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(54) Title: SMALL MOLECULE INHIBITORS OF ACETYL COENZYME A SYNTHETASE SHORT CHAIN 2 (ACSS2)

(57) Abstract: The present invention relates to compounds of formula (I). The compounds may be used to modulate the acetyl coenzyme A synthetase short chain 2 (ACSS2) protein and may thereby treat, ameliorate or prevent a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, neurodegenerative disease, neurological disorder, cerebrovascular disease, cardiovascular disease, non-alcoholic fatty liver disease and obesity. Alternatively, or additionally, the compounds may be used to promote healthy ageing.



Small molecule inhibitors of acetyl coenzyme A synthetase short chain 2 (ACSS2)

The present invention relates to small molecules for use in inhibiting the enzymatic activity of the acetyl coenzyme A synthetase short chain 2 (ACSS2) protein. Accordingly, the small molecules may be for use in the treatment of diseases, such as cancer, cardiac disorders, metabolic disorders, neurological disorders, fibrotic disease, ageing disorders, bacterial and viral infections and so on. The invention extends to the compounds *per se* pharmaceutical compositions, methods of making the compounds and methods of inhibiting the ACSS2 protein.

Acetyl CoA synthetases (ACSS 1 to 3) are a family of cellular enzymes that carry out the first enzymatic step in the conversion of acetate to the multifunctional metabolite acetyl coenzyme A (acetyl-CoA) through ligation of acetate with CoA in an ATP-driven process (Knowles, S.E.; Jarrett, I.G.; Filsell, O.H.; Ballard, F.J., *Biochem. J.*, **1974**, 142, 401-411). ACSS1 and ACSS3 are predominantly expressed in the mitochondria of cells, while ACSS2 is expressed in both nuclear and cytoplasmic compartments (Fujino, T.; Kondo, J.; Ishikawa, M.; Morikawa, K.; Yamamoto, T.T., *J. Biol. Chem.*, **2001**, 276, 11423-11426; Luong, A.; Hannah, V.C.; Brown, M.S.; Goldstein, J.L., *J. Biol. Chem.*, **2000**, 275, 26458-26466; Ariyannur, P.S.; Moffett, J.R.; Madhavarao, C.N.; Arun, P. *et. al.*, *J. Comp. Neurol.*, **2010**, 518, 2952-2977).

Acetyl-CoA fulfils a central role in cellular metabolism and is involved in multiple cellular processes (Pietrocola, F.; Galluzzi, L.; Bravo-San Pedro, J. M. *et. al.*, *Cell. Metab.*, **2015**, 21, 805-821). In well-nourished mammalian cells, acetyl-CoA enters the citric acid cycle by condensing with oxaloacetate to form citrate and therefrom a range of other metabolites (Srere, P.A., *J. Biol. Chem.*, **1959**, 234, 2544-2547). It is a key intermediate of carbon sources and is an essential building block for the synthesis of fatty acids, amino acids and sterols.

Cell growth and proliferation are closely co-ordinated with metabolism and the availability of acetyl-CoA. One of the hallmarks of cancer is rapid, uncontrolled cellular proliferation, which requires increased production of energy and biomass *via* ATP and lipid production. This involves changes in both the way extracellular nutrients are captured and how they are metabolised. Targeting the strategies adopted by cancer

cells to increase rates of metabolism and enhance proliferative capacity under nutrient-limited conditions is an attractive anti-cancer therapeutic approach. It is especially compelling to target sources of the key cytosolic regulator of lipid, cholesterol and amino acid synthesis, namely acetyl-CoA.

5

In nutrient-limited conditions, such as in cancer cells, aerobic glycolysis takes place and the pyruvate formed from glucose metabolism is preferentially converted by reduction into lactate instead of being taken on to synthesise acetyl-CoA (the 'Warburg Effect'). In response, both acetate uptake and ACSS2 are upregulated and there is a significant
10 shift in the sourcing of acetyl-CoA from other nutrients, a process which relies heavily on ACSS2 for acetyl-CoA synthesis.

Acetate is taken up and metabolized to biomass by proliferating hypoxic and lipid depleted tumor cells (Corbet, C.; Feron, O., *Curr. Op. Clin. Nutr. Metab. Care*, **2015**,
15 18, 346-353). The propensity of certain tumors for acetate uptake has been exploited for over a decade to detect primary tumors and identify distant metastases by using ¹¹C-acetate guided positron emission tomography (PET) imaging to detect or grade gliomas, hepatocellular carcinomas, non-small cell lung cancer and metastases in prostate cancer patients. This reinforces early studies demonstrating that tumor cells
20 take up significant amounts of acetate often in preference to glucose as a nutrient to satisfy their increased demand for acetyl-CoA (Yoshimoto, M.; Waki, A.; Yonekura, Y.; Sadato, N. et. al., *Nucl. Med. Biol.*, **2001**, 28, 117-122).

There is an increasing body of clinical evidence that places acetate and ACSS2 at a
25 critical metabolic node in tumor cells under nutritional and hypoxic stress. Genome analysis reveals that ACSS2 copy number is associated with higher and more invasive stages of breast cancer and metastatic prostate cancer (Schug, Z.T.; Peck, B.; Jones, D.T.; Zhang, Q.; Grosskurth, S. et. al., *Cancer Cell*, **2015**, 27, 57-71).

Immunohistochemistry (IHC) using anti-ACSS2 antibodies on human breast, ovarian,
30 kidney and lung tumor samples showed significant expression compared to matched normal samples which showed little or no ACSS2 expression. Survival analyses of patients with grade-2/3 gliomas (Mashimo, T.; Pichumani, K.; Vemireddy, V.; Hatanpaa, K.J., *Cell*, **2014**, 159, 1603-1614) or triple negative breast cancer (Comerford, S.A.; Huang, Z.; Du, X.; Wang, Y. et. al., *Cell*, **2014**, 159, 1591-1602) reveal
35 that high ACSS2 expression is associated with shorter overall survival. These clinical findings show a strong correlation between acetate uptake, ACSS2 expression and

cancer progression. This suggests that inhibiting ACSS2 activity could benefit patients with acetate metabolizing tumors.

5 Hypoxic tumor cells express high levels of cytosolic ACSS2. Knockdown of ACSS2 by RNA interference in tumor cells enhanced tumor cell death under long term hypoxia in vitro and slowed tumor growth in vivo (Yoshii, Y.; Furukawa, T.; Yoshii, H.; Mori, T. et al., *Cancer Sci.*, **2009**, 100, 821-827), supporting a role for ACSS2 in tumor progression and providing the rationale for a pharmacological inhibitor. Interfering with the metabolism of acetate by curtailing ACSS2 activity would deprive resilient
10 tumor cells of a critical nutrient source and could arrest or terminate the growth of intractable tumors.

ACSS2 contributes acetyl-CoA for histone acetyltransferases to acetylate lysine residues on histones (Takahashi, H.; McCaffery, J.M.; Irizarry, R.A.; Boeke, J.D., *Mol. Cell*,
15 **2006**, 23, 207-217) and thereby regulate transcription of growth genes through epigenetic modification of chromatin (Kaelin, W.G.; McKnight, S.L., *Cell*, **2013**, 153, 56-69). Aberrant regulation of chromatin can affect diverse cellular processes reliant on acetylation such as glucose homeostasis, neuronal gene transcription, autophagy and mitochondrial respiration and is linked to conditions such as neurodegeneration,
20 neurological disorders, immunodeficiency and metabolic disease (Mirabella, A.C.; Foster, B.M.; Bartke, T., *Chromosoma*, **2016**, 125, 75-93). Given the extent to which cancer cells exploit metabolic adaptations to meet their elevated energy and biomass demands, it has been proposed that cancer cells may also produce major shifts in their epigenetic footprint to favour tumor growth and survival (Lu, C.; Thompson, C.B., *Cell*
25 *Metab.*, **2012**, 16, 9-17).

The heterodimeric stress-responsive transcription factor Hypoxia Inducible Factor 2 α (HIF-2 α) is regulated through acetylation by Creb binding protein (CBP), and this acetylation is in turn regulated by acetyl-CoA production by ACSS2 (Chen, R.; Xu, M.;
30 Nagati, J.S.; Hogg, R.T.; Das, A. et. al., *PLoS One*, **2015**, 10, e0116515). Knockdown of ACSS2 or HIF-2 α in tumor cells impairs cell proliferation, cell migration and invasion during hypoxia and leads to significant reduction in tumor burden in mice carrying HT1080 flank tumors.

35 ACSS2 is post-translationally modified by the NAD-dependent deacetylase sirtuins. Sirtuins play a central role in energy homeostasis and ageing and it has therefore been

proposed that the regulation of ACSS2 and acetate metabolism may also play a central role in ageing (Shimazu, T.; Hirschey, M.D.; Huang, Y.; Ho, L.T.Y.; Verdin, E., *Mech. Ageing Develop.*, **2010**, 131, 511-516).

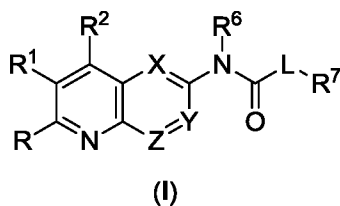
- 5 The causes of ageing are multifactorial but are manifest in a progressive decline in metabolic performance. As individuals age, there is an accompanying build-up of cellular damage and changes to the endogenous repair and detoxification processes. Healthy ageing depends on the efficient removal of damaged cellular material that is mediated in part by autophagy (Eisenberg, T.; Schroeder, S.; Andryushkova, A. et. al.,
10 *Cell Metab.*, **2014**, 19, 431-444). Knockdown of ACCS2 in mammalian cells results in a strong induction of autophagy and maintenance of lifespan, while nutrient starvation of cells achieves the same effect (Marino, G.; Pietrocola, F.; Eisenberg, T.; Kong, Y. et. al., *Mol. Cell*, **2014**, 53, 710-725).
- 15 Human cytomegalovirus (HCMV) induces a robust increase in lipid synthesis to boost the chances of a productive infection. It has recently been shown that in ACSS2 knockout human fibroblasts both HCMV induced lipogenesis and viral growth were sharply reduced compared to normal controls (Vysochan, A.; Sengupta, A.; Weljie, A.M.; Alwine, J.C.; Yu, Y., *PNAS*, **2017**, 114, E1528-E1535) suggesting that impairment
20 of ACSS2 may have some utility as an antiviral therapy in some types of infections. Martinez-Micaelo et. al. have shown that ACSS2 is a nutrient-sensing protein and a key regulator of metabolic homeostasis (Martinez-Micaelo, N.; Gonzalez-Abuin, N.; Terra, X.; Ardevol, A.; Pinent, M. et. al., *Disease Mod. Mechan.*, **2016**, 9, 1231-1239). ACSS2 gene expression was correlated with hepatic concentrations of TCA-involved
25 metabolites and with glucose plasma levels. Phosphoprotein analysis of mice fed with a high fat diet (Shaik, A.A.; Qiu, B.; Wee, S.; Choi, H. et. al., *Nature*, **2016**, 6, 25844) showed an array of phosphorylation changes on several enzymes involved in lipid and glucose homeostasis, including reduced phosphorylation of ACSS2, indicating a role in obesity for this protein. Huang et. al. observed significant reductions in body weight
30 and hepatic steatosis in a diet-induced obesity model following knockdown of ACSS2. ACSS2 deficiency appears to reduce dietary lipid absorption, lipid transport to the liver (Huang, Z.; Zhang, M.; Plec, A.A.; Estill, S.J. et. al., *PNAS*, **2018**, 115, E9499-E9506) and controls systemic lipid metabolism according to acetate availability. These studies indicate that a selective inhibitor of ACSS2 could have therapeutic benefit in obesity
35 and fatty liver disease.

This developing knowledge has stimulated considerable research into possible therapeutic applications of ACSS2 inhibition.

Accordingly, there remains a need in the art for improved therapies for treating diseases, such as cancer, neurological disorders and metabolic disorders, which can be refractory to traditional therapeutic approaches. There is a need to develop improved compositions and methods in this field. In particular, there is a need for compounds that inhibit the human ACSS2 protein, as well as methods for treating diseases that can benefit from such modulation.

The present invention has arisen from the inventors work in attempting to identify ACSS2 protein inhibitors.

In a first aspect of the invention, there is provided a compound of formula (I):



, wherein X is CR³ or N;

Y is CR⁴ or N;

Z is CR⁵ or N;

L is NR⁸ or is absent;

R and R¹ are each independently selected from the group consisting of H, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted C₁-C₁₀ alkoxy and NR⁹R¹⁰;

R² is H, halogen, COOR⁹, CN, CONR⁹R¹⁰, NR⁹SO₂R¹⁰, SO₂NR⁹R¹⁰, NR⁹COR¹⁰, optionally substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted C₁-C₁₀ alkylsulfonyl, NR⁹R¹⁰, optionally substituted C₁-C₁₀ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl or mono or bicyclic optionally substituted 5 to 10 membered heteroaryl;

R³ is H, CN, halogen, COOH, CONR⁹R¹⁰, NR⁹R¹⁰, NO₂, optionally substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted C₁-C₁₀ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl or mono or bicyclic optionally substituted 5 to 10 membered heteroaryl;

R⁴ and R⁵ are each independently selected from the group consisting of H, halogen, OH, CN, mono or bicyclic optionally substituted C₆-C₁₂ aryl, optionally substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted C₁-C₁₀ alkoxy and optionally substituted mono or bicyclic C₃-C₆ cycloalkyl; R⁶ is H or optionally substituted C₁-C₁₀ alkyl;

R⁷ is H, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, or optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

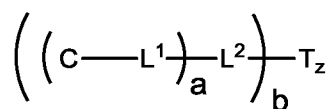
R⁸ is selected from the group consisting of H, halogen and optionally substituted C₁-C₁₀ alkyl; and

R⁹ and R¹⁰ are each independently selected from the group consisting of H, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₁-C₁₀ alkoxy and NH₂; or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

The inventors have found that the compounds of formula (I) are useful in therapy or as a medicament.

The invention also extends to a conjugate of a compound of formula (I).

Accordingly, in a second aspect of the invention, there is provided a conjugate of formula (II):



(II)

wherein, C is a compound of formula (I);

5 L¹ and L² are linkers;

T is a targeting moiety; and

a is an integer between 1 and 5;

b is an integer between 1 and 10; and

z is an integer between 1 and 5.

10

It may be appreciated that a hydrogen may be removed from the compound of formula (I) and L¹ may be bonded to the position where the hydrogen would otherwise be present.

15 Such conjugates may be designed to specifically target certain cell types or tumor types via the targeting moiety, which directs the compound of formula (I) to just those cells or tumors and delivers the ACSS2 inhibitor in a cell-specific manner. The principle of this targeted delivery will be known to those skilled in the art as being closely related to ADC (antibody-drug conjugate) technology, for example as described in Polakis, P.,
 20 *Pharmacol. Revs.*, **2016**, 68, 3-19. The linker will then be designed to cleave and the active compound would then diffuse into the cell and contact the ACSS2 protein.

Hence, in a third aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic
 25 form thereof, or a conjugate of formula (II) for use in therapy.

The inventors have also found that compounds of formula (I) and conjugates of formula (II) are useful in modulating the acetyl coenzyme A synthetase short chain 2 (ACSS2) protein.

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Hence, in a fourth aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate of formula (II) for use in modulating the acetyl coenzyme A synthetase short chain 2 (ACSS2) protein.

Preferably, the compound of formula (I) or the conjugate of formula (II) is for use in inhibiting, or inactivating, the ACSS2 protein. The compound of formula (I) or the conjugate of formula (II) may be for use in inhibiting, or inactivating, ACSS2 enzymatic activity as evidenced by a reduction of one or more biological effects selected from the group consisting of production of acetyl-CoA, acetate incorporation into lipids, acetate incorporation into histones and incorporation of acetate into tumor cells.

By inhibiting the ACSS2 protein, it is possible to treat, ameliorate or prevent cancer, bacterial infection, viral infection, parasitic infection, neurodegenerative disease, cardiovascular disease, fatty liver disease, a metabolic disorder and promote healthy ageing.

Advantageously, the compounds and conjugates of the invention selectively inhibit only one subtype of the human ACCS family of proteins. Compounds of the invention are potent inhibitors of ACCS2, but do not inhibit ACSS1 or ACSS3.

By inhibiting the ACSS2 protein, it is possible to treat, ameliorate or prevent cancer, bacterial infection, viral infection, parasitic infection, fungal infection, neurodegenerative disease, neurological disorder, cerebrovascular disease, cardiovascular disease, non-alcoholic fatty liver disease, obesity and promote healthy ageing.

Accordingly, in a fifth aspect there is provided a compound of formula (I), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate of formula (II) for use in treating, ameliorating or preventing a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, neurodegenerative disease, neurological disorder, cerebrovascular disease, cardiovascular disease, non-alcoholic fatty liver disease and obesity or for use in promoting healthy ageing.

Preferably, the disease is cancer.

In a sixth aspect, there is provided a method of inhibiting the ACSS2 protein in a subject, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically

acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate of formula (II).

Preferably, the method comprises inhibiting the ACSS2 protein.

5

In a seventh aspect, there is provided a method of treating, ameliorating or preventing a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, neurodegenerative disease, neurological disorder, cerebrovascular disease, cardiovascular disease, metabolic disorder, non-alcoholic fatty liver disease and obesity or promoting healthy ageing; the method comprising administering, to a
10 subject in need of such treatment, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate of formula (II).

15 It may be appreciated that the term “preventing” can mean “reducing the likelihood of”.

The neurodegenerative disorder may be amyotrophic lateral sclerosis, Parkinson’s disease, Alzheimer’s disease or Huntington’s disease. The neurological disorder may be anxiety, depression, autism or post-traumatic stress disorder.

20

The parasitic infection may be malaria.

The metabolic disorder may be obesity or fatty liver disease, for example non-alcoholic steatohepatitis.

25

Promoting healthy ageing may include restoring or enhancing autophagy and autophagic protein clearance.

In one preferred embodiment, the disease is cancer. The cancer may be selected from
30 the group consisting of colorectal cancer, aero-digestive squamous cancer, gastrointestinal stromal tumors, lung cancer, brain cancer, neuroblastoma, glial tumors, astrocytoma, glioblastoma, liver cancer, stomach cancer, sarcoma, leukaemia, lymphoma, multiple myeloma, ovarian cancer, uterine cancer, breast cancer, melanoma, prostate cancer, bladder cancer, pancreatic carcinoma or renal carcinoma.
35 In some embodiments, the cancer may have upregulated ACSS2 expression and /or ACSS2 activity in a tissue compared to that of a healthy subject.

In an alternative preferred embodiment, the disease is a viral infection. The viral infection may be a hepatitis C virus (HCV) infection or human cytomegalovirus (HCMV) infection.

5

The following definitions are used in connection with the compounds of the present invention unless the context indicates otherwise.

Throughout the description and the claims of this specification the word “comprise”
10 and other forms of the word, such as “comprising” and “comprises,” means including but not limited to, and is not intended to exclude for example, other additives, components, integers, or steps.

As used in the description and the appended claims, the singular forms “a,” “an,” and
15 “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a composition” includes mixtures of two or more such compositions.

“Optional” or “optionally” means that the subsequently described event, operation or
20 circumstances can or cannot occur, and that the description includes instances where the event, operation or circumstance occurs and instances where it does not.

The term “alkyl” as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In certain embodiments, the alkyl group is a
25 primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyl group includes one to ten carbon atoms, *i.e.* C₁-C₁₀ alkyl. C₁-C₁₀ alkyl includes for example methyl, ethyl, n-propyl (1-propyl) and isopropyl (2-propyl, 1-methylethyl), butyl, pentyl, hexyl, *isobutyl*, *sec-butyl*, *tert-butyl*, *isopentyl*, *neopentyl*, *isohexyl*, heptyl, octyl, nonyl and decyl. An alkyl group can be unsubstituted or substituted with one or more of
30 halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle.
35 Accordingly, it will be appreciated that an optionally substituted C₁-C₁₀ alkyl may be an optionally substituted C₁-C₁₀ haloalkyl, *i.e.* a C₁-C₁₀ alkyl substituted with at least one

halogen, and optionally further substituted with one or more of OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, CONR⁹R¹⁰, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. The optionally substituted C₁-C₁₀ alkyl may be a polyfluoroalkyl, preferably a C₁-C₃ polyfluoroalkyl. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

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The term “alkylene”, as used herein, unless otherwise specified, refers to a bivalent saturated straight or branched hydrocarbon. In certain embodiments, the alkylene group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkylene group includes one to six carbon atoms, *i.e.* C₁-C₆ alkylene. C₁-C₆ alkylene includes for example methylene, ethylene, *n*-propylene and isopropylene, butylene, pentylene, hexylene, *isobutylene*, *sec*-butylene, *tert*-butylene, *isopentylene*, *neopentylene*, and *isohexylene*. An alkylene group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)NR⁹R¹⁰, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C₁-C₆ alkylene may be an optionally substituted C₁-C₆ haloalkylene, *i.e.* a C₁-C₆ alkylene substituted with at least one halogen, and optionally further substituted with one or more of optionally substituted C₁-C₆ alkyl, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, CONR⁹R¹⁰, CN, oxo, azido, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. It will be appreciated that an optionally substituted C₁-C₆ alkylene may be an optionally substituted polyfluoroalkylene, preferably a C₁-C₃ polyfluoroalkylene. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

The term “halo” or “halogen” includes fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I).

5 The term “polyfluoroalkyl” may denote a C₁-C₃ alkyl group in which two or more hydrogen atoms are replaced by fluorine atoms. The term may include perfluoroalkyl groups, *i.e.* a C₁-C₃ alkyl group in which all the hydrogen atoms are replaced by fluorine atoms. Accordingly, the term C₁-C₃ polyfluoroalkyl includes, but is not limited to, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-
10 trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl.

“Alkoxy” refers to the group R¹¹-O- where R¹¹ is an optionally substituted C₁-C₆ alkyl group, an optionally substituted C₃-C₆ cycloalkyl group, an optionally substituted C₂-
15 C₆ alkenyl or an optionally substituted C₂-C₆ alkynyl. Exemplary C₁-C₆ alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy (1-propoxy), n-butoxy and *tert*-butoxy. An alkoxy group can be unsubstituted or substituted with one or more of halogen, OH, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted aryloxy,
20 optionally substituted heteroaryloxy, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, C₃-C₆ cycloalkyl and 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

25 “Aryl” refers to an aromatic 6 to 12 membered hydrocarbon group. Examples of a C₆-C₁₂ aryl group include, but are not limited to, phenyl, α-naphthyl, β-naphthyl, biphenyl, tetrahydronaphthyl and indanyl. An aryl group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl,
30 optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be
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selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

“Arylene” refers to a bivalent aromatic 5 to 10 membered hydrocarbon group. An
5 arylene group may be as defined above in relation the aryl group, but with a hydrogen atom removed therefrom to cause the group to be bivalent.

“Aryloxy” refers to the group aryl-O- where “aryl” is an optionally substituted C₆-C₁₂ aryl group.

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The term “bicycle” or “bicyclic” as used herein refers to a molecule that features two fused rings, which rings are a cycloalkyl, heterocyclyl, or heteroaryl. In one embodiment, the rings are fused across a bond between two atoms. The bicyclic moiety formed therefrom shares a bond between the rings. In another embodiment,
15 the bicyclic moiety is formed by the fusion of two rings across a sequence of atoms of the rings to form a bridgehead. Similarly, a “bridge” is an unbranched chain of one or more atoms connecting two bridgeheads in a polycyclic compound. In another embodiment, the bicyclic molecule is a “spiro” or “spirocyclic” moiety. The spirocyclic group may be a C₃-C₆ cycloalkyl or a mono or bicyclic 3 to 8 membered heterocycle
20 which is bound through a single carbon atom of the spirocyclic moiety to a single carbon atom of a carbocyclic or heterocyclic moiety. In one embodiment, the spirocyclic group is a cycloalkyl and is bound to another cycloalkyl. In another embodiment, the spirocyclic group is a cycloalkyl and is bound to a heterocyclyl. In a further embodiment, the spirocyclic group is a heterocyclyl and is bound to another
25 heterocyclyl. In still another embodiment, the spirocyclic group is a heterocyclyl and is bound to a cycloalkyl. A spirocyclic group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹,
30 CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group
35 consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

- “Cycloalkyl” refers to a non-aromatic, saturated, partially saturated, monocyclic, bicyclic or polycyclic hydrocarbon 3 to 6 membered ring system. Representative examples of a C₃-C₆ cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. A cycloalkyl group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.
- “Cycloalkylene” refers to a bivalent non-aromatic, saturated, partially saturated, monocyclic, bicyclic or polycyclic hydrocarbon 3 to 6 membered ring system. A cycloalkylene group may be as defined above in relation the cycloalkyl group, but with a hydrogen atom removed therefrom to cause the group to be bivalent.
- “Heteroaryl” refers to a monocyclic or bicyclic aromatic 5 to 10 membered ring system in which at least one ring atom is a heteroatom. The or each heteroatom may be independently selected from the group consisting of oxygen, sulfur and nitrogen. Examples of 5 to 10 membered heteroaryl groups include furan, thiophene, indole, azaindole, oxazole, thiazole, isoxazole, isothiazole, imidazole, N-methylimidazole, pyridine, pyrimidine, pyrazine, pyrrole, N-methylpyrrole, pyrazole, N-methylpyrazole, 1,3,4-oxadiazole, 1,2,4-triazole, 1-methyl-1,2,4-triazole, 1H-tetrazole, 1-methyltetrazole, benzoxazole, benzothiazole, benzofuran, benzisoxazole, benzimidazole, N-methylbenzimidazole, azabenzimidazole, indazole, quinazoline, quinoline, and isoquinoline. Bicyclic 5 to 10 membered heteroaryl groups include those where a phenyl, pyridine, pyrimidine, pyrazine or pyridazine ring is fused to a 5 or 6-membered monocyclic heteroaryl ring. A heteroaryl group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10

membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

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“Heteroaryloxy” refers to the group heteroaryl-O- where “heteroaryl” is an optionally substituted 5 to 10 membered heteroaryl group.

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“Heteroarylene” refers to a bivalent monocyclic or bicyclic aromatic 5 to 10 membered ring system in which at least one ring atom is a heteroatom. A heteroarylene group may be as defined above in relation the heteroaryl group, but with a hydrogen atom removed therefrom to cause the group to be bivalent.

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“Heterocycle” or “heterocyclyl” refers to 3 to 8 membered monocyclic, bicyclic or bridged molecules in which at least one ring atom is a heteroatom. The or each heteroatom may be independently selected from the group consisting of oxygen, sulfur and nitrogen. A heterocycle may be saturated or partially saturated. Exemplary 3 to 8 membered heterocyclyl groups include but are not limited to aziridine, oxirane, oxirene, thiirane, pyrroline, pyrrolidine, dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, dithiolane, piperidine, 1,2,3,6-tetrahydropyridine-1-yl, tetrahydropyran, pyran, morpholine, piperazine, thiane, thiine, piperazine, azepane, diazepane, oxazine. A heterocyclyl group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido, OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

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“Heterocyclene” refers to a bivalent 3 to 8 membered monocyclic, bicyclic or bridged molecules in which at least one ring atom is a heteroatom. A heterocyclene group may be as defined above in relation the heterocycle group, but with a hydrogen atom removed therefrom to cause the group to be bivalent.

“Alkenyl” refers to olefinically unsaturated hydrocarbon groups which can be unbranched or branched. In certain embodiments, the alkenyl group has 2 to 6 carbons, *i.e.* it is a C₂-C₆ alkenyl. C₂-C₆ alkenyl includes for example vinyl, allyl, propenyl, butenyl, pentenyl and hexenyl. An alkenyl group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

“Alkynyl” refers to acetylenically unsaturated hydrocarbon groups which can be unbranched or branched. In certain embodiments, the alkynyl group has 2 to 6 carbons, *i.e.* it is a C₂-C₆ alkynyl. C₂-C₆ alkynyl includes for example propargyl, propynyl, butynyl, pentynyl and hexynyl. An alkynyl group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R⁹ and R¹⁰ may be as defined in relation to the first aspect. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

The term “alkyne”, as used herein, unless otherwise specified, refers to a bivalent unsaturated straight or branched hydrocarbon. In certain embodiments, the alkyne group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyne group includes one to six carbon atoms, *i.e.* C₂-C₆ alkyne. C₂-C₆ alkyne includes for example ethyne, propyne, butyne, pentyne or hexyne. An alkyne group can be unsubstituted or substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl,

halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C₂-C₆ alkyne may be an optionally substituted C₂-C₆ haloalkyne, *i.e.* a C₂-C₆ alkyne substituted with at least one halogen, and optionally further substituted with one or more of optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkenyl, optionally substituted C₁-C₆ alkynyl, halogen, OH, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, NR⁹R¹⁰, C(O)R⁹, CN, oxo, azido OP(O)(OH)₂, OC(O)R⁹, COOR⁹, C₁-C₆ alkenyl, =NOR⁹, NR⁹C(O)R¹⁰, SO₂R⁹, SO₂NR⁹R¹⁰, optionally substituted C₆-C₁₂ aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl and optionally substituted 3 to 8 membered heterocycle. It will be appreciated that an optionally substituted C₂-C₆ alkyne may be an optionally substituted polyfluoroalkyne. R⁹ and R¹⁰ may be as defined above. R⁹ and R¹⁰ may each independently be selected from the group consisting of H, halogen and optionally substituted C₁-C₆ alkyl.

“Alkylsulfonyl” refers to the group alkyl-SO₂- where alkyl is an optionally substituted C₁-C₆ alkyl, and is as defined as above.

A complex of the compound of formula (I) may be understood to be a multi-component complex, wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. The complex may be other than a salt or solvate. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see *Chem Commun*, **17**, 1889-1896, by O. Almarsson and M. J. Zaworotko (**2004**), incorporated herein by reference. For a general review of multi-component complexes, see *J Pharm Sci*, **64** (8), 1269-1288, by Halebian (August **1975**), incorporated herein by reference.

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The term “pharmaceutically acceptable salt” may be understood to refer to any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Such salts include, but are not limited to: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, adipic, aspartic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; or (2) base addition salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminium ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminium, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, N-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Pharmaceutically acceptable salts may include, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrohalides, e.g. hydrochloride, hydrobromide and hydroiodide, carbonate or bicarbonate, sulfate or bisulfate, borate, phosphate, hydrogen phosphate, dihydrogen phosphate, pyroglutamate, saccharate, stearate, sulfamate, nitrate, orotate, oxalate, palmitate, pamoate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, tannate, tartrate, tosylate, sorbate, ascorbate, malate, maleate, fumarate, tartarate,

camsylate, citrate, cyclamate, benzoate, isethionate, esylate, formate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), methylsulphate, naphthylate, 2-napsylate, nicotinate, ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, 5 camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, tert-butylacetate, lauryl sulfate, gluceptate, gluconate, glucoronate, hexafluorophosphate, hibenzate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, 10 muconate, xinofoate and the like.

Hemisalts of acids and bases may also be formed, for example, hemisulphate salts. The skilled person will appreciate that the aforementioned salts include ones wherein the counterion is optically active, for example D-lactate, or racemic, for example DL- 15 tartrate.

For a review on suitable salts, see “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

20 Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

- (i) by reacting the compound of formula (I) with the desired acid or base;
- (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) using the desired acid or base; or
- 25 (iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the 30 solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The term “solvate” may be understood to refer to a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent 35 bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate. Pharmaceutically acceptable solvates in accordance with the invention

include those wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone and d₆-DMSO.

5 A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995), incorporated herein by reference. Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they
10 are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly
15 bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The compounds of the invention may exist in a continuum of solid states ranging from
20 fully amorphous to fully crystalline, including polymorphs of said crystalline material. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally
25 described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the
30 properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is
35 intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described

as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-\text{COO}^-\text{Na}^+$, $-\text{COO}^-\text{K}^+$, or $-\text{SO}_3^-\text{Na}^+$) or non-ionic (such as $-\text{N}^+\text{N}^+(\text{CH}_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970), incorporated herein by reference.

R and R¹ may each independently be selected from the group consisting of H, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted C₁-C₆ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₆ alkenyl and optionally substituted C₂-C₆ alkynyl. More preferably, R and R¹ are each independently selected from an optionally substituted phenyl ring, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl or an optionally substituted 5 or 6 membered heteroaryl. Most preferably R and R¹ are each an optionally substituted phenyl ring or methyl.

When R and/or R¹ is an optionally substituted C₆-C₁₂ aryl, the aryl is preferably optionally substituted phenyl. The phenyl may be unsubstituted or substituted with one or more of halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, COR, NR⁹R¹⁰, CN, R⁹COR¹⁰, optionally substituted C₆-C₁₂ aryl or optionally substituted 5 to 10 membered heteroaryl, wherein R⁹ and R¹⁰ are each H or an optionally substituted C₁-C₆ alkyl. More preferably, the phenyl is unsubstituted or substituted with one or more of fluorine, C₁-C₆ alkoxy, COR⁹, NR⁹R¹⁰, CN, R⁹COR¹⁰ or C₆-C₁₂ aryl, wherein R⁹ and R¹⁰ are each H or a C₁-C₆ alkyl. Most preferably, the phenyl is unsubstituted or substituted with one or more of fluorine, OH, OCH₃, OCH₂CH₃, OCH₂CH(CH₃)₂, COCH₃, N(CH₃)₂, NH₂, CN, NHC(O)CH₃ or phenyl.

When R and/or R¹ is an optionally substituted 5 to 10 membered heteroaryl, the heteroaryl is preferably an optionally substituted 5 or 6 membered heteroaryl, and more preferably an optionally substituted pyridinyl or an optionally substituted pyrazolyl. The heteroaryl may be unsubstituted or substituted with optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy or OH. More preferably, the

heteroaryl is unsubstituted or substituted with one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy or OH. Most preferably, the heteroaryl is unsubstituted or substituted with one or more of methyl, OCH₃ or OH.

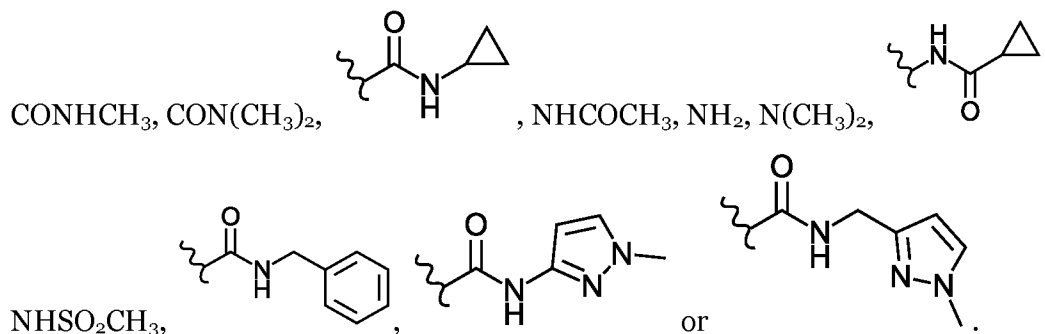
- 5 When R and/or R¹ is an optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, the cycloalkyl is preferably unsubstituted.

When R and/or R¹ is an optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl or optionally substituted C₂-C₆ alkynyl, the alkyl, alkenyl or alkynyl is preferably
 10 an optionally substituted C₁-C₃ alkyl, optionally substituted C₂-C₃ alkenyl or optionally substituted C₂-C₃ alkynyl, and more preferably an optionally substituted C₁-C₂ alkyl, optionally substituted C₂ alkenyl or optionally substituted C₂ alkynyl. The alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more of a halogen, an optionally substituted C₆-C₁₂ aryl or an optionally substituted 5 to 10 membered
 15 heteroaryl. Preferably, the alkyl, alkenyl or alkynyl is unsubstituted or substituted with one or more of fluorine or a C₆-C₁₂ aryl. Most preferably, the alkyl, alkenyl or alkynyl is unsubstituted or substituted with one or more of fluorine or phenyl.

R² may be H, COOR⁹, CONR⁹R¹⁰, CN, NR⁹COR¹⁰, NR⁹R¹⁰, NR⁹SO₂R¹⁰, optionally
 20 substituted C₁-C₆ alkyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted C₁-C₆ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl or a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl.

When R² is COOR⁹, CONR⁹R¹⁰, CN, NR⁹COR¹⁰, NR⁹R¹⁰ or NR⁹SO₂R¹⁰, R⁹ and R¹⁰ may
 25 independently be H or an optionally substituted C₁-C₆ alkyl, an optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl or a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl. More preferably, R⁹ and R¹⁰ are independently H or an optionally substituted C₁-C₃ alkyl, a C₃-C₆ cycloalkyl, optionally substituted phenyl or an optionally substituted 5 or 6
 30 membered heteroaryl. R⁹ and R¹⁰ may be H, optionally substituted methyl, cyclopropyl or optionally substituted pyrazolyl. When R⁹ or R¹⁰ is an optionally substituted alkyl or cycloalkyl, the alkyl or cycloalkyl may be substituted with a mono or bicyclic optionally substituted C₆-C₁₂ aryl or a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, preferably with an optionally substituted phenyl or a mono or bicyclic
 35 optionally substituted 5 or 6 membered heteroaryl, more preferably with phenyl or an optionally substituted pyrazolyl. When R⁹ or R¹⁰ is an optionally substituted heteroaryl,

the heteroaryl may be substituted with a C₁-C₆ alkyl, more preferably a C₁-C₃ alkyl, and most preferably methyl. Accordingly, R² may be H, COOH, COOCH₃, CONH₂,



5

When R² is an optionally substituted C₁-C₆ alkyl or an optionally substituted C₁-C₆ alkoxy, R² may be an optionally substituted C₁-C₃ alkyl or an optionally C₁-C₃ alkoxy and is preferably CH₃ or OCH₃.

- 10 When R² is a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, the heteroaryl may be an optionally substituted 5 or 6 membered heteroaryl, and may be an optionally substituted oxazolyl. The heteroaryl may be unsubstituted.

X may be CR³.

15

Y may be CR⁴.

Z may be CR⁵.

- 20 In a preferred embodiment, X is CR³, Y is CR⁴ and Z is CR⁵.

- Alternatively, X may be N. Y may be CR⁴ and Z may be CR⁵. Accordingly, in an alternative embodiment, X is N, Y is CR⁴ and Z is CR⁵. Alternatively, Y may be N and Z may be CR⁵. Accordingly, in a further alternative embodiment, X is N, Y is N and Z is CR⁵. Alternatively, Y may be CR⁴ and Z may be N. Accordingly, in a still further alternative embodiment, X is N, Y is CR⁴ and Z is N.

- Alternatively, Y may be N. X may be CR³ and Z may be CR⁵. Accordingly, in a further alternative embodiment, X is CR³, Y is N and Z is CR⁵.

30

Alternatively, Z may be N. X may be CR³ and Y may be CR⁴. Accordingly, in a still further embodiment, X is CR³, Y is CR⁴ and Z is N.

R³ may be H, CN, halogen, COOH, CONR₂, NR₂, NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle. Preferably, R³ is H, CN, halogen, optionally substituted C₁-C₆ alkyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl or mono or bicyclic optionally substituted 5 to 10 membered heteroaryl. More preferably, R³ is H, CN, F, Br, cyclopropyl or an optionally substituted 5 or 6 membered heteroaryl. Most preferably, R³ is H.

15

When R³ is a halogen it may be F, Cl, Br or I, and more preferably is Br.

When R³ is optionally substituted C₁-C₆ alkyl it is preferably an optionally substituted C₁-C₃ alkyl, and more preferably is an optionally substituted methyl. Preferably, the C₁-C₆ alkyl is unsubstituted.

20

When R³ is optionally substituted C₃-C₆ cycloalkyl it is preferably an optionally substituted cyclopropyl. Preferably, the C₃-C₆ cycloalkyl is unsubstituted.

When R³ is an optionally substituted 5 to 10 membered heteroaryl, the heteroaryl is preferably an optionally substituted 5 or 6 membered heteroaryl, and more preferably an optionally substituted pyridinyl or pyrazolyl. The heteroaryl may be unsubstituted or substituted with optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy or OH. More preferably, the heteroaryl is unsubstituted or substituted with one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy or OH. Most preferably, the heteroaryl is unsubstituted or substituted with one or more of methyl, OCH₃ or OH.

25

30

R⁴ and R⁵ may each independently be selected from the group consisting of H, halogen, OH, CN, mono or bicyclic optionally substituted C₆-C₁₂ aryl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, or optionally substituted mono or bicyclic C₃-C₆ cycloalkyl.

35

More preferably, R⁴ and R⁵ may be H, halogen, OH, CN or an optionally substituted C₁-C₆ alkyl. Most preferably, R⁴ and R⁵ are H.

When R⁴ and/or R⁵ is a halogen it may be F, Cl, Br or I, and more preferably is F.

5

R⁶ may be H or optionally substituted C₁-C₆ alkyl. Most preferably, R⁶ is H.

R⁷ may be H, optionally substituted C₁-C₁₀ alkyl or optionally substituted mono or bicyclic C₃-C₆ cycloalkyl. More preferably, R⁷ may be an optionally substituted C₁-C₁₀
10 alkyl or an optionally substituted mono or bicyclic C₃-C₆ cycloalkyl. Even more preferably, R⁷ is an optionally substituted C₁-C₆ alkyl, and most preferably is an optionally substituted C₃-C₅ alkyl.

R⁷ may be H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl,
15 optionally substituted C₂-C₆ alkynyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, or optionally substituted mono or bicyclic 3 to 8 membered heterocycle. More preferably, R⁷ is optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally
20 substituted phenyl, optionally substituted 5 or 6 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3 to 6 membered heterocycle.

When R⁷ is an optionally substituted alkyl, an optionally substituted alkenyl or an optionally substituted alkynyl, the alkyl, alkenyl or alkynyl may be unsubstituted or
25 substituted with one or more substituents selected from the group consisting of halogen, -OH, oxo, optionally substituted C₁-C₆ alkoxy, NR⁹R¹⁰, C(O)R⁹, OC(O)R⁹, COOR⁹, OP(O)(OH)₂ and NR⁹C(O)R¹⁰. R⁹ and R¹⁰ may each be H, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl or optionally substituted C₂-C₆ alkynyl. More preferably, the alkyl, alkenyl or alkynyl may be unsubstituted or
30 substituted with one or more substituents selected from the group consisting of F, -OH, oxo, C₁-C₃ alkoxy, C(O)R⁹, OP(O)(OH)₂ and NHC(O)R¹⁰, wherein R⁹ and R¹⁰ are each H or a C₁-C₆ alkyl. Most preferably, the alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more substituents selected from the group consisting of F, -OH, oxo, OCH₃, C(O)CH₃, OP(O)(OH)₂ and NHC(O)CH₃.

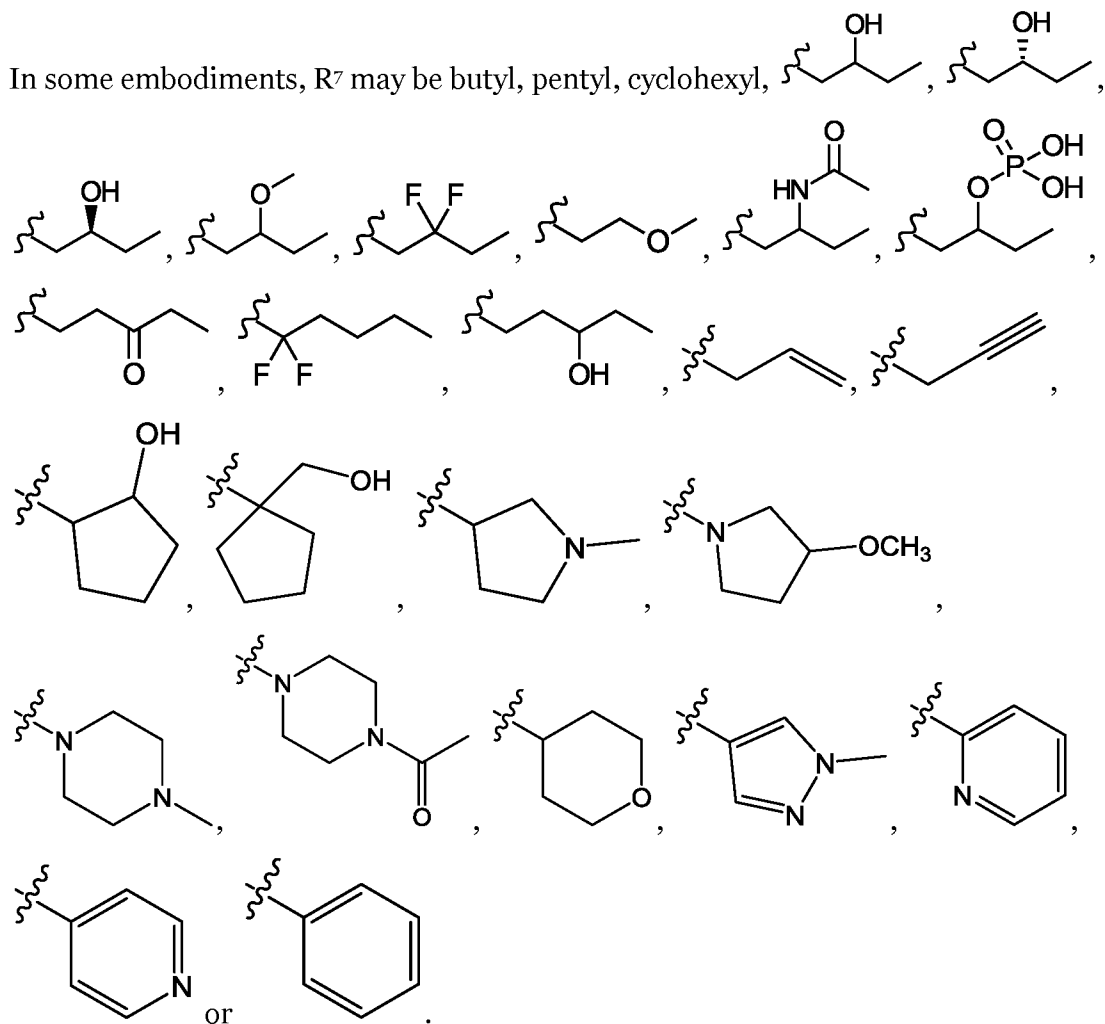
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When R⁷ is an optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocycle, the heteroaryl, cycloalkyl or heterocycle may be unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, oxo, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkenyl, optionally substituted C₁₋₆ alkynyl, optionally substituted C₁₋₆ alkoxy, NR⁹R¹⁰, C(O)R⁹, OC(O)R⁹, COOR⁹, OP(O)(OH)₂ and NR⁹C(O)R¹⁰. R⁹ and R¹⁰ may each be H, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl or optionally substituted C₂₋₆ alkynyl. When the heteroaryl, cycloalkyl or heterocycle is substituted, either directly or indirectly, with an alkyl, alkenyl and/or alkynyl, the or each alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH and oxo. Preferably, the heteroaryl, cycloalkyl or heterocycle is unsubstituted or substituted with one or more substituents selected from the group consisting of F, -OH, oxo, optionally substituted C₁₋₃ alkyl, optionally substituted C₁₋₃ alkenyl, optionally substituted C₁₋₃ alkynyl, C₁₋₃ alkoxy, C(O)R⁹, OP(O)(OH)₂ and NHC(O)R¹⁰, wherein R⁹ and R¹⁰ are each H or a C₁₋₆ alkyl. Most preferably, the heteroaryl, cycloalkyl or heterocycle may be unsubstituted or substituted with one or more substituents selected from the group consisting of F, -OH, oxo, CH₃, CH₂OH, OCH₃, C(O)CH₃, OP(O)(OH)₂ and NHC(O)CH₃.

20

When R⁷ is an optionally substituted aryl, the aryl may be unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkenyl, optionally substituted C₁₋₆ alkynyl, optionally substituted C₁₋₆ alkoxy, NR⁹R¹⁰, C(O)R⁹, OC(O)R⁹, COOR⁹, OP(O)(OH)₂ and NR⁹C(O)R¹⁰. R⁹ and R¹⁰ may each be H, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl or optionally substituted C₂₋₆ alkynyl. When the aryl is substituted, either directly or indirectly, with an alkyl, alkenyl and/or alkynyl, the or each alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH and oxo. Preferably, the aryl is unsubstituted or substituted with one or more substituents selected from the group consisting of F, -OH, optionally substituted C₁₋₃ alkyl, optionally substituted C₁₋₃ alkenyl, optionally substituted C₁₋₃ alkynyl, C₁₋₃ alkoxy, C(O)R⁹, OP(O)(OH)₂ and NHC(O)R¹⁰, wherein R⁹ and R¹⁰ are each H or a C₁₋₆ alkyl. Most preferably, the aryl may be unsubstituted or substituted with one or more substituents selected from the group consisting of F, -OH, CH₃, CH₂OH, OCH₃, C(O)CH₃, OP(O)(OH)₂ and NHC(O)CH₃.

35



In some embodiments, L is absent. In alternative embodiments, L is NR⁸. R⁸ may be H or an optionally substituted C₁-C₆ alkyl. More preferably, R⁸ is H.

Compounds of formula (I) may include one or more stereogenic centers and so may exist as optical isomers, such as enantiomers and diastereomers. All such isomers and mixtures thereof are included within the scope of the present invention.

Stereogenic centres may arise within any of the groups R and R¹-R⁹.

It will be understood that the above compounds may exist as enantiomers and as diastereoisomeric pairs. These isomers also represent further embodiments of the invention.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

5

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be
 10 separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in
 15 enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

20

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art; see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

25

The structure $(-L^1)_a-L^2-$ may be referred to as "the linker".

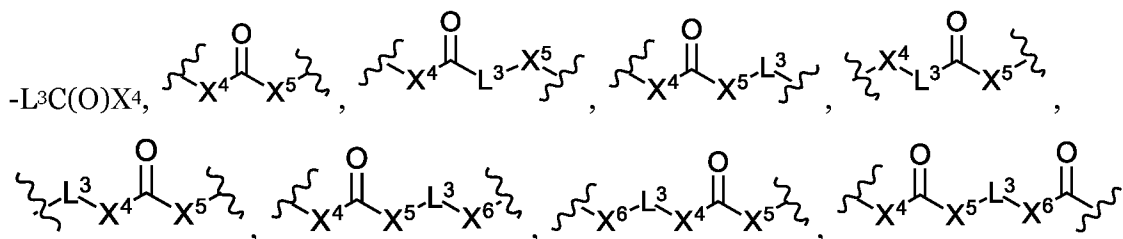
L^1 may be absent or may be:

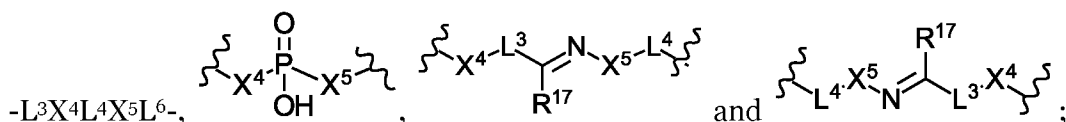
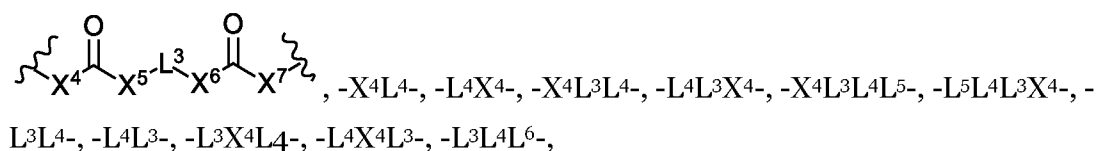


30

wherein:

A is absent or is selected from the group consisting of $-L^3-$, $-X^4L^3-$, $-L^3X^4-$, $-C(O)X^4$,





W is either absent or is selected from the group consisting of $-\text{L}^7\text{NH}-$, $-\text{L}^3\text{L}^7\text{NH}-$,
 5 $-\text{L}^7\text{NHC(O)}-$, $-\text{L}^3\text{L}^7\text{NHC(O)}-$, $-\text{L}^7\text{L}^8\text{NH}-$, $-\text{L}^3\text{L}^7\text{L}^8\text{NH}-$, $-\text{L}^7\text{L}^8\text{NHC(O)}-$, and $-\text{L}^3\text{L}^7\text{L}^8\text{NHC(O)}-$;

D is either absent or has formula $-(\text{D}^1)_q-$ or $-(\text{D}^1)_q\text{C(O)}-$, wherein $(\text{D}^1)_q$ is either linear or cyclic;

the or each L^3 and L^6 are each independently an optionally substituted $\text{C}_1\text{-C}_{25}$ alkylene
 10 or an optionally substituted $\text{C}_2\text{-C}_{25}$ alkylyne;

L^4 and L^5 are each independently selected from the group consisting of an optionally substituted mono or bicyclic $\text{C}_6\text{-C}_{12}$ aryl; an optionally mono or bicyclic 5 to 10 membered heteroaryl; an optionally $\text{C}_3\text{-C}_{12}$ cycloalkyl; and an optionally mono or bicyclic 3 to 12 membered heterocycle;

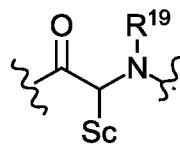
15 L^7 and L^8 are each independently an optionally substituted mono or bicyclic $\text{C}_6\text{-C}_{12}$ aryl; or an optionally substituted mono or bicyclic 5 to 10 membered heteroaryl, wherein the aryl or heteroaryl is optionally further substituted with at least one $-\text{OR}^{18}$ group;

the or each of X^4 , X^5 , X^6 and X^7 is independently O, S or NR^{16} ;

R^{16} is selected from the group consisting of H, halogen, CN, hydroxyl, COOH,
 20 $\text{CONR}^9\text{R}^{10}$, NR^9R^{10} , NHCOR^9 , optionally substituted $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_3$ polyfluoroalkyl, optionally substituted $\text{C}_1\text{-C}_6$ alkylsulfonyl, optionally substituted mono or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ alkynyl, optionally substituted $\text{C}_1\text{-C}_6$ alkoxy, optionally substituted $\text{C}_1\text{-C}_6$ alkoxycarbonyl, mono or bicyclic optionally substituted $\text{C}_5\text{-C}_{10}$ aryl, mono or bicyclic optionally substituted 5
 25 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted aryloxy, optionally substituted heteroaryloxy, and optionally substituted heterocycloxy;

R^{17} is hydrogen or an optionally substituted C_{1-6} alkyl;

R^{18} is an optionally substituted $\text{C}_3\text{-C}_6$ cycloalkyl, or an optionally substituted mono or
 30 bicyclic 3 to 8 membered heterocycle;

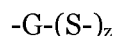


each D¹ independently has general formula

Sc is a side chain of a natural or unnatural amino acid and R¹⁹ is H, or Sc and R¹⁹ together with the atoms to which they are attached form a ring; and
q is an integer between 2 and 20.

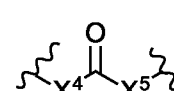
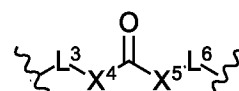
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L² may be absent or may be:

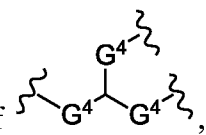


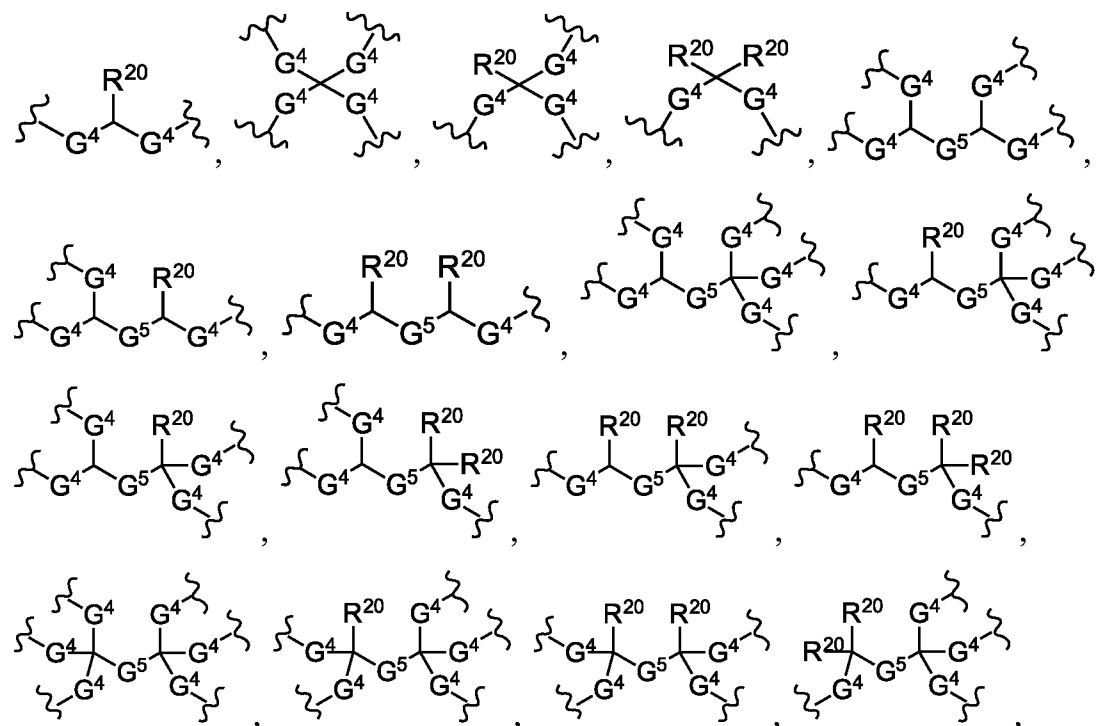
wherein, G is either absent or is $(-G^1)_a-G^2-(G^3-)_z$,

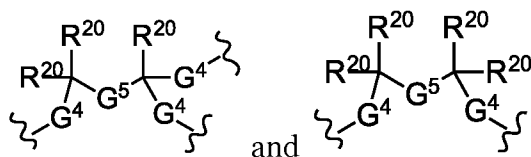
wherein, the or each G¹ is independently either absent or selected from the group
10 consisting of $-L^3-$, $-(X^4L^3)_p-$, $-(L^3X^4)_p-$, $-L^4-$, $-X^4-$, $-X^8-$, $-X^4C(O)-$, $-C(O)X^4-$,

, $-L^3X^4C(O)-$, $-L^3C(O)X^4$, , $-L^9-$, $-L^9L^3-$, $-L^9L^3C(O)-$, $-C(O)L^3-$, $-C(O)L^9-$, $-C(O)L^3X^4L^6-$, $-C(O)L^3X^4C(O)L^6-$, $-C(O)L^9L^3-$, $-C(O)L^3C(O)-$, $-C(O)L^9C(O)-$, $-C(O)L^9L^3C(O)-$, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

15

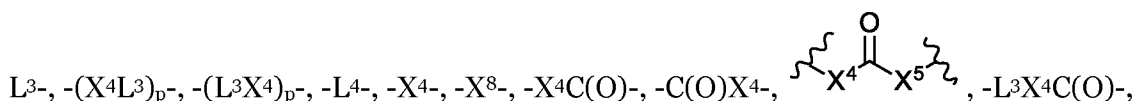
G² is either absent or is selected from the group consisting of ,

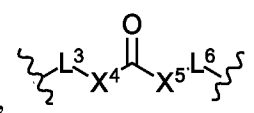




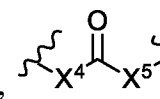
wherein a wavy line indicates either the attachment of G² to G¹ or, in embodiments where G¹ is absent, to L¹, or the attachment of the G² to G³ or, in embodiments where G³ is absent, to S, and each G², in embodiments where it is present, is attached to at least one G¹ or, in embodiments where G¹ is absent, to at least one group L¹, and each G², in embodiments where it is present, is attached to at least one G³ or, in embodiments where G³ is absent, to at least one group S;

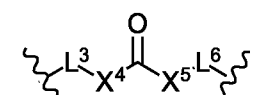
the or each G³ is independently either absent or selected from the group consisting of –

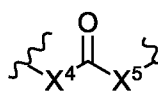


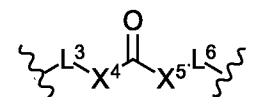
–L³C(O)X⁴–, –L³X⁴C(O)L⁶–, –L³C(O)X⁴L⁶–, , –L⁹–, –X⁴L⁹–, –L⁹L³–, –L⁹L³C(O)–, –C(O)L³–, –C(O)L⁹–, –C(O)L³X⁴L⁶–, –C(O)L³X⁴C(O)L⁶–, –C(O)L⁹L³–, –C(O)L³C(O)–, –C(O)L⁹C(O)–, –C(O)L⁹L³C(O)–, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

the or each G⁴ is independently either absent or selected from the group consisting of

–L³–, –(X⁴L³)_p–, –(L³X⁴)_p–, –X⁴–, –X⁸–, –X⁴C(O)–, –C(O)X⁴–, , –L³X⁴C(O)–, –C(O)X⁴L³–, –L³C(O)X⁴–, –X⁴C(O)L³–, –X⁴L³C(O)X⁵–, –X⁴C(O)L³X⁵–, –L³X⁴L⁶C(O)X⁵–,

–X⁴C(O)L³X⁵L³–, , –L⁹–, –L⁹L³–, –L⁹L³C(O)–, –C(O)L³–, –C(O)L⁹–, –C(O)L³X⁴L⁶–, –C(O)L³X⁴C(O)L⁶–, –C(O)L⁹L³–, –C(O)L³C(O)–, –C(O)L⁹C(O)–, –C(O)L⁹L³C(O)–, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

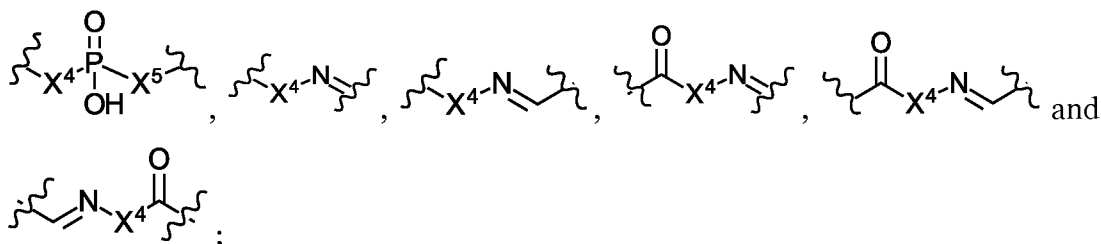
G⁵ is either –L³–, –(X⁴L³)_p–, –(L³X⁴)_p–, –X⁴–, –X⁸–, –X⁴C(O)–, –C(O)X⁴–, ,

–L³X⁴C(O)–, –L³C(O)X⁴–, –L³X⁴C(O)L⁶–, –L³C(O)X⁴L⁶–, , –L⁹–, –X⁴L⁹–, –L⁹L³–, –L⁹L³C(O)–, –C(O)L³–, –C(O)L⁹–, –C(O)L³X⁴L⁶–, –C(O)L³X⁴C(O)L⁶–, –C(O)L⁹L³–, –C(O)L³C(O)–, –C(O)L⁹C(O)–,

-C(O)L⁹L³C(O)-, a poly(ethylene glycol) (PEG) chain of between 1 and 25 units and a cyclodextrin;

S is either absent or is selected from the group consisting of -X⁴-, -X⁴-, -X⁸-, -C(X⁹)-, -X⁴C(X⁹)-, -X⁴C(X⁹)L³-, -X⁴C(X⁹)L³C(O)-, -X⁸L³-, -X⁴X⁸L³-, X⁸L³C(O)-, -L³-, -L⁴-,

5 -L⁴L³-, -L⁴C(O)-, -C(O)L⁴C(O)-, -L³C(O)L⁴C(O)-, -L⁴L³L⁵-, L⁴L³L⁵C(O)-,



L³ to L⁸ and X⁴ to X⁷ are as defined above,

L⁹ is a poly(ethylene glycol) (PEG) chain between 1 and 25 units long;

10 X⁸ is -S(O)- or -SO₂-;

X⁹ is O or S;

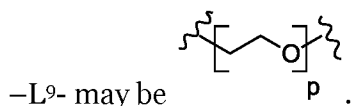
R²⁰ is an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, -L⁹H, -C(O)L³H, -C(O)L⁹H, -X⁴L³H, -X⁴L⁹H, -X⁴C(O)L³H, -X⁴C(O)L⁹H, -C(O)X⁴L³H or -C(O)X⁴L⁹H; and

15 p is an integer between 1 and 25.

a may be 1, 2, 3, 4 or 5. Preferably, a is an integer between 1 and 3.

z may be 1, 2, 3, 4 or 5. Preferably, z is an integer between 1 and 3.

20



-L⁹- may be

Preferably, at least one of L¹ and L² is present.

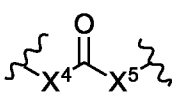
25 Preferably, 3 or less of A, W, D, G and S are absent, and more preferably 2 or less or 1 or less of A, W, D, G and S are absent. In some embodiments, none of A, W, D, G and S are absent.

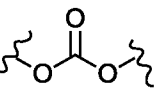
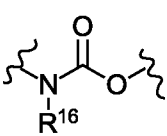
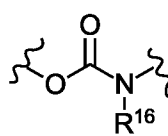
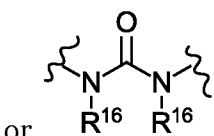
A may be -L³-. L³ may be an optionally substituted C₁-C₆ alkylene. Preferably, L³ is an optionally substituted C₁-C₂ alkylene or an optionally substituted C₁ alkylene.

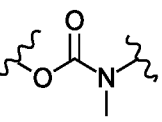
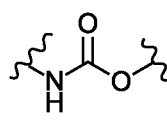
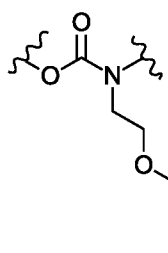
30

A may be $-L^3X^4-$. L^3 may be an optionally substituted C_1 - C_6 alkylene, and is preferably $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2\text{CH}_2-$. Accordingly, A may be $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{CH}_2\text{S}-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{S}-$.

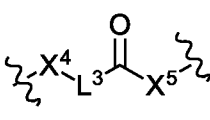
- 5 A may be $-\text{C}(\text{O})\text{X}^4$ or $-\text{L}^3\text{C}(\text{O})\text{X}^4$. X^4 may be O. L^3 may be an optionally substituted C_1 - C_6 alkylene, and is preferably a C_1 - C_3 alkylene, and most preferably is $-\text{CH}_2-$. Accordingly A may be $-\text{C}(\text{O})\text{O}-$ or $-\text{CH}_2\text{C}(\text{O})\text{O}-$.

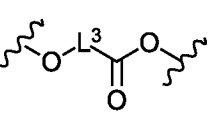
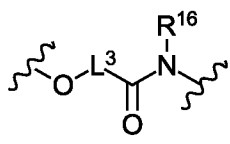
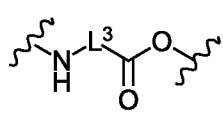
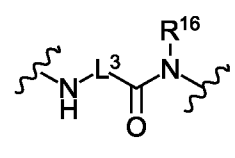
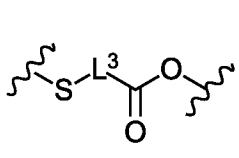
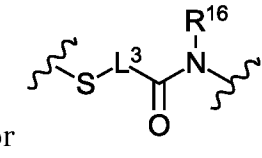
A may be . X^4 may be $-\text{O}-$ or $-\text{NR}^{16}-$. X^5 may be $-\text{O}-$ or $\text{NR}^{16}-$.

- 10 Accordingly, A may be , ,  or . R^{16} may be an optionally substituted C_1 - C_6 alkyl or hydrogen. The optionally substituted C_1 - C_6 alkyl may be substituted with an optionally substituted C_1 - C_6 alkoxy, which may be substituted with an $-\text{OH}$. Accordingly, R^{16} may be methyl or $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$.

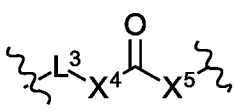
Accordingly, A may be ,  or .

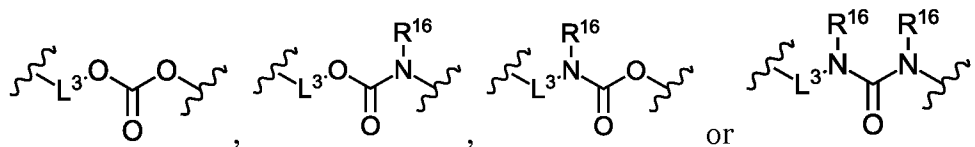
15

A may be . X^4 may be $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$. X^5 may be $-\text{O}-$ or $-\text{NR}^{16}-$.

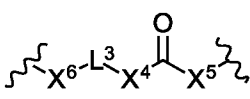
Accordingly, A may be , , , ,  or . L^3 may be an optionally substituted C_1 - C_{10} alkylene, and is preferably an optionally substituted C_1 - C_6 alkylene.

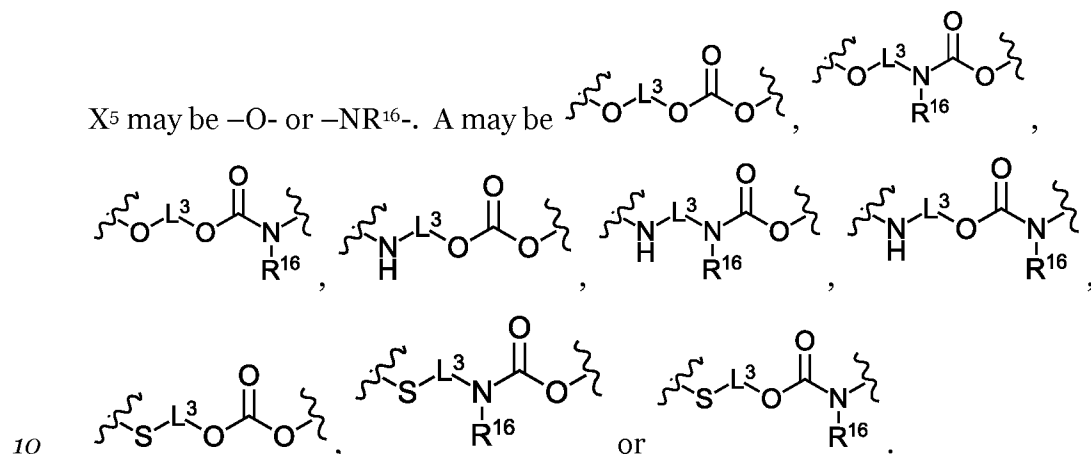
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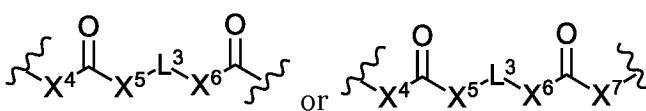
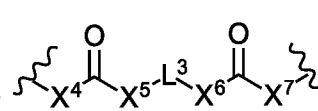
A may be . X⁴ may be -O- or -NR¹⁶-. X⁵ may be -O- or NR¹⁶-. L³ may be an optionally substituted C₁-C₆ alkylene. Accordingly, A may be

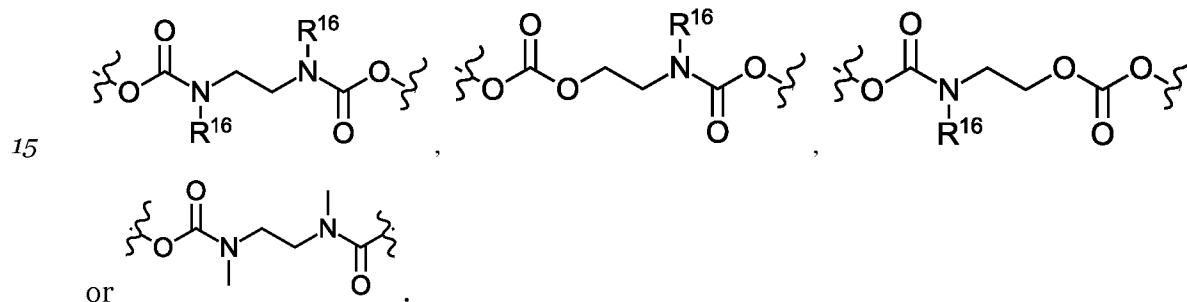


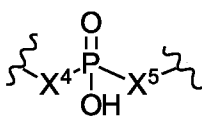
Preferably, L³ is an optionally substituted C₁-C₂ alkylene or an optionally substituted C₁ alkylene.

A may be . X⁶ may be -O-, -S- or -NH-. X⁴ may be -O- or -NR¹⁶-. X⁵ may be -O- or -NR¹⁶-. A may be

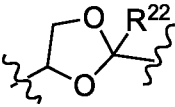
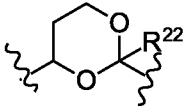


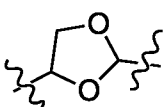
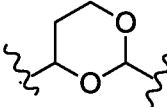
A may be  or . X⁴ may be -O-. X⁵ may be -O- or NR¹⁶-. L³ may an optionally substituted C₁-C₆ alkylene, and is preferably -CH₂CH₂-. X⁶ may be -O- or NR¹⁶-. X⁷ may be -O-. Accordingly, A may be:

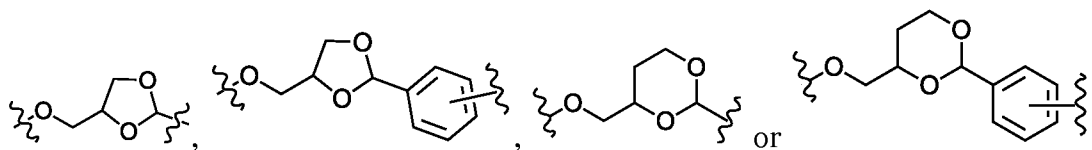


A may be . Preferably, X⁴ is -O-. Preferably, X⁵ is -O-.

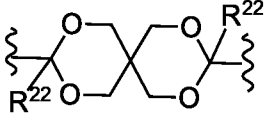
A may be $-X^4L^3L^4-$ or $-X^4L^3L^4L^5-$. X^4 may be $-O-$. L^3 may be an optionally substituted C_1-C_6 alkylene, and is preferably a C_1-C_2 alkylene, and more preferably is $-CH_2-$. L^4 may be an optionally substituted 3 to 12 membered heterocycle, preferably L^4 may be an optionally substituted 3 to 8 membered heterocycle, and most preferably L^4 is an

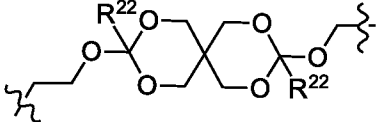
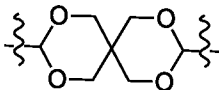
optionally substituted 5 or 6 membered heterocycle. L^4 may be  or , where R^{22} may be a hydrogen, a C_1-C_6 alkyl or a mono or bicyclic C_6-C_{12}

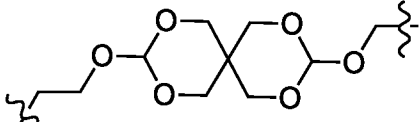
aryl. Accordingly, L^4 may be  or . L^5 may be an optionally substituted mono or bicyclic C_6-C_{12} aryl. Preferably, L^5 is an optionally substituted phenyl, and in some embodiments is an unsubstituted phenyl. Accordingly, A may be

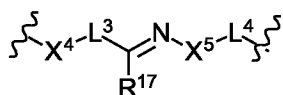


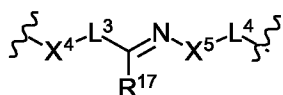
A may be $-L^3X^4L^4X^5L^6-$. L^3 and L^6 may independently be an optionally substituted C_1-C_6 alkylene, and are preferably independently a C_1-C_2 alkylene. L^3 may be $-CH_2CH_2-$. L^6 may be $-CH_2-$. X^4 may be $-O-$. X^5 may be $-O-$. L^4 may be an optionally substituted 3 to 12 membered heterocycle. L^4 is preferably an optionally substituted 6 to 12 membered bicyclic heterocycle, and more preferably an optionally substituted 6 to 12

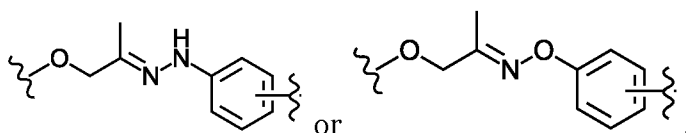
membered spirocyclic heterocycle. Accordingly, L^4 may be , where R^{22} may be a hydrogen, a C_1-C_6 alkyl or a mono or bicyclic C_6-C_{12} aryl. Accordingly, L^4

may be  and is preferably . Accordingly,

A may be .



A may be . X⁴ is preferably –O–. L³ may be an optionally substituted C₁–C₆ alkylene, and preferably is a C₁–C₂ alkylene, and more preferably is –CH₂–. R¹⁷ may be an optionally substituted C_{1–6} alkyl, and is preferably a C_{1–3} alkyl and more preferably is a methyl. X⁵ is preferably –NH– or –O–. L⁴ may be an optionally substituted mono or bicyclic C₆–C₁₂ aryl. Preferably, L⁴ is an optionally substituted phenyl, and in some embodiments is an unsubstituted phenyl. Accordingly, A may be



As explained above, W is –L⁷NH–, –L³L⁷NH–, –L⁷NHC(O)–, –L³L⁷NHC(O)–, –L⁷L⁸NH–, –L³L⁷L⁸NH–, –L⁷L⁸NHC(O)–, or –L³L⁷L⁸NHC(O)–.

L³ may an optionally substituted C₁–C₆ alkylene or C₁–C₆ alkylyne, preferably C₁–C₃ alkylene or C₁–C₃ alkylyne, and most preferably is –CH₂– or –CH₂CHCH–.

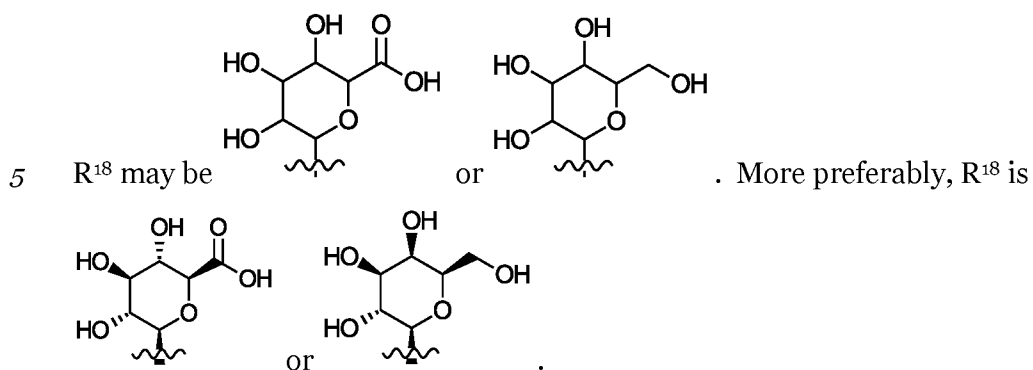
Preferably, L⁷ and L⁸ are each independently a mono or bicyclic C₆–C₁₂ aryl; or a mono or bicyclic 5 to 10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one –OR¹⁸ group.

L⁷ may be a phenyl, naphthalenyl or a 2H-chromen-2-onyl group, wherein each group may be further substituted with one –OR¹⁸ group.

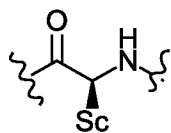
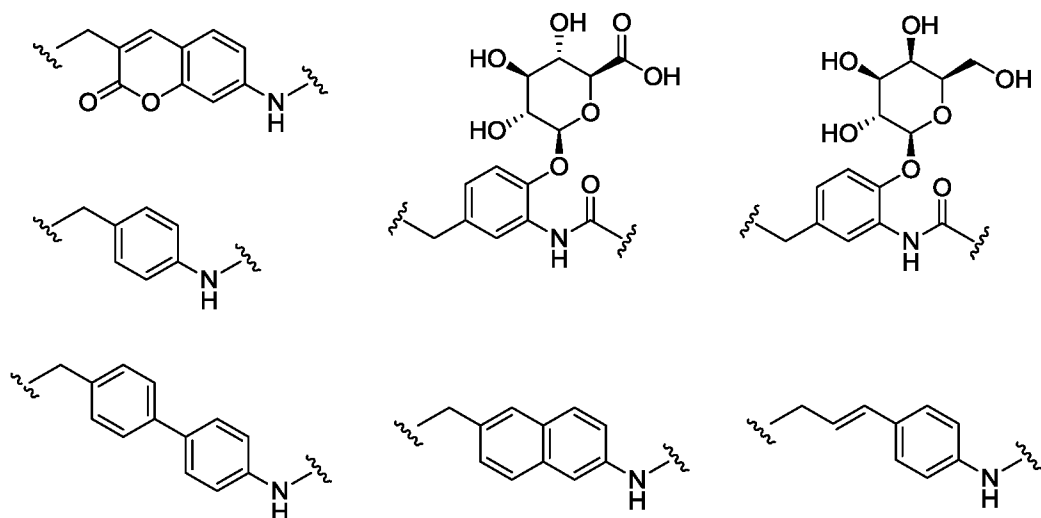
L⁸ is preferably a phenyl.

R¹⁸ is preferably an optionally substituted mono or bicyclic 3 to 8 membered heterocycle. More preferably, R¹⁸ is an optionally substituted 6 membered heterocycle, and most preferably an optionally substituted tetrahydropyranyl. Preferably, the heterocycle is substituted with between 1 and 9 substituents, more preferably between 2 and 7 or between 3 and 5 substituents, and most preferably with 4 substituents. The substituents may be selected from C₁–C₆ alkoxy, OH and COOH. Preferably, the C₁–C₆ alkoxy is a C₁–C₄ alkoxy, more preferably a C₁–C₂ alkoxy, and most preferably –CH₂OH. Preferably, the heterocycle is substituted with between 1 and 9 OH groups, more preferably between 2 and 5 OH groups, and most preferably with 3 OH groups.

Preferably, the heterocycle is substituted with between 1 and 9 C₁-C₆ alkoxy and/or COOH groups, more preferably between 1 and 5 C₁-C₆ alkoxy and/or COOH groups, and most preferably with 1 C₁-C₆ alkoxy or COOH group.



Accordingly, W may be:



D¹ may have general formula

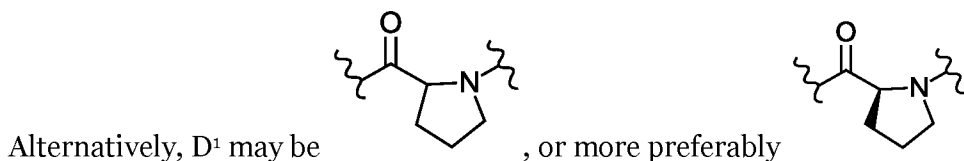
Sc may be H, an optionally substituted C₁-C₆ alkyl, an optionally substituted mono or bicyclic C₆-C₁₂ aryl, an optionally mono or bicyclic 5 to 10 membered heteroaryl, an optionally C₃-C₁₂ cycloalkyl, or an optionally mono or bicyclic 3 to 12 membered heterocycle. Preferably, Sc is H, an optionally substituted C₁-C₆ alkyl, a mono or bicyclic C₆-C₁₂ aryl, a mono or bicyclic 5 to 10 membered heteroaryl, a C₃-C₁₂ cycloalkyl, or a mono or bicyclic 3 to 12 membered heterocycle.

In embodiments where Sc is an optionally substituted C₁-C₆ alkyl, the alkyl may be substituted with at least one of NR⁹R¹⁰, NHC(NH)NH₂, OH, COOH, CONR⁹R¹⁰, SeH, SR⁹, an optionally substituted C₆-C₁₂ aryl, an optionally substituted 5 to 10 membered heteroaryl, an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3 to 8 membered heterocycle. When the alkyl is substituted with NR⁹R¹⁰ then R¹⁰ may be H. R⁹ may also be H. Alternatively, R⁹ may be C(O)NH₂. Accordingly, the alkyl may be substituted with NHC(O)NH₂. When the alkyl is substituted with CONR⁹R¹⁰ then R¹⁰ may be H. R⁹ may also be H. Alternatively, R⁹ may be C(O)NH₂. When the alkyl is substituted with SR⁹, R⁹ may be H or a C₁-C₆ alkyl, preferably R⁹ is H or methyl. When the alkyl is substituted with an optionally substituted C₆-C₁₂ aryl, the optionally substituted C₆-C₁₂ aryl is preferably optionally substituted phenyl. The phenyl may optionally be substituted with an -OH. When the alkyl is substituted with an optionally substituted 5 to 10 membered heteroaryl, the optionally substituted 5 to 10 membered heteroaryl is preferably imidazolyl or 1H-indolyl.

In embodiments where Sc is NC(O)R⁹, R⁹ may be a C₁-C₆ alkyl, and preferably is methyl.

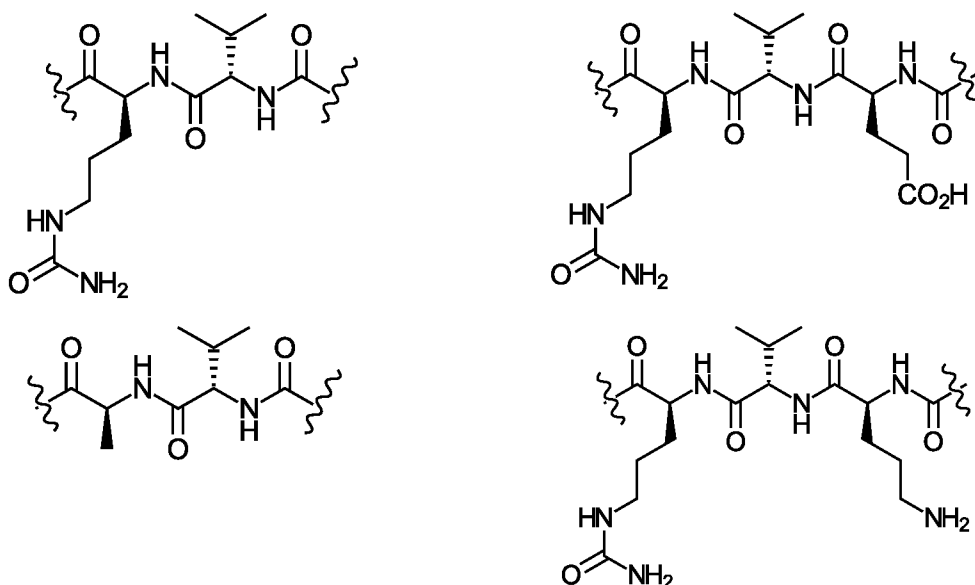
Accordingly, in some embodiments, Sc is H or a C₁-C₆ alkyl optionally substituted with at least one substituent selected from the group consisting of NH₂, NHC(NH)NH₂, OH, COOH, CONR⁹H, SeH, SH, SCH₃, a phenyl optionally substituted with an OH, imidazolyl and 1H-indolyl.

Preferably, Sc is a C₁-C₆ alkyl optionally substituted with NHC(O)NH₂ or COOH. More preferably, Sc is methyl, isopropyl, -CH₂CH₂CH₂NHC(O)NH₂ or -CH₂CH₂COOH.



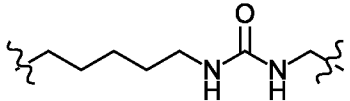
q may be an integer between 1 and 10, more preferably between 2 and 7, and most preferably between 3 and 5.

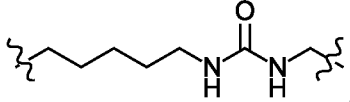
Accordingly, D may be:



- G¹ and G³ may each independently be $-L^3-$, $-(X^4L^3)_p-$ or $-(L^3X^4)_p-$. p may be 1 or 2. L³ may be an optionally substituted C₁-C₁₅ alkylene, more preferably an optionally substituted C₁-C₁₀ alkylene, and most preferably optionally substituted C₁-C₆ alkylene.
- 5 L³ may be substituted with one or more optionally substituted C₁-C₆ alkyl. Preferably, the C₁-C₆ alkyl is unsubstituted. Accordingly, G¹ and G³ may each independently be substituted with one or more methyl groups. G¹ and G³ may each independently be $-\text{CH}_2-$, $-(\text{CH}_2)_2-$, $-(\text{CH}_2)_3-$, $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$, $-\text{CH}_2\text{C}(\text{Me})\text{H}-$, CH_2CMe_2- , $-\text{CH}_2\text{CMe}_2\text{S}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}-$ or $-(\text{CH}_2)_5\text{NH}-$. In embodiments where G²
- 10 and G³ are absent, G may be $-\text{CH}_2-$, $-(\text{CH}_2)_2-$, $-(\text{CH}_2)_3-$, $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$, $-\text{CH}_2\text{C}(\text{Me})\text{H}-$, CH_2CMe_2- , $-\text{CH}_2\text{CMe}_2\text{S}-$ or $-(\text{CH}_2)_5\text{NH}-$. In some embodiments where G¹ and G³ are present, but G² is absent, G may be $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}-$.

- G¹ and G³ may each independently be $\text{---}L^3\text{---}X^4\text{---}C(=O)\text{---}X^5\text{---}L^6\text{---}$. L³ and L⁶ may independently
- 15 be an optionally substituted C₁-C₁₀ alkylene, and more preferably an optionally substituted C₁-C₆ alkylene. X⁴ may be NH. X⁵ may be NH. Accordingly, G¹ and/or G³

may be . In embodiments where G² and G³ are absent, G

may be .

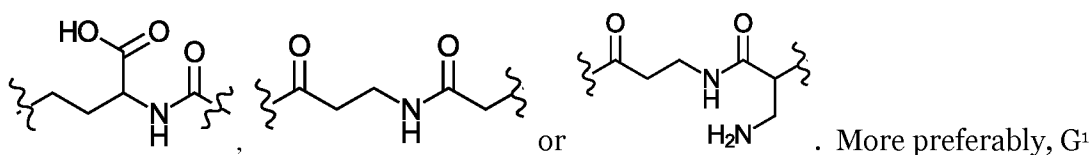
G^1 and G^3 may each independently be may be $-L^3X^4C(O)-$ or $-C(O)L^3X^4C(O)L^6-$.

Preferably, L^3 is an optionally substituted C_1 - C_{15} alkylene, more preferably an optionally substituted C_1 - C_{10} alkylene, and most preferably an optionally substituted C_1 - C_6

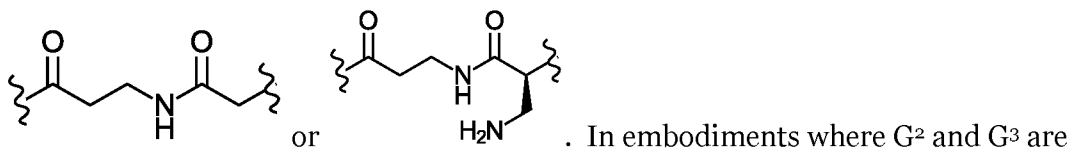
5 alkylene. The alkylene may be substituted with an optionally substituted C_1 - C_6 alkyl or $-COOH$. The alkyl may be substituted with NH_2 . Preferably X^4 is $-NH-$. L^6 is

preferably, an optionally substituted C_1 - C_{15} alkylene, more preferably an optionally substituted C_1 - C_{10} alkylene, and most preferably an optionally substituted C_1 - C_6

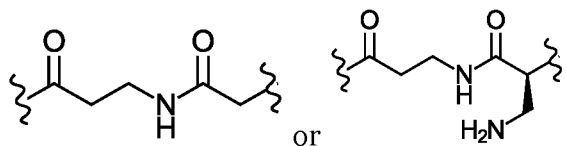
10 alkylene. The alkylene may be substituted with an optionally substituted C_1 - C_6 alkyl or $-COOH$. The alkyl may be substituted with NH_2 . Alternatively, the alkylene may be unsubstituted. Accordingly, G^1 and G^3 may each independently be $-(CH_2)_5NHC(O)-$,



and G^3 may each independently be $-(CH_2)_5NHC(O)-$,

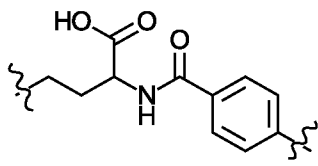


15 absent, G may be $-(CH_2)_5NHC(O)-$,

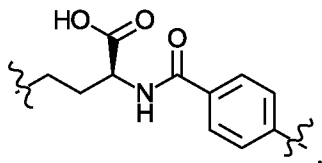


G^1 and G^3 may each independently be an optionally substituted C_3 - C_6 cycloalkyl, a mono or bicyclic optionally substituted C_6 - C_{12} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or a mono or bicyclic optionally substituted 5
20 to 10 membered heterocycle.

In some embodiments G may be $-L^3X^4C(O)-$. G^2 may be absent. G^3 may be $-L^4-$.



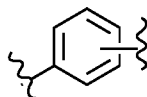
Accordingly, G may be



, and is preferably

- 5 G^1 and G^3 may each independently be $-O-$, $-S-$, $-NR^9-$, $-S(O)-$, $-SO_2-$, $-C(O)L^3-$, $-C(O)L^3C(O)-$, $-OC(O)-$, $-C(O)O-$, $-OC(O)O-$, $-L^3OC(O)-$, $-L^3C(O)O-$, $-(OL^3)_p-$, $-(L^3O)_p-$, $-C(O)NR^9-$, $-NR^9C(O)O-$ or $-NR^9C(O)NR^{10}-$. In some embodiments, G^1 and G^3 may each independently be $-C(O)L^3-$ or $-C(O)L^3C(O)-$ where L^3 is an optionally substituted C_1-C_6 alkylene, and more preferably an optionally substituted C_4-C_5 alkylene. In
- 10 embodiments where G^2 and G^3 are absent, G may be $-C(O)L^3-$ or $-C(O)L^3C(O)-$ where L^3 is an optionally substituted C_1-C_6 alkylene, and more preferably an optionally substituted C_4-C_5 alkylene.

- G^1 and/or G^3 may be $-L^4-$. Accordingly, G^1 and/or G^3 may be an optionally substituted
- 15 mono or bicyclic C_6-C_{12} aryl. G^1 and/or G^3 may be an optionally substituted phenyl. In

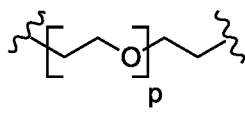


embodiments where G^2 and G^3 are absent, G may be

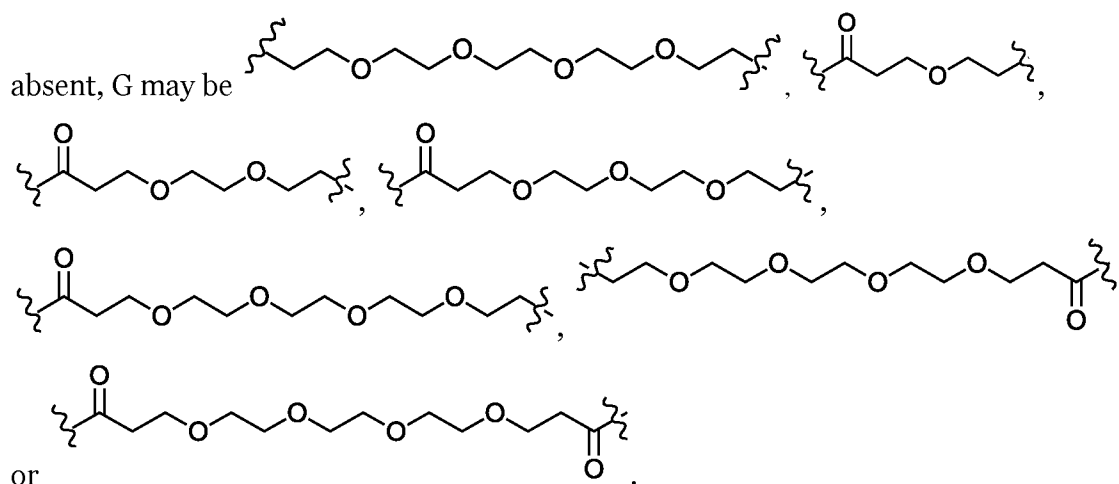
- G^1 and/or G^3 may be a poly(ethylene glycol) (PEG) chain of between 1 and 25 units. The PEG chain may be a cyclic PEG chain, branched PEG chain or a linear PEG chain.
- 20

G^1 and/or G^3 may be a cyclodextrin. The cyclodextrin may be α , β or γ cyclodextrin.

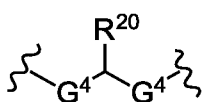
G^1 and/or G^3 may be $-C(O)L^9L^3-$, $-L^9L^3C(O)-$, $-C(O)L^9L^3C(O)-$ or $-L^9L^3-$. L^3 may be an optionally substituted C_1-C_6 alkylene, and is more preferably methylene or ethylene. G^1

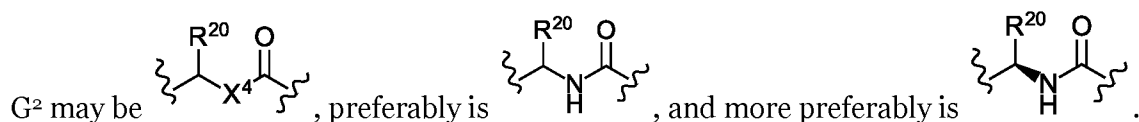


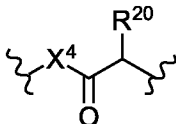
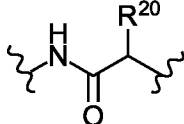
- 25 and/or G^3 may be . p may be an integer between 1 and 15, more preferably between 2 and 10 or between 3 and 5. In embodiments where G^2 and G^3 are

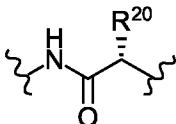


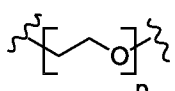
5

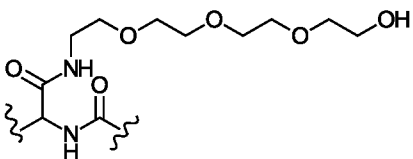
G² may be . Each G⁴ may be absent, -L³- or -X⁴C(O)-. In one embodiment, one G⁴ is absent and one G⁴ is -X⁴C(O)-. X⁴ may be -NH-. Accordingly,

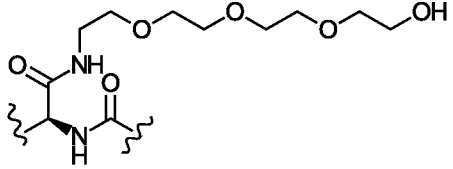


Alternatively, G² may be , preferably is , and more

10 preferably is . In one embodiment, R²⁰ may be -L⁹H, -C(O)L⁹H, -X⁴L⁹H, -X⁴C(O)L⁹H or -C(O)X⁴L⁹H. Preferably R²⁰ is -C(O)X⁴L⁹H. X⁴ may be -NH-. L⁹- may

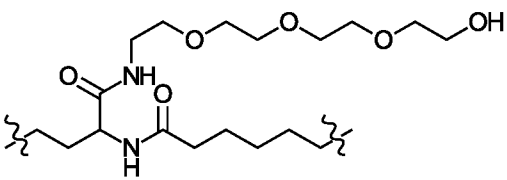
be . p may be an integer between 2 and 10, more preferably between 3 and

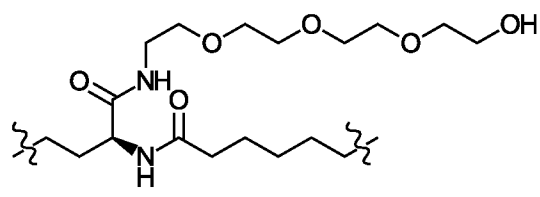
5, and most preferably 4. Accordingly, G² may be , and

more preferably is .

15

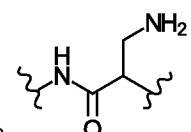
G¹ and G³ may each independently be an optionally substituted C₁-C₁₀ alkylene, more preferably an optionally substituted C₁-C₆ alkylene. G¹ may be ethylene. G³ may be

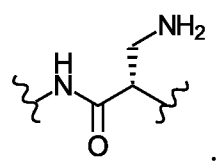
pentylene. Accordingly, G may be , and

preferably is .

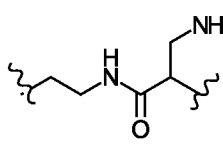
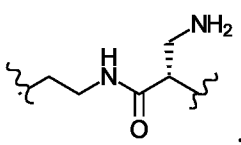
5

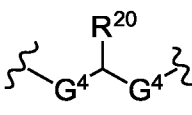
In an alternative embodiment, R²⁰ may be an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl or an optionally substituted C₂-C₆ alkynyl. More preferably, R²⁰ is an optionally substituted C₁-C₃ alkyl, and most preferably is optionally substituted methyl. Preferably, the alkyl, alkenyl or C₂-C₆ alkynyl is substituted with –

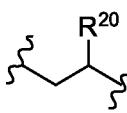
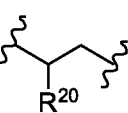
10 NR⁹R¹⁰. Preferably, R⁹ and R¹⁰ are H. Accordingly, G² may be  and more

preferably is .

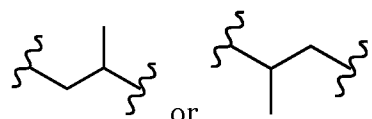
G¹ may be an optionally substituted C₁-C₁₀ alkylene, more preferably an optionally substituted C₁-C₆ alkylene. G¹ may be ethylene. G³ may be absent. Accordingly, G may

15 be , and preferably is .

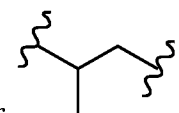
In an alternative embodiment, G² may be  and one G⁴ is absent if –L³–. –L³– may be an optionally substituted C₁-C₁₂ alkylene, more preferably an optionally substituted C₁-C₆ alkylene, and most preferably methylene or ethylene. Accordingly, G²

20 may be  or . R²⁰ may be an optionally substituted C₁-C₆ alkyl, and

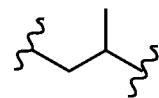
in some embodiments is methyl. Accordingly, G^2 may be



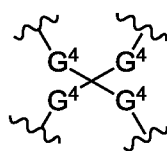
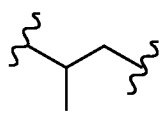
or



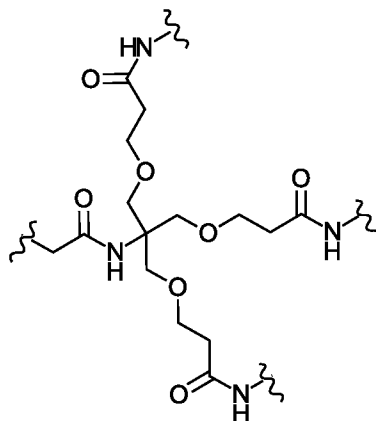
G^1 and G^3 may be absent. Accordingly, in some embodiments, G may be



or



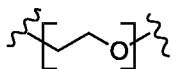
- 5 In some embodiments, G^2 may be . Each G^4 may independently be absent, or selected from the group consisting of $-L^3X^4C(O)-$, $-C(O)X^4L^3-$, $-L^3C(O)X^4$, $-X^4C(O)L^3-$, $-X^4L^3C(O)X^5-$, $-X^4C(O)L^3X^5-$, $-L^3X^4L^6C(O)X^5-$ and $-X^4C(O)L^3X^5L^3-$. At least one G^4 group may be $-X^4C(O)L^3-$. X^4 may be $-NH-$. $-L^3-$ may be an optionally substituted C_1 - C_{12} alkylene, more preferably an optionally substituted C_1 - C_6 alkylene, and most
- 10 preferably methylene or ethylene. At least one G^4 group may be $-L^3X^4L^6C(O)X^5-$. Preferably, at least two or at least three G^4 groups are $-L^3X^4L^6C(O)X^5-$. Each X^4 may be $-NH-$. Each X^5 may be $-NH-$. Each $-L^3-$ and $-L^6-$ may independently be an optionally substituted C_1 - C_{12} alkylene, more preferably an optionally substituted C_1 - C_6 alkylene, and most preferably methylene or ethylene. Accordingly, G^2 may be:



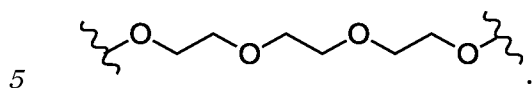
15

Each G^1 and G^3 may independently be absent, $-L^3-$, $-L^9-$, $-X^4L^9-$, $-L^9L^3-$, $-L^3X^4C(O)-$, $-L^3C(O)X^4$, $-L^3X^4C(O)L^6-$ or $-L^3C(O)X^4L^6-$.

The G group may comprise at least one G¹ group. Accordingly, a may be 1, 2 or 3. Preferably, a is 1. G¹ may be -L⁹- or -X⁴L⁹-. Preferably, G¹ is -X⁴L⁹-. Preferably, X⁴ is -

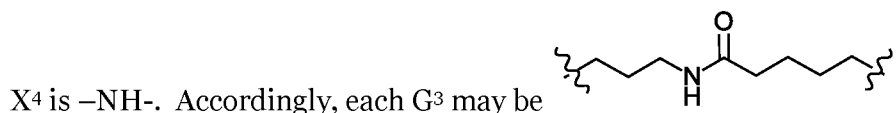


O-. Preferably, -L⁹- is $\left[\text{O}-\text{CH}_2-\text{CH}_2-\text{O} \right]_p$ and p is an integer between 1 and 10, more preferably between 2 and 5, most preferably p is 3. Accordingly, G¹ may be

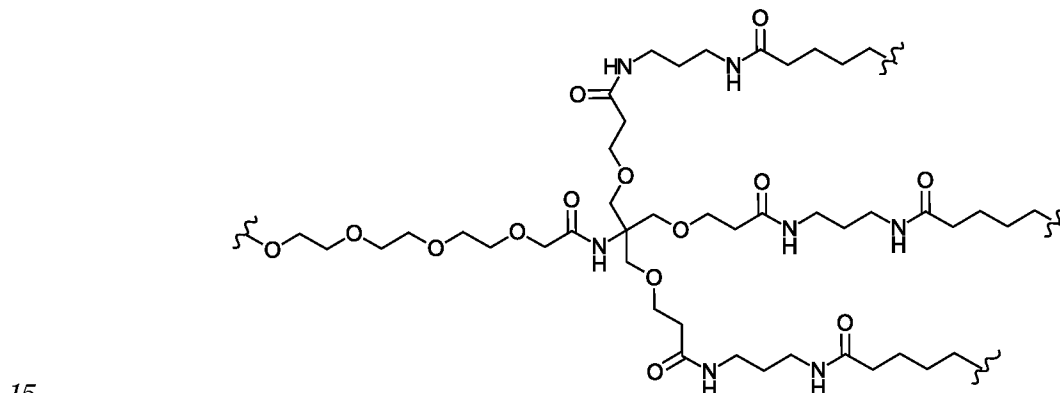


The G group may comprise at least one, at least two or at least three G³ groups.

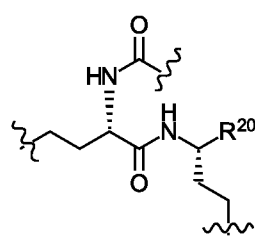
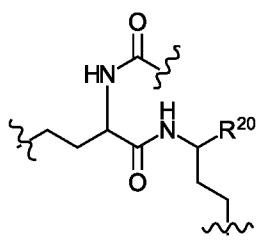
Accordingly, z may be 1, 2 or 3. Preferably, z is 3. G³ may be -L³X⁴C(O)-, -L³C(O)X⁴-, -L³X⁴C(O)L⁶- or -L³C(O)X⁴L⁶-. Preferably, G³ is -L³X⁴C(O)L⁶-. -L³- and -L⁶- may
10 independently be an optionally substituted C₁-C₁₂ alkylene, more preferably an optionally substituted C₁-C₆ alkylene, and most preferably a C₂-C₅ alkylene. Preferably,



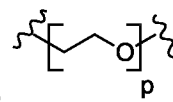
Accordingly, in some embodiments, G may be:



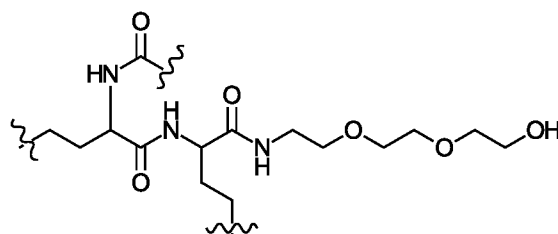
G² may be . Each G⁴ may independently be absent, -L³-, -X⁴-, -X⁸-, -X⁴C(O)- or -C(O)X⁴-. Preferably, at least one, and more preferably at least two G⁴ groups are -L³-. -L³- may be an optionally substituted C₁-C₁₂ alkylene, more preferably an optionally substituted C₁-C₆ alkylene, and most preferably methylene or ethylene.
20 Preferably, at least one G⁴ group is -X⁴C(O)-. Preferably X⁴ is -NH-. Preferably, G⁵ is -X⁴C(O)- or -C(O)X⁴-. Preferably, X⁴ is -NH-. Accordingly, G² may be



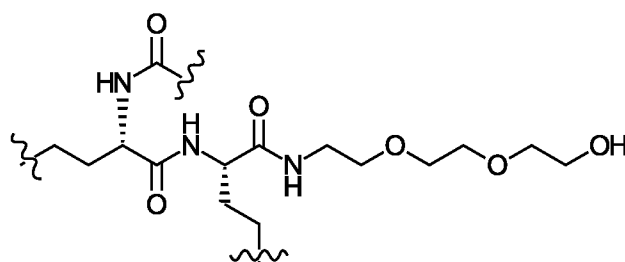
, and more preferably is R^{20} may be -
 $\text{X}^4\text{C}(\text{O})\text{L}^3\text{H}$, $-\text{X}^4\text{C}(\text{O})\text{L}^9\text{H}$, $-\text{C}(\text{O})\text{X}^4\text{L}^3\text{H}$ or $-\text{C}(\text{O})\text{X}^4\text{L}^9\text{H}$. Preferably, X^4 is $-\text{NH}-$.



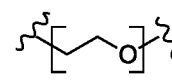
Preferably, R^{20} is $-\text{C}(\text{O})\text{X}^4\text{L}^9\text{H}$. Preferably, $-\text{L}^9-$ is p and p is an integer between 1 and 10, more preferably between 2 and 5, and most preferably p is 3.



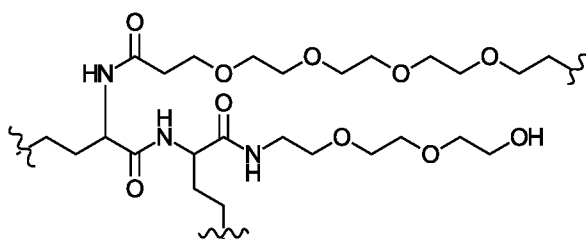
5 Accordingly, G^2 may be , and more



preferably is .

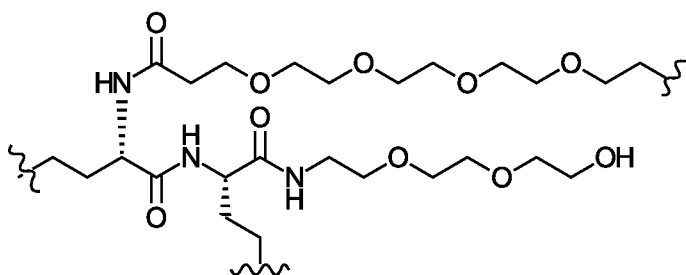


G^1 may be absent. G^3 may be $-\text{L}^3-$, $-\text{L}^9-$, or $-\text{L}^9\text{L}^3-$. Preferably, $-\text{L}^9-$ is p and p is an integer between 1 and 10, more preferably between 2 and 5, and most preferably p is 4. $-\text{L}^3-$ may be an optionally substituted C_1 - C_{12} alkylene, more preferably an optionally substituted C_1 - C_6 alkylene, and most preferably ethylene.



Accordingly, G may be

, and is more



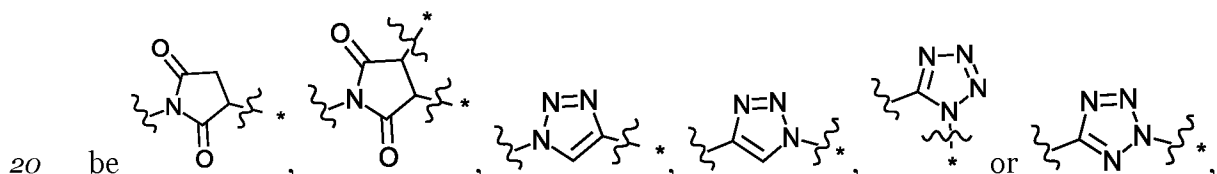
preferably

S may be $-L^3-$. L^3 may be an optionally substituted C_1 - C_{10} alkylene, more preferably an
 5 optionally substituted C_1 - C_6 alkylene. Preferably, the alkylene is unsubstituted.

S may be $-X^4L^3-$. X^4 may be $-NH-$. L^3 may be a C_1 - C_{12} optionally substituted alkylene,
 more preferably a C_1 - C_6 optionally substituted alkylene and most preferably methylene
 or ethylene. Accordingly, S may be $-NHCH_2-$.

10

S may be an optionally substituted mono or bicyclic C_6 - C_{12} aryl, an optionally
 substituted mono or bicyclic 5 to 10 membered heteroaryl, an optionally substituted C_3 -
 C_{12} cycloalkyl, or an optionally substituted mono or bicyclic 3 to 12 membered
 heterocycle. Preferably S is an optionally substituted mono or bicyclic 5 to 10
 15 membered heteroaryl or an optionally substituted mono or bicyclic 3 to 12 membered
 heterocycle. More preferably, S is an optionally substituted mono or bicyclic 5
 membered heteroaryl or an optionally substituted mono or bicyclic 5 membered
 heterocycle. In some embodiments, G is a succinimidyl group, a triazolyl group or a
 tetrazolyl group. The triazolyl group may be a 1,2,3-triazolyl group. Accordingly, S may

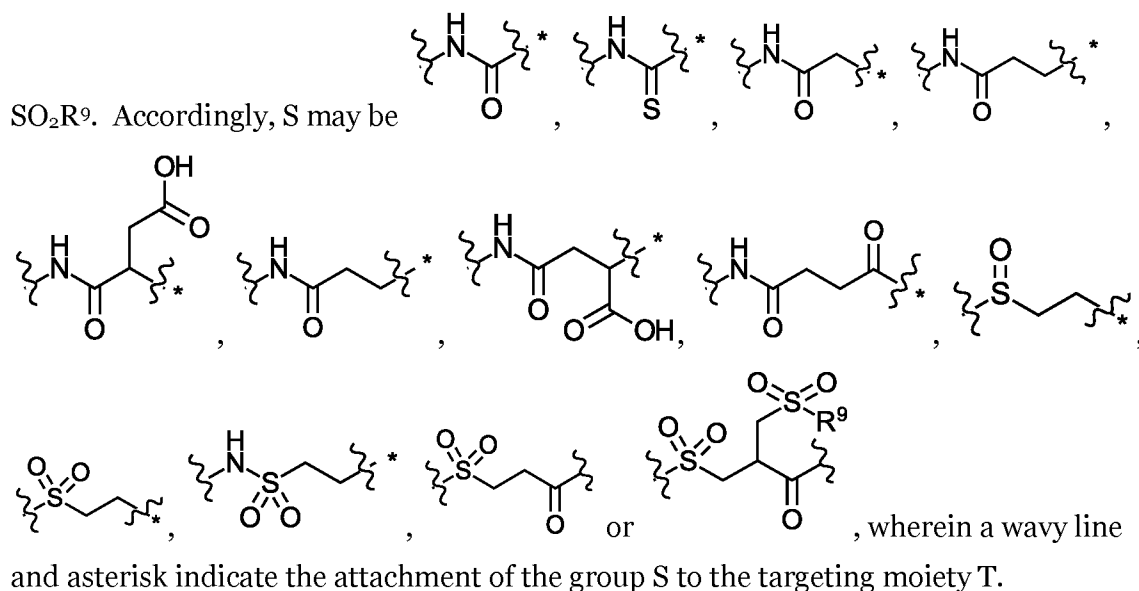


wherein a wavy line and asterisk indicate the attachment of the group S to the targeting
 moiety T. It may be appreciated that where two attachment sites are shown then S
 may be attached to the same targeting moiety at two separate points.

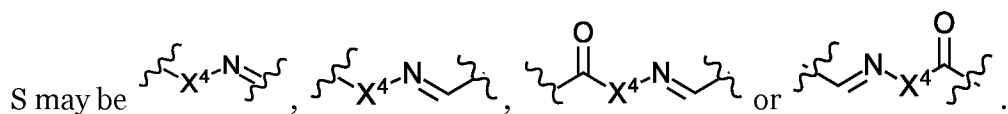
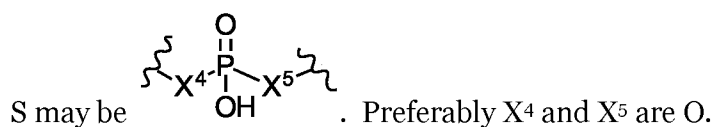
S may be -O-, -NH-, -S- or -C(O)-.

S may be L³. L³ may be an optionally substituted C₁-C₁₅ alkylene, more preferably an optionally substituted C₁-C₁₀ alkylene, and most preferably an optionally substituted C₁-C₆ alkylene. In some embodiments, the alkylene is unsubstituted.

S may be -X⁴C(X⁹)L³-, -X⁴C(X⁹)-, -X⁴C(X⁹)L³C(O)-, -X⁸L³-, -X⁴X⁸L³- or -X⁸L³C(O)-. X⁴ may be NH. X⁹ may be O or S. L³ may be an optionally substituted C₁-C₆ alkylene, and more preferably an optionally substituted C₁-C₂ alkylene. The alkylene may be substituted with COOH or a C₁-C₆ alkyl which is optionally substituted with COOH or

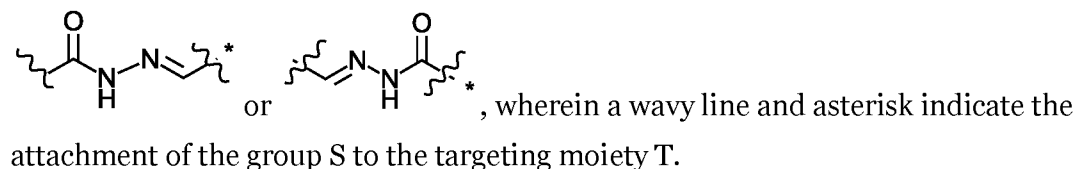


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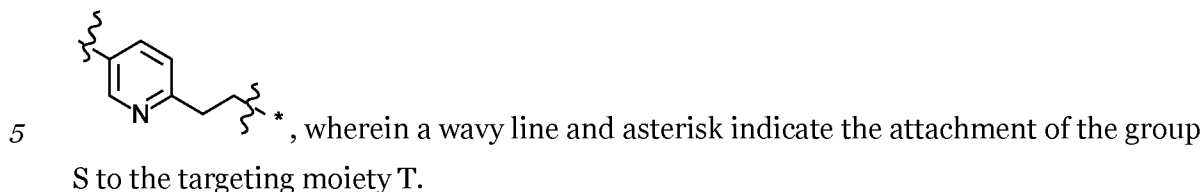


Preferably, X⁴ is O or NH. Accordingly, S may be

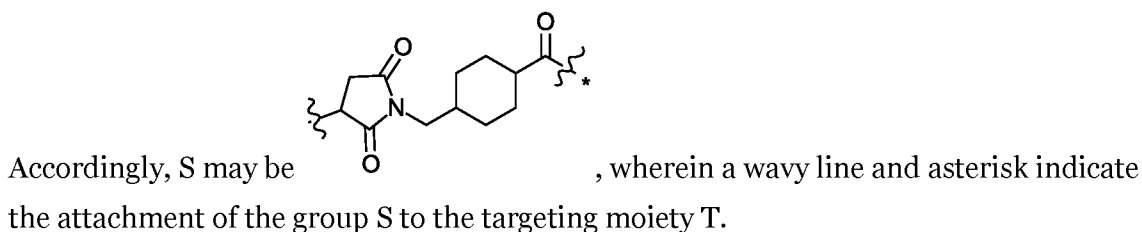
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S may be $-L^4L^3-$. L^3 may be an optionally substituted C_1 - C_6 alkylene, and more preferably a C_1 - C_2 alkylene. L^4 may be an optionally substituted mono or bicyclic C_6 - C_{12} aryl or an optionally substituted mono or bicyclic 5 to 10 membered heteroaryl, and preferably is a phenyl or a 6 membered heteroaryl. Accordingly, S may be

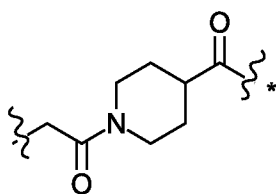


S may be $-L^4L^3L^5C(O)-$. L^3 may be an optionally substituted C_1 - C_6 alkylene, more preferably a C_1 - C_2 alkylene, and most preferably methylene. L^4 may be an optionally substituted C_3 - C_{12} cycloalkyl or an optionally substituted mono or bicyclic 3 to 12 membered heterocycle, more preferably is an optionally substituted C_3 - C_6 cycloalkyl or an optionally substituted mono or bicyclic 3 to 6 membered heterocycle, even more preferably is an optionally substituted mono or bicyclic 5 membered heterocycle, and most preferably is a succinimidyl. L^5 may be an optionally substituted C_3 - C_{12} cycloalkyl or an optionally substituted mono or bicyclic 3 to 12 membered heterocycle, more preferably is an optionally substituted C_3 - C_6 cycloalkyl or an optionally substituted mono or bicyclic 3 to 6 membered heterocycle, and most preferably is a cyclohexyl.



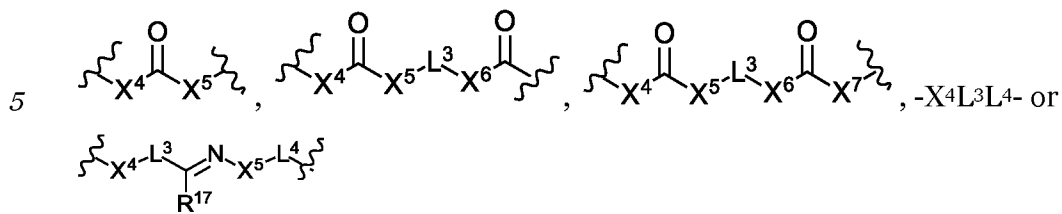
20 S may be $-L^3C(O)L^4C(O)-$. L^3 may be an optionally substituted C_1 - C_6 alkylene, more preferably a C_1 - C_2 alkylene, and most preferably methylene. L^4 may be an optionally substituted C_3 - C_{12} cycloalkyl or an optionally substituted mono or bicyclic 3 to 12 membered heterocycle, more preferably is an optionally substituted C_3 - C_6 cycloalkyl or an optionally substituted mono or bicyclic 3 to 6 membered heterocycle, most preferably is a mono or bicyclic 6 membered heterocycle. Accordingly, S may be

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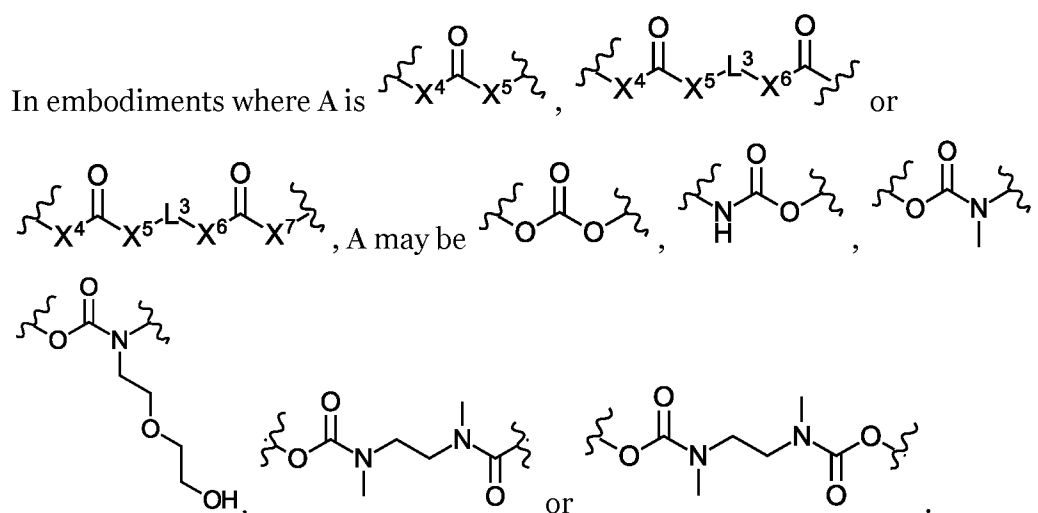
wherein a wavy line and asterisk indicate the attachment of the group S to the targeting moiety T.

In a preferred embodiment, A may be absent, $-L^3X^4$ -, $-C(O)X^4$ -, $-L^3C(O)X^4$,



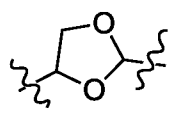
In embodiments where A is -L³X⁴-, L³ may be an optionally substituted C₁-C₁₂ alkylene, and is preferably a C₁-C₆ alkylene, and more preferably is -CH₂-, -CH₂CH₂- or -CH₂CH₂CH₂-. Preferably X⁴ is O. Accordingly, A may be -CH₂O-, -CH₂CH₂O- or -CH₂CH₂CH₂O-.

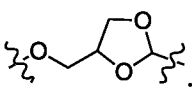
In embodiments where A is $-\text{C}(\text{O})\text{X}^4-$ or $-\text{L}^3\text{C}(\text{O})\text{X}^4$, X^4 may be $-\text{O}-$. L^3 may be an optionally substituted $\text{C}_1\text{-C}_6$ alkylene, and is preferably a $\text{C}_1\text{-C}_3$ alkylene, and most preferably is $-\text{CH}_2-$. Accordingly A may be $-\text{C}(\text{O})\text{O}-$ or $-\text{CH}_2\text{C}(\text{O})\text{O}-$.



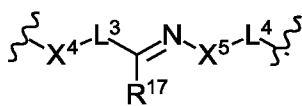
In embodiments where A is -X⁴L³L⁴-, X⁴ is preferably -O-. L³ may be an optionally substituted C₁-C₆ alkylene, and is preferably a C₁-C₂ alkylene, and more preferably is -

CH₂-. L⁴ may be an optionally substituted 3 to 12 membered heterocycle, preferably L⁴ may be an optionally substituted 3 to 8 membered heterocycle, and most preferably L⁴ is

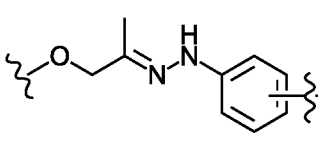
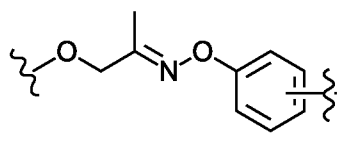
an optionally substituted 5 or 6 membered heterocycle. L⁴ may be .

Accordingly, A may be .

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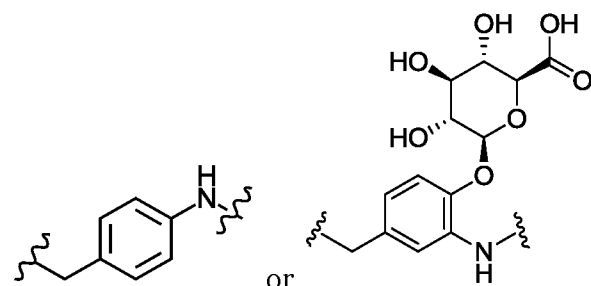
In embodiments where A is , X⁴ is preferably -O-. L³ may be an optionally substituted C₁-C₆ alkylene, and preferably is a C₁-C₂ alkylene, and more preferably is -CH₂-. R¹⁷ may be an optionally substituted C₁₋₆ alkyl, and is preferably a C₁₋₃ alkyl and more preferably is a methyl. X⁵ is preferably -NH- or -O-. L⁴ may be an optionally substituted mono or bicyclic C₆-C₁₂ aryl. Preferably, L⁴ is an optionally substituted phenyl, and in some embodiments is an unsubstituted phenyl. Accordingly,

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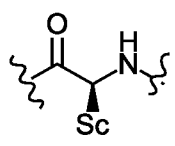
A may be  or .

In a preferred embodiment, W is absent or is -L³L⁷NH-. More preferably W is

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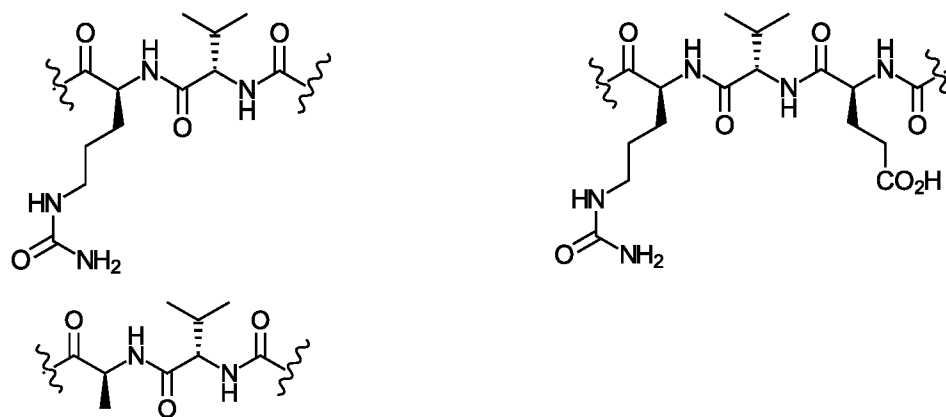


In a preferred embodiment, D is absent or is -(D¹)_qC(O)-, where q is an integer between 2 and 10, and more preferably between 3 and 4. Preferably, D¹ may have general

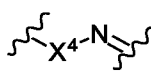
formula . Preferably, each Sc group is an optionally substituted C₁-C₆

20

alkyl. Preferably, the alkyl is optionally substituted with NHC(O)NH₂ or COOH. Accordingly, D may be



In a preferred embodiment, S is $-L^3-$, $-X^4-$, $-X^4L^3-$, $-C(X^9)-$, $-L^4-$, $-X^4C(X^9)L^3-$, $-X^8L^3-$, $-$

$X^4X^8L^3-$,  or $-L^4L^3-$.

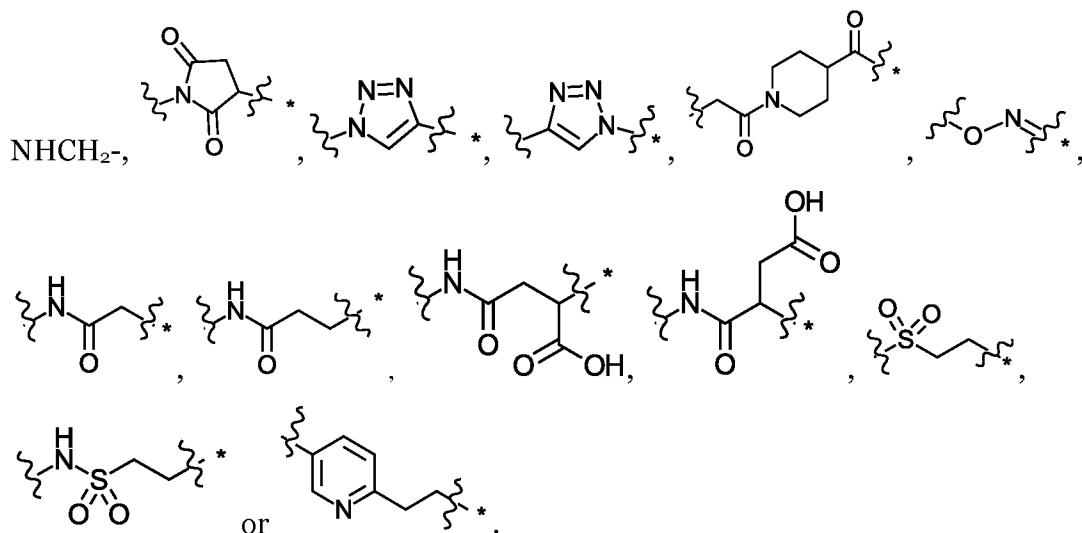
- 5 In embodiments where S is $-X^4L^3-$, X^4 may be $-NH-$. L^3 may be a C_1 - C_{12} optionally substituted alkylene, more preferably a C_1 - C_6 optionally substituted alkylene and most preferably methylene or ethylene.

- 10 In embodiments where S is $-L^4-$, S may be an optionally substituted mono or bicyclic 5 to 10 membered heteroaryl or an optionally substituted mono or bicyclic 3 to 12 membered heterocycle. More preferably, S is an optionally substituted mono or bicyclic 5 membered heteroaryl or an optionally substituted mono or bicyclic 5 membered heterocycle.

- 15 In embodiments where S is $-X^4C(X^9)L^3-$, $-X^8L^3-$ or $-X^4X^8L^3-$, X^4 may be NH. X^9 may be O. C^8 may be $-SO_2-$. L^3 may be an optionally substituted C_1 - C_6 alkylene, and more preferably an optionally substituted C_1 - C_2 alkylene. The alkylene may be unsubstituted or substituted with COOH or a C_1 - C_6 alkyl which is optionally substituted with COOH.

- 20 In embodiments where S is $-L^4L^3-$, L^3 may be an optionally substituted C_1 - C_6 alkylene, and more preferably a C_1 - C_2 alkylene. L^4 may be an optionally substituted mono or bicyclic C_6 - C_{12} aryl or an optionally mono or bicyclic 5 to 10 membered heteroaryl, and preferably is a phenyl or a 6 membered heteroaryl.

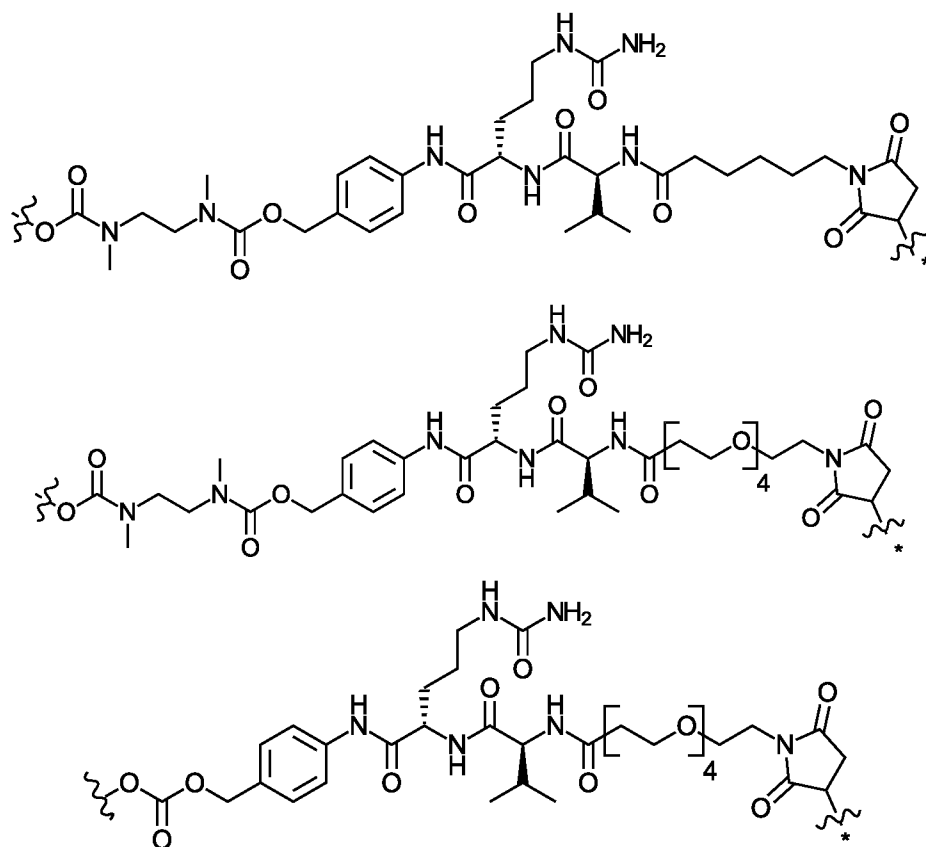
Accordingly, in a preferred embodiment, S may be $-(CH_2)_5-$, $-NH-$, $-S-$, $-C(O)-$, -



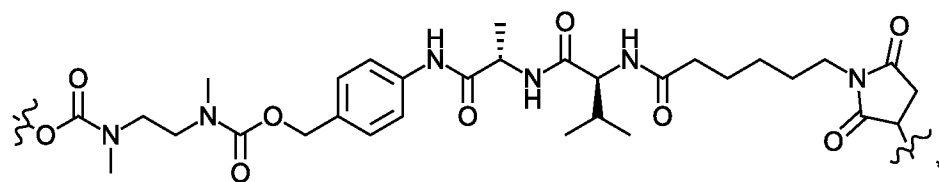
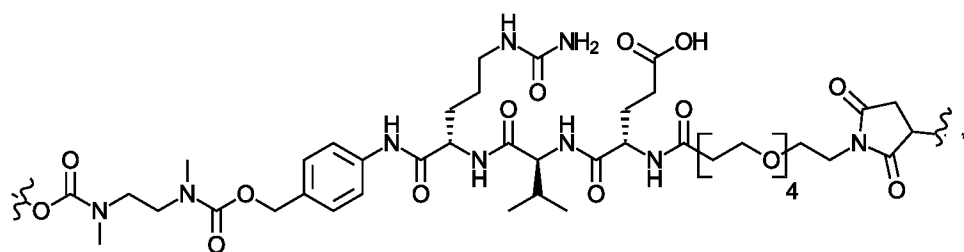
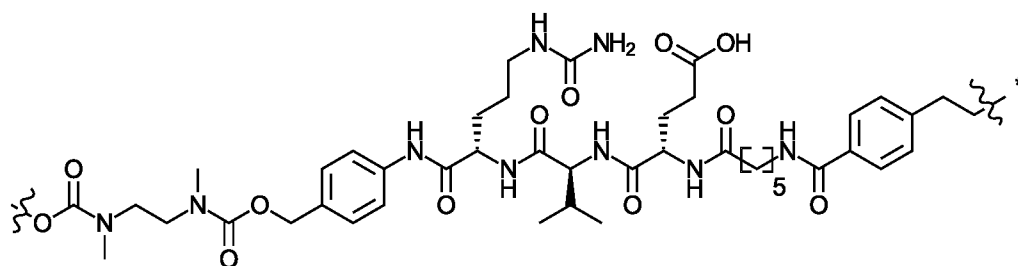
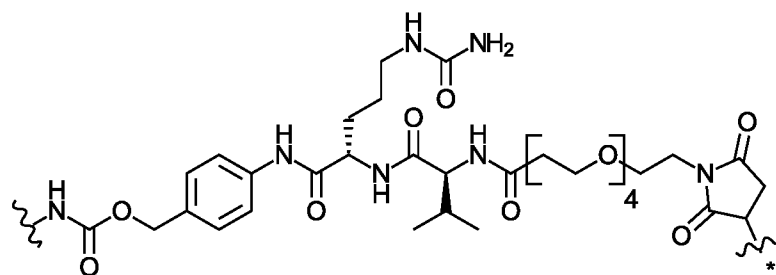
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A, W, D, G and S may all be present. In some embodiments, a is 1 and z is 1.

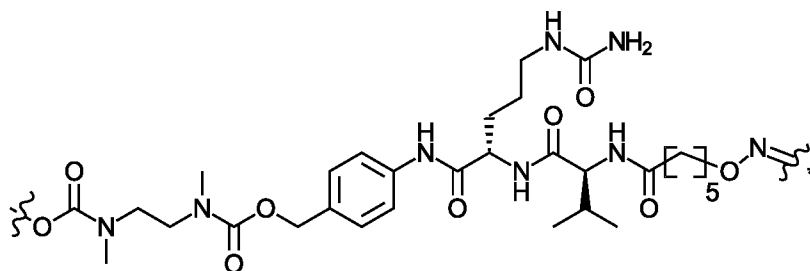
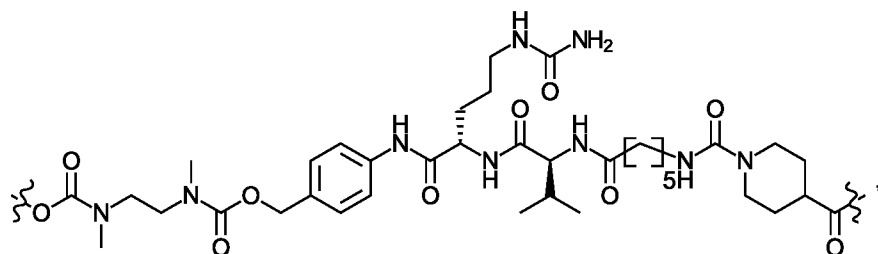
Accordingly, the linker may be:

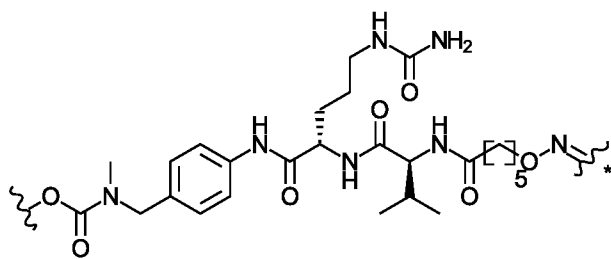
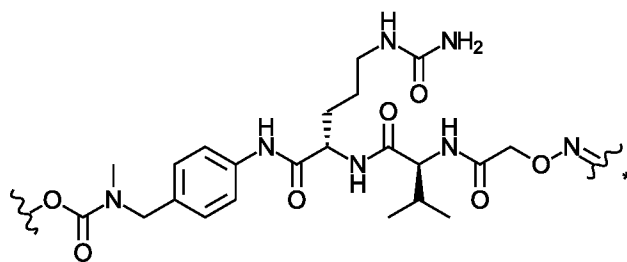
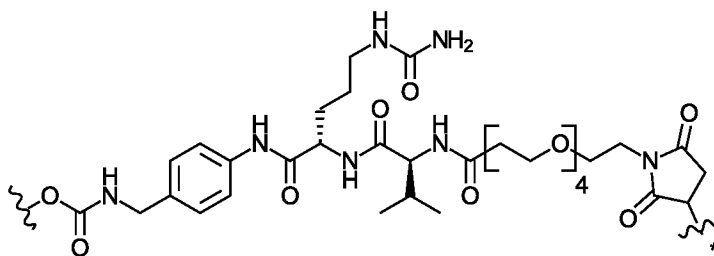
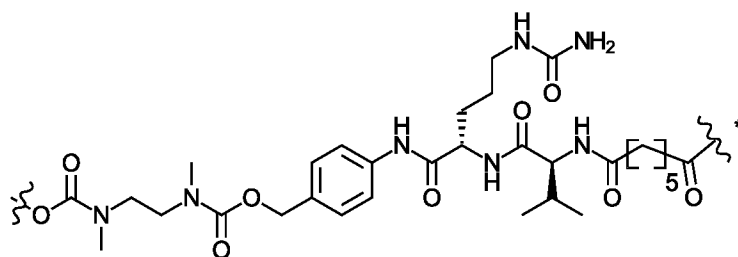
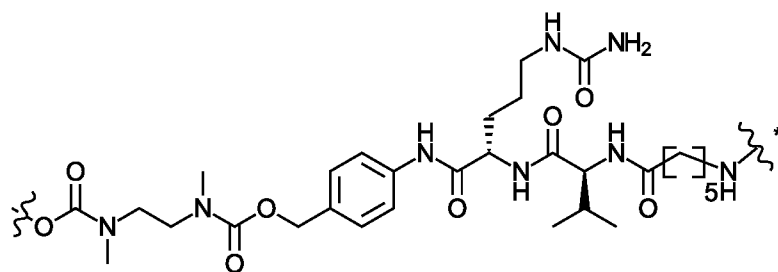


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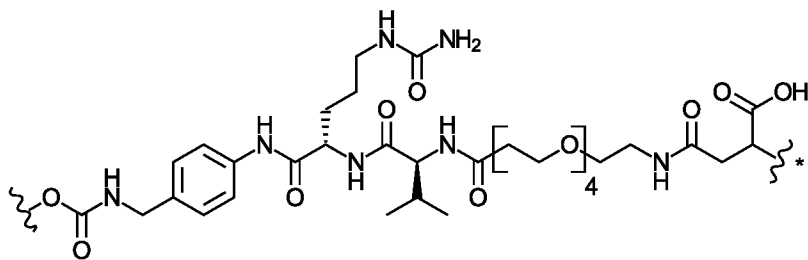


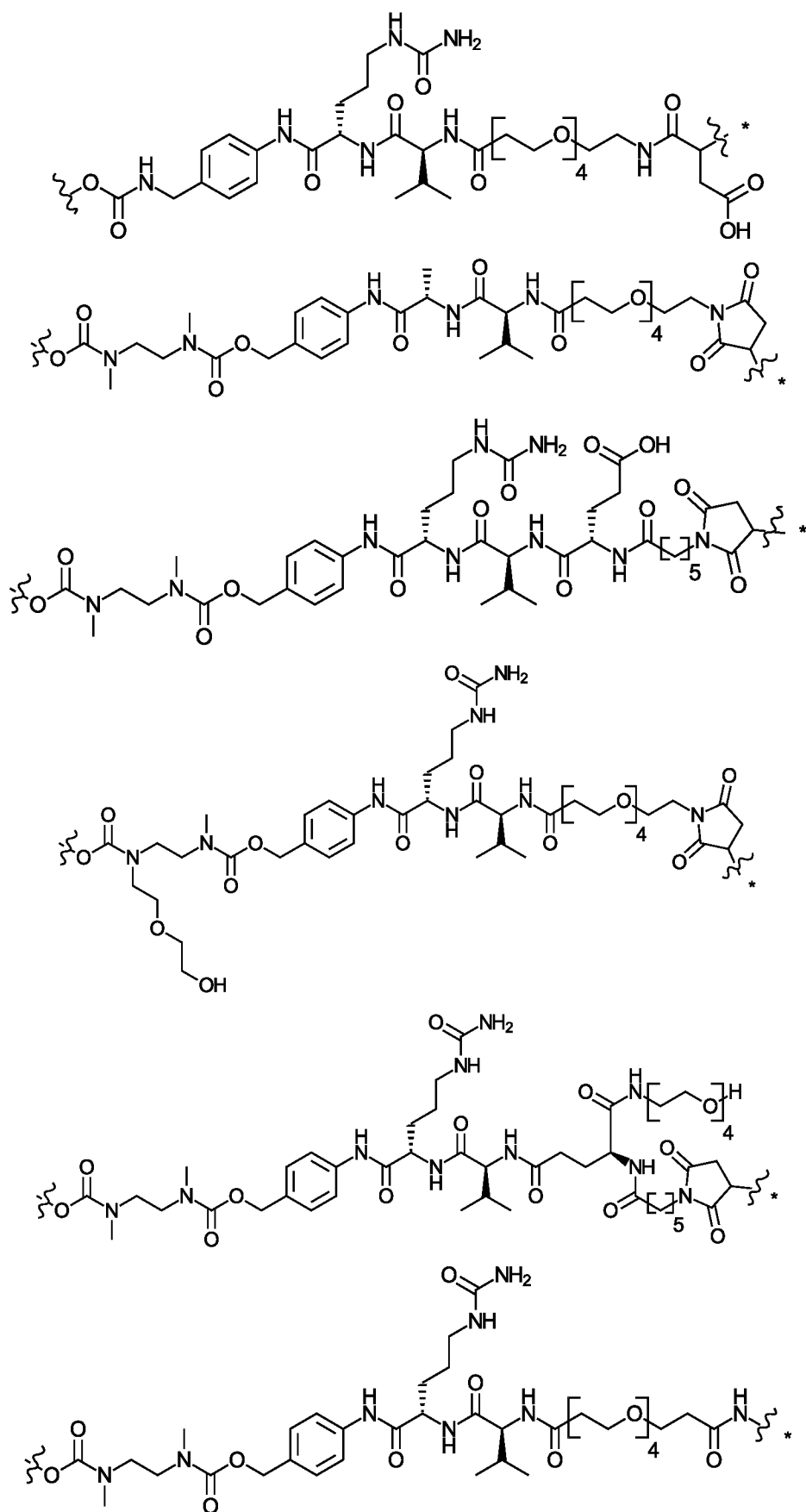
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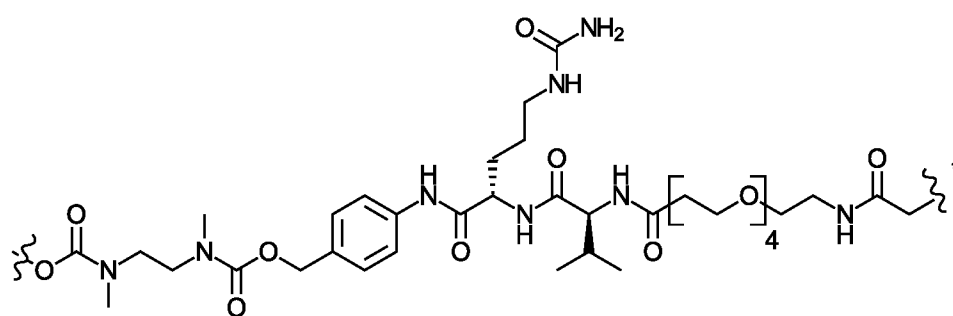
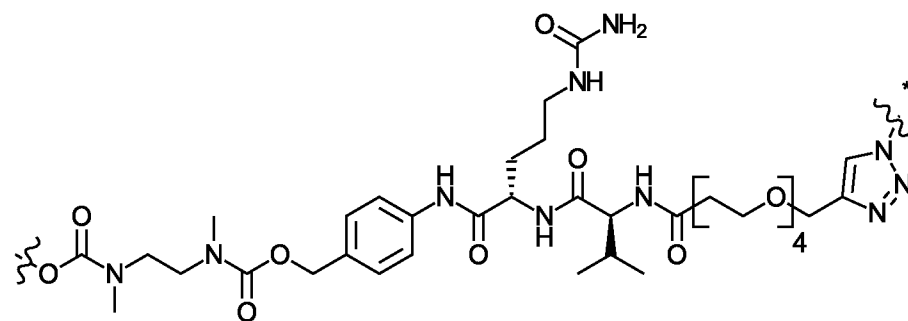
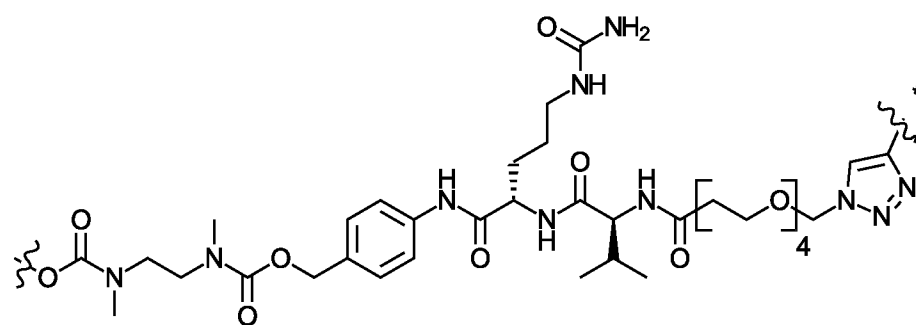
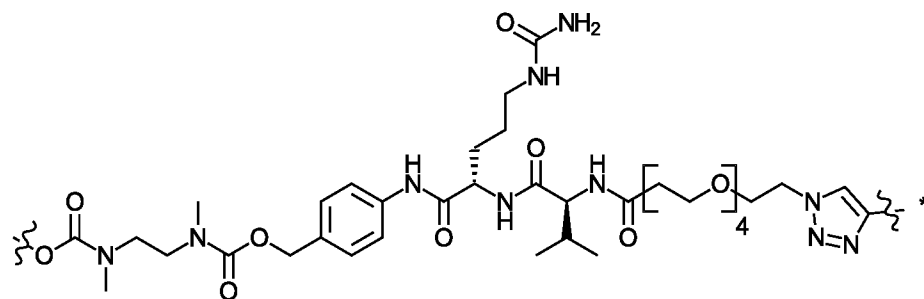
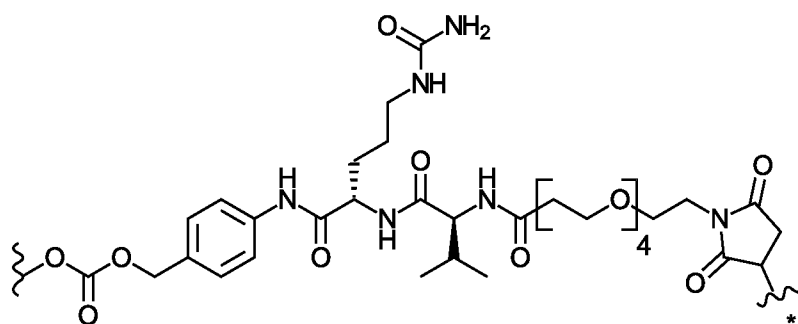


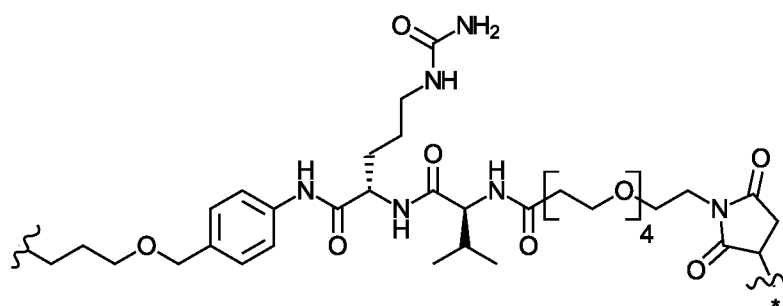
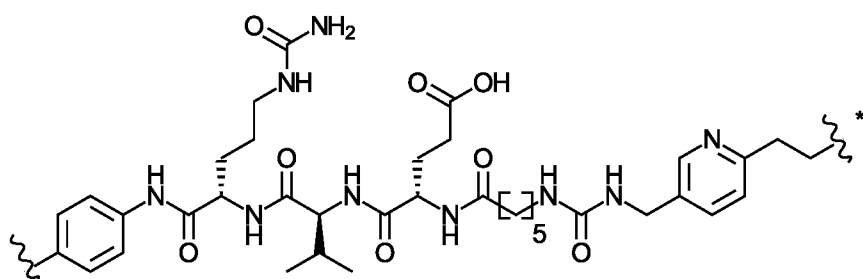
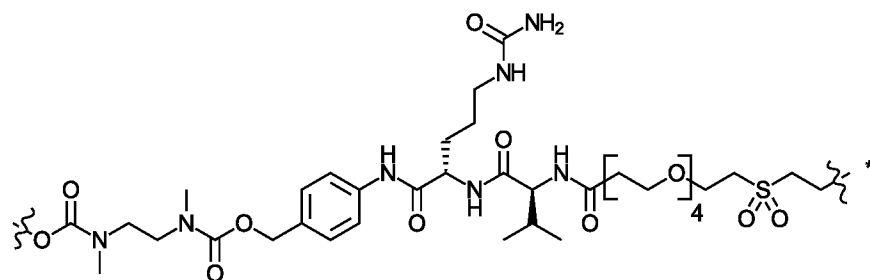
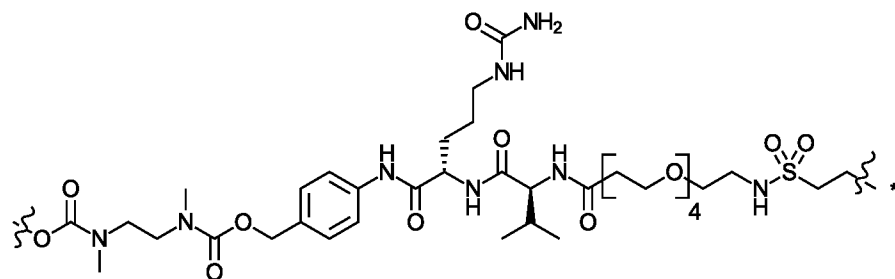
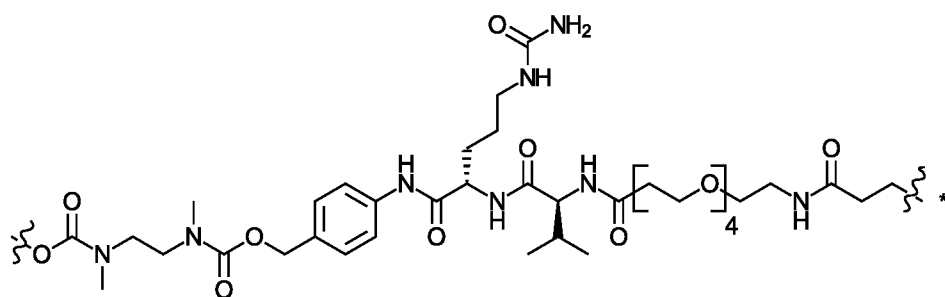


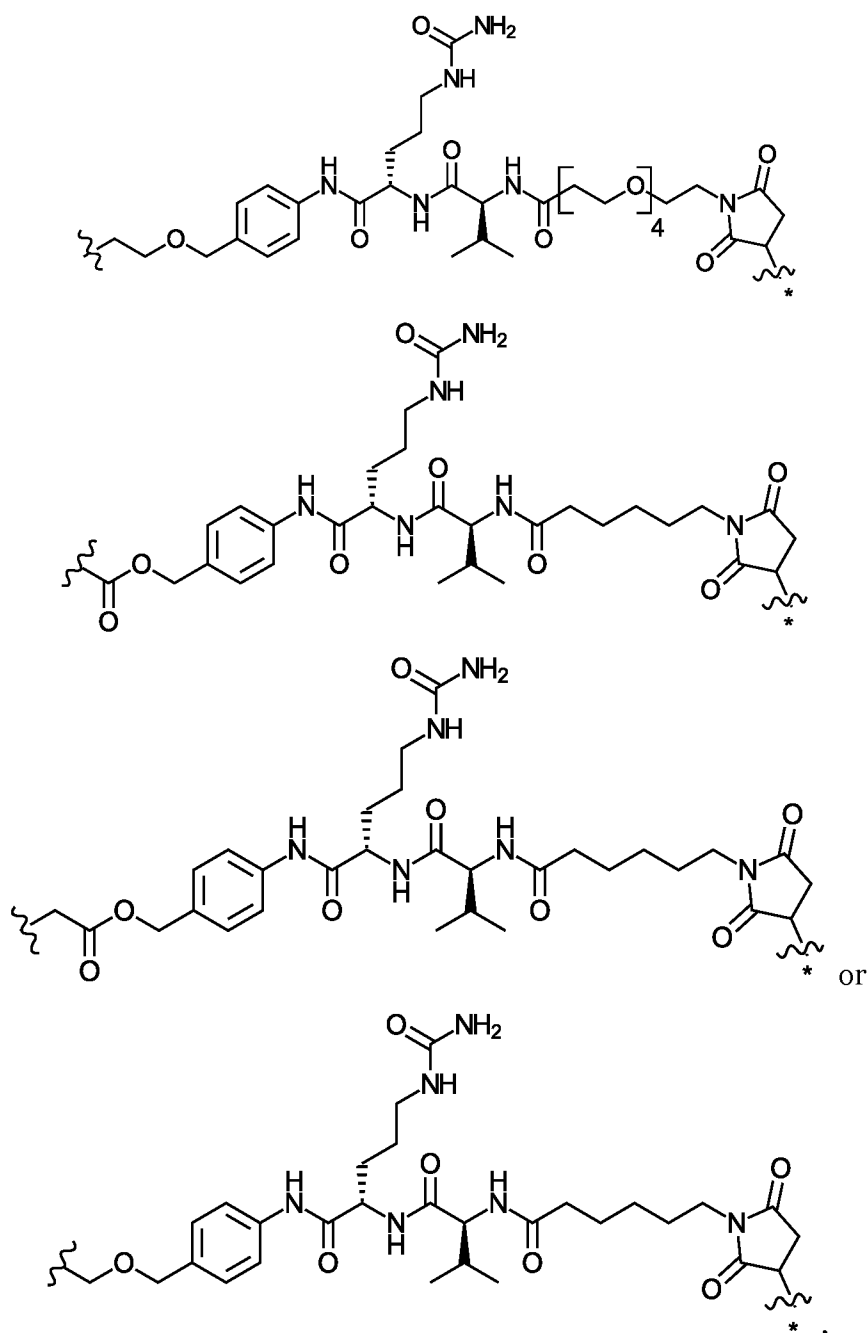
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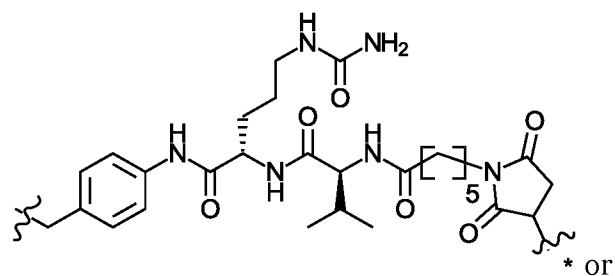
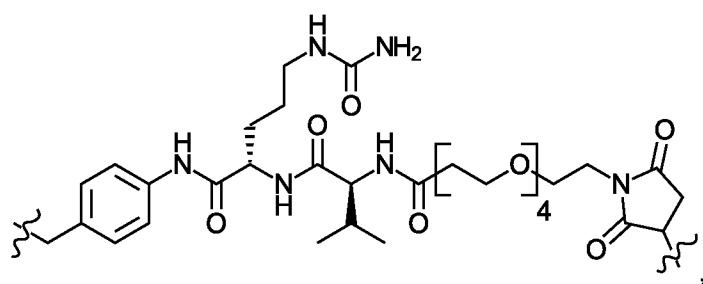
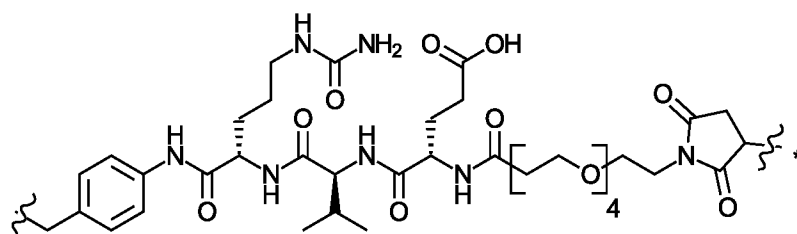
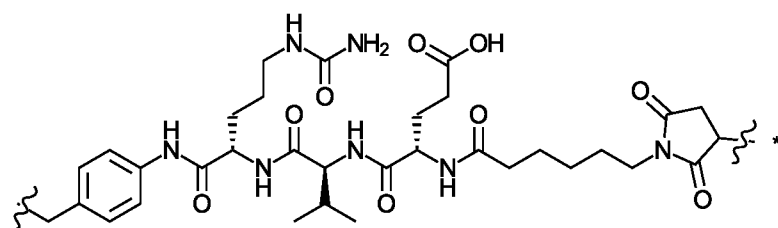
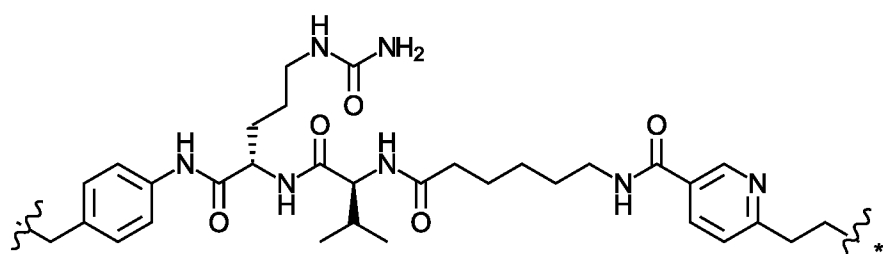




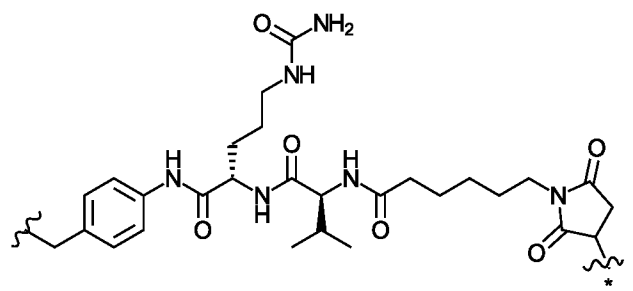


- 5 wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

W, D, G and S may all be present. A may be absent. In some embodiments, a is 1 and z
 10 is 1. Accordingly, the linker may be:



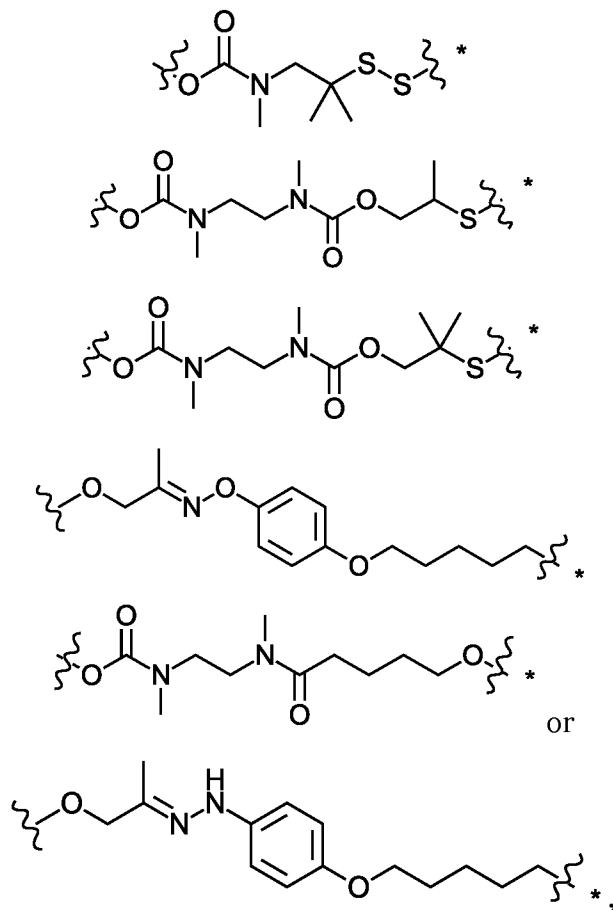
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wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

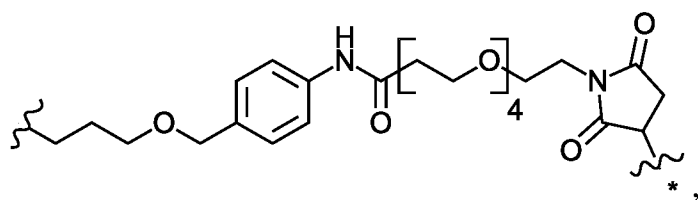
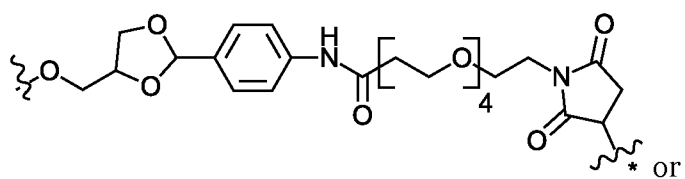
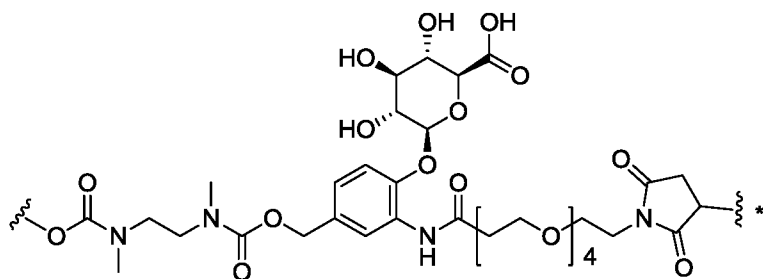
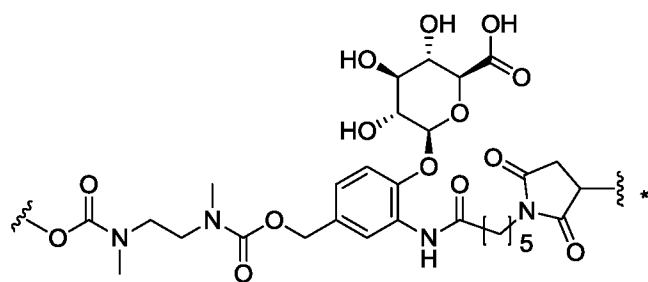
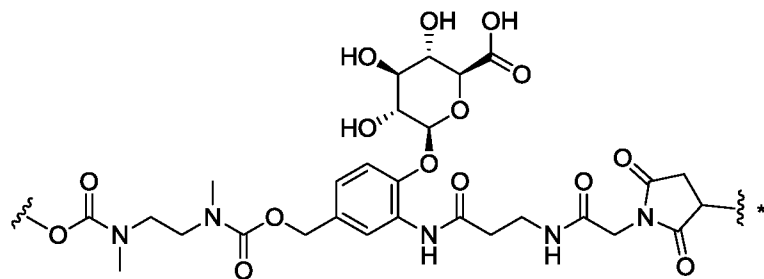
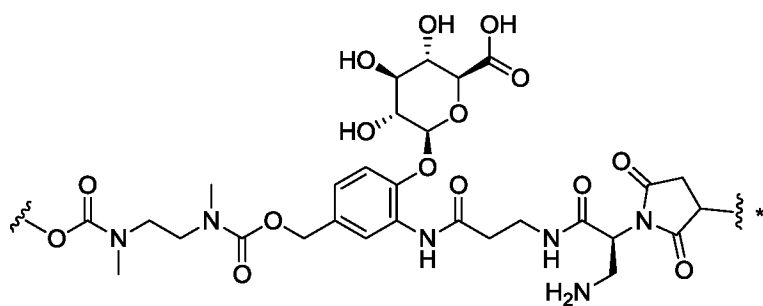
A, G and S may all be present. D may be absent. W may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:

5



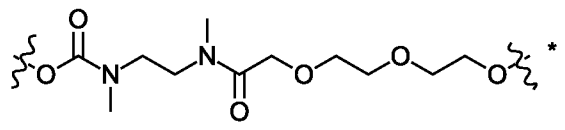
10 wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

15 A, W, G and S may all be present. D may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:



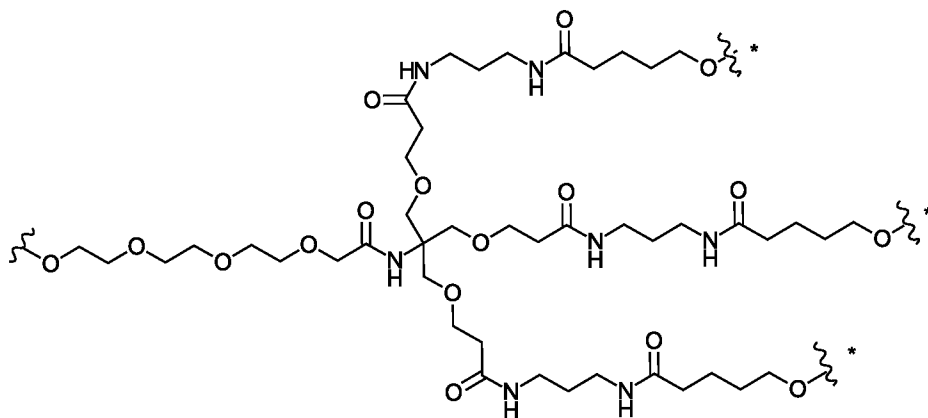
wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

- 5 A and G may both be present. D may be absent. W may be absent. S may be absent. In some embodiments, a is 1 and z is 1. Accordingly, the linker may be:



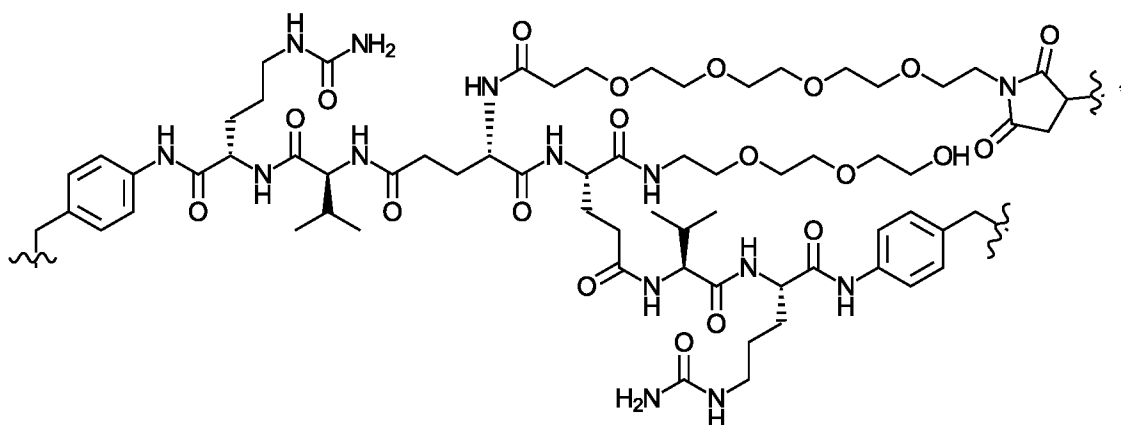
- 10 wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

In some embodiments, a is 1 and z is 2 or 3. Accordingly, a may be 1 and z may be 3. In some embodiments, G and S may both be present. A may be absent. D may be absent. W may be absent. Accordingly, the linker may be:



- 15 wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

- 20 In some embodiments, a is 2 or 3 and z is a. Accordingly, a may be 2 and z may be a. In some embodiments, W, D, G and S may all be present. A may be absent. Accordingly, the linker may be:



wherein a wavy line and asterisk indicates the attachment of the linker to the targeting moiety T, and a wavy line and no asterisk indicates the attachment of the linker to the active compound C.

5

The linker will be known to those skilled in the art as either 'stable' linkers which are resistant to degradation in cells and in the systemic circulation or 'cleavable' or 'conditionally labile' linkers which are designed to degrade under intracellular conditions and/or in the systemic circulation following a defined trigger event, which may be a change in pH or a metabolic process such as ester or amide hydrolysis.

Conjugates of the present invention may comprise two or more cleavage elements which may be selected from acid-induced cleavage, peptidase-induced cleavage (for example, a peptide linker cleaved by an intracellular protease, such as a lysosomal protease or an endosomal protease, see Trout *et. al.*, **1982**, *PNAS USA*, 79, 626-629),

esterase-induced cleavage, glycosidase-induced cleavage, glucuronidase-induced cleavage, phosphodiesterase-induced cleavage, phosphatase-induced cleavage, lipase-induced cleavage or disulfide bond cleavage. Certain intracellular compartments, such as endosomes and lysosomes, have an acidic pH (pH 4.5), and provide conditions suitable to cleave acid-labile linkers. Specific hydrolysis processes have been described,

such as the protease cleavage of a dipeptide e.g. the valine-citrulline dipeptide moiety (Ducry *et. al.*, *Bioconj. Chem.*, **2010**, 21, 5-13) contained in the clinically precedented ADC brentuximab vedotin, a phenylalanine-lysine dipeptide, maleimidocaproyl or a maleimidocaproyl-valine-citrulline linker. The self-immolative group para-aminobenzyloxycarbonyl (PABC) may also form part of the linker structure in which, in response to a suitable trigger event, will eliminate from the conjugate to release the parent structure (Carl *et. al.*, *J. Med. Chem.*, **1981**, 24, 479 and Chakravarty *et. al.*, *J. Med. Chem.*, **1983**, 26, 638), for example in the maleimidocaproyl-valine-citrulline-

PABC linker. Other linkers include those linkers that are cleaved at a specific pH or pH range such as a hydrazone e.g. the hydrazone moiety in gemtuzumab ozogamicin.

5 A non-cleavable linker may be protease insensitive. Non-cleavable linkers include that contained in the clinically precedented ADC trastuzumab emtansine and will require the conjugate to be degraded intracellularly to release the active drug C. See for example; Wong, Chemistry of Protein Conjugation and Cross-Linking, CRC Press Inc., Boca Raton, **1991**.

10 The linker may be dendritic in nature, in that more than one small molecule C may be covalently attached through a branched, multifunctional unit to the targeting moiety (US2006/116422, US2005/271615). Dendritic linkers can increase the molar ratio of drug to targeting group which is related to the potency of the conjugate. Thus, where a targeting group contains for example just a single thiol group, a multitude of small
15 molecules may be attached through a dendritic or branched linker.

The linker may be attached to a targeting moiety T in a variety of ways at any suitable available position on the targeting moiety through a reactive group thereon. Examples of suitable reactive groups include a surface lysine, an oxidised carbohydrate and a
20 cysteine residue. Suitable reactive groups will be known by the skilled person. For instance, a variety of antibody-drug conjugate (ADC) linkage technologies are known in the art, including via alkylation, reductive amination, transesterification, amidation and thiol Michael additions. The resulting linkages include hydrazone, disulphide, maleimide, succinimide and peptide-based functional groups. For example thiol
25 groups, or cysteine residues may be bonded to the linker or spacer group via a maleimide group. Alternative conjugation chemistries include lysine-reactive groups, such as succinyl or HOBt esters, pentafluorophenyl esters, β -lactam amides, isocyanates, and isothiocyanates; azide reactive groups, such as alkynes and strained alkynes; cysteine reactive groups, such as maleimides, α -haloacetamides, pyridyl
30 disulfides and vinyl sulfoxides; and ketone reactive groups, such as hydroxylamines, hydrazines and acyl hydrazides.

In some embodiments, the number of drug/linker moieties conjugated per antibody molecule ranges from 1 to 10. The drug antibody ratio (DAR) is typically from 1 to 10,
35 and may be from 2 to 5 or 2 to 3. Accordingly, b may be 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

Such conjugates may be designed to specifically target certain cell types or tumour types via the targeting moiety. Accordingly, the targeting moiety may be configured to direct the compound of formula (I) to a specific cell or tumour type, and thereby deliver the STING modulator in a cell-specific manner. The conjugate can therefore be used
5 accordingly in a therapeutic setting. The principle of this targeted delivery will be known to those skilled in the art as being closely related to ADC technology, for example as described in Polakis, P., *Pharmacol. Revs.*, **2016**, 68, 3-19 and Beck *et. al.*, *Nat. Revs. Drug Disc.*, **2017**, 16, 315-337. The conjugate may then be taken up inside a cell or tumour through receptor-mediated endocytosis. The target antigen or receptor
10 may be part of a cell or tumour or can be an extracellular matrix protein within the microenvironment of the cell or tumour. Once inside a cell or tumour, one or more specific peptide sequences within the conjugate may be hydrolytically cleaved by one or more cell or tumour proteases. For example, a tumour-associated protease, cathepsin B, C or D, or a plasmin protease to cleave the linker and release the active compound
15 either in the target cells or in the tumour microenvironment of the target cells. The active drug is then free to migrate within the cell or microenvironment and thereby contact and subsequently modulate the STING protein. In some embodiments, the active drug may be cleaved from the targeting moiety outside of cells or tumours and the active drug subsequently acts at the cell surface or penetrates the cell or tumour.

20

T is a targeting moiety and may comprise an antibody, an antibody fragment, a nucleic acid based molecule, a carbohydrate, a peptide, a modified peptide or a small molecule.

In one embodiment, T may be configured to target a tumour antigen. Accordingly, T
25 may be configured to target the Human Epidermal Growth Factor Receptor (EGFR), a plasminogen activator, a cytotoxic T-lymphocyte associated antigen (CTLA) such as CTLA-4, vascular endothelial growth factor (VEGF), neurotrophic factors such as BDNF, fibroblast growth factor receptor (FGFR), a nerve growth factor, platelet-derived growth factor (PDGF), transforming growth factor (TGF), tissue factor (TF), EpCAM,
30 CEACAM5, CEACAM6, colon-specific antigen p, FLT3, PSA, PSMA, PSCA, STEAP, BCMA, CEA, folate receptor, cathepsin D, estrogen receptor, progesterone receptor, NCA-95, NCA-90, A3, A33, Ep-CAM, the CD33/CD30/CD37/CD52/CD66e, CD56/CD74/CD79/CD22 receptors, the SLC34A2 gene product, SLC44A4, the mesothelin protein, the integrin $\alpha_v\beta_3$, PD-1, PD-L1, EGP-1, EGP-2, the EphA2 tyrosine
35 kinase, the mucin cell-surface antigens e.g. MUC16, the hLewis Y antigen, carbonic anhydrase IX, 5T4, EFNA4, DLL4, Axl, B7, ALK, Fyn3, HLA, HIF, IGF, CC49, AFP,

NaPi2b, bcr-abl, caspase-8, guanylyl cyclase C, CD19, CD20, CD21, CD22, CD40, CD79a, CD79b, CD98, CD123, PTK7, CDK4, RANTES, CD44, CD48, CD133, CD70, CD72, CD74, CD166, c-kit, cMet, ErbB2/Her2, ErbB3/Her3, ErbB4/Her4, OX40, p53, α -fetoprotein, R1, PAP, PAX3, PAX5, Ras, Rho, ROR2, nectin-4, E-cadherin, P-
 5 cadherin, cadherin-6, LRRC15, BMPR1B, E16, Sema 5b, ETBR, MSG783, Trop2, TRPM4, ENPP3, SLITRK6, LIV-1, CRIPTO, FcRH1, IRTA2, TENB2, FcRH2, NCA, MDP, IL30R α , ERK, gpNMB, LYPD3, GEDA, CXCR5, HLA-DOB, P2X5, LY64 or LY75.

In a preferred embodiment, T is configured to target Her2. It may be appreciated that
 10 HER2 may also be called Erbb2, and is a biomarker for breast cancer, gastric cancer, ovarian cancer and/or lung cancer.

In a preferred embodiment, T is an antibody, or a fragment thereof. Certain antibodies have been applied in the field of immune oncology previously. Exemplary anti-PD1
 15 antibodies include lambrolizumab (MK-3475, Merck), nivolumab (BMS-936558, Bristol-Myers Squibb), AMP-224 (Merck) and pidilizumab (CT-O11, Curetech Ltd.). Known anti-PDL1 antibodies include MDX-1105 (Medarex), MEDI4736 (Medimmune), MPDL4280A (Genentech) and BMS-936559 (Bristol-Myers Squibb). Exemplary anti-CTLA4 antibodies include ipilimumab (Yervoy, Bristol-Myers Squibb) and
 20 tremelimumab (Pfizer). Exemplary anti-ErbB2/Her2 antibodies include trastuzumab (Roche), pertuzumab (Genentech), margetuximab (Macrogenics) and HT-19 (Mersana Therapeutics). In a preferred embodiment, T is trastuzumab or a fragment or derivative thereof.

25 As an example, conjugates which comprise an anti-HER2 antibody can be specifically targeted to HER2-positive cancer cells or tumours. Trastuzumab (Herceptin or Herclon) is a humanized monoclonal antibody that binds to the juxtamembrane portion of the extracellular domain of the HER2 receptor (Hudis et. al., *N. Engl. J. Med.*, **2007**, 357, 39-51; Cho et. al., *Nature*, **2003**, 421, 756-760). Trastuzumab gained
 30 US FDA approval in September 1998 for the treatment of metastatic breast cancer in patients whose tumours overexpress HER2 and who received one or more chemotherapy regimens for their metastatic disease.

The invention extends to both whole antibodies, as well as to antigen-binding
 35 fragments or regions of the corresponding full-length antibody.

The antibody or antigen-binding fragment thereof may be monovalent, divalent or polyvalent. Monovalent antibodies are dimers (HL) comprising a heavy (H) chain associated by a disulphide bridge with a light chain (L). Divalent antibodies are tetramer (H₂L₂) comprising two dimers associated by at least one disulphide bridge.

5 Polyvalent antibodies may also be produced, for example by linking multiple dimers. The basic structure of an antibody molecule consists of two identical light chains and two identical heavy chains which associate non-covalently and can be linked by disulphide bonds. Each heavy and light chain contains an amino-terminal variable region of about 110 amino acids, and constant sequences in the remainder of the chain.

10 The variable region includes several hypervariable regions, or Complementarity Determining Regions (CDRs), that form the antigen-binding site of the antibody molecule and determine its specificity for the antigen or variant or fragment thereof (e.g. an epitope). On either side of the CDRs of the heavy and light chains is a framework region, a relatively conserved sequence of amino acids that anchors and

15 orients the CDRs. Antibody fragments may include a bi-specific antibody (BsAb) or a chimeric antigen receptor (CAR).

The constant region consists of one of five heavy chain sequences (μ , γ , ζ , α , or ϵ) and one of two light chain sequences (κ or λ). The heavy chain constant region sequences

20 determine the isotype of the antibody and the effector functions of the molecule.

Preferably, the antibody or antigen-binding fragment thereof is isolated or purified.

In one preferred embodiment, the antibody or antigen-binding fragment thereof

25 comprises a polyclonal antibody, or an antigen-binding fragment thereof. The antibody or antigen-binding fragment thereof may be generated in a rabbit, mouse or rat.

In another preferred embodiment, the antibody or antigen-binding fragment thereof comprises a monoclonal antibody or an antigen-binding fragment thereof. Preferably,

30 the antibody is a human antibody. As used herein, the term "human antibody" can mean an antibody, such as a monoclonal antibody, which comprises substantially the same heavy and light chain CDR amino acid sequences as found in a particular human antibody exhibiting immunospecificity. An amino acid sequence, which is substantially the same as a heavy or light chain CDR, exhibits a considerable amount of sequence

35 identity when compared to a reference sequence. Such identity is definitively known or recognizable as representing the amino acid sequence of the particular human

antibody. Substantially the same heavy and light chain CDR amino acid sequence can have, for example, minor modifications or conservative substitutions of amino acids.

5 The term “human monoclonal antibody” can include a monoclonal antibody with substantially or entirely human CDR amino acid sequences produced, for example by recombinant methods such as production by a phage library, by lymphocytes or by hybridoma cells.

10 The term “humanised antibody” can mean an antibody from a non-human species (e.g. mouse or rabbit) whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans.

The antibody may be a recombinant antibody. The term “recombinant human antibody” can include a human antibody produced using recombinant DNA technology.
15

The term “antigen-binding region” can mean a region of the antibody having specific binding affinity for its target antigen or a variant or fragment thereof. Preferably, the fragment is an epitope. The binding region may be a hypervariable CDR or a functional portion thereof. The term “functional portion” of a CDR can mean a sequence within
20 the CDR which shows specific affinity for the target antigen. The functional portion of a CDR may comprise a ligand which specifically binds to the target antigen or a fragment thereof.

The term “CDR” can mean a hypervariable region in the heavy and light variable
25 chains. There may be one, two, three or more CDRs in each of the heavy and light chains of the antibody. Normally, there are at least three CDRs on each chain which, when configured together, form the antigen-binding site, i.e. the three-dimensional combining site with which the antigen binds or specifically reacts. It has however been postulated that there may be four CDRs in the heavy chains of some antibodies.

30 The definition of CDR also includes overlapping or subsets of amino acid residues when compared against each other. The exact residue numbers which encompass a particular CDR or a functional portion thereof will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a
35 particular CDR given the variable region amino acid sequence of the antibody.

The term “functional fragment” of an antibody can mean a portion of the antibody which retains a functional activity. A functional activity can be, for example antigen binding activity or specificity. A functional activity can also be, for example, an effector function provided by an antibody constant region. The term “functional fragment” is
5 also intended to include, for example, fragments produced by protease digestion or reduction of a human monoclonal antibody and by recombinant DNA methods known to those skilled in the art. Human monoclonal antibody functional fragments include, for example individual heavy or light chains and fragments thereof, such as VL, VH and Fd; monovalent fragments, such as Fv, Fab, and Fab'; bivalent fragments such as
10 F(ab')₂; single chain Fv (scFv); and Fc fragments.

The term “VL fragment” can mean a fragment of the light chain of a human monoclonal antibody which includes all or part of the light chain variable region, including the CDRs. A VL fragment can further include light chain constant region sequences.
15

The term “VH fragment” can means a fragment of the heavy chain of a human monoclonal antibody which includes all or part of the heavy chain variable region, including the CDRs.

20 The term “Fd fragment” can mean the heavy chain variable region coupled to the first heavy chain constant region, i.e. VH and CH-1. The “Fd fragment” does not include the light chain, or the second and third constant regions of the heavy chain.

The term “Fv fragment” can mean a monovalent antigen-binding fragment of a human
25 monoclonal antibody, including all or part of the variable regions of the heavy and light chains, and absent of the constant regions of the heavy and light chains. The variable regions of the heavy and light chains include, for example, the CDRs. For example, an Fv fragment includes all or part of the amino terminal variable region of about 110 amino acids of both the heavy and light chains.

30 The term “Fab fragment” can mean a monovalent antigen-binding fragment of a human monoclonal antibody that is larger than an Fv fragment. For example, a Fab fragment includes the variable regions, and all or part of the first constant domain of the heavy and light chains. Thus, a Fab fragment additionally includes, for example, amino acid
35 residues from about 110 to about 220 of the heavy and light chains.

The term “Fab' fragment” can mean a monovalent antigen-binding fragment of a human monoclonal antibody that is larger than a Fab fragment. For example, a Fab' fragment includes all of the light chain, all of the variable region of the heavy chain, and all or part of the first and second constant domains of the heavy chain. For example, a
5 Fab' fragment can additionally include some or all of amino acid residues 220 to 330 of the heavy chain.

The term “F(ab')₂ fragment” can mean a bivalent antigen-binding fragment of a human monoclonal antibody. An F(ab')₂ fragment includes, for example, all or part of the
10 variable regions of two heavy chains-and two light chains, and can further include all or part of the first constant domains of two heavy chains and two light chains.

The term “single chain Fv (scFv)” can mean a fusion of the variable regions of the heavy (VH) and light chains (VL) connected with a short linker peptide.
15

The term “bispecific antibody (BsAb)” can mean a bispecific antibody comprising two scFv linked to each other by a shorter linked peptide.

One skilled in the art knows that the exact boundaries of a fragment of an antibody are
20 not important, so long as the fragment maintains a functional activity. Using well-known recombinant methods, one skilled in the art can engineer a polynucleotide sequence to express a functional fragment with any endpoints desired for a particular application. A functional fragment of the antibody may comprise or consist of a fragment with substantially the same heavy and light chain variable regions as the
25 human antibody.

The antigen-binding fragment thereof may comprise or consist of any of the fragments selected from a group consisting of VH, VL, Fd, Fv, Fab, Fab', scFv, F(ab')₂ and Fc fragment.
30

The antigen-binding fragment thereof may comprise or consist of any one of the antigen binding region sequences of the VL, any one of the antigen binding region sequences of the VH, or a combination of VL and VH antigen binding regions of a human antibody. The appropriate number and combination of VH and VL antigen
35 binding region sequences may be determined by those skilled in the art depending on the desired affinity and specificity and the intended use of the antigen-binding

fragment. Functional fragments or antigen-binding fragments of antibodies may be readily produced and isolated using methods well known to those skilled in the art. Such methods include, for example, proteolytic methods, recombinant methods and chemical synthesis. Proteolytic methods for the isolation of functional fragments
5 comprise using human antibodies as a starting material. Enzymes suitable for proteolysis of human immunoglobulins may include, for example, papain, and pepsin. The appropriate enzyme may be readily chosen by one skilled in the art, depending on, for example, whether monovalent or bivalent fragments are required. For example, papain cleavage results in two monovalent Fab' fragments that bind antigen and an Fc
10 fragment. Pepsin cleavage, for example, results in a bivalent F (ab') fragment. An F (ab')₂ fragment of the invention may be further reduced using, for example, DTT or 2-mercaptoethanol to produce two monovalent Fab' fragments.

Functional or antigen-binding fragments of antibodies produced by proteolysis may be
15 purified by affinity and column chromatographic procedures. For example, undigested antibodies and Fc fragments may be removed by binding to protein A. Additionally, functional fragments may be purified by virtue of their charge and size, using, for example, ion exchange and gel filtration chromatography. Such methods are well known to those skilled in the art.

20 The antibody or antigen-binding fragment thereof may be produced using techniques well known in the art. For example, by recombinant methodology (see US Pat. No. 4,816,567), hybridoma technology (Kohler et. al., *Nature*, **1975**, 256, 495), phage display technologies (for example, see Clackson et. al., *Nature*, **1991**, 352, 624 and
25 Marks et. al., *J. Mol. Biol.*, **1991**, 222, 581), synthetic technologies or combinations of such technologies. Preferably, one initially isolates a polynucleotide encoding desired regions of the antibody heavy and light chains. Such regions may include, for example, all or part of the variable region of the heavy and light chains. Preferably, such regions can particularly include the antigen binding regions of the heavy and light chains,
30 preferably the antigen binding sites, most preferably the CDRs.

The polynucleotide encoding the antibody or antigen-binding fragment thereof according to the invention may be produced using methods known to those skilled in the art. The polynucleotide encoding the antibody or antigen-binding fragment thereof
35 may be directly synthesized by methods of oligonucleotide synthesis known in the art. Alternatively, smaller fragments may be synthesized and joined to form a larger

functional fragment using recombinant methods known in the art. Antibodies of use may be commercially obtained from a wide variety of known sources e.g. the American Type Culture Collection (ATCC, Manassas, Va.). A large number of antibodies against a wide variety of disease targets and tumor-associated antigens have been deposited at the ATCC and/or have published variable region sequences and are available for use in the claimed methods and compositions.

Cysteine-engineered antibodies have been designed as Fab antibody fragments (ThioFab) and expressed as full-length IgG monoclonal (thioMab) antibodies (US. Pat. 7,521,541). ThioFab and ThioMab antibodies have been conjugated through linkers at the newly introduced cysteine thiols to prepare site-specific antibody-drug conjugates (US. Pat. 7521541, US2008/0050310, WO2008/052187).

Polytherics have described a method for bridging a pair of sulfhydryl groups contained in antibody proteins derived from reduction of a native disulfide hinge (Badescu *et. al.*, *Bioconjugate Chem.*, **2014**, 25, 1124-1136) to synthesise homogenous drug-loaded ADCs. Similar methods have been described by Concortis (US Patent 0105540, April 26 2015), Thiologics (Schumacher *et. al.*, *Org Biomol. Chem.*, **2014**, 12, 7261-7269) and Igenica (Behrens *et. al.*, *Mol. Pharm.*, **2015**, 12, 3986-3998). Related methods have been described in Frigerio *et. al.*, *Curr. Top. Med. Chem.*, **2018**, 18, 1-32.

Other recent methods that have been used to target homogeneous drug-loaded ADCs include the incorporation of unnatural amino acids such as selenocysteine (Hofer, T. *et. al.*, *Biochem.*, **2009**, 48, 12047-12057) or formyl glycine (Drake, P.M. *et. al.*, *Bioconj. Chem.*, **2014**, 25, 1331-1341) groups into antibodies. Glycoengineering has been used to introduce sialic acid residues at specific sites (Zhou, Q. *et. al.*, *Bioconj. Chem.*, **2014**, 25, 510-520) and transglutaminases used to enzymatically conjugate primary amine-containing linker/payloads to glutamine residues (Dorywalska, M. *et. al.*, *Bioconj. Chem.*, **2015**, 26, 650-659). These, and other, methods are described in Sochaj, A.M. *et. al.*, *Biotech. Adv.*, **2015**, 33, 775-784.

As used herein, the term “immunospecificity” can mean the binding region is capable of immunoreacting with the target antigen, or a variant or fragment thereof, by specifically binding therewith. The antibody or antigen-binding fragment thereof can selectively interact with an antigen with an affinity constant of approximately 10^{-5} to 10^{-13} M⁻¹, preferably 10^{-6} to 10^{-9} M⁻¹, even more preferably, 10^{-10} to 10^{-12} M⁻¹.

The term “immunoreact” can mean the binding region is capable of eliciting an immune response upon binding with the target antigen, or an epitope thereof.

- 5 The term “epitope” can mean any region of an antigen with the ability to elicit, and combine with, a binding region of the antibody or antigen-binding fragment thereof.

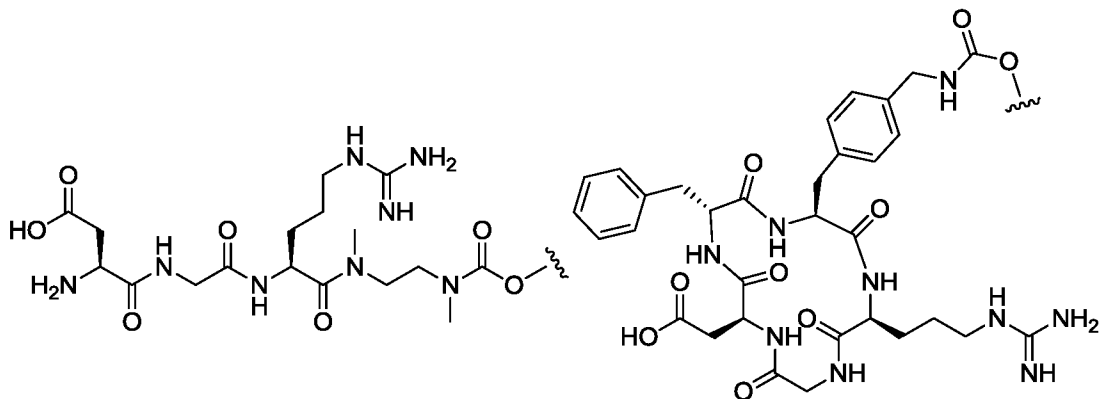
In one embodiment, T comprises a nucleic acid based molecule. The nucleic acid based molecule may be an aptamer. The nucleic acid based molecule may target the
10 CD33/CD34 antigen as described in Zaimy, M.A. et. al., *Cancer Gene Ther.*, **2016**, 23, 315-320 or PSMA tumor antigens such as A9, A10 and A9L described by Lupold, S.E. et. al., *Cancer Res.*, **2002**, 62, 4029-4033; Dassie, J.P. et. al., *Nat. Biotech.*, **2009**, 27, 839-849; Rockey, W.M. et. al., *Nucleic Acid Ther.*, **2011**, 21, 299-314, or any other tumor antigen known to those skilled in the art, for example as described in Orava, E.,
15 *Biochem. Biophys. Acta*, **2010**, 1798, 2190-2200.

Aptamers are nucleic acid or peptide molecules that assume a specific, sequence-dependent shape and bind to specific target ligands based on a lock-and-key fit between the aptamer and ligand. Typically, aptamers may comprise either single-
20 or double-stranded DNA molecules (ssDNA or dsDNA) or single-stranded RNA molecules (ssRNA). Peptide aptamers consist of a short variable peptide domain, attached at both ends to a protein scaffold. Aptamers may be used to bind both nucleic acid and non-nucleic acid targets.

25 Suitable aptamers may be selected from random sequence pools, from which specific aptamers may be identified which bind to the selected antigen with high affinity. Methods for the production and selection of aptamers having desired specificity are well known to those skilled in the art, and include the SELEX (systematic evolution of ligands by exponential enrichment) process. Briefly, large
30 libraries of oligonucleotides are produced, allowing the isolation of large amounts of functional nucleic acids by an iterative process of *in vitro* selection and subsequent amplification through polymerase chain reaction. Preferred methodologies for producing aptamers include those disclosed in WO 2004/042083.

35

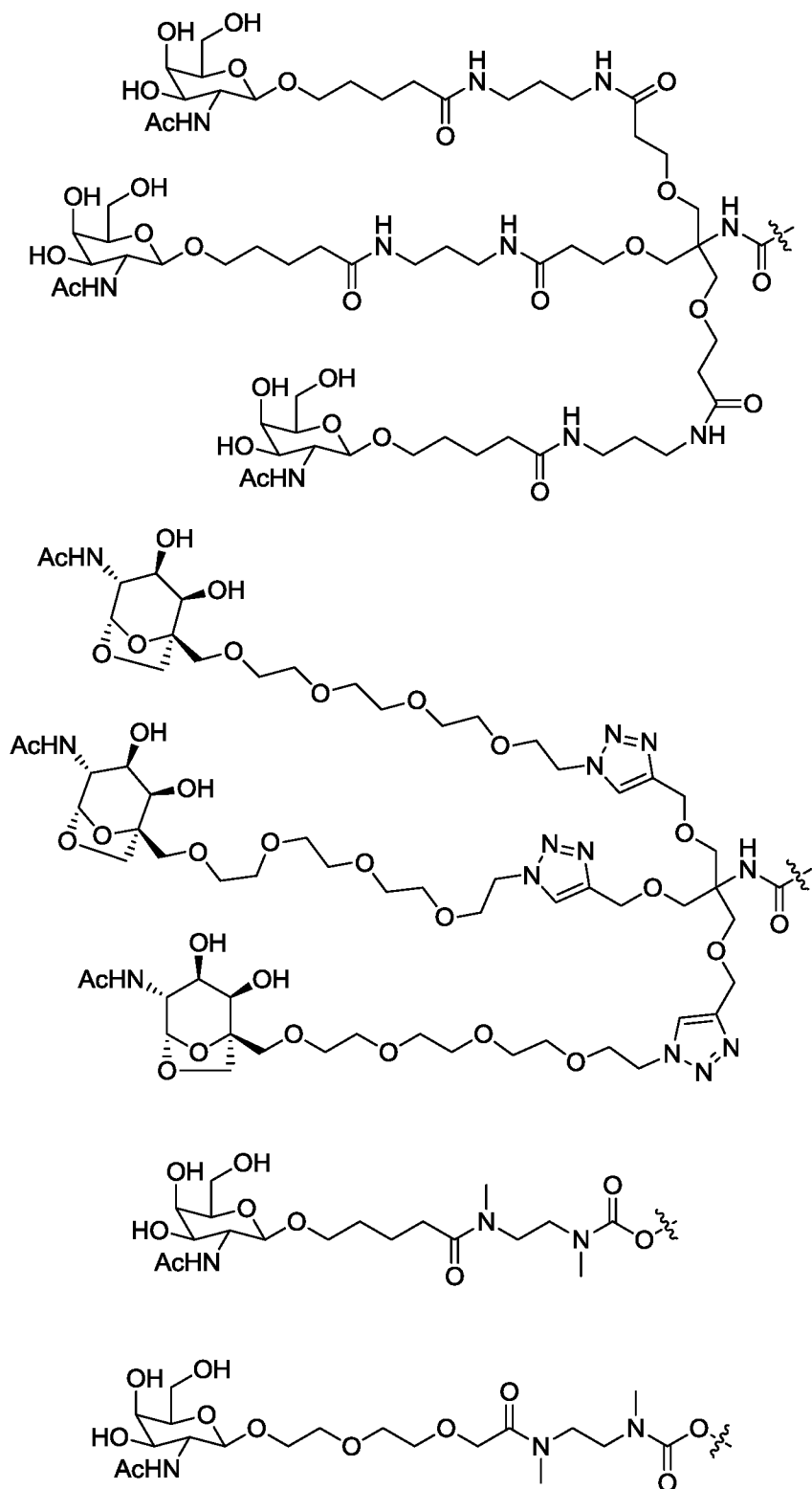
In an alternative embodiment, T comprises a peptide or a modified peptide. The peptide or modified peptide may comprise the RGD sequence motif, as described in Mousavizadeh, A., *Colloids Surfaces B.*, **2017**, 158, 507-517 to include linear RGD peptide sequences or cyclised versions thereof as described in Belvisi, L et. al., *Curr. Top., Med Chem.*, **2016**, 16, 314-329. Exemplary embodiments of an RGD ligand which the targeting moiety may target and bind are as follows:

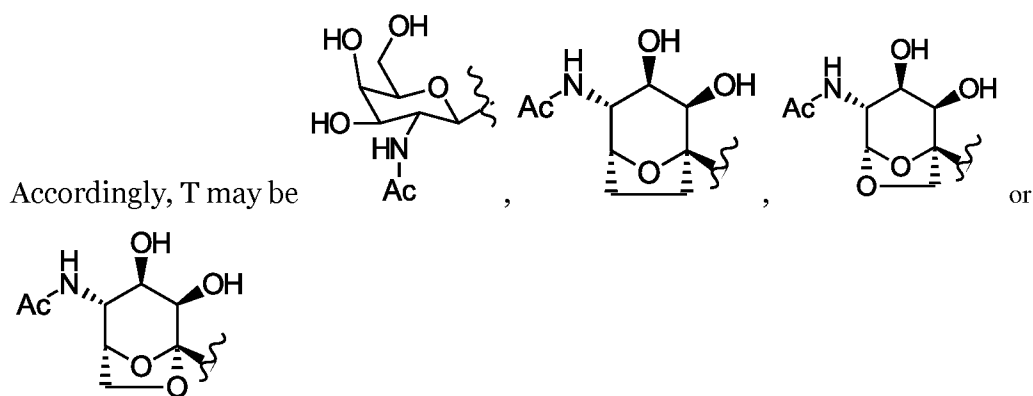


The peptide or modified peptide may comprise transferrin, or modified versions of transferrin, which has been described as showing promise for the targeted delivery of xenobiotics (Kratz *et. al.*, *Cancer Chemother. Pharmacol.*, **1998**, 41, 155-160), including crossing the blood-brain barrier (Fishman *et. al.*, *J. Cell Biol.*, **1987**, 101, 423-427). The peptide or modified peptide may also comprise albumin, or modified versions of albumin, in which the albumin protein may be conjugated to a suitable linker via Cys34 or other suitable residue as described in Larsen *et. al.*, *Mol Cell Ther.*, **2016**, 4, 3.

In an alternative embodiment, T comprises a carbohydrate or a modified carbohydrate molecule which can target a tumour-associated carbohydrate antigen receptor on target tumours and cells. For example, glycosphingolipids, gangliosides, sialic acids and mucins are indicative of malignant transformation and an aberrant glycosylation pattern on cancer cells (as reviewed in Feng, D. *et. al.*, *ACS Chem. Biol.* **2016**, 11, 850-863; Hakomori, S., *Ann. Rev. Immunol.*, **1984**, 2, 103-126; Dube, D.H. and Bertozzi, C.R., *Nat. Rev. Drug Disc.*, **2005**, 4, 477-488) and targeting ligands based on carbohydrate molecules have been designed against them, for example mannose, galactose or cerebroside derivatives. In a related method, cell-surface receptors on tissues of interest may also be targeted; a recent example includes derivatives of N-acetyl-galactosamine (GalNAc) which have been developed to target the asialoglycoprotein receptor on hepatocytes (reviewed in D'Souza, A. *et. al.*, *J. Controlled Rel.*, **2015**, 203, 126-139 and a recent example in Sanhueza, C.A. *et. al.*,

JACS, **2017**, *139*, 3528-3536). Exemplary embodiments of carbohydrates which may be used as the targeting moiety are as follows:

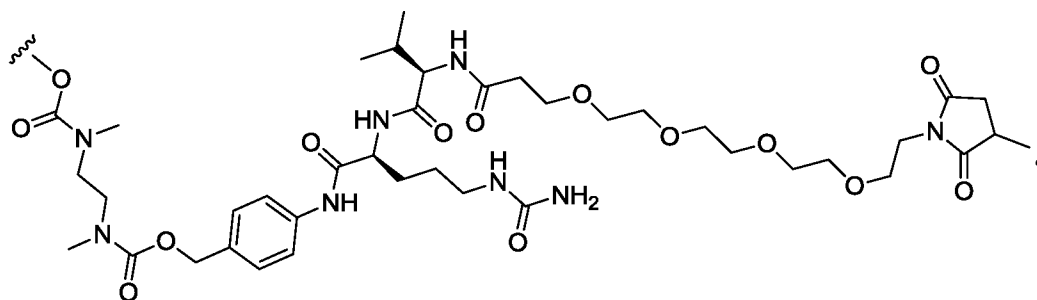


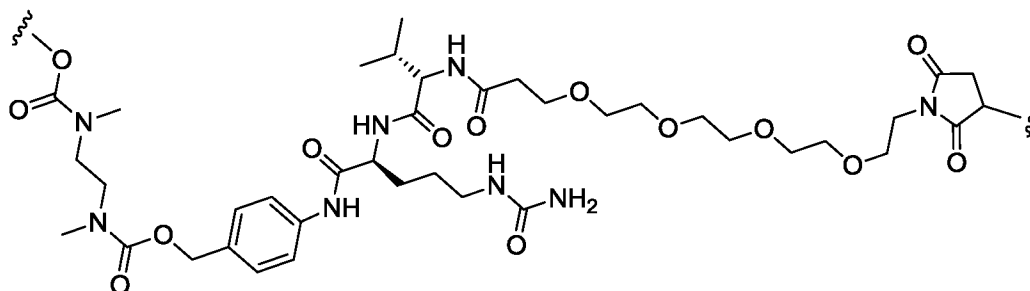
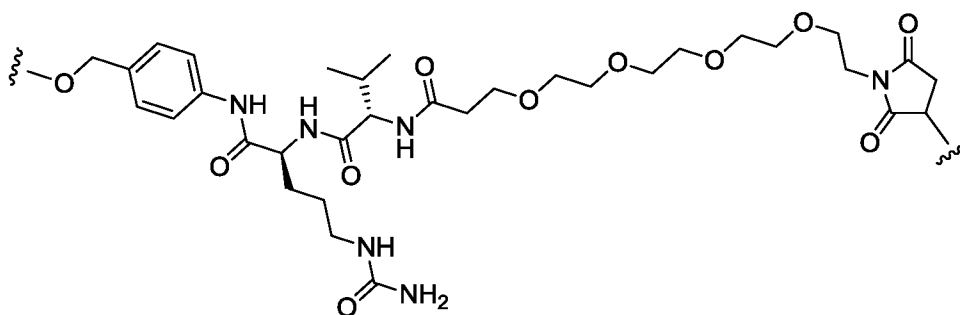
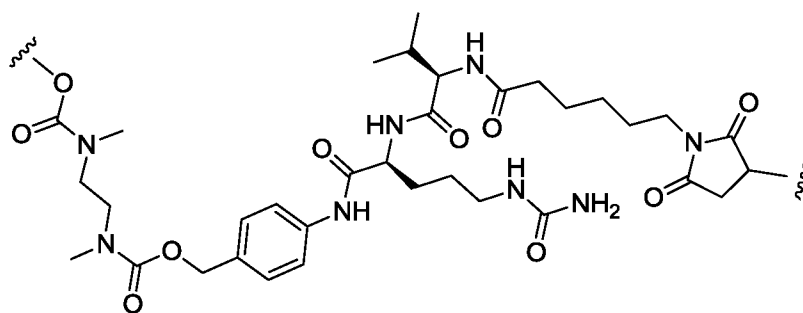


In another embodiment, T comprises a small molecule ligand with affinity for a cell or
 5 tumour-surface receptor. For example, folic acid or derivatives thereof may be used to
 target folate receptors α , β or γ (FR α , FR β and FR γ). FR α in particular is known to be
 expressed in multiple endothelial tumour types such as breast, lung and kidney (see
 Fernandez, M. *et. al.*, **2018**, 4, 790-810 for a recent review) and conjugates of folate
 derivatives and toxins have been described previously (Vlahov, I. and Leamon, C.P.,
 10 *Bioconjugate Chem.*, **2012**, 23, 1357-1369).

Linkers may be joined to a compound of formula (I) through a C atom, an O atom, a N
 atom or a S atom.

15 Linkers may be cleavable, non-cleavable, hydrophilic or hydrophobic. A cleavable linker
 can be sensitive to enzymes and may be cleaved by enzymes such as proteases. For
 example, a cleavable linker can be a valine-citrulline linker or a valine-alanine linker.
 For example:





5

A non-cleavable linker may be protease insensitive.

The inventors have found that compounds of the current invention may be functionalised in various locations with a variety of linkers and spacers to provide conjugate molecules. Said linkers may include self-immolating groups (for example a p-aminobenzyl ether or amine and/or a valine-citrulline unit) that are designed to release the parent ACSS2 inhibitor upon a hydrolytic event, for example following amide, peptide or carbamate hydrolysis.

The term 'ACSS2' refers to acetyl coenzyme A synthetase short chain 2, and ATP-dependent enzyme that catalyses the synthesis of acetyl coenzyme A from acetate. ACSS2 is responsible for acetate incorporation in cells, including the uptake of acetate into lipids and histones.

It will be appreciated that an ‘antagonist’, or ‘inhibitor’ as it relates to a ligand and ACSS2, comprises a molecule, combination of molecules, or a complex, that inhibits, counteracts, downregulates, and/or desensitizes ACSS2 activity. ‘Antagonist’ encompasses any reagent that inhibits a constitutive activity of ACSS2. A constitutive activity is one that is manifest in the absence of a ligand/ACSS2 interaction. ‘Antagonist’ also encompasses any reagent that inhibits or prevents a stimulated (or regulated) activity of ACSS2.

Preferably, the compound of formula (I) or the conjugate of formula (II) is an inhibitor of the ACSS2 protein.

It will be appreciated that the compounds described herein or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof may be used in a medicament which may be used in a monotherapy (i.e. use of the compound alone), for modulating the ACSS2 protein and/or treating, ameliorating or preventing a disease.

Alternatively, the compounds or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof may be used as an adjunct to, or in combination with, known therapies for modulating the ACSS2 protein and/or treating, ameliorating or preventing a disease.

Accordingly, in one aspect, a second therapeutic agent may be administered with a compound of Formula (I) or a conjugate of formula (II). The compound of Formula (I) or the conjugate of formula (II) may be administered before, after, and/or together with the second therapeutic agent. The second therapeutic agent may comprise an antiviral agent, an anti-inflammation agent, conventional chemotherapy, an anti-cancer vaccine and/or hormonal therapy. Alternatively, or additionally, the second therapeutic agent may comprise a B7 costimulatory molecule, interleukin-2, interferon- γ , GM-CSF, a CTLA-4 antagonist (such as Ipilimumab and tremilimumab), an IDO inhibitor or IDO/TDO inhibitor (such as Epacadostat and GDC-0919), a PD-1 inhibitor (such as Nivolumab, Pembrolizumab, Pidilizumab, AMP-224, and MDX-1106), a PD-L1 inhibitor (such as Durvalumab, Avelumab and Atezolizumab), an OX-40 ligand, a LAG3 inhibitor, a CD40 ligand, a 41BB/CD137 ligand, a CD27 ligand, Bacille Calmette-Guerin (BCG), liposomes, alum, Freund’s complete or incomplete adjuvant, a TLR agonist (such as Poly I:C, MPL, LPS, bacterial flagellin, imiquimod, resiquimod, loxoribine and a CpG dinucleotide) and/or detoxified endotoxins.

Methods for co-administration with an additional therapeutic agent are well known in the art (Hardman et. al. (eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed., **2001**, McGraw-Hill New York, NY; Poole and Peterson (eds.), Pharmacotherapeutics for Advanced Practice: A Practical Approach, **2001**, Lippincott, Williams and Wilkins, Philadelphia, PA; Chabner and Longo (eds.), Cancer Chemotherapy and Biotherapy, **2001**, Lippincott, Williams and Wilkins, Philadelphia, PA).

In one aspect, the disease is cancer and a chemotherapeutic agent may be administered with a compound of Formula (I) or a conjugate of formula (II). The chemotherapeutic agent may be selected from a group further consisting of a cancer vaccine, a targeted drug, a targeted antibody, an antibody fragment, an antimetabolite, an antineoplastic, an antifolate, a toxin, an alkylating agent, a DNA strand breaking agent, a DNA minor groove binding agent, a pyrimidine analogue, a ribonucleotide reductase inhibitor, a tubulin interactive agent, an anti-hormonal agent, an immunomodulator, an anti-adrenal agent, a cytokine, radiation therapy, a cell therapy, cell depletion therapy such as B-cell depletion therapy and a hormone therapy. Alternatively or additionally, the chemotherapeutic agent may comprise abiraterone, altretamine, anhydrovinblastine, auristatin, bexarotene, bicalutamide, bleomycin, cachectin, cemadotin, chlorambucil, cyclophosphamide, docetaxol, doxetaxel, carboplatin, cisplatin, cytarabine, dactinomycin, daunorubicin, decitabine, doxorubicin, etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea, streptozocin, mitomycin, methotrexate, taxanes, tamoxifen, vinblastine, vincristine and/or vindesine.

The compound of Formula (I) or the conjugate of formula (II) may be combined in compositions having a number of different forms depending, in particular, on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micellar solution, transdermal patch, liposome suspension or any other suitable form that may be administered to a person or animal in need of treatment. It will be appreciated that the vehicle of medicaments according to the invention should be one which is well-tolerated by the subject to whom it is given.

Medicaments comprising the compounds described herein may be used in a number of ways. Suitable modes of administration include oral, intra-tumoral, parenteral, topical, inhaled/intranasal, rectal/intravaginal, and ocular/aural administration.

Formulations suitable for the aforementioned modes of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

5

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include
10 solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays, liquid formulations and buccal/mucoadhesive patches.

15 Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of
20 a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in *Expert Opinion in Therapeutic Patents*, 11 (6), 981-986, by Liang and Chen (2001).

25

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose,
30 calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

35

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as
5 lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl
10 sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with
15 sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

20 Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-
25 granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

30 Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in "Pharmaceutical Technology On-line", 25(2), 1-14, by Verma et al (2001). The use of chewing gum to
35 achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) and conjugates of formula (II) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(dl-lactic-co-glycolic)acid (PLGA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

5 The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser
10 using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

15 The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

20 Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure
25 homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or
30 starch and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

35 A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention

per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I) or the conjugate of formula (II), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

5

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

10 In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or “puff” containing from 1µg to 100mg of the compound of formula (I) or the conjugate of formula (II). The overall daily dose will typically be in the range 1µg to 200mg which may be
15 administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, microbicide, vaginal ring or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as
20 appropriate.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration
25 include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a
30 heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

The compounds of the invention may also be administered directly to a site of interest
35 by injection of a solution or suspension containing the active drug substance. The site of interest may be a tumour and the compound may be administered via intratumoral

injection. Typical injection solutions are comprised of propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

- 5 The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

10

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most
15 commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

It will be appreciated that the amount of the compound that is required is determined
20 by its biological activity and bioavailability, which in turn depends on the mode of administration, the physiochemical properties of the compound, and whether it is being used as a monotherapy, or in a combined therapy. The frequency of administration will also be influenced by the half-life of the compound within the subject being treated. Optimal dosages to be administered may be determined by those skilled in the art, and
25 will vary with the particular compound in use, the strength of the pharmaceutical composition, the mode of administration, and the advancement of the disease. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

30

Generally, for administration to a human, the total daily dose of the compounds of the invention is typically in the range 100µg to 10g, such as 1mg to 1g, for example 10mg to 500mg. For example, oral administration may require a total daily dose of from 25mg to 250mg. The total daily dose may be administered in single or divided doses and may,
35 at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg.

The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

5 The compound may be administered before, during or after onset of the disease to be treated.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. *in vivo* experimentation, clinical trials, etc.), may be used to form specific formulations comprising the compounds according to the invention and precise
10 therapeutic regimes (such as daily doses of the compounds and the frequency of administration). The inventors believe that they are the first to describe a pharmaceutical composition for treating a disease, based on the use of the compounds of the invention.

15 Hence, in a eighth aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate according to the second aspect, and a pharmaceutically acceptable vehicle.

20 The invention also provides, in a ninth aspect, a process for making the composition according to the eighth aspect, the process comprising contacting a therapeutically effective amount of a compound of the first aspect, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate according to
25 the second aspect, and a pharmaceutically acceptable vehicle.

A “subject” may be a vertebrate, mammal, or domestic animal. Hence, compounds, compositions and medicaments according to the invention may be used to treat any mammal, for example livestock (e.g. a horse), pets, or may be used in other veterinary
30 applications. Most preferably, however, the subject is a human being.

A “therapeutically effective amount” of compound is any amount which, when administered to a subject, is the amount of drug that is needed to treat the target disease, or produce the desired effect, i.e. inhibit the ACSS2 protein.

35

For example, the therapeutically effective amount of compound used may be from about 0.01 mg to about 800 mg, and preferably from about 0.01 mg to about 500 mg. It is preferred that the amount of compound is an amount from about 0.1 mg to about 250 mg, and most preferably from about 0.1 mg to about 20 mg.

5

A “pharmaceutically acceptable vehicle” as referred to herein, is any known compound or combination of known compounds that are known to those skilled in the art to be useful in formulating pharmaceutical compositions.

10 In one embodiment, the pharmaceutically acceptable vehicle may be a solid, and the composition may be in the form of a powder or tablet. A solid pharmaceutically acceptable vehicle may include one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, dyes, fillers, glidants, compression aids, inert binders, sweeteners, preservatives, dyes, coatings, or tablet-
15 disintegrating agents. The vehicle may also be an encapsulating material. In powders, the vehicle is a finely divided solid that is in admixture with the finely divided active agents (i.e. the compound according to the first, second and third aspects) according to the invention. In tablets, the active compound may be mixed with a vehicle having the necessary compression properties in suitable proportions and compacted in the shape
20 and size desired. The powders and tablets preferably contain up to 99% of the active compound. Suitable solid vehicles include, for example calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins. In another embodiment, the pharmaceutical vehicle may be a gel and the composition may be in the form of a cream
25 or the like.

However, the pharmaceutical vehicle may be a liquid, and the pharmaceutical composition is in the form of a solution. Liquid vehicles are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The compound
30 according to the invention may be dissolved or suspended in a pharmaceutically acceptable liquid vehicle such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid vehicle can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity
35 regulators, stabilizers or osmo-regulators. Suitable examples of liquid vehicles for oral and parenteral administration include water (partially containing additives as above,

e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the vehicle can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid vehicles are useful in sterile liquid form compositions for parenteral administration. The liquid vehicle for pressurized compositions can be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intrathecal, epidural, intraperitoneal, intravenous and particularly subcutaneous injection. The compound may be prepared as a sterile solid composition that may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium.

The compound and compositions of the invention may be administered in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like. The compounds used according to the invention can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

It will be known to those skilled in the art that active drug ingredients may be converted into a prodrug, which is a metabolically labile derivative that is converted within the body into the active drug substance. Also included within the scope of the invention are prodrugs which are compounds of formula (I) which contain metabolically or hydrolytically labile moieties which in vivo are converted into the active drug of formula (I). The processes by which the prodrug is converted into the active drug substance include, but are not limited to, ester or carbonate or carbamate hydrolysis, phosphate ester hydrolysis, S-oxidation, N-oxidation, dealkylation and metabolic oxidation as described in Beaumont et. al., *Curr. Drug Metab.*, **2003**, 4, 461-485 and Huttenen et. al., *Pharmacol. Revs.*, **2011**, 63, 750-771. Such prodrug derivatives may offer improved

solubility, stability or permeability compared to the parent drug substance, or may better allow the drug substance to be administered by an alternative route of administration, for example as an intravenous solution.

- 5 Also included within the scope of the invention are soft drugs or antedugs which are compounds of formula (I) which contain metabolically or hydrolytically labile moieties which *in vivo* are converted into inactive derivatives. The processes by which the active drug substance is converted into an inactive derivative include, but are not limited to, ester hydrolysis, *S*-oxidation, *N*-oxidation, dealkylation and metabolic oxidation as
10 described for example in Pearce et al., *Drug Metab. Dispos.*, **2006**, 34, 1035-1040 and B. Testa, Prodrug and Soft Drug Design, in *Comprehensive Medicinal Chemistry II*, Volume 5, Elsevier, Oxford, 2007, pp. 1009-1041 and Bodor, N. *Chem. Tech.* **1984**, 14, 28-38.
- 15 The scope of the invention includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.
- 20 Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .
- 25 Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with isotopes such as deuterium, i.e. ^2H , may afford
30 certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

35

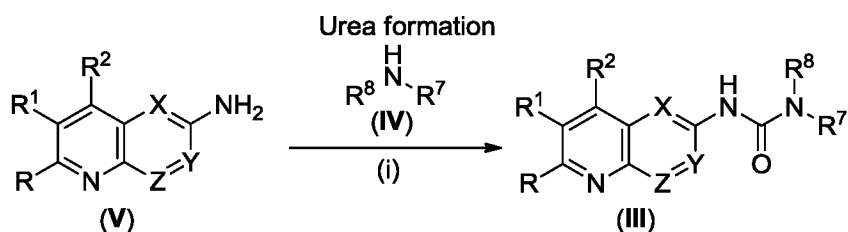
Isotopically-labelled compounds of formula (I) or conjugates of formula (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

All features described herein (including any accompanying claims, drawings and abstract), and/or all of the steps of any method or process so disclosed, may be combined with any of the above aspects in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

General Schemes

General Scheme 1:

Compounds of formula (III) may be prepared from compounds of formula (IV) and (V) using a urea bond forming reaction, as shown below.

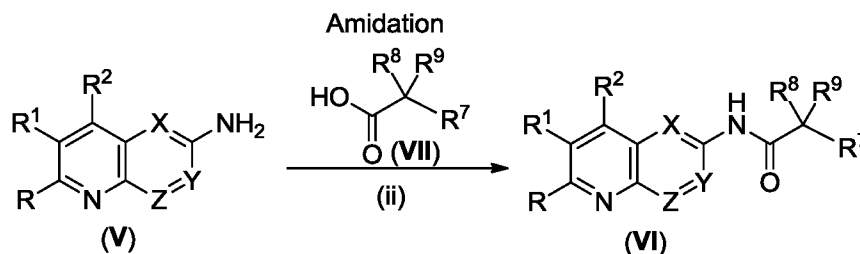


Typical reaction conditions for the activation of the aromatic amine of the compound of formula (V) employ 4-nitrophenyl chloroformate to generate an intermediate which can be attacked by a suitable nucleophile such as amine (IV) to give a urea as a compound of formula (III). Preferred organic bases include DIPEA or TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature.

Compounds of formula (IV) and (V) are commercially available or may be synthesized by those skilled in the art. In particular, methods of synthesizing compounds of formula (V) are described in General Schemes 3 to 10.

General Scheme 2:

Compounds of formula (VI) may be prepared from compounds of formula (V) and (VII) using an amide bond forming reaction, as shown below.

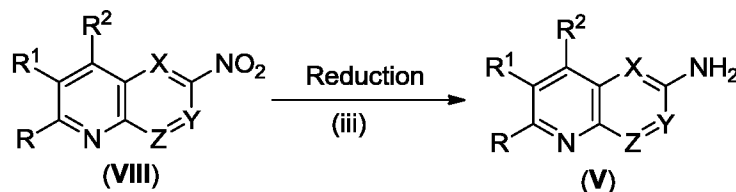


Typical conditions employ activation of the carboxylic acid of the compound of formula (VII) using a suitable organic base and a suitable coupling agent. Preferred coupling agents are either EDCI with HOBt, T₃P, HATU, HBTU or BOP. Preferred organic bases include DIPEA or TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature.

Compounds of formula (V) and (VII) are commercially available or may be synthesized by those skilled in the art. In particular, methods of synthesizing compounds of formula (V) or derivatives thereof, are described in General Schemes 3-10.

General Scheme 3:

Compounds of formula (V) may be prepared from nitro compounds of formula (VIII) by simple reduction.

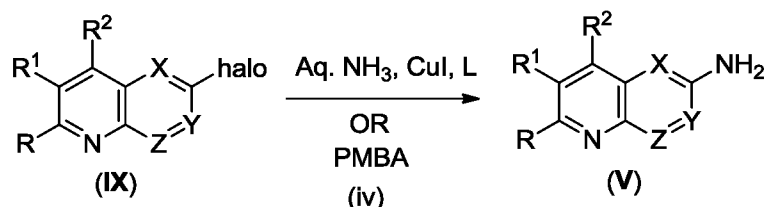


Typical reduction conditions may include Pd catalyzed or Ra-Ni catalyzed hydrogenation methods, or reduction in the presence of a transition metal reagent, for example Fe-AcOH, Zn-AcOH or SnCl₂-H₂O-HCl in a suitable solvent such as methanol or ethanol.

Compounds of formula (VIII) are commercially available or may be synthesized by those skilled in the art. In particular, methods of synthesizing compounds of formula (VIII) are described in General Schemes 6, 7, 9 and 11-14 shown below.

General Scheme 4:

Compounds of formula (V) may be prepared from haloaromatic compounds of formula (IX) by a direct ammonolysis reaction.

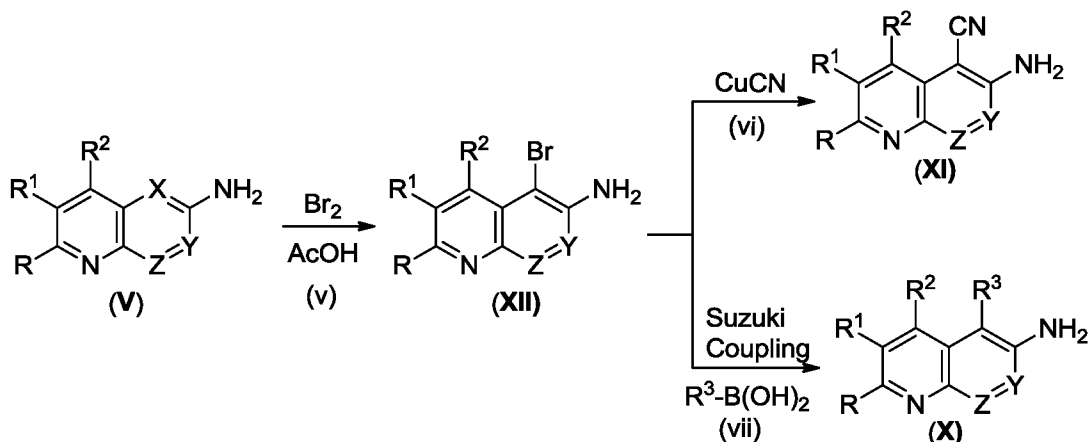


Typical amination conditions use liquid or aqueous solutions of ammonia in the presence of a suitable catalyst, typically CuI in the presence of a suitable activating ligand such as dimethylethylenediamine (DMEDA), amino acids such as proline, pyridine-based ligands such as phenanthroline, diols and diketones. Alternatively, the halide may be aminated with para-methoxybenzylamine and then deprotected using methods known to those skilled in the art, for example using TFA, ceric ammonium nitrate or a Pd-catalyzed hydrogenation reaction.

- Compounds of formula (IX) are commercially available or may be synthesized by those skilled in the art. In particular, methods of synthesizing compounds of formula (IX) are described in General Schemes 8 and 10 shown below.

General Scheme 5:

- The amines of formula (V) may be further functionalized at the X position according to the below scheme.



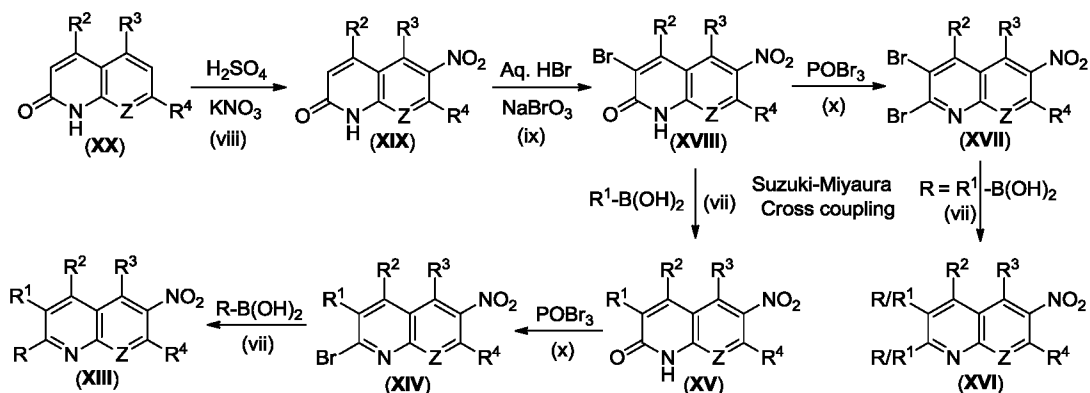
- Compounds of formula (V) may be halogenated, for example brominated using bromine in AcOH to provide the bromides of formula (XII). Said bromides may then be reacted with a suitable cyano source such as CuCN or Zn(CN)₂ in a suitable polar solvent such as DMF, DMA, NMP or pyridine, optionally in the presence of a catalyst such as tetrakis(triphenylphosphine) palladium(0) usually at reflux temperature to give the nitriles of formula (XI). Alternatively, the bromides of formula (XII) may undergo a Suzuki reaction with a suitable boronic acid R³-B(OH)₂ or boronate ester in the

presence of a transition metal catalyst, typically Pd for example Pd(OAc)₂, Pd₂dba₃ or Pd(dppf)Cl₂, a suitable base such as KO^tBu, K₃PO₄, K₂CO₃, Cs₂CO₃ or Na₂CO₃ and a suitable solvent system such as THF-water, ethanol-water, DMF, dioxane or toluene. Reactions are typically heated to give the R³ functionalized amines (X).

5

General Scheme 6:

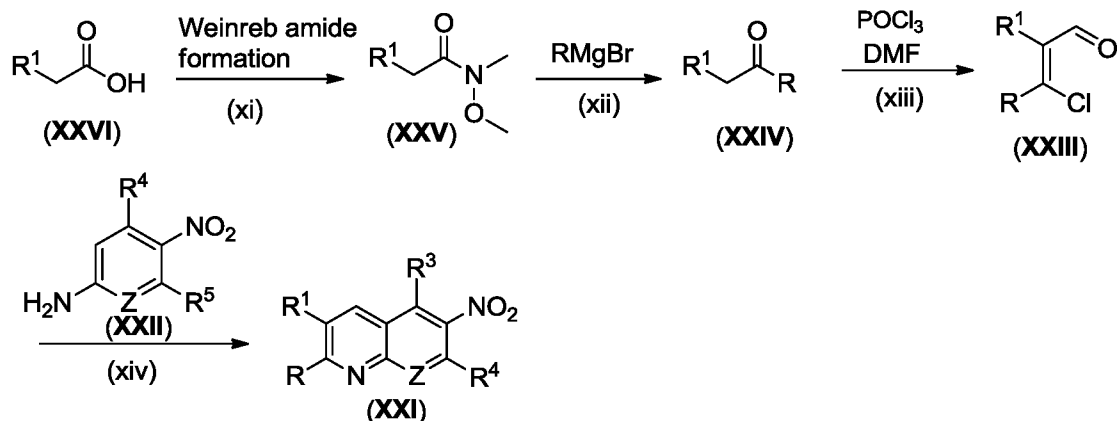
Nitro compounds of formula (XIII) may be synthesized starting from benzopyridones of formula (XX).



- 10 Benzopyridones of formula (XX) may undergo a nitration reaction, for example in mixtures of sulfuric acid and fuming nitric acid, typically at room temperature to give nitro compounds of formula (XIX). These nitro compounds may then be halogenated, for example brominated with sodium bromate and a strong acid such as aqueous HBr under heating to provide bromo derivatives of formula (XVIII). Treatment of a
- 15 compound of formula (XVIII) with POBr₃ converts a pyridine into the corresponding bromopyridine to give dibromo compounds of formula (XVII). Compounds of formula (XVII) may then undergo a Suzuki reaction as described in General Scheme 5 with boronates or boronic acids R¹-B(OH)₂ and/or R-B(OH)₂ to provide a quinoline of formula (XVI). Alternatively, the bromopyridones of formula (XVIII) may also be
- 20 reacted in a Suzuki reaction with boronates or a boronic acid of formula R¹-B(OH)₂ to provide the functionalized pyridine of formula (XV) which may then be further brominated to a bromopyridine (XIV) and subjected to a Suzuki reaction with a boronate or boronic acid R-B(OH)₂ to provide a quinoline of formula (XIII).
- 25 Compounds of formula (XX) are commercially available or may be synthesized by those skilled in the art.

General Scheme 7:

Nitro-quinolines may also be built up according to the below scheme, starting from a nitro aniline of formula (XXII) and an acetic acid derivative of formula (XXVI).

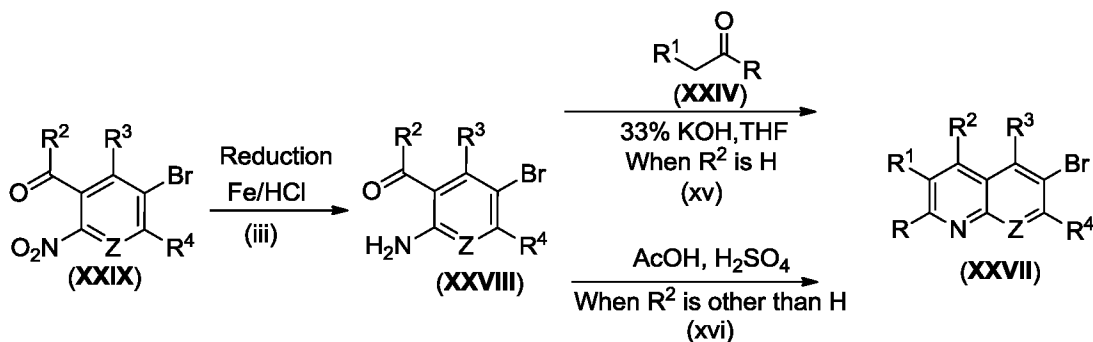


- 5 An acid of formula (XXVI) may be converted into a Weinreb amide of formula (XXV) with, for example, N,O-diMe-hydroxylamine using a suitable organic base and a suitable coupling agent. Preferred coupling agents are either EDCI with HOBT, T₃P, HATU, HBTU or BOP. Preferred organic bases include DIPEA or TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature. The Weinreb amides may then be reacted with a suitable nucleophilic species, typically a Grignard or organolithium reagent in a suitable solvent such as THF or diethyl ether, to give a ketone of formula (XXIV). Treatment of a ketone of formula (XXIV) with POCl₃ in a suitable solvent such as DMF or DCM provides vinylogous aldehydes of formula (XXIII), which when combined with aniline of formula (XXII) in a suitable solvent such as DMF, DMA or DMSO can provide a functionalized quinoline of formula (XXI).

Compounds of formula (XXVI) and (XXII) are commercially available or may be synthesized by those skilled in the art.

General Scheme 8:

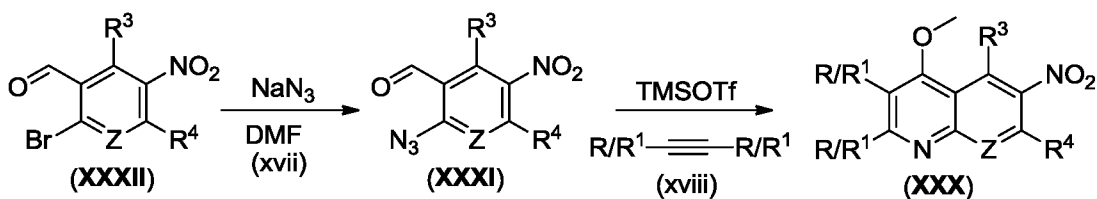
Bromoquinolines of formula (XXVII) may be prepared starting from a nitro carbonyl compound of formula (XXIX), for example a ketone or an aldehyde.



The nitro carbonyl compound of formula (XXIX) may be subjected to a reduction of the nitro group, for example using a transition metal catalyst such as Fe in a suitable acid, for example HCl. Alternative reduction methods include any of those described in General Scheme 3. The product of the reduction is an aniline compound of formula (XXVIII) which may be condensed in a Friedlander quinoline synthesis with a ketone of formula (XXIV) using either a strong base such as KOH or NaOH in a suitable solvent such as THF, dioxane or ethanol, or alternatively using a strong acid such as sulfuric acid or para-toluene sulfonic acid in a suitable solvent such as AcOH depending on the nature of the group R². The product of the condensation reaction is a quinoline of formula (XXVII).

General Scheme 9:

An alternative synthesis of a nitro-quinoline of formula (XXX) starts from a bromo-nitro benzaldehyde of formula (XXXII). The halide may be displaced using a nitrogen nucleophile such as NaN₃ or KN₃ in a suitable solvent such as DMF, DMA or NMP typically at elevated temperature to give an azide compound of formula (XXXI).

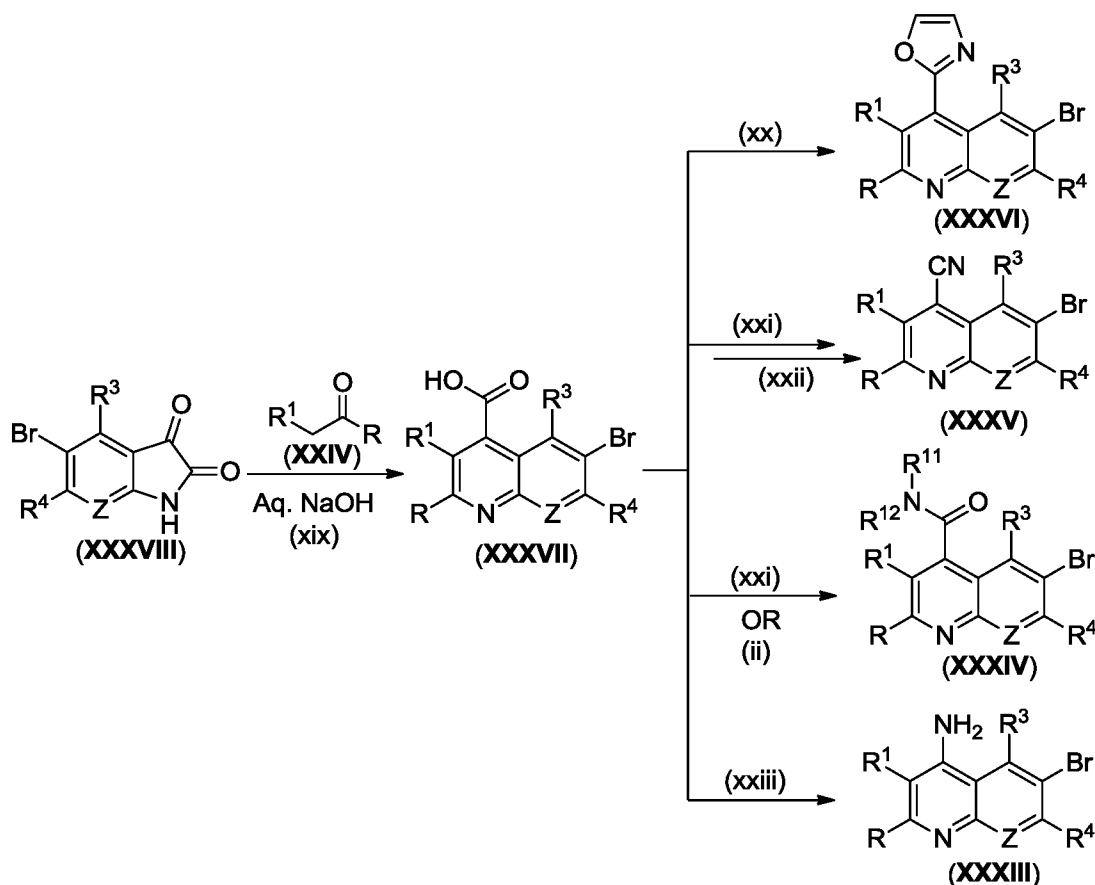


The azide compound of formula (XXXI) may then undergo reaction with an alkyne and suitable reagent such as TMSOTf or AgNTf₂ in a suitable solvent such as MeOH to give a functionalized quinoline compound of formula (XXX).

General Scheme 10:

A flexible method of making halo-quinolines is shown in the below scheme, starting from an oxindole of formula (XXXVIII). An oxindole compound of formula (XXXVIII) may be reacted with a ketone of formula (XXIV) in the presence of a

strong base such as NaOH or KOH, typically with heating or under reflux conditions to provide the key intermediate bromo-quinoline carboxylic acid of formula (XXXVII).



The acid function of (XXXVII) may then be elaborated into several different functional groups at the R² position according to the above scheme. For example, the acid of formula (XXXVII) may be converted into an α-acylaminocarbonyl compound which can then undergo a cyclodehydration reaction to form an oxazole compound of formula (XXXVI). Typically, this transformation will involve activation of the carboxylic acid followed by treating with an aminocarbonyl reagent such as 2-aminoacetaldehyde or a derivative thereof. Preferred activating agents include DCC, CDI, T₃P, HATU, HBTU or treatment of the acid with oxalyl chloride and a catalytic amount of DMF. Preferred organic bases include DIPEA or TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature. Subsequently, the intermediate α-acylaminocarbonyl compound is then treated with a strong acid such as H₂SO₄ to provide the oxazoles of formula (XXXVI).

Alternatively, an acid of formula (XXXVII) may be converted to a nitrile of formula (XXXV) in a 2-step process that first converts the acid into a primary carboxamide. Typical conditions employ activation of the carboxylic acid of the compound of formula

(**XXXVII**) using a suitable organic base and a suitable activating agent, and then treating the activated acid with an ammonia source. Preferred activating agents are DCC, CDI, T₃P, HATU, HBTU or treatment of the acid with oxalyl chloride and a catalytic amount of DMF. Preferred organic bases include DIPEA or TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. Preferred ammonia sources are NH₄OH and NH₄OAc. The reaction may be shaken or stirred at room temperature. The primary carboxamides thus formed may subsequently be dehydrated to provide the nitriles of formula (**XXXV**). Typical conditions involve treating the carboxamide with a suitable reagent, preferably SOCl₂, Burgess' Reagent, POCl₃ or TFAA at temperatures between room temperature and reflux to provide the nitriles of formula (**XXXV**).

Alternatively, an acid of formula (**XXXVII**) may be converted to an amide of formula (**XXXIV**) using the methods described in General Scheme 2. Typical conditions employ activation of the carboxylic acid of the compound of formula (**XXXVII**) using a suitable organic base and a suitable coupling agent. Preferred coupling agents are either EDCI with HOBT, T₃P, HATU, HBTU or BOP. Preferred organic bases include DIPEA or TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature.

Alternatively, an acid of formula (**XXXVII**) may be converted to an amine of formula (**XXXIII**) using a suitable azido reagent such as diphenyl phosphorazide in a suitable solvent such as DMF, DMA, MeCN or NMP in the presence of a suitable base such as DIPEA or TEA. Reactions are typically carried out at room temperature. The intermediate acyl azide thus formed is then typically treated with water under heating or reflux conditions to provide an amine of formula (**XXXIII**).

General Synthetic Procedures

General Purification and Analytical Methods

All final compounds were purified by either Combi-flash or prep-HPLC purification, and analyzed for purity and product identity by UPLC or LCMS according to one of the following methods.

Prep-HPLC

Preparative HPLC was carried out on a Waters auto purification instrument using either an YMC Triart C18 column (250 x 20 mm, 5 µm) or a Phenyl Hexyl column (250

x 21.2 mm, 5 µm) or a Kinetex C18 column (250 x 21.2 mm, 10 µm) operating at between ambient temperature and 50 °C with a flow rate of 16.0 – 50.0 mL/min.

Mobile phase 1: A = 20mM Ammonium Bicarbonate in water, B = Acetonitrile;

Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then 60% A

5 and 40% B after 3 min., then 30% A and 70% B after 20 min., then 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to initial composition for 3 min.

Mobile phase 2: A = 10mM Ammonium Acetate in water, B = Acetonitrile; Gradient

10 Profile: Mobile phase initial composition of 90% A and 10% B, then 70% A and 30% B after 2 min., then 20% A and 80% B after 20 min., then 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to initial composition for 3 min.

15 Mobile phase 3: A = 0.1% Formic acid in water, B = Acetonitrile; Gradient Profile:

Mobile phase initial composition of 90% A and 10% B, then 70% A and 30% B after 2 min., then 20% A and 80% B after 20 min., then 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to initial composition for 3 min.

20

LCMS method

General 5 min method: Zorbax Extend C18 column (50 x 4.6 mm, 5 µm) or Luna C18 column (50 x 4.6 mm, 5 µm) operating at ambient temperature and a flow rate of 1.2 mL/min. Mobile phase: A = 10 mM Ammonium Acetate in water, B = Acetonitrile;

25 Gradient profile: from 90 % A and 10 % B to 70 % A and 30% B in 1.5 min, and then to 10 % A and 90 % B in 3.0 min, held at this composition for 1.0 min, and finally back to initial composition for 2.0 min.

UPLC method

30 UPLC was carried out on a Waters auto purification instrument using a Zorbax Extend C18 column (50 x 4.6 mm, 5 µm) or Kinetex Evo C18 column (100 x 2.1 mm, 1.7 µm) at ambient temperature and a flow rate of 0.3 to 1.5ml/min.

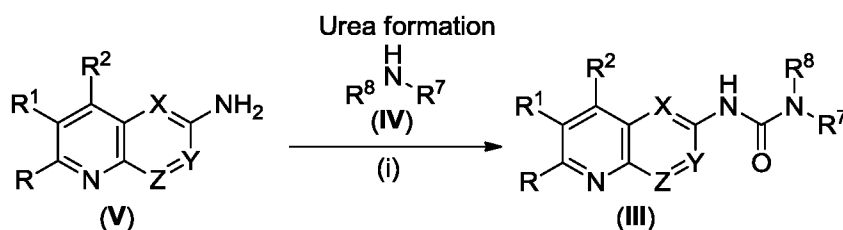
Mobile phase 1: A = 5 mM Ammonium Acetate in water, B = 5 mM Ammonium Acetate

35 in 90/10 Acetonitrile/water; Gradient profile from 95% A and 5% B to 65% A and 35%

B in 2 min., then to 10% A and 90% B in 3.0 min., held at this composition for 4.0 min. and finally back to the initial composition for 5.0 min.

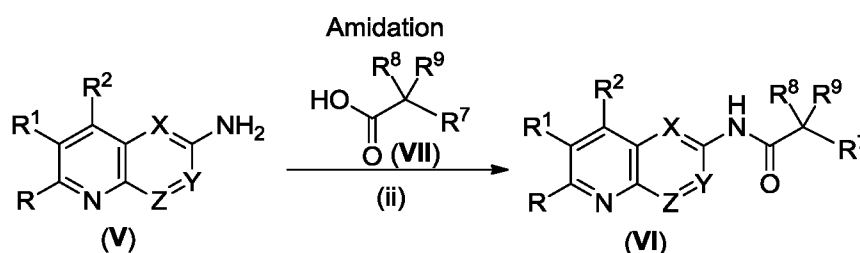
Mobile phase 2: A = 0.05 % formic acid in water, B = Acetonitrile; Gradient profile
 5 from 98 % A and 2 % B over 1 min., then 90 % A and 10 % B for 1 min., then 2 % A and 98 % B for 2 min. and then back to the initial composition for 3 min.

General Procedure 1: Urea formation



10 To a stirred solution of aromatic amine (V) (1.0 eq.) in a suitable solvent, such as DCM, DMF, MeCN or THF (8 mL/mmol) was added p-nitrophenyl chloroformate (1.1 eq.) at 0-5 °C and the whole stirred for 1-3 h at RT. TEA or DIPEA (6 eq.) and amine R⁸-NH-R⁷ (IV) (2.0 eq.) were then added dropwise and the whole further stirred for 1-5 h at RT. Progress of the reaction was monitored by TLC/LCMS and after completion the
 15 reaction mass was diluted with EtOAc and washed with a dilute solution of a suitable inorganic base such as NaHCO₃ or 1N NaOH and finally with brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated in vacuo to give a residue which was purified by column chromatography or combi-flash or prep-HPLC to afford a compound of formula (III) (yield 4-80%) as an off white to white solid. A similar
 20 procedure can be followed to synthesize all ureas of formula (III).

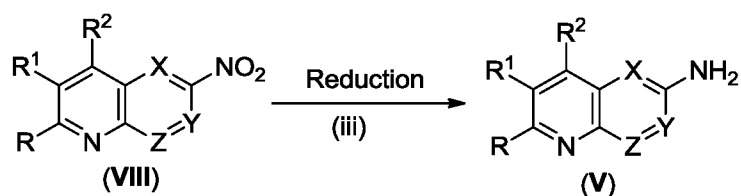
General Procedure 2: Amidation



25 To a stirred solution of carboxylic acid (VII) (1.5 eq.) in a suitable solvent, such as DCM, DCE, DMA, THF, MeCN or DMF (5 mL/mmol) was added a suitable organic base, such as TEA or DIPEA (1.5 eq.) and a coupling reagent, such as T₃P, HATU, EDC.HCl, HOBT, BOP, HBTU or HATU (1.5 eq.). Stirring was continued for 10 min.

and then the aromatic amine (V) (1.0 eq.) was added. The whole was stirred at RT for 1-5 h. Progress of the reaction was confirmed by TLC/LCMS and after completion the reaction mixture was diluted with water and extracted with MTBE or EtOAc or DCM, washed with brine, dried over anhydrous Na₂SO₄ and evaporated in vacuo to give the crude product which was purified by column chromatography or combi-flash or prep-HPLC to afford a compound of formula (VI) (25-90 %) as an off white to white solid. A similar procedure can be followed to synthesize all amides of formula (VI).

General Procedure 3: Nitro group Reduction

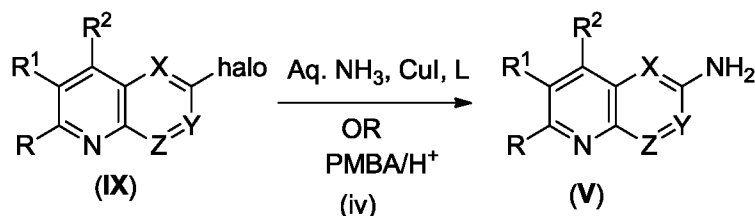


Option A:

To a stirred solution of a compound of formula (VIII) (1.0 eq.) in a suitable solvent such as DMF, EtOH, MeOH or THF (4 mL/mmol) was added aq. HCl (0.12 mL/mmol, 36% w/w in water) followed by SnCl₂·2H₂O or SnCl₂ (4.0 eq.) at RT and the resulting reaction mixture was stirred at RT to 100 °C for 1-5 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc and washed with a saturated solution of NaHCO₃ or 0.5N NaOH solution and finally with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography to give a compound of formula (V) (yield 70-80%) as an off white to yellow solid.

Option B:

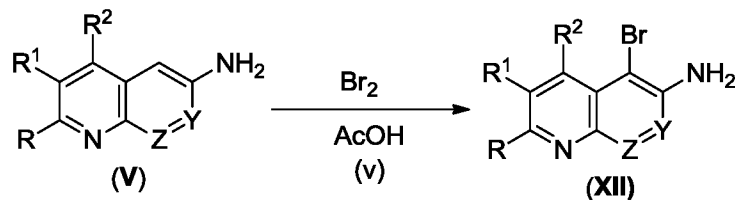
To a stirred solution of a compound of formula (VIII) (1.0 eq.) in a suitable solvent, such as EtOAc, EtOH or MeOH (7 mL/mmol) was added 10% Pd-C (68 mg/mmol, 50% w/w in water) under an inert atmosphere and the resulting reaction mixture was stirred under H₂ gas balloon pressure at RT for 2-12 h. Progress of the reaction was monitored by TLC and UPLC-MS which showed complete conversion of the nitro group to its corresponding amino group. The H₂ gas balloon was removed and the reaction mixture filtered under an inert atmosphere. The obtained filtrate was evaporated in vacuo to give a compound of formula (V) as crude which was used in the next step without any further purification.

General Procedure 4: AminationOption A: Amination by Aq. NH₃

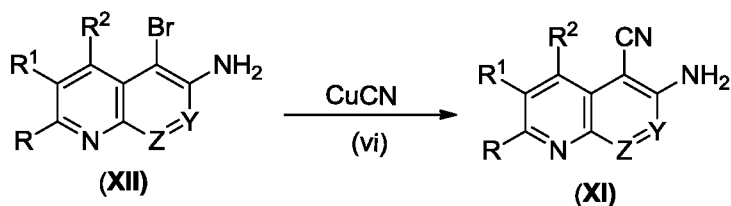
5 A solution of a compound of formula (IX) (1.0 eq.), CuI (0.05 eq.), a suitable ligand such as BINAP, N1,N2-bis(4-phenoxyphenyl)oxalamide, *trans*-4-hydroxy-L-proline or L-proline (0.05 eq.) and a suitable base, such as KHCO₃, K₃PO₄ or K₂CO₃ (1.0 eq.) and DMSO (11 mL/mmol) in a sealed tube was purged with argon for 30 min. then aq. NH₃ (0.5 mL/mmol, 36% w/w in water) was added and the whole stirred at 60-100 °C for 4-
10 16 h. After completion of the reaction (monitored by TLC and LCMS) the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound as a crude brown solid.

Option B: Amination using p-methoxy benzyl amine

15 To a stirred solution of a compound of formula (IX) (1.0 eq.) in a suitable solvent, such as DMF or DMSO (4 mL/mmol) was added p-methoxy benzyl amine (6 eq.) followed by a suitable base, such as KHCO₃, K₃PO₄ or K₂CO₃ (2.5 eq.) under an inert atmosphere. CuI (1.0 eq.) and a suitable ligand, such as BINAP, N1,N2-bis(4-phenoxyphenyl)oxalamide, *trans*-4-hydroxy-L-proline or L-proline (0.5 eq.) were then
20 added. The resulting reaction mixture was transferred to a sealed tube and heated at 60-100 °C for 4-16 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was poured into ice-water. The aqueous reaction mixture was extracted with EtOAc and washed with brine. The organic layer was dried
25 over anhydrous Na₂SO₄ and concentrated in vacuo to give a residue which was stirred with a suitable acid, such as HCl or TFA at RT. The resulting reaction mixture was quenched in ice-water, basified with solid K₂CO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated in vacuo to give the crude product which was purified by column chromatography/combi-flash to
30 afford a compound of formula (V) (yield 60-90%) as a light brown to yellow solid.

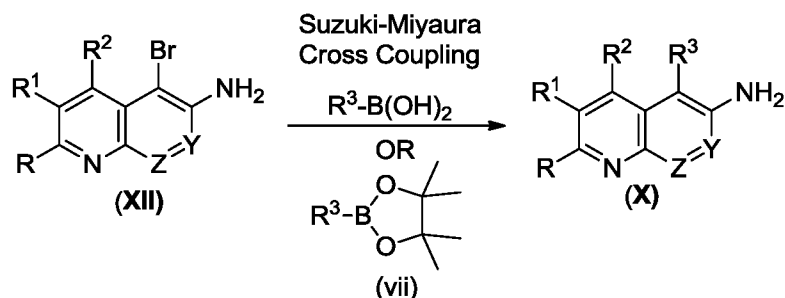
General Procedure 5: Bromination

To a stirred solution of a compound of formula (V) (1.0 eq.) in AcOH (8 mL/mmol) was added Br₂ (1.0 eq.) in AcOH (2mL/mmol) at 0-5 °C. The whole was stirred at RT for 1-4 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was quenched with a saturated aqueous solution of sodium metabisulfite. The aqueous mass was basified with solid NaHCO₃ and extracted with EtOAc, washed with brine, dried and concentrated to give the crude product which was purified by column chromatography to afford a compound of formula (XII) (80-95% yield) as an off white solid.

General Procedure 6: Cyanation

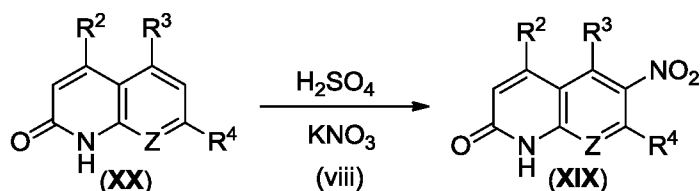
To a stirred solution of a compound of formula (XII) (1.0 eq.) in NMP (3 mL/mmol) was added CuCN (4 eq.) and the whole stirred in a sealed tube at 100-120 °C for 10-16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with water and extracted with MTBE. The organic layer was washed with a saturated solution of NH₄Cl and finally with brine, dried and concentrated in vacuo to give the crude product which was purified by column chromatography to afford a compound of formula (XI) (60-80% yield) as an off white to light brown solid.

General Procedure 7: Suzuki-Miyaura Cross Coupling Reaction

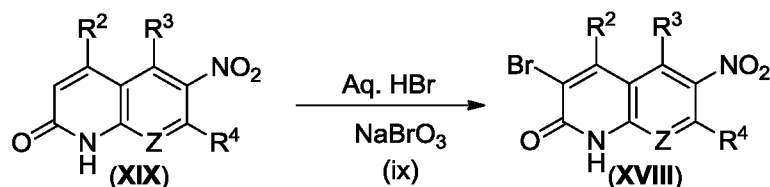


A solution of a compound of formula **XII** (4.805 mmol, 1.0 eq.), $\text{R}^3\text{-B(OH)}_2$ (2.0 eq.) and a suitable base, such as K_2CO_3 , TEA, NaHCO_3 or K_3PO_4 (3.0 eq.) in a mixture of solvents 1,4-dioxane (4 mL/mmol) and water (0.5 mL/mmol) was degassed with argon for 30 min. then a suitable transition metal catalyst, such as Pd(OAc)_2 , $\text{Pd(PPh}_3)_4$, $\text{Pd(PPh}_3)_2\text{Cl}_2$ or $\text{Pd}_2(\text{dba})_3$ (0.1 eq.) and a suitable ligand, such as BINAP or PCy_3 (0.2 eq.) were added. The resulting reaction mixture was stirred at 80-100 °C for 4-16 h under an inert atmosphere. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc, filtered and the filtrate was partitioned by the addition of water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product which was purified by column chromatography to give a compound of formula (yield 50-80%) as a pale yellow solid

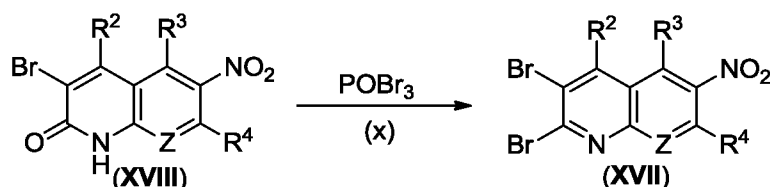
General Procedure 8: Nitration



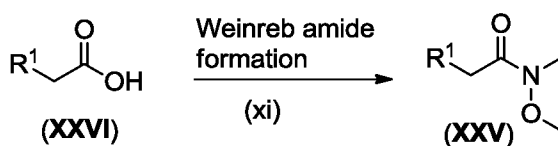
To a stirred solution of a compound of formula **XX** (1.0 eq.) in H_2SO_4 (3 mL/mmol) was added KNO_3 (1.1 eq.) portionwise at -10-0 °C. The whole was stirred at 0-5 °C for 30 min. Completion of the reaction was confirmed by TLC/LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford a compound of formula **(XIX)** as a crude yellow solid.

General Procedure 9: Bromination by Aq. HBr

To a stirred solution of a compound of formula (XIX) (1.0 eq.) in water (0.6 mL/mmol) was added NaBrO₃ (1.2 eq.) at -10-5 °C, then aq. 48% HBr (3.5 mL/mmol) was added dropwise at the same temperature. The whole was then refluxed at 90-100 °C for 2-6 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was quenched with ice-water and stirred at 0-5 °C for 1 h. The resulting solid precipitate was filtered off and washed with water to give a solid material which was slurry washed with hexane to afford a compound of formula (XVIII) (yield 65-80%) as a yellow solid.

General Procedure 10: Bromination by POBr₃

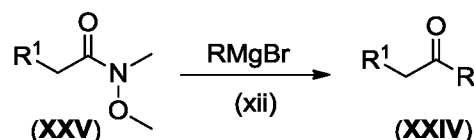
A solution of a compound of formula (XVIII) (1.0 eq.) in POBr₃ (2.0 eq.) was heated at 120-140 °C for 10-16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was quenched with cold water and basified with aqueous NaHCO₃ to pH 7-8. Then the aqueous mass was extracted with EtOAc and washed with brine. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a compound of formula (XVII) as a crude brown solid.

General Procedure 11: Weinreb amide formation

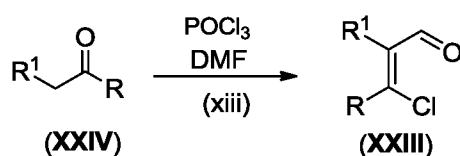
To a stirred solution of a compound of formula (XXVI) (1.0 eq.) in DCM (1.3 mL/mmol) was added a catalytic amount of DMF (2 drops) and oxalyl chloride (1.5 eq.) dropwise at 0-5 °C. The resulting reaction mixture was stirred at RT for 1-2 h and then commercially available N,O-dimethylhydroxylamine hydrochloride (1.0 eq.) added,

followed by TEA (4.0 eq.) at 0-5 °C and the mixture was further stirred at RT for 30 min. Progress of the reaction was monitored by TLC and LCMS, and after completion the reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography or combi-flash to afford a compound of formula (**XXV**) (yield 65-80%) as an off white solid.

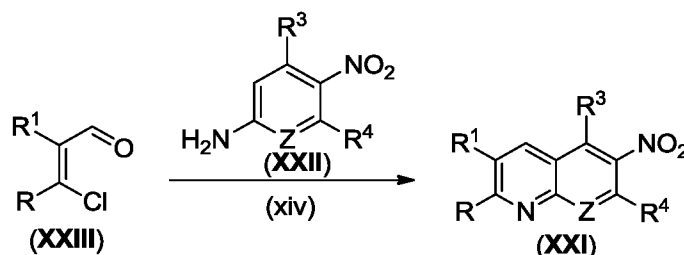
General Procedure 12: Grignard Reaction



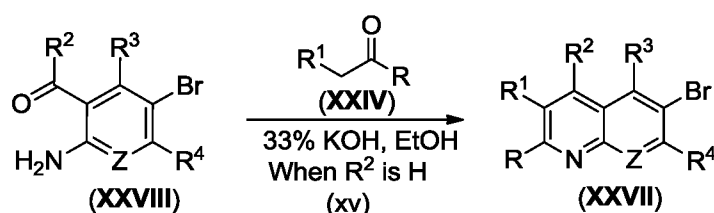
To a stirred solution of a compound of formula (**XXV**) (1.0 eq.) in a suitable solvent, such as dry diethyl ether or dry THF (3.2 mL/mmol) was added R-MgBr (0.67 mL/mmol, 3M solution in diethyl ether) at -78 °C. The mixture was warmed to RT and stirred at RT for 2-3 h. The reaction was monitored by TLC and LCMS which now showed completion of the reaction. The reaction mixture was quenched with a saturated solution of ammonium chloride and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography or combi-flash to afford a compound of formula (**XXIV**) (yield 80-90%) as a white solid.

20 General Procedure 13: Vilsmeier-Haack Reaction

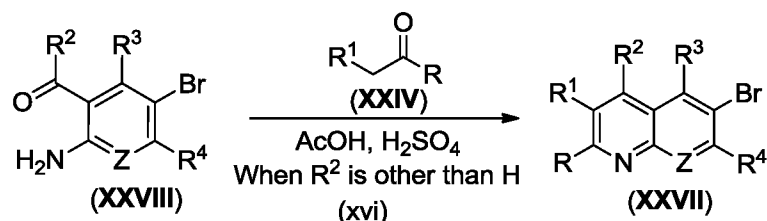
To a stirred DMF (0.24 mL/mmol) was added POCl₃ (3.0 eq.) dropwise at 0-5 °C and the whole was stirred at RT for 1-2 h, before a compound of formula (XXIV) (1.0 eq.) was added slowly at RT. The resulting reaction mixture was stirred at 55-60 °C for 10-16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was poured into crushed ice and stirred at RT for 1-2 h. The obtained solid precipitate was collected by filtration, dissolved in EtOAc, dried over anhydrous Na₂SO₄ and the solvent removed in vacuo to afford a compound of formula (XXIII) (yield 85-95%) as a crude off white solid which was used in the next step without any further purification.

General Procedure 14: Condensation

A stirred solution of a compound of formula (XXII) (1.0 eq.) and a compound of formula (XXIII) (1.0 eq.) in AcOH (0.36 mL/mmol) was refluxed for 10-16 h. TLC showed formation of new polar spot. The mass of the product was confirmed by LCMS. The reaction mixture was diluted with cold water and the product was extracted with EtOAc. The organics were washed with water followed by brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography or combi-flash to afford a compound of formula (XXI) (yield 30-45%) as a yellow solid.

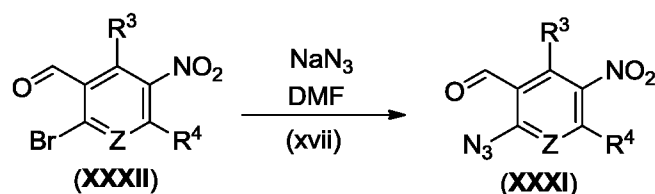
General Procedure 15: Condensation

To a stirred solution of a compound of formula (XXIV) (1.0 eq.) and a compound of formula (XXVIII) (1.0 eq.) in ethanol (8 mL/mmol) was added 33% aq. KOH solution (0.81 mL/mmol) or piperidine at RT. The resulting reaction mixture was refluxed at 70-75 °C for 1-4 h. The reaction was monitored by TLC and LCMS and after completion the solvents were evaporated to give a residue which was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography or combi-flash to afford a compound of formula (XXVII) (yield 30-50%) as a white solid.

General Procedure 16: Condensation

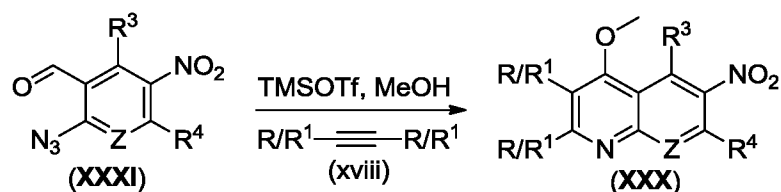
To a stirred solution of a compound of formula (XXVIII) (1.0 eq.) in glacial acetic acid (4.4 mL/mmol) was added a compound of formula (XXIV) (1.0 eq.) and conc. H₂SO₄ (0.1 mL/mmol). The whole was heated at 110-120 °C for 4-6 h. The reaction was monitored by TLC and LCMS and after completion the solvents were partially
 5 evaporated under reduced pressure to give a residue which was dissolved in water and extracted with EtOAc. The organic layer was washed with a saturated solution of NaHCO₃ followed by brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography or combi-flash to afford a compound of formula (XXVII) (yield 40-
 10 50%) as a light yellow solid.

General Procedure 17: Azide formation



To a stirred solution of a compound of formula (XXXII) (1.0 eq.) in a suitable solvent, such as HMPA or DMF was added NaN₃ (1.5 eq.) at 45-50 °C and stirring was continued at the same temperature for 30 min. The reaction was monitored by TLC and after complete consumption of the bromide reagent the reaction mixture was quenched with ice-water and stirred for another 30 min. to give a solid precipitate which was filtered off. The filtrate was then extracted with MTBE, washed with brine, dried over
 20 anhydrous Na₂SO₄ and concentrated in vacuo to afford a compound of formula (XXXI) (yield 75-85 %) as a yellow solid.

General Procedure 18: Condensation

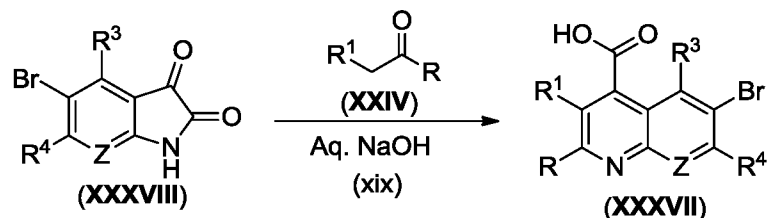


To a stirred solution of a compound of formula (XXXI) (1.0 eq.) in dry DCM (2.5 mL/mmol) was added MeOH (0.16 mL/mmol) followed by an acetylene derivative (1.0 eq.) at RT. The reaction mixture was cooled to 0-5 °C and TMSOTf (4.0 eq.) then added dropwise. The resulting reaction mixture was stirred at RT for 10-16 h. Progress of the reaction mixture was monitored by TLC/LCMS and after completion the reaction

mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography or combi-flash to give a compound of formula (XXX) (yield 80-90%) as a yellow solid.

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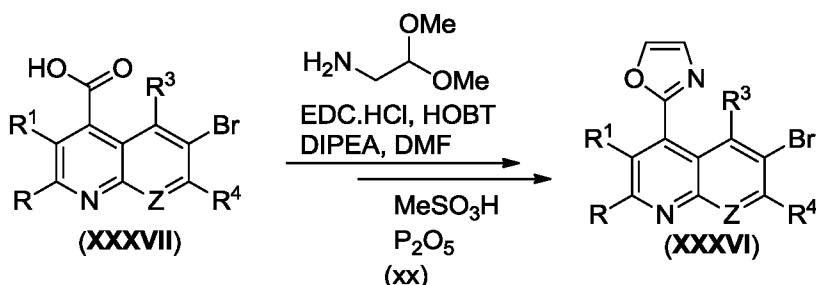
General Procedure 19: Pfitzinger Reaction



A stirred solution of a compound of formula (XXXVIII) (1.0 eq.) in 2N NaOH solution (4.5 mL/mmol) was refluxed at 85-90 °C for 30 min. The reaction mixture was then cooled to RT and a compound of formula (XXIV) (1.1 eq.) was added at RT. The whole was refluxed at 85-90 °C for 10-16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was filtered and the obtained solid was dissolved in water and acidified with 2N HCl solution to give a solid precipitate which was filtered and washed with water to afford a compound of formula (XXXVII) (25-45%) as a white solid.

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General Procedure 20: Oxazole formation



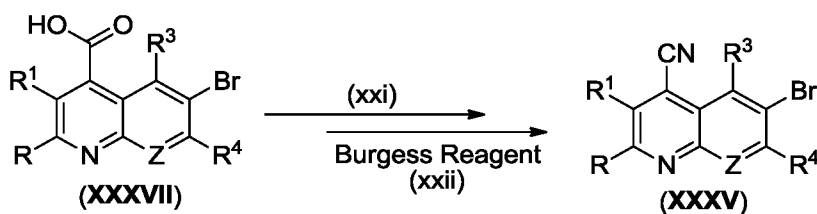
To a stirred solution of a compound of formula (XXXVII) (1.0 eq.) in a suitable solvent, such as DCM, THF or DMF (2.5 mL/mmol) was added an organic base, such as TEA or DIPEA (4.0 eq.), and a coupling agent such as EDC.HCl (1.5 eq.) and HOBT (1.5 eq.) at RT and the whole stirred at RT for 10-15 min. 2,2-dimethoxyethanamine (1.2 eq.) was then added and the whole allowed to stir at RT for 10-12 h. Progress of the reaction mixture was monitored by TLC/LCMS and after completion the reaction mixture was diluted with water and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the

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crude product which was purified by column chromatography to afford a corresponding amide intermediate (40-50%) as an off white solid.

The obtained amide intermediate (1.0 eq.) was dissolved in methanesulfonic acid (5 mL/mmol) at RT and then P₂O₅ (3.0 eq.) added. The whole was heated at 120-130 °C for 3-5 h. Progress of the reaction was monitored by TLC and after complete consumption of amide; the reaction mixture was poured into ice-water and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography to afford a compound of formula (XXXVI) (yield 35-40%) as an off white solid.

General Procedure 21: Amide/cyanide via acid chloride formation



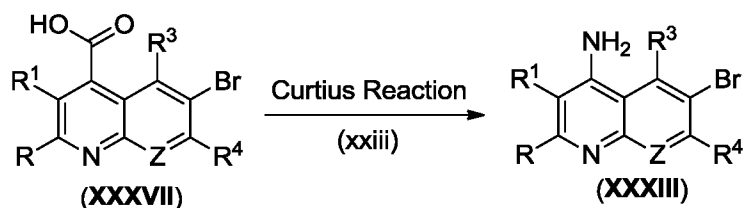
To a stirred solution of a compound of formula (XXXVII) (1.0 eq.) in a mixture of solvents DCM (4 mL/mmol) and DMF (0.015 mL/mmol) was added oxalyl chloride (2.0 eq.) dropwise at -5 to 0 °C and the mixture stirred at RT for 1-2 h. Formation of the corresponding acid chloride was confirmed by LCMS. Then aq. NH₃ or another amine (3.0 eq., 33% in water) was added dropwise at 0-5 °C. The resulting reaction mixture was stirred at RT for 2-3 h. Progress of the reaction was confirmed by TLC/LCMS and after completion the obtained solid was filtered and washed with hexane. The filtrate was extracted to recover the dissolved material with 10% MeOH in DCM and washed with brine. The combined organic layers were dried over anhydrous Na₂SO₄ and evaporated in vacuo to give the corresponding amide intermediate as crude.

General Procedure 22: Burgess Reaction

The obtained amide intermediate (1.0 eq.) was dissolved in dry THF (12 mL/mmol), then Burgess Reagent (2.0 eq.) added at 0-5 °C. The whole was heated at 50-60 °C for 1-2 h under an inert atmosphere. After completion of the reaction (monitored by TLC/LCMS) the solid obtained was filtered off and the filtrate was diluted with water and extracted with 5% MeOH in DCM. The combined organic layers were washed with

brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a compound of formula (XXXV) (yield 70-80%) as a white solid.

General Procedure 23: Curtius Reaction



To a stirred solution of a compound of formula (XXXVII) (1.0 eq.) in DMF (6 mL/mmol) was added DIPEA or TEA (1.5 eq.), and diphenyl phosphorazide (2.0 eq.) at 0-5 °C under a N₂ atmosphere. The whole was stirred at RT for 1-3 h then water (6 mL/mmol) was added and the whole refluxed at 100-110 °C for 2-6 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was diluted with water to give a solid precipitate which was filtered and washed with water followed by hexane. The obtained solid was dried in a vacuum oven to afford a compound of formula (XXXIII) (yield 80-85%) as a pale yellow solid.

Examples

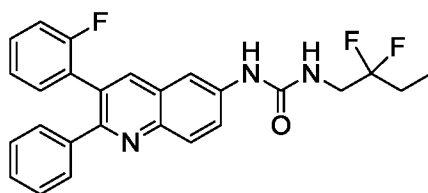
Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane (for ¹H-NMR) and upfield from trichloro-fluoro-methane (for ¹⁹F NMR) using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents: CDCl₃, deuteriochloroform; d₆-DMSO, deuterodimethylsulphoxide; and CD₃OD, deuteromethanol.

Mass spectra, MS (m/z), were recorded using electrospray ionisation (ESI). Where relevant and unless otherwise stated the m/z data provided are for isotopes ¹⁹F, ³⁵Cl, ⁷⁹Br and ¹²⁷I.

All chemicals, reagents and solvents were purchased from commercial sources and used without further purification. All reactions were performed under an atmosphere of nitrogen unless otherwise noted.

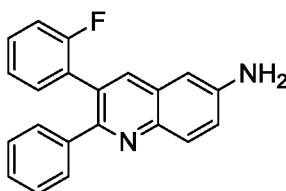
Flash column chromatography was carried out using pre-packed silica gel cartridges in a Combi-Flash platform. Prep-HPLC purification was carried out according to the General purification and analytical methods described above. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). All final compounds were >95% pure as judged by the LCMS or UPLC analysis methods described in the General purification and analytical methods above unless otherwise stated.

Example 45: 1-(2,2-Difluorobutyl)-3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)urea

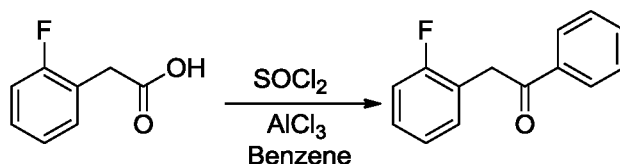


Example 45 was prepared according to the methods described in General Procedures 1, 3, 13, 14 and the methods described below.

Preparation 1: 3-(2-Fluorophenyl)-2-phenylquinolin-6-amine



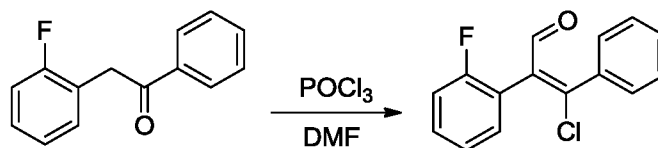
Step 1: 2-(2-Fluorophenyl)-1-phenylethanone



To a stirred solution of commercially available 2-(2-fluorophenyl)acetic acid (35.0 g, 222.93 mmol) in benzene (350 mL) was added thionyl chloride (105 mL) at 0-5 °C and the resulting reaction mixture was allowed to slowly warmup to RT and was then refluxed for 4 h. The solvent was removed under high vacuum and the leftover residue was diluted with benzene (105 mL). AlCl₃ (32.615 g, 245.22 mmol) was then added carefully portionwise at 0-5 °C, and the reaction mixture then allowed to slowly warm to RT and stir at this temperature for 3 h. The reaction was monitored by TLC/ LCMS and after completion the reaction mixture was poured into crushed ice, extracted with

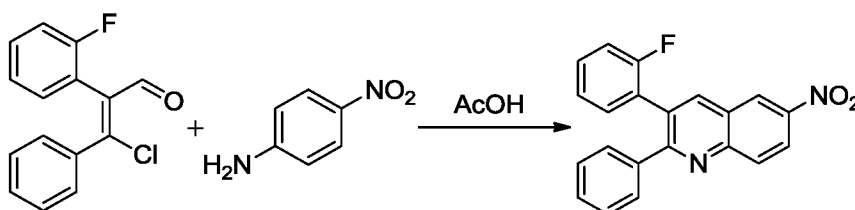
EtOAc and then washed with water followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound (35 g, yield 73.3%) as a white solid. LCMS m/z: 215 [M+H].

5 Step 2: 3-Chloro-2-(2-fluorophenyl)-3-phenylacrylaldehyde

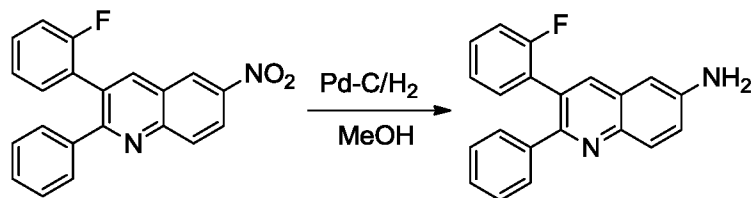


To a stirred DMF (55 mL, 700.93 mmol) was added POCl_3 (65.4 mL, 700.93 mmol) dropwise at 0-5 °C and the whole was stirred at RT for 1 h, before 2-(2-fluorophenyl)-1-phenylethanone (Preparation 1, Step 1) (50.0 g, 233.65 mmol) was added slowly at RT.
 10 The resulting reaction mixture was stirred at 60 °C for overnight. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was poured into crushed ice and stirred at RT for 1 h. The obtained solid precipitate was collected by filtration, dissolved in EtOAc, dried over anhydrous Na_2SO_4 and the solvent removed in vacuo to afford the title compound (55.0 g, yield 90%) as a crude off
 15 white solid which was used in the next step without any further purification. LCMS m/z: 261 [M+H].

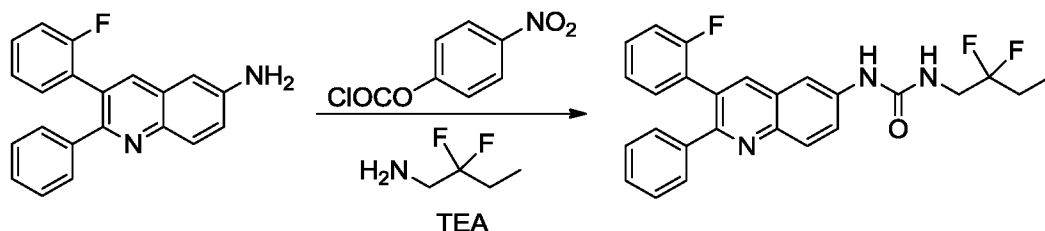
Step 3: 3-(2-Fluorophenyl)-6-nitro-2-phenylquinoline



20 A stirred solution of commercially available p-nitroaniline (26.54 g, 192.307 mmol) and 3-chloro-2-(2-fluorophenyl)-3-phenylacrylaldehyde (Preparation 1, Step 2) (50.0 g, 192.307 mmol) in AcOH (70 mL) was refluxed for 16 h. TLC showed formation of new polar spot. The mass of the product was confirmed by LCMS. The reaction mixture was diluted with cold water and the product was extracted with EtOAc. The organics were
 25 washed with water followed by brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography to afford the titled compound (21 g, yield 31.7%) as a yellow solid. LCMS m/z: 245 [M+H].

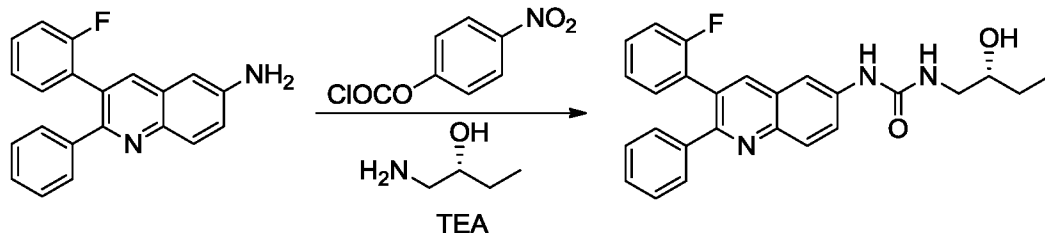
Step 4: 3-(2-Fluorophenyl)-2-phenylquinolin-6-amine

To a stirred solution of 3-(2-fluorophenyl)-6-nitro-2-phenylquinoline (Preparation 1, Step 3) (500 mg, 1.453 mmol) in MeOH (10 mL) was added 10% Pd-C (100 mg, 50%
 5 w/w in water) under an inert atmosphere and the resulting reaction mixture was stirred under H₂ gas balloon pressure at RT for 2 h. Progress of the reaction was monitored by TLC and UPLC-MS which showed complete conversion of the nitro group into its corresponding amino group. The H₂ gas balloon was removed and the reaction mixture filtered under an inert atmosphere. The obtained filtrate was evaporated in vacuo to
 10 give the title compound (450 mg) as crude which was used in the next step without any further purification. LCMS m/z: 315 [M+H].

Preparation 2: 1-(2,2-Difluorobutyl)-3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)urea (Example 45)

To a stirred solution of 3-(2-fluorophenyl)-2-phenylquinolin-6-amine (Preparation 1, Step 4) (404 mg, 1.286 mmol) in THF (10 mL) was added p-nitrophenyl chloroformate (285 mg, 1.415) at 0-5 °C and the whole stirred for 1 h at RT. TEA (781 mg, 7.718 mmol) and 2,2-difluorobutan-1-amine (280.06 mg, 2.573 mmol) were then added dropwise
 20 and further stirred for 3 h at RT. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mas was diluted with EtOAc and washed with 1N NaOH solution and finally with brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated in vacuo to give a residue which was purified by prep-HPLC to afford the title compound (25 mg, yield 4%) as a white solid. LCMS m/z: 450.21
 25 [M+H]; Purity 99.86%; ¹H NMR (500 MHz; DMSO-d₆): δ 0.99 (t, J = 7.5 Hz, 3H), 1.86-1.97 (m, 2H), 3.59-3.66 (m, 2H), 6.71 (t, J = 6.2 Hz, 1H), 7.09-7.13 (m, 1H), 7.25-7.30 (m 4H), 7.35-7.42 (m 3H), 7.46-7.49 (m, 1H), 7.76-7.78 (m, 1H), 7.99 (d, J = 9.05 Hz, 1H), 8.15 (d, J = 2.2 Hz, 1H), 8.28 (s, 1H), 9.08 (s, 1H).

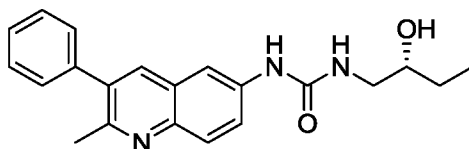
Example 15: (R)-1-(3-(2-Fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea



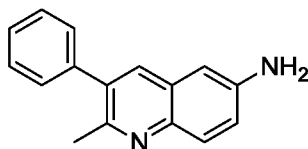
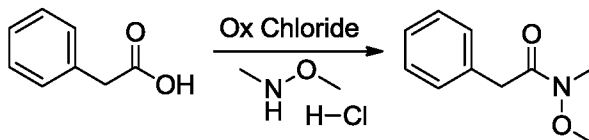
- 5 Example 15 was prepared according to the methods described for the preparation of Example 45 and the method described below.

To a stirred solution of 3-(2-fluorophenyl)-2-phenylquinolin-6-amine (Preparation 1, Step 4) (9.0 g, 28.66 mmol) in THF (90 mL) was added p-nitrophenyl chloroformate
 10 (6.4 g, 31.526 mmol) at 0-5 °C and the whole stirred at RT for 3 h. TEA (11.58 g, 114.64 mmol) and (R)-1-aminobutan-2-ol (2.55 g, 28.66 mmol) were then added dropwise and further stirred for 2 h at RT. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 1N NaOH solution to remove any p-nitrophenol and
 15 with 1N HCl to remove unreacted amine, and finally with brine solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by trituration with acetone and hexane to afford the title compound (7.0 g, yield 57%) as a white solid. LCMS m/z: 430.34 [M+H]; Purity 99.46%; ¹H NMR (500 MHz; DMSO-d₆): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.34-1.46 (m 2H),
 20 2.99-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.44 (t, *J* = 6.5 Hz, 1H), 4.80 (d, *J* = 5.15 Hz, 1H), 6.34 (t, *J* = 5.55 Hz, 1H), 7.11 (t, *J* = 8.95 Hz, 1H), 7.25-7.29 (m, 4H), 7.35-7.46 (m, 3H), 7.46-7.49 (m, 1H), 7.74 (d, *J* = 6.9 Hz, 1H), 7.97 (d, *J* = 9.05 Hz, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 8.25 (s, 1H), 9.06 (s, 1H).

25 **Example 72: (R)-1-(2-Hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea**



Example 72 was prepared according to the methods described in General Procedures 1, 4, 11, 14, 15 and the methods described below.

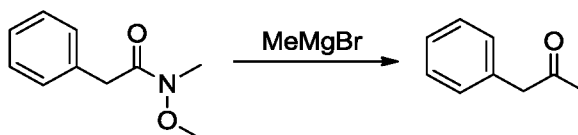
Preparation 3: 2-Methyl-3-phenylquinolin-6-amineStep 1: N-Methoxy-N-methyl-2-phenylacetamide

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To a stirred solution of commercially available phenyl acetic acid (4.18 g, 30.753 mmol) in DCM (40 mL) was added a catalytic amount of DMF (2 drops) and oxalyl chloride (5.855 g, 46.135 mmol) dropwise at 0-5 °C. The resulting reaction mixture was stirred at RT for 2 h and then commercially available N,O-dimethylhydroxylamine hydrochloride (3.0 g, 30.75 mmol) added, followed by TEA (12.45 g, 123.03 mmol) at 0-5 °C and the mixture was further stirred at RT for 30 min. Progress of the reaction was monitored by TLC and LCMS, and after completion the reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography to afford the title compound (4.0 g, yield 72.7%) as an off white solid. LCMS m/z: 180 [M+H].

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Step 2: 1-Phenylpropan-2-one

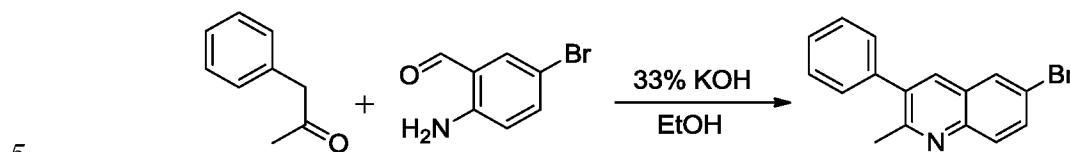
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To a stirred solution of N-methoxy-N-methyl-2-phenylacetamide (Preparation 3, Step 1) (1.0 g, 5.586 mmol) in dry THF (18 mL) was added methyl magnesium bromide (1.332 g, 3.72 mL, 3M solution in diethyl ether) at -78 °C under an inert atmosphere and the reaction mixture was maintained at the same temperature for 1 h. LCMS indicated that the reaction was ~ 60% complete. The mixture was warmed to RT and stirred at RT for 2 h. The reaction was monitored by TLC and LCMS which now showed completion of the reaction. The reaction mixture was quenched with a saturated solution of ammonium chloride and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the

crude product which was purified by column chromatography to afford the title compound (0.7 g, yield 93%) as a white solid. LCMS m/z: 135 [M+H].

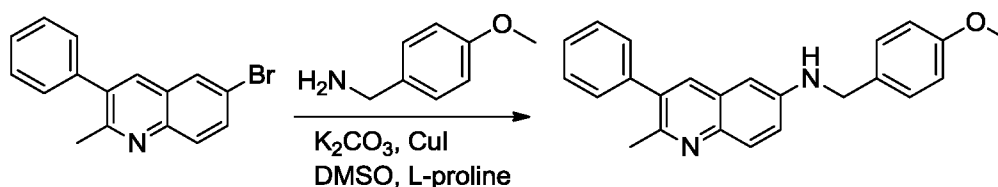
Step 3: 6-Bromo-2-methyl-3-phenylquinoline



To a stirred solution of 1-phenylpropan-2-one (Preparation 3, Step 2) (1.098 g, 8.146 mmol) and commercially available 2-amino-5-bromobenzaldehyde (1.646 g, 8.146 mmol) in ethanol (65 mL) was added a 33% aq. KOH solution (6.584 mL) at RT. The resulting reaction mixture was refluxed at 70 °C for 1 h. The reaction was monitored by
 10 TLC and LCMS and after completion the solvents were evaporated to give a residue which was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography to afford the title compound (0.94 g, yield 38%) as a white solid. LCMS m/z: 298 [M+H].

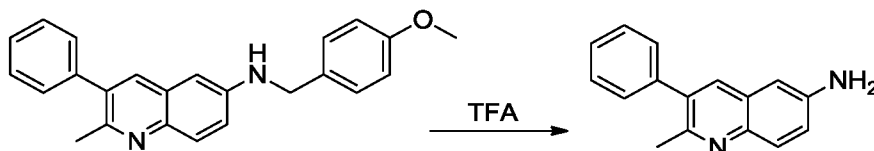
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Step 4: N-(4-Methoxybenzyl)-2-methyl-3-phenylquinolin-6-amine



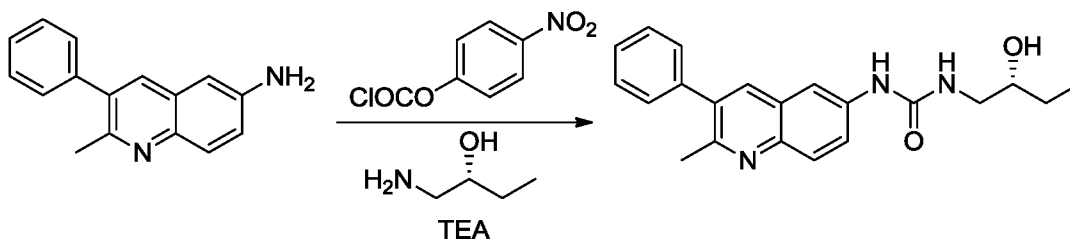
To a stirred solution of 6-bromo-2-methyl-3-phenylquinoline (Preparation 3, Step 3) (921 mg, 3.099 mmol) in DMSO (12 mL) was added p-methoxy benzyl amine (2.44 mL, 18.594 mmol) followed by K₂CO₃ (1070 mg, 7.747 mmol) under an inert atmosphere, then CuI (590 mg, 3.099 mmol) and L-proline (178.68 mg, 1.549 mmol) were added. The resulting reaction mixture was transferred to a sealed tube and heated at 90 °C for 12 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was poured into ice-water. The aqueous reaction mixture was
 20 extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a crude product which was purified by column chromatography to afford the title compound (951 mg, yield 87%) as a yellow solid. LCMS m/z: 355 [M+H].

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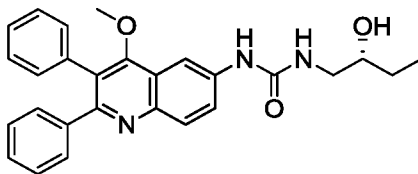
Step 5: 2-Methyl-3-phenylquinolin-6-amine

A solution of N-(4-methoxybenzyl)-2-methyl-3-phenylquinolin-6-amine (Preparation 3, Step 4) (920 mg, 2.137 mmol) in TFA (10 mL) was stirred at RT for 12 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was neutralized with an aqueous solution of NaHCO₃, extracted with EtOAc and washed with a saturated solution of NaHCO₃ followed by brine. The combined organics were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound (644 mg, purity 90%) as a crude solid which was used in the next step without any further purification. LCMS m/z: 235 [M+H].

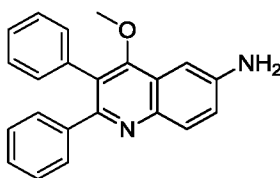
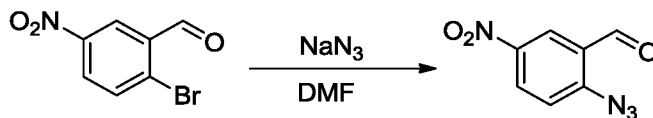
Preparation 4: (R)-1-(2-Hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea
(Example 72)



To a stirred solution of 2-methyl-3-phenylquinolin-6-amine (Preparation 3, Step 5) (644 mg, 2.751 mmol) in THF (6 mL) was added p-nitrophenyl chloroformate (609.8 mg, 3.026 mmol) and the whole stirred at RT for 1 h. After complete consumption of the amine by TLC, TEA (1.535 mL, 11.00 mmol) and (R)-1-aminobutan-2-ol (269.68 mg, 3.025 mmol) were added dropwise and the combined mixture was further stirred at RT for 3 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc, washed with 1N NaOH solution thrice followed by brine and 1N HCl solution and again with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by crystallization with acetone and hexane to afford the title compound (393 mg, yield 41%) as a white solid. LCMS m/z: 350.22 [M+H]; Purity 99.71%; ¹H NMR (400 MHz; DMSO-d₆): δ 0.88 (t, *J* = 7.44 Hz, 3H), 1.28-1.44 (m, 2H), 2.50 (s, 3H), 2.93-2.99 (m, 1H), 3.18-3.32 (m, 1H), 3.40 (d, *J* = 4.84 Hz, 1H), 4.76 (d, *J* = 4.96 Hz, 1H), 6.25 (t, *J* = 5.72 Hz, 1H), 7.40-7.50 (m, 5H), 7.61-7.64 (m, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.95 (s, 1H), 7.99 (s, 1H), 8.90 (s, 1H).

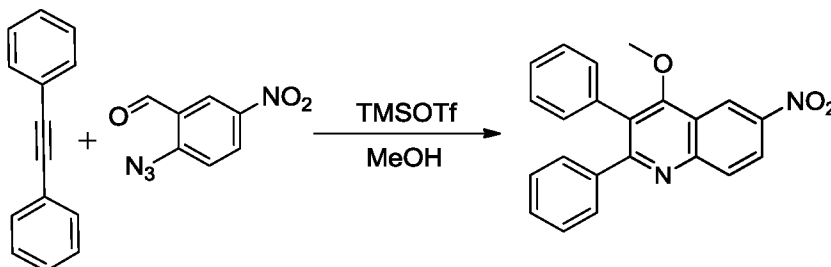
Example 101: (R)-1-(2-Hydroxybutyl)-3-(4-methoxy-2,3-diphenylquinolin-6-yl)urea

- 5 Example 101 was prepared according to the methods described in General Procedures 1, 3, 17, 18 and the method described below.

Preparation 5: 4-Methoxy-2,3-diphenylquinolin-6-amine**Step 1: 2-Azido-5-nitrobenzaldehyde**

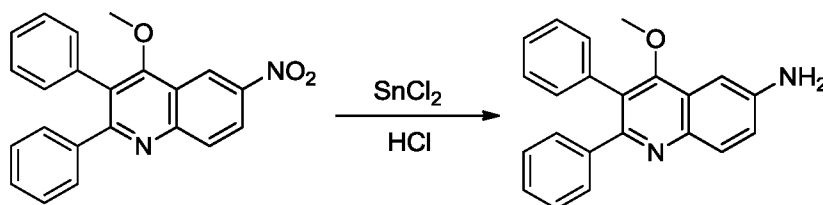
- To a stirred solution of commercially available 2-bromo-5-nitrobenzaldehyde (2.0 g, 8.684 mmol) in DMF was added NaN_3 (0.869 g, 13.378 mmol) at 50 °C and the reaction mixture maintained at this temperature for 30 min. The reaction was monitored by
- 15 TLC and after complete consumption of the starting material; the reaction mixture was quenched with ice-water and stirred for another 30 min. to give a solid precipitate which was filtered off. The filtrate was then extracted with MTBE, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the title compound (1.35 g, yield 80.8 %) as a yellow solid. LCMS m/z : 193 $[\text{M}+\text{H}]$.

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Step 2: 4-Methoxy-6-nitro-2,3-diphenylquinoline

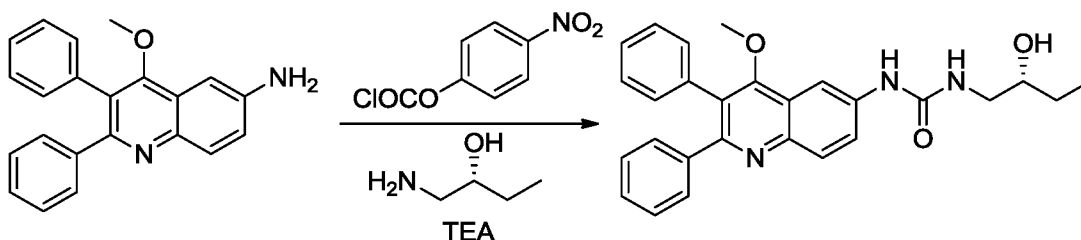
To a stirred solution of 2-azido-5-nitrobenzaldehyde (Preparation 5, Step 1) (1.35 g, 5.862 mmol) in dry DCM was added MeOH (0.94 mL, 23.44 mmol) followed by diphenyl acetylene (1.044 g, 5.86 mmol) at RT. The reaction mixture was cooled to 0-5 °C and TMSOTf (5.22 g, 23.44 mmol) then added dropwise. The resulting reaction mixture was stirred at RT for 12 h. Progress of the reaction mixture was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc and washed with brine. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography to give the title compound (2.2 g, yield 88%) as a yellow solid. LCMS m/z: 357.25 [M+H].

Step 3: 4-Methoxy-2,3-diphenylquinolin-6-amine



To a stirred solution of 4-methoxy-6-nitro-2,3-diphenylquinoline (Preparation 5, Step 2) (832 mg, 2.335 mmol) in THF (10 mL) was added aq. HCl (0.3 mL) followed by SnCl₂ (1742 mg, 9.338 mmol) at RT and the resulting reaction mixture was refluxed at 60 °C for 2 h. Progress of the reaction mixture was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc and washed with 0.5N NaOH and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography to give the title compound (605 mg, yield 79.5%) as a yellow solid. LCMS m/z: 327 [M+H].

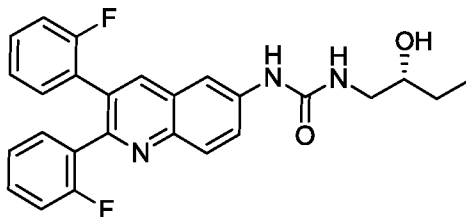
Preparation 6: (R)-1-(2-Hydroxybutyl)-3-(4-methoxy-2,3-diphenylquinolin-6-yl)urea (Example 101)



To a stirred solution of 4-methoxy-2,3-diphenylquinolin-6-amine (Preparation 5, Step 3) (605 mg, 1.855 mmol) in THF (6 mL) was added p-nitrophenyl chloroformate

(411.29 mg, 2.041 mmol) and the whole stirred at RT for 1 h. After complete consumption of the amine by TLC, TEA (1.035 mL, 7.42 mmol) and (R)-1-aminobutan-2-ol (181.87 mg, 2.0405 mmol) were added dropwise and the combined mixture was further stirred at RT for 3 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc, washed with 1N NaOH solution thrice followed by brine and 0.02N HCl solution and again with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by crystallization with acetone and hexane to afford the title compound (400 mg, yield 49%) as a white solid. LCMS m/z: 442.27 [M+H]; Purity 99.51%; ¹H NMR (400 MHz; DMSO-d₆): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.32-1.42 (m, 2H), 2.96-3.01 (m, 1H), 3.21-3.25 (m, 1H), 3.42 (d, *J* = 4.76 Hz, 1H), 3.49 (s, 3H), 4.75 (d, *J* = 5.16 Hz, 1H), 6.26 (t, *J* = 5.48 Hz, 1H), 7.16-7.33 (m, 10H), 7.67 (dd, *J'* = 2.36 Hz, *J''* = 9.04 Hz, 1H), 7.93 (d, *J* = 9.08 Hz, 1H), 8.29 (d, *J* = 2.44 Hz, 1H), 9.04 (s, 1H).

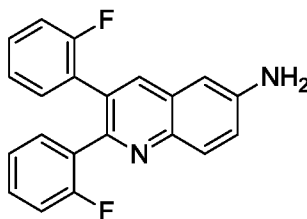
Example 20: (R)-1-(2,3-Bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea



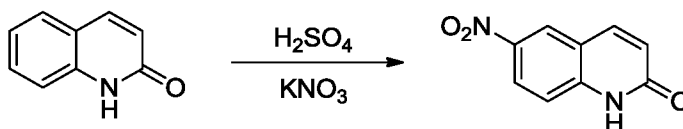
Example 20 was prepared according to the methods described in General Procedures 1, 3, 7, 8, 9, 10 and the method described below.

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Preparation 7: 2,3-Bis(2-fluorophenyl)quinolin-6-amine



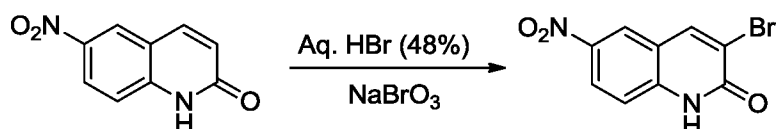
Step 1: 6-Nitroquinolin-2(1H)-one



To a stirred solution of commercially available quinolin-2(1H)-one (5.0 g, 34.44 mmol) in H₂SO₄ (100 mL, 1.876 mmol) was added KNO₃ (3.83 g, 37.884 mmol) portionwise at

-10 to 0 °C. The whole was stirred at 0-5 °C for 30 min. Completion of the reaction was confirmed by TLC/LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the title compound (7.4 g, crude) as a yellow solid. LCMS m/z: 188.97 [M-H].

Step 2: 3-Bromo-6-nitroquinolin-2(1H)-one

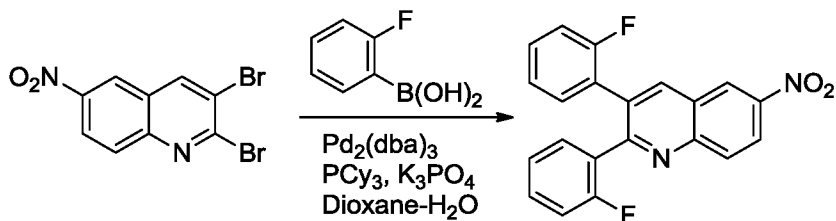


To a stirred solution of 6-nitroquinolin-2(1H)-one (Preparation 7, Step 1) (7.315 g, 38.46 mmol) in water (25.15 mL) was added NaBrO₃ (6.965 g, 46.16 mmol) at -10 to 5 °C, then aq. 48% HBr (133.8 mL) was added dropwise at the same temperature. The whole was then refluxed at 100 °C for 4 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was quenched in ice-water and stirred at 0-5 °C for 1 h. The resulting solid precipitate was filtered off and washed with water to give a solid material which was slurry washed with hexane (500 mL) to afford the title compound (8.0 g, yield 77.3 %) as a yellow solid. LCMS m/z: 266.98 [M-H].

Step 3: 2,3-Dibromo-6-nitroquinoline

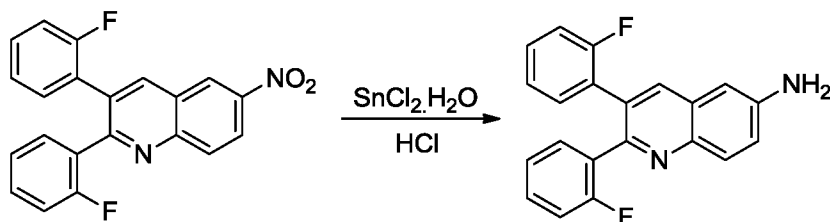


A solution of 3-bromo-6-nitroquinolin-2(1H)-one (Preparation 7, Step 2) (2.0 g, 7.435 mmol) in POBr₃ (4.263 g, 14.869 mmol) was heated at 140 °C for 12 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was quenched with cold water and basified with aqueous NaHCO₃ to pH 7-8. The aqueous mixture was extracted with EtOAc and washed with brine. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the title compound (1.6 g crude) as a crude brown solid. LCMS m/z: 231 [M+H].

Step 4: 2,3-Bis(2-fluorophenyl)-6-nitroquinoline

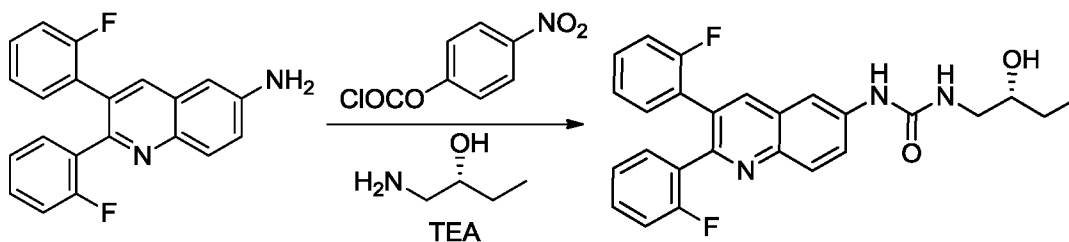
A solution of 2,3-dibromo-6-nitroquinoline (Preparation 7, Step 3) (1.6 g, 4.805 mmol), (2-fluorophenyl)boronic acid (1.7 g, 12.151 mmol) and K₃PO₄ (4.118 g, 19.399 mmol) in
 5 a mixture of solvents 1,4-dioxane (20 mL) and water (2 mL) was degassed with argon for 30 min. then Pd₂(dba)₃ (444 mg, 0.485 mmol) and PCy₃ (272 mg, 0.969 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 16 h under an inert atmosphere. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc, filtered and the filtrate was
 10 partitioned with water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was purified by column chromatography to give the title compound (1.2 g, yield 68.73%) as a pale yellow solid. LCMS m/z: 363 [M+H].

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Step 5: 2,3-Bis(2-fluorophenyl)quinolin-6-amine

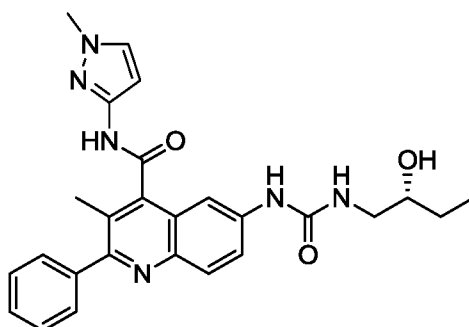
To a stirred solution of 2,3-bis(2-fluorophenyl)-6-nitroquinoline (Preparation 7, Step 4) (1.2 g, 3.312 mmol) in THF (15 mL) was added aq. HCl (0.2 mL) followed by
 20 SnCl₂.H₂O (2.98 g, 13.22 mmol) at RT and the resulting reaction mixture was then refluxed at 60 °C for 2 h. Progress of the reaction mixture was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO₃ and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the crude product which was
 25 purified by column chromatography to give the title compound (1.0 g, yield 91%) as a light yellow solid. LCMS m/z: 333 [M+H].

Preparation 8: (R)-1-(2,3-Bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea
(Example 20)



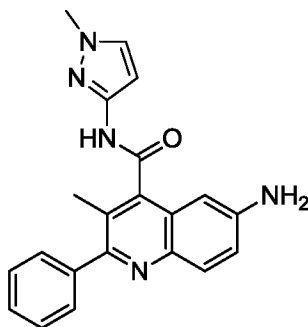
To a stirred solution of 2,3-bis(2-fluorophenyl)quinolin-6-amine (Preparation 7, Step 5) (1.0 g, 3.008 mmol) in THF (15 mL) was added p-nitrophenyl chloroformate (758 mg, 3.761 mmol) and the whole stirred at RT for 2 h. After complete consumption of the amine by TLC, TEA (1.257 g, 12.445 mmol) and (R)-1-aminobutan-2-ol (0.335 g, 3.764 mmol) were added dropwise and the combined mixture was further stirred at RT for 2 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc, washed with saturated solution of NaHCO₃ thrice followed by brine and 0.02N HCl solution and again with brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by column chromatography to afford the title compound (0.6 g, yield 45%) as a white solid. LCMS m/z: 448.37 [M+H]⁺; Purity 98.05%; ¹H NMR (500 MHz; DMSO-d₆): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.34-1.45 (m, 2H), 2.99-3.03 (m, 1H), 3.24-3.27 (m, 1H), 3.44 (d, *J* = 4.9 Hz, 1H), 4.81 (d, *J* = 5.1 Hz, 1H), 6.39 (t, *J* = 5.45 Hz, 1H), 7.04-7.20 (m, 4H), 7.30-7.36 (m, 3H), 7.44 (t, *J* = 7.35 Hz, 1H), 7.75-7.77 (m, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 8.17 (d, *J* = 2.05 Hz, 1H), 8.29 (s, 1H), 9.15 (s, 1H)

Example 115: (R)-6-(3-(2-Hydroxybutyl)ureido)-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide

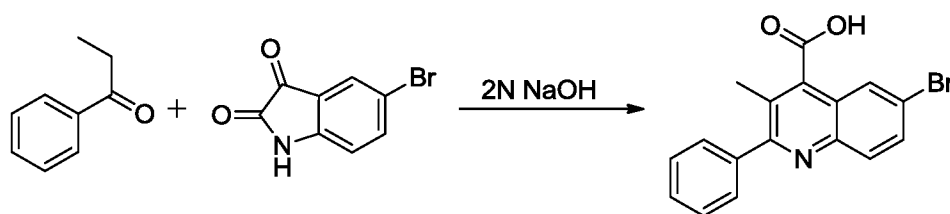


Example 115 was prepared according to the methods described in General Procedures 1, 4, 19, 23 and the method described below.

Preparation 9: 6-Amino-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide



Step 1: 6-Bromo-3-methyl-2-phenylquinoline-4-carboxylic acid

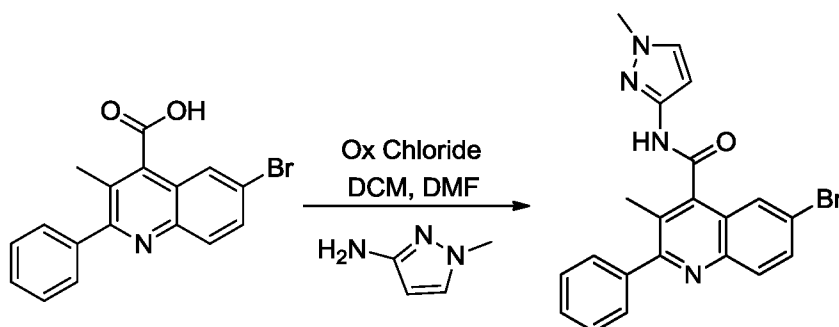


5

A stirred solution of commercially available 5-bromoisatin (3.0 g, 13.272 mmol) in 2N NaOH (60 mL) solution was refluxed at 90 °C for 30 min. The reaction mixture was then cooled to RT and commercially available propiophenone (1.959 g, 14.60 mmol) was added at RT. The whole was refluxed at 85-90 °C for 16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was filtered and the obtained solid was dissolved in water and acidified with 2N HCl solution to give a solid precipitate which was filtered and washed with water to afford the title compound (1.3 g, yield 28.6%) as a white solid. LCMS m/z: 342 [M+H].

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Step 2: 6-Bromo-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide

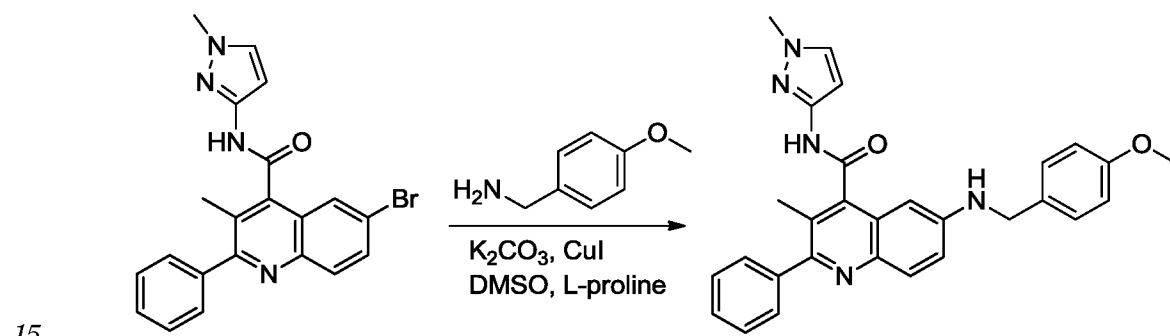


To a stirred solution of 6-bromo-3-methyl-2-phenylquinoline-4-carboxylic acid (Preparation 9, Step 1) (600 mg, 1.753 mmol) in a mixture of solvents DCM (10 mL) and DMF (10 mL) was added oxalyl chloride (0.229 mL, 2.63 mmol) dropwise at 0-5

20

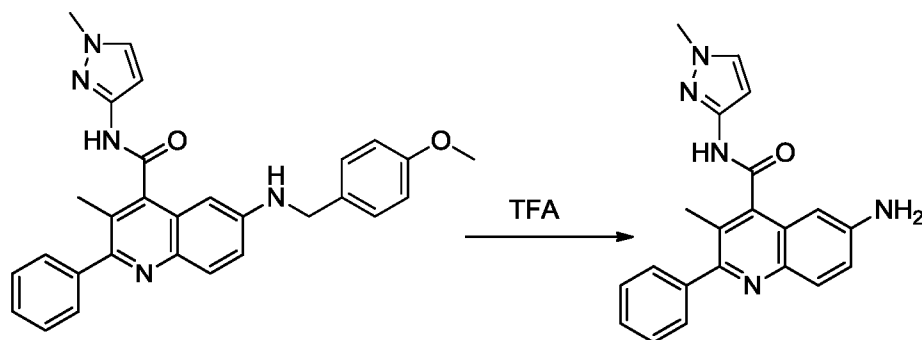
°C. The whole was stirred at RT for 1 h under an inert atmosphere. After formation of the corresponding acid chloride (a small aliquot was quenched in MeOH and checked by LCMS), excess oxalyl chloride was evaporated in vacuo to give a residue. A pre-prepared mixture of 1-methyl-1H-pyrazol-3-amine (340 mg, 3.506 mmol) and TEA (0.977 mL, 7.01 mmol) in DCM (5 mL) was added dropwise into the concentrated acid chloride residue at low temperature and the resulting reaction mixture was further stirred at RT for 16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with DCM, washed with brine solution and dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure to give the crude compound which was purified by combi-flash to afford the title compound (603 mg, yield 79.0%) as a yellow solid. LCMS m/z: 421.30 [M+H].

Step 3: 6-((4-Methoxybenzyl)amino)-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide



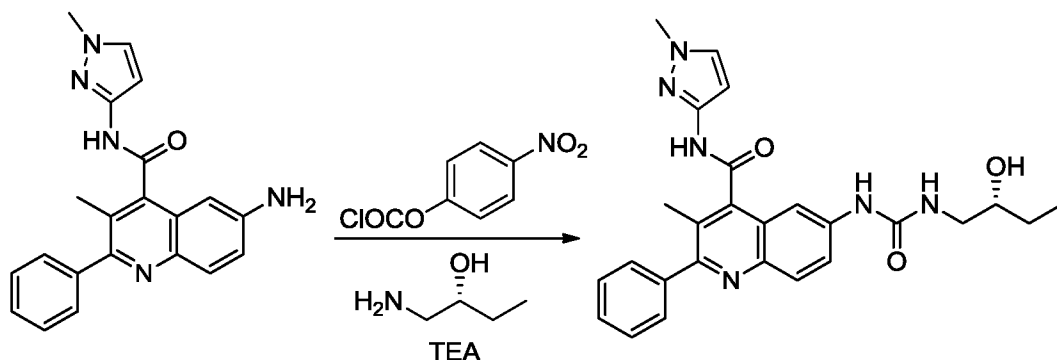
To a stirred solution of 6-bromo-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide (Preparation 9, Step 2) (550 mg, 1.306 mmol) in DMSO (10 mL) was added p-methoxy benzyl amine (899 mg, 6.527 mmol) followed by K₂CO₃ (451 g, 2.263 mmol) under an inert atmosphere, then CuI (497 mg, 2.611 mmol) and L-proline (171 mg, 1.305 mmol) were added. The resulting reaction mixture was transferred to a sealed tube and heated at 90 °C for 14 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was poured into ice-water. The aqueous reaction mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a crude product which was purified by column chromatography to afford the title compound (484 mg, yield 77.5%) as a yellow solid. LCMS m/z: 478 [M+H].

Step 4: 6-Amino-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide



A solution of 6-((4-methoxybenzyl)amino)-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide (Preparation 9, Step 3) (484 mg, 1.014 mmol) in TFA (5 mL) was stirred at RT for 14 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was neutralized with an aqueous solution of NaHCO₃, extracted with 5% MeOH in DCM and washed with a saturated solution of NaHCO₃ followed by brine. The combined organics were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound (450 mg, purity 91.69%) as a crude solid which was used in the next step without any further purification. LCMS m/z: 358.34 [M+H].

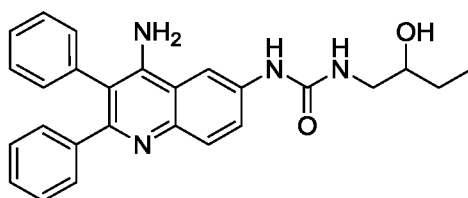
Preparation 10: (R)-6-(3-(2-Hydroxybutyl)ureido)-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide (Example 115)



To a stirred solution of 6-amino-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide (Preparation 9, Step 4) (212 mg, 0.593 mmol) in THF (5 mL) was added p-nitrophenyl chloroformate (132 mg, 0.653 mmol) and the whole stirred at RT for 1 h. After complete consumption of the amine by TLC, TEA (0.33 mL, 2.374 mmol) and (R)-1-aminobutan-2-ol (63.47 mg, 0.712 mmol) were added dropwise and the combined mixture was further stirred at RT for 3 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted

with EtOAc, washed with a saturated solution of NaHCO₃ thrice followed by brine and 0.02N HCl solution and again with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by prep-HPLC to afford the title compound (89.6 mg, yield 32%) as a white solid. LCMS m/z: 473.5 [M+H]; Purity 98.83%; ¹H NMR (500 MHz; DMSO-d₆): δ 0.88 (bs, 3H), 1.33-1.41 (m, 2H), 2.31 (s, 3H), 2.95 (bs, 1H), 3.20 (bs, 1H), 3.41 (s, 1H), 3.79 (s, 3H), 4.77 (s, 1H), 6.20 (s, 1H), 6.72 (s, 1H), 7.49-7.57 (m, 5H), 7.68 (s, 1H), 7.79-7.82 (m, 2H), 7.91 (d, *J* = 10.1 Hz, 1H), 9.07 (s, 1H) 11.12 (s, 1H).

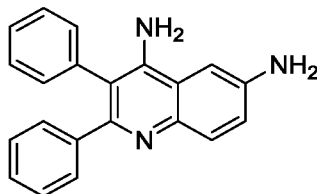
Example 95: 1-(4-Amino-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea



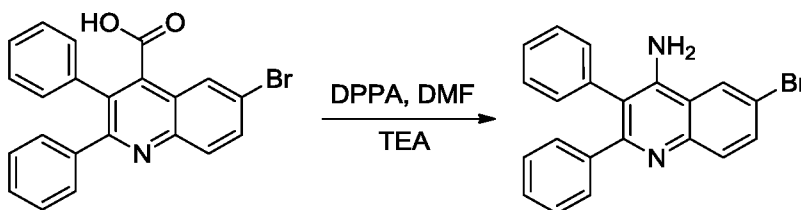
Example 95 was prepared according to the methods described in General Procedures 1, 4, 19, 22 and the method described below.

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Preparation 11: 2,3-Diphenylquinoline-4,6-diamine



Step 1: 6-Bromo-2,3-diphenylquinolin-4-amine

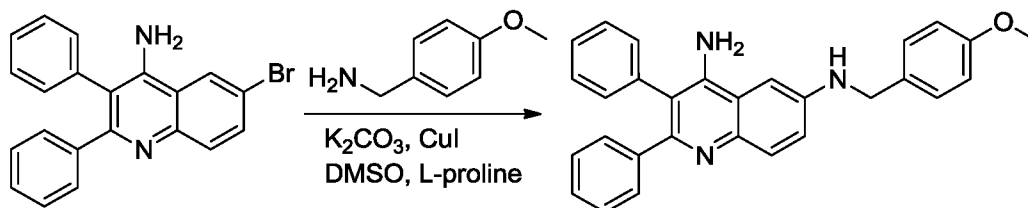


To a stirred solution of 6-bromo-2,3-diphenylquinoline-4-carboxylic acid (Synthesized according to method described in preparation 9, Step 1) (2.0 g, 4.948 mmol) in DMF (30 mL) was added TEA (1.03 mL, 7.42 mmol) at 0-5 °C under a N₂ atmosphere, and diphenyl phosphorazide (2.126 mL, 9.896 mmol) was added. The whole was stirred at RT for 2 h then water (30 mL) was added and refluxed at 100 °C for 4 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was diluted

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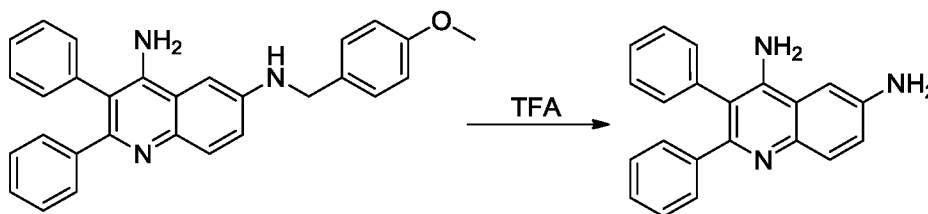
with water to give a solid precipitate which was filtered and washed with water followed by hexane. The obtained solid was dried in a vacuum oven to afford the title compound (1.5 g, yield 81%) as a pale yellow solid. LCMS m/z: 375.40/377.35 [M+H].

5 Step 2: N6-(4-Methoxybenzyl)-2,3-diphenylquinoline-4,6-diamine

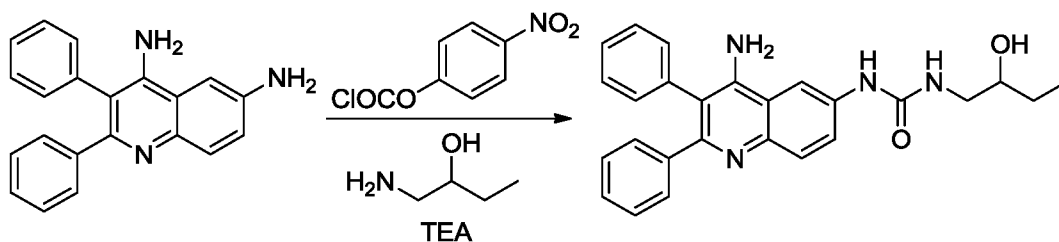


To a stirred solution of 6-bromo-2,3-diphenylquinolin-4-amine (Preparation 11, Step 1) (500 mg, 1.06 mmol) in DMSO (15 mL) was added p-methoxy benzyl amine (0.83 mL, 6.39 mmol) followed by K₂CO₃ (365.7 mg, 2.65 mmol) under an inert atmosphere, then
 10 CuI (100.9 mg, 0.53 mmol) and L-proline (48.8 mg, 0.424 mmol) were added. The resulting reaction mixture was transferred to a sealed tube and heated at 90 °C for 16 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was poured into ice-water. The aqueous reaction mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and
 15 concentrated in vacuo to give a crude product which was purified by column chromatography to afford the title compound (329 mg, yield 71.5%) as a yellow solid. LCMS m/z: 432.35 [M+H].

Step 3: 2,3-Diphenylquinoline-4,6-diamine

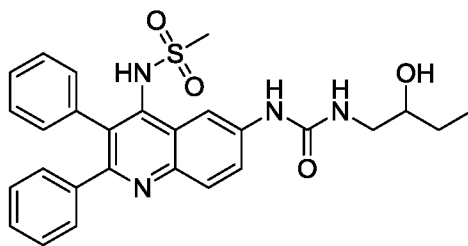


A solution of N6-(4-methoxybenzyl)-2,3-diphenylquinoline-4,6-diamine (Preparation 11, Step 2) (320 mg, 0.742 mmol) in TFA (7 mL) was stirred at RT for 16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with water and neutralized with solid NaHCO₃, extracted with EtOAc and
 25 washed with a saturated solution of NaHCO₃ followed by brine. The combined organics were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound (400 mg, purity 88%) as a crude solid which was used in the next step without any further purification. LCMS m/z: 312.19 [M+H].

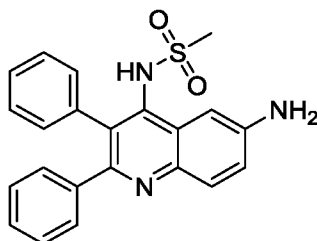
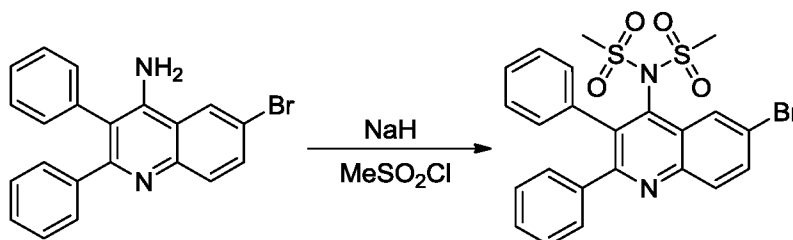
Preparation 12: 1-(4-Amino-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea(Example 95)

To a stirred solution of 2,3-diphenylquinoline-4,6-diamine (Preparation 11, Step 3) (80
 5 mg, 0.257 mmol) in THF (3 mL) was added p-nitrophenyl chloroformate (64.78 mg,
 0.321 mmol) and the whole stirred at RT for 1 h. After complete consumption of the
 amine by TLC, TEA (0.14 mL, 1.06 mmol) and 1-aminobutan-2-ol (0.03 mL, 0.312
 mmol) were added dropwise and the combined mixture was further stirred at RT for 3
 h. Progress of the reaction was monitored by TLC/LCMS and after completion the
 10 reaction mixture was diluted with EtOAc and washed with 0.5N NaOH solution
 followed by brine. The organic layer was dried over anhydrous Na₂SO₄ and
 concentrated in vacuo to give the crude product which was purified by prep-HPLC to
 afford the title compound (20 mg, yield 18.3%) as a white solid. LCMS m/z: 427.37
 [M+H]⁺; Purity 98.19%; ¹H NMR (500 MHz; DMSO-d₆): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.42-
 15 1.47 (m, 2H), 2.98-3.03 (m, 1H), 3.24-3.28 (m, 1H), 3.44-3.45 (m, 1H), 4.82 (d, *J* = 4.95
 Hz, 1H), 6.53 (s, 1H), 7.21 (d, *J* = 7.05 Hz, 2H), 7.36-7.39 (m, 10H), 7.87-7.92 (m, 2H),
 8.34 (s, 1H), 8.99 (s, 1H).

Example 94: N-(6-(3-(2-Hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)methanesulfonamide



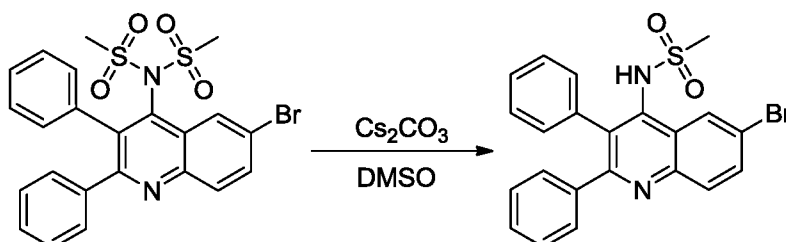
Example 94 was prepared according to the methods described in General Procedures 1,
 4, 19, 22 and the method described below.

Preparation 13: N-(6-Amino-2,3-diphenylquinolin-4-yl)methanesulfonamideStep 1: N-(6-Bromo-2,3-diphenylquinolin-4-yl)-N-(methylsulfonyl)methanesulfonamide

5

To a stirred solution of 6-bromo-2,3-diphenylquinolin-4-amine (Preparation 11, Step 1) (800 mg, 2.12 mmol) in dry DMF (10 mL) was added NaH (153 mg, 6.38 mmol, 60% suspension in mineral oil) at 0-5 °C and the whole stirred at RT for 20 min. Then MeSO₂Cl (0.5 mL, 6.36 mmol) was added dropwise at 0-5 °C and the whole stirred at
 10 RT for a further 2 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was quenched with a saturated solution of NH₄Cl and extracted with MTBE and washed with water followed by brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound (1.132 g crude) as a yellow gummy solid. LCMS m/z: 531.25 [M+H].

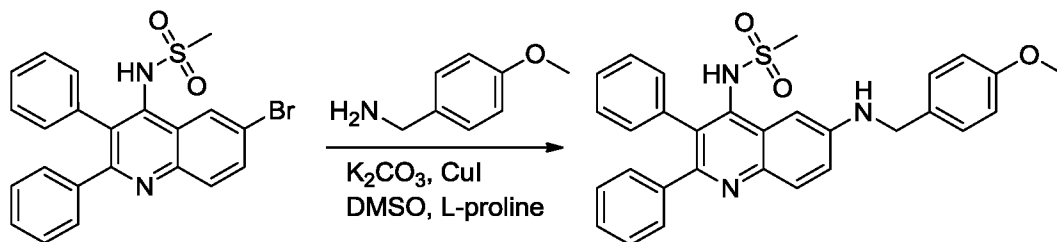
15

Step 2: N-(6-Bromo-2,3-diphenylquinolin-4-yl)methanesulfonamide

To a stirred solution of N-(6-bromo-2,3-diphenylquinolin-4-yl)-N-(methylsulfonyl)methane-sulfonamide (Preparation 13, Step 1) (1.132 g, 2.13 mmol) in
 20 DMSO (10 mL) was added Cs₂CO₃ (2.776 g, 8.5 mmol) and the mixture heated in a sealed tube at 120 °C for 16 h. The reaction was checked by TLC/LCMS and after completion the reaction mixture was quenched with ice-water and extracted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to

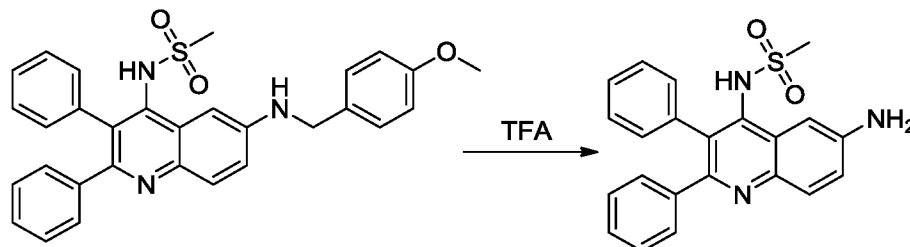
give the crude product which was purified by combi-flash to afford the title compound (900 mg, yield 93%) as a brown solid. LCMS m/z : 453.17 [M+H].

Step 3: N-(6-((4-Methoxybenzyl)amino)-2,3-diphenylquinolin-4-yl)methanesulfonamide



To a stirred solution of N-(6-bromo-2,3-diphenylquinolin-4-yl)methanesulfonamide (Preparation 13, Step 2) (383 mg, 0.84 mmol) in DMSO (15 mL) was added p-methoxy benzyl amine (0.667 mL, 5.06 mmol) followed by K₂CO₃ (289.8 mg, 2.1 mmol) under an inert atmosphere, then CuI (80 mg, 0.50 mmol) and L-proline (39 mg, 0.336 mmol) were added. The resulting reaction mixture was transferred to a sealed tube and heated at 90 °C for 16 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was poured into ice-water. The aqueous reaction mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a crude product which was purified by column chromatography to afford the title compound (300 mg, yield 69.7%) as a yellow solid. LCMS m/z : 510.37 [M+H].

Step 4: N-(6-Amino-2,3-diphenylquinolin-4-yl)methanesulfonamide

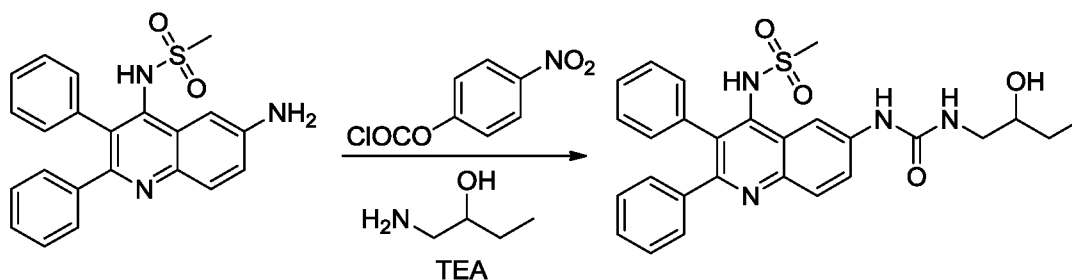


A solution of N-(6-((4-methoxybenzyl)amino)-2,3-diphenylquinolin-4-yl)methanesulfonamide (Preparation 13, Step 3) (293 mg, 0.575 mmol) in TFA (4 mL) was stirred at RT for 16 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with water and neutralized with solid NaHCO₃, extracted with EtOAc and washed with a saturated solution of NaHCO₃ followed by brine. The combined organics were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound (400 mg, crude) as a yellow gummy

semisolid which was used in the next step without any further purification. LCMS m/z: 390.31 [M+H].

Preparation 14: N-(6-(3-(2-Hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)methanesulfonamide (Example 94)

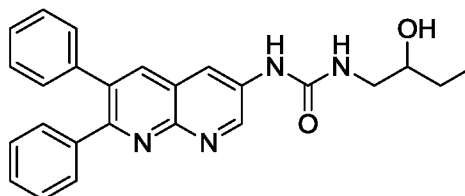
5



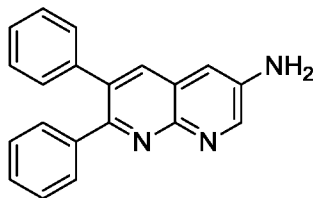
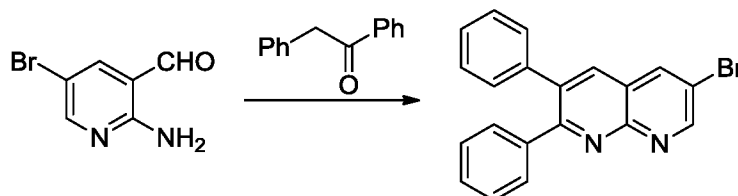
To a stirred solution of N-(6-amino-2,3-diphenylquinolin-4-yl)methanesulfonamide (Preparation 13, Step 4) (400 mg, 1.02 mmol) in THF (5 mL) was added p-nitrophenyl chloroformate (258.86 mg, 1.28 mmol) and the whole stirred at RT for 1 h. After
 10 complete consumption of the amine by TLC, TEA (0.58 mL, 4.207 mmol) and 1-aminobutan-2-ol (0.12 mL, 1.28 mmol) were added dropwise and the combined mixture was further stirred at RT for 3 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mixture was diluted with EtOAc and washed with 0.5N NaOH solution followed by brine. The organic layer was dried over
 15 anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product which was purified by prep-HPLC to afford the title compound (150 mg, yield 29%) as a white solid. LCMS m/z: 505.37 [M+H]; Purity 98.16%; ¹H NMR (500 MHz; DMSO-d₆): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.34-1.46 (m, 2H), 2.24 (s, 3H), 2.98-3.03 (m, 1H), 3.24-3.35 (m, 1H), 3.45 (s, 1H), 4.81 (d, *J* = 5.1 Hz, 1H), 6.36 (d, *J* = 5.1 Hz, 1H), 7.22-7.34 (m,
 20 10H), 7.97 (d, *J* = 9 Hz, 1H), 8.05 (d, *J* = 9.15 Hz, 1H), 8.17 (s, 1H), 9.16 (s, 1H), 9.56 (bs, 1H).

Example 145: 1-(6,7-Diphenyl-1,8-naphthyridin-3-yl)-3-(2-hydroxybutyl)urea

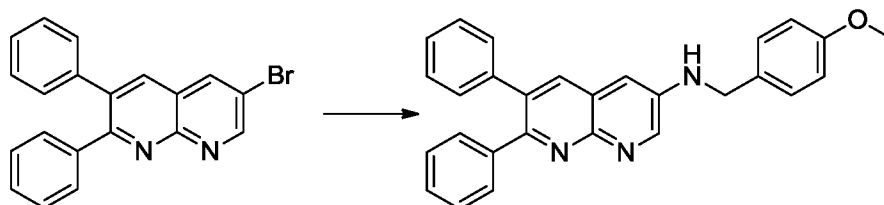
25



Example 145 was prepared according to the methods described in General Procedures 1, 4, 15 and the method described below.

Preparation 16: 6,7-Diphenyl-1,8-naphthyridin-3-amineStep-1: 6-Bromo-2,3-diphenyl-1,8-naphthyridine

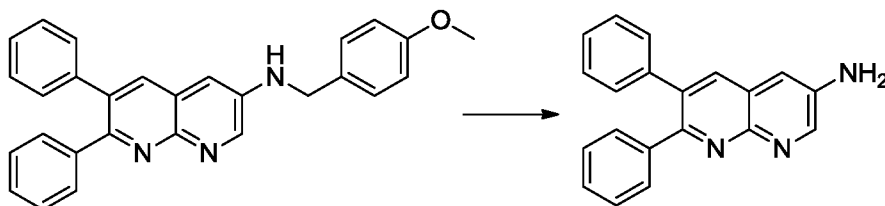
5 To a stirred solution of commercially available 2-amino-5-bromonicotinaldehyde (250 mg, 1.24 mmol) in piperidine (3 mL), 1,2-diphenylethan-1-one (244 mg, 1.24 mmol) was added at room temperature and the resulting reaction mixture was heated at 120 °C for 16 h in a sealed tube. The reaction was monitored by LCMS and after completion of the reaction, it was quenched with saturated sodium bicarbonate solution and extracted with EtOAc (3 x 50 mL) and washed with water (3 x 50 mL) followed by brine (3 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude product which was purified by column chromatography on silica gel to give the title compound (200 mg, 45% yield) as an off white solid. LCMS m/z: 361 [M+H].

Step-2: N-(4-Methoxybenzyl)-6,7-diphenyl-1,8-naphthyridin-3-amine

To a stirred solution of 6-bromo-2,3-diphenyl-1,8-naphthyridine (Preparation 16, Step 1) (400 mg, 1.108 mmol) in toluene (10 mL), p-methoxy benzyl amine (227.70 mg, 1.66 mmol), K₃PO₄ (704.70 mg, 3.32 mmol) and X-Phos (105.48 mg, 0.222 mmol) were added and the reaction mixture was degassed with N₂ gas for 10 min. After that Pd₂(dba)₃ (101.38 mg, 0.111 mmol) was added to the reaction mixture. The whole reaction mixture was capped and stirred at 100 °C for 16 h. The reaction was monitored by LCMS and after completion of the reaction the reaction mixture was quenched with water and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine solution (3 x 50 mL), dried over anhydrous Na₂SO₄ and evaporated in vacuo

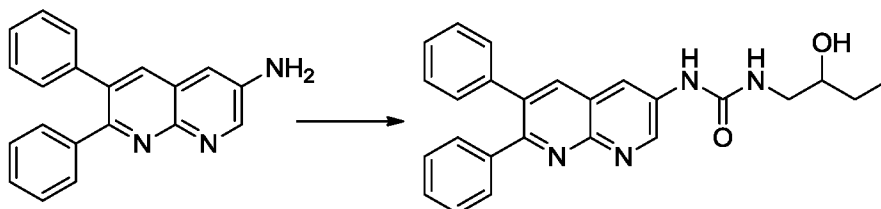
to give a crude product which was purified by column chromatography (silica gel, eluent: 60% EtOAc in hexane) to afford the title compound (300 mg, 65% yield) as a reddish gummy solid. LCMS m/z: 418.0 [M+H].

5 Step-3: 6,7-Diphenyl-1,8-naphthyridin-3-amine



To a stirred solution of N-(4-methoxybenzyl)-6,7-diphenyl-1,8-naphthyridin-3-amine (Preparation 16, Step 2) (190 mg, 0.455 mmol) in DCM (1 mL) was added TFA (1.8 mL) and the whole stirred for 2 h. The reaction was monitored by LCMS and after
 10 completion of the reaction it was basified with saturated sodium bicarbonate solution and extracted with EtOAc (3 x 50 mL), washed with water (3 x 50 mL) followed by brine (3 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, eluent: 80% EtOAc in hexane) to afford the title compound (100 mg, 73%
 15 yield) as a yellowish gum. LCMS m/z: 297.9 [M+H].

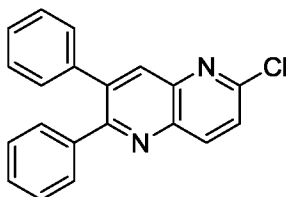
Preparation 17: 1-(6,7-Diphenyl-1,8-naphthyridin-3-yl)-3-(2-hydroxybutyl)urea
 (Example 145)



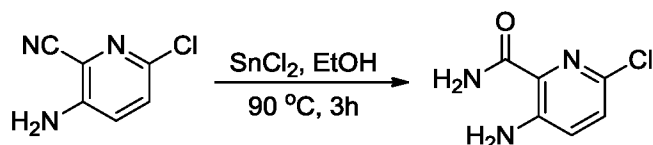
20 To a stirred solution of 6,7-diphenyl-1,8-naphthyridin-3-amine (Preparation 16, Step 3) (150 mg, 0.504 mmol) in THF (3 mL) was added p-nitrophenyl chloroformate (152.51 mg, 0.757 mmol) at 0-5 °C and the whole stirred at room temperature for 3 h. To the reaction mixture was added TEA (0.352 mL, 2.52 mmol) and 1-aminobutan-2-ol (0.053 mL, 0.555 mmol) at the same temperature and the whole stirred for another 6 h. The
 25 reaction was monitored by LCMS and after completion the solvent was evaporated to give the crude product. The crude was purified by reverse phase prep-HPLC to afford the title compound (23 mg, 11% yield) as an off white solid. LCMS m/z: 413.5 [M+H]; Purity 99.45%; ¹H NMR (400 MHz; DMSO-d₆): δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.32-1.39 (m,

1H), 1.41-1.48 (m, 1H), 2.98-3.05 (m, 1H), 3.23-3.28 (m, 1H), 3.45 (d, $J = 4.8$ Hz, 1H), 4.78 (d, $J = 5.08$ Hz, 1H), 6.48 (d, $J = 5.32$ Hz, 1H), 7.26-7.39 (m, 10H), 8.35 (s, 1H), 8.57 (d, $J = 2.72$ Hz, 1H), 8.93 (d, $J = 2.72$ Hz, 1H), 9.28 (s, 1H).

5 Preparation 18: 6-Chloro-2,3-diphenyl-1,5-naphthyridine

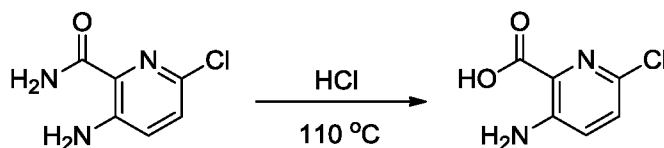


Step-1: 3-Amino-6-chloropicolinamide

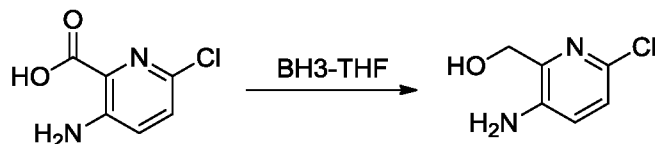


To a stirred solution of commercially available 3-amino-6-chloropicolinonitrile (4.0 g, 26.1 mmol) in EtOH (40.0 mL) was added SnCl₂ (9.92 g, 52.3 mmol) and the reaction mixture was stirred at 90 °C for 16 h. Progress of the reaction was monitored by LCMS and after completion of the reaction, the excess solvent was concentrated under reduced pressure and the reaction mixture was quenched with 2M NaOH solution to make the pH 8-9 and the product was then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine solution (1 x 30 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to afford the title compound (3.2 g, 71.2% yield) as a crude light yellow solid which was used in the next step without any further purification. LCMS m/z: 172.0 [M+H].

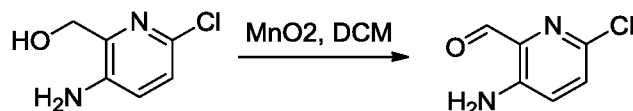
20 Step-2: 3-Amino-6-chloropicolinic acid



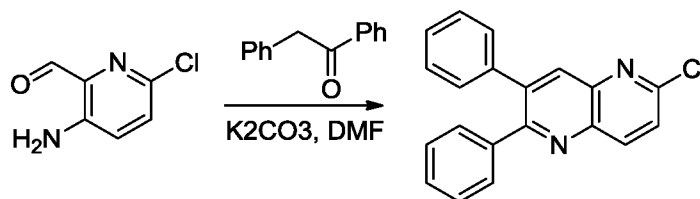
3-Amino-6-chloropicolinamide (Preparation 18, Step-1) (3.0 g, 17.5 mmol) was taken up in cone. HCl (15 mL) and heated to 110 °C for 5 h. The solvent was removed under reduced pressure to afford the title compound (3.0 g, crude) as a yellow solid. The crude was used in the next step without any further purification. LCMS m/z: 173.09 [M+H].

Step-3: (3-Amino-6-chloropyridin-2-yl)methanol

To a stirred solution of 3-amino-6-chloropicolinic acid (Preparation 18, Step-2) (3.0 g, 17.4 mmol) in THF (30.0 mL) was added BH₃-THF (1M in THF) (69.5 mL, 69.5 mmol) and the reaction mixture was stirred at room temperature for 48 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was diluted with HCl and H₂O, then neutralized with NaHCO₃ and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to afford the title compound (2.5 g, crude) as a yellow sticky solid which was used in the next step without any further purification.

Step-4: 3-Amino-6-chloropicolinaldehyde

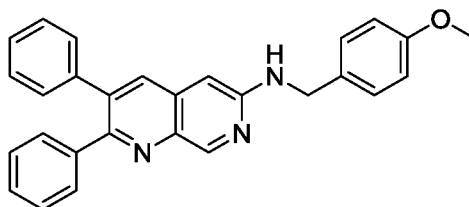
To a stirred solution of (3-amino-6-chloropyridin-2-yl)methanol (Preparation 18, Step-3) (2.5 g, 15.8 mmol) in DCM (50 mL) was added MnO₂ (2.75 g, 31.6 mmol). After 24 h another portion of MnO₂ (2 eq.) was added to the mixture and the whole was stirred for a further 24 h at RT. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was filtered through Celite, and the solvent was removed *in vacuo* to afford the title compound (950 mg, 38.4% yield) as a yellow solid. LCMS m/z: 156.84 [M+H].

Step-5: 6-Chloro-2,3-diphenyl-1,5-naphthyridine

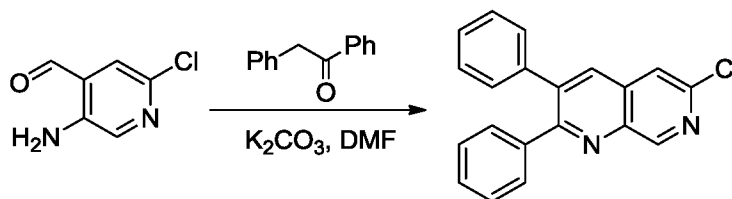
To a stirred solution of 3-amino-6-chloropicolinaldehyde (Preparation 18, Step-4) (100 mg, 0.64 mmol) in DMF (2.0 mL) was added K₂CO₃ (88.6 mg, 0.64 mmol) and 1,2-diphenylethan-1-one (126 mg, 0.64 mmol) and the reaction mixture was stirred at 90 °C for 16 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was quenched with crushed ice and cold water (20 mL). The product

was extracted using EtOAc (3 x 20 mL) and the combined organic layers were washed with brine solution (1 x 30 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by preparative-TLC (20% EtOAc-Hexane) to afford the title compound (3 mg, 1.48%
 5 yield) as an off white solid. LCMS m/z: 316.9 [M+H]; ¹H NMR (400 MHz; DMSO-d₆): δ 8.53 (d, *J* = 8.8 Hz, 1H), 8.36 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.31-7.40 (m, 10H),

Preparation 19: N-(4-Methoxybenzyl)-2,3-diphenyl-1,7-naphthyridin-6-amine

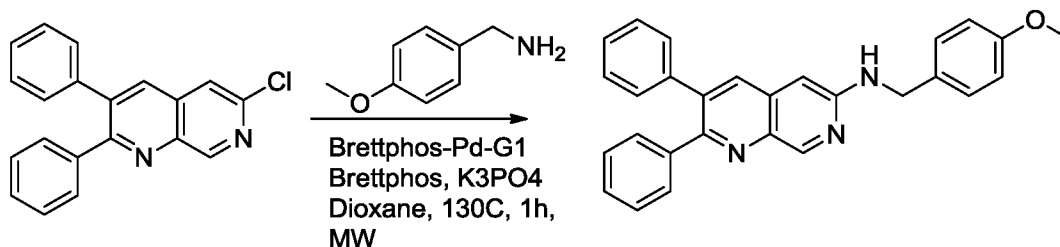


10 Step-1: 6-Chloro-2,3-diphenyl-1,7-naphthyridine

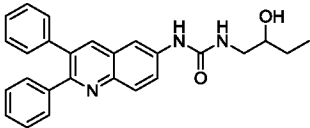
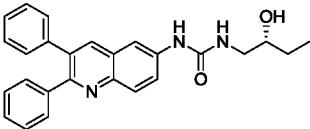


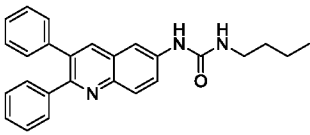
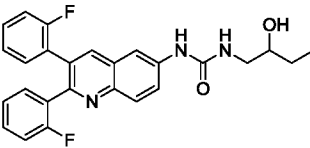
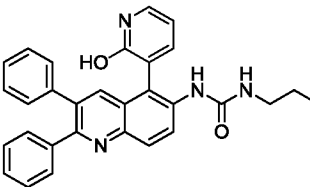
To a stirred solution of commercially available 5-amino-2-chloroisonicotinaldehyde (300 mg, 1.92 mmol) in DMF (6.0 mL) were added K₂CO₃ (265.7 mg, 1.92 mmol) and 1,2-diphenylethan-1-one (377 mg, 1.92 mmol) and the reaction mixture was stirred at
 15 90 °C for 16 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was quenched with crushed ice and cold water (20 mL). The product was extracted using EtOAc (3 x 20 mL) and the combined organic layers were washed with brine solution (3 x 20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to afford the crude product which was
 20 purified by preparative-TLC (20% EtOAc-Hexane) to afford the title compound (240 mg, 34.9% yield) as an off white solid. LCMS m/z: 316.9 [M+H].

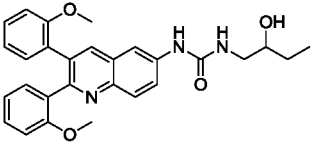
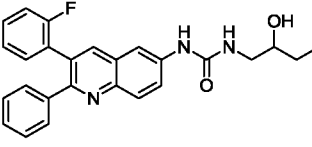
Step-2: N-(4-Methoxybenzyl)-2,3-diphenyl-1,7-naphthyridin-6-amine

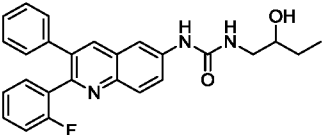
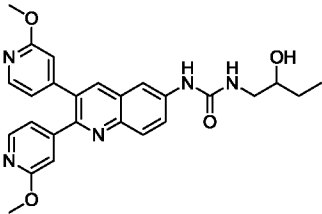


To a degassed solution of 6-chloro-2,3-diphenyl-1,7-naphthyridine (Preparation 19, Step-1) (100 mg, 0.32 mmol) in toluene (1 mL) were added p-methoxy benzyl amine (0.08 mL, 0.63 mmol), K₃PO₄ (201 mg, 0.95 mmol), Brett-phos (57.23 mg, 0.063 mmol) and Brettphos-Pd-G1 (50.43 mg, 0.063 mmol). The whole reaction mixture was capped and stirred at 130 °C for 1 h in the microwave. After completion of the reaction (monitored by LCMS) the reaction mixture was quenched with water and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine solution (1 x 10mL), dried over anhydrous Na₂SO₄ and evaporated to give the crude product which was purified by column chromatography (silica gel, eluent: 50% EtOAc in hexane) followed by prep-TLC to afford the title compound (10 mg, crude) as a brown solid. LCMS m/z: 418.0 [M+H].

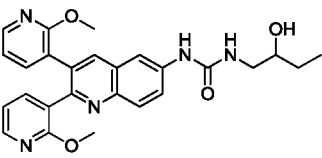
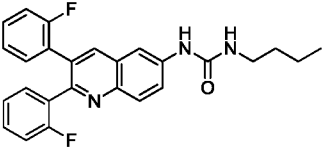
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
1		1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.3 Hz, 3H), 1.33-1.46 (m, 2H), 2.99-3.03 (m, 1H), 3.25 (t, <i>J</i> = 7.85 Hz, 1H), 3.44 (d, <i>J</i> = 4.4 Hz, 1H), 4.81 (d, <i>J</i> = 4.85 Hz, 1H), 6.35 (s, 1H), 7.26-7.36 (m, 10H), 7.72 (d, <i>J</i> = 8.85 Hz, 1H), 7.95 (d, <i>J</i> = 9.0 Hz, 1H), 8.13 (s, 1H), 8.20 (s, 1H), 9.05 (s, 1H)	412.19	97.58
2		(R)-1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.42 (m, 1H), 1.44-1.47 (m, 1H), 2.99-3.04 (m, 1H), 3.21-3.26 (m, 1H), 3.42-3.46 (m, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.47 (s, 1H), 7.25-7.36 (m, 10H), 7.73 (dd, <i>J</i> ' = 2.3 Hz,	412.17	96.82

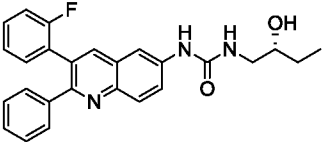
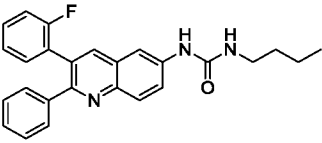
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			$J'' = 9.05$ Hz, 1H), 7.95 (d, $J = 9.1$ Hz, 1H), 8.14 (s, 1H), 8.19 (s, 1H), 9.26 (s, 1H)		
3		1-butyl-3-(2,3-diphenylquinolin-6-yl)urea	(500 MHz; DMSO- d_6): δ 0.92 (t, $J = 7.3$ Hz, 3H), 1.30-1.38 (m, 2H), 1.42-1.48 (m, 2H), 3.12-3.16 (m, 2H), 6.31 (t, $J = 5.55$ Hz, 1H), 7.25-7.36 (m, 10H), 7.72-7.74 (m, 1H), 7.95 (d, $J = 9.05$ Hz, 1H), 8.13 (s, 1H), 8.22 (s, 1H), 8.87 (s, 1H)	396.20	98.79
4		1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO- d_6): δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.35-1.45 (m, 2H), 2.99-3.03 (m, 1H), 3.24-3.27 (m, 1H), 3.45-3.46 (m, 1H), 4.81 (d, $J = 5.1$ Hz, 1H), 6.34 (t, $J = 5.55$ Hz, 1H), 7.02-7.20 (m, 4H), 7.30-7.36 (m, 3H), 7.42-7.45 (m, 1H), 7.75-7.77 (m, 1H), 7.98 (d, $J = 9.05$ Hz, 1H), 8.16 (d, $J = 2.15$ Hz, 1H), 8.29 (s, 1H), 9.07 (s, 1H)	448.15	99.15
5		1-butyl-3-(5-(2-hydroxypyridin-3-yl)-2,3-diphenylquinolin-6-yl)urea	(500 MHz; DMSO- d_6): δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.28-1.33 (m, 2H), 1.38-1.42 (m, 2H), 3.05-3.10 (m, 2H), 6.41 (t, $J = 6.6$	489.20	98.58

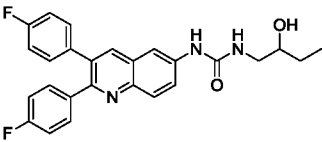
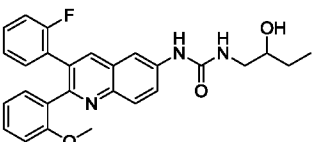
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		in-6-yl)urea	Hz, 1H), 6.84 (t, <i>J</i> = 5.3 Hz, 1H), 7.11-7.13 (m, 2H), 7.28-7.36 (m, 8H), 7.52-7.59 (m, 4H), 8.00 (d, <i>J</i> = 9.3 Hz, 1H), 8.59 (d, <i>J</i> = 9.3 Hz, 1H), 11.99 (s, 1H)		
6		1-(2,3-bis(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.45 (m, 2H), 3.00-3.02 (m, 1H), 1.20-1.24 (m, 1H), 3.33 (s, 3H), 3.42 (bs, 4H), 4.78 (d, <i>J</i> = 5.15 Hz, 1H), 6.29-6.31 (m, 1H), 6.73 (d, <i>J</i> = 8.3 Hz, 1H), 6.83-6.85 (m, 2H), 6.93 (t, <i>J</i> = 7.3 Hz, 1H), 7.1 (bs, 1H), 7.18-7.23 (m, 2H), 7.30 (dd, <i>J'</i> = 1.5 Hz, <i>J''</i> = 7.45 Hz, 1H), 7.67 (dd, <i>J'</i> = 2.3 Hz, <i>J''</i> = 9.05 Hz, 1H), 7.89 (d, <i>J</i> = 9.05 Hz, 1H), 8.00 (s, 1H), 8.07 (d, <i>J</i> = 2.25 Hz, 1H), 8.96 (s, 1H)	472.23	99.36
7		1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.3 Hz, 3H), 1.33-1.47 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.45 (bs, 1H), 4.80 (d, <i>J</i> = 4.55 Hz, 1H), 6.36 (t, <i>J</i> = 5.2 Hz, 1H), 7.11 (t, <i>J</i> = 9.2 Hz, 1H), 7.25-7.29 (m, 4H), 7.35-	430.18	99.27

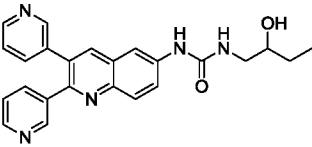
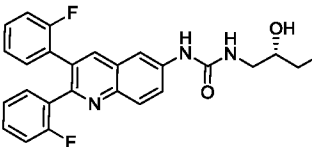
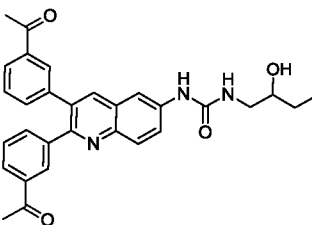
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.42 (m, 3H), 7.46-7.49 (m, 1H), 7.75 (t, <i>J</i> = 7.55 Hz, 1H), 7.98 (d, <i>J</i> = 9.0 Hz, 1H), 8.13 (s, 1H), 8.24 (s, 1H), 9.07 (s, 1H)		
8		1-(2-(2-fluorophenyl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.35-1.46 (m, 2H), 2.99-3.03 (m, 1H), 3.24-3.29 (m, 1H), 3.45-3.46 (m, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.34 (t, <i>J</i> = 5.5 Hz, 1H), 7.04 (t, <i>J</i> = 9.3 Hz, 1H), 7.23-7.30 (m, 6H), 7.37-7.39 (m, 1H), 7.51-7.54 (m, 1H), 7.72-7.74 (m, 1H), 7.96 (d, <i>J</i> = 9.05 Hz, 1H), 8.17 (d, <i>J</i> = 2.1 Hz, 1H), 8.25 (s, 1H), 9.05 (s, 1H)	430.18	98.15
9		1-(2,3-bis(2-methoxypyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.47 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.45-3.46 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.35 (t, <i>J</i> = 5.5 Hz, 1H), 6.81-6.85 (m, 3H), 6.93 (d, <i>J</i> = 5.25 Hz, 1H), 7.75-7.78 (m, 1H), 7.99 (d, <i>J</i> = 9.1 Hz, 1H), 8.10-8.11 (m, 2H), 8.18 (d, <i>J</i> = 2.1	474.24	99.76

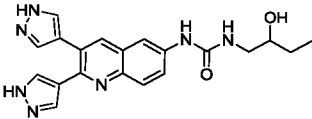
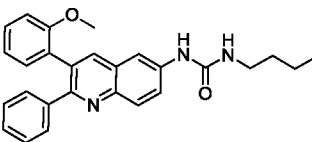
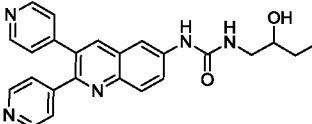
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			Hz, 1H), 8.34 (s, 1H), 9.10 (s, 1H)		
10		1-(2-hydroxybutyl)-3-(3-(2-methoxyphenyl)-2-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.46 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.25 (m, 1H), 3.27 (s, 3H), 3.44-3.45 (m, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.5 Hz, 1H), 6.87 (d, <i>J</i> = 8.05 Hz, 1H), 7.2 (t, <i>J</i> = 7.4 Hz, 1H), 7.20-7.25 (m, 3H), 7.31-7.34 (m, 4H), 7.69-7.71 (m, 1H), 7.94 (d, <i>J</i> = 9.05 Hz, 1H), 8.08 (s, 2H), 9.00 (s, 1H)	442.22	99.73
11		1-(2,3-bis(6-methoxypyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.3 Hz, 3H), 1.34-1.46 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.44-3.45 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.80 (d, <i>J</i> = 5.0 Hz, 1H), 6.33 (t, <i>J</i> = 5.25 Hz, 1H), 6.78-6.82 (m, 2H), 7.55 (d, <i>J</i> = 8.05 Hz, 1H), 7.68-7.71 (m, 2H), 7.96 (d, <i>J</i> = 9.05 Hz, 1H), 8.16 (d, <i>J</i> = 9.25 Hz, 3H), 8.25 (s, 1H), 9.04 (s, 1H)	474.22	99.06
12		1-(2-hydroxybutyl)-3-(2-(2-methoxyphenyl)-2-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.46 (m, 2H), 2.98-	442.22	98.90

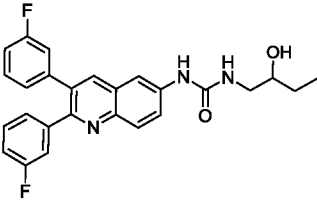
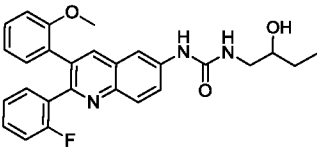
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		methoxyphenyl-3-phenylquinolin-6-yl)urea	3.03 (m, 1H), 3.20 (s, 3H), 3.24-3.28 (m, 1H), 3.45-3.46 (m, 1H), 4.79 (d, <i>J</i> = 4.9 Hz, 1H), 6.31 (t, <i>J</i> = 5.45 Hz, 1H), 6.79 (d, <i>J</i> = 8.3 Hz, 1H), 7.02 (t, <i>J</i> = 7.4 Hz, 1H), 7.18-7.24 (m, 5H), 7.29-7.33 (m, 1H), 7.42 (d, <i>J</i> = 7.35 Hz, 1H), 7.68-7.70 (m, 1H), 7.91 (d, <i>J</i> = 9.0 Hz, 1H), 8.12 (s, 2H), 8.99 (s, 1H)		
13		1-(2,3-bis(2-methoxypyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.35-1.45 (m, 2H), 3.99-3.02 (m, 1H), 3.25-3.27 (m, 1H), 3.44 (s, 4H), 3.58 (s, 3H), 4.79 (d, <i>J</i> = 5.1 Hz, 1H), 6.33 (t, <i>J</i> = 5.45 Hz, 1H), 6.94-6.97 (m, 1H), 7.02-7.04 (m, 1H), 7.53 (s, 1H), 7.70-7.72 (m, 1H), 7.76-7.78 (m, 1H), 7.93 (d, <i>J</i> = 9.0 Hz, 1H), 8.06-8.10 (m, 2H), 8.13-8.15 (m, 2H), 9.03 (s, 1H)	474.25	98.07
14		1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-butylurea	(500 MHz; DMSO-d ₆): δ 0.92 (t, <i>J</i> = 7.3 Hz, 3H), 1.32-1.37 (m, 2H), 1.43-1.47 (m, 2H), 3.12-3.16 (m, 2H), 6.32 (t, <i>J</i> = 5.55 Hz, 1H), 7.04 (t, <i>J</i> = 9.4 Hz, 1H), 7.10-7.20 (m, 3H),	432.2	98.88

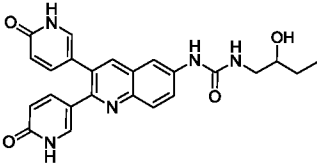
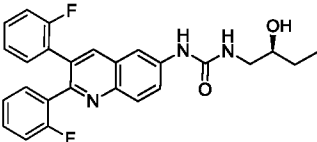
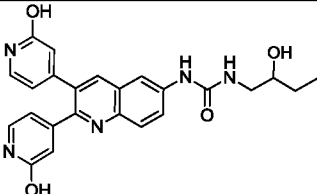
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.29-7.38 (m, 3H), 7.43 (t, <i>J</i> = 7.5 Hz, 1H), 7.77-7.79 (m, 1H), 7.97 (d, <i>J</i> = 9.05 Hz, 1H), 8.16 (d, <i>J</i> = 2.15 Hz, 1H), 8.28 (s, 1H), 8.91 (s, 1H)		
15		(R)-1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.46 (m, 2H), 2.99-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.44 (t, <i>J</i> = 6.5 Hz, 1H), 4.80 (d, <i>J</i> = 5.15 Hz, 1H), 6.34 (t, <i>J</i> = 5.55 Hz, 1H), 7.11 (t, <i>J</i> = 8.95 Hz, 1H), 7.25-7.29 (m, 4H), 7.35-7.46 (m, 3H), 7.46-7.49 (m, 1H), 7.74 (d, <i>J</i> = 6.9 Hz, 1H), 7.97 (d, <i>J</i> = 9.05 Hz, 1H), 8.13 (d, <i>J</i> = 2.1 Hz, 1H), 8.25 (s, 1H), 9.06 (s, 1H).	430.19	99.58
16		1-butyl-3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.92 (t, <i>J</i> = 7.3 Hz, 3H), 1.31-1.38 (m, 2H), 1.43-1.49 (m, 2H), 3.12-3.15 (m, 2H), 6.30 (t, <i>J</i> = 5.5 Hz, 1H), 7.11 (t, <i>J</i> = 9.2 Hz, 1H), 7.25-7.30 (m, 4H), 7.35-7.42 (m, 3H), 7.45-7.48 (m, 1H), 7.76 (dd, <i>J'</i> = 2.25 Hz, <i>J''</i> = 9.05 Hz, 1H), 7.97 (d, <i>J</i> = 9.05 Hz, 1H), 8.15 (s, 1H), 8.25 (s, 1H),	414.21	98.18

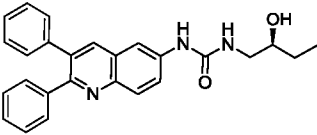
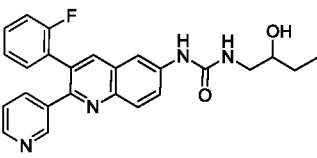
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			8.87 (s, 1H)		
17		1-(2,3-bis(4-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.47 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.42-3.48 (m, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.33 (t, <i>J</i> = 5.5 Hz, 1H), 7.12-7.21 (m, 4H), 7.28-7.31 (m, 2H), 7.36-7.39 (m, 2H), 7.70-7.73 (m, 1H), 7.95 (d, <i>J</i> = 9.1 Hz, 1H), 8.13 (s, 1H), 8.21 (s, 1H), 9.04 (s, 1H)	448.19	98.18
18		1-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.46 (m, 2H), 2.98-3.03 (m, 1H), 3.24-3.29 (m, 1H), 3.35 (s, 3H), 3.45 (d, <i>J</i> = 4.8 Hz, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.45 Hz, 1H), 6.75 (d, <i>J</i> = 8.3 Hz, 1H), 6.99 (t, <i>J</i> = 7.4 Hz, 1H), 7.05 (t, <i>J</i> = 7.4 Hz, 1H), 7.12 (t, <i>J</i> = 8.9 Hz, 2H), 7.26-7.30 (m, 2H), 7.41 (d, <i>J</i> = 7.35 Hz, 1H), 7.71-7.73 (m, 1H), 7.93 (d, <i>J</i> = 9.05 Hz, 1H), 8.12 (s, 1H), 8.16 (s, 1H), 9.02 (s, 1H)	460.22	98.08

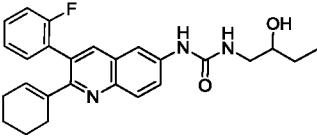
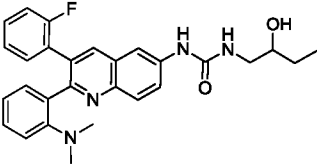
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
19		1-(2,3-di(pyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.3 Hz, 3H), 1.33-1.47 (m, 2H), 2.99-3.04 (m, 1H), 3.24-3.35 (m, 1H), 3.46 (bs, 1H), 4.81 (d, <i>J</i> = 5.0 Hz, 1H), 6.36 (t, <i>J</i> = 5.35 Hz, 1H), 7.34-7.40 (m, 2H), 7.70-7.77 (m, 3H), 8.01 (d, <i>J</i> = 9.05 Hz, 1H), 8.19 (d, <i>J</i> = 1.9 Hz, 1H), 8.37 (s, 1H), 8.50-8.53 (m, 4H), 9.11 (s, 1H)	414.20	95.66
20		(R)-1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.45 (m, 2H), 2.99-3.03 (m, 1H), 3.24-3.27 (m, 1H), 3.44 (d, <i>J</i> = 4.9 Hz, 1H), 4.81 (d, <i>J</i> = 5.1 Hz, 1H), 6.39 (t, <i>J</i> = 5.45 Hz, 1H), 7.04-7.20 (m, 4H), 7.30-7.36 (m, 3H), 7.44 (t, <i>J</i> = 7.35 Hz, 1H), 7.75-7.77 (m, 1H), 7.97 (d, <i>J</i> = 9.1 Hz, 1H), 8.17 (d, <i>J</i> = 2.05 Hz, 1H), 8.29 (s, 1H), 9.15 (s, 1H)	448.19	98.38
21		1-(2,3-bis(3-acetylphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (s, 3H), 1.36-1.44 (m, 2H), 2.44 (s, 3H), 2.51 (s, 3H), 3.02 (bs, 1H), 3.25-3.27 (m, 1H), 3.46 (bs, 1H), 4.80 (s, 1H), 6.34 (s,	496.26	99.40

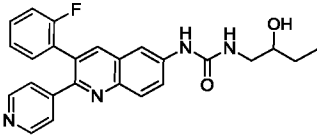
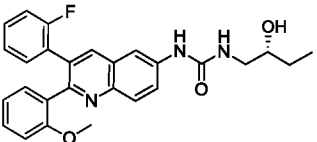
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			1H), 7.44-7.48 (m, 3H), 7.59 (d, <i>J</i> = 6.7 Hz, 1H), 7.75 (d, <i>J</i> = 8.75 Hz, 1H), 7.88 (t, <i>J</i> = 6.7 Hz, 2H), 7.93 (s, 1H), 7.98-8.02 (m, 2H), 8.20 (s, 1H), 8.37 (s, 1H), 9.06 (s, 1H)		
22		1-(2,3-di(1H-pyrazol-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.47 (m, 2H), 2.97-3.02 (m, 1H), 3.21-3.26 (m, 1H), 3.43 (d, <i>J</i> = 5.1 Hz, 1H), 4.79 (d, <i>J</i> = 4.9 Hz, 1H), 6.37 (s, 1H), 7.55-7.62 (m, 4H), 7.83 (d, <i>J</i> = 9.05 Hz, 2H), 7.99 (s, 1H), 8.03 (s, 1H), 9.00 (s, 1H), 12.88 (s, 1H), 13.03 (s, 1H)	392.17	98.09
23		1-butyl-3-(3-(2-methoxyphenyl)-2-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.92 (t, <i>J</i> = 7.3 Hz, 3H), 1.31-1.38 (m, 2H), 1.43-1.48 (m, 2H), 3.12-3.16 (m, 2H), 3.34 (s, 3H), 6.28 (t, <i>J</i> = 5.55 Hz, 1H), 6.88 (t, <i>J</i> = 8.1 Hz, 1H), 7.02 (t, <i>J</i> = 7.4 Hz, 1H), 7.21-7.25 (m, 3H), 7.31-7.34 (m, 4H), 7.71-7.73 (m, 1H), 7.93 (d, <i>J</i> = 9.0 Hz, 1H), 8.08 (s, 2H), 8.81 (s, 1H)	426.26	99.92
24		1-(2,3-di(pyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 5.5 Hz, 3H), 1.36-1.44 (m, 2H), 3.01-	414.21	98.35

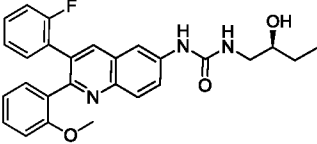
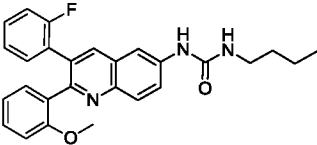
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		yl)-3-(2-hydroxybutyl) urea	3.02 (m, 1H), 3.25-3.28 (m, 1H), 3.45 (bs, 1H), 4.81 (s, 1H), 6.36 (s, 1H), 7.34 (t, <i>J</i> = 5.95 Hz, 4H), 7.78 (s, 1H), 8.02 (s, 1H), 8.21 (s, 1H), 8.38 (s, 1H), 8.54 (bs, 4H), 9.13 (s, 1H)		
25		1-(2,3-bis(3-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.88 (d, <i>J</i> = 3.6 Hz, 3H), 1.36 (s, 1H), 1.34 (s, 1H), 3.01 (s, 1H), 3.23 (s, 2H), 4.90 (s, 1H), 6.34 (s, 1H), 7.08-7.15 (m, 6H), 7.33-7.37 (m, 2H), 7.73 (s, 1H), 7.98 (s, 1H), 8.13 (s, 1H), 8.25 (s, 1H), 9.07 (s, 1H)	448.19	98.05
26		1-(2-(2-fluorophenyl)-3-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.42 (m, 1H), 1.43-1.47 (m, 1H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.38 (s, 3H), 3.45 (d, <i>J</i> = 4.9 Hz, 1H), 4.80 (d, <i>J</i> = 5.0 Hz, 1H), 6.33 (t, <i>J</i> = 5.4 Hz, 1H), 6.82 (d, <i>J</i> = 8.6 Hz, 1H), 6.95 (t, <i>J</i> = 7.4 Hz, 1H), 7.02-7.05 (m, 1H), 7.08-7.11 (m, 1H), 7.25-7.32 (m, 4H), 7.00-7.72 (m, 1H), 7.93 (d, <i>J</i> = 9.05 Hz, 1H), 8.12 (s, 2H), 9.02 (s, 1H)	460.22	99.31

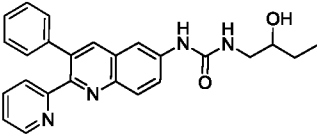
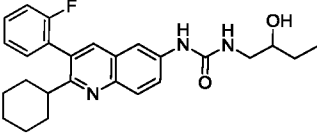
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
27		1-(2,3-bis(6-oxo-1,6-dihydropyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.45 (m, 2H), 2.99-3.02 (m, 1H), 3.23-3.27 (m, 1H), 3.43-3.46 (m, 1H), 4.79 (d, <i>J</i> = 4.4 Hz, 1H), 6.30-6.35 (m, 3H), 7.33 (d, <i>J</i> = 9.25 Hz, 1H), 7.45 (s, 1 H), 7.50 (s, 1H), 7.62-7.66 (m, 2H), 7.89 (d, <i>J</i> = 8.95 Hz, 1H), 8.08 (s, 1H), 8.15 (s, 1H), 8.99 (s, 1H), 11.77 (bs, 2H)	446.18	98.56
28		(S)-1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.39 (m, 1H), 1.42-1.45 (m, 1H), 2.99-3.02 (m, 1H), 3.25-3.27 (m, 1H), 3.45 (d, <i>J</i> = 4.85 Hz, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.36 (t, <i>J</i> = 5.45 Hz, 1H), 7.04 (t, <i>J</i> = 9.35 Hz, 1H), 7.10-7.20 (m, 3H), 7.30-7.36 (m, 3H), 7.42-7.45 (m, 1H), 7.75-7.77 (m, 1H), 7.98 (d, <i>J</i> = 9.05 Hz, 1H), 8.16 (d, <i>J</i> = 2.15 Hz, 1H), 8.29 (s, 1H), 9.09 (s, 1H)	448.22	99.35
29		1-(2,3-bis(2-hydroxypyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.3 Hz, 3H), 1.33-1.38 (m, 1H), 1.42-1.47 (m, 1H), 2.98-3.03	446.21	98.75

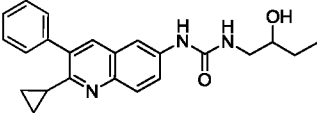
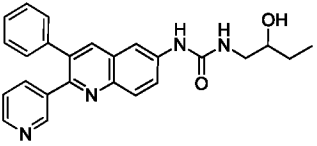
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		yl)-3-(2-hydroxybutyl) urea	(m, 1H), 3.23-3.27 (m, 1H), 3.44 (d, <i>J</i> = 4.8 Hz, 1H), 4.80 (d, <i>J</i> = 4.95 Hz, 1H), 6.07 (d, <i>J</i> = 5.7 Hz, 1H), 6.29-6.40 (m, 4H), 7.38 (dd, <i>J'</i> = 6.8 Hz, <i>J''</i> = 10.35 Hz, 2H), 7.76-7.78 (m, 1H), 7.97 (d, <i>J</i> = 9.1 Hz, 1H), 8.15 (d, <i>J</i> = 1.85 Hz, 1H), 8.29 (s, 1H), 9.14 (s, 1H), 11.64 (s, 2H)		
30		(S)-1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.47 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.45 (d, <i>J</i> = 4.85 Hz, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.5 Hz, 1H), 7.25-7.36 (m, 10H), 7.72 (dd, <i>J'</i> = 2.15 Hz, <i>J''</i> = 9.05 Hz, 1H), 7.95 (d, <i>J</i> = 9.05 Hz, 1H), 8.12 (d, <i>J</i> = 2.15 Hz, 1H), 8.20 (s, 1H), 9.02 (s, 1H)	412.26	98.98
31		1-(3-(2-fluorophenyl)-2-(pyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.36-1.37 (m, 1H), 1.43-1.45 (m, 1H), 3.01 (d, <i>J</i> = 7.1 Hz, 1H), 3.24-3.27 (m, 1H), 3.45 (d, <i>J</i> = 4.85 Hz, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.34 (t, <i>J</i> = 5.4 Hz, 1H), 7.11-7.15 (m, 1H),	431.2	98.90

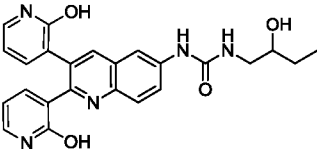
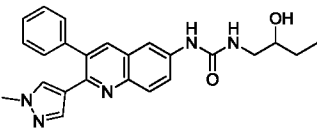
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.30-7.33 (m, 2H), 7.43 (d, <i>J</i> = 7.35 Hz, 1H), 7.53-7.56 (m, 1H), 7.73-7.79 (m, 2H), 8.01 (d, <i>J</i> = 9.1 Hz, 1H), 8.16 (s, 1H), 8.31 (s, 1H), 8.48-8.49 (m, 1H), 8.51 (d, <i>J</i> = 1.75 Hz, 1H), 9.08 (s, 1H)		
32		1-(2-(cyclohex-1-en-1-yl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.36 (m, 1H), 1.42 (d, <i>J</i> = 7.5 Hz, 1H), 1.48-1.51 (m, 2H), 1.61-1.63 (m, 2H), 1.84 (s, 2H), 2.40 (s, 2H), 2.97-3.02 (m, 1H), 3.23-3.25 (m, 1H), 3.43 (d, <i>J</i> = 4.9 Hz, 1H), 4.79 (d, <i>J</i> = 5.1 Hz, 1H), 5.39 (s, 1H), 6.30 (t, <i>J</i> = 5.55 Hz, 1H), 7.25-7.32 (m, 2H), 7.42-7.745 (m, 2H), 7.47-7.50 (m, 1H), 7.68-7.70 (m, 1H), 7.86 (d, <i>J</i> = 9.05 Hz, 1H), 8.04 (s, 1H), 8.10 (s, 1H), 8.97 (s, 1H)	434.26	99.85
33		1-(2-(2-(dimethylamino)phenyl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.36-1.39 (m, 1H), 1.42-1.46 (m, 1H), 2.08 (s, 6H), 2.99-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.44 (d, <i>J</i> = 4.9 Hz, 1H), 4.80 (d, <i>J</i> = 5.05 Hz, 1H), 6.32 (t, <i>J</i> =	473.27	98.09

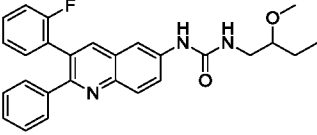
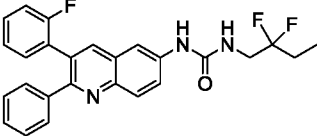
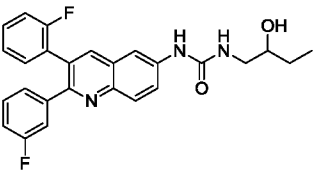
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		urea	5.45 Hz, 1H), 6.68 (d, <i>J</i> = 8.1 Hz, 1H), 6.92 (d, <i>J</i> = 6.35 Hz, 2H), 7.02 (t, <i>J</i> = 7.4 Hz, 1H), 7.11 (t, <i>J</i> = 9.65 Hz, 1H), 7.19-7.22 (m, 2H), 7.44 (d, <i>J</i> = 7.4 Hz, 1H), 7.71 (d, <i>J</i> = 9.15 Hz, 1H), 7.96 (d, <i>J</i> = 9.05 Hz, 1H), 8.09 (s, 1H), 8.14 (s, 1H), 9.00 (s, 1H)		
34		1-(3-(2-fluorophenyl)-2-(pyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.39 (m, 1H), 1.42-1.46 (m, 1H), 2.98-3.03 (m, 1H), 3.24-3.28 (m, 1H), 3.45 (d, <i>J</i> = 4.9 Hz, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.35 (t, <i>J</i> = 5.55 Hz, 1H), 7.15 (t, <i>J</i> = 9.25 Hz, 1H), 7.30-7.33 (m, 3H), 7.45 (d, <i>J</i> = 7.45 Hz, 1H), 7.52-7.55 (m, 1H), 7.77-7.79 (m, 1H), 8.02 (d, <i>J</i> = 9.1 Hz, 1H), 8.17 (d, <i>J</i> = 2.1 Hz, 1H), 8.33 (s, 1H), 8.48 (s, 2H), 9.10 (s, 1H)	431.21	98.91
35		(R)-1-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.40 (m, 1H), 1.42-1.47 (m, 1H), 2.98-3.03 (m, 1H), 3.24-3.26 (m, 1H), 3.29 (s, 3H), 3.45 (d, <i>J</i> = 4.8 Hz, 1H), 4.80 (d, <i>J</i>	460.25	98.12

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		urea	= 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.55 Hz, 1H), 6.76 (d, <i>J</i> = 8.3 Hz, 1H), 6.99 (t, <i>J</i> = 7.45 Hz, 1H), 7.05 (t, <i>J</i> = 7.4 Hz, 1H), 7.12 (t, <i>J</i> = 8.95 Hz, 2H), 7.27 (t, <i>J</i> = 7.4 Hz, 2H), 7.41 (d, <i>J</i> = 7.35 Hz, 1H), 7.71-7.73 (m, 1H), 7.93 (d, <i>J</i> = 9.05 Hz, 1H), 8.11 (s, 1H), 8.12 (s, 1H), 9.04 (s, 1H)		
36		(S)-1-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.39 (m, 1H), 1.42-1.46 (m, 1H), 2.98-3.03 (m, 1H), 3.24-3.26 (m, 1H), 3.29 (s, 3H), 3.43-3.46 (m, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.55 Hz, 1H), 6.75 (d, <i>J</i> = 8.3 Hz, 1H), 6.99 (t, <i>J</i> = 7.4 Hz, 1H), 7.05 (t, <i>J</i> = 7.35 Hz, 1H), 7.12 (t, <i>J</i> = 9.25 Hz, 2H), 7.27 (t, <i>J</i> = 7.05 Hz, 2H), 7.41 (d, <i>J</i> = 7.4 Hz, 1H), 7.71-7.73 (m, 1H), 7.93 (d, <i>J</i> = 9.05 Hz, 1H), 8.12 (s, 1H), 8.15 (s, 1H), 9.01 (s, 1H)	460.25	99.21
37		1-butyl-3-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.92 (t, <i>J</i> = 7.3 Hz, 3H), 1.32-1.37 (m, 2H), 1.43-1.47 (m, 2H), 3.12-3.16 (m,	444.24	99.23

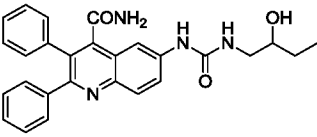
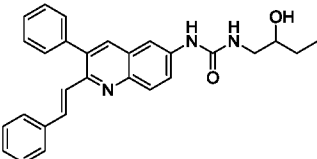
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		methoxyphenylquinolin-6-yl)urea	2H), 3.29 (s, 3H), 6.29 (t, $J = 5.55$ Hz, 1H), 6.75 (d, $J = 8.25$ Hz, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.05 (t, $J = 7.4$ Hz, 1H), 7.12 (t, $J = 9.02$ Hz, 2H), 7.26-7.29 (m, 2H), 7.41 (dd, $J' = 1.4$ Hz, $J'' = 7.45$ Hz, 1H), 7.72-7.75 (m, 1H), 7.92 (d, $J = 9.05$ Hz, 1H), 8.11 (d, $J = 2.2$ Hz, 1H), 8.15 (s, 1H), 8.82 (s, 1H)		
38		1-(2-hydroxybutyl)-3-(3-phenyl-2-(pyridin-2-yl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.35-1.39 (m, 1H), 1.42-1.45 (m, 1H), 3.00-3.04 (m, 1H), 3.24-3.28 (m, 1H), 3.45 (d, $J = 4.8$ Hz, 1H), 4.80 (d, $J = 5.05$ Hz, 1H), 6.34 (t, $J = 5.45$ Hz, 1H), 7.18 (d, $J = 6.3$ Hz, 2H), 7.24-7.32 (m, 4H), 7.71-7.75 (m, 2H), 7.83-7.86 (m, 1H), 7.97 (d, $J = 9.05$ Hz, 1H), 8.16 (s, 1H), 8.25 (s, 1H), 8.34 (d, $J = 4.45$ Hz, 1H), 9.06 (s, 1H)	413.23	98.04
39		1-(2-cyclohexyl-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-cyclohexyl-3-(2-fluorophenyl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.06 (bh, 2H), 1.19-1.24 (m, 1H), 1.32-1.37 (m, 1H), 1.39-1.46 (m, 1H), 1.61-1.74 (m, 7H), 2.64 (bs,	436.27	98.12

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		hydroxybutyl) urea	1H), 2.97-3.06 (m, 1H), 3.21-3.28 (m, 1H), 3.43 (d, <i>J</i> = 4.95 Hz, 1H), 4.78 (d, <i>J</i> = 5.0 Hz, 1H), 6.28 (t, <i>J</i> = 5.45 Hz, 1H), 7.34-7.39 (m, 2H), 7.44 (t, <i>J</i> = 7.4 Hz, 1H), 7.51-7.55 (m, 1H), 7.69 (t, <i>J</i> = 7.3 Hz, 1H), 7.87 (d, <i>J</i> = 9.05 Hz, 1H), 7.98 (s, 2H), 8.94 (s, 1H)		
40		1-(2-cyclopropyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.88-0.92 (m, 5H), 1.16 (t, <i>J</i> = 6.3 Hz, 2H), 1.33-1.37 (m, 1H), 1.40-1.43 (m, 1H), 2.07-2.10 (m, 1H), 2.29-3.00 (m, 1H), 3.21-3.24 (m, 1H), 3.42 (d, <i>J</i> = 4.9 Hz, 1H), 4.78 (d, <i>J</i> = 5.05 Hz, 1H), 6.26 (t, <i>J</i> = 5.5 Hz, 1H), 7.46 (d, <i>J</i> = 7.1 Hz, 1H), 7.52-7.57 (m, 4H), 7.62-7.64 (m, 1H), 7.74 (d, <i>J</i> = 9.05 Hz, 1H), 7.95 (s, 1H), 7.98 (s, 1H), 8.88 (s, 1H)	376.24	98.44
41		1-(2-hydroxybutyl)-3-(3-phenyl-2-(pyridin-3-yl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.39 (m, 1H), 1.42-1.46 (m, 1H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.45 (d, <i>J</i> = 5.05 Hz, 1H), 4.80 (d, <i>J</i> = 5.05 Hz, 1H), 6.34 (t, <i>J</i> = 5.5 Hz,	413.23	98.26

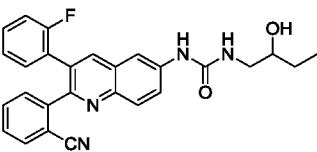
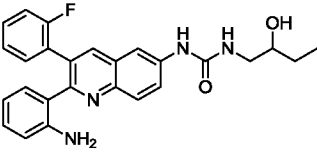
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			1H), 7.28-7.36 (m, 6H), 7.73-7.75 (m, 2H), 7.99 (d, <i>J</i> = 9.1 Hz, 1H), 8.15 (s, 1H), 8.26 (s, 1H), 8.47-8.50 (m, 2H), 9.06 (s, 1H)		
42		1-(2,3-bis(2-hydroxypyridin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.3 Hz, 3H), 1.32-1.38 (m, 1H), 1.42-1.47 (m, 1H), 2.97-3.02 (m, 1H), 3.22-3.27 (m, 1H), 3.44 (s, 1H), 4.82 (s, 1H), 6.10 (t, <i>J</i> = 6.6 Hz, 1H), 6.22 (t, <i>J</i> = 6.6 Hz, 1H), 6.55 (s, 1H), 7.29 (t, <i>J</i> = 6.6 Hz, 2H), 7.35 (d, <i>J</i> = 4.85 Hz, 1H), 7.54-7.56 (m, 1H), 7.66-7.68 (m, 1H), 7.86 (d, <i>J</i> = 9.05 Hz, 1H), 7.07-7.08 (m, 2H), 9.21 (s, 1H), 11.57 (s, 2H)	446.15	98.35
43		1-(2-(1-methyl-1H-pyrazol-4-yl)-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 4.3 Hz, 3H), 1.32-1.38 (m, 1H), 1.40-1.46 (m, 1H), 2.97-3.02 (m, 1H), 3.22-3.27 (m, 1H), 3.44 (d, <i>J</i> = 4.8 Hz, 1H), 3.76 (s, 3H), 4.77 (d, <i>J</i> = 5.15 Hz, 1H), 6.28 (s, 1H), 6.96 (s, 1H), 7.37-7.39 (m, 2H), 7.48-7.50 (m, 3H), 7.56 (s, 1H), 7.69 (dd, <i>J'</i> = 2.25 Hz, <i>J''</i> = 9.1 Hz, 1H), 7.86 (d, <i>J</i> = 9.05 Hz, 1H),	416.23	98.83

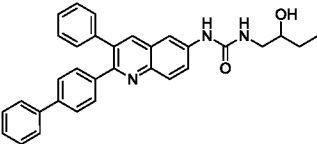
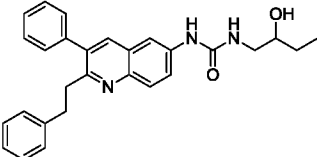
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			8.00 (d, <i>J</i> = 2.3 Hz, 2H), 8.94 (s, 1H),		
44		1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-methoxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.47-1.52 (m, 2H), 2.51 (s, 1H), 3.16-3.22 (m, 2H), 3.32 (s, 3H), 6.31 (t, <i>J</i> = 5.12 Hz, 1H), 7.11 (t, <i>J</i> = 9.2 Hz, 1H), 7.25-7.29 (m, 4H), 7.35-7.41 (m, 3H), 7.47 (t, <i>J</i> = 7.15 Hz, 1H), 7.75 (dd, <i>J'</i> = 1.8 Hz, <i>J''</i> = 9.0 Hz, 1H), 7.98 (d, <i>J</i> = 9.05 Hz, 1H), 8.13 (d, <i>J</i> = 1.55 Hz, 1H), 8.25 (s, 1H), 8.98 (s, 1H)	444.18	99.79
45		1-(2,2-difluorobutyl)-3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.99 (t, <i>J</i> = 7.5 Hz, 3H), 1.86-1.97 (m, 2H), 3.59-3.66 (m, 2H), 6.71 (t, <i>J</i> = 6.2 Hz, 1H), 7.09-7.13 (m, 1H), 7.25-7.30 (m, 4H), 7.35-7.42 (m, 3H), 7.46-7.49 (m, 1H), 7.76-7.78 (m, 1H), 7.99 (d, <i>J</i> = 9.05 Hz, 1H), 8.15 (d, <i>J</i> = 2.2 Hz, 1H), 8.28 (s, 1H), 9.08 (s, 1H).	450.15	99.86
46		1-(3-(2-fluorophenyl)-2-(3-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.39 (m, 1H), 1.42-1.46 (m, 1H), 2.98-3.03 (m, 1H), 3.23-3.28 (m,	448.15	99.44

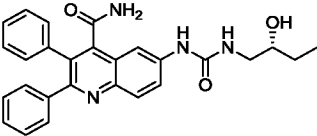
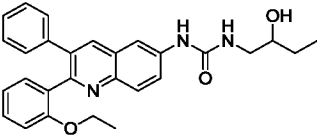
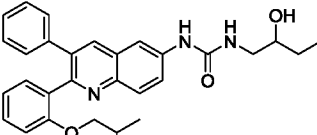
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		3-(2-hydroxybutyl) urea	1H), 3.44 (d, J = 4.8 Hz, 1H), 4.80 (d, J = 5.15 Hz, 1H), 6.34 (t, J = 5.45 Hz, 1H), 7.12-7.16 (m, 4H), 7.30 (dd, J = 6.05 Hz, J' = 13.6 Hz, 2H), 7.41-7.45 (m, 1H), 7.50-7.53 (m, 1H), 7.76 (dd, J = 2.2 Hz, J' = 9.05 Hz, 1H), 7.99 (d, J = 9.05 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 8.28 (s, 1H), 9.07 (s, 1H)		
47		1-(3-(2-fluorophenyl)-2-(4-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, J = 7.42 Hz, 3H), 1.34-1.39 (m, 1H), 1.42-1.46 (m, 1H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.44 (d, J = 4.75 Hz, 1H), 4.80 (d, J = 5.05 Hz, 1H), 6.33 (t, J = 5.5 Hz, 1H), 7.09-7.15 (m, 3H), 7.29 (t, J = 7.4 Hz, 1H), 7.37-7.44 (m, 3H), 7.49 (t, J = 7.5 Hz, 1H), 7.75 (dd, J = 2.1 Hz, J' = 9.05 Hz, 1H), 7.97 (d, J = 9.1 Hz, 1H), 8.13 (d, J = 2.05 Hz, 1H), 8.25 (s, 1H), 9.05 (s, 1H)	448.15	99.88
48		methyl 6-(3-(2-hydroxybutyl)ureido)-2,3-	(500 MHz; DMSO-d ₆): δ 0.90 (t, J = 7.45 Hz, 3H), 1.34-1.38 (m, 1H), 1.41-1.44 (m, 1H), 2.97-3.01 (m,	470.16	99.79

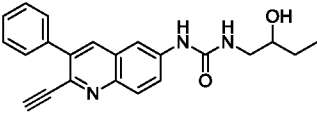
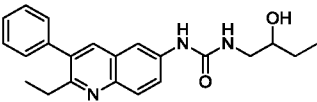
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		diphenylquinoline-4-carboxylate	1H), 3.23-3.27 (m, 1H), 3.42-3.45 (m, 1H), 3.61 (s, 3H), 4.79 (d, <i>J</i> = 5.15 Hz, 1H), 6.31 (t, <i>J</i> = 5.5 Hz, 1H), 7.16 (dd, <i>J'</i> = 3.0 Hz, <i>J''</i> = 6.4 Hz, 2H), 7.22-7.26 (m, 3H), 7.30-7.32 (m, 5H), 7.74-7.76 (m, 1H), 8.02-8.06 (m, 2H), 9.17 (s, 1H)		
49		6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.38 (m, 1H), 1.40-1.45 (m, 1H), 2.96-3.01 (m, 1H), 3.23-3.28 (m, 1H), 3.44 (d, <i>J</i> = 4.9 Hz, 1H), 4.79 (d, <i>J</i> = 5.1 Hz, 1H), 6.25 (t, <i>J</i> = 5.4 Hz, 1H), 7.21-7.26 (m, 10H), 7.66 (s, 1H), 7.79-7.81 (m, 1H), 7.92 (s, 1H), 7.98 (d, <i>J</i> = 9.05 Hz, 1H), 8.10 (d, <i>J</i> = 2.0 Hz, 1H), 9.12 (s, 1H)	455.19	98.04
50		(E)-1-(2-(3-(3-phenyl-2-styrylquinolin-6-yl)urea)-2-hydroxybutyl)-3-(3-phenyl-2-styrylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.23 (s, 1H), 1.34-1.38 (m, 1H), 1.42-1.44 (m, 1H), 2.99-3.02 (m, 1H), 3.24-3.26 (m, 1H), 3.44 (d, <i>J</i> = 4.9 Hz, 1H), 4.80 (d, <i>J</i> = 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.5 Hz, 1H), 7.23 (d, <i>J</i> = 15.65 Hz, 1H), 7.30 (t, <i>J</i> = 7.25	438.17	98.48

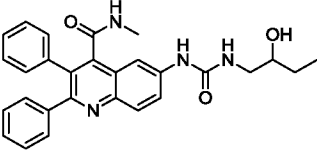
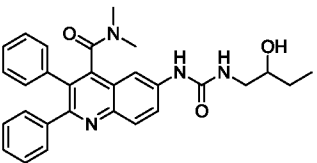
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			Hz, 1H), 7.37 (t, <i>J</i> = 7.4 Hz, 2H), 7.39-7.59 (m, 7H), 7.72 (dd, <i>J'</i> = 2.2 9.1 Hz, <i>J''</i> = Hz, 1H), 7.85 (d, <i>J</i> = 15.65 Hz, 1H), 7.96 (d, <i>J</i> = 9.1 Hz, 1H), 8.05 (s, 1H), 8.09 (s, 1H), 9.00 (s, 1H)		
51		N-(2-(3-(2-fluorophenyl)-6-(3-(2-hydroxybutyl)ureido)quinolin-2-yl)phenyl)acetamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.36-1.45 (m, 2H), 1.87 (s, 3H), 2.99-3.03 (m, 1H), 3.24-3.28 (m, 1H), 3.45 (d, <i>J</i> = 4.75 Hz, 1H), 4.79 (d, <i>J</i> = 5.15 Hz, 1H), 6.34 (t, <i>J</i> = 5.4 Hz, 1H), 6.97 (d, <i>J</i> = 7.5 Hz, 1H), 7.09-7.13 (m, 3H), 7.22-7.30 (m, 3H), 7.76 (dd, <i>J'</i> = 2.25 Hz, <i>J''</i> = 9.05 Hz, 1H), 7.80 (d, <i>J</i> = 8.1 Hz, 1H), 7.99 (d, <i>J</i> = 9.05 Hz, 1H), 8.14 (d, <i>J</i> = 2.2 Hz, 1H), 8.27 (s, 1H), 9.06 (s, 1H), 9.45 (s, 1H)	487.16	99.28
52		1-(2-hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.37 (m, 1H), 1.41-1.44 (m, 1H), 2.53 (s, 3H), 2.96-3.01 (m, 1H), 3.22-3.26 (m, 1H), 3.43 (d, <i>J</i> = 4.8 Hz, 1H), 4.78 (d, <i>J</i> = 5.1 Hz, 1H), 6.28 (t, <i>J</i> = 5.55 Hz, 1H), 7.43-7.45 (m, 1H), 7.49-7.53 (m, 4H),	350.17	98.98

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.65 (dd, $J = 2.1$ Hz, $J'' = 9.05$ Hz, 1H), 7.84 (d, $J = 9.0$ Hz, 1H), 7.97 (s, 1H), 8.01 (d, $J = 2.0$ Hz, 1H), 8.92 (s, 1H)		
53		1-(2-(2-cyanophenyl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.33-1.39 (m, 1H), 1.42-1.48 (m, 1H), 3.00-3.02 (m, 1H), 3.25-3.28 (m, 1H), 3.45 (d, $J = 3.1$ Hz, 1H), 4.80 (d, $J = 5.05$ Hz, 1H), 6.36 (s, 1H), 7.08 (t, $J = 9.25$ Hz, 1H), 7.24-7.28 (m, 2H), 7.36 (d, $J = 6.2$ Hz, 1H), 7.46-7.55 (m, 3H), 7.79 (d, $J = 9.25$ Hz, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 8.00 (d, $J = 9.0$ Hz, 1H), 8.21 (s, 1H), 8.38 (s, 1H), 9.12 (s, 1H)	455.17	95.21
54		1-(2-(2-aminophenyl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.34-1.39 (m, 1H), 1.42-1.45 (m, 1H), 2.95-3.03 (m, 1H), 3.23-3.28 (s, 1H), 3.45 (d, $J = 4.55$ Hz, 1H), 4.79 (d, $J = 5.05$ Hz, 1H), 5.32 (s, 2H), 6.27-6.33 (m, 2H), 6.63 (d, $J = 7.35$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.93 (t, $J = 7.1$ Hz, 1H), 7.09-7.18 (m, 2H),	445.16	98.97

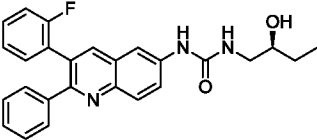
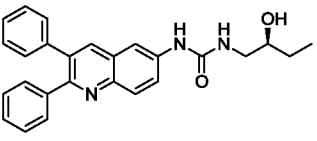
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.31-7.37 (m, 2H), 7.74 (dd, $J' = 2.1$ Hz, $J'' = 9.05$ Hz, 1H), 7.92 (d, $J = 9.1$ Hz, 1H), 8.10 (d, $J = 1.95$ Hz, 1H), 8.25 (s, 1H), 9.03 (s, 1H)		
55		1-(2-([1,1'-biphenyl]-4-yl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.35-1.39 (m, 1H), 1.43-1.46 (m, 1H), 3.00-3.03 (m, 1H), 3.25-3.26 (m, 1H), 3.45 (s, 1H), 4.79 (d, $J = 4.4$ Hz, 1H), 6.34 (s, 1H), 7.34-7.47 (m, 10H), 7.60 (d, $J = 7.75$ Hz, 1H), 7.68-7.74 (m, 4H), 7.97 (d, $J = 8.9$ Hz, 1H), 8.14 (s, 1H), 8.21 (s, 1H), 9.06 (s, 1H)	488.20	99.64
56		1-(2-(2-phenylethyl)-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.34-1.38 (m, 1H), 1.42-1.45 (m, 1H), 2.94-3.01 (m, 3H), 3.07 (d, $J = 7.65$ Hz, 2H), 3.23-3.25 (m, 1H), 3.44 (s, 1H), 4.78 (s, 1H), 6.31 (s, 1H), 7.01 (d, $J = 6.7$ Hz, 2H), 7.13 (d, $J = 6.7$ Hz, 1H), 7.19 (d, $J = 6.8$ Hz, 2H), 7.42-7.50 (m, 5H), 7.69 (d, $J = 8.25$ Hz, 1H), 7.90-8.02 (m, 3H), 8.97 (s, 1H)	440.21	93.56

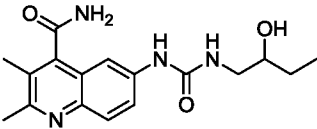
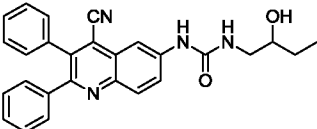
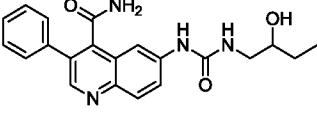
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
57		(R)-6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.38 (m, 1H), 1.41-1.45 (m, 1H), 3.23-3.27 (m, 1H), 3.28-3.36 (m, 1H), 3.44 (d, <i>J</i> = 4.95 Hz, 1H), 4.79 (d, <i>J</i> = 5.05 Hz, 1H), 6.24 (t, <i>J</i> = 5.45 Hz, 1H), 7.21-7.26 (m, 10H), 7.64 (s, 1H), 7.79-7.81 (dd, <i>J</i> ₁ = 2.15 Hz, <i>J</i> ₂ = 9.1 Hz, 1H), 7.92 (s, 1H), 7.98 (d, <i>J</i> = 9.05 Hz, 1H), 8.10 (d, <i>J</i> = 2.05 Hz, 1H), 9.11 (s, 1H)	455.18	99.16
58		1-(2-(2-ethoxyphenyl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.66(t, <i>J</i> = 6.15 Hz, 5H), 1.36-1.37 (m, 1H), 1.43 (bs, 1H), 1.91 (s, 1H), 3.01 (bs, 1H), 3.14 (bs, 1H), 3.25 (bs, 1H), 3.45 (s, 1H), 3.75 (bs, 1H), 4.80 (s, 1H), 6.34 (s, 1H), 6.77 (d, <i>J</i> = 6.95 Hz, 1H), 7.02 (s, 1H), 7.15-7.28 (m, 5H), 7.30 (s, 1H), 7.44 (bs, 1H), 7.69 (d, <i>J</i> = 6.8 Hz, 1H), 7.91 (d, <i>J</i> = 8.05 Hz, 1H), 8.13 (s, 2H), 9.04 (s, 1H)	456.19	99.78
59		1-(2-(2-isobutoxyphenyl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.66 (d, <i>J</i> = 6.6 Hz, 6H), 0.84-0.88 (m, 2H), 0.90 (t, <i>J</i> = 7.35 Hz, 3H), 1.34-1.40 (m, 1H), 1.42-1.47 (m,	484.22	99.14

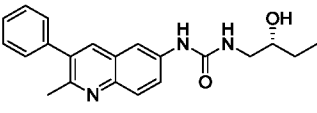
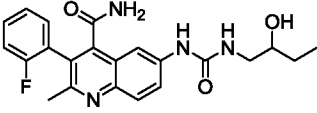
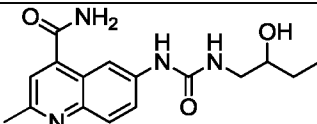
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		phenylquinolin-6-yl)urea	1H), 1.63 1.67 (m, 1H), 2.98-3.03 (m, 1H), 3.23-3.34 (m, 1H), 3.45 (bs, 1H), 4.80 (d, <i>J</i> = 3.95 Hz, 1H), 6.32 (t, <i>J</i> = 5.15 Hz, 1H), 6.85 (d, <i>J</i> = 8.3 Hz, 1H), 6.97 (t, <i>J</i> = 7.35 Hz, 1H), 7.22 (s, 5H), 7.28 (t, <i>J</i> = 7.4 Hz, 1H), 7.33 (d, <i>J</i> = 7.3 Hz, 1H), 7.68 (d, <i>J</i> = 7.7 Hz, 1H), 7.90 (d, <i>J</i> = 8.95 Hz, 1H), 8.15 (d, <i>J</i> = 19 Hz, 2H), 9.007 (s, 1H)		
60		1-(2-ethynyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.35 Hz, 3H), 1.30-1.39 (m, 1H), 1.41-1.48 (m, 1H), 2.97-3.02 (m, 1H), 3.22-3.27 (m, 1H), 3.44-3.45 (m, 1H), 4.5 (s, 1H), 4.79 (d, <i>J</i> = 5.1 Hz, 1H), 6.34 (t, <i>J</i> = 5.55 Hz, 1H), 7.46-7.47 (m, 1H), 7.51 (t, <i>J</i> = 7.55 Hz, 2H), 7.67 (d, <i>J</i> = 7.25 Hz, 2H), 7.72 (d, <i>J</i> = 2 Hz, 1H), 7.70 (d, <i>J</i> = 9.1 Hz, 1H), 8.11 (d, <i>J</i> = 2.05 Hz, 1H), 8.21 (s, 1H), 9.09 (s, 1H)	360.12	98.65
61		1-(2-ethyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.35 Hz, 3H), 1.15 (t, <i>J</i> = 7.45 Hz, 3H), 1.36-1.39 (m, 1H), 1.41-1.47 (m, 1H), 2.80-2.85	364.15	98.04

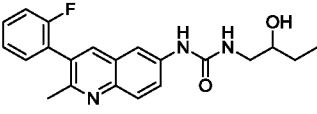
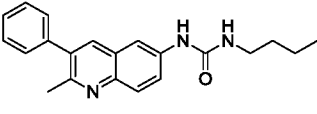
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			(dd, $J_1 = 7.4$ Hz, $J_2 = 14.85$ Hz, 2H), 2.96-3.01 (m, 1H), 3.17-3.26 (m, 1H), 3.41-3.42 (m, 1H), 4.80 (d, $J = 3.2$ Hz, 1H), 6.36 (s, 1H), 7.44-7.52 (m, 5H), 7.67 (d, $J = 8.65$ Hz, 1H), 7.86 (d, $J = 8.95$ Hz, 1H), 7.93 (s, 1H), 8.01 (s, 1H), 9.01 (s, 1H)		
62		6-(3-(2-hydroxybutyl)ureido)-N-methyl-2,3-diphenylquinoline-4-carboxamide	(500 MHz; DMSO- d_6): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.32-1.38 (m, 1H), 1.40-1.46 (m, 1H), 2.50 (s, 3H), 2.78 (s, 3H), 2.94-3.01 (m, 1H), 3.21-3.35 (m, 1H), 3.43-3.44 (m, 1H), 4.80 (d, $J = 5.15$ Hz, 1H), 6.26 (t, $J = 5.45$ Hz, 1H), 7.01 (bs, 1H), 7.21-7.32 (m, 9H), 7.79-7.85 (m, 2H), 8.01 (d, $J = 8.95$ Hz, 1H), 9.13 (s, 1H)	469.11	98.44
63		6-(3-(2-hydroxybutyl)ureido)-N,N-dimethyl-2,3-diphenylquinoline-4-carboxamide	(500 MHz; DMSO- d_6): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.31-1.38 (m, 1H), 1.40-1.46 (m, 1H), 2.50 (s, 3H), 2.78 (s, 3H), 2.94-3.03 (m, 1H), 3.21-3.35 (m, 1H), 3.43-3.44 (m, 1H), 4.80 (d, $J = 5.15$ Hz, 1H), 6.26 (t, $J = 5.40$ Hz, 1H), 7.01 (bs, 1H), 7.21-7.32 (m,	483.14	98.72

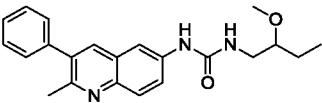
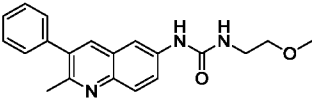
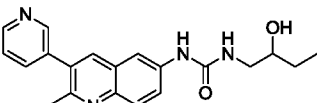
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			9H), 7.94-7.85 (m, 2H), 8.01 (d, <i>J</i> = 8.95 Hz, 1H), 9.13 (s, 1H)		
64		N-cyclopropyl-6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.08 (bs, 2H), 0.49-0.50 (m, 2H), 0.90 (t, <i>J</i> = 7.35 Hz, 3H), 1.31-1.38 (m, 1H), 1.40-1.47 (m, 1H), 2.97-3.02 (m, 1H), 3.23-3.27 (m, 1H), 3.39-3.44 (m, 2H), 4.81 (d, <i>J</i> = 5.0 Hz, 1H), 6.26 (t, <i>J</i> = 5.40 Hz, 1H), 7.21-7.26 (m, 10H), 7.81 (d, <i>J</i> = 9.15 Hz, 1H), 7.97-7.99 (m, 2H), 8.43 (d, <i>J</i> = 3.45 Hz, 1H), 9.13 (s, 1H)	495.27	99.70
65		6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxylic acid	(500 MHz; DMSO-d ₆): δ 0.87-0.95 (m, 5H), 1.24-1.34 (m, 2H), 1.41-1.44 (m, 1H), 1.57 (bs, 1H), 2.96-2.99 (m, 1H), 3.15-3.20 (m, 2H), 3.35 (m, 2H), 4.78 (s, 1H), 6.45 (s, 1H), 7.20-7.24 (m, 10H), 7.89-8.0 (m, 3H), 9.35 (s, 1H)	456.22	98.22
66		6-(3-(2-hydroxybutyl)ureido)-2-methyl-3-phenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.31-1.38 (m, 1H), 1.40-1.44 (m, 1H), 2.33 (s, 3H), 2.94-3.00 (m, 1H), 3.21-3.34 (m, 1H), 3.42-3.43 (m, 1H), 4.78 (d, <i>J</i> = 5.10	393.27	99.38

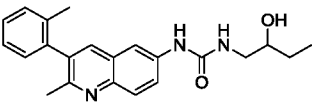
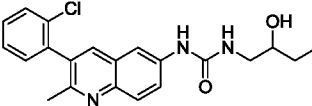
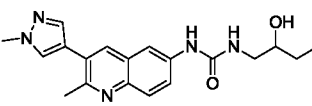
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			Hz, 1H), 6.20 (t, <i>J</i> = 5.45 Hz, 1H), 7.35-7.47 (m, 5H), 7.57 (s, 1H), 7.71-7.74 (dd, <i>J</i> ₁ = 2.15 Hz, <i>J</i> ₂ = 9 Hz, 2H), 7.85-7.87 (m, 2H), 8.00 (s, 1H), 9.01 (s, 1H)		
67		(S)-1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.35 Hz, 3H), 1.31-1.47 (m, 2H), 2.99-3.02 (m, 1H), 3.24-3.26 (m, 1H), 3.43-3.44 (m, 1H), 4.80 (d, <i>J</i> = 5.0 Hz, 1H), 6.33 (t, <i>J</i> = 5.15 Hz, 1H), 7.13 (t, <i>J</i> = 9.025 Hz, 1H), 7.25-7.47 (m, 8H), 7.74-7.76 (m, 1H), 7.98 (d, <i>J</i> = 9.0 Hz, 1H), 8.13 (s, 1H), 8.25 (s, 1H), 9.13 (s, 1H)	430.26	98.60
68		(S)-1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.31-1.48 (m, 2H), 2.98-3.03 (m, 1H), 3.23-3.28 (m, 1H), 3.44-3.45 (m, 1H), 4.83 (d, <i>J</i> = 5.10 Hz, 1H), 6.34 (t, <i>J</i> = 5.35 Hz, 1H), 7.25-7.36 (m, 10H), 7.70-7.72 (dd, <i>J</i> ₁ = 2.10 Hz, <i>J</i> ₂ = 9.05 Hz, 1H), 7.95 (d, <i>J</i> = 7.25 Hz, 1H), 8.13-8.21 (2H), 9.01 (s, 1H)	412.28	99.58

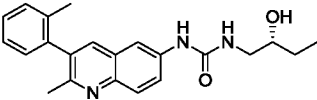
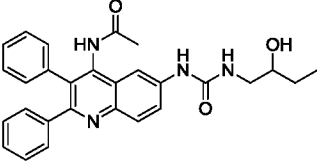
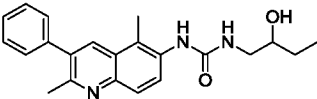
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
69		6-(3-(2-hydroxybutyl)ureido)-2,3-dimethylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.39 (m, 1H), 1.41-1.45 (m, 1H), 2.32 (s, 3H), 2.58 (s, 3H), 2.94- 2.99 (m, 1H), 3.20-3.25 (m, 1H), 3.36-3.42 (m, 1H), 4.80 (d, <i>J</i> = 5.0 Hz, 1H), 6.20 (t, <i>J</i> = 5.25 Hz, 1H), 7.63 (d, <i>J</i> = 8.95 Hz, 1H), 7.77 (d, <i>J</i> = 9Hz, 1H), 7.90 (s, 2H), 8.06 (s, 1H), 8.97 (s, 1H)	331.24	97.70
70		1-(4-cyano-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.39 (m, 1H), 1.40-1.47 (m, 1H), 2.99- 3.04 (m, 1H), 3.26-3.36 (m, 1H), 3.46-3.47 (m, 1H), 4.84 (d, <i>J</i> = 5.05 Hz, 1H), 6.41 (t, <i>J</i> = 5.35 Hz, 1H), 7.24-7.31 (m, 5H), 7.37-7.41 (m, 5H), 7.80 (d, <i>J</i> = 7.85 Hz, 1H), 8.12 (d, <i>J</i> = 9.1 Hz, 1H), 8.54 (d, <i>J</i> = 1.4 Hz, 1H), 9.40 (s, 1H)	437.28	99.79
71		6-(3-(2-hydroxybutyl)ureido)-3-phenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.37 (m, 1H), 1.42-1.44 (m, 1H), 2.97- 2.99 (m, 1H), 3.73-3.74 (m, 2H), 4.81 (bs, 1H), 6.28 (s, 1H), 7.46-7.51 (m, 3H),	379.28	86.58

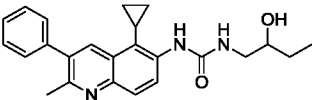
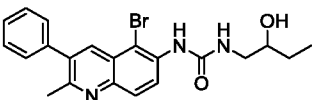
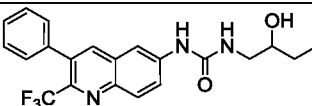
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.63 (d, <i>J</i> = 7.15 Hz, 2H), 7.78-7.82 (m, 2H), 7.96 (d, <i>J</i> = 9.05 Hz, 1H), 8.05 (s, 1H), 8.12 (s, 1H), 8.71 (s, 1H), 9.15 (s, 1H)		
72		(R)-1-(2-hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea	(400 MHz; DMSO-d ₆): δ 0.88 (t, <i>J</i> = 7.44 Hz, 3H), 1.28-1.44 (m, 2H), 2.50 (s, 3H), 2.93-2.99 (m, 1H), 3.18-3.32 (m, 1H), 3.40 (d, <i>J</i> = 4.84 Hz, 1H), 4.76 (d, <i>J</i> = 4.96 Hz, 1H), 6.25 (t, <i>J</i> = 5.72 Hz, 1H), 7.40-7.50 (m, 5H), 7.61-7.64 (m, 1H), 7.82 (d, <i>J</i> = 9.0 Hz, 1H), 7.95 (s, 1H), 7.99 (s, 1H), 8.90 (s, 1H)	350.28	98.20
73		3-(2-fluorophenyl)-6-(3-(2-hydroxybutyl)ureido)-2-methylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.36 (m, 1H), 1.40-1.45 (m, 1H), 2.32 (s, 3H), 2.95-2.98 (m, 1H), 3.21-3.24 (m, 1H), 3.42-3.43 (m, 1H), 4.81 (d, <i>J</i> = 4.9 Hz, 1H), 6.39 (s, 1H), 7.28-7.30 (m, 2H), 7.31-34 (m, 1H), 7.41-7.43 (m, 1H), 7.47-7.50 (m, 1H), 7.68-7.74 (m, 1H), 7.87-7.89 (m, 1H), 7.98 (s, 1H), 8.07 (s, 1H), 9.20 (s, 1H)	411.28	98.90
74		6-(3-(2-hydroxybutyl)ureido)-2-methylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.35 Hz, 3H),	317.18	99.10

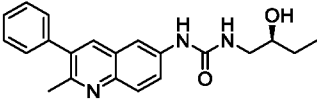
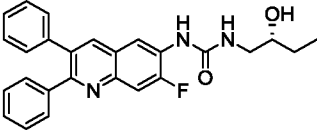
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		ureido)-2-methylquinoline-4-carboxamide	1.31-1.38 (m, 1H), 1.40-1.45 (m, 1H), 2.61 (s, 3H), 2.94-2.99 (m, 1H), 3.20-3.36 (m, 1H), 3.42-3.43 (m, 1H), 4.80 (d, <i>J</i> = 5 Hz, 1H), 6.25 (s, 1H), 7.34 (s, 1H), 7.78-7.83 (m, 3H), 8.11 (s, 1H), 8.18 (s, 1H), 9.03 (s, 1H)		
75		1-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(400 MHz; DMSO-d ₆): δ 0.86 (t, <i>J</i> = 7.4 Hz, 3H), 1.30-1.42 (m, 2H), 2.48 (t, <i>J</i> = 1.64 Hz, 3H), 2.94-2.99 (m, 1H), 3.18-3.31 (m, 1H), 3.41 (bs, 1H), 4.76 (bs, 1H), 6.27 (t, <i>J</i> = 5.36 Hz, 1H), 7.49-7.53 (m, 1H), 7.62-7.65 (m, 1H), 7.83 (d, <i>J</i> = 9.04 Hz, 1H), 7.93-7.96 (m, 1H), 8.02-8.04 (m, 2H), 8.61-8.69 (m, 2H), 8.93 (s, 1H)	368.28	98.13
76		1-butyl-3-(2-methyl-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.3 Hz, 3H), 1.31-1.36 (m, 2H), 1.41-1.47 (m, 2H), 2.53 (s, 3H), 3.11 (t, <i>J</i> = 6.25 Hz, 2H), 6.25 (t, <i>J</i> = 5.45 Hz, 1H), 7.44-7.45 (m, 1H), 7.50-7.53 (m, 4H), 7.65-7.67 (m, 1H), 7.84 (d, <i>J</i> = 9.05 Hz, 1H), 7.96 (s, 1H), 8.02 (m, 1H), 8.75 (s, 1H)	334.29	97.40

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
77		1-(2-methoxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.88 (t, <i>J</i> = 7.3 Hz, 3H), 1.43-1.52 (m, 2H), 2.53 (s, 3H), 3.14-3.20 (m, 2H), 3.35 (s, 4H), 6.28 (s, 1H), 7.44-7.50 (m, 5H), 7.65 (d, <i>J</i> = 8.75 Hz, 1H), 7.85 (d, <i>J</i> = 8.95 Hz, 1H), 7.98 (s, 1H), 8.03 (s, 1H), 8.89 (s, 1H)	364.32	98.15
78		1-(2-methoxyethyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 2.52 (d, <i>J</i> = 11.95 Hz, 3H), 3.29 (t, <i>J</i> = 8.55 Hz, 5H), 3.41 (t, <i>J</i> = 5.35 Hz, 2H), 6.33 (t, <i>J</i> = 5.35 Hz, 1H), 7.44-7.53 (m, 5H), 7.65 (d, <i>J</i> = 9.1 Hz, 1H), 7.85 (d, <i>J</i> = 9.05 Hz, 1H), 7.98 (s, 1H), 8.02 (s, 1H), 8.88 (s, 1H)	336.25	98.34
79		1-(2-hydroxybutyl)-3-(2-methyl-3-(pyridin-3-yl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.44 (m, 2H), 2.54 (s, 3H), 2.96-3.01 (m, 1H), 3.21-3.23 (m, 1H), 3.41 (bs, 1H), 4.81 (d, <i>J</i> = 6.45 Hz, 1H), 6.29 (t, <i>J</i> = 5.2 Hz, 1H), 7.53-7.55 (m, 1H), 7.65-7.67 (m, 1H), 7.86 (d, <i>J</i> = 8.6 Hz, 1H), 7.98 (d, <i>J</i> = 7.8 Hz, 1H), 8.06 (d, <i>J</i> = 10.1 Hz, 2H), 8.66 (d, <i>J</i> = 4.3 Hz, 1H), 8.72 (s, 1H),	351.26	99.28

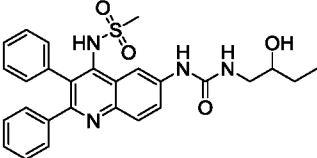
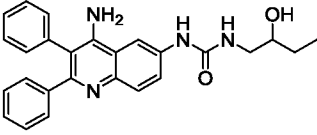
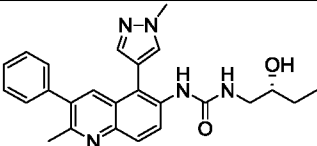
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			8.96 (s, 1H)		
80		1-(2-hydroxybutyl)-3-(2-methyl-3-(o-tolyl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.44 (m, 2H), 2.04 (s, 3H), 2.31 (s, 3H), 2.97-2.99 (m, 1H), 3.21-3.23 (m, 1H), 3.41 (bs, 1H), 4.80 (d, <i>J</i> = 3.6 Hz, 1H), 6.28 (t, <i>J</i> = 5.0 Hz, 1H), 7.21 (d, <i>J</i> = 7.2 Hz, 1H), 7.29-7.36 (m, 3H), 7.65 (d, <i>J</i> = 8.85 Hz, 1H), 7.85 (d, <i>J</i> = 9.05 Hz, 1H), 7.88 (s, 1H), 7.99 (s, 1H), 8.93 (s, 1H)	364.33	98.04
81		1-(3-(2-chlorophenyl)-2-methylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.30-1.45 (m, 2H), 2.35 (s, 3H), 2.95-3.0 (m, 1H), 3.21-3.37 (m, 1H), 3.42-3.43 (m, 1H), 4.81 (d, <i>J</i> = 4.6 Hz, 1H), 6.30 (t, <i>J</i> = 5.25 Hz, 1H), 7.45-7.51 (m, 3H), 7.63-7.69 (m, 2H), 7.85-7.87 (m, 1H), 7.96 (s, 1H), 8.01 (s, 1H), 8.97 (s, 1H)	384.29	98.44
82		1-(2-hydroxybutyl)-3-(2-methyl-3-(1-methyl-1H-pyrazol-4-yl)quinolin-6-yl)urea	NA	354.25	98.25

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		yl)urea			
83		(R)-1-(2-hydroxybutyl)-3-(2-methyl-3-(o-tolyl)quinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.30-1.45 (m, 2H), 2.04 (s, 3H), 2.30 (s, 3H), 2.97-2.99 (m, 1H), 3.22-3.36 (m, 1H), 3.42-3.50 (m, 1H), 4.81 (d, <i>J</i> = 4.65 Hz, 1H), 6.28 (t, <i>J</i> = 5.25 Hz, 1H), 7.20-7.21 (m, 1H), 7.29-7.38 (m, 3H), 7.64-7.66 (m, 1H), 7.84-7.88 (m, 2H), 7.99 (s, 1H), 8.92 (s, 1H)	364.33	98.37
84		N-(6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)acetamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.38 (m, 1H), 1.40-1.47 (m, 1H), 1.88 (s, 3H), 2.89-3.01 (m, 1H), 3.23-3.36 (m, 1H), 3.43-3.44 (m, 1H), 4.82 (s, 1H), 6.29 (s, 1H), 7.10 (d, <i>J</i> = 5.55 Hz, 2H), 7.20-7.28 (m, 8H), 7.72-7.80 (m, 1H), 7.98 (d, <i>J</i> = 9.0 Hz, 1H), 8.04 (s, 1H), 9.09 (s, 1H), 9.72 (s, 1H)	469.40	98.15
85		1-(2,5-dimethyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.33-1.38 (m, 1H), 1.40-1.47 (m, 1H), 2.47 (s, 3H), 2.55 (s, 3H), 2.97-3.01 (m, 1H), 3.21-3.37 (m, 1H),	364.04	98.24

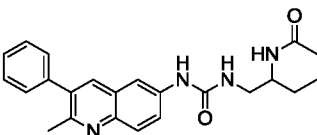
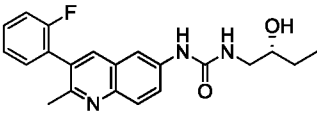
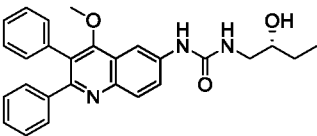
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			3.4-3.45 (m, 1H), 4.82 (d, $J = 4.30$ Hz, 1H), 6.62 (t, $J = 5.35$ Hz, 1H), 7.45-7.48 (m, 1H), 7.50-7.53 (m, 4H), 7.74 (d, $J = 9.15$ Hz, 1H), 8.12-8.16 (m, 2H), 8.23 (s, 1H)		
86		1-(5-cyclopropyl-2-methyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.50 (d, $J = 4.3$ Hz, 2H), 0.91 (t, $J = 7.4$ Hz, 3H), 1.67-1.24 (m, 2H), 1.33-1.39 (m, 1H), 1.44-1.49 (m, 1H), 1.85-1.99 (m, 1H), 2.54 (s, 3H), 3.02-3.07 (m, 1H), 3.20-3.36 (m, 1H), 3.44-3.46 (m, 1H), 4.79 (s, 1H), 6.96 (s, 1H), 7.46-7.52 (m, 5H), 7.76 (d, $J = 9.25$ Hz, 1H), 8.28 (bs, 2H), 8.44 (s, 1H)	390.05	98.73
87		1-(5-bromo-2-methyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.33-1.48 (m, 2H), 2.58 (s, 3H), 3.00-3.05 (m, 1H), 3.22-3.35 (m, 1H), 3.43 (bs, 1H), 4.86 (s, 1H), 7.39 (s, 1H), 7.48-7.49 (m, 1H), 7.50-7.54 (m, 4H), 7.92 (d, $J = 9.30$ Hz, 1H), 8.10 (s, 1H), 8.45 (s, 1H), 8.52 (d, $J = 9.3$ Hz, 1H)	428.28	99.67
88		1-(2-(trifluoromethyl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl) urea	(500 MHz; DMSO-d ₆): δ 0.88 (t, $J = 7.32$ Hz, 3H),	404.20	99.43

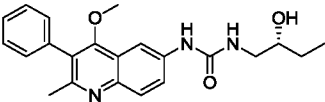
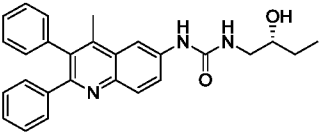
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		3-(3-phenyl-2-(trifluoromethyl)quinolin-6-yl)urea	1.34-1.43 (m, 2H), 2.97-3.01 (m, 1H), 3.22-3.31 (m, 1H), 3.44 (s, 1H), 4.78 (d, <i>J</i> = 4.2 Hz, 1H), 6.37 (s, 1H), 7.44-7.48 (m, 4H), 7.85 (d, <i>J</i> = 9.52 Hz, 1H), 8.07 (d, <i>J</i> = 9.52 Hz, 1H), 8.17 (s, 1H), 8.30 (s, 1H), 9.17 (s, 1H) (one proton missing).		
89		(S)-1-(2-hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.45 Hz, 3H), 1.31-1.46 (m, 2H), 2.53 (s, 3H), 2.96-3.01 (m, 1H), 3.21-3.36 (m, 1H), 3.42-3.43 (m, 1H), 4.81 (d, <i>J</i> = 5.1 Hz, 1H), 6.32 (t, <i>J</i> = 5.45 Hz, 1H), 7.43-7.50 (m, 5H), 7.63-7.66 (m, 1H), 7.97 (m, 1H), 8.02 (d, <i>J</i> = 1.85 Hz, 2H), 8.96 (s, 1H)	350.25	99.23
90		(R)-1-(7-fluoro-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.45 Hz, 3H), 1.35-1.45 (m, 2H), 3.00-3.05 (m, 1H), 3.24-3.36 (m, 1H), 3.43-3.44 (m, 1H), 4.82 (d, <i>J</i> = 3.9 Hz, 1H), 6.97 (t, <i>J</i> = 5.4 Hz, 1H), 7.25-7.35 (m, 10H), 7.85 (d, <i>J</i> = 12.6 Hz, 1H), 8.26 (s, 1H), 8.75 (d, <i>J</i> = 8.9 Hz, 1H), 8.87 (s, 1H)	430.32	96.47

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
91		1-(4-(dimethylamino)-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.45 Hz, 3H), 1.35-1.38 (m, 1H), 1.42-1.44 (m, 1H), 2.57 (s, 6H), 2.97-3.00 (m, 1H), 3.25-3.27 (m, 1H), 3.44-3.45 (m, 1H), 4.82 (d, <i>J</i> = 5.2 Hz, 1H), 6.26 (t, <i>J</i> = 5.35 Hz, 1H), 7.11-7.17 (m, 7H), 7.25-7.30 (m, 3H), 7.65-7.67 (m, 1H), 7.86 (d, <i>J</i> = 9 Hz, 1H), 8.32 (d, <i>J</i> = 2.25 Hz, 1H), 9.01 (s, 1H)	455.40	99.66
92		(R)-N-(6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)cyclopropanecarboxamide	(500 MHz; DMSO-d ₆): δ 0.62-0.66 (m, 4H), 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.38 (m, 1H), 1.42-1.46 (m, 1H), 1.68-1.70 (m, 1H), 2.98-3.02 (m, 1H), 3.22-3.36 (m, 1H), 3.44-3.45 (m, 1H), 4.82 (d, <i>J</i> = 5.1 Hz, 1H), 6.34 (t, <i>J</i> = 5.10 Hz, 1H), 7.08 (t, <i>J</i> = 3.1 Hz, 2H), 7.20-7.27 (m, 8H), 7.81-8.00 (m, 3H), 9.14 (s, 1H), 9.88 (s, 1H)	495.41	98.53
93		N-(6-(3-(2-hydroxybutyl)ureido)-2-methyl-3-phenylquinolin-4-yl)acetamide	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.31-1.36 (m, 1H), 1.40-1.44 (m, 1H), 1.82 (s, 3H), 2.35 (s, 3H), 2.95-3.00 (m, 1H), 3.20-3.36 (m, 1H), 3.40-3.42 (m, 1H), 4.80	407.34	98.54

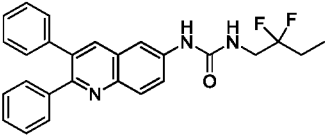
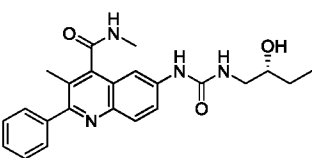
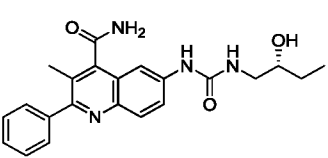
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			(bs, 1H), 6.27 (t, <i>J</i> = 5.45 Hz, 1H), 7.26 (d, <i>J</i> = 7.05 Hz, 2H), 7.40-7.48 (m, 3H), 7.70-7.72 (m, 1H), 7.86 (d, <i>J</i> = 9.05 Hz, 1H), 7.94 (s, 1H), 9.01 (s, 1H), 9.60 (s, 1H)		
94		N-(6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)methanesulfonamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.34-1.46 (m, 2H), 2.24 (s, 3H), 2.98-3.03 (m, 1H), 3.24-3.35 (m, 1H), 3.45 (s, 1H), 4.81 (d, <i>J</i> = 5.1 Hz, 1H), 6.36 (d, <i>J</i> = 5.1 Hz, 1H), 7.22-7.34 (m, 10H), 7.97 (d, <i>J</i> = 9 Hz, 1H), 8.05 (d, <i>J</i> = 9.15 Hz, 1H), 8.17 (s, 1H), 9.16 (s, 1H), 9.56 (bs, 1H)	505.37	98.16
95		1-(4-amino-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.42-1.47 (m, 2H), 2.98-3.03 (m, 1H), 3.24-3.28 (m, 1H), 3.44-3.45 (m, 1H), 4.82 (d, <i>J</i> = 4.95 Hz, 1H), 6.53 (s, 1H), 7.21 (d, <i>J</i> = 7.05 Hz, 2H), 7.36-7.39 (m, 10H), 7.87-7.92 (m, 2H), 8.34 (s, 1H), 8.99 (s, 1H)	427.37	98.19
96		(R)-1-(2-hydroxybutyl)-3-(2-methyl-5-(1-methyl-1H-imidazol-2-yl)-2-phenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.30-1.39 (m, 1H), 1.41-	430.37	98.23

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		(1-methyl-1H-pyrazol-4-yl)-3-phenylquinolin-6-yl)urea	1.43 (m 1H), 2.53 (s, 3H), 2.93-3.98 (m, 1H), 3.14-3.19 (m, 1H), 3.38-3.40 (m, 1H), 4.01 (s, 3H), 4.73 (d, <i>J</i> = 5.1 Hz, 1H), 6.99 (t, <i>J</i> = 5.25 Hz, 1H), 7.39-7.43 (m, 3H), 7.45-7.48 (m, 2H), 7.53 (s, 1H), 7.57 (s, 1H), 7.69 (s, 1H), 7.87 (d, <i>J</i> = 7.0 Hz, 2H), 8.52 (d, <i>J</i> = 9.3 Hz, 1H)		
97		1-(2-hydroxybutyl)-3-(4-(oxazol-2-yl)-2,3-diphenylquinolin-6-yl)urea	(400 MHz; DMSO-d ₆): δ 0.87 (t, <i>J</i> = 7.44 Hz, 3H), 1.15-1.19 (m, 1H), 1.33-1.40 (m 1H), 1.98 (s, 2H), 2.93 (bs, 1H), 3.18-3.22 (m, 1H), 4.02 (d, <i>J</i> = 6.84 Hz, 1H), 6.23 (s, 1H), 6.99 (s, 2H), 7.15-7.23 (m, 5H), 7.29 (bs, 2H), 7.36 (s, 1H), 7.78 (s, 1H), 7.85 (d, <i>J</i> = 11.2 Hz, 1H), 8.06 (d, <i>J</i> = 8.64 Hz, 1H), 8.11 (s, 1H), 9.10 (s, 1H)	479.20	98.15
98		1-(4-cyano-2-methyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(400 MHz; DMSO-d ₆): δ 0.87 (d, <i>J</i> = 7.44 Hz, 3H), 1.30-1.43 (m, 2H), 2.42 (s, 3H), 2.95-3.00 (m, 1H), 3.20-3.32 (m, 1H), 3.41-3.42 (m, 1H), 4.78 (d, <i>J</i> = 5.12 Hz, 1H), 6.33 (t, <i>J</i> = 5.32 Hz, 1H), 7.50-7.58 (m, 5H), 5.69-5.72 (dd, <i>J</i> 1	375.30	97.03

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			= 2.24 Hz, <i>J</i> 2 = 9.08 Hz, 1H), 7.98 (d, <i>J</i> = 9.08 Hz, 1H), 8.40 (d, <i>J</i> = 2.16 Hz, 1H), 9.27 (s, 1H)		
99		N-(1-(3-(2-methyl-3-phenylquinolin-6-yl)ureido)butan-2-yl)acetamide	NA	391.36	95.08
100		(R)-1-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.89 (d, <i>J</i> = 7.4 Hz, 3H), 1.30-1.46 (m, 2H), 2.43 (s, 3H), 2.96-3.01 (m, 1H), 3.22-3.34 (m, 1H), 3.43-3.44 (m, 1H), 4.80 (d, <i>J</i> = 4.95 Hz, 1H), 6.29 (t, <i>J</i> = 5.05 Hz, 1H), 7.35-7.47 (m, 2H), 7.48-7.55 (m, 2H), 7.68 (d, <i>J</i> = 8.85 Hz, 1H), 7.86 (d, <i>J</i> = 9 Hz, 1H), 8.04 (d, <i>J</i> = 6.8 Hz, 2H), 8.95 (s, 1H)	368.32	99.15
101		(R)-1-(2-hydroxybutyl)-3-(4-methoxy-2,3-diphenylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.88 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.42 (m, 2H), 2.96-3.01 (m, 1H), 3.21-3.25 (m, 1H), 3.42 (d, <i>J</i> = 4.76 Hz, 1H), 3.49 (s, 3H), 4.75 (d, <i>J</i> = 5.16 Hz, 1H), 6.26 (t, <i>J</i> = 5.48 Hz, 1H), 7.16-7.33 (m, 10H), 7.67 (dd, <i>J</i> ' =	442.27	99.51

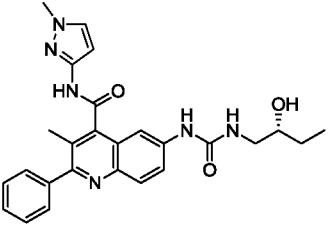
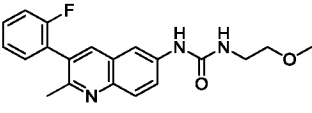
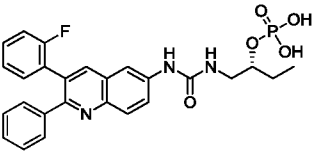
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			2.36 Hz, $J'' = 9.04$ Hz, 1H), 7.93 (d, $J = 9.08$ Hz, 1H), 8.29 (d, $J = 2.44$ Hz, 1H), 9.04 (s, 1H)		
102		(R)-1-(2-hydroxybutyl)- 3-(4-methoxy- 2-methyl-3- phenylquinolin -6-yl)urea	(500 MHz; DMSO- d_6): δ 0.90 (d, $J = 7.45$ Hz, 3H), 1.33-1.47 (m, 2H), 2.31 (s, 3H), 2.98-3.02 (m, 1H), 3.24-3.36 (m, 1H), 3.44- 3.45 (m, 1H), 3.95 (s, 3H), 4.82 (d, $J = 5.1$ Hz, 1H), 6.29 (t, $J = 5.3$ Hz, 1H), 7.45-7.51 (m, 3H), 7.58- 7.59 (m, 3H), 7.85-7.87 (m, 1H), 8.26 (d, $J = 1.85$ Hz, 1H), 9.04 (s, 1H)	380.32	98.69
103		(R)-1-(2-hydroxybutyl)- 3-(4-methyl- 2,3- diphenylquinol in-6-yl)urea	(400 MHz; DMSO- d_6): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.32-1.42 (m, 2H), 2.35 (s, 3H), 2.98-3.03 (m, 1H), 3.21-3.39 (m, 1H), 3.42- 3.43 (m, 1H), 4.76 (d, $J =$ 5.08 Hz, 1H). 3.49 (s, 3H), 6.28 (t, $J = 5.24$ Hz, 1H), 7.12-7.20 (m, 5H), 7.31- 7.25 (m, 2H), 7.27-7.31 (m, 3H), 7.63-7.65 (dd, $J' = 2.2$ Hz, $J'' = 9.08$ Hz, 1H), 7.91 (d, $J = 8.96$ Hz, 1H), 8.31 (d, $J = 2.08$ Hz, 1H), 9.01 (s, 1H)	426.37	99.69

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
104		(R)-N-benzyl-6-(3-(2-hydroxybutyl)ureido)-3-methyl-2-phenylquinoline-4-carboxamide	(400 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.32-1.43 (m, 2H), 2.23 (s, 3H), 2.98-3.02 (m, 1H), 3.22-3.30 (m, 1H), 3.43-3.45 (m, 1H), 4.57-4.58 (m, 2H), 4.77 (d, <i>J</i> = 5.16 Hz, 1H), 6.26 (t, <i>J</i> = 5.12 Hz, 1H), 7.23-7.26 (m, 1H), 7.33-7.37 (m, 2H), 7.42-7.53 (m, 7H), 7.63-7.66 (m, 1H), 7.86 (d, <i>J</i> = 9.04 Hz, 1H), 8.03 (d, <i>J</i> = 2.16 Hz, 1H), 9.03 (s, 1H), 9.17 (t, <i>J</i> = 5.96 Hz, 1H)	483.40	96.33
105		1-(2,2-difluorobutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea	(400 MHz; DMSO-d ₆): δ 0.96 (d, <i>J</i> = 7.52 Hz, 3H), 1.81-1.95 (m, 2H), 2.47-2.48 (m, 3H), 3.58-3.63 (m, 2H), 6.62 (d, <i>J</i> = 6.12 Hz, 1H), 7.39-7.51 (m, 5H), 7.63-7.66 (dd, <i>J</i> ₁ = 2.36 Hz, <i>J</i> ₂ = 9.04 Hz, 1H), 7.84 (d, <i>J</i> = 9.08 Hz, 1H), 7.96 (s, 1H), 8.01 (d, <i>J</i> = 2.2 Hz, 1H), 8.89 (s, 1H)	370.31	99.67
106		6-(3-(2,2-difluorobutyl)ureido)-2,3-diphenylquinoline-4-carboxamide	(400 MHz; DMSO-d ₆): δ 0.97 (d, <i>J</i> = 7.44 Hz, 3H), 1.81-2.06 (m, 2H), 3.60-3.64 (m, 2H), 6.66 (t, <i>J</i> = 6.16 Hz, 1H), 7.20-7.24 (m, 10H), 7.62 (s, 1H), 7.77-7.79 (dd, <i>J</i> ₁ = 11.4 Hz,	475.40	98.87

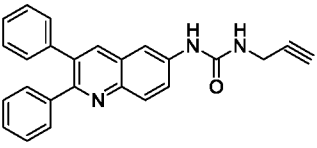
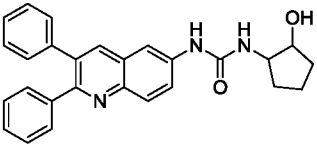
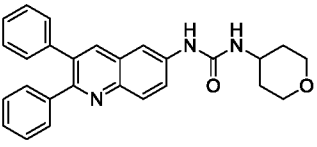
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			$J_2 = 1.12$ Hz, 1H), 7.89 (s, 1H), 7.97 (d, $J = 9.08$ Hz, 1H), 8.12 (d, $J = 2.24$ Hz, 1H), 9.20 (s, 1H)		
107		1-(2,2-difluorobutyl)-3-(2,3-diphenylquinolin-6-yl)urea	(400 MHz; DMSO- d_6): δ 0.97 (d, $J = 7.48$ Hz, 3H), 1.81-1.96 (m, 2H), 3.56-3.65 (m, 2H), 6.66 (t, $J = 6.2$ Hz, 1H), 7.22-7.34 (m, 10H), 7.70-7.73 (dd, $J_1 = 2.36$ Hz, $J_2 = 9.08$ Hz, 1H), 7.95 (d, $J = 9.04$ Hz, 1H), 8.12 (d, $J = 2.24$ Hz, 1H), 8.20 (s, 1H), 9.01 (s, 1H)	432.38	98.09
108		(R)-6-(3-(2-hydroxybutyl)ureido)-N,3-dimethyl-2-phenylquinoline-4-carboxamide	(400 MHz; DMSO- d_6): δ 0.87 (t, $J = 7.4$ Hz, 3H), 1.30-1.45 (m, 2H), 2.24 (s, 3H), 2.87 (d, $J = 4.56$ Hz, 3H), 2.93-2.99 (m, 1H), 3.18-3.29 (m, 1H), 3.41 (bs, 1H), 4.75 (s, 1H), 6.27 (t, $J = 5.56$ Hz, 1H), 7.42-7.52 (m, 5H), 7.70-7.73 (dd $J_1 = 2.2$ Hz, $J_2 = 9.04$ Hz, 1H), 7.80-7.86 (m, 2H), 8.56 (t, $J = 4.64$ Hz, 1H), 9.07 (s, 1H)	407.38	98.14
109		(R)-6-(3-(2-hydroxybutyl)ureido)-3-methyl-2-phenylquinolin-4-amine	(400 MHz; DMSO- d_6): δ 0.87 (t, $J = 7.4$ Hz, 3H), 1.31-1.44 (m, 2H), 2.30 (s, 3H), 2.90-2.99 (m, 1H), 3.19-3.29 (m, 1H), 3.41	393.37	98.27

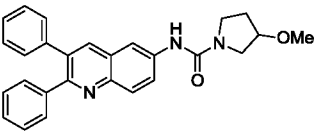
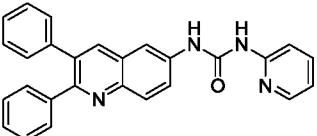
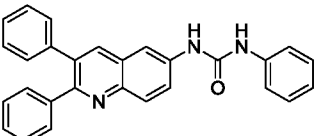
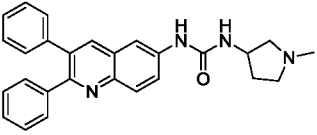
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		e-4-carboxamide	(bs, 1H), 4.75 (d, <i>J</i> = 4.44 Hz, 1H), 6.24 (t, <i>J</i> = 5.40 Hz, 1H), 7.42-7.54 (m, 5H), 7.67-7.70 (dd <i>J</i> ₁ = 2.16 Hz, <i>J</i> ₂ = 9.08 Hz, 1H), 7.84 (d, <i>J</i> = 9.04 Hz, 1H), 7.91 (s, 1H), 7.972 (s, 1H), 7.978 (s, 1H), 8.10 (bs, 1H), 9.05 (s, 1H)		
110		1-(2,2-difluorobutyl)-3-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)urea	(500 MHz; DMSO-d ₆): δ 0.99 (d, <i>J</i> = 7.45 Hz, 3H), 1.87-1.93 (m, 2H), 2.44 (s, 3H), 3.58-3.65 (m, 2H), 6.80 (t, <i>J</i> = 4.6 Hz, 1H), 7.35-7.38 (m, 2H), 7.40-7.54 (m, 2H), 7.70-7.72 (dd, <i>J</i> ₁ = 2.0 Hz, <i>J</i> ₂ = 8.95 Hz, 1H), 7.88 (d, <i>J</i> = 9.05 Hz, 1H), 8.07 (d, <i>J</i> = 2.7 Hz, 2H), 9.12 (s, 1H)	388.35	98.57
111		(R)-1-(3-(2-fluorophenyl)-2-methyl-5-(2-oxo-1,2-dihydropyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea	(500 MHz; DMSO-d ₆): δ 0.88 (t, <i>J</i> = 7.4 Hz, 3H), 1.31-1.41 (m, 2H), 2.45 (s, 3H), 2.89-3.00 (m, 1H), 3.12-3.19 (m, 1H), 3.47 (bs, 2H), 4.72 (bs, 1H), 6.36 (t, <i>J</i> = 6.6 Hz, 1H), 6.93 (d, <i>J</i> = 4.9 Hz, 1H), 7.29-7.53 (m, 7H), 7.67 (s, 1H), 7.90 (d, <i>J</i> = 9.3 Hz, 1H), 8.56 (t, <i>J</i> = 9.05 Hz, 1H)	461.44	95.19

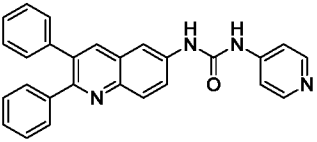
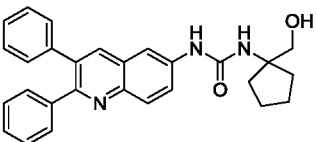
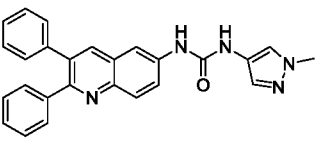
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
112		(R)-6-(3-(2-hydroxybutyl)ureido)-N-(1-methyl-1H-pyrazol-3-yl)-2,3-diphenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 7.4 Hz, 3H), 1.31-1.43 (m, 2H), 2.92-2.97 (m, 1H), 3.19-3.34 (m, 1H), 3.40-3.41 (m, 1H), 3.70 (s, 3H), 4.77 (d, <i>J</i> = 5.15 Hz, 1H), 6.22 (t, <i>J</i> = 5.55 Hz, 1H), 6.39 (d, <i>J</i> = 2 Hz, 1H), 7.20-7.28 (m, 10H), 7.53 (d, <i>J</i> = 1.9 Hz, 1H), 7.87 (d, <i>J</i> ' = 1.95 Hz, 1H), 7.91-7.93 (dd, <i>J</i> ₁ = 2.0 Hz, <i>J</i> ₂ = 9.1 Hz, 1H), 8.02 (d, <i>J</i> = 2.0 Hz, 1H), 9.12 (s, 1H), 10.85 (s, 1H)	535.71	99.72
113		(R)-1-(2,4-dimethyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea	(400 MHz; DMSO-d ₆): δ 0.87 (d, <i>J</i> = 7.36 Hz, 3H), 1.30-1.44 (m, 2H), 2.21 (s, 3H), 2.24 (s, 3H), 2.93-2.99 (m, 1H), 3.19-3.32 (m, 1H), 3.41-3.42 (m, 1H), 4.76 (d, <i>J</i> = 4.8 Hz, 1H), 6.27 (d, <i>J</i> = 5 Hz, 1H), 7.24 (d, <i>J</i> = 7.16 Hz, 2H), 7.41-7.59 (m, 4H), 7.80 (d, <i>J</i> = 8.96 Hz, 1H), 7.82 (s, 1H), 8.94 (s, 1H)	364.58	99.28
114		(R)-6-(3-(2-hydroxybutyl)ureido)-3-methyl-N-((1-methyl-1H-pyrazol-4-yl)methyl)-2-phenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.91 (bs, 3H), 1.37-1.45 (m, 2H), 2.25 (s, 3H), 3.02 (bs, 1H), 3.27 (bs, 1H), 3.46 (bs, 1H), 3.84 (s, 3H), 4.43 (bs, 2H), 4.82 (s, 1H),	487.51	98.60

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
		yl)methyl)-2-phenylquinoline-4-carboxamide	6.32 (s, 1H), 7.43-7.54 (m, 7H), 7.61-7.89 (m, 2H), 8.04 (s, 1H), 9.02-9.08 (m, 2H)		
115		(R)-6-(3-(2-hydroxybutyl)ureido)-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-phenylquinoline-4-carboxamide	(500 MHz; DMSO-d ₆): δ 0.88 (bs, 3H), 1.33-1.41 (m, 2H), 2.31 (s, 3H), 2.95 (bs, 1H), 3.20 (bs, 1H), 3.41 (s, 1H), 3.79 (s, 3H), 4.77 (s, 1H), 6.20 (s, 1H), 6.72 (s, 1H), 7.49-7.57 (m, 5H), 7.68 (s, 1H), 7.79-7.82 (m, 2H), 7.91 (d, <i>J</i> = 10.1 Hz, 1H), 9.07 (s, 1H), 11.12 (s, 1H).	473.57	98.83
116		1-(3-(2-fluorophenyl)-2-methylquinoline-6-yl)-3-(2-methoxyethyl)urea	(500 MHz; DMSO-d ₆): δ 2.43 (s, 3H), 3.29-3.50 (m, 7H), 6.32 (d, <i>J</i> = 5.4 Hz, 1H), 7.35-7.39 (m, 2H), 7.46-7.54 (m, 2H), 7.68-7.70 (dd, <i>J</i> ₁ = 2.15 Hz, <i>J</i> ₂ = 9.05 Hz, 1H), 7.86 (d, <i>J</i> = 9.05 Hz, 1H), 8.03 (d, <i>J</i> = 9.1 Hz, 2H), 8.88 (s, 1H)	354.21	99.68
117		(R)-1-(3-(3-(2-fluorophenyl)-2-phenylquinoline-6-yl)ureido)butan-2-yl dihydrogen phosphate	(500 MHz; DMSO-d ₆): δ 0.92 (bs, 3H), 1.60 (s, 2H), 3.36-3.39 (m, 3H), 4.16 (bs, 2H), 6.43 (s, 1H), 7.12-7.13 (m, 1H), 7.28-7.47 (m, 8H), 7.79 (d, <i>J</i> = 8.55 Hz, 1H), 8.01 (d, <i>J</i> = 8.75 Hz, 1H), 8.18 (s, 1H), 8.33 (s, 1H), 9.14 (s, 1H)	510.24	99.66

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
131		1-cyclohexyl-3-(2,3-diphenylquinolin-6-yl)urea	(400 MHz; DMSO-d ₆): δ 1.15-1.24 (m, 3H), 1.28-1.34 (m, 2H), 1.53 (bs, 1H), 1.66 (bs, 2H), 1.84 (d, <i>J</i> = 9.52 Hz, 2H), 3.51 (bs, 1H), 6.23 (d, <i>J</i> = 7.88 Hz, 1H), 7.24-7.35 (m, 10H), 7.7-7.72 (m, 1H), 7.94 (d, <i>J</i> = 9 Hz, 1H), 8.09 (d, <i>J</i> = 1.96 Hz, 1H), 8.18 (s, 1H), 8.72 (s, 1H).	422.42	99.04
132		N-(2,3-diphenylquinolin-6-yl)-4-methylpiperazine-1-carboxamide	(400 MHz; DMSO-d ₆): δ 2.17 (s, 3H), 2.21 (s, 4H), 3.50 (s, 4H), 7.26-7.35 (m, 10H), 7.87 (d, <i>J</i> = 9.96 Hz, 1H), 7.95 (d, <i>J</i> = 9.04 Hz, 1H), 8.15 (s, 1H), 8.19 (s, 1H), 8.90 (s, 1H).	423.28	99.78
133		4-acetyl-N-(2,3-diphenylquinolin-6-yl)piperazine-1-carboxamide	(400 MHz; DMSO-d ₆): δ 2.05 (s, 3H), 3.50-3.54 (m, 8H), 7.27-7.36 (m, 10H), 7.87-7.97 (q, 2H), 8.15 (s, 1H), 8.21 (s, 1H), 9.0 (s, 1H)	451.26	99.44
134		1-allyl-3-(2,3-diphenylquinolin-6-yl)urea	(400 MHz; DMSO-d ₆): δ 3.78 (s, 2H), 5.09 (d, <i>J</i> = 10.4 Hz, 1H), 5.20 (d, <i>J</i> = 17.52 Hz, 1H), 5.87-5.93 (m, 1H), 6.44 (d, <i>J</i> = 5.18 Hz, 1H), 7.26-7.35 (m, 10H), 7.73-7.75 (m, 1H), 7.95 (d, <i>J</i> = 9.04 Hz, 1H), 8.12 (s, 1H), 8.19 (s, 1H),	380.17	99.89

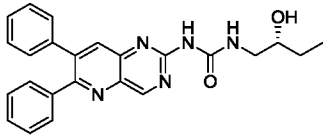
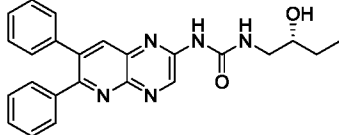
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			8.95 (s, 1H).		
135		1-(2,3-diphenylquinolin-6-yl)-3-(prop-2-yn-1-yl)urea	(400 MHz; DMSO-d ₆): δ 3.13 (s, 1H), 3.93 (d, <i>J</i> = 3.2 Hz, 2H), 6.61-6.62 (m, 1H), 7.26-7.35 (m, 10H), 7.74 (d, <i>J</i> = 7.2 Hz, 1H), 7.95 (d, <i>J</i> = 8.96 Hz, 1H), 8.13 (s, 1H), 8.21 (s, 1H), 9.02 (s, 1H).	378.49	99.62
136		1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxycyclopentyl)urea	(400 MHz; DMSO-d ₆): δ 1.13-1.23 (m, 1H), 1.37-1.48 (m, 1H), 1.62-1.67 (m, 2H), 1.76-1.82 (m, 1H), 1.99-2.08 (m, 1H), 3.74 (s, 1H), 3.84 (s, 1H), 6.31-6.33 (d, <i>J</i> = 6.2 Hz, 1H), 7.26-7.33 (m, 10H), 7.71 (d, <i>J</i> = 8.68 Hz, 1H), 7.94 (d, <i>J</i> = 8.64 Hz, 1H), 8.11 (s, 1H), 8.19 (s, 1H), 8.77 (s, 1H).	424.50	99.74
137		1-(2,3-diphenylquinolin-6-yl)-3-(tetrahydro-2H-pyran-4-yl)urea	(400 MHz; DMSO-d ₆): δ 1.41-1.46 (m, 2H), 1.71 (s, 1H), 1.82 (d, <i>J</i> = 11.88 Hz, 2H), 3.37-3.42 (m, 3H), 3.73 (bs, 1H), 3.84 (d, <i>J</i> = 11.68 Hz, 2H), 6.69 (s, 1H), 7.24-7.35 (m, 8H), 7.74 (d, <i>J</i> = 9.16, 1H), 7.94 (d, <i>J</i> = 9.04 Hz, 1H), 8.12 (s, 1H), 8.17 (s, 1H), 9.11 (s, 1H).	424.21	97.17

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
138		N-(2,3-diphenylquinolin-6-yl)-3-methoxypyrrolidine-1-carboxamide	(400 MHz; DMSO-d ₆): δ 2.00 (s, 2H), 3.32-3.27 (m, 3H), 3.39-3.56 (m, 4H), 4.01 (s, 1H), 7.26-7.35 (m, 10H), 7.95 (d, <i>J</i> = 9.08 Hz, 2H), 8.18-8.20 (m, 2H), 8.56 (s, 1H).	424.40	99.74
139		1-(2,3-diphenylquinolin-6-yl)-3-(pyridin-2-yl)urea	(400 MHz; DMSO-d ₆): δ 7.04 (t, <i>J</i> = 5.94 Hz, 1H), 7.28-7.44 (m, 10H), 7.55 (d, <i>J</i> = 8.2 Hz, 1H), 7.78 (t, <i>J</i> = 6.92 Hz, 1H), 7.86 (d, <i>J</i> = 7.52 Hz, 1H), 8.04 (d, <i>J</i> = 9 Hz, 1H), 8.30-8.33 (m, 3H), 9.60 (s, 1H), 10.90 (s, 1H).	417.43	97.23
140		1-(2,3-diphenylquinolin-6-yl)-3-phenylurea	(400 MHz; DMSO-d ₆): δ 6.99 (t, <i>J</i> = 7.3 Hz, 1H), 7.26-7.37 (m, 12H), 7.50 (d, <i>J</i> = 8.08 Hz, 2H), 7.77-7.80 (dd, <i>J'</i> = 2.24 Hz, <i>J''</i> = 2.2 Hz, 1H), 8.0 (d, <i>J</i> = 9 Hz, 1H), 8.21 (d, <i>J</i> = 2.08 Hz, 1H), 8.26 (s, 1H), 8.82 (s, 1H), 9.10 (s, 1H).	416.44	99.47
141		1-(2,3-diphenylquinolin-6-yl)-3-(1-methylpyrrolidin-3-yl)urea	(400 MHz; DMSO-d ₆): δ 1.55-1.58 (m, 1H), 2.17-2.23 (m, 1H), 2.28-2.43 (m, 4H), 2.35-2.43 (m, 1H), 2.49-2.56 (m, 1H), 2.58-2.72 (m, 1H), 4.17 (s, 1H), 6.57 (d, <i>J</i> = 7.52 Hz, 1H), 7.72-7.35 (m, 10H),	423.46	99.13

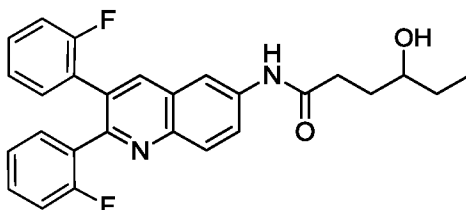
Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			7.69-7.71 (dd, $J' = 2.12$ Hz, $J'' = 1.96$ Hz, 1H), 7.94 (d, $J = 9.2$ Hz, 1H), 8.10 (d, $J = 1.88$ Hz, 1H), 8.18-8.21 (m, 1H), 8.83 (s, 1H).		
142		1-(2,3-diphenylquinolin-6-yl)-3-(pyridin-4-yl)urea	(400 MHz; DMSO-d ₆): δ 7.28-7.37 (m, 10H), 7.49 (d, $J = 5.96$ Hz, 2H), 7.78-7.81 (dd, $J' = 2.08$ Hz, $J'' = 2.08$ Hz, 1H), 8.03 (d, $J = 9.04$ Hz, 1H), 8.14 (s, 1H), 8.23 (d, $J = 1.76$ Hz, 1H), 8.30 (s, 1H), 8.38 (d, $J = 5.88$ Hz, 2H), 9.30 (d, $J = 15.75$ Hz, 1H).	417.39	98.44
143		1-(2,3-diphenylquinolin-6-yl)-3-(1-(hydroxymethyl)cyclopentyl)urea	(400 MHz; DMSO-d ₆): δ 1.54-1.59 (m, 2H), 1.65-1.72 (m, 4H), 1.82-1.89 (m, 2H), 3.49 (d, $J = 5.44$ Hz, 2H), 4.94 (t, $J = 5.46$ Hz, 1H), 6.20 (s, 1H), 7.23-7.35 (m, 10H), 7.64-7.67 (dd, $J' = 2.32$ Hz, $J'' = 2.28$ Hz, 1H), 7.93 (d, $J = 9.08$ Hz, 1H), 8.12 (d, $J = 2.24$ Hz, 1H), 8.19 (s, 1H), 8.87 (s, 1H).	438.50	99.25
144		1-(2,3-diphenylquinolin-6-yl)-3-(1-methyl-1H-pyrazol-4-yl)urea	(400 MHz; DMSO-d ₆): δ 3.79 (s, 3H), 7.25-7.36 (m, 10H), 7.41 (s, 1H), 7.75-7.77 (m, 2H), 7.98 (d, $J = 9.04$ Hz, 1H), 8.18 (d, $J = 2.12$ Hz, 1H), 8.23 (s, 1H),	420.42	98.5

Ex	Structure	IUPAC Name	¹ H-NMR	LCMS [M+H]	Purity (%)
			8.53 (s, 1H), 9.04 (s, 1H).		

Ex.	Structure	IUPAC name	Ex.	Structure	IUPAC name
146		1-(6,7-diphenyl-1,5-naphthyridin-2-yl)-3-(2-hydroxybutyl)urea	147		1-(2,3-diphenyl-1,7-naphthyridin-6-yl)-3-(2-hydroxybutyl)urea
148		(R)-1-(6,7-diphenyl-1,8-naphthyridin-3-yl)-3-(2-hydroxybutyl)urea	149		(R)-1-(6,7-diphenyl-1,5-naphthyridin-2-yl)-3-(2-hydroxybutyl)urea
150		(R)-1-(2,3-diphenyl-1,7-naphthyridin-6-yl)-3-(2-hydroxybutyl)urea	151		N-(6,7-diphenyl-1,8-naphthyridin-3-yl)-3-methoxypyrrolidine-1-carboxamide
152		N-(6,7-diphenyl-1,5-naphthyridin-2-yl)-3-methoxypyrrolidine-1-carboxamide	153		N-(2,3-diphenyl-1,7-naphthyridin-6-yl)-3-methoxypyrrolidine-1-carboxamide

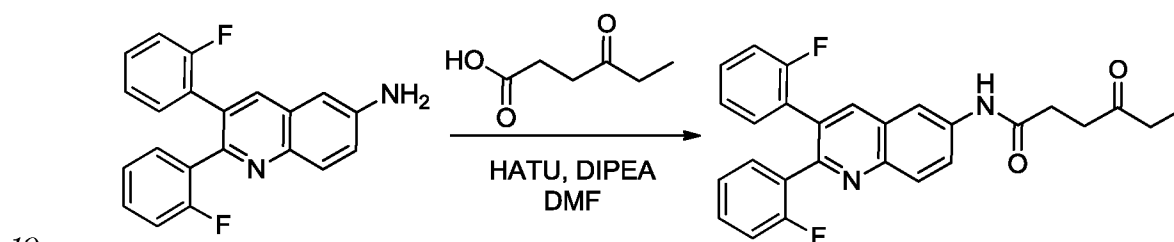
Ex.	Structure	IUPAC name	Ex.	Structure	IUPAC name
		methoxypyrrolidine-1-carboxamide			olidine-1-carboxamide
154		(R)-1-(6,7-diphenylpyrido[3,2-d]pyrimidin-2-yl)-3-(2-hydroxybutyl)urea	155		(R)-1-(6,7-diphenylpyrido[2,3-b]pyrazin-2-yl)-3-(2-hydroxybutyl)urea

Example 128: N-(2,3-Bis(2-fluorophenyl)quinolin-6-yl)-4-hydroxyhexanamide



- 5 Example 128 was prepared according to the methods described in General Procedures 1, 2, 3, 7, 8, 9, 10 and the method described below.

Preparation 15: N-(2,3-Bis(2-fluorophenyl)quinolin-6-yl)-4-oxohexanamide (Example 124)

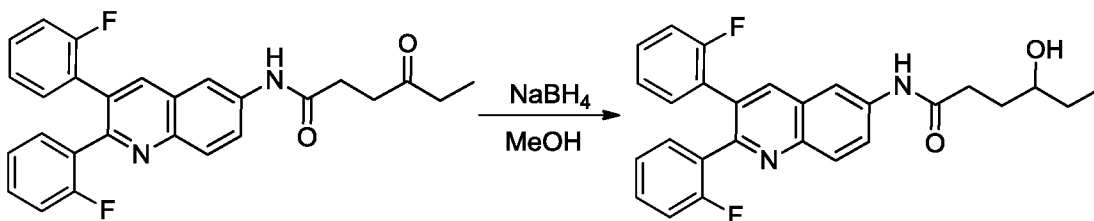


To a stirred solution of 4-oxohexanoic acid (56.2 mg, 0.432 mmol) in DMF (2 mL) was added DIPEA (0.103 mL, 0.602 mmol) and HATU (171.68 mg, 0.452 mmol). Stirring was continued for 10 min., then 2,3-bis(2-fluorophenyl)quinolin-6-amine (Preparation 7 Step 5) (100 mg, 0.301 mmol) was added. The whole was stirred at RT for 2 h.

- 15 Progress of the reaction was confirmed by TLC/LCMS and after completion the

reaction mixture was diluted with water and extracted with MTBE, washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the crude product which was purified by prep-HPLC to afford the title compound (39 mg, yield 29 %) as a white solid. LCMS m/z : 445.2 $[\text{M}+\text{H}]$; Purity 98.04%; ^1H NMR (500 MHz; $\text{DMSO}-d_6$): δ 0.96 (t, $J = 7.3$ Hz, 3H) 2.52 (t, $J = 7.35$ Hz, 2H), 2.66 (t, $J = 6.65$ Hz, 2H), 2.79 (t, $J = 6.6$ Hz, 2H), 7.03-7.21 (m, 4H), 7.31-7.39 (m, 3H), 7.45 (t, $J = 7.55$ Hz, 1H), 7.89 (dd, $J' = 2.1$ Hz, $J'' = 9.15$ Hz, 1H), 8.04 (d, $J = 9.1$ Hz, 1H), 8.37 (s, 1H), 8.45 (d, $J = 1.85$ Hz, 1H), 10.41 (s, 1H).

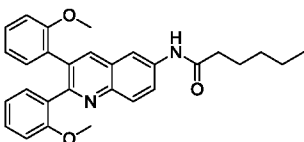
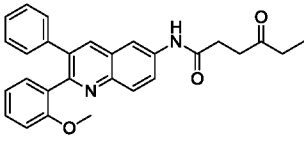
10 Preparation 16: N-(2,3-Bis(2-fluorophenyl)quinolin-6-yl)-4-hydroxyhexanamide
(**Example 128**)

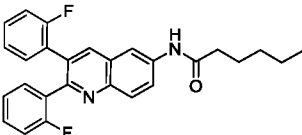
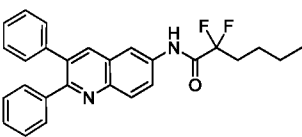
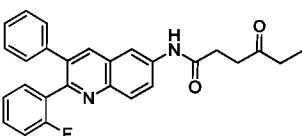
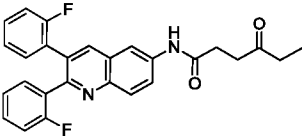


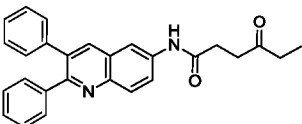
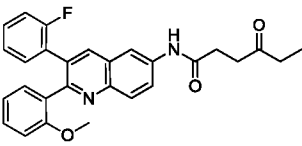
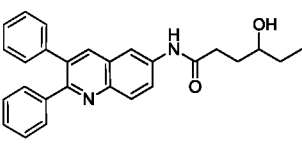
To a stirred solution of N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-4-oxohexanamide (Preparation 15) (50 mg, 0.113 mmol) in MeOH (2 mL) was added NaBH_4 (4.26 mg, 0.113 mmol) at 0-5 °C and the whole stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC and LCMS) the reaction mixture was quenched with water and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the crude product which was purified by prep-HPLC to afford the title compound (15 mg, yield 29.8%) as a white solid. LCMS m/z : 447.22 $[\text{M}+\text{H}]$; Purity 98.69%; ^1H NMR (500 MHz; $\text{DMSO}-d_6$): δ 0.89 (t, $J = 7.35$ Hz, 3H), 1.23 (s, 1H), 1.36-1.45 (m, 2H), 1.60-1.63 (m, 1H), 1.78-1.81 (m, 1H), 2.46-2.48 (m, 1H), 3.39 (d, $J = 3.75$ Hz, 1H), 4.49 (d, $J = 5.3$ Hz, 1H), 7.05 (t, $J = 9.4$ Hz, 1H), 7.10-7.21 (m, 3H), 7.31-7.37 (m, 3H), 7.45 (t, $J = 7.25$ Hz, 1H), 7.90 (t, $J = 7.15$ Hz, 1H), 7.92-7.05 (m, 1H), 8.38 (s, 1H), 8.49 (s, 1H), 10.34 (s, 1H)

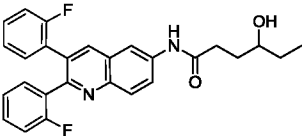
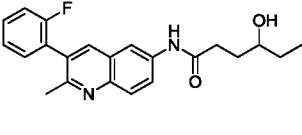
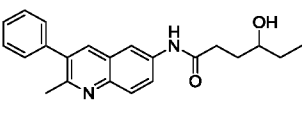
25

Ex	Structure	IUPAC Name	^1H NMR	LCMS $[\text{M}+\text{H}]$	Purity (%)
118		N-(2,3-diphenylquinolin-6-yl)hexanamide	(500 MHz; $\text{DMSO}-d_6$): δ 0.90 (t, $J = 6.77$ Hz, 3H), 1.32-1.35 (m, 4H), 1.64-1.68 (m, 2H), 2.40 (t, $J = 7.45$ Hz,	395.19	99.68

Ex	Structure	IUPAC Name	¹ H NMR	LCMS [M+H]	Purity (%)
		de	2H), 7.26-7.37 (m, 10H), 7.84-7.87 (m, 1H), 8.01 (d, <i>J</i> = 9.0 Hz, 1H), 8.28 (s, 1H), 8.44 (d, <i>J</i> = 1.85 Hz, 1H), 10.27 (s, 1H).		
119		N-(2,3-bis(2-methoxyphenyl)quinolin-6-yl)hexanamide	(500 MHz; DMSO-d ₆): δ 0.90 (t, <i>J</i> = 6.82 Hz, 3H), 1.32-1.35 (m, 4H), 1.63-1.68 (m, 2H), 2.39 (t, <i>J</i> = 7.45 Hz, 2H), 3.30 (s, 3H), 3.44 (bs, 3H), 6.74 (d, <i>J</i> = 8.25 Hz, 1H), 6.85 (bs, 2H), 6.93 (t, <i>J</i> = 7.37 Hz, 1H), 7.11 (bs, 1H), 7.19-7.23 (m, 2H), 7.32 (dd, <i>J'</i> = 1.4 Hz, <i>J''</i> = 1.35 Hz, 1H), 7.82 (dd, <i>J'</i> = 2.15 Hz, <i>J''</i> = 2.1 Hz, 1H), 7.96 (d, <i>J</i> = 9.05 Hz, 1H), 8.08 (s, 1H), 8.38 (d, <i>J</i> = 1.7 Hz, 1H), 10.22 (s, 1H).	455.23	98.32
120		N-(2-(2-methoxyphenyl)-3-phenylquinolin-6-yl)-4-oxohexanamide	(500 MHz; DMSO-d ₆): δ 0.96 (t, <i>J</i> = 7.3 Hz, 3H), 2.54 (s, 2H), 2.65 (t, <i>J</i> = 6.5 Hz, 2H), 2.78 (t, <i>J</i> = 6.55 Hz, 2H), 3.20 (s, 2H), 6.80 (d, <i>J</i> = 8.2 Hz, 1H), 7.02 (t, <i>J</i> = 7.4 Hz, 1H), 7.18-7.25 (m, 6H), 7.30-7.34 (m, 1H), 7.45 (dd, <i>J'</i> = 1.55 Hz, <i>J''</i> = 1.3 Hz, 1H), 7.82 (dd, <i>J'</i> = 2.1 Hz, <i>J''</i> = 1.95 Hz, 1H), 7.98 (d, <i>J</i> = 9 Hz, 1H), 8.20 (s, 1H), 8.41 (d, <i>J</i> = 1.75 Hz, 1H), 10.35 (s,	439.23	72.11

Ex	Structure	IUPAC Name	¹ H NMR	LCMS [M+H]	Purity (%)
			1H).		
121		N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)hexanamide	(500 MHz; DMSO-d ₆): δ 0.89 (s, 3H), 1.33 (s, 4H), 1.66 (t, <i>J</i> = 6.3 Hz, 2H), 2.41 (t, <i>J</i> = 7.4 Hz, 2H), 7.03-7.21 (m, 4H), 7.31-7.39 (m, 3H), 7.45 (t, <i>J</i> = 7.4 Hz, 1H), 7.90 (d, <i>J</i> = 9.05 Hz, 1H), 8.04 (d, <i>J</i> = 9.05 Hz, 1H), 8.38 (s, 1H), 8.49 (s, 1H), 10.32 (s, 1H).	431.20	98.17
122		N-(2,3-diphenylquinolin-6-yl)-2,2-difluorohexanamide	(500 MHz; DMSO-d ₆): δ 0.91 (t, <i>J</i> = 7.2 Hz, 3H), 1.37-1.48 (m, 4H), 2.17-2.26 (m, 2H), 7.27-7.39 (m, 10H), 8.02-8.09 (m, 2H), 8.37 (s, 1H), 8.51 (d, <i>J</i> = 1.95 Hz, 1H), 10.92 (s, 1H).	31.20	98.52
123		N-(2-(2-fluorophenyl)-3-phenylquinolin-6-yl)-4-oxohexanamide	(500 MHz; DMSO-d ₆): δ 0.96 (t, <i>J</i> = 7.3 Hz, 3H), 2.52 (s, 2H), 2.66 (t, <i>J</i> = 6.52 Hz, 2H), 2.79 (t, <i>J</i> = 6.52 Hz, 2H), 7.04 (t, <i>J</i> = 9.2 Hz, 1H), 7.24-7.29 (m, 6H), 7.37-7.42 (m, 1H), 7.53-7.56 (m, 1H), 7.84-7.87 (m, 1H), 8.02 (d, <i>J</i> = 9.05 Hz, 1H), 8.33 (s, 1H), 8.46 (d, <i>J</i> = 1.9 Hz, 1H), 10.39 (s, 1H).	427.24	98.60
124		N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-4-oxohexanamide	(500 MHz; DMSO-d ₆): δ 0.96 (t, <i>J</i> = 7.3 Hz, 3H), 2.52 (t, <i>J</i> = 7.35 Hz, 2H), 2.66 (t, <i>J</i> = 6.65 Hz, 2H), 2.79 (t, <i>J</i> =	445.20	98.04

Ex	Structure	IUPAC Name	¹ H NMR	LCMS [M+H]	Purity (%)
		oxohexanamide	6.6 Hz, 2H), 7.03-7.21 (m, 4H), 7.31-7.39 (m, 3H), 7.45 (t, <i>J</i> = 7.55 Hz, 1H), 7.89 (dd, <i>J'</i> = 2.1 Hz, <i>J''</i> = 9.15 Hz, 1H), 8.04 (d, <i>J</i> = 9.1 Hz, 1H), 8.37 (s, 1H), 8.45 (d, <i>J</i> = 1.85 Hz, 1H), 10.41 (s, 1H).		
125		N-(2,3-diphenylquinolin-6-yl)-4-oxohexanamide	(500 MHz; DMSO-d ₆): δ 0.96 (t, <i>J</i> = 7.3 Hz, 3H), 2.54 (s, 2H), 2.65 (t, <i>J</i> = 6.55 Hz, 2H), 2.79 (t, <i>J</i> = 6.52 Hz, 2H), 7.26-7.37 (m, 10H), 7.83-7.85 (m, 1H), 8.02 (d, <i>J</i> = 9.05 Hz, 1H), 8.28 (s, 1H), 8.42 (d, <i>J</i> = 1.85 Hz, 1H), 10.37 (s, 1H).	409.23	91.99
126		N-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-4-oxohexanamide	(500 MHz; DMSO-d ₆): δ 0.96 (t, <i>J</i> = 7.27 Hz, 3H), 2.52 (s, 2H), 2.65 (t, <i>J</i> = 6.47 Hz, 2H), 2.79 (t, <i>J</i> = 6.5 Hz, 2H), 3.38 (bs, 3H), 6.77 (d, <i>J</i> = 8.35 Hz, 1H), 6.98-7.15 (m, 4H), 7.27-7.30 (m, 2H), 7.43 (d, <i>J</i> = 7.3 Hz, 1H), 7.86 (d, <i>J</i> = 9.15 Hz, 1H), 8.01 (d, <i>J</i> = 9.05 Hz, 1H), 8.26 (s, 1H), 8.41 (s, 1H), 10.38 (s, 1H).	457.18	84.89
127		N-(2,3-diphenylquinolin-6-yl)-4-hydroxyhexanamide	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.40-1.45 (m, 2H), 1.59-1.63 (m, 1H), 1.78-1.80 (m, 1H), 2.46-2.48 (m, 2H), 3.40 (d, <i>J</i> = 3.8 Hz, 1H), 4.49 (d, <i>J</i> =	411.20	98.15

Ex	Structure	IUPAC Name	¹ H NMR	LCMS [M+H]	Purity (%)
			5.35 Hz, 1H), 7.26-7.37 (m, 10H), 7.85-7.87 (m, 1H), 8.01 (d, <i>J</i> = 9.05 Hz, 1H), 8.28 (s, 1H), 8.45 (d, <i>J</i> = 1.6 Hz, 1H), 10.29 (s, 1H).		
128		N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-4-hydroxyhexanamide	(500 MHz; DMSO-d ₆): δ 0.89 (t, <i>J</i> = 7.35 Hz, 3H), 1.23 (s, 1H), 1.36-1.45 (m, 2H), 1.60-1.63 (m, 1H), 1.78-1.81 (m, 1H), 2.46-2.48 (m, 1H), 3.39 (d, <i>J</i> = 3.75 Hz, 1H), 4.49 (d, <i>J</i> = 5.3 Hz, 1H), 7.05 (t, <i>J</i> = 9.4 Hz, 1H), 7.10-7.21 (m, 3H), 7.31-7.37 (m, 3H), 7.45 (t, <i>J</i> = 7.25 Hz, 1H), 7.90 (t, <i>J</i> = 7.15 Hz, 1H), 7.92-7.05 (m, 1H), 8.38 (s, 1H), 8.49 (s, 1H), 10.34 (s, 1H)	447.22	98.69
129		N-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-4-hydroxyhexanamide	(500 MHz; DMSO-d ₆): δ 0.88 (t, <i>J</i> = 6.17 Hz, 3H), 1.34-1.42 (m, 2H), 1.60 (bs, 1H), 1.78 (bs, 1H), 2.45 (s, 6H), 4.48 (bs, 1H), 7.37-7.40 (m, 2H), 7.47-7.54 (m, 2H), 7.81-7.93 (m, 2H), 8.14 (d, <i>J</i> = 21.5 Hz, 1H), 8.34 (s, 1H), 10.22 (s, 1H).	367.28	98.05
130		4-hydroxy-N-(2-methyl-3-phenylquinolin-6-yl)-4-hydroxyhexanamide	(500 MHz; DMSO-d ₆): δ 1.41 (t, <i>J</i> = 6.3 Hz, 3H), 1.56-1.62 (m, 2H), 1.75-1.79 (m, 2H), 2.41-2.47 (m, 2H), 2.62 (s, 3H), 3.38-3.40 (m, 1H),	349.30	99.85

Ex	Structure	IUPAC Name	¹ H NMR	LCMS [M+H]	Purity (%)
		yl)hexanamide	4.42 (bs, 1H), 7.48-7.53 (m, 5H), 7.98-8.02 (m, 2H), 8.30 (s, 1H), 8.43 (s, 1H), 10.29 (s, 1H).		

Biological assays

ACSS2 enzyme assay

Novel compounds were screened in a human ACSS2 enzyme assay. Briefly, the ACSS2 enzyme reaction was monitored by directly measuring acetyl-CoA formation. The cytosolic fraction of BT474 cells was used as a source of the ACSS2 enzyme. A short protocol for this assay is provided below.

Preparation of cytosolic fraction from BT474 cells

9 x 10⁶ cells were harvested by trypsinization followed by centrifugation. The cell pellet was washed with PBS and dissolved in 500μl STM buffer (50mM Tris-HCl pH7.4, 250mM sucrose, 5mM MgCl₂ & protease-phosphatase inhibitor cocktail) and homogenized at 600-1000 rpm for 1 min. on ice followed by incubation for 30 min. with intermittent vortexing. Supernatant was collected by centrifugation at 800g for 15 min. at 4 °C. Cytosolic fraction was prepared by further centrifugation of the supernatant at 12000g for 15 min. at 4 °C. Total protein content of the cytosolic fraction was estimated & diluted to 1 mg/ml concentration in storage buffer (25mM Tris-HCl pH7.4, 1mM MgCl₂, 1mM DTT & 10% glycerol) and stored at -80 °C for further use.

Assay protocol

100ng of cytosolic fraction in buffer composed of 25mM Tris-HCl pH7.4 1mM MgCl₂, 1mM DTT & 0.05% Tween20 was preincubated with desired concentrations of novel compounds for 5 min. maintaining 1% DMSO. Reaction was started with addition of substrate mix (100μM of acetate, CoA and ATP) and incubated for 2 h at 25 °C with constant shaking at 500 rpm. Post incubation the reaction was terminated by addition of 10% TCA followed by 5 fold dilution in water. The reaction mixture was centrifuged at 800g for 10 min. at RT and acetyl-CoA detected in supernatant by LC-MS/MS (QTrap5500 ABSCIEX).

Cell based [¹⁴C] acetate incorporation assay

In the cellular assay, ACSS2 inhibitors were screened against [¹⁴C] acetate incorporation in macromolecules. 4 x 10⁴ BT474 cells were plated in 96 well plates in growth media composed of DMEM & 10% FBS and incubated overnight in a 37 °C, 5% CO₂ incubator. The following day the cells were washed in HBSS and the assay was performed in 100 µl of HBSS. 50 µl of 4x compound in 4% DMSO was added to the cells and preincubated for 10min. at 37 °C. 50 µl of acetate solution (0.1 µCi ¹⁴C acetate + 10 µM ¹²C acetate) was added to each well of the plate and incubated for 3 h in a 37 °C, 5% CO₂ incubator. Following incubation, cells were harvested with water on polyethylene imine (PEI) presoaked GF/C filtermat, air dried and radioactive count were recorded in Trilux micro beta Liquid Scintillation Counter (PerkinElmer).

In the tables below, IC₅₀ value ranges for exemplary compounds are given. The IC₅₀ ranges are indicated as “A” for values less than 100 nM, “B” for values less than or equal to 1 µM, “C” for values less than or equal to 10 µM, and “D” for values greater than 10 µM.

ACSS2 activity

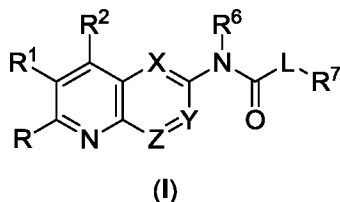
Ex	Enzyme Activity	Cellular Activity	Ex	Enzyme Activity	Cellular Activity
1	A	A	75	A	A
2	A	A	76	B	A
3	A	A	77	A	B
4	A	A	78	B	B
5	A	A	79	A	B
6	A	A	80	A	A
7	A	A	81	A	A
8	A	A	82	B	D
9	D	C	83	A	A
10	A	A	84	A	A
11	B	C	85	A	A
12	A	A	86	A	A
13	B	B	87	A	A
14	A	A	88	C	D
15	A	A	89	B	B

Ex	Enzyme Activity	Cellular Activity	Ex	Enzyme Activity	Cellular Activity
16	A	A	90	B	B
17	A	A	91	A	A
18	A	A	92	A	A
19	A	C	93	A	B
20	A	A	94	A	A
21	C	C	95	A	A
22	C	D	96	A	A
23	A	A	97	A	A
24	B	C	98	B	A
25	B	B	99	B	B
26	A	A	100	A	A
27	B	C	101	A	A
28	A	A	102	A	A
29	D	D	103	A	A
30	A	A	104	A	A
31	A	A	105	A	A
32	B	B	106	A	A
33	A	A	107	A	A
34	A	A	108	A	A
35	A	A	109	A	B
36	A	A	110	A	A
37	A	A	111	A	B
38	A	B	112	A	A
39	D	C	113	A	A
40	B	C	114	A	B
41	A	A	115	A	B
42	D	D	116	B	A
43	A	B	117	A	A
44	A	A	118	B	B
45	A	A	119	A	A
46	A	A	120	A	A
47	A	A	121	A	B

Ex	Enzyme Activity	Cellular Activity	Ex	Enzyme Activity	Cellular Activity
48	A	A	122	C	D
49	A	A	123	A	A
50	C	D	124	A	A
51	A	A	125	A	A
52	A	A	126	A	A
53	A	B	127	A	A
54	A	A	128	A	A
55	C	D	129	A	A
56	C	C	130	A	B
57	A	A	131	B	B
58	A	A	132	C	D
59	A	A	133	C	D
60	A	A	134	B	B
61	A	A	135	B	B
62	A	A	136	B	B
63	A	A	137	B	B
64	A	A	138	A	A
65	A	C	139	D	D
66	A	B	140	D	D
67	A	A	141	C	D
68	A	A	142	D	D
69	C	D	143	D	C
70	A	A	144	B	A
71	B	D	145	B	B
72	A	A			
73	A	B			
74	C	D			

Claims

1. A compound of formula (I):



5 , wherein X is CR³ or N;

Y is CR⁴ or N;

Z is CR⁵ or N;

L is NR⁸ or is absent;

R and R¹ are each independently selected from the group consisting of H, mono or
 10 bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to
 10 membered heteroaryl, optionally substituted C₁-C₁₀ alkyl, optionally substituted
 mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆
 cycloalkenyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀
 alkynyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle,
 15 optionally substituted C₁-C₁₀ alkoxy and NR⁹R¹⁰;
 R² is H, halogen, COOR⁹, CN, CONR⁹R¹⁰, NR⁹SO₂R¹⁰, SO₂NR⁹R¹⁰, NR⁹COR¹⁰, optionally
 substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic 3 to 8 membered
 heterocycle, optionally substituted C₁-C₁₀ alkylsulfonyl, NR⁹R¹⁰, optionally substituted
 C₁-C₁₀ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl or mono or bicyclic
 20 optionally substituted 5 to 10 membered heteroaryl;
 R³ is H, CN, halogen, COOH, CONR⁹R¹⁰, NR⁹R¹⁰, NO₂, optionally substituted C₁-C₁₀
 alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted
 mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₁₀ alkenyl, optionally
 substituted C₂-C₁₀ alkynyl, optionally substituted mono or bicyclic 3 to 8 membered
 25 heterocycle, optionally substituted C₁-C₁₀ alkoxy, mono or bicyclic optionally
 substituted C₆-C₁₂ aryl or mono or bicyclic optionally substituted 5 to 10 membered
 heteroaryl;
 R⁴ and R⁵ are each independently selected from the group consisting of H, halogen, OH,
 CN, mono or bicyclic optionally substituted C₆-C₁₂ aryl, optionally substituted C₁-C₁₀
 30 alkyl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally
 substituted C₁-C₁₀ alkoxy and optionally substituted mono or bicyclic C₃-C₆ cycloalkyl;
 R⁶ is H or optionally substituted C₁-C₁₀ alkyl;

R⁷ is H, optionally substituted C₁-C₁₀ alkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, or optionally substituted mono or bicyclic
 5 3 to 8 membered heterocycle;
 R⁸ is selected from the group consisting of H, halogen and optionally substituted C₁-C₁₀ alkyl; and
 R⁹ and R¹⁰ are each independently selected from the group consisting of H, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to
 10 10 membered heteroaryl, optionally substituted C₁-C₁₀ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₁-C₁₀ alkoxy and NH₂;
 or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or
 15 polymorphic form thereof.

2. The compound according to claim 1, wherein R and R¹ are each independently be selected from the group consisting of H, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl,
 20 optionally substituted C₁-C₆ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₆ alkenyl and optionally substituted C₂-C₆ alkynyl.

3. The compound according to claim 2, wherein R and R¹ are each independently
 25 selected from an optionally substituted phenyl ring, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl or an optionally substituted 5 or 6 membered heteroaryl.

4. The compound according to claim 3, wherein R and R¹ are each an optionally
 30 substituted phenyl ring or methyl.

5. The compound according to any preceding claim, wherein R² is H, COOR⁹, CONR⁹R¹⁰, CN, NR⁹COR¹⁰, NR⁹R¹⁰, NR⁹SO₂R¹⁰, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl
 35 or a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl.

6. The compound according to any preceding claim, wherein X is CR³, Y is CR⁴ and Z is CR⁵.
7. The compound according to any one of claims 1 to 5, wherein:
- 5 - X is N, Y is CR⁴ and Z is CR⁵;
- X is N, Y is N and Z is CR⁵;
- X is N, Y is CR⁴ and Z is N;
- X is CR³, Y is N and Z is CR⁵; or
- X is CR³, Y is CR⁴ and Z is N.
- 10
8. The compound according to any preceding claim, wherein R³ is H, CN, halogen, COOH, CONR₂, NR₂, NO₂, optionally substituted C₁-C₆ alkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, optionally substituted mono or bicyclic C₃-C₆ cycloalkenyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, 15 optionally substituted C₁-C₆ alkoxy, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl.
9. The compound according to claim 8, wherein R³ is H, CN, halogen, optionally substituted C₁-C₆ alkyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl, optionally 20 substituted mono or bicyclic C₃-C₆ cycloalkyl or mono or bicyclic optionally substituted 5 to 10 membered heteroaryl.
10. The compound according to any preceding claim, wherein R⁴ and R⁵ are each independently selected from the group consisting of H, halogen, OH, CN, mono or 25 bicyclic optionally substituted C₆-C₁₂ aryl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy or optionally substituted mono or bicyclic C₃-C₆ cycloalkyl.
11. The compound according to claim 10, wherein R⁴ and R⁵ are H, halogen, OH, CN or an optionally substituted C₁-C₆ alkyl.
- 30
12. The compound according to claim 11, wherein R⁴ and R⁵ are H.
13. The compound according to any preceding claim, wherein R⁶ is H or optionally substituted C₁-C₆ alkyl.
- 35

14. The compound according to any preceding claim, wherein R⁷ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, mono or bicyclic optionally substituted C₆-C₁₂ aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic C₃-C₆ cycloalkyl, or optionally substituted mono or bicyclic 3 to 8 membered heterocycle.

15. The compound according to claim 14, wherein R⁷ is optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3 to 6 membered heterocycle.

16. The compound according to any preceding claim, wherein L is absent.

17. The compound according to any one of claims 1 to 15, wherein L is NR⁸ and R⁸ is H or an optionally substituted C₁-C₆ alkyl.

18. The compound according to claim 1, wherein the compound is:
1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
(R)-1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-butyl-3-(2,3-diphenylquinolin-6-yl)urea;
1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-butyl-3-(5-(2-hydroxypyridin-3-yl)-2,3-diphenylquinolin-6-yl)urea;
1-(2,3-bis(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-(2-fluorophenyl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2,3-bis(2-methoxypyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-hydroxybutyl)-3-(3-(2-methoxyphenyl)-2-phenylquinolin-6-yl)urea;
1-(2,3-bis(6-methoxypyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-hydroxybutyl)-3-(2-(2-methoxyphenyl)-3-phenylquinolin-6-yl)urea;
1-(2,3-bis(2-methoxypyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-butylurea;
(R)-1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-butyl-3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)urea;
1-(2,3-bis(4-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;

- 1-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2,3-di(pyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
(R)-1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2,3-bis(3-acetylphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
5 1-(2,3-di(1H-pyrazol-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-butyl-3-(3-(2-methoxyphenyl)-2-phenylquinolin-6-yl)urea;
1-(2,3-di(pyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2,3-bis(3-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-(2-fluorophenyl)-3-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
10 1-(2,3-bis(6-oxo-1,6-dihydropyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
(S)-1-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2,3-bis(2-hydroxypyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
(S)-1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(3-(2-fluorophenyl)-2-(pyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
15 1-(2-(cyclohex-1-en-1-yl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-(2-(dimethylamino)phenyl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(3-(2-fluorophenyl)-2-(pyridin-4-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
(R)-1-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
20 (S)-1-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-butyl-3-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)urea;
1-(2-hydroxybutyl)-3-(3-phenyl-2-(pyridin-2-yl)quinolin-6-yl)urea;
1-(2-cyclohexyl-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-cyclopropyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
25 1-(2-hydroxybutyl)-3-(3-phenyl-2-(pyridin-3-yl)quinolin-6-yl)urea;
1-(2,3-bis(2-hydroxypyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-hydroxybutyl)-3-(2-(1-methyl-1H-pyrazol-4-yl)-3-phenylquinolin-6-yl)urea;
1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-methoxybutyl)urea;
1-(2,2-difluorobutyl)-3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)urea;
30 1-(3-(2-fluorophenyl)-2-(3-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(3-(2-fluorophenyl)-2-(4-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
methyl 6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxylate;
6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxamide;
(E)-1-(2-hydroxybutyl)-3-(3-phenyl-2-styrylquinolin-6-yl)urea;
35 N-(2-(3-(2-fluorophenyl)-6-(3-(2-hydroxybutyl)ureido)quinolin-2-yl)phenyl)acetamide;

- 1-(2-hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea;
1-(2-(2-cyanophenyl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-(2-aminophenyl)-3-(2-fluorophenyl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-([1,1'-biphenyl]-4-yl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
5 1-(2-hydroxybutyl)-3-(2-phenethyl-3-phenylquinolin-6-yl)urea;
(R)-6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxamide;
1-(2-(2-ethoxyphenyl)-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-hydroxybutyl)-3-(2-(2-isobutoxyphenyl)-3-phenylquinolin-6-yl)urea;
1-(2-ethynyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
10 1-(2-ethyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
6-(3-(2-hydroxybutyl)ureido)-N-methyl-2,3-diphenylquinoline-4-carboxamide;
6-(3-(2-hydroxybutyl)ureido)-N,N-dimethyl-2,3-diphenylquinoline-4-carboxamide;
N-cyclopropyl-6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxamide;
6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinoline-4-carboxylic acid;
15 6-(3-(2-hydroxybutyl)ureido)-2-methyl-3-phenylquinoline-4-carboxamide;
(S)-1-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
(S)-1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
6-(3-(2-hydroxybutyl)ureido)-2,3-dimethylquinoline-4-carboxamide;
1-(4-cyano-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
20 6-(3-(2-hydroxybutyl)ureido)-3-phenylquinoline-4-carboxamide;
(R)-1-(2-hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea;
3-(2-fluorophenyl)-6-(3-(2-hydroxybutyl)ureido)-2-methylquinoline-4-carboxamide;
6-(3-(2-hydroxybutyl)ureido)-2-methylquinoline-4-carboxamide;
1-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
25 1-butyl-3-(2-methyl-3-phenylquinolin-6-yl)urea;
1-(2-methoxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea;
1-(2-methoxyethyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea;
1-(2-hydroxybutyl)-3-(2-methyl-3-(pyridin-3-yl)quinolin-6-yl)urea;
1-(2-hydroxybutyl)-3-(2-methyl-3-(o-tolyl)quinolin-6-yl)urea;
30 1-(3-(2-chlorophenyl)-2-methylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(2-hydroxybutyl)-3-(2-methyl-3-(1-methyl-1H-pyrazol-4-yl)quinolin-6-yl)urea;
(R)-1-(2-hydroxybutyl)-3-(2-methyl-3-(o-tolyl)quinolin-6-yl)urea;
N-(6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)acetamide;
1-(2,5-dimethyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
35 1-(5-cyclopropyl-2-methyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
1-(5-bromo-2-methyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;

- 1-(2-hydroxybutyl)-3-(3-phenyl-2-(trifluoromethyl)quinolin-6-yl)urea;
 (S)-1-(2-hydroxybutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea;
 (R)-1-(7-fluoro-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
 1-(4-(dimethylamino)-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
 5 (R)-N-(6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)cyclopropanecarboxamide;
 N-(6-(3-(2-hydroxybutyl)ureido)-2-methyl-3-phenylquinolin-4-yl)acetamide;
 N-(6-(3-(2-hydroxybutyl)ureido)-2,3-diphenylquinolin-4-yl)methanesulfonamide;
 1-(4-amino-2,3-diphenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
 10 (R)-1-(2-hydroxybutyl)-3-(2-methyl-5-(1-methyl-1H-pyrazol-4-yl)-3-phenylquinolin-6-yl)urea;
 1-(2-hydroxybutyl)-3-(4-(oxazol-2-yl)-2,3-diphenylquinolin-6-yl)urea;
 1-(4-cyano-2-methyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
 N-(1-(3-(2-methyl-3-phenylquinolin-6-yl)ureido)butan-2-yl)acetamide;
 15 (R)-1-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
 (R)-1-(2-hydroxybutyl)-3-(4-methoxy-2,3-diphenylquinolin-6-yl)urea;
 (R)-1-(2-hydroxybutyl)-3-(4-methoxy-2-methyl-3-phenylquinolin-6-yl)urea;
 (R)-1-(2-hydroxybutyl)-3-(4-methyl-2,3-diphenylquinolin-6-yl)urea;
 (R)-N-benzyl-6-(3-(2-hydroxybutyl)ureido)-3-methyl-2-phenylquinoline-4-
 20 carboxamide;
 1-(2,2-difluorobutyl)-3-(2-methyl-3-phenylquinolin-6-yl)urea;
 6-(3-(2,2-difluorobutyl)ureido)-2,3-diphenylquinoline-4-carboxamide;
 1-(2,2-difluorobutyl)-3-(2,3-diphenylquinolin-6-yl)urea;
 (R)-6-(3-(2-hydroxybutyl)ureido)-N,3-dimethyl-2-phenylquinoline-4-carboxamide;
 25 (R)-6-(3-(2-hydroxybutyl)ureido)-3-methyl-2-phenylquinoline-4-carboxamide;
 1-(2,2-difluorobutyl)-3-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)urea;
 (R)-1-(3-(2-fluorophenyl)-2-methyl-5-(2-oxo-1,2-dihydropyridin-3-yl)quinolin-6-yl)-3-(2-hydroxybutyl)urea;
 (R)-6-(3-(2-hydroxybutyl)ureido)-N-(1-methyl-1H-pyrazol-3-yl)-2,3-
 30 diphenylquinoline-4-carboxamide;
 (R)-1-(2,4-dimethyl-3-phenylquinolin-6-yl)-3-(2-hydroxybutyl)urea;
 (R)-6-(3-(2-hydroxybutyl)ureido)-3-methyl-N-((1-methyl-1H-pyrazol-4-yl)methyl)-2-phenylquinoline-4-carboxamide;
 (R)-6-(3-(2-hydroxybutyl)ureido)-3-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2-
 35 phenylquinoline-4-carboxamide;
 1-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-3-(2-methoxyethyl)urea;

- (R)-1-(3-(3-(2-fluorophenyl)-2-phenylquinolin-6-yl)ureido)butan-2-yl dihydrogen phosphate;
- N-(2,3-diphenylquinolin-6-yl)hexanamide;
- N-(2,3-bis(2-methoxyphenyl)quinolin-6-yl)hexanamide;
- 5 N-(2-(2-methoxyphenyl)-3-phenylquinolin-6-yl)-4-oxohexanamide;
- N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)hexanamide;
- N-(2,3-diphenylquinolin-6-yl)-2,2-difluorohexanamide;
- N-(2-(2-fluorophenyl)-3-phenylquinolin-6-yl)-4-oxohexanamide;
- N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-4-oxohexanamide;
- 10 N-(2,3-diphenylquinolin-6-yl)-4-oxohexanamide;
- N-(3-(2-fluorophenyl)-2-(2-methoxyphenyl)quinolin-6-yl)-4-oxohexanamide;
- N-(2,3-diphenylquinolin-6-yl)-4-hydroxyhexanamide;
- N-(2,3-bis(2-fluorophenyl)quinolin-6-yl)-4-hydroxyhexanamide;
- N-(3-(2-fluorophenyl)-2-methylquinolin-6-yl)-4-hydroxyhexanamide;
- 15 4-hydroxy-N-(2-methyl-3-phenylquinolin-6-yl)hexanamide;
- 1-cyclohexyl-3-(2,3-diphenylquinolin-6-yl)urea;
- N-(2,3-diphenylquinolin-6-yl)-4-methylpiperazine-1-carboxamide;
- 4-acetyl-N-(2,3-diphenylquinolin-6-yl)piperazine-1-carboxamide;
- 1-allyl-3-(2,3-diphenylquinolin-6-yl)urea;
- 20 1-(2,3-diphenylquinolin-6-yl)-3-(prop-2-yn-1-yl)urea;
- 1-(2,3-diphenylquinolin-6-yl)-3-(2-hydroxycyclopentyl)urea;
- 1-(2,3-diphenylquinolin-6-yl)-3-(tetrahydro-2H-pyran-4-yl)urea;
- N-(2,3-diphenylquinolin-6-yl)-3-methoxypyrrolidine-1-carboxamide;
- 1-(2,3-diphenylquinolin-6-yl)-3-(pyridin-2-yl)urea;
- 25 1-(2,3-diphenylquinolin-6-yl)-3-phenylurea;
- 1-(2,3-diphenylquinolin-6-yl)-3-(1-methylpyrrolidin-3-yl)urea;
- 1-(2,3-diphenylquinolin-6-yl)-3-(pyridin-4-yl)urea;
- 1-(2,3-diphenylquinolin-6-yl)-3-(1-(hydroxymethyl)cyclopentyl)urea;
- 1-(2,3-diphenylquinolin-6-yl)-3-(1-methyl-1H-pyrazol-4-yl)urea;
- 30 1-(6,7-diphenyl-1,8-naphthyridin-3-yl)-3-(2-hydroxybutyl)urea;
- 1-(6,7-diphenyl-1,5-naphthyridin-2-yl)-3-(2-hydroxybutyl)urea;
- 1-(2,3-diphenyl-1,7-naphthyridin-6-yl)-3-(2-hydroxybutyl)urea;
- (R)-1-(6,7-diphenyl-1,8-naphthyridin-3-yl)-3-(2-hydroxybutyl)urea;
- (R)-1-(6,7-diphenyl-1,5-naphthyridin-2-yl)-3-(2-hydroxybutyl)urea;
- 35 (R)-1-(2,3-diphenyl-1,7-naphthyridin-6-yl)-3-(2-hydroxybutyl)urea;
- N-(6,7-diphenyl-1,8-naphthyridin-3-yl)-3-methoxypyrrolidine-1-carboxamide;

N-(6,7-diphenyl-1,5-naphthyridin-2-yl)-3-methoxypyrrolidine-1-carboxamide; or
N-(2,3-diphenyl-1,7-naphthyridin-6-yl)-3-methoxypyrrolidine-1-carboxamide.

19. A conjugate of formula (II):



wherein, C is a compound of formula (I), as defined by any one of claims 1 to 18;

L¹ and L² are linkers;

10 T is a targeting moiety; and

a is an integer between 1 and 5;

b is an integer between 1 and 10; and

z is an integer between 1 and 5.

15 20. A pharmaceutical composition comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, or a conjugate according to claim 19, and a pharmaceutically acceptable vehicle.

20 21. A compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, a conjugate according to claim 19, or a pharmaceutical composition according to claim 20, for use in therapy.

25 22. A compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, a conjugate according to claim 19, or a pharmaceutical composition according to claim 20, for use in modulating the acetyl coenzyme A synthetase short chain 2 (ACSS2) protein.

30 23. A compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, a conjugate according to claim 19, or a pharmaceutical composition according to claim 20, for use in treating, ameliorating or preventing a disease selected from cancer, bacterial infection, viral infection, parasitic infection, fungal infection, neurodegenerative

disease, neurological disorder, cerebrovascular disease, cardiovascular disease, non-alcoholic fatty liver disease and obesity or for use in promoting healthy ageing.

24. A compound, conjugate or pharmaceutical composition for use according to
5 claim 23, wherein the disease is cancer, and the cancer is selected from the group
consisting of colorectal cancer, aero-digestive squamous cancer, gastrointestinal
stromal tumors, lung cancer, brain cancer, neuroblastoma, glial tumors, astrocytoma,
glioblastoma, liver cancer, stomach cancer, sarcoma, leukaemia, lymphoma, multiple
myeloma, ovarian cancer, uterine cancer, breast cancer, melanoma, prostate cancer,
10 bladder cancer, pancreatic carcinoma or renal carcinoma.

25. A compound, conjugate or pharmaceutical composition for use according to
claim 23, wherein the disease is a viral infection, and the viral infection is a hepatitis C
virus (HCV) infection or a human cytomegalovirus (HCMV) infection.
15