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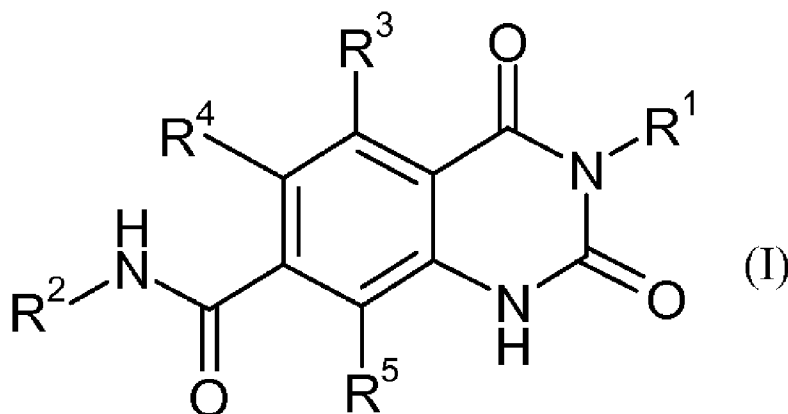
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(54) **Title:** PROLYL HYDROXYLASE INHIBITORS



(57) **Abstract:** The invention described herein relates to certain 2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide derivatives of formula (I) which are antagonists of HIF prolyl hydroxylases and are useful for treating diseases benefiting from the inhibition of this enzyme, anemia being one example.

Prolyl Hydroxylase Inhibitors

FIELD OF THE INVENTION

This invention relates to certain 2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide derivatives that are inhibitors of HIF prolyl hydroxylases, and thus have use in treating diseases benefiting from the inhibition of this enzyme, anemia being one example.

BACKGROUND OF THE INVENTION

Anemia occurs when there is a decrease or abnormality in red blood cells, which leads to reduced oxygen levels in the blood. Anemia occurs often in cancer patients, particularly those receiving chemotherapy. Anemia is often seen in the elderly population, patients with renal disease, and in a wide variety of conditions associated with chronic disease.

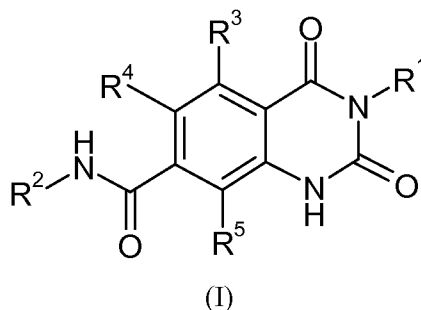
Frequently, the cause of anemia is reduced erythropoietin (Epo) production resulting in prevention of erythropoiesis (maturation of red blood cells). Epo production can be increased by inhibition of prolyl hydroxylases that regulate hypoxia inducible factor (HIF).

One strategy to increase erythropoietin (Epo) production is to stabilize and thus increase the transcriptional activity of the HIF. HIF-alpha subunits (HIF-1alpha, HIF-2alpha, and HIF-3alpha) are rapidly degraded by proteasome under normoxic conditions upon hydroxylation of proline residues by prolyl hydroxylases (EGLN1, 2, 3). Proline hydroxylation allows interaction with the von Hippel Lindau (VHL) protein, a component of an E3 ubiquitin ligase. This leads to ubiquitination of HIF-alpha and subsequent degradation. Under hypoxic conditions, the inhibitory activity of the prolyl hydroxylases is suppressed, HIF-alpha subunits are therefore stabilized, and HIF-responsive genes, including Epo, are transcribed. Thus, inhibition of prolyl hydroxylases results in increased levels of HIF-alpha and thus increased Epo production.

The compounds of this invention provide a means for inhibiting these hydroxylases, increasing Epo production, and thereby treating anemia. Ischemia, stroke, and cytoprotection may also be treated by administering these compounds.

SUMMARY OF THE INVENTION

In the first instance, this invention relates to a compound of formula (I):



wherein:

R¹ is an unsubstituted or substituted 4 to 6-membered mono-cyclic heteroaryl or a 9- to 11-membered bicyclic heteroaryl ring containing one or more hetero atoms selected from the group consisting of N, O and S;

5 R² is unsubstituted or substituted aryl, C₁-C₆ alkyl-aryl, heteroaryl, or C₁-C₆ alkyl-heteroaryl;

R³, R⁴ and R⁵ each independently selected from the group consisting of hydrogen, nitro, cyano, halogen, CF₃, -C(O)R⁶, -C(O)OR⁶, -OR⁶, -SR⁶, -S(O)R⁶, -S(O)₂R⁶, -NR⁷R⁸, -CONR⁷R⁸, -N(R⁷)C(O)R⁶, -N(R⁷)C(O)OR⁶, -OC(O)NR⁷R⁸, -N(R⁷)C(O)N⁷R⁸, -P(O)(OR⁶)₂, -SO₂NR⁷R⁸, -N(R⁷)SO₂R⁶, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₅-C₆ cycloalkenyl, aryl, and heteroaryl;

each R⁶ is independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl, and heteroaryl;

15 R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₄-C₆ heterocycloalkyl, aryl, and heteroaryl; or R⁷ and R⁸ taken together with the nitrogen to which they are attached form a 5- or 6- membered saturated ring optionally containing one other heteroatom which is oxygen, nitrogen or sulphur;

If any carbon or heteroatom of R¹ or R² is substituted, it may be substituted with one or more substituents independently selected from the group consisting of C₁-C₆ alkyl, aryl, heteroaryl, 20 halogen, -OR⁶, -NR⁷R⁸, cyano, nitro, -C(O)R⁶, -C(O)OR⁶, -SR⁶, -S(O)R⁶, -S(O)₂R⁶, -CONR⁷R⁸, -N(R⁷)C(O)R⁶, -N(R⁷)C(O)OR⁶, -OC(O)NR⁷R⁸, -N(R⁷)C(O)NR⁷R⁸, -SO₂NR⁷R⁸, -N(R⁷)SO₂R⁶, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ heterocycloalkyl, C₅-C₈ cycloalkenyl, aryl or heteroaryl, wherein R⁶, R⁷, and R⁸ are the same as defined above;

or a pharmaceutically acceptable salt or solvate thereof.

25 In a second aspect of the present invention, there is provided a compound of formula (I) or a salt or solvate thereof for use in mammalian therapy, e.g. treating amenia. An example of this therapeutic approach is that of a method for treating anemia caused by increasing the production of erythropoietin (Epo) by inhibiting HIF prolyl hydroxylases comprising administering a compound of formula (I) to a patient in need thereof, neat or admixed with a pharmaceutically acceptable 30 excipient, in an amount sufficient to increase production of Epo.

In a third aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a salt, solvate, or the like thereof, and one or more of pharmaceutically acceptable carriers, diluents and excipients.

35 In a fourth aspect, there is provided the use of a compound of formula (I) or a salt or solvate thereof in the preparation of a medicament for use in the treatment of a disorder mediated

by inhibiting HIF prolyl hydroxylases, such as an anemia, that can be treated by inhibiting HIF prolyl hydroxylases.

DETAILED DESCRIPTION OF THE INVENTION

5 For the avoidance of doubt, unless otherwise indicated, the term “substituted” means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

The term “independently” means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

10 An “effective amount” means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term “therapeutically effective amount” means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder,
15 or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein the term “alkyl” refers to a straight- or branched-chain hydrocarbon radical having the specified number of carbon atoms, so for example, as used herein, the terms “C₁-C₆ alkyl” refers to an alkyl group having at least 1 and up to 6 carbon atoms respectively. Examples
20 of such branched or straight-chained alkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *n*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *n*-hexyl, and branched analogs of the latter normal alkanes.

When the term “alkenyl” (or “alkenylene”) is used it refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and at least 1 and up to 3
25 carbon-carbon double bonds. Examples include ethenyl (or ethenylene) and propenyl (or propenylene).

When the term “alkynyl” (or “alkynylene”) is used it refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and at least 1 carbon-carbon triple bonds. Examples include ethynyl (or ethynylene) and propynyl (or propynylene).

30 When “cycloalkyl” is used it refers to a non-aromatic, saturated, cyclic hydrocarbon ring containing the specified number of carbon atoms. So, for example, the term “C₃-C₆ cycloalkyl” refers to a non-aromatic cyclic hydrocarbon ring having from three to six carbon atoms. Exemplary “C₃-C₆ cycloalkyl” groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "C₅-C₆ cycloalkenyl" refers to a non-aromatic monocyclic carboxycyclic ring having the specified number of carbon atoms at least 1 carbon-carbon double bonds.

"Cycloalkenyl" includes by way of example cyclopentenyl and cyclohexenyl.

Where "C₃-C₆ heterocycloalkyl" is used, it means a non-aromatic heterocyclic ring
5 containing the specified number of ring atoms being, saturated or having one or more degrees of unsaturation and containing one or more heteroatom substitutions selected from O, S and/or N. Examples of "heterocyclic" moieties include, but are not limited to, aziridine, thiirane, oxirane, azetidine, oxetane, thietane, tetrahydrofuran, pyran, 1,4-dioxane, 1,4-dithiane, 1,3-dioxane, 1,3-dioxolane, piperidine, piperazine, 2,4-piperazinedione, pyrrolidine, 2-imidazoline, imidazolidine,
10 pyrazolidine, pyrazoline, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

"Aryl" refers to optionally substituted monocyclic and polycarbocyclic unfused or fused groups having 6 to 14 carbon atoms and having at least one aromatic ring that complies with Hückel's Rule. Examples of aryl groups are phenyl, biphenyl, naphthyl, anthracenyl,
15 phenanthrenyl and the like.

"Heteroaryl" means an optionally substituted aromatic monocyclic ring or polycarbocyclic fused ring system wherein at least one ring complies with Hückel's Rule, has the specified number of ring atoms, and that ring contains at least one heteroatom selected from N, O, and/or S. Examples of "heteroaryl" groups include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl,
20 triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzthiazolyl, indoliziny, indolyl, isoindolyl, and indazolyl.

25 The substituents on aryl or heteroaryl can be selected from the group consisting of hydrogen, nitro, cyano, halogen, CF₃, -C(O)R⁶, -C(O)OR⁶, -OR⁶, -SR⁶, -S(O)R⁶, -S(O)₂R⁶, -NR⁷R⁸, -CONR⁷R⁸, -N(R⁷)C(O)R⁶, -N(R⁷)C(O)OR⁶, -OC(O)NR⁷R⁸, -N(R⁷)C(O)N⁷R⁸, -P(O)(OR⁶)₂, -SO₂NR⁷R⁸, -N(R⁷)SO₂R⁶, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₆ heterocycloalkyl, C₅-C₆ cycloalkenyl, aryl, and heteroaryl;

30 The term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

The term "solvate" refers to a complex of variable stoichiometry formed by a solute and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water,
35 methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable

solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

Herein, the term "pharmaceutically-acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects.

5 These pharmaceutically-acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

In certain embodiments, compounds according to Formula I may contain an acidic functional group, one acidic enough to form salts. Representative salts include pharmaceutically-
10 acceptable metal salts such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc salts; carbonates and bicarbonates of a pharmaceutically-acceptable metal cation such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc; pharmaceutically-acceptable organic primary, secondary, and tertiary amines including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines such as methylamine, ethylamine, 2-
15 hydroxyethylamine, diethylamine, triethylamine, ethylenediamine, ethanolamine, diethanolamine, and cyclohexylamine.

In certain embodiments, compounds according to Formula (I) may contain a basic functional group and are therefore capable of forming pharmaceutically-acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically-acceptable
20 inorganic acids and pharmaceutically-acceptable organic acids. Representative pharmaceutically-acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenylacetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, *p*-aminosalicylate, glycolate, lactate, heptanoate, phthalate, oxalate, succinate,
25 benzoate, *o*-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pantoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), *p*-aminobenzenesulfonate, *p*-toluenesulfonate (tosylate), and naphthalene-2-sulfonate.

30 Compounds of particular interest include those wherein:

R¹ is an unsubstituted or substituted 4 to 6-membered mono-cyclic heteroaryl or a 9- to 11-membered bicyclic heteroaryl ring containing one or more hetero atoms selected from the group consisting of N, O and S;

R² is aryl, C₁-C₆ alkyl-aryl;

R^3 , R^4 and R^5 each independently selected from the group consisting of hydrogen, nitro, cyano, halogen, CF_3 , $-C(O)R^6$, $-C(O)OR^6$, $-OR^6$, $-SR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NR^7R^8$, $-CONR^7R^8$, $-N(R^7)C(O)R^6$, $-N(R^7)C(O)OR^6$, $-OC(O)NR^7R^8$, $-N(R^7)C(O)N^7R^8$, $-P(O)(OR^6)_2$, $-SO_2NR^7R^8$, $-N(R^7)SO_2R^6$, C_1 - C_{10} alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_5 - C_6 cycloalkenyl, aryl, and heteroaryl;

each R^6 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, aryl, and heteroaryl;

R^7 and R^8 are each independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, aryl, and heteroaryl; or R^7 and R^8 taken together with the nitrogen to which they are attached form a 5- or 6- or 7-membered saturated ring optionally containing one other heteroatom which is oxygen, nitrogen or sulphur;

If any carbon or heteroatom of R^1 or R^2 is substituted, it may be substituted with one or more substituents independently selected from the group consisting of C_1 - C_6 alkyl, aryl, heteroaryl, halogen, $-OR^6$, $-NR^7R^8$, cyano, nitro, $-C(O)R^6$, $-C(O)OR^6$, $-SR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-CONR^7R^8$, $-N(R^7)C(O)R^6$, $-N(R^7)C(O)OR^6$, $-OC(O)NR^7R^8$, $-N(R^7)C(O)N^7R^8$, $-SO_2NR^7R^8$, $-N(R^7)SO_2R^6$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, C_5 - C_6 cycloalkenyl, aryl or heteroaryl, wherein R^6 , R^7 , and R^8 are the same as defined above;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of further interest are those wherein:

R^1 is an unsubstituted or substituted 4 to 6-membered mono-cyclic heteroaryl containing one or more hetero atoms selected from the group consisting of N, O and S;

R^2 is aryl, C_1 - C_6 alkyl-aryl;

R^3 , R^4 and R^5 each independently selected from the group consisting of hydrogen, nitro, cyano, halogen, CF_3 , $-C(O)R^6$, $-C(O)OR^6$, $-OR^6$, $-SR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NR^7R^8$, $-CONR^7R^8$, $-N(R^7)C(O)R^6$, $-N(R^7)C(O)OR^6$, $-OC(O)NR^7R^8$, $-N(R^7)C(O)N^7R^8$, $-P(O)(OR^6)_2$, $-SO_2NR^7R^8$, $-N(R^7)SO_2R^6$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, C_5 - C_6 cycloalkenyl, aryl, and heteroaryl;

each R^6 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, aryl, and heteroaryl;

R^7 and R^8 are each independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, aryl, and heteroaryl; or R^7 and R^8 taken together with the nitrogen to which they are attached form a 5- or 6- membered saturated ring optionally containing one other heteroatom which is oxygen, nitrogen or sulphur;

or a pharmaceutically acceptable salt or solvate thereof.

Specific compounds exemplified herein via the Examples set out below are:

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

5 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chloro-3-fluorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-*N*-{[4-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

10 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-{[4-(1-methylethyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

15 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-{[4-(methylsulfonyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-{[4-(dimethylamino)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

20 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)-1-methylethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

25 3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

30 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

35 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[6-chloro-5-(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

5 *N*-[(4-chlorophenyl)methyl]-3-[6-(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[4,5-bis(methyloxy)-2-pyrimidinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

10 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

15 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

20 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide; or

25 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

or a pharmaceutically acceptable salt or solvate thereof.

30 Processes for preparing the compound of formula (I) are also within the ambit of this invention (see Illustrated Methods of Preparation section). The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

35 Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. The compounds claimed below include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures.

Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), or claimed below, as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the claimed compounds as mixtures with isomers thereof in which one or more chiral centers are inverted.

5 Also, it is understood that any tautomers and mixtures of tautomers of the claimed compounds are included within the scope of the compounds of formula (I) as disclosed herein above or claimed herein below.

Where there are different isomeric forms they may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic
10 methods or by stereospecific or asymmetric syntheses.

While it is possible that, for use in therapy, a compound of formula (I), as well as salts, solvates and the like, may be administered as a neat preparation, i.e. no additional carrier, the more usual practice is to present the active ingredient confectioned with a carrier or diluent. Accordingly, the invention further provides pharmaceutical compositions, which includes a compound of
15 formula (I) and salts, solvates and the like, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and salts, solvates, etc, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the
20 preparation of a pharmaceutical formulation including admixing a compound of the formula (I), or salts, solvates etc, with one or more pharmaceutically acceptable carriers, diluents or excipients.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally
25 and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of
30 Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by
35 reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention. Preferred prodrugs for compounds of the invention include : esters,

carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 1 g, or 1 mg to 700 mg, or further, 5 mg to 100 mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association a compound of formula (I) with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is

prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture
5 can be granulated by tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material
10 and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of a compound of formula (I). Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are
15 prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

20 Where appropriate, dosage unit pharmaceutical compositions for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and
25 solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The pharmaceutical compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections,
30 immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the pharmaceutical compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include
35 flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the intended recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant prescribing the medication. However, an effective amount of a compound of formula (I) for the treatment of anemia will generally be in the range of 0.1 to 100 mg/kg body weight of recipient per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, etc., may be determined as a proportion of the effective amount of the compound of formula (I) *per se*. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

Chemical Background:

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention as prepared are given in the examples.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I) and (II). Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I) and (II). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic and/or enzymatic processes.

The following abbreviations are used in the following pages:

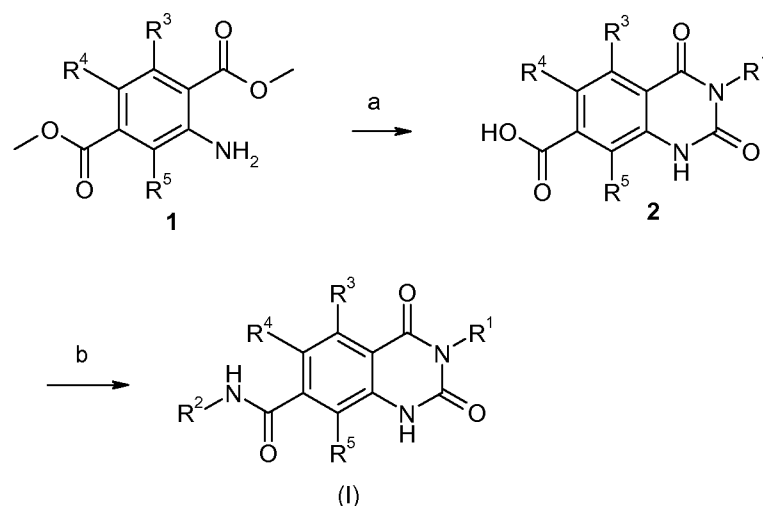
ACN	Acetonitrile
DCE	1,2-dichloroethane
DCM	Dichloromethane
DIEA	Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMHB resin	2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde
DMSO	Dimethylsulfoxide
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide HCl
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOAc	Acetic acid
NMP	<i>N</i> -methylpyrrolidone
PS-DCC	Polymer supported dicyclohexylcarbodiimide
Rt or rt	room temperature
Sat.	Saturated
TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
DMC	2-chloro-1,3-dimethylimidazolinium chloride

5 Illustrated Methods of Preparation

Schemes

Included in the present invention is a process according to Schemes 1-3 for the synthesis of the compounds:

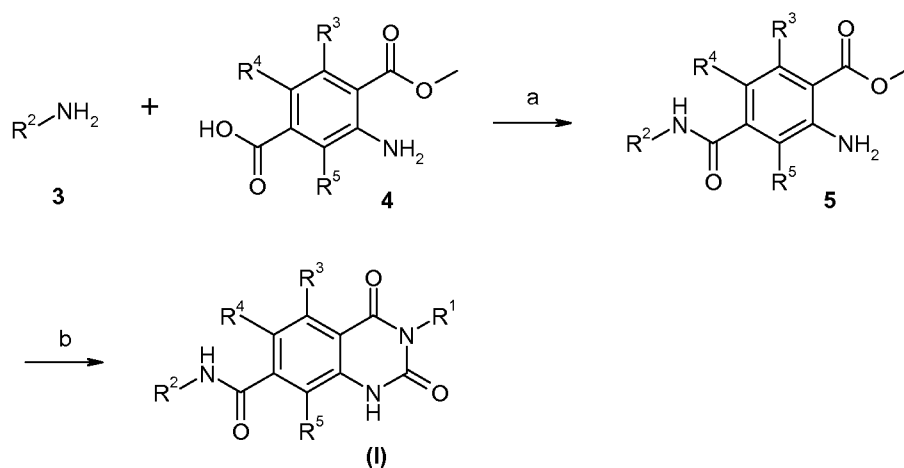
Scheme 1



Conditions: a) (i) triphosgene, DIEA, DCM, 0 °C; NH₂-R¹, DCM, rt; ii) 6N NaOH, MeOH, rt; b) R²NH₂, HATU, DIEA, DMF, rt.

Dimethyl 2-amino-1,4-benzenedicarboxylate or appropriately substituted dimethyl 2-amino-1,4-benzenedicarboxylates **1** react with with triphosgene in the presence of a base such as DIEA to give isocyanates. A variety of amines, such as appropriately substituted aminopyridines, aminopyrimidines and aminothiazoles, are added to isocyanates in an appropriate solvent, such as DCM, DMF or DMSO, by heating or in room temperature to afford cyclized methyl 2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylates. Upon addition of an appropriate base, such as NaOH, the methyl 2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylates are hydrolyzed to the corresponding acids **2**. Amide formation of the acids **2** with a variety of amines or anilines, such as appropriately substituted benzylamines, in the presence of a coupling reagent, such as DMC, HATU, EDC, and base, such as DIEA, in an appropriate solvent like DMF or DCM/DMF at rt produces the desired compounds of formula (I).

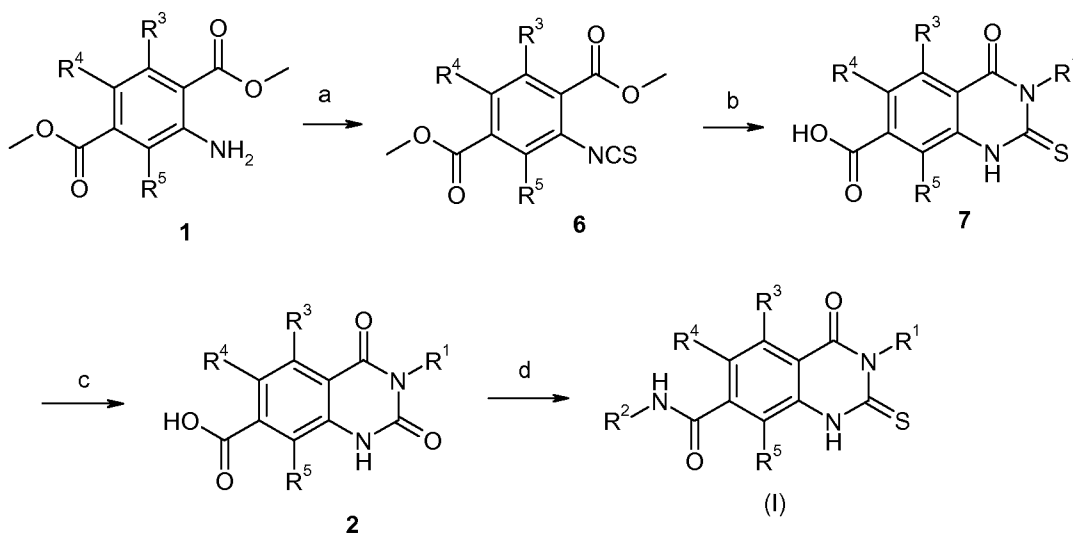
Scheme 2



Conditions: a) HATU, DIEA, DMF, rt; b) (i) triphosgene, DMAP, DCM, -77 °C; $\text{NH}_2\text{-R}^1$, rt; DMF, 50 °C; (ii) 2N NaOH, DMF, rt

3-Amino-4-[(methyloxy)carbonyl]benzoic acid or appropriately substituted 3-amino-4-
 5 [(methyloxy)carbonyl]benzoic acids **4** react with amines **3**, such as appropriately substituted
 benzylamines, in the presence of a coupling reagent, such as HATU, and base, such as DIEA, in an
 appropriate solvent like DMF at rt to give the amides **5**. The amides **5** react with triphosgene in the
 presence of base such as DMAP in DCM to give isocyanates. A variety of amines, such as
 appropriately substituted aminopyridines, aminopyrimidines and aminothiazoles, are added to
 10 isocyanates in an appropriate solvent, such as DCM, DMF or DMSO, by heating or in room
 temperature to afford the desired compounds of formula (I).

Scheme 3



15 Conditions: a) thiophosgene, sat. NaHCO_3 aqueous solution, CHCl_3 , rt; b) i) $\text{NH}_2\text{-A-R}^1$, DMF,
 heating; ii) 10% NaOH; c) (i) $\text{C}_2\text{H}_5\text{I}$, 5N NaOH, DMF, rt; (ii) 6N HCl, EtOH, 100 °C; c) R^2NH_2 ,
 HATU, DIEA, DMF, rt.

Dimethyl 2-amino-1,4-benzenedicarboxylate or appropriately substituted dimethyl 2-
 20 amino-1,4-benzenedicarboxylates **1** react with thiophosgene in sat NaHCO_3 and CHCl_3 at the room
 temperature to give isothiocyanates **6**. A variety of amines or anilines, such as appropriately
 substituted aminopyridines, aminopyrimidines and aminothiazoles, are added to isothiocyanates **6**
 in an appropriate solvent, such as DMF or DMSO, by heating or in room temperature to afford
 cyclized 4-oxo-2-thioxoquinazolinecarboxylates. Upon addition of an appropriate base, such as
 25 NaOH, the 4-oxo-2-thioxoquinazolinecarboxylates are hydrolyzed to the corresponding acids **7**.
 Converting thiocarbonyl to ethyl sulfide in the presense of a base such as NaOH followed by acidic

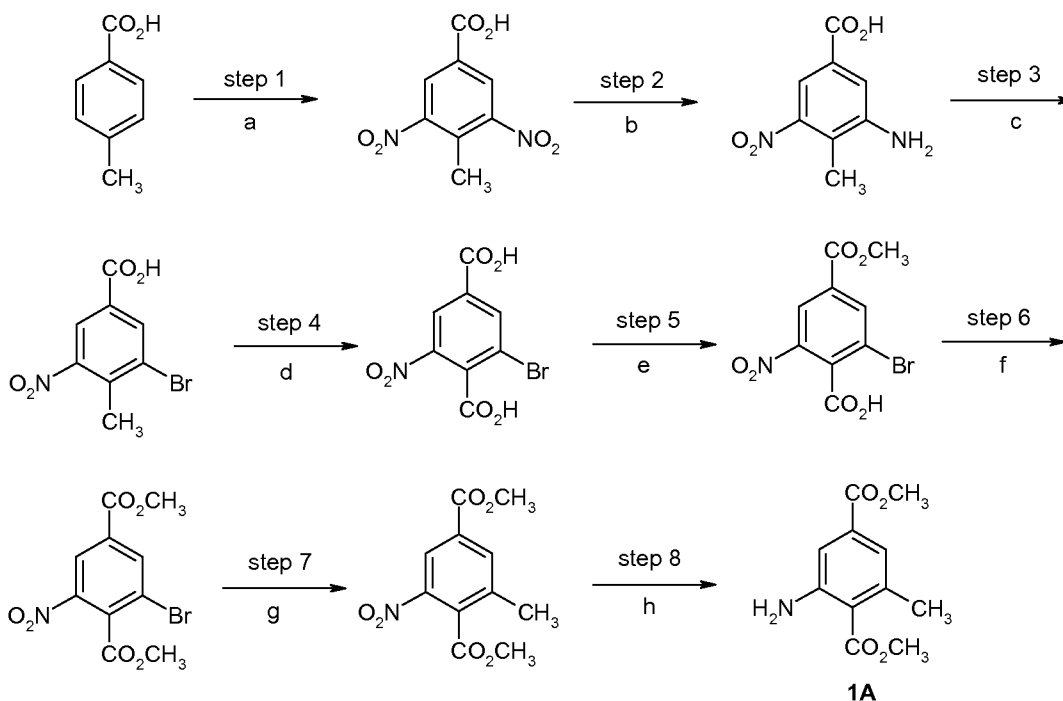
hydrolysis with HCl in ethanol under heating gave the diones **2**. Amide formation of **2** with a variety of amines or anilines, such as appropriately substituted benzylamines, in the presence of a coupling reagent, such as DMC, HATU, EDC, and base, such as DIEA and DMAP, in an appropriate solvent like DMF or DCM/DMF at rt produces the desired compounds of formula (I).

5

Substituted dimethyl 2-amino-1,4-benzenedicarboxylates **1A-1G** were prepared according to the following procedures.

Preparation 1A) dimethyl 2-amino-6-methyl-1,4-benzenedicarboxylate

10



Conditions: a) 0-5 °C, conc. H₂SO₄, conc. HNO₃; b) NaSH, MeOH, reflux; c) 0-5 °C, conc. HCl:H₂O (1:1), NaNO₂; d) H₂O, KMnO₄, reflux 5h; e) MeOH, cat. conc. H₂SO₄, reflux; f) i) N-nitroso methylurea, 50% aq. KOH, ether, ii) MeOH; g) Toluene, CsCO₃, trimethylboroxine, Pd(PPh₃)₄, 100-110 °C, 16 h; h) MeOH, H₂ (g), Pd/C

15

Step 1: 4-Methyl benzoic acid (50 g, 368 mmole) was dissolved in conc. sulfuric acid (500 ml) and conc. nitric acid (200 ml) was added slowly at 18-20°C over a period of 3 h. After addition, the reaction mixture was then allowed to come to room temperature and stirred for 2 h. During this period, the dark viscous reaction mixture turned yellow in color with some amount of yellow solid precipitation. TLC revealed the disappearance of starting material. The reaction mixture was poured over crushed ice water (1 kg) and stirred for 30 minutes. The pale yellow solid obtained was filtered, washed with water (100 ml) and dried under vacuum to yield 70 g of 4-

20

methyl-3,5-dinitrobenzoic acid (83%). $^1\text{H-NMR}$ in $\text{DMSO}-d_6$ δ ppm : 2.52 (3H, s, CH_3), 8.58 (2H, s, Ar-H).

Step 2: A solution of 4-methyl-3,5-dinitrobenzoic acid (70 g, 307 mmole) in methanol (750 ml) was warmed to 60°C and a 30% solution of sodium hydrogen sulfide (133 ml, 539 mmole) was added slowly over a period of 30 minutes. The reaction mixture was refluxed for 3 h. The reaction mixture was evaporated to dryness and the resulting residue was treated with water (500 ml). The mixture was acidified to pH 3 using dil. HCl. The precipitated product was extracted with ethyl acetate (3×250 ml) and the ethyl acetate layer was dried and evaporated to yield 50 g of 3-amino-4-methyl-5-nitrobenzoic acid as yellow solid (83%). $^1\text{H-NMR}$ in $\text{DMSO}-d_6$ δ ppm: 2.14 (3H, s, CH_3), 5.85 (2H, bs, NH_2), 7.41 (1H, s, Ar-H), 7.56 (1H, s, Ar-H), 13.31 (1H, bs, COOH).

Step 3: To a suspension of 3-amino-4-methyl-5-nitrobenzoic acid (50 g, 254 mmole) in a mixture of conc. hydrochloric acid (350 ml) and water (350 ml) was added at between $0-5^\circ\text{C}$ a solution of sodium nitrite (18.6 g, 270 mmole) in water (30 ml) over a period of 15 to 20 minutes. After stirring at $0-5^\circ\text{C}$ for another 30 minutes, the reaction mixture was then slowly added to a cold cuprous bromide (73.21 g, 516 mmole) solution in conc. hydrochloric acid (220 ml) with stirring. The reaction mixture was stirred at $0-5^\circ\text{C}$ for 30 minutes and then at room temperature for another 30 minutes. Finally, after stirring at $30-35^\circ\text{C}$ for 30 minutes, precipitated solid was filtered, washed with water (50 ml) and dried under vacuum to yield 58 g of 3-bromo-4-methyl-5-nitrobenzoic acid as pink solid (88%). $^1\text{H-NMR}$ in $\text{CD}_3\text{OD}-d_4$ δ ppm : 2.6 (3H, s, CH_3), 8.21 (1H, d, $J = 1.4$ Hz, Ar-H), 8.27 (1H, d, $J = 1.2$ Hz, Ar-H).

Step 4: To a solution of KMnO_4 (176.85 g, 1.12 mole) in water (2650 ml) was added at ambient temperature 3-bromo-4-methyl-5-nitrobenzoic acid (97 g, 373 mmole) and the mixture was then heated to reflux. After every 3 h, additional lots of KMnO_4 (58.95g, 373 mmole; 117.9g, 746 mmole; 58.95g, 373 mmole) were added and thereafter refluxing continued for a further 5 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated to approximately 400 ml on a rotavap. The concentrated aqueous mixture was cooled to $0-5^\circ\text{C}$ and acidified to pH 2 with conc. HCl. The precipitated solid was filtered and washed with water (50 ml) to yield 85 g of 2-bromo-6-nitroterephthalic acid as an off-white solid after drying (79%). $^1\text{H-NMR}$ in $\text{DMSO}-d_6$ δ ppm : 8.12 (1H, s, Ar-H) 8.31 (1H, s, Ar-H).

Step 5: To a suspension of 2-bromo-6-nitroterephthalic acid (80 g, 276 mmole) in methanol (2000 ml) was added, at ambient temperature, conc. sulfuric acid (25 ml) and the mixture was refluxed for 10 h. The reaction mixture was filtered and concentrated on a rota-vap. The resulting residue was dissolved in ethyl acetate (800 ml) and washed with water (2×50 ml). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to yield 70 g of 2-bromo-6-

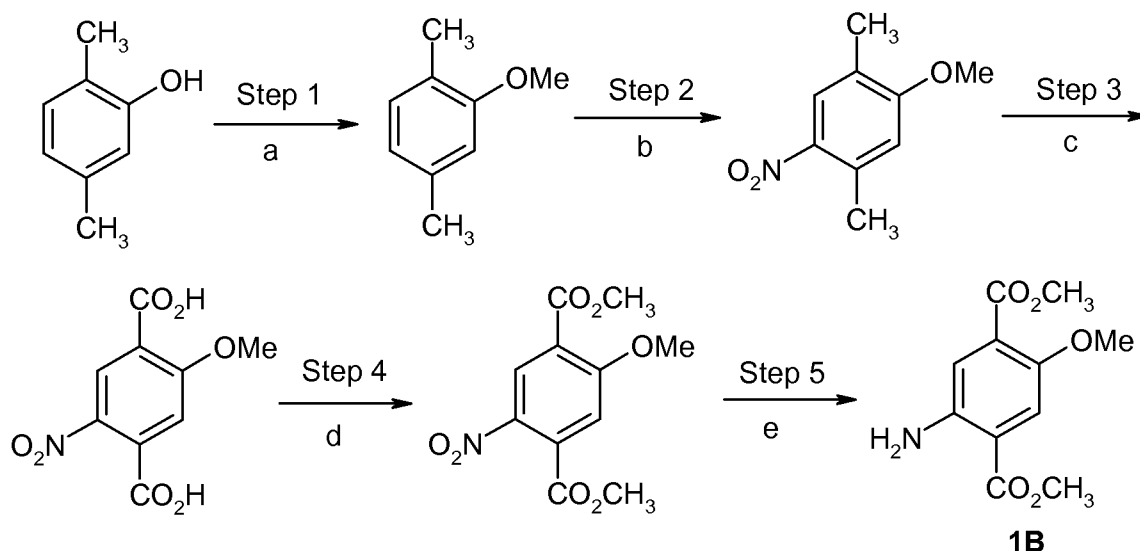
nitro-terephthalic acid 4-methyl ester as colorless solid (83%). ¹H-NMR in CD₃OD-d₄ δ ppm : 3.97 (3H, s, OCH₃), 8.35 (1H, d, J = 1.2 Hz, Ar-H), 8.59 (1H, d, J = 1.2 Hz, Ar-H).

Step 6: To a solution of 2-bromo-6-nitro-terephthalic acid 4-methyl ester (25 g, 82 mmole) in methanol (50 ml) maintained between 0-5°C was added an ethereal solution of
5 diazomethane (340 ml) [prepared from 50% aq. KOH (156 ml) and N-nitroso methylurea (34 g, 330mmole)] over a period of 30 minutes. The reaction mixture was stirred between 0-5°C for 1 h and then allowed to come to room temperature. Excess diazomethane was quenched by adding acetic acid. The reaction mixture was dried over Na₂SO₄ and concentrated under vacuum to yield
10 19 g of dimethyl 2-bromo-6-nitroterephthalate (73%) as a colorless solid. ¹H-NMR in CDCl₃ δ ppm: 4.01 (3H, s, OCH₃), 4.03 (3H, s, OCH₃), 8.36 (1H, s, Ar-H), 8.7 (1H, s, Ar-H).

Step 7: To a solution of dimethyl 2-bromo-5-nitroterephthalate (12 g; 38 mmole) in toluene (50ml) maintained at ambient temperature were added cesium carbonate (36 g; 110 mmole), tetrakis(triphenylphosphine)palladium (4.32 g; 3.8 mmole) and trimethylboroxine (5.28 ml; 38 mmole) sequentially under an inert atmosphere (nitrogen). The mixture was heated to 100-
15 110°C for 8 h. Another lot of trimethylboroxine (5.28 ml; 38 mmole) was added and the mixture was heated at 100-110°C for another 8 h. The reaction mass was cooled to ambient temperature and filtered. The filtrate was concentrated on a rotavap and the resulting brown solid (11 g) was purified by column chromatography over silica gel (2.5% ethyl acetate in hexane) to yield 5.8 g (60%) of dimethyl 2-methyl-6-nitroterephthalate as colorless solid. ¹H-NMR in CDCl₃ δ ppm:
20 2.47 (3H, s, CH₃), 3.99 (6H, s, OCH₃), 8.19 (1H, s, Ar-H), 8.6 (1H, s, Ar-H).

Step 8: Mixture of dimethyl 2-methyl-6-nitroterephthalate (5.7 g; 22.4 mmoles), 5% Pd/C (0.7 g) in methanol (228 ml) was hydrogenated under a hydrogen pressure of 40 psi for 2 h in a Parr hydrogenator. The mixture was filtered under nitrogen and filtrate was concentrated to give
25 4.2 g (84%) of dimethyl 2-amino-6-methylterephthalate as yellow solid. ¹H NMR in DMSO-d₆ δ ppm : 2.44 (3H, s, CH₃), 3.94 (3H, s, OCH₃), 3.96 (3H, s, OCH₃), 5.15 (2H, bs, NH₂), 8.45 (1H, d, J = 1.0 Hz, Ar-H), 8.55 (1H, d, J = 1.2 Hz, Ar-H).

Preparation 1B) dimethyl 2-amino-5-(methoxy)-1,4-benzenedicarboxylate



Conditions: a) acetone, anh. K_2CO_3 , $(CH_3)_2SO_4$, reflux; b) conc. HNO_3 , $NaNO_2$;

c) H_2O , $KMnO_4$, reflux; d) i) N-nitroso methylurea, 50% aq. KOH , ether, ii) $MeOH$;

e) $MeOH$, H_2 , Pd/C

Step 1: To a mixture of 2,5-dimethyl phenol (50 g, 410 mmole), and potassium carbonate (68 g; 490 mmole) in acetone (600 ml), dimethyl sulfate (31.02g, 246 mmole) was added at ambient temperature. The mixture was refluxed for 9 h after which TLC revealed presence of the starting material. Additional dimethyl sulfate (31.02 g, 246 mmole) was added and the reaction mixture was refluxed for another 9 h. The reaction mixture was filtered and acetone was removed on a rotavap. The resulting oil was stirred with 20% $NaOH$ (100 ml) for 10 minutes. The organic layer was washed with water (2 X 500 ml) till the aqueous layer was neutral. The organic layer was dried over sodium sulfate and concentrated under vacuum to yield 45.5 g of 2-methoxy-1,4-dimethylbenzene (81%). ^1H NMR in $CDCl_3$ δ ppm: 2.2 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 6.65 (1H, s, Ar-H), 6.7 (1H, d, $J = 7.2$ Hz, Ar-H), 7.03 (1H, d, $J = 7.2$ Hz, Ar-H).

Step 2: To an ice-cold conc. nitric acid (500 ml) was added slowly under stirring over a period of 20 minutes 2-methoxy-1,4-dimethylbenzene (45 g, 330 mmole). To this cold reaction mixture, sodium nitrite (67.5g, 990 mmole) was added slowly in lots over a period of 1 h while maintaining the temperature below $2^\circ C$. The reaction mixture was stirred at between $0-5^\circ C$ for 5 h. The reaction mass was poured over ice-cold water (2000 ml) and the precipitated solid was filtered, washed with cold water (200 ml) and dried. The crude solid was crystallized from ethanol and water (7:1) to yield 28 g of 2-methoxy-5-nitro-1,4-dimethylbenzene (46%). ^1H NMR in $CDCl_3$ δ ppm: 2.21 (3H, s, CH_3), 2.63 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 6.64 (1H, s, Ar-H), 7.9 (1H, s, Ar-H).

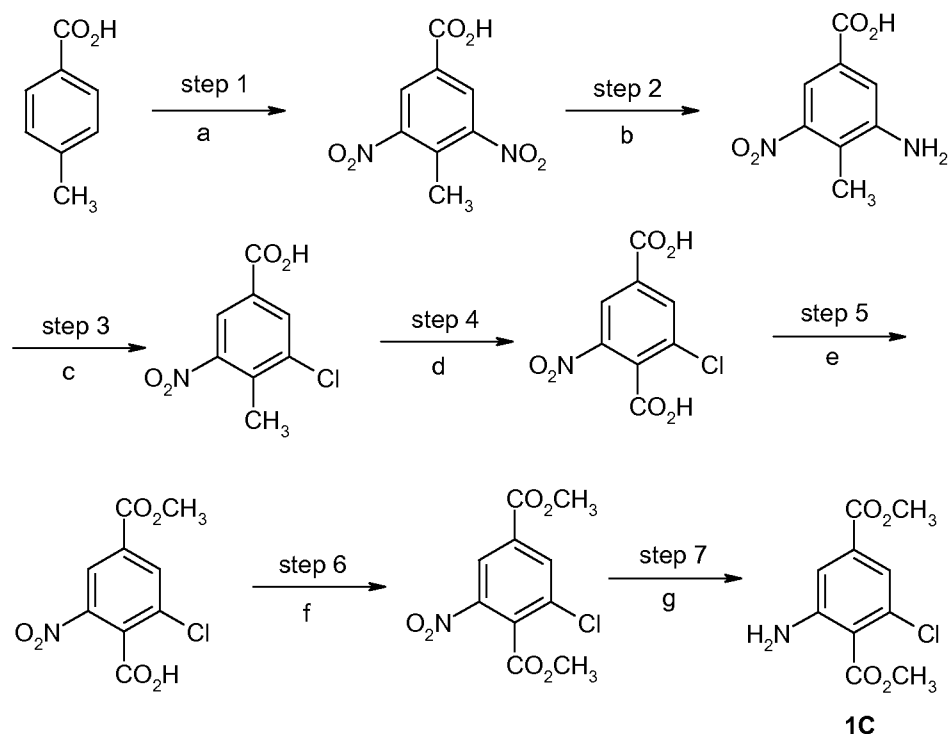
Step 3: A mixture of 2-methoxy-5-nitro-1,4-dimethylbenzene (28 g, 153 mmole) and $KMnO_4$ (79 g; 500 mmole) in water (1500 ml) was reflux for 5 h under stirring. After the

disappearance of KMnO_4 color, TLC showed the presence of starting material. Additional KMnO_4 (79 g; 500 mmole) was added and refluxing continued for 5 h. TLC showed the presence of starting material, another lot of KMnO_4 (50.5 g; 320 mmole) was added and refluxing continued for 5 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated to approx. 300ml on a rotavap. The concentrated aqueous mixture was cooled to 0-5°C and acidified to pH 2 with conc. HCl. The precipitated solid was filtered and washed with water to yield 18.5 g of 2-methoxy-5-nitroterephthalic acid as a colorless solid after drying (50%).
 $^1\text{H-NMR}$ in DMSO-d_6 δ ppm: 3.98 (3H, s, OCH_3), 7.41 (1H, s, Ar-H), 8.3 (1H, s, ArH).

Step 4: To a solution of 2-methoxy-5-nitroterephthalic acid (15 g, 61 mmole) in methanol (200 ml), an ethereal solution of diazomethane (1000 ml) [prepared from 50% aq. KOH (100 ml) and N-nitroso methylurea (60 g, 580 mmole)] was added maintaining the temperature at between 0-5°C over a period of 30 minutes. The reaction mixture was stirred at between 0-5°C for 1 h and then allowed to come to room temperature. Excess of diazomethane was quenched with acetic acid. The reaction mixture was dried over Na_2SO_4 and concentrated to yield 15.5 g of dimethyl 2-methoxy-5-nitroterephthalate (94%) as colorless solid. $^1\text{H-NMR}$ in CDCl_3 δ ppm: 3.92 (3H, s, OCH_3), 3.95 (3H, s, COOCH_3), 4.02 (3H, s, COOCH_3), 7.11 (1H, s, Ar-H), 8.53 (1H, s, Ar-H).

Step 5: A mixture of dimethyl 2-methoxy-5-nitroterephthalate (15.5 g; 57 mmoles), 5% Pd/C (1 g) in methanol (160 ml) was hydrogenated under hydrogen pressure of 50 psi for 1 h in a Parr hydrogenator. This mixture was filtered under nitrogen and the filtrate was concentrated to get 13.5 g (99%) of dimethyl 2-amino-5-methoxyterephthalate as yellow solid. $^1\text{H-NMR}$ in CDCl_3 δ ppm: 3.38 (3H, s, OCH_3), 3.88 (3H, s, COOCH_3), 3.89 (3H, s, COOCH_3), 5.42 (2H, bs, NH_2), 7.07 (1H, s, Ar-H), 7.41 (1H, s, Ar-H).

Preparation 1C) dimethyl 2-amino-6-chloro-1,4-benzenedicarboxylate



Conditions: a) 0-50 °C conc. H₂SO₄, conc. HNO₃; b) NaSH, MeOH, reflux; c) 0-5 °C, conc. HCl:H₂O (1:1), NaNO₂; d) H₂O, KMnO₄, reflux 5h; e) MeOH, cat. conc. H₂SO₄, reflux; f) i) N-nitroso methyleneurea, 50% aq. KOH, ether, ii) MeOH; g) Toluene, Fe/AcOH

5

Step 1: 4-Methyl benzoic acid (50 g, 368 mmole) was dissolved in conc. sulfuric acid (500 ml) and conc. nitric acid (200 ml) was added slowly at 18-20°C over a period of 3 h. After addition, the reaction mixture was then allowed to come to room temperature and stirred for 2 h. During this period, the dark viscous reaction mixture turned yellow in color with some amount of yellow solid precipitation. TLC revealed disappearance of starting material. The reaction mixture was poured over crushed ice water (1 kg) and stirred for 30 minutes. Pale yellow solid obtained was filtered, washed with water (100 ml) and dried under vacuum to yield 70 g of 4-methyl-3,5-dinitrobenzoic acid (83%). ¹H-NMR in DMSO-d₆ δ ppm : 2.52 (3H, s, CH₃), 8.58 (2H, s, Ar-H).

Step 2: A solution of 4-methyl-3,5-dinitrobenzoic acid (70 g, 307 mmole) in methanol (750 ml) was warmed to 60°C and a 30% solution of sodium hydrogen sulfide (133 ml, 539 mmole) was added slowly over a period of 30 minutes. The reaction mixture was refluxed for 3 h. It was evaporated to dryness and resulting residue was treated with water (500 ml). The mixture was acidified to pH 3 using dil. HCl. The precipitated product was extracted with ethyl acetate (3 × 250 ml) and the ethyl acetate layer was dried and evaporated to yield 50 g of 3-amino-4-methyl-5-nitrobenzoic acid as yellow solid (83%). ¹H-NMR in DMSO-d₆ δ ppm: 2.14 (3H, s, CH₃), 5.85 (2H, bs, NH₂), 7.41 (1H, s, Ar-H), 7.56 (1H, s, Ar-H), 13.31 (1H, bs, COOH).

Step 3: To a suspension of 3-amino-4-methyl-5-nitrobenzoic acid (25 g, 127 mmole) in a mixture of conc. hydrochloric acid (100 ml) and water (100 ml), a solution of sodium nitrite (9.3 g, 135 mmole) in water (25 ml) was added at between 0-5°C over a period of 15 to 20 minutes. After stirring at 0-5°C for another 30 minutes, the reaction mixture was slowly added to cold cuprous chloride (27.8 g, 280 mmole) solution in conc. hydrochloric acid (60 ml) with stirring. The reaction mixture was allowed to come to room temperature and stirred for 1 h. Precipitated solid was filtered off, washed with ice-cold water (25 ml) and dried under vacuum to yield 21.5 g of 3-chloro-4-methyl-5-nitrobenzoic acid as off-white solid (78%). ¹H-NMR in CD₃OD-*d*₄ δ ppm : 2.58 (3H, s, CH₃), 8.22 (1H, d, J = 1.4 Hz, Ar-H), 8.23 (1H, d, J = 1.4 Hz, Ar-H).

Step 4: A mixture of 3-chloro-4-methyl-5-nitrobenzoic acid (21.5 g, 100 mmole) and KMnO₄ (31.6 g; 200 mmole) in water (475 ml) was refluxed for 4 h under stirring. After the disappearance of KMnO₄ color, TLC showed the presence of starting material. Additional KMnO₄ (15.8 g; 100 mmole) was added and refluxing continued for 4 h. When TLC revealed the disappearance of starting material, the reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated to ca. 150 ml on a rotavap. The concentrated aqueous mixture was cooled to 0-5°C and acidified to pH 2 with conc. HCl. The precipitated solid was filtered and washed with water to yield 12 g of 2-chloro-6-nitroterephthalic acid as a colorless solid (49%). ¹H-NMR in DMSO-*d*₆ δ ppm : 8.35 (1H, s, ArH) 8.49 (1H, s, ArH).

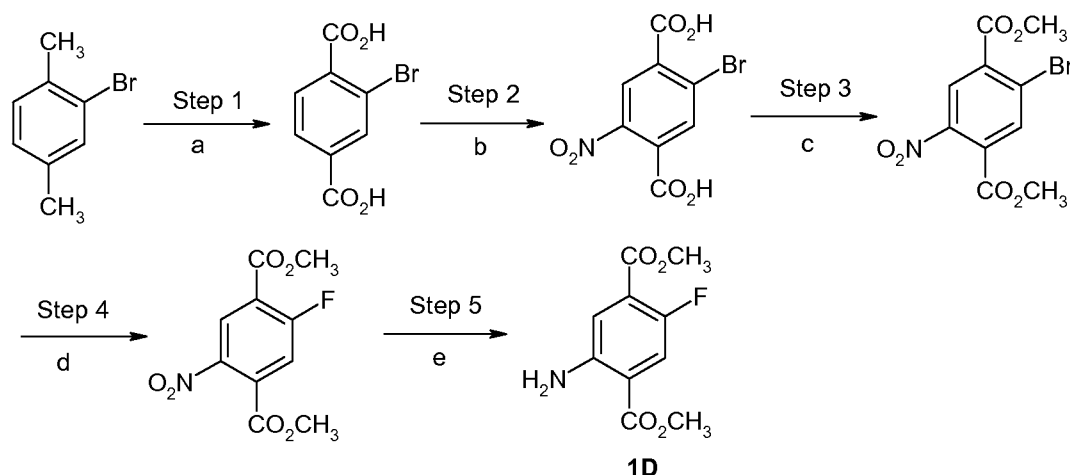
Step 5: To a suspension of 2-chloro-6-nitroterephthalic acid (12 g, 48 mmole) in methanol (300 ml) was added conc. sulfuric acid (7.5 ml) at ambient temperature and the mixture was refluxed for 18 h. The reaction mixture was concentrated on a rotavap and the resulting residue was dissolved in ethyl acetate (25 ml) and washed with water (2 × 20 ml). The organic phase was dried over anhydrous Na₂SO₄ and evaporated under vacuum to yield 10 g of 2-chloro-6-nitroterephthalic acid 4-methyl ester as colorless solid (80%). ¹H-NMR in CD₃OD-*d*₄ δ ppm : 4.0 (3H, s, COOCH₃), 8.44 (1H, d, J = 1.6 Hz, Ar-H), 8.67 (1H, d, J = 1.4 Hz, Ar-H).

Step 6: To a solution of 2-chloro-6-nitroterephthalic acid 4-methyl ester (10g, 38 mmole) in methanol (200 ml), an ethereal solution of diazomethane (100 ml) [prepared from 50% aq. KOH (56 ml) and N-nitroso methylurea (14 g, 135 mmole)] was added at between 0-5°C over a period of 30 minutes. The reaction mixture was stirred between 0-5°C for 1 h and then allowed to come to ambient temperature. Excess of diazomethane was quenched by adding acetic acid. The reaction mixture was dried and concentrated to yield 10 g of dimethyl 2-chloro-6-nitroterephthalate (96%) as a colorless solid. ¹H NMR in CDCl₃ δ ppm : 4.0 (3H, s, COOCH₃), 4.03 (3H, s, COOCH₃), 8.36 (1H, d, J = 1.4 Hz, Ar-H), 8.71 (1H, d, J = 1.4 Hz, Ar-H).

Step 7: To a solution of dimethyl 2-chloro-6-nitroterephthalate (9.5 g, 35 mmole) in toluene (400 ml), iron (20g, 357 mmole) was added at ambient temperature and mixture was heated

to reflux. Under reflux condition, acetic acid (33 ml) was added slowly over a period of 1 h and refluxing continued for 2 h. Another lot of acetic acid (33 ml) was added over a period of 1 h and refluxing continued for 2 h. As TLC revealed presence of the starting material, another lot of acetic acid (33 ml) was added over a period of 1 h and refluxing continued for 2 h. Upon complete
 5 disappearance of starting material, the mixture was cooled to room temperature and filtered through celite. Filtrate was concentrated on a rotavap and resulting residue was subjected to column chromatography purification over silica gel to yield 5 g of dimethyl 2-amino-6-chloroterephthalate as yellow solid (59%). ¹H NMR in CDCl₃ δ ppm : 3.89 (3H, s, COOCH₃), 3.94 (3H, s, COOCH₃), 6.03 (2H, s, NH₂), 7.18 (1H, s, Ar-H), 7.3 (1H, s, Ar-H).

Preparation 1D) dimethyl 2-amino-5-fluoro-1,4-benzenedicarboxylate



Conditions: a) H₂O, KMnO₄, reflux, 6 h; b) conc. H₂SO₄, conc. HNO₃, c) MeOH, conc. H₂SO₄;
 15 d) DMSO, PEG 400, KF, 90 °C; e) MeOH, H₂ (g), Pd/C

Step 1: A mixture of 2-bromo-p-xylene (18.5 g, 100 mmole) and KMnO₄ (15.8 g; 100 mmole) in water (225 ml) was refluxed for 2 h under stirring. After the disappearance of KMnO₄-color, TLC showed the presence of starting material. Additional KMnO₄ (15.8 g; 100 mmole) was added and refluxing continued for 2 h. TLC showed the presence of starting material, another lot of KMnO₄ (15.8 g; 100 mmole) was added and refluxing continued for 2 h. TLC showed the presence of starting material, however, the reaction was worked up. The mixture was cooled to RT and filtered. The filtrate was extracted with ethyl acetate (2 X 25 ml). The ethyl acetate layer was dried and evaporated to recover 6.15 g (33%) of the starting material. The aqueous filtrate was
 20 concentrated to half volume on a rotavap. The concentrated aqueous mixture was cooled to 0-5°C and acidified to pH 2 with conc. HCl. The precipitated solid was filtered and washed with water and dried to yield 11.39 g (47%) of 2-bromo terephthalic acid as a colorless solid. ¹H NMR in

CD₃OD-d₄ δ ppm : 7.86 (1H, d, J = 7.8 Hz, Ar-H), 8.05 (1H, dd, J = 8.4 Hz & 1.6 Hz, Ar-H), 8.28 (1H, d, J = 1.6 Hz, Ar-H).

Step 2: 2-Bromo terephthalic acid (13.8 g, 56.3 mmole) was slowly added under stirring to conc. H₂SO₄ (78 ml) at 0-5°C over 5 minutes. To the resulting mixture was added 1:1 mixture of conc. H₂SO₄ and conc. HNO₃ (15 ml) dropwise over 20 min. at 0-5°C. The mixture was then heated to 100°C for 2 h. After cooling and stirring for 18 h at ambient temperature, mixture was poured into 100 g of ice-water. The resulting colorless solid was filtered and dried. The solid was recrystallized from ethanol to give 10.5 g (64%) of 2-bromo-5-nitroterephthalic acid. ¹H NMR in CD₃OD-d₄ δ ppm : 3.96 (3H, s, OCH₃) 4.01 (3H, s, OCH₃) 8.16 (1H, s, ArH) 8.41 (1H, s, ArH).

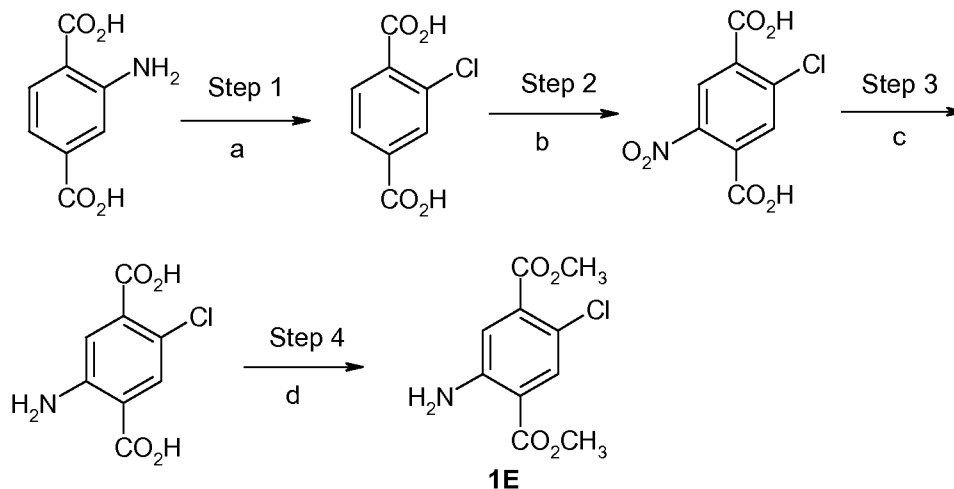
Step 3: To a suspension of 2-bromo-5-nitroterephthalic acid (10.5 g; 36.2 mmole) in methanol (200 ml) was added dropwise conc H₂SO₄ (5 ml) at rt. The mixture was refluxed for 18 h. TLC showed the disappearance of starting material and formation of non-polar product along with small amount of monoester. Methanol was distilled out on a rotavap and the resulting solid was stirred with water (25 ml), filtered and washed with water. The wet solid was dissolved in ethyl acetate (100 ml) and washed with saturated solution of NaHCO₃ (25 ml). The organic layer was dried and evaporated to get 8 g (69%) of dimethyl 2-bromo-5-nitroterephthalate as a colorless solid. ¹H NMR in CD₃OD-d₄ δ ppm : 3.96 (3H, s, OCH₃) 4.01 (3H, s, OCH₃) 8.16 (1H, s, ArH) 8.41 (1H, s, ArH).

Step 4: A mixture of dimethyl 2-bromo-5-nitroterephthalate (8.5 g; 26.7 mmole), PEG 400 (1.92 g) and KF (5.35 g, 92.1mmole) in DMSO (250 ml) was heated at 90°C for 8 h. ¹H-NMR of the reaction mass showed disappearance of starting material along with the formation of a phenolic impurity. The reaction mixture was quenched with water (500 ml) and the mass was extracted with ethyl acetate (3 × 100 ml). Combined ethyl acetate extract was washed with water (25 ml), dried and evaporated to get an oily residue which after silica gel column chromatography purification gave 4.5 g of product contaminated with the phenolic impurity as revealed by ¹H-NMR. The column purified material was washed with 10% sodium hydroxide solution to yield 3.2 g of dimethyl 2-fluoro-5-nitroterephthalate as yellow solid (46%). ¹H-NMR, CDCl₃ δ ppm: 3.96 (3H, s, COOCH₃), 3.99 (3H, s, COOCH₃), 7.45 (1H, d, J = 9.2 Hz, Ar-H), 8.59 (1H, d, J = 5.8 Hz, Ar-H).

Step 5: A mixture of dimethyl 2-fluoro-5-nitroterephthalate (0.5 g; 2 mmoles) in toluene (30 ml), containing iron (0.9 g, 16.2 mmole) was heated to reflux. Under reflux condition, acetic acid (0.3 ml) was added slowly over a period of 1 h and refluxing continued for 2 h. TLC revealed the presence of starting material, so another lot of acetic acid (0.3 ml) was added over a period of 1 h and refluxing continued for 2 h. Addition of acetic acid was repeated again, after which TLC revealed the disappearance of the starting material. The reaction mixture was cooled to rt and

filtered through celite. The filtrate was concentrated on a rotavap and resulting residue was subjected to column chromatography purification over silica gel to yield 0.25 g of dimethyl 2-amino-5-fluoroterephthalate as a yellow solid (55%). $^1\text{H-NMR}$, CDCl_3 - d_4 δ ppm: 3.88 (3H, s, COOCH_3), 3.91 (3H, s, COOCH_3), 5.6 (2H, br s, NH_2), 7.18 (1H, d, $J = 5.8$ Hz, Ar-H), 7.36 (1H, d, $J = 11.8$ Hz, Ar-H).

1E) dimethyl 2-amino-5-chloro-1,4-benzenedicarboxylate



Conditions: a) conc. HCl : H_2O (1:2), $0\sim 5^\circ\text{C}$, NaNO_2 , CuCl ; b) conc. H_2SO_4 , conc. HNO_3 ; c) EtOAc , $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ overnight; d) SOCl_2 , MeOH

Step 1: To a suspension of 2-amino terephthalic acid (10 g, 55 mmole) in conc. hydrochloric acid (14.3 ml) and water (28.6 ml) a solution of sodium nitrite (3.8 g, 55 mmole) in water (18 ml) was added between $0\sim 5^\circ\text{C}$ over a period of 15 to 20 minutes. After stirring at $0\sim 5^\circ\text{C}$ for another 30 minutes, the reaction mixture was slowly added to cold cuprous chloride (12 g, 122 mmole) solution in conc. hydrochloric acid (60 ml) under stirring. The reaction mixture was then allowed to come to RT and stirred for 3 h. It was filtered and the solid obtained was washed with ice-cold water (25 ml). The crude solid was dried under vacuum and then crystallized from water and ethanol (9:1) to get 8 g of 2-chloro terephthalic acid as an off-white solid (73%). $^1\text{H NMR}$ in $\text{CD}_3\text{OD}-d_4$ δ ppm : 7.87 (1H, d, $J = 7.8$ Hz, Ar-H), 7.98 (1H, d, $J = 7.8$ Hz, Ar-H), 8.07 (1H, s, Ar-H).

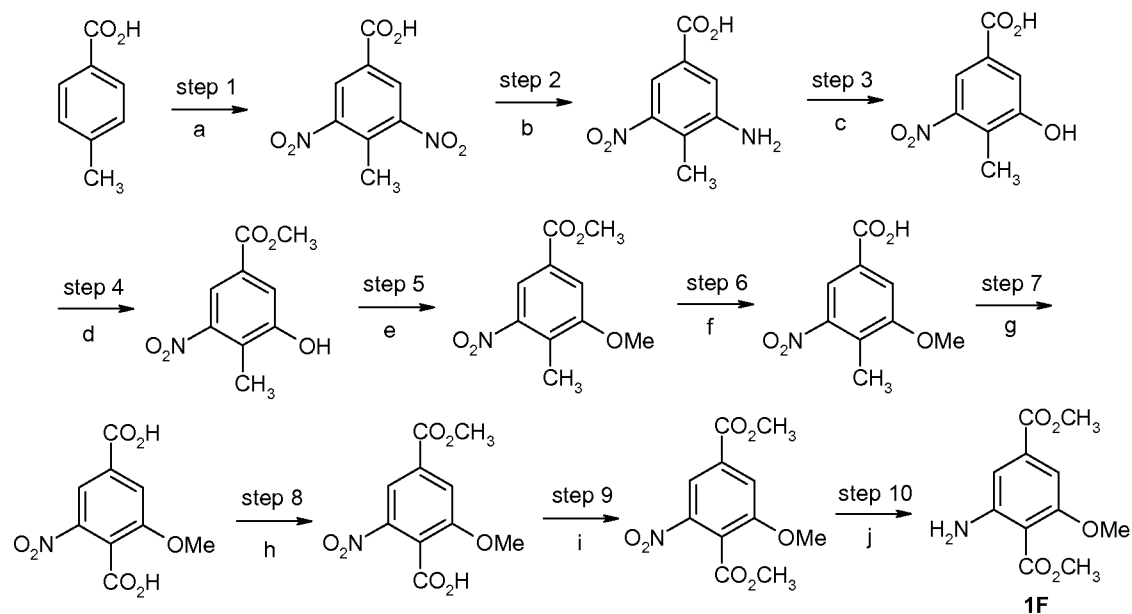
Step 2: 2-Chloro terephthalic acid (8 g, 40 mmole) was dissolved in conc. sulfuric acid (33 ml) under ice-cooling. To the cold reaction mixture, 1:1 mixture of conc. nitric acid (3.6 ml) and conc. sulfuric acid (3.6 ml) was added slowly between $0\sim 5^\circ\text{C}$ over a period of 15 minutes. After addition reaction mixture was heated at 100°C for 2 h after which TLC revealed disappearance of starting material. Mixture was then cooled to rt and quenched with cold water

(250 ml). Precipitated solid was filtered and washed with cold water (25 ml) and dried under vacuum to get 6 g of product (61%). ^1H NMR in $\text{CD}_3\text{OD}-d_4$ δ ppm : 7.93 (1H, s Ar-H) 8.34 (1H, s, Ar-H).

Step 3: Mixture of 2-chloro-5-nitroterephthalic acid (10 g, 41 mmole) and stannous chloride dihydrate (27.5 g, 132 mmole) in ethyl acetate (375 ml) was stirred overnight at ambient temperature. TLC indicated disappearance of starting material. Mixture was diluted with ethyl acetate (200 ml) and washed with saturated aq. sodium chloride solution (75 ml). Ethyl acetate layer was evaporated and resulting residue was treated with 5% aq. sodium bicarbonate solution till the pH was ~ 7 . The semi-solid reaction mass was then stirred with ethyl acetate (500 ml) and filtered. The organic layer of the biphasic filtrate was separated, dried and evaporated to get 9 g of crude product. This was dissolved in methanol (200 ml), treated with charcoal, filtered and evaporated to yield 8.1 g of 2-amino-5-chloro-1,4-benzenedicarboxylic acid (92%) as yellow solid. ^1H NMR in $\text{CD}_3\text{OD}-d_4$ δ ppm : 6.75 (1H, s ArH) 7.76 (1H, s, ArH).

Step 4: To a stirred solution of 2-amino-5-chloro-1,4-benzenedicarboxylic acid (2.16 g, 10 mmol, 1 eq.) in methanol (25 mL) cooled in an ice bath, thionyl chloride (3.57 g, 30 mmol, 3.0 eq.) was added dropwise. After stirring the mixture at rt for 3 hours, the reaction was checked with LCMS. It was concentrated, diluted with ethyl acetate (75 mL) and water (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the title product which was used without purification. Yield: 0.307 g, 12%; LC/MS: $M+1=244$

Preparation 1F) dimethyl 2-amino-6-(methoxy)-1,4-benzenedicarboxylate



Conditions: a) 0-5 °C conc. H_2SO_4 , conc. HNO_3 ; b) NaSH , MeOH , reflux; c) 0-50 °C conc. H_2SO_4 : H_2O (3:1), NaNO_2 , 90-100 °C; d) 0-5 °C MeOH , SOCl_2 , reflux; e) Acetone, anh. K_2CO_3 ,

CH₃I; f) 1M NaOH, MeOH, RT, overnight; g) H₂O, KMnO₄, reflux 5h; h) 0-5 °C MeOH, SOCl₂, reflux; i) i) N-nitroso methylurea, 50% aq. KOH, ether, ii) MeOH; j) Toluene, Fe/AcOH, reflux

Step 1: 4-Methyl benzoic acid (50 g, 368 mmole) was dissolved in conc. sulfuric acid (500 ml) and conc. nitric acid (200 ml) was added slowly 18-20°C over a period of 3 h. After addition, the reaction mixture was then allowed to come to room temperature and stirred for 2 h. During this period, the dark viscous reaction mixture turned yellow in color with some amount of yellow solid precipitated. TLC revealed disappearance of starting material. The reaction mixture was poured over crushed ice water (1 kg) and stirred for 30 minutes. The pale yellow solid obtained was filtered, washed with water (100 ml) and dried under vacuum to yield 70 g of 4-methyl-3,5-dinitrobenzoic acid (83%). ¹H-NMR in DMSO-d₆ δ ppm : 2.52 (3H, s, CH₃), 8.58 (2H, s, Ar-H).

Step 2: A solution of 4-methyl-3,5-dinitrobenzoic acid (70 g, 307 mmole) in methanol (750 ml) was warmed to 60°C and a 30% solution of sodium hydrogen sulfide (133 ml, 539 mmole) was added slowly over a period of 30 minutes. The reaction mixture was refluxed for 3 h. The reaction mixture was evaporated to dryness and resulting residue was treated with water (500 ml). The mixture was acidified to pH 3 using dil. HCl. The precipitated product was extracted with ethyl acetate (3 × 250 ml) and the ethyl acetate layer was dried and evaporated to yield 50 g of 3-amino-4-methyl-5-nitrobenzoic acid as yellow solid (83%). ¹H-NMR in DMSO-d₆ δ ppm : 2.14 (3H, s, CH₃), 5.85 (2H, bs, NH₂), 7.41 (1H, s, Ar-H), 7.56 (1H, s, Ar-H), 13.31 (1H, bs, COOH).

Step 3: A mixture of conc. sulfuric acid (367.5 ml) and water (117.6 ml) was heated to 90-100°C and 3-amino-4-methyl-5-nitrobenzoic acid (29.4 g, 149 mmole) was added in small portion over a period of 30 minutes. The reaction mixture was then cooled to 0-5°C and a solution of sodium nitrite (20.7 g, 300 mmole) in water (117.6 ml) was added over a period of 60 minutes. After addition, reaction mixture was stirred at 0-5°C for another 30 minutes. The reaction mixture was then slowly allowed to come to 15-20°C and then heated to 90-100°C on a preheated oil-bath for 2 -3 h. It was cooled to RT and water (630 ml) was added. Precipitated solid was filtered and dried under vacuum to yield 15 g of 3-hydroxy-4-methyl-5-nitrobenzoic acid as buff colored solid (51%). ¹H-NMR in DMSO-d₆ δ ppm : 2.29 (3H, s, CH₃), 7.65 (1H, s, Ar-H), 7.78 (1H, s, Ar-H), 10.77 (1H, s, OH).

Step 4: At 0-5°C, to a solution of 3-hydroxy-4-methyl-5-nitrobenzoic acid (28 g, 141 mmole) in methanol (280 ml), thionyl chloride (15.5ml, 212 mmole) was added dropwise over a period of 30 minutes. After the addition, the reaction mixture was brought to room temperature and then refluxed for 4 h. The reaction mixture was concentrated under vacuum. The resulting solid residue was dissolved in ethyl acetate (500 ml) and washed with sodium bicarbonate solution.

Ethyl acetate extract was dried over Na_2SO_4 and concentrated under vacuum to yield 30 g of methyl 3-hydroxy-4-methyl-5-nitrobenzoate as colorless solid (quantitative). The crude product was used as such for the next step without characterization.

Step 5: To a mixture of methyl 3-hydroxy-4-methyl-5-nitrobenzoate (30 g, 141 mmole),
5 and K_2CO_3 (38.9 g; 282 mmole) in acetone (300 ml) under inert atmosphere (nitrogen) was added methyl iodide (22.2 g, 156 mmole) at ambient temperature. The mixture was stirred overnight at the same temperature. The reaction mixture was filtered and acetone was removed on a rotavap. The resulting residue was dissolved in ethyl acetate (500 ml) and washed with dil. HCl. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to yield 30 g of methyl 3-
10 methoxy-4-methyl-5-nitrobenzoate as off-white solid (94%). ^1H NMR in DMSO-d_6 δ ppm : 2.33 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 7.7 (1H, s, Ar-H), 7.96 (1H, s, Ar-H).

Step 6: To a solution of methyl 3-methoxy-4-methyl-5-nitrobenzoate (30 g, 132 mmole) in methanol (200 ml) was added at room temperature 1M NaOH solution (158 ml, 158 mmole) and stirred overnight. The reaction mixture was concentrated on a rotavap and the resulting mixture
15 was cooled to 5-10°C and acidified with dil HCl to pH 2. Precipitated solid was filtered, washed with water and partly dried under vacuum. Partially dried colorless 3-methoxy-4-methyl-5-nitrobenzoic acid, weighing 30 g was used as such for the next step. ^1H NMR in DMSO-d_6 δ ppm : 2.32 (3H, s, CH_3) 3.95 (3H, s, OCH_3) 7.69 (1H, s, ArH) 7.93 (1H, s, ArH).

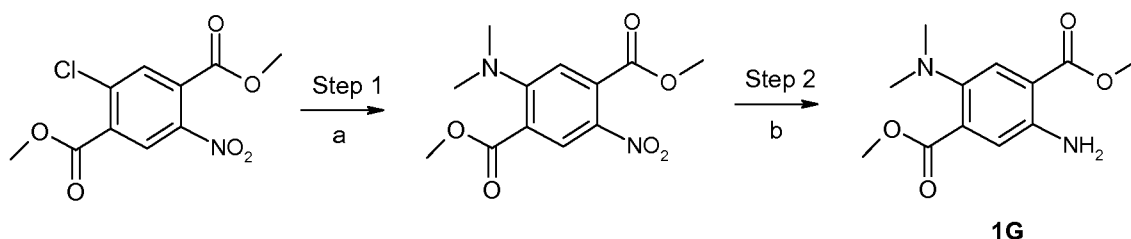
Step 7: To a solution of KMnO_4 (44.56 g, 282 mmole) in water (675 ml) was added at
20 room temperature 3-methoxy-4-methyl-5-nitrobenzoic acid (30 g, 141 mmole) and the mixture was heated to reflux. After 2 h and 4h of refluxing another lot of KMnO_4 44.56g (282 mmole) and 22.28 g (141mmole) were added respectively. After complete consumption of starting material, the reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated to ca. 200ml on a rotavap. The concentrated aqueous mixture was cooled to 0-5°C
25 and acidified to pH 2 with conc. HCl. The precipitated solid was filtered and washed with water to yield 15 g of 2-methoxy-6-nitroterephthalic acid as a colorless solid after drying (44%). ^1H NMR in DMSO-d_6 δ ppm : 3.9 (3H, s, OCH_3), 7.81 (1H, s, Ar-H), 8.06 (1H, s, Ar-H).

Step 8: To a solution of 2-methoxy-6-nitroterephthalic acid (5 g, 21 mmole) in methanol (280 ml) maintained at 0-5°C was added dropwise thionyl chloride (2.4ml, 32 mmole) over a
30 period of 5 minutes. The mixture was slowly brought to ambient temperature and was then refluxed for 4 h. The reaction mixture was concentrated under vacuum. The resulting solid residue was dissolved in ethyl acetate (150 ml) and washed with saturated Na_2CO_3 solution. Ethyl acetate extract was dried over Na_2SO_4 and evaporated to yield 5 g of 2-methoxy-6-nitro-terephthalic acid 4-methyl ester as colorless solid (93%). ^1H NMR in DMSO-d_6 δ ppm : 3.93 (3H, s, OCH_3), 3.97
35 (3H, s, OCH_3), 7.92 (1H, s, Ar-H) 8.17 (1H, s, Ar-H).

Step 9: To a solution of 2-methoxy-6-nitro-terephthalic acid 4-methyl ester (7g, 27 mmole) in methanol (100 ml) was added between 0-5°C an ethereal solution of diazomethane (100 ml) [prepared from 50% aq. KOH (45 ml) and N-nitroso methylurea (11.3 g, 108 mmole)] over a period of 30 minutes. The reaction mixture was stirred between 0-5°C for 1 h and then allowed to come to room temperature. Excess diazomethane was then quenched by adding acetic acid. The reaction mixture was dried over Na₂SO₄ and concentrated to yield 7 g of dimethyl 2-methoxy-6-nitroterephthalate (96%) as a pale yellow solid. ¹H-NMR in CDCl₃ δ ppm: 3.98 (3H, s, OCH₃), 3.99 (3H, s, OCH₃), 4.36 (3H, s, OCH₃), 7.88 (1H, d, J = 1.2 Hz, Ar-H), 8.4 (1H, d, J = 1.2 Hz, Ar-H).

Step 10: To a solution of dimethyl 2-methoxy-6-nitroterephthalate (9.45 g, 35 mmole) in toluene (400 ml) was added at room temperature iron (20g, 357 mmole) and the mixture was heated to reflux. Under reflux condition, acetic acid (33 ml) was added slowly over a period of 1 h and refluxing continued for 2 h. Two more lots of acetic acid (33 ml each) were added after a gap of 2 h for complete conversion. The reaction mass was cooled to room temperature and filtered through celite. The filtrate was concentrated on a rotavap and the resulting residue was subjected to column chromatographic purification over silica gel to yield 4.3 g of dimethyl 2-amino-6-methoxyterephthalate as yellow solid (51%). ¹H-NMR in CDCl₃ δ ppm: 3.86 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.9 (3H, s, OCH₃), 5.05 (2H, bs, NH₂), 6.86 (1H, d, J = 1.2 Hz, Ar-H), 6.97 (1H, d, J = 1.2 Hz, Ar-H).

Preparation 1G) dimethyl 2-amino-5-(dimethylamino)-1,4-benzenedicarboxylate



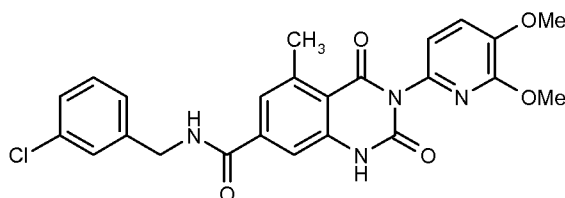
Conditions: a) (CH₃)₂NH, THF; b) Zn dust, acetic acid

Step 1: To a tetrahydrofuran solution (2 mL) of dimethyl 2-chloro-5-nitro-1,4-benzenedicarboxylate (547 mg, 2 mmol) in a 5 mL microwave tube, was added dimethylamine (90mg, 2.0 mmol) to give a yellow solution. The reaction was heated via Biotage Microwave reactor at 85°C for 15 minutes and checked by LCMS. The reaction mixture was concentrated, diluted with ethyl acetate (75 mL), washed with water (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the title product (564 mg, 100 %) which was used without purification. LC/MS: M+1=283

Step 2: In a 25 mL round-bottomed flask was added the dimethyl ester (13a, 564 mg, 2 mmol), zinc dust (1.3g, 20 mmol) and acetic acid (10 mL) to give a yellow suspension. The reaction was stirred for 30 minutes at which time LCMS ($m+1 = 252.8$) showed that the reaction was complete. The reaction mixture was diluted with ethyl acetate (25 mL), filtered through celite and rinsed with ethyl acetate (10 mL). The filtrate was concentrated to dryness, and then characterized by LCMS and NMR. Yield: 505mg., 100 %. LC/MS: $M+1=253$

Examples

Example 1



3-[5,6-Bis(methoxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

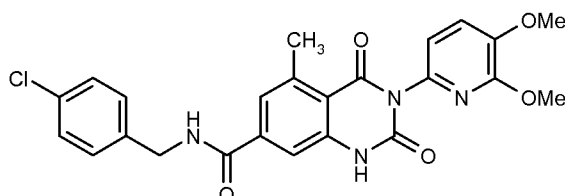
1a) 3-[5,6-bis(methoxy)-2-pyridinyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

To a mixture of triphosgene (178 mg, 0.6 mmol) in dichloromethane (2 mL) at 0 °C was added a solution of dimethyl 2-amino-6-methyl-1,4-benzenedicarboxylate (**1A**, 335 mg, 1.5 mmol) in dichloromethane (2 mL) and DIEA (233 mg, 1.8 mmol). After stirring at 0 °C for 15 min, the mixture was stirred at room temperature for 90 min. To the mixture was added a solution of 2-amino-5,6-dimethoxypyridine (231 mg, 1.5 mmol) in dichloromethane (2 mL) and DIEA (233 mg, 1.8 mmol). The mixture was stirred at room temperature overnight then concentrated in vacuo and dissolved in methanol (6 mL). To the suspension was added 6N NaOH (2 mL) and the suspension was stirred at 50 °C for 3h then acidified with 6N HCl. The precipitate was collected, washed with water, and dried in vacuo to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**1a**). (365 mg, 68%); MS(ES^+) m/e 358 (MH^+).

1b) 3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**1a**, 72 mg, 0.2 mmol) in DMF (2.4 mL) was added DIEA (39 mg, 0.3 mmol) and HATU (114 mg, 0.3 mmol). The mixture was stirred at room temperature for 30 min, then 3-chlorobenzylamine (43 mg, 0.3 mmol) was added. The mixture was stirred at room temperature for 2h and purified by reversed-phase HPLC to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**1b**). (48.1 mg, 50%); MS(ES⁺) *m/e* 480 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.68 (s, 3 H) 3.80 (s, 3 H) 3.85 (s, 3 H) 4.49 (d, *J*=5.81 Hz, 2 H) 7.02 (d, *J*=8.08 Hz, 1 H) 7.28 - 7.42 (m, 4 H) 7.45 (d, *J*=8.08 Hz, 1 H) 7.49 (s, 1 H) 7.55 (s, 1 H) 9.32 (t, *J*=5.94 Hz, 1 H) 11.63 (s, 1 H).

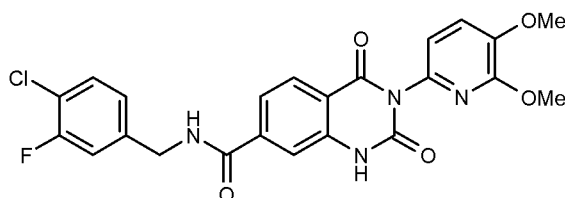
Example 2



3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**1a**, 72 mg, 0.2 mmol) in DMF (2.4 mL) was added DIEA (39 mg, 0.3 mmol) and HATU (114 mg, 0.3 mmol). The mixture was stirred at room temperature for 30 min, then 4-chlorobenzylamine (43 mg, 0.3 mmol) was added. The mixture was stirred at room temperature for 2h and purified by reversed-phase HPLC to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**2**). (40.7 mg, 42%); MS(ES⁺) *m/e* 480 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.68 (s, 3 H) 3.80 (s, 3 H) 3.85 (s, 3 H) 4.47 (d, *J*=6.06 Hz, 2 H) 7.02 (d, *J*=8.08 Hz, 1 H) 7.33 - 7.47 (m, 5 H) 7.49 (s, 1 H) 7.55 (s, 1 H) 9.31 (t, *J*=5.94 Hz, 1 H) 11.62 (s, 1 H).

Example 3



3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chloro-3-fluorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

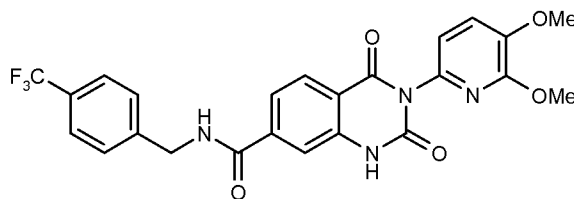
3a) 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

To a mixture of triphosgene (0.890 g, 3.00 mmol) in Dichloromethane (DCM) (14.93 ml) at 0 °C was added a solution of dimethyl 2-amino-1,4-benzenedicarboxylate (2.092 g, 10 mmol) in Dichloromethane (DCM) (26.9 ml) and DIEA (2.096 ml, 12.00 mmol). The mixture was stirred at room temperature for 90 min, then cooled in an ice bath and a solution of 5,6-bis(methyloxy)-2-pyridinamine (1.542 g, 10.00 mmol) in Dichloromethane (DCM) (8.96 ml) and DIEA (2.096 ml, 12.00 mmol) was added. The mixture was stirred at room temperature overnight, then concentrated in vacuo. To the residue was added methanol (35 mL) and 6N NaOH (14.3 mL, 86 mmol), the mixture was stirred at 45 °C for 1h. The mixture was acidified with 6N HCl. The precipitate was collected by filtration, washed with ice cold water, and dried in vacuo to provide 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**). (2.98 g, 87%); MS(ES⁺) m/e 344 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.47 (d, *J*=8.08 Hz, 1 H) 7.73 (dd, *J*=8.08, 1.26 Hz, 1 H) 7.82 (s, 1 H) 8.04 (d, *J*=8.34 Hz, 1 H) 11.78 (s, 1 H) 13.58 (br. s., 1 H).

3b) 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chloro-3-fluorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 86 mg, 0.25 mmol) in N,N-Dimethylformamide (DMF) (1667 μl) was added DIEA (87 μl, 0.500 mmol) and HATU (190 mg, 0.500 mmol). The mixture was stirred at room temperature for 1h, then [(4-chloro-3-fluorophenyl)methyl]amine (80 mg, 0.500 mmol) was added. The mixture was stirred at room temperature overnight and purified by reversed-phase HPLC to provide 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chloro-3-fluorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**3b**). (63 mg, 52%); MS(ES⁺) m/e 485 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 4.50 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.22 (dd, *J*=8.21, 1.39 Hz, 1 H) 7.38 (dd, *J*=10.61, 1.77 Hz, 1 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.57 (t, *J*=8.08 Hz, 1 H) 7.68 (d, *J*=1.26 Hz, 2 H) 8.03 (d, *J*=8.34 Hz, 1 H) 9.39 (t, *J*=5.94 Hz, 1 H) 11.75 (s, 1 H).

Example 4

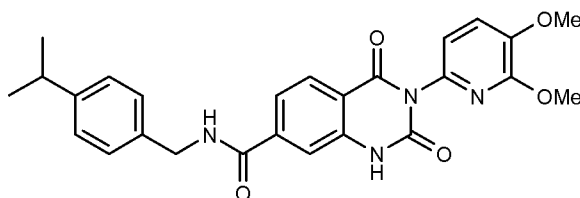


3-[5,6-bis(methoxy)-2-pyridinyl]-2,4-dioxo-N-{[4-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

- 5 To a solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 86 mg, 0.25 mmol) in N,N-dimethylformamide (DMF) (1667 μ l) was added DIEA (87 μ l, 0.500 mmol) and HATU (190 mg, 0.500 mmol). The mixture was stirred at room temperature for 1h, then {[4-(trifluoromethyl)phenyl]methyl} amine (88 mg, 0.500 mmol) was added. The mixture was stirred at room temperature overnight and purified by reversed-phase
- 10 HPLC to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-2,4-dioxo-N-{[4-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**4**). (64 mg, 51%); MS(ES⁺) m/e 501 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 4.58 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.56 (d, *J*=8.08 Hz, 2 H) 7.67 - 7.76 (m, 4 H) 8.04 (d, *J*=8.59 Hz, 1 H) 9.45 (t, *J*=5.94 Hz, 1 H) 11.75 (s, 1 H).

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Example 5



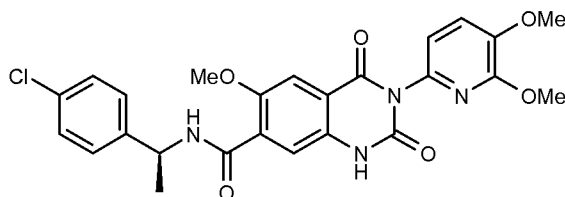
3-[5,6-bis(methoxy)-2-pyridinyl]-N-{[4-(1-methylethyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

20

- To a solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 86 mg, 0.25 mmol) in N,N-dimethylformamide (DMF) (1.66 mL) was added DIEA (0.087 mL, 0.500 mmol) and HATU (190 mg, 0.500 mmol). The mixture was stirred at room temperature for 1h, then {[4-(1-methylethyl)phenyl]methyl} amine (74.6 mg, 0.500
- 25 mmol) was added. The mixture was stirred at room temperature overnight and purified by reversed-phase HPLC to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-N-{[4-(1-methylethyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**5**). (44 mg, 37%); MS(ES⁺) m/e 475 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.18 (s, 3 H) 1.20 (s, 3 H) 2.87 (dt, *J*=13.71, 6.92 Hz, 1 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 4.45 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08

Hz, 1 H) 7.18 - 7.29 (m, 4 H) 7.46 (d, $J=8.34$ Hz, 1 H) 7.65 - 7.73 (m, 2 H) 8.01 (d, $J=8.08$ Hz, 1 H) 9.30 (t, $J=5.94$ Hz, 1 H) 11.74 (s, 1 H).

Example 6



3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(1S)-1-(4-chlorophenyl)ethyl]-6-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

6a) 3-[5,6-bis(methoxy)-2-pyridinyl]-6-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

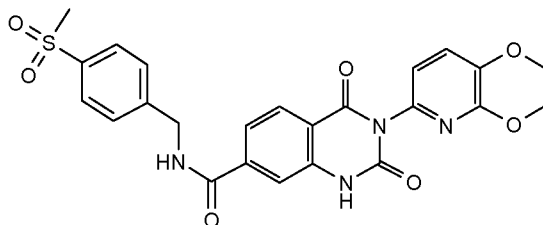
To a mixture of triphosgene (0.093 g, 0.314 mmol) in dichloromethane (DCM) (1.560 ml) at 0 °C was added a solution of dimethyl 2-amino-5-(methoxy)-1,4-benzenedicarboxylate (**1B**, 0.250 g, 1.045 mmol) in dichloromethane (DCM) (2.81 ml) and DIEA (0.219 ml, 1.254 mmol). The mixture was stirred at room temperature for 90 min, then cooled in an ice bath and a solution of 5,6-bis(methoxy)-2-pyridinamine (0.161 g, 1.045 mmol) in dichloromethane (DCM) (0.936 ml) and DIEA (0.219 ml, 1.254 mmol) was added. The mixture was stirred at room temperature overnight, then concentrated in vacuo. To the residue was added methanol (3.5 mL) and 6N NaOH (1.43 mL, 8.6 mmol), the mixture was stirred at 45 °C for 1h. The mixture was acidified with 6N HCl. The precipitate was collected by filtration, washed with ice cold water, and dried in vacuo to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-6-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**6a**). (200 mg, 51%); MS(ES⁺) m/e 374 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 3.86 (s, 3 H) 7.03 (d, $J=8.08$ Hz, 1 H) 7.40 - 7.49 (m, 3 H) 11.57 (s, 1 H) 13.41 (br. s., 1 H).

6b) 3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(1S)-1-(4-chlorophenyl)ethyl]-6-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a mixture of 3-[5,6-bis(methoxy)-2-pyridinyl]-6-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**6a**, 74.7 mg, 0.2 mmol), [(1S)-1-(4-chlorophenyl)ethyl]amine (31.1 mg, 0.200 mmol) and 2-chloro-1,3-dimethylimidazolium chloride (50.7 mg, 0.300 mmol) in N,N-dimethylformamide (DMF) (1.2 ml) was added DIEA (0.052 ml, 0.300 mmol). The mixture

was stirred at room temperature overnight and purified by reversed-phase HPLC to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**6b**). (27 mg, 27%); MS(ES⁺) *m/e* 511 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.44 (d, *J*=6.82 Hz, 3 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 3.91 (s, 3 H) 5.13 (qd, *J*=7.24, 7.07 Hz, 1 H) 7.03 (d, *J*=8.08 Hz, 1 H) 7.38 (s, 1 H) 7.42 - 7.51 (m, 6 H) 8.83 (d, *J*=7.83 Hz, 1 H) 11.55 (s, 1 H).

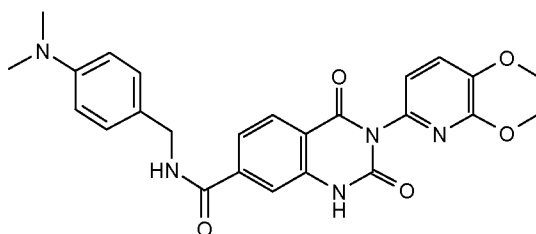
Example 7



3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-{[4-(methylsulfonyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 100 mg, 0.291 mmol) in *N,N*-dimethylformamide (DMF) (1.5 ml) were added HATU (166 mg, 0.437 mmol) and DIEA (0.153 ml, 0.874 mmol). The reaction was stirred for 30 minutes, which was followed by addition of {[4-(methylsulfonyl)phenyl]methyl}amine (64.8 mg, 0.350 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-{[4-(methylsulfonyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**7**) (Yield: 28 mg, 19%); MS(ES⁺) *m/e* 511 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.20 (s, 3 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 4.60 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.60 (m, *J*=8.34 Hz, 2 H) 7.66 - 7.77 (m, 2 H) 7.91 (m, *J*=8.34 Hz, 2 H) 8.04 (d, *J*=8.84 Hz, 1 H) 9.47 (t, *J*=5.94 Hz, 1 H) 11.76 (s, 1 H).

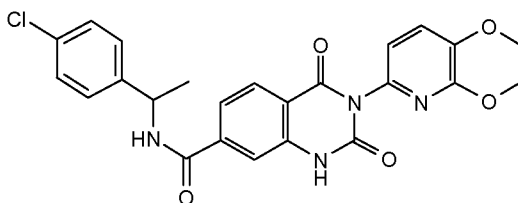
Example 8



3-[5,6-bis(methyloxy)-2-pyridinyl]-N-{[4-(dimethylamino)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

- 5 To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 100 mg, 0.291 mmol) in N,N-dimethylformamide (DMF) (1.5 ml) were added HATU (166 mg, 0.437 mmol) and DIEA (0.153 ml, 0.874 mmol). The reaction was stirred for 30 minutes, which was followed by addition of [4-(aminomethyl)phenyl]dimethylamine (52.5 mg, 0.350 mmol). Reaction was allowed to stir overnight at room temperature. The solvent
- 10 was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-{[4-(dimethylamino)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**8**) (Yield: 20 mg, 14%); MS(ES⁺) m/e 476 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.90 (s, 6 H) 3.80 (s, 3 H) 3.85 (s, 3 H) 4.39 (d, *J*=5.56 Hz, 2 H) 6.85 (br. s., 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.23 (d, *J*=7.83 Hz, 2 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.60 - 7.73 (m, 2 H) 8.01 (d, *J*=8.34 Hz, 1 H) 9.23 (br. s., 1 H) 11.73 (s, 1 H).
- 15

Example 9

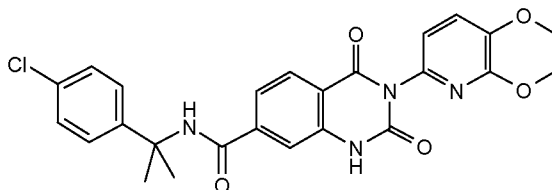


- 20 **3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide**

- To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 100 mg, 0.291 mmol) in N,N-dimethylformamide (DMF) (1.5 ml) were added 2-chloro-1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium (DMC, 0.224 ml, 0.437 mmol) and DIEA (0.153 ml, 0.874 mmol). The reaction was stirred for 30 minutes, which was followed by addition of [1-(4-chlorophenyl)ethyl]amine (54.4 mg, 0.350 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material
- 25

was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**9**) (Yield: 32 mg, 23%); MS(ES⁺) *m/e* 481 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.48 (d, *J*=7.07 Hz, 3 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 5.16 (qd, *J*=7.20, 6.95 Hz, 1 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.36 - 7.52 (m, 5 H) 7.61 - 7.76 (m, 2 H) 8.02 (d, *J*=8.08 Hz, 1 H) 9.16 (d, *J*=7.83 Hz, 1 H) 11.71 (s, 1 H).

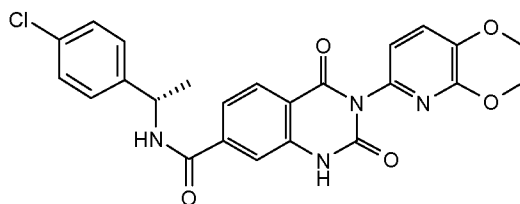
Example 10



3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)-1-methylethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 100 mg, 0.291 mmol) in *N,N*-dimethylformamide (DMF) (1.5 ml) were added 2-chloro-1,3-dimethyl-4,5-dihydro-1*H*-imidazol-3-ium (DMC, 0.224 ml, 0.437 mmol, 25% wt. in CH₂Cl₂) and DIEA (0.153 ml, 0.874 mmol). The reaction was stirred for 30 minutes, which was followed by addition of [1-(4-chlorophenyl)-1-methylethyl]amine (59.3 mg, 0.350 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)-1-methylethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**10**) (Yield: 28 mg, 19%); MS(ES⁺) *m/e* 495 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.67 (s, 6 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.38 (m, 4 H) 7.46 (d, *J*=8.08 Hz, 1 H) 7.57 (d, *J*=1.26 Hz, 1 H) 7.71 (dd, *J*=8.34, 1.26 Hz, 1 H) 8.01 (d, *J*=8.34 Hz, 1 H) 8.83 (s, 1 H) 11.71 (s, 1 H).

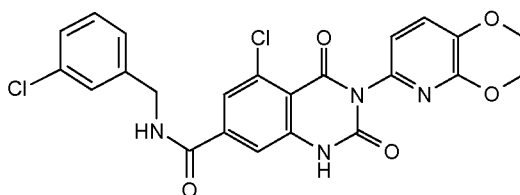
Example 11



3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(1S)-1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**3a**, 100 mg, 0.291 mmol) in N,N-dimethylformamide (DMF) (1.5 ml) were added 2-chloro-1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium (DMC, 0.224 ml, 0.437 mmol, 25% wt. in CH₂Cl₂), DIEA (0.153 ml, 0.874 mmol) and [(1S)-1-(4-chlorophenyl)ethyl]amine (0.049 ml, 0.350 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(1S)-1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**11**) (Yield: 28 mg, 19%); MS(ES⁺) m/e 481 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.48 (d, *J*=7.07 Hz, 3 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 5.16 (qd, *J*=7.24, 7.07 Hz, 1 H) 7.00 - 7.09 (m, 1 H) 7.36 - 7.50 (m, 5 H) 7.63 - 7.74 (m, 2 H) 8.02 (d, *J*=8.08 Hz, 1 H) 9.16 (d, *J*=7.83 Hz, 1 H) 11.71 (s, 1 H).

Example 12



3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

12a) 3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

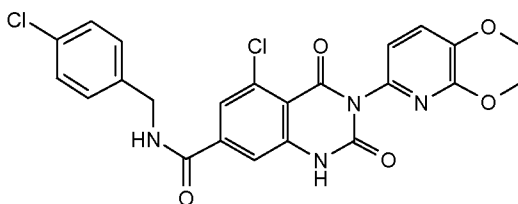
To a stirred solution of triphosgene (80 mg, 0.271 mmol) in dichloromethane (DCM) (2 mL) having been cooled to 0°C was added in drop-wise fashion dimethyl 2-amino-5-chloro-1,4-benzenedicarboxylate (**1C**, 200 mg, 0.821 mmol) and DIEA (0.287 mL, 1.642 mmol) having been dissolved in dichloromethane (DCM) (1 mL). The reaction was allowed to stir at 0° C for fifteen minutes followed by another fifteen minutes at room temperature. To this solution was added a solution of 5,6-bis(methyloxy)-2-pyridinamine (139 mg, 0.903 mmol) and DIEA (0.430 mL, 2.463 mmol) having been dissolved in dichloromethane (DCM) (1 mL). The reaction was allowed to stir for one hour. The solvent was removed by rotary evaporation, and the crude solid was redissolved

in methanol (4 mL). With stirring, NaOH (0.410 mL, 4.10 mmol) was added and the reaction was heated to 50°C. The reaction was allowed to stir for one hour, reaction pH was lowered to ~3 using 6N HCl. Solid precipitate was filtered off by vacuum filtration to afford 3-[5,6-bis(methoxy)-2-pyridinyl]-5-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid, which was used in future steps without further purification (**12a**) (Yield: 251 mg, 81%); MS(ES⁺) m/e 378 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 7.03 (d, *J*=8.08 Hz, 1 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.63 (d, *J*=1.26 Hz, 1 H) 7.75 (d, *J*=1.52 Hz, 1 H) 11.90 (s, 1 H).

12b) 3-[5,6-bis(methoxy)-2-pyridinyl]-5-chloro-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-5-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**12a**, 100 mg, 0.265 mmol) in N,N-dimethylformamide (DMF) (2.5 mL) was added HATU (221 mg, 0.582 mmol) and DIEA (0.231 mL, 1.324 mmol). Reaction stirred for 30 minutes, which was followed by addition of 1-(3-chlorophenyl)methanamine (0.065 mL, 0.529 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed by rotary evaporation and the resulting crude material was dissolved in ethyl acetate (50 mL). Organic solution was washed with water twice (50 mL) and brine (50 mL). Organic layer was dried with magnesium sulfate, was filtered and the solvent was removed by rotary evaporation. The resulting oil was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methoxy)-2-pyridinyl]-5-chloro-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**12b**) (Yield: 25 mg, 19%); MS(ES⁺) m/e 501 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.81 (s, 3 H) 3.86 (s, 3 H) 4.49 (d, *J*=5.81 Hz, 2 H) 7.04 (d, *J*=8.08 Hz, 1 H) 7.27 - 7.43 (m, 4 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.67 (d, *J*=1.52 Hz, 1 H) 7.75 (d, *J*=1.52 Hz, 1 H) 9.44 (t, *J*=5.81 Hz, 1 H) 11.87 (s, 1 H).

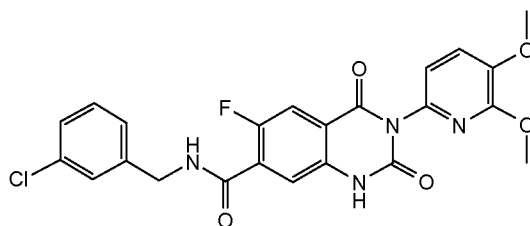
Example 13



3-[5,6-bis(methoxy)-2-pyridinyl]-5-chloro-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**12a**, 100 mg, 0.265 mmol) in N,N-dimethylformamide (DMF) (2.5 mL) was added HATU (221 mg, 0.582 mmol) and DIEA (0.231 mL, 1.324 mmol). The reaction stirred for 30 minutes, which was followed by addition of 1-(4-chlorophenyl)methanamine (0.065 mL, 0.529 mmol). It was allowed to stir overnight at room temperature. The solvent was removed by rotary evaporation and the resulting crude material was dissolved in ethyl acetate (50 mL). The organic solution was washed with water twice (50 mL) and brine (50 mL). The organic layer was dried with magnesium sulfate, was filtered and the solvent was removed by rotary evaporation. The resulting oil was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**13**) (Yield: 34 mg, 26%); MS(ES⁺) m/e 501 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.81 (s, 3 H) 3.85 (s, 3 H) 4.47 (d, *J*=5.81 Hz, 2 H) 7.04 (d, *J*=8.08 Hz, 1 H) 7.33 - 7.44 (m, 4 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.66 (d, *J*=1.52 Hz, 1 H) 7.74 (d, *J*=1.52 Hz, 1 H) 9.43 (t, *J*=5.94 Hz, 1 H) 11.87 (s, 1 H).

Example 14



3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

14a) 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

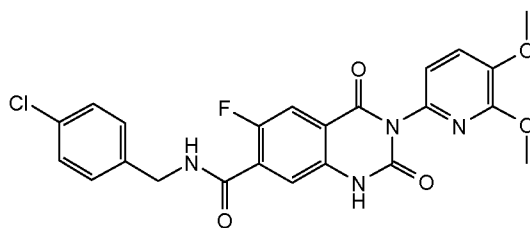
To a stirred solution of Triphosgene (86 mg, 0.291 mmol) in dichloromethane (DCM) (2 mL) having been cooled to 0°C was added in drop-wise fashion dimethyl 2-amino-5-fluoro-1,4-benzenedicarboxylate (**1D**, 200 mg, 0.880 mmol) and DIEA (0.308 mL, 1.761 mmol) having been dissolved in dichloromethane (DCM) (1 mL). The reaction was allowed to stir at 0° C for fifteen minutes followed by another fifteen minutes at room temperature. To this solution was added a solution of 5,6-bis(methyloxy)-2-pyridinamine (271 mg, 1.761 mmol) and DIEA (0.461 mL, 2.64 mmol) having been dissolved in dichloromethane (DCM) (1 mL). The reaction was allowed to stir for one hour. The solvent was removed by rotary evaporation, and the crude solid was redissolved in methanol (2 mL). With stirring, NaOH (0.440 mL, 4.40 mmol) was added and the reaction was

heated to 50°C. The reaction was allowed to stir for one hour, reaction pH was lowered to ~3 using 6N HCl. Solid precipitate was filtered off by vacuum filtration to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid, which was used in future steps without further purification (**14a**) (Yield: 202 mg, 64%); MS(ES⁺) m/e 362 (MH⁺)

14b) 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**14a**, 90mg, 0.249 mmol) in N,N-dimethylformamide (DMF) (1.5 ml) were added HATU (189 mg, 0.498 mmol) and DIEA (0.131 ml, 0.747 mmol). The reaction stirred for 30 minutes, which was followed by addition of [(3-chlorophenyl)methyl]amine (0.061 ml, 0.498 mmol). It was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**14b**) (Yield: 25 mg, 21%); MS(ES⁺) m/e 585 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 4.50 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.29 - 7.50 (m, 6 H) 7.77 (d, *J*=9.60 Hz, 1 H) 9.24 (t, *J*=6.32 Hz, 1 H) 11.75 (s, 1 H).

Example 15



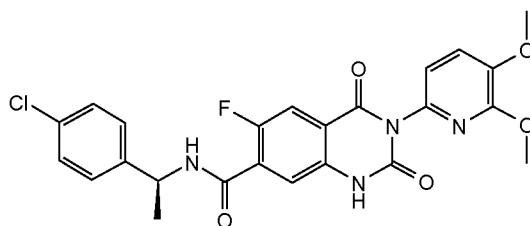
3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**14a**, 90mg, 0.249 mmol) in N,N-dimethylformamide (DMF) (1.5 ml) were added HATU (189 mg, 0.498 mmol) and DIEA (0.131 ml, 0.747 mmol). The reaction stirred for 30 minutes, followed by addition of [(4-chlorophenyl)methyl]amine (0.061 ml, 0.498 mmol). It was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative

reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**15**)

(Yield: 31 mg, 26%); MS(ES⁺) *m/e* 585 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 4.48 (d, *J*=6.06 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.33 - 7.53 (m, 6 H) 7.76 (d, *J*=9.60 Hz, 1 H) 9.22 (t, *J*=5.56 Hz, 1 H) 11.74 (s, 1 H).

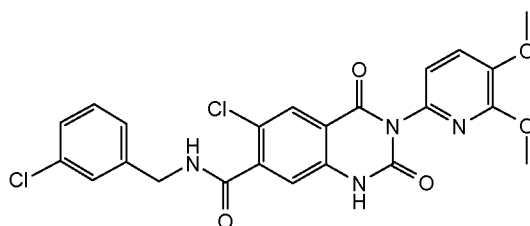
Example 16



3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**14a**, 100 mg, 0.277 mmol) in *N,N*-dimethylformamide (DMF) (1.5 ml) were added 2-chloro-1,3-dimethyl-4,5-dihydro-1*H*-imidazol-3-ium (DMC, 0.212 ml, 0.415 mmol, 25% wt. in CH₂Cl₂), DIEA (0.145 ml, 0.830 mmol) and [(1*S*)-1-(4-chlorophenyl)ethyl]amine (0.047 ml, 0.332 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**16**) (Yield: 39 mg, 27%); MS(ES⁺) *m/e* 499 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.45 (d, *J*=7.07 Hz, 3 H) 3.82 (s, 3 H) 3.86 (s, 3 H) 5.13 (qd, *J*=7.24, 7.07 Hz, 1 H) 7.05 (d, 1 H) 7.35 (d, *J*=5.56 Hz, 1 H) 7.40 - 7.49 (m, 5 H) 7.70 - 7.80 (m, 1 H) 9.17 (d, *J*=7.83 Hz, 1 H) 11.73 (s, 1 H).

Example 17



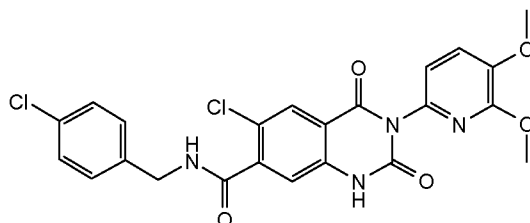
3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

17a) 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

To a stirred solution of triphosgene (76 mg, 0.257 mmol) in dichloromethane (DCM) (2 mL) having been cooled to 0°C was added in drop-wise fashion dimethyl 2-amino-5-chloro-1,4-benzenedicarboxylate (**1E**, 190 mg, 0.780 mmol) and DIEA (0.272 mL, 1.560 mmol) having been dissolved in dichloromethane (DCM) (2 mL). The reaction was allowed to stir at 0° C for fifteen minutes followed by another fifteen minutes at room temperature. To this solution was added a solution of 5,6-bis(methyloxy)-2-pyridinamine (240 mg, 1.560 mmol) and DIEA (0.409 mL, 2.339 mmol) having been dissolved in Dichloromethane (DCM) (2 ml). The reaction was allowed to stir for one hour. The solvent was removed by rotary evaporation, and the crude solid was redissolved in methanol (5 mL). With stirring, NaOH (1.300 mL, 7.80 mmol) was added and the reaction was heated to 50°C. The reaction was allowed to stir for one hour, reaction pH was lowered to ~3 using 6N HCl. Solid precipitate was filtered off by vacuum filtration to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**17a**) (Yield: 170 mg, 58%); MS(ES⁺) m/e 378 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 7.04 (d, *J*=8.08 Hz, 1 H) 7.46 (d, *J*=8.08 Hz, 1 H) 7.57 (s, 1 H) 7.95 (s, 1 H) 11.84 (s, 1 H) 14.02 (br. s., 1 H).

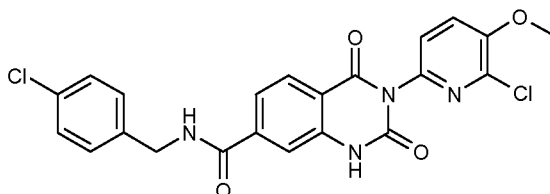
17b) 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**17a**, 85 mg, 0.225 mmol) in N,N-dimethylformamide (DMF) (2 ml) were added HATU (171 mg, 0.450 mmol) and DIEA (0.157 ml, 0.900 mmol). The reaction was stirred for 30 minutes, followed by the addition of [(3-chlorophenyl)methyl]amine (0.055 ml, 0.450 mmol). It was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**17b**) (Yield: 14 mg, 13%); MS(ES⁺) m/e 501 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 4.50 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.25 (s, 1 H) 7.32 - 7.51 (m, 5 H) 7.94 (s, 1 H) 9.30 (t, *J*=5.94 Hz, 1 H) 11.81 (s, 1 H).

Example 18

3-[5,6-bis(methoxy)-2-pyridinyl]-6-chloro-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of 3-[5,6-bis(methoxy)-2-pyridinyl]-6-chloro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**17a**, 85 mg, 0.225 mmol) in N,N-dimethylformamide (DMF) (2 ml) were added HATU (171 mg, 0.450 mmol) and DIEA (0.157 ml, 0.900 mmol). The reaction stirred for 30 minutes, followed by addition of [(4-chlorophenyl)methyl]amine (0.055 ml, 0.450 mmol). The reaction was allowed to stir overnight at room temperature. The solvent was removed and the resulting crude material was dissolved in DMSO (1 mL), which then underwent preparative reversed phase HPLC under acidic conditions to afford 3-[5,6-bis(methoxy)-2-pyridinyl]-6-chloro-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**18**) (Yield: 14 mg, 13%); MS(ES⁺) m/e 501 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.85 (s, 3 H) 4.47 (d, *J*=6.06 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.23 (s, 1 H) 7.33 - 7.53 (m, 5 H) 7.93 (s, 1 H) 9.27 (t, *J*=5.94 Hz, 1 H) 11.79 (s, 1 H).

Example 19

3-[6-chloro-5-(methoxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

19a) methyl 2-amino-4-([(4-chlorophenyl)methyl]amino)benzoate

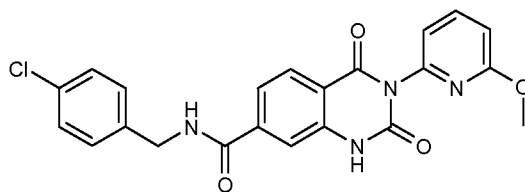
3-Amino-4-[(methoxy)carbonyl]benzoic acid (5g, 25.6 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 10.71g, 28.2 mmol) and N,N-

diisopropylethylamine (DIEA, 3.64 g, 28.2 mmol) were stirred 30 min at rt in N,N-dimethylformamide (DMF, 51 ml). To the same was added [(4-chlorophenyl)methyl]amine (3.63 g, 25.6 mmol) and stirred overnight. The mixture was poured into a rapidly stirred ice bath (20 ml) and made acidic with 1N HCl (5 ml). The solid was collected and dried *in-vacuo* to produce the title compound methyl 2-amino-4-({[(4-chlorophenyl)methyl]amino}carbonyl)benzoate (**19a**) as an off-white solid. (Yield: 7.5 g., 91 %); MS(ES⁺) m/e 318.9 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H), 4.42 (d, *J*=6.06 Hz, 2 H), 6.80 (s, 2 H), 6.96 (dd, *J*=8.34, 1.52 Hz, 1 H), 7.26 (d, *J*=1.77 Hz, 1 H), 7.29 - 7.36 (m, 2 H), 7.36 - 7.42 (m, 2 H), 7.76 (d, *J*=8.59 Hz, 1 H), 9.06 (t, *J*=6.06 Hz, 1 H)

19b) 3-[6-chloro-5-(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Under inert atmosphere (N₂) in dichloromethane (DCM, 20 ml) were combined methyl 2-amino-4-({[(4-chlorophenyl)methyl]amino}carbonyl)benzoate (**19a**, 200 mg, .627 mmol) and *N,N*-dimethyl-4-pyridinamine (DMAP, 460 mg, 3.76 mmol). The solution was stirred 30 min at -78°C (CO₂/acetone) before slowly adding a DCM (2.5 ml) solution of bis(trichloromethyl) carbonate (triphosgene, 61.4 mg, .207 mmol). The cooling was removed after 10 min and stirring continued 1 hour before adding a prestirred (30 min) solution of 6-chloro-5-(methyloxy)-2-pyridinamine (129 mg, .816 mmol) and sodium hydride (NaH, 15 mg, .627 mmol) in DCM (4 ml) and *N,N*-dimethylformamide (DMF, .5 ml) and stirring continued 2 hours. The solvent was removed *in-vacuo* and the residue dissolved in methyl sulfoxide (DMSO, 3.5 ml) and 2N sodium hydroxide (NaOH, 1 ml); stirring continued overnight. The DMSO solution was poured into rapidly stirred acidic water (20 ml / 1 ml 1N HCl). The solid was collected and dissolved in DMSO filtered and purified by HPLC (0.1% TFA, acetonitrile, 0.1% TFA water) to produce the title compound (3-[6-chloro-5-(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**19b**) as a white solid. (Yield: 150 mg, 43%); MS(ES⁺) m/e 471 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.98 (s, 3 H), 4.48 (d, *J*=6.06 Hz, 2 H), 7.33 - 7.45 (m, 4 H), 7.58 (d, *J*=8.34 Hz, 1 H), 7.66 - 7.73 (m, 2 H), 7.81 (d, *J*=8.34 Hz, 1 H), 8.03 (d, *J*=8.08 Hz, 1 H), 9.38 (t, *J*=5.94 Hz, 1 H), 11.84 (s, 1 H)

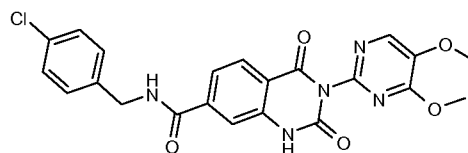
Example 20



N-[(4-chlorophenyl)methyl]-3-[6-(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Under inert atmosphere (N₂) in dichloromethane (DCM, 20 ml) were combined methyl 2-amino-4-
 ([(4-chlorophenyl)methyl]amino)benzoate (**19a**, 200 mg, .627 mmol), *N,N*-dimethyl-4-
 pyridinamine (DMAP, 460 mg, 3.76 mmol) and a DCM (2.5 ml) solution of bis(trichloromethyl)
 carbonate (triphosgene, 63.3 mg, .213 mmol). The contents were stirred at room temperature 2
 hours before adding a prestirred solution of 6-(methyloxy)-2-pyridinamine (86 mg, .690 mmol) and
 sodium hydride (NaH, 15 mg, .627 mmol) in DCM (2 ml) and stirring continued overnight. The
 solvent was removed in-vacuo and the residue dissolved in DMSO (10 ml) and 2N NaOH (1.5 ml)
 and stirred at room temperature overnight. The DMSO solution was poured into rapidly stirred
 water and the pH adjusted to 7 with 1N HCl (1.5 ml). The solid was collected, dissolved in DMSO,
 filtered and purified by HPLC (0.1% TFA, acetonitrile, 0.1% TFA water) to produce the title
 compound (*N*-[(4-chlorophenyl)methyl]-3-[6-(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-
 tetrahydro-7-quinazolinecarboxamide (**20**) as a white solid. (Yield: 37 mg, 13.3%); MS(ES⁺) *m/e*
 437.1 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.81 (s, 3 H), 4.48 (d, *J*=5.81 Hz, 2 H), 6.95
 (d, *J*=8.34 Hz, 1 H), 7.12 (d, *J*=7.33 Hz, 1 H), 7.34 - 7.44 (m, 4 H), 7.66 - 7.74 (m, 2 H), 7.91 (t,
J=7.83 Hz, 1 H), 8.03 (d, *J*=8.34 Hz, 1 H), 9.38 (t, *J*=5.94 Hz, 1 H), 11.81 (br. s., 1 H)

Example 21



3-[4,5-bis(methyloxy)-2-pyrimidinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

21a) Dimethyl 2-isothiocyanato-1,4-benzenedicarboxylate

To a stirred solution of dimethyl 2-amino-1,4-benzenedicarboxylate (41.84 g, 0.20 mol, 1 eq.) in saturated sodium bicarbonate (500 mL) and chloroform (500 mL) was slowly added thiophosgene (20.5 mL, 0.24 mol, 1.2 eq.) and the mixture was stirred at rt for 2.5 hours. Phases were separated

and the aqueous was extracted with DCM (3x). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated to give dimethyl 2-isothiocyanato-1,4-benzenedicarboxylate (**21a**) as a solid which was used for next step without purification. (Yield: 50.3 g, 100%); MS(ES⁺) m/e 252 (MH⁺); ¹H-NMR (400 MHz, CDCl₃) δ ppm: 8.01 - 8.09 (m, 1H), 7.92-8.00 (m, 1H), 4.00 (s, 3H), 3.96 (s, 3H).

21b) 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-4-oxo-2-thioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

To a solution of dimethyl 2-isothiocyanato-1,4-benzenedicarboxylate (**21a**, 1.03 g, 4.1 mmol, 1 eq.) in DMF (5 mL) was added 2-amino-5,6-dimethoxypyrimidine (636 mg, 4.1 mmol, 1 eq.) and the mixture was stirred at rt. After 20 minutes, more DMF (2 mL) was added to give a clear solution and the reaction was stirred at rt for another 2 hours, and then heated at 50°C for 10 hours (solid started to precipitate out after 3 hours' heating). 10% Sodium hydroxide (5 mL) was added and the mixture was stirred at 50 °C for another hour. The cooled mixture was acidified with 6N hydrochloric acid to pH 6-7 and the resulting solid was collected by filtration and washed with water. The product, 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-4-oxo-2-thioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21b**), was used without further purification. (Yield: 1.1 g, 75%); MS(ES⁺) m/e 361 (MH⁺); ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm: 13.71 (br. s., 1H), 13.40 (s, 1H), 8.39 (s 1H), 8.09 (d, *J* 8.08 Hz, 1H), 8.03 (s, 1H), 7.85 (d, *J* 9.60 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H).

21c) 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-2-(ethylthio)-4-oxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

A solution of 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-4-oxo-2-thioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21b**, 739 mg, 2.05 mmol) in DMF was treated with 5N NaOH (0.82 mL, 4.1 mmol) at rt, and reaction mixture was stirred at rt for one hour. Ethyl iodide was then added dropwise, and the reaction mixture was stirred at rt for another two hours. The reaction mixture was acidified to pH 5 and concentrated. The product was suspended in water and sonicated for 2 minutes. The resulting solid was collected, washed and dried. The crude product 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-2-(ethylthio)-4-oxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21c**) was used for next step without further purification. (Yield: 720 mg, 90 %)

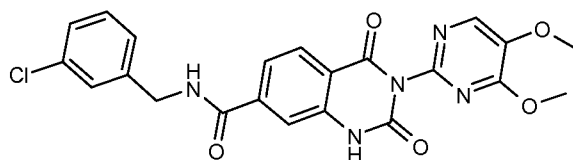
21d) 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

To a suspension of 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-2-(ethylthio)-4-oxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21c**, 720 mg, 1.8 mmol) in ethanol was added 6N HCl (20 mL). The reaction mixture was refluxed at 100 °C for 2 hours. Reaction mixture was concentrated and the residue was dissolved in DMF (4 mL) to which was added 10 % NaOH (5 mL). The reaction mixture was stirred at rt for 2.5 hours. The reaction mixture was concentrated and the residue was dissolved in DMSO (6 mL). The DMSO solution was filtered and the filtrate purified with a Gilson HPLC system. Desired product, 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21d**), was obtained. (Yield: 35 mg, 5%)

21e) 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

3-[4,5-Bis(methyloxy)-2-pyrimidinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21d**, 17.2 mg, 0.05 mmol), 4-chlorobenzylamine (8 mg, 0.06mmol, 1.1 eq.), and DIEA (8 mg, 0.06 mmol, 1.1 eq.) were added into dry DMF (1 mL). HATU (21 mg, 0.06 mmol) was then added into the reaction mixture. It was stirred at rt overnight. The reaction mixture was poured into cold water (35 mL), and the precipitate was filtered and collected. The solid was dissolved in DMSO, filtered and purified on a Gilson HPLC system (15-75% gradient in 8 minutes). Desired product, 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**21e**), was obtained. (Yield 4.2 mg. 18 %); MS(ES⁺) m/e 468.2 (MH⁺) ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.95 (d, *J*=14.15 Hz, 6 H) 4.48 (d, *J*=6.06 Hz, 2 H) 7.35 - 7.46 (m, 4 H) 7.72 (s, 1 H) 7.70 (d, *J*=1.52 Hz, 1 H) 8.05 (d, *J*=8.08 Hz, 1 H) 8.39 (s, 1 H) 9.34 - 9.45 (m, 1 H) 11.93 (s, 1 H)

Example 22

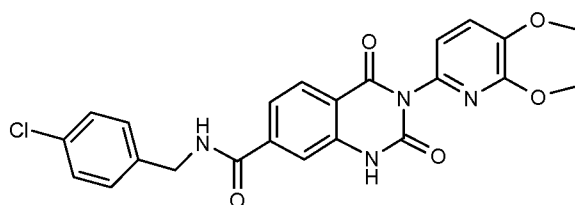


3-[4,5-bis(methyloxy)-2-pyrimidinyl]-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

3-[4,5-Bis(methyloxy)-2-pyrimidinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**21d**, 17.2 mg, 0.05 mmol), 3-chlorobenzylamine (8 mg, 0.06mmol, 1.1 eq.), and DIEA (8 mg, 0.06 mmol, 1.1 eq.) were added into dry DMF (1 mL). HATU (21 mg, 0.06 mmol) was added into

the reaction mixture. It was stirred at rt overnight. The reaction mixture was poured into cold water (35 mL), and the precipitate was filtered and collected. The solid was dissolved in DMSO, filtered and purified on a Gilson HPLC system (15-75% gradient in 8 minutes). The desired product, 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**22**), was obtained. Yield 13.9 mg, 59 %; MS(ES⁺) m/e 468.2 (MH⁺) ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.93 (s, 3 H) 3.96 (s, 3 H) 4.50 (d, *J*=6.06 Hz, 2 H) 7.30 - 7.42 (m, 4 H) 7.70 (d, *J*=1.52 Hz, 1 H) 7.72 (s, 1 H) 8.05 (d, *J*=8.08 Hz, 1 H) 8.39 (s, 1 H) 9.40 (s, 1 H) 11.93 (s, 1 H)

Example 23



3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

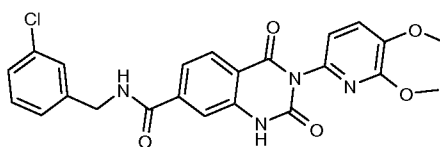
23a) methyl 2-amino-4-({[(4-chlorophenyl)methyl]amino}carbonyl)benzoate

To a stirred suspension of 3-amino-4-(methoxycarbonyl)benzoic acid (20 g, 0.10 mol, 1 eq.) in DMF (205 mL) was added HATU (43 g, 0.11 mol, 1.1 eq.) and DIEA (19.6 mL, 0.11 mol, 1.1 eq.) and the mixture stirred at rt for 10 min until all dissolved. To this stirred solution was added a 9M solution of 4-chlorobenzylamine (13.7 mL, 0.11 mol, 1.1 eq.) in DMF (12 mL) via syringe. The solution was stirred at rt overnight, and after confirmation by LCMS that the reaction was complete the product was precipitated from ice water (2 L, crush ice, dionized water). The product was collected by vacuum filtration and dried in a vacuum oven at 30°C for 48 hours to yield the title product methyl 2-amino-4-({[(4-chlorophenyl)methyl]amino}carbonyl)benzoate (**23a**) as a pale cream powder which was used without further purification. (Yield: 30 g, 94%); MS(ES⁺) m/e 319 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 3.81 (s, 3 H), 4.42 (d, *J* 6.06 Hz, 2 H), 6.80 (s, 2 H), 6.96 (dd, *J* 8.34, 1.77 Hz, 1 H), 7.26 (d, *J* 1.52 Hz, 1 H), 7.29 - 7.36 (m, 2 H), 7.36 - 7.43 (m, 2 H), 7.76 (d, *J* 8.59 Hz, 1 H), 9.06 (t, 1 H)

23b) 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of methyl 2-amino-4-({[(4-chlorophenyl)methyl]amino}carbonyl)benzoate (**23a**, 159 mg, 0.5 mmol) and DMAP (366 mg, 3.0 mmol) in DCM (15 mL) was added dropwise of a solution of triphosgene (50 mg, 0.17 mmol) in DCM (2 mL) at -77°C . Reaction mixture was stirred at rt for 1 hour. 5,6-bis(methoxy)-2-pyridinamine (77 mg, 0.5 mmol) was added into
 5 reaction mixture. Reaction mixture was stirred at rt for one hour. Reaction was concentrated and residue was dissolved with DMF (2 mL). 2N NaOH (0.5 mL) solution was added into reaction solution. The reaction mixture was then heated at 50°C for one hour. The reaction mixture was poured into ice water and a precipitate formed. The solid was filtered off and collected. The solid was dissolved with 1.5 mL of DMSO. purified with a Gilson HPLC system (20-50% gradient in
 10 8.5 minutes). The product, 3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide, (**23b**) was obtained. (Yield: 75 mg, 32 %); MS(ES^+) m/e 467 (MH^+); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 4.48 (d, $J=5.81$ Hz, 2 H) 7.05 (d, $J=8.08$ Hz, 1 H) 7.35 - 7.43 (m, 4 H) 7.46 (d, $J=8.34$ Hz, 1 H) 7.65 - 7.72 (m, 2 H) 8.02 (d, $J=8.08$ Hz, 1 H) 9.33 - 9.42 (m, 1 H) 11.75 (s, 1 H)

Example 24



3-[5,6-bis(methoxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

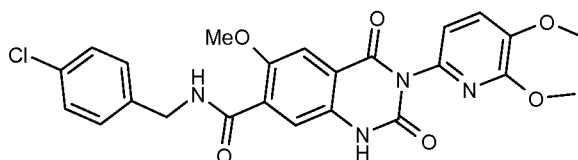
24a) Methyl 2-amino-4-(3-chlorobenzylaminocarbonyl)benzoate

To a stirred suspension of 3-amino-4-(methoxycarbonyl)benzoic acid (1.0 g, 5.13 mmol, 1 eq.) in
 25 DMF (7 mL) was added HATU (2.1 g, 0.564 mmol, 1.1 eq.) and DIEA (0.98 mL, 0.11 mol, 1.1 eq.) and the mixture was stirred at rt for 5 minutes until all dissolved. The resulting solution was added to 3-chlorobenzylamine (0.69 mL, 5.64 mmol, 1.1 eq.) in DMF (3 mL) via syringe and stirred at rt for 30 minutes when LCMS showed that the reaction was complete. The solution was added dropwise to ice-water with stirring and the precipitate collected by vacuum filtration,
 30 washed with ice-water and dried under vacuum to yield the title product methyl 2-amino-4-(3-chlorobenzylaminocarbonyl)benzoate (**24a**) which was used without further purification. (Yield: 1.52g, 93%); MS(ES^+) m/e 319 (MH^+); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 3.81 (s, 3 H) 4.44 (d, J 6.06 Hz, 2 H) 6.81 (s, 2 H) 6.97 (d, J 8.59 Hz, 1 H) 7.24 - 7.40 (m, 5 H) 7.77 (d, J 8.59 Hz, 1 H) 9.07 (t, J 6.06 Hz, 1 H)

24b) 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

To a stirred solution of methyl 2-amino-4-({[(3-chlorophenyl)methyl]amino}carbonyl)benzoate (**24a**, 159 mg, 0.5 mmol) and DMAP (366 mg, 3.0 mmol) in DCM (15 mL) was added dropwise of a solution of triphosgene (50 mg, 0.17 mmol) in DCM (2 mL) at -77 °C. The reaction mixture was stirred at rt for 1 hour. 5,6-Bis(methyloxy)-2-pyridinamine (77 mg, 0.5 mmol) was added to the reaction mixture and it was stirred at rt for one hour. It was concentrated and residue was dissolved with DMF (2 mL). 2N NaOH solution was added into reaction solution and the mixture was then heated at 40-50 °C for one hour. The reaction mixture was poured into ice water while stirring. Precipitate was filtered off and collected. The solid was dissolved with DMSO (1.5 mL) and purified with a Gilson HPLC system (20-50% gradient in 8.5 minutes). The product, 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**24b**), was obtained. (Yield: 64 mg, 27%); LCMS MS(ES⁺) m/e 467 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 4.50 (d, *J*=5.81 Hz, 2 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.30 - 7.42 (m, 4 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.65 - 7.73 (m, 2 H) 8.03 (d, *J*=8.08 Hz, 1 H) 9.38 (s, 1 H) 11.75 (s, 1 H)

Example 25

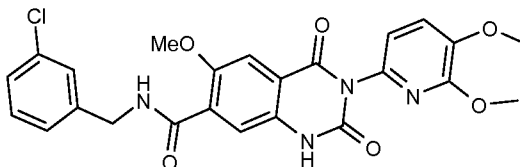


3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Into a 5 mL round-bottomed flask were added 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**6a**, 93 mg, 0.25 mmol), 1-(4-chlorophenyl)methanamine (35 mg, 0.25 mmol), and TEA (0.105 mL, 0.75 mmol) in N,N-dimethylformamide (DMF) (2 mL). HATU (124 mg, 0.33 mmol) was added slowly into the solution. The reaction mixture was then stirred at rt for one hour. LCMS showed that the reaction was complete. The reaction mixture was then poured into 100 mL of ice water and a precipitate formed immediately. The resulted solid was filtered, rinsed with water (50 mL), and collected. The residue was dissolved with DMSO, the solution was filtered and purified with a Gilson preparative

HPLC system. The desired product, 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**25**), was obtained. (Yield: 20 mg, 16%); LCMS MS(ES⁺) *m/e* 497 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 3.92 (s, 3 H) 4.49 (d, *J*=6.06 Hz, 2 H) 6.56 (s, 1 H) 7.03 (d, *J*=8.08 Hz, 2 H) 7.34 - 7.43 (m, 2 H) 7.47 (s, 1 H) 7.44 (d, *J*=4.55 Hz, 1 H) 7.50 (s, 1 H) 7.54 (s, 1 H) 9.01 (s, 1 H)

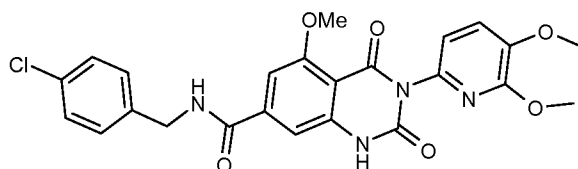
Example 26



3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Into a 5 mL round-bottomed flask were added 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**6a**, 112 mg, 0.3 mmol), 1-(3-chlorophenyl)methanamine (43 mg, 0.3 mmol), and TEA (0.06 mL, 0.45 mmol) in *N,N*-dimethylformamide (DMF) (2 mL). HATU (148 mg, 0.39 mmol) was added slowly into the solution. The reaction mixture was then stirred at rt for one hour. LCMS showed that the reaction was complete. The reaction mixture was then poured into 100 ml of icy water and precipitate formed immediately. The resulted solid was filtered, rinsed with water (50 mL), and collected. The residue was dissolved with DMSO which was filtered and purified with Gilson preparative HPLC system. The desired product 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**26**) was obtained. (Yield: 21 mg), 14%; LCMS MS(ES⁺) *m/e* 497 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.80 (s, 3 H) 3.86 (s, 3 H) 3.94 (s, 3 H) 4.51 (d, *J*=6.06 Hz, 2 H) 7.04 (d, *J*=7.83 Hz, 1 H) 7.33 (d, *J*=6.57 Hz, 1 H) 7.34 (s, 1 H) 7.39 (d, *J*=7.58 Hz, 1 H) 7.43 (s, 1 H) 7.46 (d, *J*=8.08 Hz, 1 H) 7.51 (s, 2 H) 9.04 (s, 1 H)

Example 27



3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-5-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

5

27a) 3-[5,6-bis(methoxy)-2-pyridinyl]-5-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

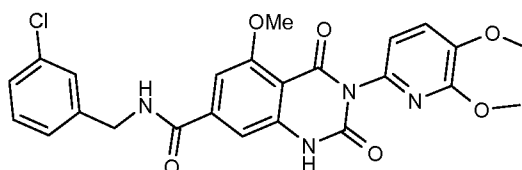
Into a 100 mL round-bottomed flask were added dimethyl 2-amino-6-(methoxy)-1,4-benzenedicarboxylate (**1F**, 478 mg, 2 mmol), and DMAP (1466 mg, 12 mmol) in tetrahydrofuran (THF) (40 mL). The resulted reaction mixture was cooled to -77 °C. Triphosgene (198 mg, 0.67 mmol) was added slowly into the mixture. The reaction mixture was stirred at -77 °C for 1 hour. 5,6-Bis(methoxy)-2-pyridinamine (308 mg, 2 mmol) in DCM solution was added slowly into reaction mixture. The reaction mixture was stirred overnight. The reaction mixture was concentrated and dissolved into DMF (5 mL). Then it was stirred at 50 °C for 30 minutes. 2N NaOH solution (2.5 mL) was added and the resulted reaction mixture was stirred for 60 minutes. LCMS showed that reaction was completed. The reaction mixture was acidified with 6N HCl to pH 2. The solution was precipitated and filtered. Solid was collected and dried to provide 3-[5,6-bis(methoxy)-2-pyridinyl]-5-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**27a**) (Yield: 337 mg, 45 %); LCMS MS(ES⁺) m/e 374 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.79 (s, 3 H) 3.85 (s, 6 H) 6.97 (d, *J*=8.08 Hz, 1 H) 7.20 (br. s., 1 H) 7.34 (s, 1 H) 7.44 (d, *J*=8.08 Hz, 1 H)

27b) 3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-5-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Into a 25 mL round-bottomed flask were added 3-[5,6-bis(methoxy)-2-pyridinyl]-5-(methoxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**27a**, 37 mg, 0.1 mmol), 1-(4-chlorophenyl)methanamine (14 mg, 0.1 mmol), and TEA (0.02 mL, 0.15 mmol) in N,N-Dimethylformamide (DMF) (2 mL), HATU (49 mg, 0.13 mmol) was added slowly into the solution. The reaction mixture was then stirred at rt overnight. LCMS showed that the reaction was complete. The reaction mixture was then poured into 100 ml of ice water and a precipitate formed immediately. The resulted solid was filtered, rinsed with water (50 mL), and collected. The residue was dissolved with DMSO (2 mL) which was filtered and purified with a Gilson preparative

HPLC system. The desired product, 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**27b**), was obtained. (Yield: 5 mg, 10 %); LCMS MS(ES^+) m/e 497 (MH^+); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.79 (s, 3 H) 3.85 (s, 3 H) 3.89 (s, 3 H) 4.49 (s, 2 H) 6.96 (d, $J=4.55$ Hz, 2 H) 7.20 (d, $J=5.05$ Hz, 1 H) 7.19 (s, 1 H) 7.26 (d, $J=1.52$ Hz, 1 H) 7.34 - 7.45 (m, 5 H)

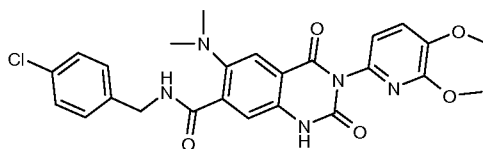
Example 28



10 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Into a 25 mL round-bottomed flask were added 3-[5,6-bis(methyloxy)-2-pyridinyl]-5-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**27a**, 37 mg, 0.1 mmol), 1-(3-chlorophenyl)methanamine (14 mg, 0.1 mmol), and TEA (0.02 mL, 0.15 mmol) in *N,N*-Dimethylformamide (DMF) (2 mL), HATU (49 mg, 0.13 mmol) was added slowly into the solution. The reaction mixture was then stirred at rt overnight. LCMS showed that the reaction was complete. The reaction mixture was then poured into 100 ml of ice water and a precipitate formed immediately. This solid was filtered, rinsed with water (50 mL), and collected. The residue was dissolved with DMSO (2 mL) which was filtered and purified with a Gilson preparative HPLC system. The desired product, 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**28**), was obtained. (Yield: 8.5 mg, 17%); LCMS MS(ES^+) m/e 497 (MH^+); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.79 (s, 3 H) 3.85 (s, 3 H) 3.89 (s, 3 H) 4.51 (d, $J=5.81$ Hz, 2 H) 6.99 (s, 1 H) 7.20 (d, $J=1.26$ Hz, 1 H) 7.27 (d, $J=1.26$ Hz, 1 H) 7.30 - 7.36 (m, 2 H) 7.39 - 7.43 (m, 2 H) 7.45 (s, 1 H) 9.33 - 9.37 (m, 1 H) 11.59 (s, 1 H)

Example 29



30

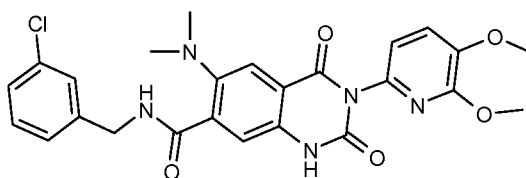
3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

29a) 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid

Into a 100 mL round-bottomed flask were added dimethyl 2-amino-5-(methyloxy)-1,4-benzenedicarboxylate (**1G**, 400 mg, 1.6 mmol), DMAP (1162 mg, 9.5 mmol) in DCM (40 mL). The resulted reaction mixture was cooled to -77 °C. Triphosgene (155 mg, 0.52 mmol) was added slowly into the mixture. The reaction mixture was stirred at -77 °C for 1 hour. Then 5,6-bis(methyloxy)-2-pyridinamine (244 mg, 1.6 mmol) in DCM solution was added slowly into reaction mixture. The reaction mixture was stirred overnight. The reaction mixture was concentrated and dissolved into DMF (5 mL). The reaction mixture was stirred at 50 °C for overnight. 2N NaOH solution (1.25 mL) was added and the resulted reaction mixture was stirred for 3.5 hours. LCMS showed that reaction was completed. The reaction mixture was acidified with 6N HCl to pH 2. The solution was precipitated and filtered. Solid was collected and dried to provide 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**29a**) (Yield: 456 mg, 74 %)

29b) 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Into a 10 mL round-bottomed flask were added 3-[5,6-bis(methyloxy)-2-pyridinyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**29a**, 58 mg, 0.15 mmol), 1-(4-chlorophenyl)methanamine (21 mg, 0.15 mmol), and TEA (23 mg, 0.23 mmol) in N,N-dimethylformamide (DMF) (3 mL). HATU (74 mg, 0.2 mmol) was added slowly into the solution. The reaction mixture was then stirred at rt for 2 hours. LCMS showed that the reaction was complete. The reaction mixture was then poured into 100 ml of icy water and a precipitate formed immediately. The resulted solid was filtered, rinsed with water (50 mL), and collected. The residue was dissolved with DMSO (2 mL) after which it was filtered and purified with a Gilson preparative HPLC system. The desired product, 3-[5,6-bis(methyloxy)-2-pyridinyl]-N-[(4-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**29c**), was obtained. (Yield 12 mg, 16%); MS(ES⁺) m/e 510 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.65 (s, 6 H) 3.79 (s, 3 H) 3.85 (s, 3 H) 4.49 (d, *J*=6.32 Hz, 2 H) 7.02 (d, *J*=8.08 Hz, 1 H) 7.40 - 7.50 (m, 6 H) 7.61 (s, 1 H) 9.68 (s, 1 H) 11.56 (s, 1 H)

Example 30

3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide

Into a 10 mL round-bottomed flask were added 3-[5,6-bis(methoxy)-2-pyridinyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxylic acid (**29a**, 58 mg, 0.15 mmol), 1-(3-chlorophenyl)methanamine (21 mg, 0.15 mmol), and TEA (23 mg, 0.23 mmol) in N,N-dimethylformamide (DMF) (3 mL). HATU (74 mg, 0.2 mmol) was added slowly into the solution. The reaction mixture was then stirred at rt for 2 hours. LCMS showed that the reaction was complete. The reaction mixture was then poured into 100 ml of ice water and a precipitate formed immediately. The resulted solid was filtered, rinsed with water (50 mL), and collected. The residue was dissolved with DMSO (2 mL) which was filtered and purified with a Gilson preparative HPLC system. The desired product, 3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide (**30**), was obtained. Yield 20 mg, 26%; MS(ES⁺) m/e 510 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.70 (s, 6 H) 3.79 (s, 3 H) 3.85 (s, 3 H) 4.51 (d, *J*=6.06 Hz, 2 H) 7.02 (d, *J*=8.08 Hz, 1 H) 7.30 - 7.42 (m, 2 H) 7.42 - 7.52 (m, 2 H) 7.67 (s, 1 H) 9.65 (s, 1 H) 11.59 (s, 1 H).

Biological Background:

The following references set out information about the target enzymes, HIF prolyl hydroxylases, and methods and materials for measuring inhibition of same by small molecules.

M. Hirsilä, P. Koivunen, V. Günzler, K. I. Kivirikko, and J. Myllyharju "Characterization of the Human Prolyl 4-Hydroxylases That Modify the Hypoxia-inducible Factor" *J. Biol. Chem.*, **2003**, 278, 30772-30780.

C. Willam, L. G. Nicholls, P. J. Ratcliffe, C. W. Pugh, P. H. Maxwell "The prolyl hydroxylase enzymes that act as oxygen sensors regulating destruction of hypoxia-inducible factor α" *Advan. Enzyme Regul.*, **2004**, 44, 75-92

M. S. Wiesener, J. S. Jürgensen, C. Rosenberger, C. K. Scholze, J. H. Hörstrup, C. Warnecke, S. Mandriota, I. Bechmann, U. A. Frei, C. W. Pugh, P. J. Ratcliffe, S. Bachmann, P. H. Maxwell, and K.-U. Eckardt "Widespread hypoxia-inducible expression of HIF-2α in distinct cell populations of different organs" *FASEB J.*, **2003**, 17, 271-273.

S. J. Klaus, C. J. Molineaux, T. B. Neff, V. Guenzler-Pukall, I. Lansetmo Parobok, T. W. Seeley, R. C. Stephenson "Use of hypoxia-inducible factor α (HIF α) stabilizers for enhancing erythropoiesis" PCT Int. Appl. (**2004**), WO 2004108121 A1

- C. Warnecke, Z. Zaborowska, J. Kurreck, V. A. Erdmann, U. Frei, M. Wiesener, and K.-U. Eckardt "Differentiating the functional role of hypoxia-inducible factor (HIF)-1 α and HIF-2 α (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2 α target gene in Hep3B and Kelly cells" *FASEB J.*, **2004**, 18, 1462-1464.

For the expression of EGLN3 see:

- 10 R. K. Bruick and S. L. McKnight "A Conserved Family of Prolyl-4-Hydroxylases That Modify HIF" *Science*, **2001**, 294, 1337-1340.

For the expression of HIF2 α -CDD see:

- a) P. Jaakkola, D. R. Mole, Y.-M. Tian, M. I. Wilson, J. Gielbert, S. J. Gaskell, A. von Kriegsheim, H. F. Hebestreit, M. Mukherji, C. J. Schofield, P. H. Maxwell, C. W. Pugh, P. J. Ratcliffe "Targeting of HIF- α to the von Hippel-Lindau Ubiquitylation Complex by O₂-Regulated Prolyl Hydroxylation" *Science*, **2001**, 292, 468-472.
- 15 b) M. Ivan, K. Kondo, H. Yang, W. Kim, J. Valiando, M. Ohh, A. Salic, J. M. Asara, W. S. Lane, W. G. Kaelin Jr. "HIF α Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O₂ Sensing" *Science*, **2001**, 292, 464-468.

20

For the expression of VHL, elongin b and elongin c see:

- A. Pause, S. Lee, R. A. Worrell, D. Y. T. Chen, W. H. Burgess, W. M. Linehan, R. D. Klausner "The von Hippel-Lindau tumor-suppressor gene product forms a stable complex with human CUL-2, a member of the Cdc53 family of proteins" *Proc. Natl. Acad. Sci. USA*, **1997**, 94, 2156-2161.
- 25

Biological Assay(s)

EGLN3 Assay

Materials:

- 30 His-MBP-EGLN3 (6HisMBPAttB1EGLN3(1-239)) was expressed in *E. Coli* and purified from an amylose affinity column. Biotin-VBC [6HisSumoCysVHL(2-213), 6HisSumoElonginB(1-118), and 6HisSumoElonginC(1-112)] and His-GB1-HIF2 α -CDD (6HisGB1tevHIF2A(467-572)) were expressed from *E. Coli*.

Method:

Cy5-labelled HIF2 α CODD, and a biotin-labeled VBC complex were used to determine EGLN3 inhibition. EGLN3 hydroxylation of the Cy5CODD substrate results in its recognition by the biotin-VBC. Addition of a Europium/streptavidin (Eu/SA) chelate results in proximity of Eu to
5 Cy5 in the product, allowing for detection by energy transfer. A ratio of Cy5 to Eu emission (LANCE Ratio) is the ultimate readout, as this normalized parameter has significantly less variance than the Cy5 emission alone.

Then 50nL of inhibitors in DMSO (or DMSO controls) were stamped into a 384-well low volume Corning NBS plate, followed by addition of 2.5 μ L of enzyme [50 mL buffer (50 mM
10 HEPES/50 mM KCl) + 1 mL of a 10 mg/mL BSA in buffer + 6.25 μ L of a 10mg/mL FeCl₂ solution in water + 100 μ L of a 200 mM solution of ascorbic acid in water + 15.63 μ L EGLN3] or control [50 mL buffer + 1 mL of a 10 mg/mL BSA in buffer + 6.25 μ L of a 10mg/mL FeCl₂ solution in water + 100 μ L of a 200 mM solution of ascorbic acid in water]. Following a 3 minutes
15 incubation, 2.5 μ L of substrate [50mL Buffer + 68.6 μ L biotin-VBC + 70.4 μ L Eu (at 710 μ g/mL stock) + 91.6 μ L Cy5CODD + 50 μ L of a 20 mM solution of 2-oxoglutaric acid in water + 0.3mM CHAPS] was added and incubated for 30 minutes. The plate was loaded into a PerkinElmer Viewlux for imaging. For dose response experiments, normalized data were fit by ABASE/XC50 using the equation $y = a + (b-a)/(1+(10^x/10^c)^d)$, where a is the minimum % activity, b is the maximum % activity, c is the pIC₅₀, and d is the Hill slope.

20 The IC₅₀ for exemplified compounds in the EGLN3 assay ranged from approximately 1 - 100 nanomolar. This range represents the data accumulated as of the time of the filing of this initial application. Later testing may show variations in IC₅₀ data due to variations in reagents, conditions and variations in the method(s) used from those given herein above. So this range is to be viewed as illustrative, and not a absolute set of numbers.

Measure Epo protein produced by Hep3B cell line using ELISA method.

Hep3B cells obtained from the American Type Culture Collection (ATCC) are seeded at 2x10⁴ cells/well in Dulbecco's Modified Eagle Medium (DMEM) + 10% FBS in 96-well plates. Cells are incubated at 37degC/5% CO2/90% humidity (standard cell culture incubation
30 conditions). After overnight adherence, medium is removed and replaced with DMEM without serum containing test compound or DMSO negative control. Following 48 hours incubation, cell culture medium is collected and assayed by ELISA to quantitate Epo protein.

The EC₅₀ for exemplar compounds in the Hep3B ELISA assay ranged from approximately 1 - 20 micromolar using the reagents and under the conditions outlined herein above. This range
35 represents the data accumulated as of the time of the filing of this initial application. Later testing

may show variations in EC₅₀ data due to variations in reagents, conditions and variations in the method(s) used from those given herein above. So this range is to be viewed as illustrative, and not a absolute set of numbers.

5 These compound are believed to be useful in therapy as defined above and to not have unacceptable or untoward effects when used in compliance with a permitted therapeutic regime.

The foregoing examples and assay have been set forth to illustrate the invention, not limit it. What is reserved to the inventors is to be determined by reference to the claims.

What is claimed is:

1. A compound of formula (I):

5 To be added.

2. A compound according to claim 1 wherein:

To be added

10 3. A compound according to claim 1 wherein:

To be added

4. A compound according to claim 1 which is:

15 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chloro-3-fluorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

20 3-[5,6-bis(methyloxy)-2-pyridinyl]-2,4-dioxo-*N*-{[4-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-{[4-(1-methylethyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

25 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-{[4-(methylsulfonyl)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-{[4-(dimethylamino)phenyl]methyl}-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

30 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[1-(4-chlorophenyl)-1-methylethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

35 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-5-chloro-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

5 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

10 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(1*S*)-1-(4-chlorophenyl)ethyl]-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-6-chloro-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

15 3-[6-chloro-5-(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

N-[(4-chlorophenyl)methyl]-3-[6-(methyloxy)-2-pyridinyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

20 3-[4,5-bis(methyloxy)-2-pyrimidinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[4,5-bis(methyloxy)-2-pyrimidinyl]-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

25 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

30 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-5-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(3-chlorophenyl)methyl]-6-(methyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

35 3-[5,6-bis(methyloxy)-2-pyridinyl]-*N*-[(4-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide; or

3-[5,6-bis(methoxy)-2-pyridinyl]-N-[(3-chlorophenyl)methyl]-6-(dimethylamino)-2,4-dioxo-1,2,3,4-tetrahydro-7-quinazolinecarboxamide;

or a pharmaceutically acceptable salt or solvate thereof.

- 5 5. A method for treating anemia in a mammal, which method comprises administering an effective amount of a compound of formula (I) or a salt thereof according to claim 1 to a mammal suffering from anemia which can be treated by inhibiting HIF prolyl hydroxylases.
6. A pharmaceutical composition comprising a compound of formula (I) or a salt thereof
- 10 according to claim 1 and one or more of pharmaceutically acceptable carriers, diluents and excipients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/64534

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/54; A61K 31/517 (2010.01) USPC - 514/266.1 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IUSPC- 514/266.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC- 514/252.17, 266.3 (see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest (US Pat, PgPub, EPO, JPO: class, keyword), DialogClassic (Derwent, EPO, JPO, USPTO, WIPO: keyword), GoogleScholar; search terms: anemia, quinazoline, carboxamide, cancer, hydroxylase, phenyl, chloro, fluoro, sulfonyl		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0293575 A1 (SEELEY et al.) 20 December 2007 (20.12.2007) Formula 1a; pg 10; para [0015], [0017], [0048], [0071], [0083], [0091], [0099]-[0107], [0262], [0267], [0281], [0285], [0296]	1-6
Y	US 4,738,971 A (ERIKSOO et al.) 19 April 1988 (19.04.1988) col 1, ln 11-15; col 3, ln 50 to col 4, ln 60; col 5, ln 1-29; col 6, ln 10-13	1-6
X/P	WO 2008/144464 A1 (ADAMS et al.) 27 November 2008 (27.11.2008) entire document	1-6
A	WO 2007/022241 A2 (DENG et al.) 22 February 2007 (22.02.2007) entire document	1-6
A	WO 2005/085227 A1 (YAMASHITA et al.) 15 September 2005 (15.09.2005) entire document	1-6
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* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 11 January 2010 (11.01.2010)		Date of mailing of the international search report 12 FEB 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774