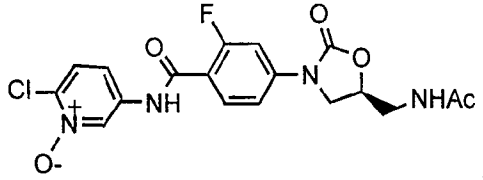

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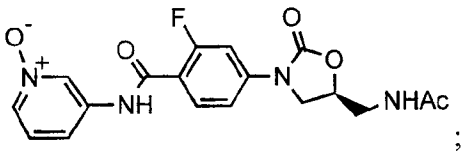
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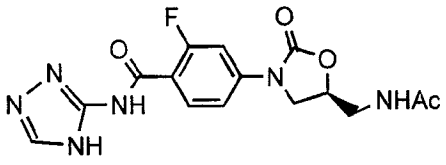
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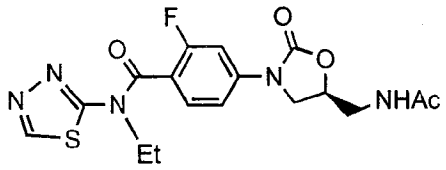
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60. The compound of claim 14 wherein:

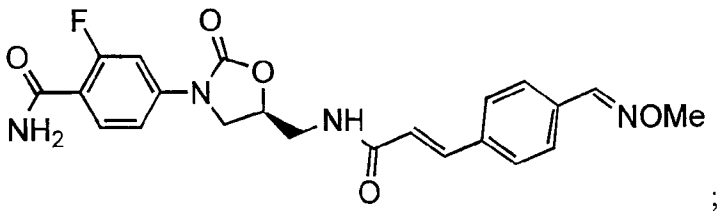
R_6 is C(=O)R, wherein R is H, alkyl, heteroalkyl, aryl or heteroaryl;

R_7 is aryl;

R_8 is NH(C=O); and

R_9 is hydrogen or OH.

61. The compound of claim 14 wherein the compound is selected from the group consisting of: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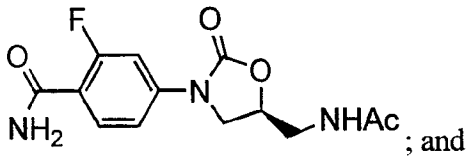
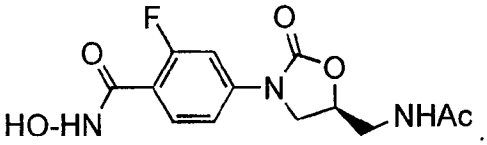
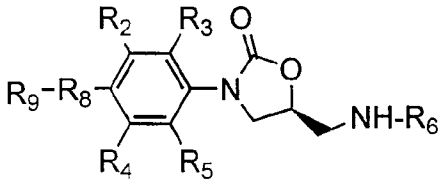

; and



62. A compound of formula **3c**



3c

wherein:

R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl; and

R_9 is alkyl, aryl, heteroalkyl, or heteroaryl.

63. The compound of claim 62, wherein

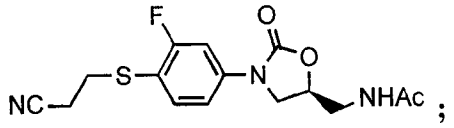
R_6 is $C(=O)CH_3$;

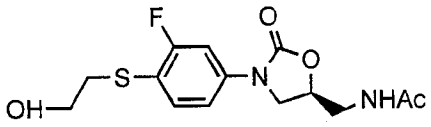
R_7 is aryl;

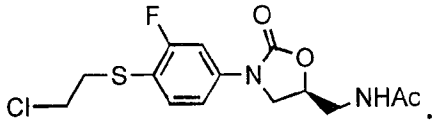
R_8 is S; and

R_9 is heteroalkyl.

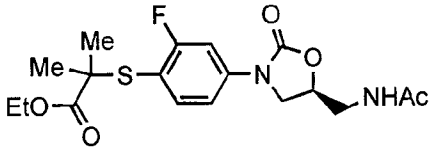
64. The compound of claim 62, wherein the compound is selected from the group consisting of

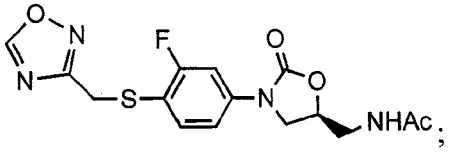

;

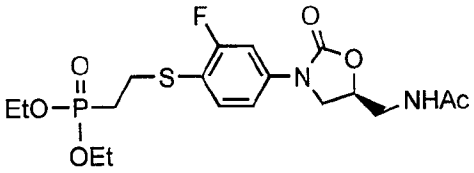

; and

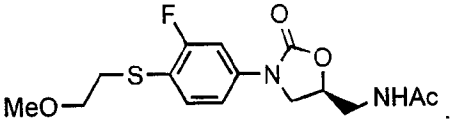

.

65. The compound of claim 62, wherein the compound is selected from the group consisting of

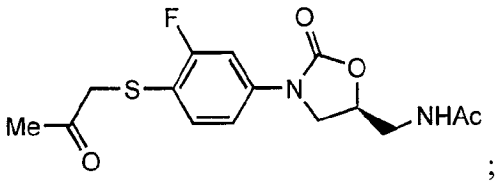

;


;

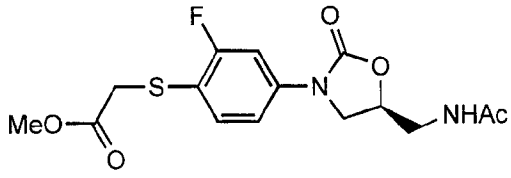

; and


.

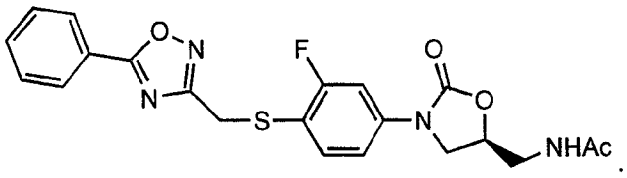
66. The compound of claim 62, wherein the compound is selected from the group consisting of



;



; and



.

67. The compound of claim 62 wherein:

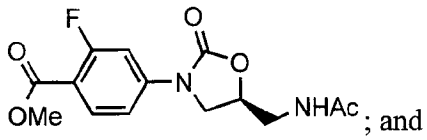
R_6 is $C(=O)CH_3$;

R_7 is aryl;

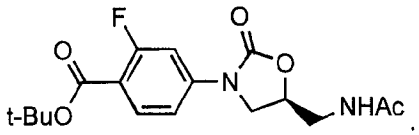
R_8 is $OC(=O)$; and

R_9 is alkyl.

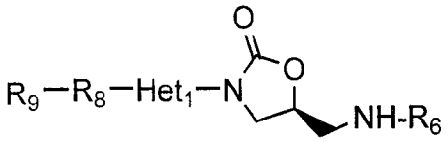
68. The compound of claim 62 selected from the group consisting of:



; and



69. A compound of formula **4c**:



4c

wherein:

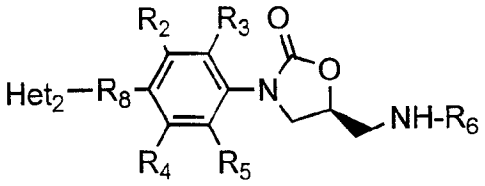
R_6 is acyl or sulfonyl;

Het_1 is heteroaryl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl; and

R_9 is alkyl, aryl, heteroalkyl, or heteroaryl.

70. A compound of formula **5c**:



wherein:

R_2, R_3, R_4 and R_5 are, independently, hydrogen, alkyl, heteroalkyl, heteroaryl or an electron withdrawing group;

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O)NOR C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl; and

Het_2 is a heterocyclic group.

71. The compound of claim 70, wherein

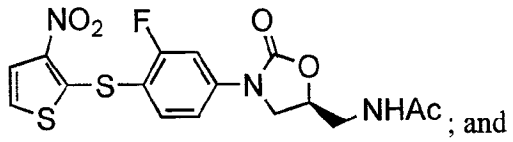
R_6 is $C(=O)CH_3$;

R_7 is aryl;

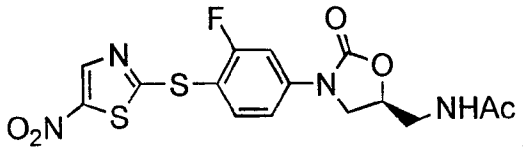
R_8 is S; and

Het_2 is a thienylphenyl or thiazolyl group.

72. The compound of claim 70 selected from the group consisting of:



; and



.

73. The compound of claim 70 wherein:

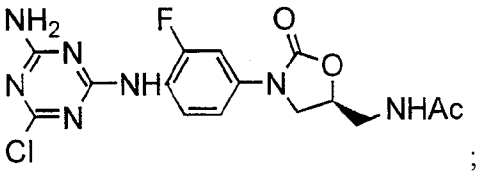
R_6 is $C(=O)CH_3$;

R_7 is aryl;

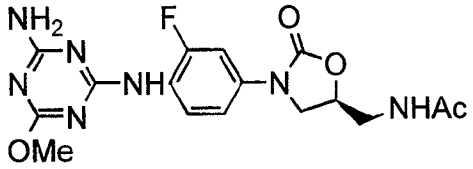
R_8 is NH; and

Het_2 is 1,3,5-triazinyl.

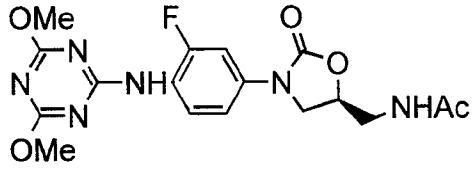
74. The compound of claim 70 selected from the group consisting of



;

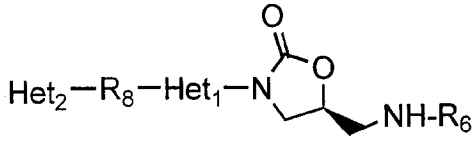


; and



.

75. A compound of formula **6c**:



6c

wherein:

R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, NRC(=O), C(=O)NOR C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl;

Het_1 is heteroaryl; and

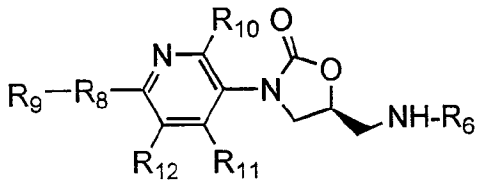
Het_2 is a heterocyclic group.

76. The compound of claim 75 wherein

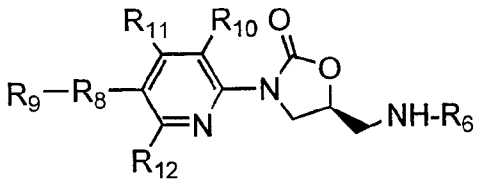
Het_1 is selected from the group consisting of thienylphenyl, thiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyrimidinyl, phenyl and fluorophenyl; and

Het_2 is selected from the group consisting of oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-oxadiazolyl, thienylphenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-triazinyl, 1,2,4-triazinyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, and 1,2,4,5-tetrazinyl.

77. A compound of formulas **7c** or **8c**:



7c



8c

wherein:

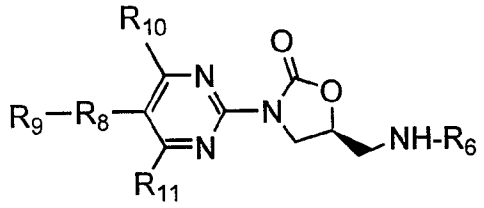
R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, $NRSO_2$, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl;

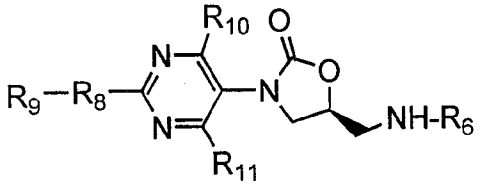
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R_{10}, R_{11} and R_{12} are independently hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in the pyridine nuclei, wherein R'' and R''' are independently H, alkyl, heteroalkyl, aryl or heteroaryl.

78. A compound of formula **9c** or **10c**:



9c



10c

wherein:

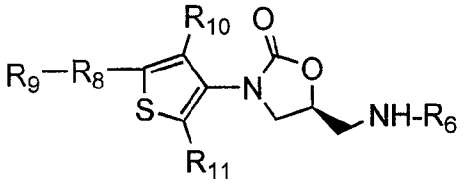
R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, where n = 0-6, and where R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl;

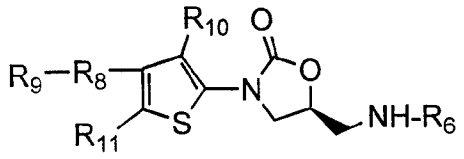
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R_{10} and R_{11} are independently hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', N(R'')C(=O)R''', or N-oxide group in the pyrimidine nuclei, wherein R' and R''' are independently H, alkyl, heteroalkyl, aryl or heteroaryl.

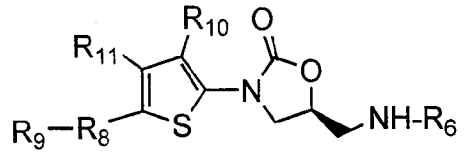
79. A compound of formula **11c, 12c** or **13c**:



11c



12c



13c

wherein:

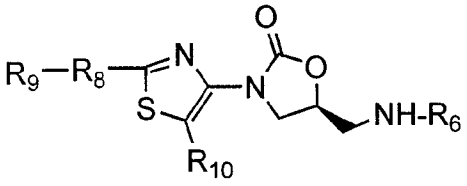
R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, wherein n = 0-6, and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl;

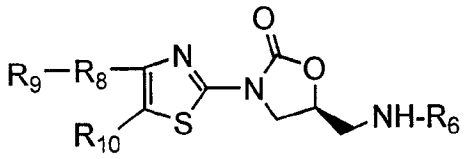
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R_{10} and R_{11} are independently hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', or N(R'')C(=O)R''', wherein R'' and R''' are independently H, alkyl, heteroalkyl, aryl or heteroaryl.

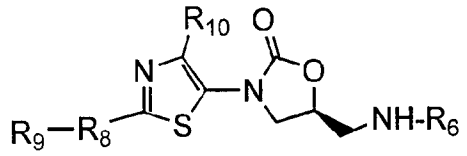
80. A compound of formula **14c, 15c** or **16c**:



14c



15c



16c

wherein:

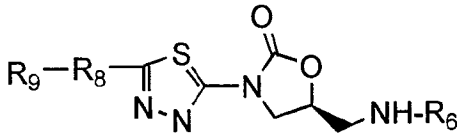
R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, wherein n = 0-6), and wherein R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl;

R_9 is alkyl, aryl, heteroalkyl, or heteroaryl; and

R_{10} is hydrogen, alkyl, aryl, heteroalkyl, electron withdrawing group, F, Cl, CN, NO_2, NR''R''', OR'', SR'', S(=O)R'', SO_2R'', C(=O)R'', C(=O)OR'', OC(=O)R'', C(=O)NR''R''', or N(R'')C(=O)R''', where R'' and R''' are independently H, alkyl, heteroalkyl, aryl or heteroaryl.

81. A compound of formula **17c**:



17c

wherein:

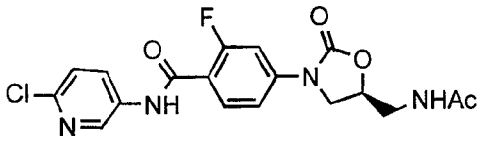
R_6 is acyl or sulfonyl;

R_8 is C_1-C_7 alkyl, NR, O, S, C(=O)NR, C(=O)NOR, NRC(=O), C(=O), C(=O)O, OC(=O), S(=O), SO_2, SO_2NR, NRSO_2, NRCONR', or $(CH_2)_nO$, where n = 0-6, and where R and R' are independently H, alkyl, heteroalkyl, aryl or heteroaryl; and

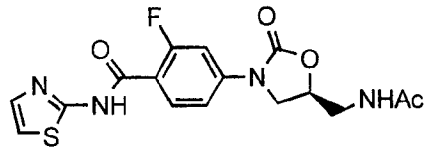
R_9 is alkyl, aryl, heteroalkyl, or heteroaryl.

82. A composition for the treatment or prevention of an infectious disorder comprising an effective amount of a compound of claim 14 and a pharmaceutically acceptable carrier.

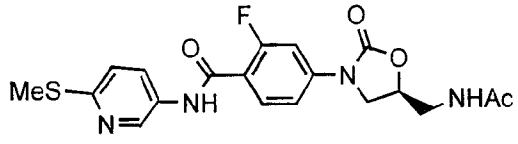
83. The composition of claim 82 wherein the compound is



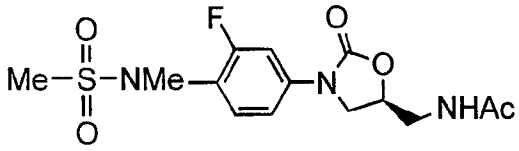
84. The composition of claim 82 wherein the compound is



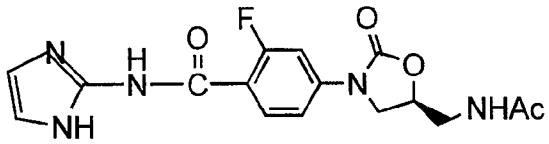
85. The composition of claim 82 wherein the compound is



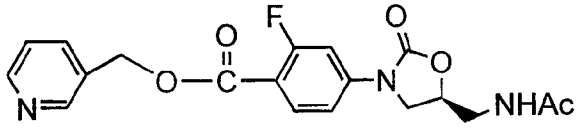
86. The composition of claim 82 wherein the compound is



87. The composition of claim 82 wherein the compound is



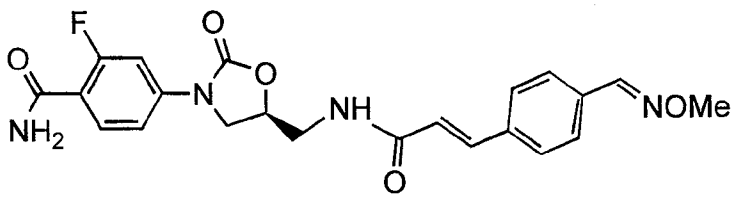
88. The composition of claim 82 wherein the compound is



89. A composition for the treatment or prevention of an infectious disorder comprising an effective amount of a compound of claim 55 and a pharmaceutically acceptable carrier.

90. A composition for the treatment or prevention of an infectious disorder comprising an effective amount of a compound of claim 57 and a pharmaceutically acceptable carrier.

91. The composition of claim 82, wherein the compound is



92. A composition for the treatment or prevention of an infectious disorder comprising an effective amount of a compound of claim 61 and a pharmaceutically acceptable carrier.

93. A composition for the treatment or prevention of an infectious disorder comprising an effective amount of a compound of claim 64 and a pharmaceutically acceptable carrier.

94. A composition for the treatment or prevention of an infectious disorder comprising an effective amount of a compound of claim 72 and a pharmaceutically acceptable carrier.

95. A method of treating or preventing an infectious disorder in a human or other animal subject, comprising administering to the subject an effective amount of a compound of claim 14.

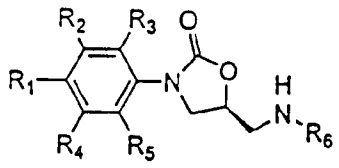
96. A method of treating or preventing an infectious disorder in a human or other animal subject, comprising administering to the subject an effective amount of a compound of claim 55.

97. A method of treating or preventing an infectious disorder in a human or other animal subject, comprising administering to the subject an effective amount of a compound of claim 57.

98. A method of treating or preventing an infectious disorder in a human or other animal subject, comprising administering to the subject an effective amount of a compound of claim 61.

99. A method of treating or preventing an infectious disorder in a human or other animal subject, comprising administering to the subject an effective amount of a compound of claim 64.

100. A method of treating or preventing an infectious disorder in a human or other animal subject, comprising administering to the subject an effective amount of a compound of claim 72.



1b

FIGURE 1

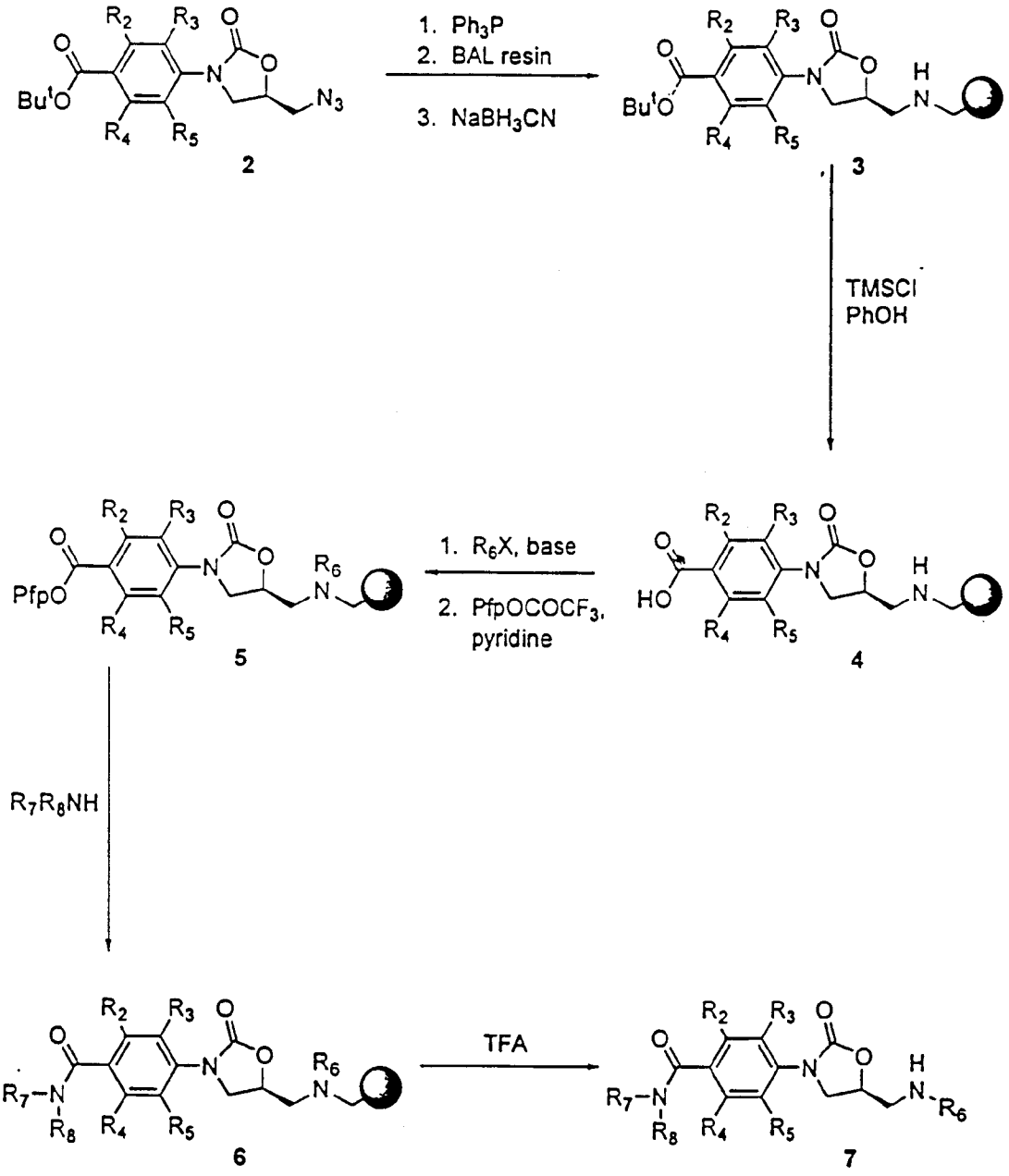

1. Ph_3P
2. BAL resin
3. $NaBH_3CN$
TMSCl
PhOH
1. R_6X, base
2. $PfpOCOCF_3$, pyridine
R_7R_8NH
TFA
2
3
4
5
6
7

FIGURE 2

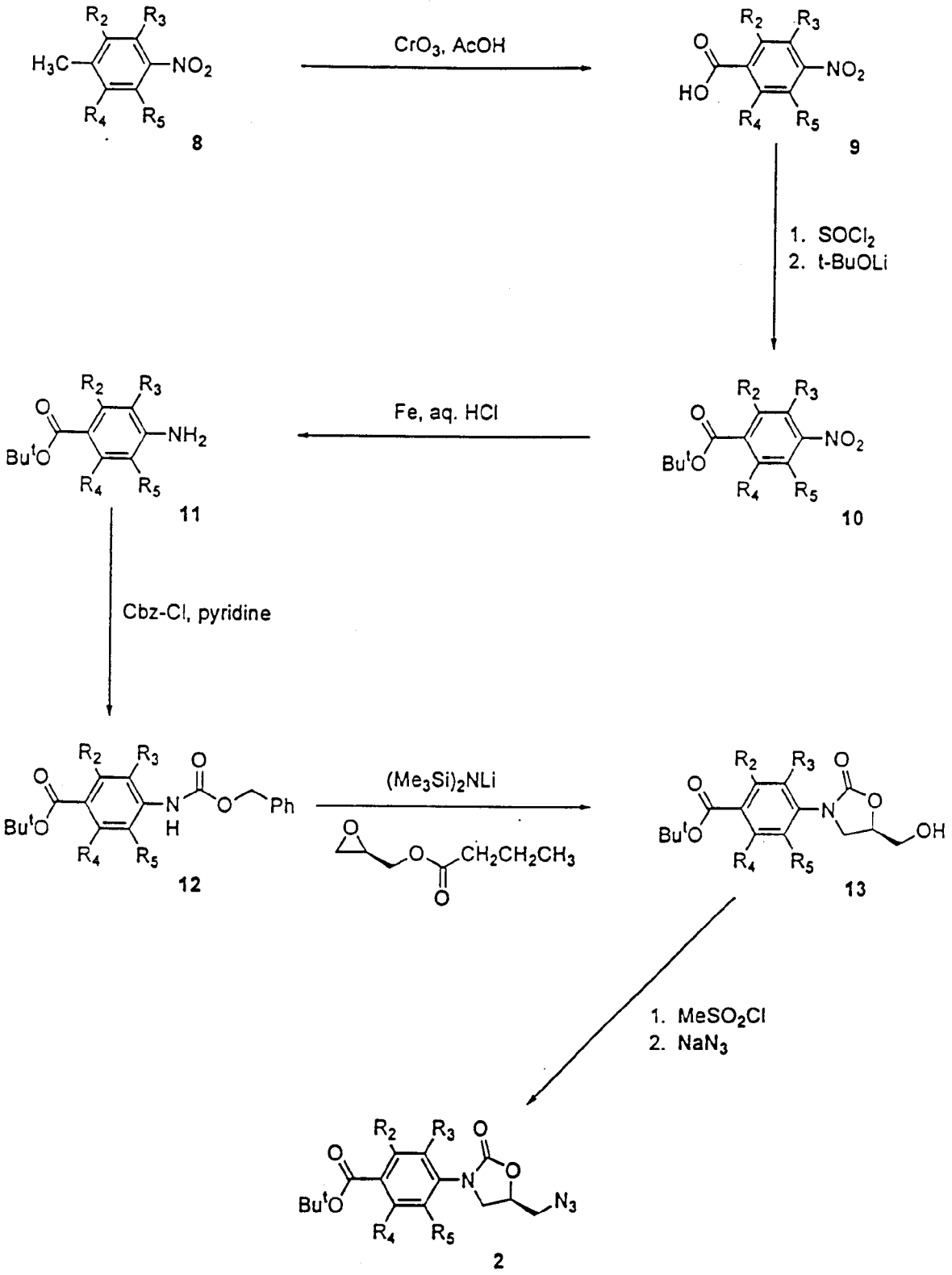

R2 R3
H3C NO2
R4 R5
8
CrO3, AcOH
R2 R3
O
HO NO2
R4 R5
9
1. SOCl2
2. t-BuOLi
R2 R3
O
Bu^tO NO2
R4 R5
10
Fe, aq. HCl
R2 R3
O
Bu^tO NH2
R4 R5
11
Cbz-Cl, pyridine
R2 R3 O
O
Bu^tO N Ph
H O
R4 R5
12
(Me3Si)2NLi
O
O CH2CH2CH3
O
R2 R3 O
O
Bu^tO N
O
R4 R5
13
OH
1. MeSO2Cl
2. NaN3
R2 R3 O
O
Bu^tO N
O
R4 R5
2
N3

FIGURE 3

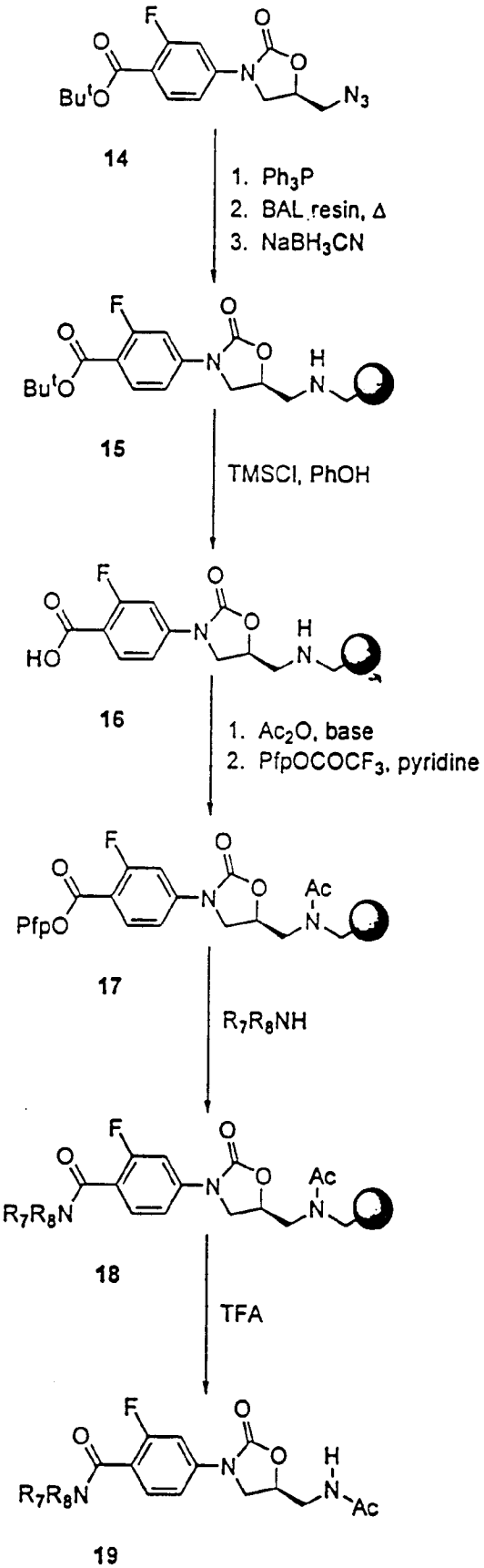

F
O
O
Bu^{t}O
N
O
N$_3$
14
1. Ph$_3$P
2. BAL resin, Δ
3. NaBH$_3$CN
H
N
15
TMSCl, PhOH
HO
16
1. Ac$_2$O, base
2. PfpOCOCF$_3$, pyridine
Ac
PfpO
17
R$_7$R$_8$NH
R$_7$R$_8$N
18
TFA
19

FIGURE 4

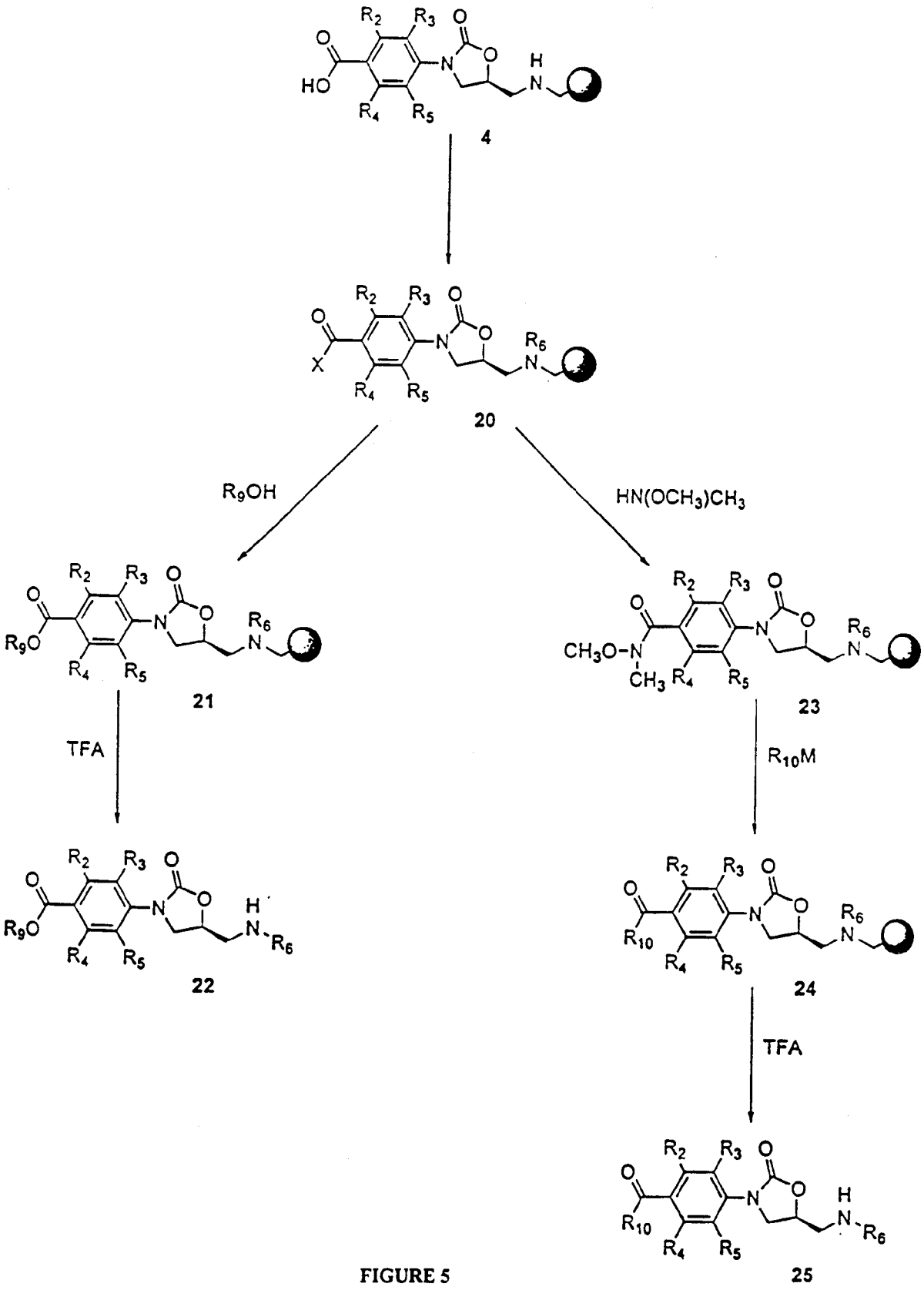


FIGURE 5

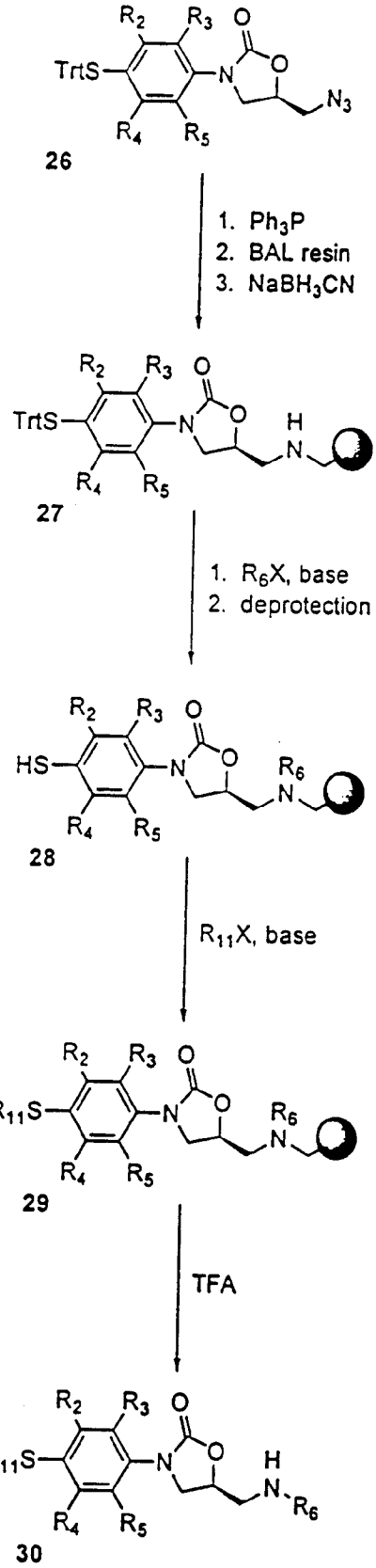
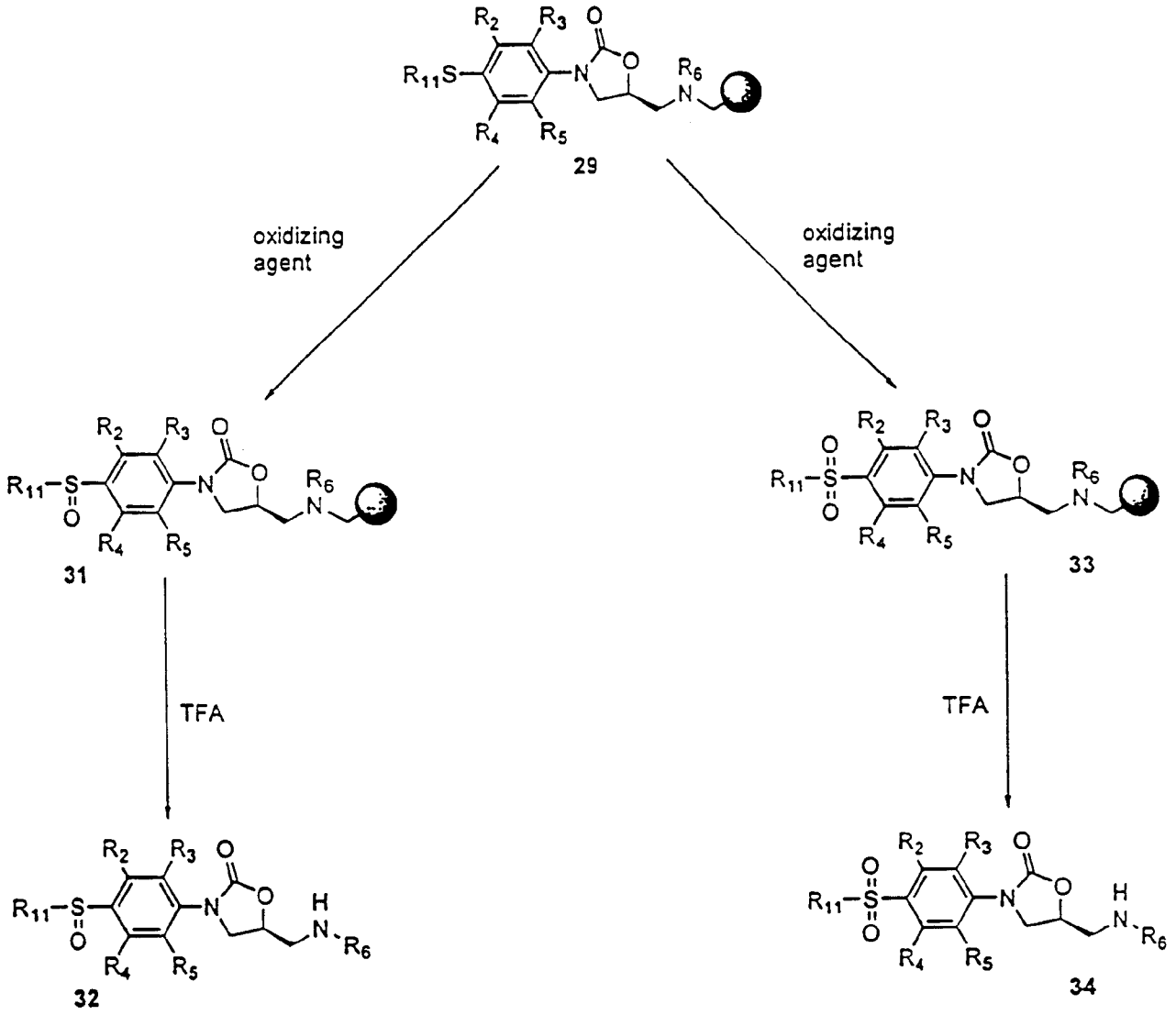

R2
R3
O
TrtS
N
O
N3
R4
R5
26
1. Ph3P
2. BAL resin
3. NaBH3CN
TrtS
H
N
27
1. R6X, base
2. deprotection
HS
R6
28
R11X, base
R11S
29
TFA
30

FIGURE 6



29 31 33 32 34

FIGURE 7

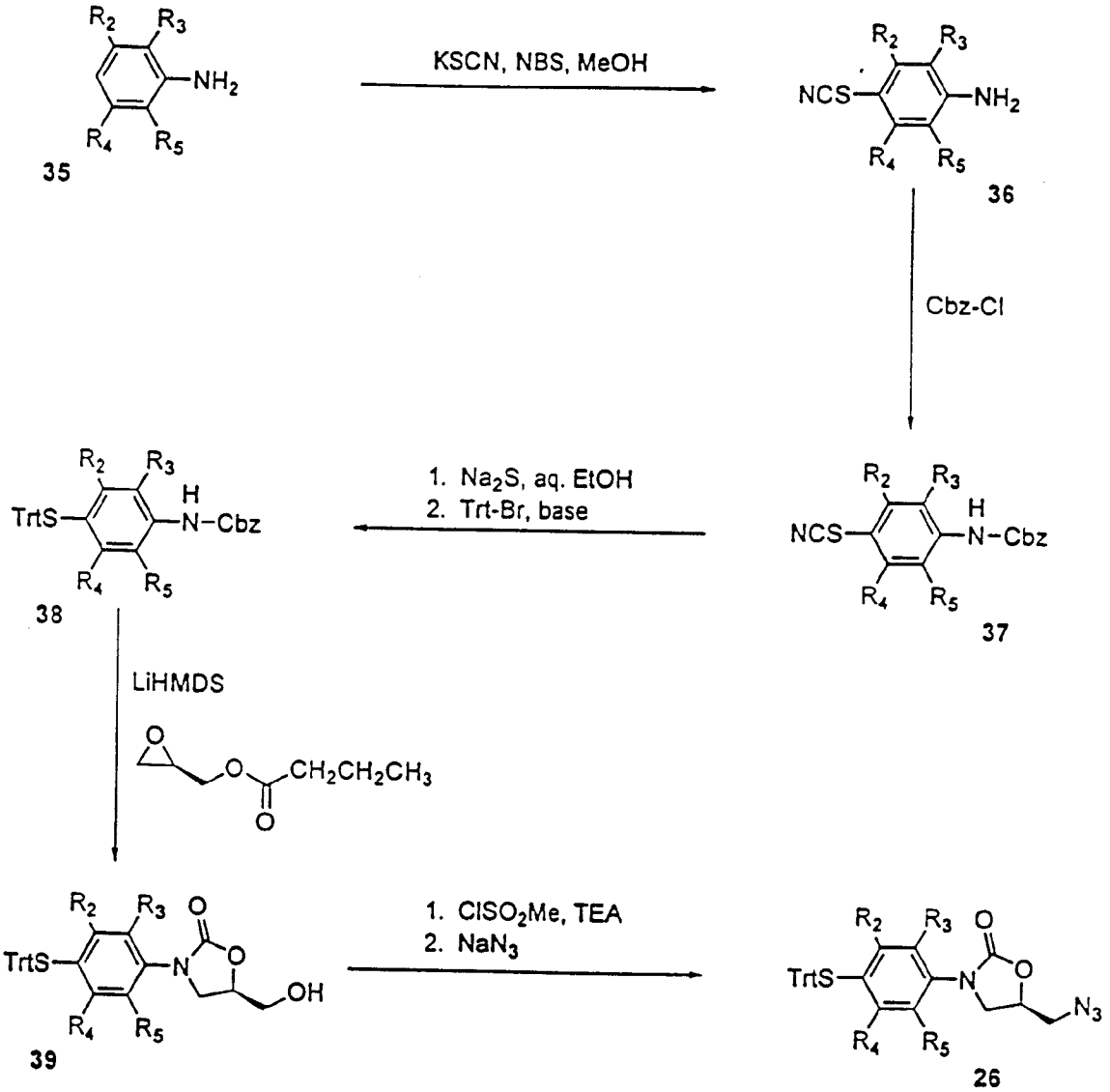

KSCN, NBS, MeOH
Cbz-Cl
1. Na_2S, aq. EtOH
2. Trt-Br, base
LiHMDS
1. $ClSO_2Me$, TEA
2. NaN_3
35
36
37
38
39
26

FIGURE 8

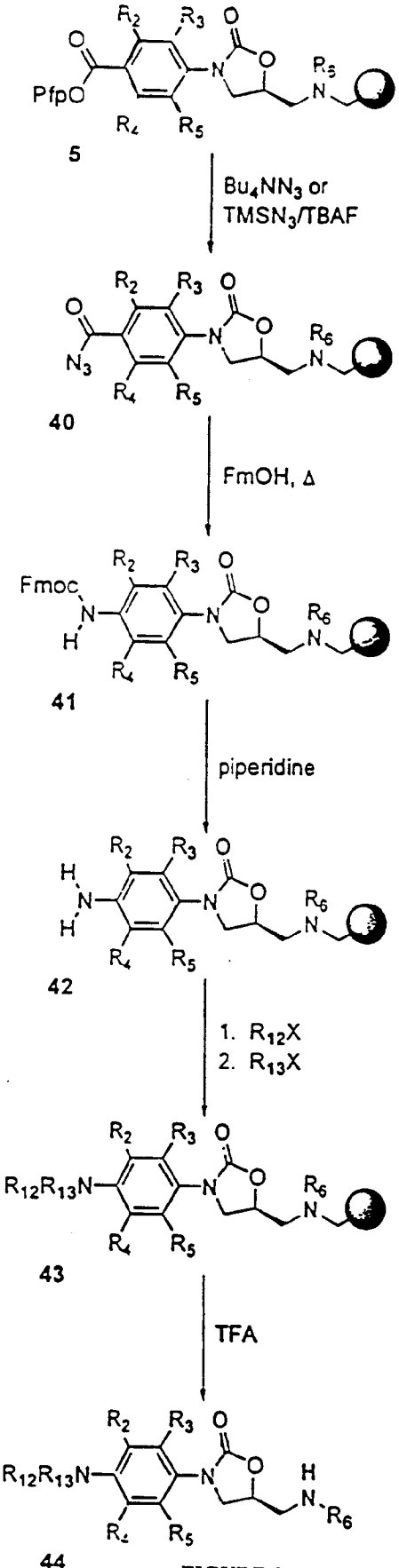

PfpO
5
Bu_4NN_3 or
$TMSN_3$/TBAF
40
FmOH, Δ
Fmoc
41
piperidine
42
1. $R_{12}X$
2. $R_{13}X$
43
TFA
44

FIGURE 9

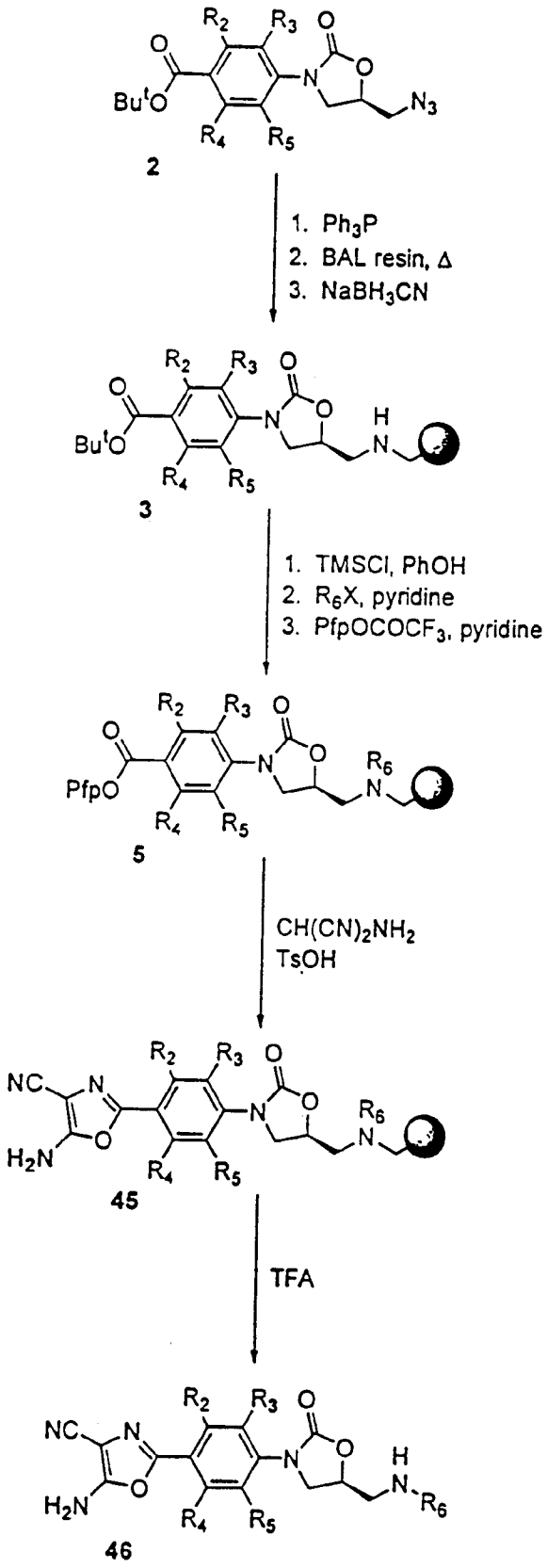

2
1. Ph_3P
2. BAL resin, Δ
3. $NaBH_3CN$
3
1. TMSCl, PhOH
2. R_6X, pyridine
3. $PfpOCOCF_3$, pyridine
5
$CH(CN)_2NH_2$
TsOH
45
TFA
46

FIGURE 10

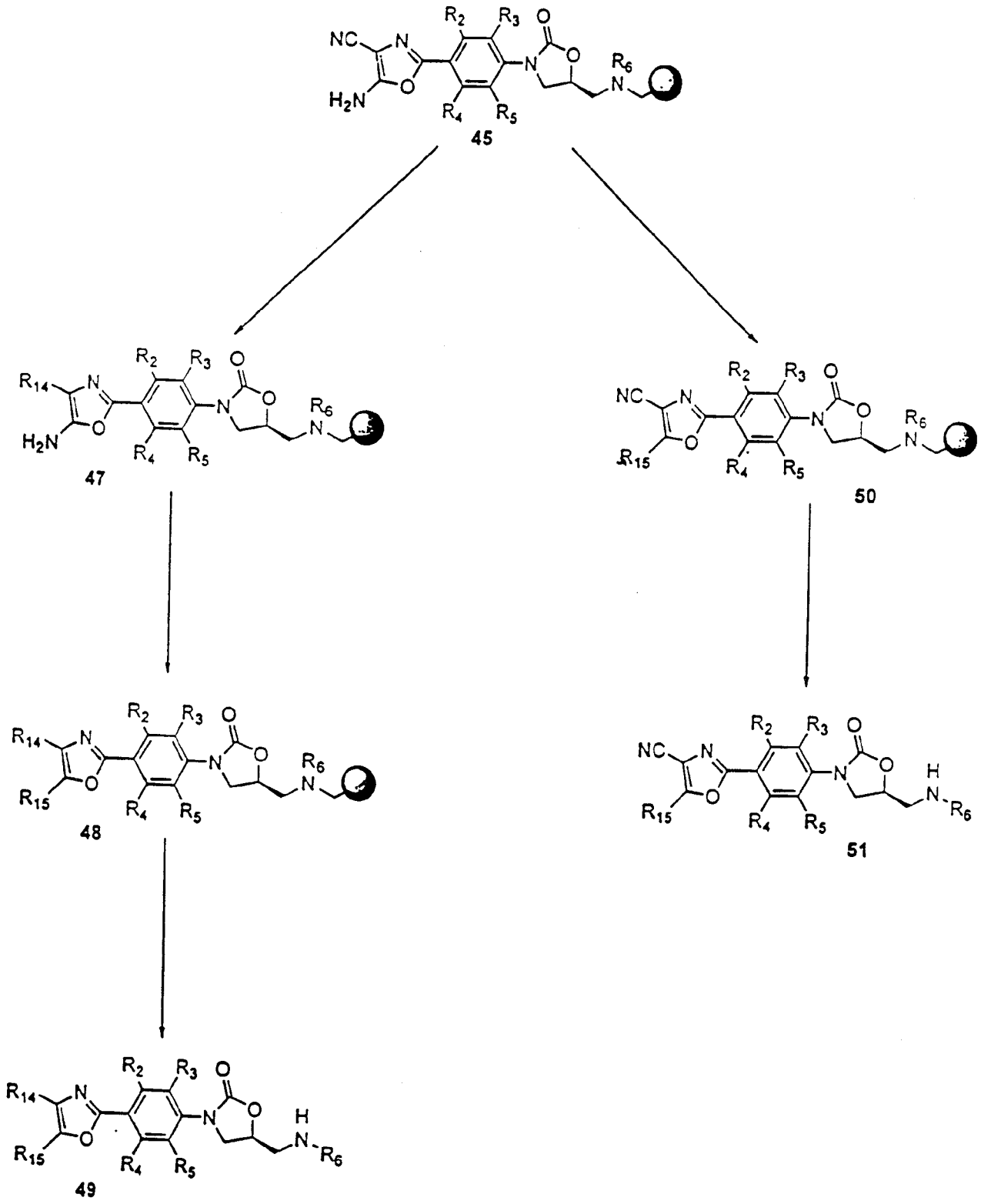


FIGURE 11

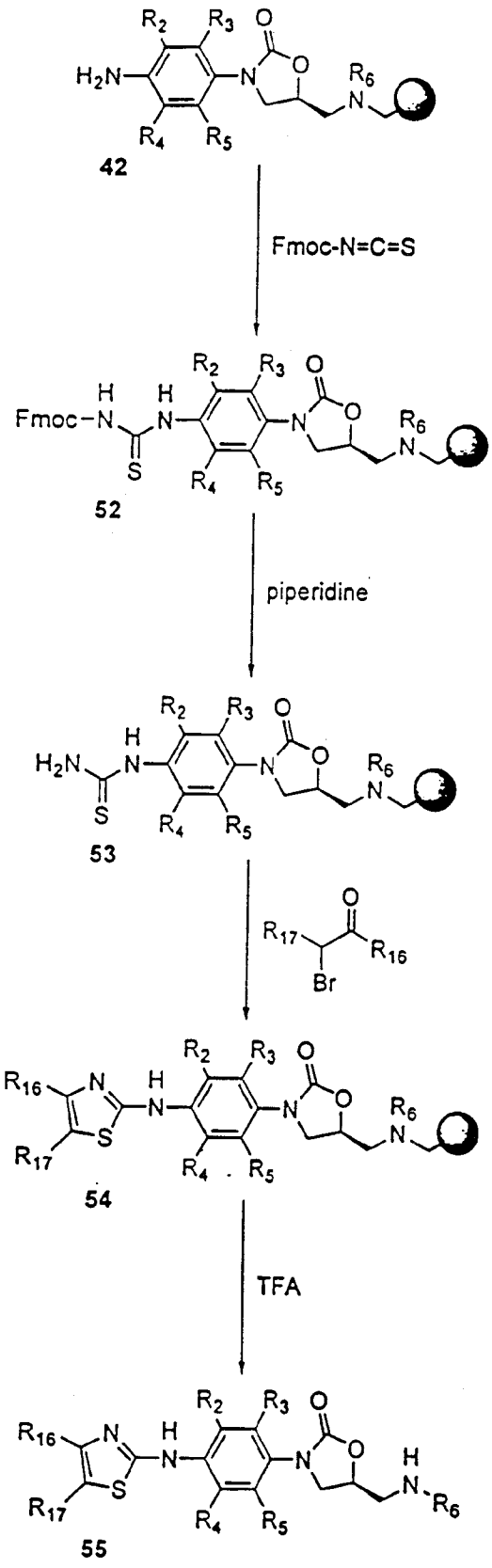


FIGURE 12

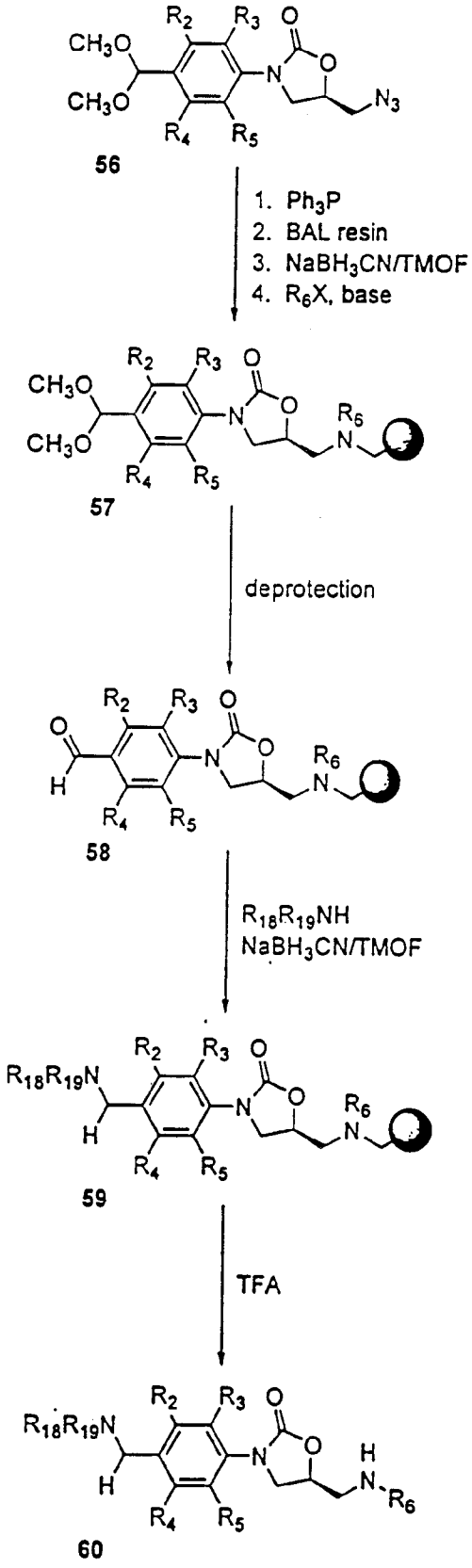

56
1. Ph_3P
2. BAL resin
3. $NaBH_3CN$/TMOF
4. R_6X, base
57
deprotection
58
$R_{18}R_{19}NH$
$NaBH_3CN$/TMOF
59
TFA
60

FIGURE 13

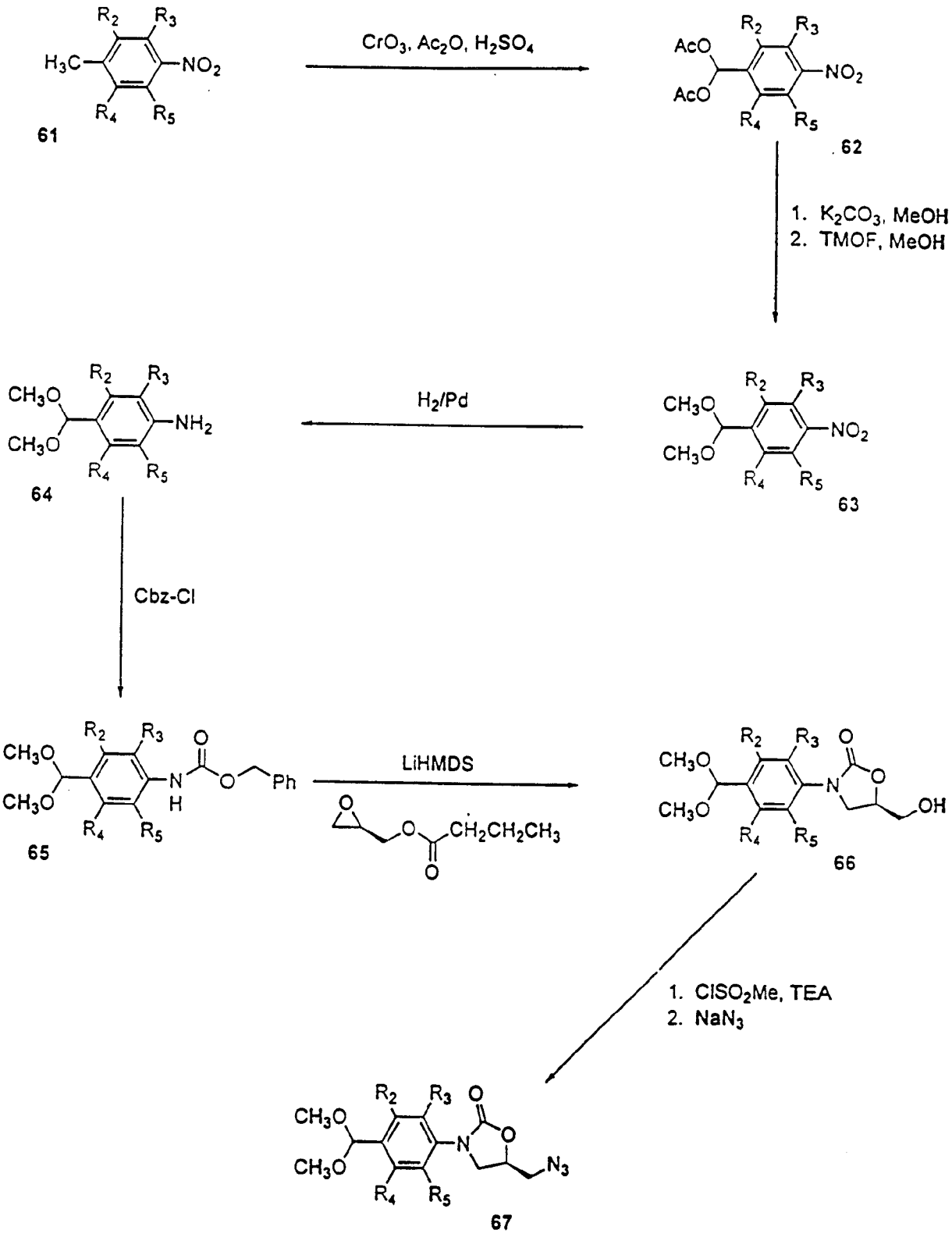

R2 R3
H3C NO2
R4 R5
61
CrO3, Ac2O, H2SO4
AcO
AcO
NO2
62
1. K2CO3, MeOH
2. TMOF, MeOH
CH3O
CH3O
NH2
64
H2/Pd
NO2
63
Cbz-Cl
LiHMDS
Ph
CH2CH2CH3
65
66
1. ClSO2Me, TEA
2. NaN3
N3
67

FIGURE 14

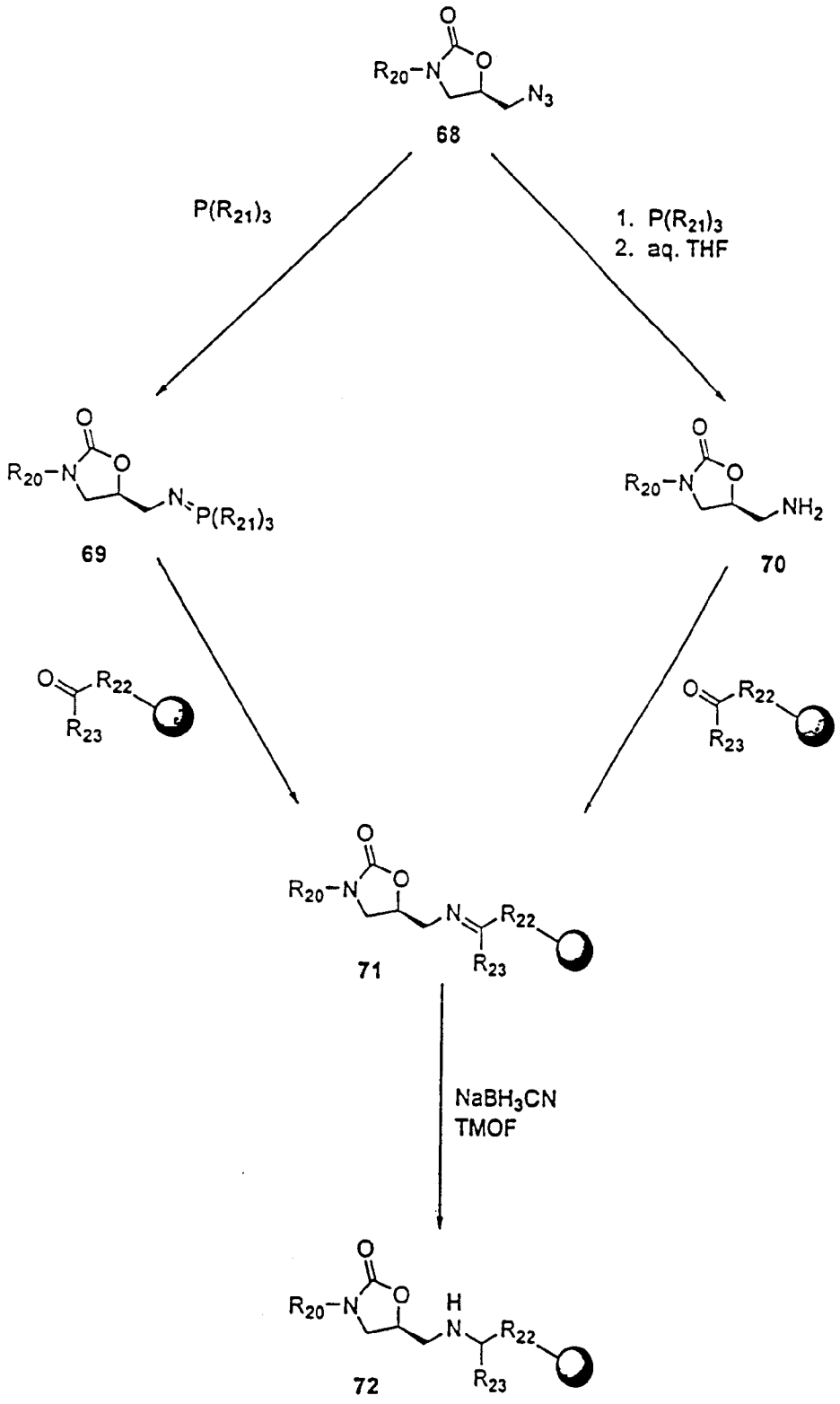


FIGURE 15

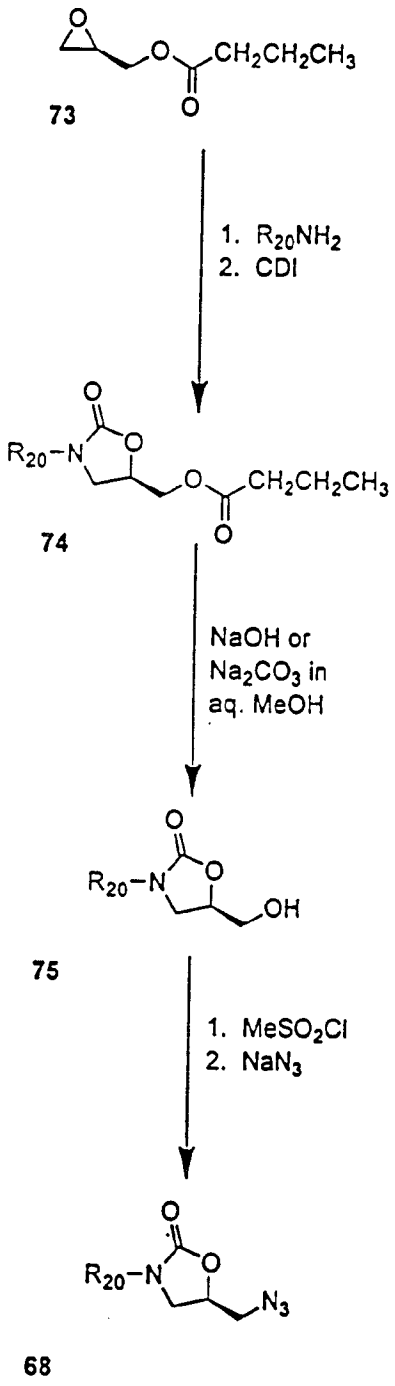
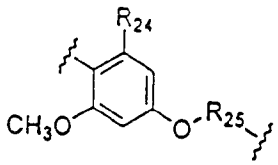

O
O
CH2CH2CH3
O
73
1. R20NH2
2. CDI
R20–N
O
O
O
CH2CH2CH3
O
74
NaOH or
Na2CO3 in
aq. MeOH
R20–N
O
O
OH
75
1. MeSO2Cl
2. NaN3
R20–N
O
O
N3
68

FIGURE 16



76

FIGURE 17

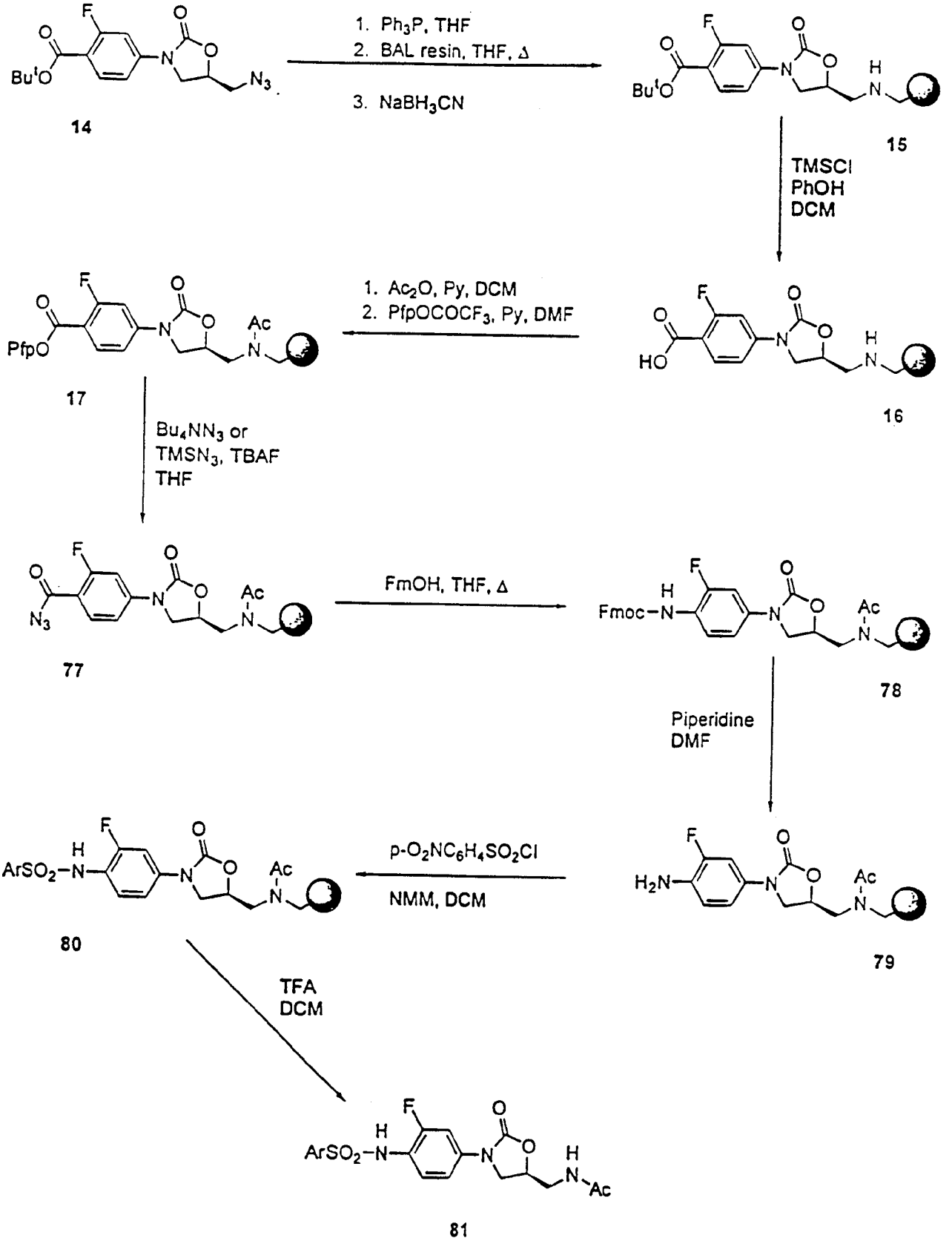

1. Ph_3P, THF
2. BAL resin, THF, Δ
3. $NaBH_3CN$
14
15
TMSCl
PhOH
DCM
1. Ac_2O, Py, DCM
2. $PfpOCOCF_3$, Py, DMF
17
16
Bu_4NN_3 or
$TMSN_3$, TBAF
THF
77
FmOH, THF, Δ
78
Piperidine
DMF
p-$O_2NC_6H_4SO_2Cl$
NMM, DCM
80
79
TFA
DCM
81

FIGURE 18

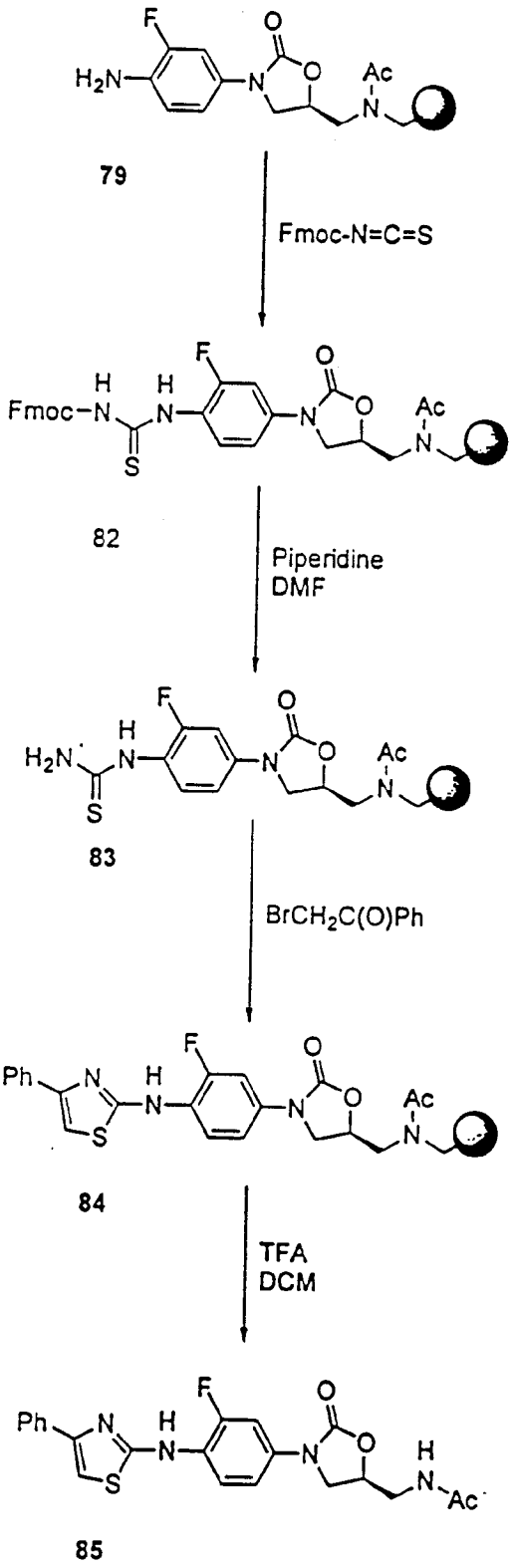


FIGURE 19