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(54) Title: HALOGENATED-HETEROARYL AND OTHER HETEROCYCLIC KINASE INHIBITORS, AND USES THEREOF

(57) Abstract: The invention relates to kinase inhibitors, in particular inhibitors of protein kinases including the SIK-family CSF1R, ABL/BCR-ABL, SRC, HCK, PDGFR, KIT and/or their mutants. Although structurally similar to dasatinib, the kinase inhibitors of the invention are distinctive; possessing a particular class of halogenated heteroaryls. Such kinase inhibitors can display one or more certain properties distinct to dasatinib and other structurally similar kinase inhibitors. The kinase inhibitors of the invention or pharmaceutical compositions comprising them may be used in the treatment of a disorder or condition, such as a proliferative disorder, for example, a leukaemia or solid tumour. In particular, these and other structurally similar kinase inhibitors may be used in the treatment of a proliferative disorder - such as a mixed phenotype acute leukaemia (MPAL) - characterised by (*inter-alia*) the presence of MEF2C protein, a human chromosomal translocation at 11q23, and/or a KMT2A fusion oncoprotein. The kinase inhibitors or pharmaceutical compositions disclosed herein may be used topically to modulate skin pigmentation in a subject, for example to impart UV protection and reduce skin cancer risk.

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HALOGENATED-HETEROARYL AND OTHER HETEROCYCLIC KINASE INHIBITORS, AND USES THEREOF

DESCRIPTION

[1] The invention relates to kinase inhibitors, in particular inhibitors of protein kinases including the SIK-family, CSF1R, ABL/BCR-ABL, SRC, HCK, PDGFR, KIT and/or their mutants. Although structurally similar to dasatinib, the kinase inhibitors of the invention are distinctive; possessing a particular class of halogenated heteroaryls. Such kinase inhibitors can display one or more certain properties distinct to dasatinib and other structurally similar kinase inhibitors. The kinase inhibitors of the invention or pharmaceutical compositions comprising them may be used in the treatment of a disorder or condition, such as a proliferative disorder, for example, a leukaemia or solid tumour. In particular, these and other structurally similar kinase inhibitors may be used in the treatment of a proliferative disorder - such as a mixed phenotype acute leukaemia (MPAL) - characterised by (*inter-alia*) the presence of MEF2C protein, a human chromosomal translocation at 11q23, and/or a KMT2A fusion oncoprotein. The kinase inhibitors or pharmaceutical compositions disclosed herein may be used topically to modulate skin pigmentation in a subject, for example to impart UV protection and reduce skin cancer risk.

[2] A kinase inhibitor is an enzyme inhibitor that blocks the action of a kinase. A partial, non-limiting, list of kinases includes ABL, AKT, BCR-ABL, BLK, BRK, c-KIT, c-MET, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRAF1, CSF1R, CSK, EGFR, ERBB2, ERBB3, ERBB4, ERK, PAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, FGR, FIT-1, FPS, FRK, FYN, HCK, IGF-1R, INS-R, JAK, KDR, LCK, LYN, MEK, p38, PDGFR, PIK, PKC, PYK2, ROS, SIK1, SIK2, SIK3, SRC, TIE, TIE2, TRK and ZAP70. Kinases are enzymes that add a phosphate group to a protein or another organic molecule, and have been shown to be key regulators in most cellular functions including cell-signalling, -proliferation, -differentiation, -metabolism, -survival, -apoptosis, -motility, DNA damage repair etc. Phosphorylation, in particular deregulated signalling due to defective control of protein phosphorylation, is implicated in a wide range of diseases; such as diseases associated with aberrant activity (e.g., increased activity) of a kinase. Such diseases include, but are not limited to, proliferative diseases (e.g., cancers, benign neoplasms, pathological angiogenesis, inflammatory diseases, and autoimmune diseases), as wells as allergies and CNS disorders.

[3] Protein-tyrosine kinases (PTKs) are enzymes that, in conjunction with ATP as a substrate, phosphorylate tyrosine residues in peptides and proteins. PTKs comprise, inter alia, receptor protein-tyrosine kinases (RPTKs), including members of the epidermal growth factor kinase family (e.g., HER1 and HER2), platelet derived growth factor (PDGF), and kinases that play a role in angiogenesis (e.g., TIE2 and KDR); and, in addition, non-receptor protein-tyrosine kinases, including members of the SYK, JAK and SRC kinase families (e.g., SRC, HCK, FYN, LYN, LCK and BLK kinases). Protein-serine/threonine kinases (STKs) are enzymes that phosphorylate the oxygen atom of a serine or threonine side-chain in in peptides and proteins. STKs comprise, inter alia, AKT1, Aurora kinases, BRAF, MAP kinases, PLK1, SIK1, SIK2 and SIK3.

[4] Inhibiting protein kinases, and therefore the phosphorylation of a substrate peptide or protein, has been shown to be useful in treating many diseases. For example, afatinib, an ERBB inhibitor, is useful in treating non-small cell lung cancer; axitinib, a VEGFR, PDGFR, and c-KIT inhibitor, is useful in treating renal cell carcinoma; bosutinib, an ABL/BCR-ABL inhibitor, is useful in treating chronic myelogenous leukaemia; cabozantinib, a c-MET and VEGFR2 inhibitor, is useful in treating thyroid cancer; crizotinib, an ALK, HGFR, and c-MET inhibitor, is useful in treating non-small cell lung cancer; dasatinib, an ABL/BCR-ABL, SRC, and c-KIT inhibitor, is useful in treating chronic myelogenous leukaemia; erlotinib, an EGFR inhibitor, is useful in treating non-small cell lung cancer and pancreatic cancer; gefitinib, an EGFR inhibitor, is useful in treating non- small cell lung cancer; imatinib, an ABL/BCR-ABL inhibitor, is useful in treating chronic myelogenous leukaemia; lapatinib, a HER2 inhibitor, is useful in treating breast cancer; nilotinib, an ABL/BCR-ABL inhibitor, is useful in treating chronic myelogenous leukaemia; pazopanib, a VEGFR, PDGFR, and c-KIT

inhibitor, is useful in treating renal cell carcinoma and soft tissue sarcoma; palbociclib, an inhibitor of CDK4 and CDK6, is useful in treating ER-positive and HER2-negative breast cancer; ponatinib, an ABL/BCR-ABL, BEGFR, PDGFR, FGFR, EPH, SRC, c-KIT, RET, TIE2, and FLT3 inhibitor, is useful in treating chronic myelogenous leukaemia and acute lymphoblastic leukaemia; regorafenib, a RET, VEGFR, and PDGFR inhibitor, is useful in treating colorectal cancer and gastrointestinal stromal tumour; ribociclib, an inhibitor of cyclin D1/CDK4 and CDK6, is useful in treating HR-positive, HER2-negative advanced or metastatic breast cancers; ruxolitinib, a JAK inhibitor, is useful in treating myelofibrosis; sorafenib, a VEGFR, PDGFR, BRAF, and c-KIT inhibitor, is useful in treating renal cell carcinoma and hepatocellular carcinoma; sunitinib, a VEGFR and PDGFR inhibitor, is useful in treating renal cell carcinoma, gastrointestinal stromal tumour, and pancreatic neuroendocrine tumour; tofacitinib, a JAK inhibitor, is useful in treating rheumatoid arthritis; vandetanib, a VEGFR, EGFR, RET and BRK inhibitor, is useful in treating thyroid cancer; and vemurafenib, a BRAF inhibitor, is useful in treating malignant melanoma.

[5] In view of the large number of kinases and associated diseases, there is an ever-existing need for new inhibitors selective for various kinases which might be useful in the treatment of related diseases; in particular there remains a need for new kinase inhibitors, pharmaceutical compositions/formulations and uses thereof (including in treatment regimens) for the treatment of diseases associated with aberrant activity of one or more kinases; in particular, there remains a need for new kinase inhibitors: (a) for use in the treatment of proliferative disorders - such as a mixed phenotype acute leukaemia (MPAL) - that are characterised by (*inter-alia*) the presence of myocyte enhancer factor 2C (MEF2C) protein, a human chromosomal translocation at 11q23, and/or a lysine methyltransferase 2A (KMT2A) fusion oncoprotein; or (b) that are alternatives to an existing kinase inhibitor, such as dasatinib.

[6] One particular kinase inhibitor is dasatinib (N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate; Figure 1A), marketed as "SPRYCEL" by Bristol-Myers Squibb, and is indicated for the treatment of adult patients with: (i) newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia (CML) in chronic phase; (ii) chronic, accelerated, or (myeloid or lymphoid) blast phase (Ph+) CML with resistance or intolerance to prior therapy including imatinib; and (iii) Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) with resistance or intolerance to prior therapy. In the EU, dasatinib is also indicated for the treatment of paediatric patients with newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib, and in the US it is indicated for paediatric patients with Ph+ CML in chronic phase.

[7] Notably, despite numerous trials being conducted with dasatinib, it is not indicated in the US or Europe for any cancer other than CML or Ph+ ALL; in particular, as of September 2018, dasatinib is not indicated for any solid tumour. Indeed, numerous clinical trials using dasatinib to investigate its possible use to treat solid tumours were terminated early (for example, due to toxicity issues) or failed to report strong or even encouraging results. For example, according to information on clincialtrials.gov on 09-Sept-2018, dasatinib has only once reached phase 3 testing for solid tumours: in a single investigation against castrate resistant prostate cancer in combination with docetaxel, the "READY" trial (NCT00744497), but dasatinib failed to improve overall survival over docetaxel alone in such trial (Araujo et al. 2013, Lancet Oncol. 14:13017), despite some suggestion of its activity against chemotherapy-naïve castrate resistant prostate in earlier-stage trials (e.g., Araujo et al. 2012, Cancer 118:63). Despite several trials against other cancers such as breast, skin, pancreatic, brain or lung cancer, dasatinib has not shown satisfactory efficacy or tolerability, and has not been progressed to phase 3 testing against any of these cancers. In particular, more recently dasatinib failed to show increased overall survival in combination with gemcitabine compared to gemcitabine alone in a double-blinded phase 2 trial against locally-advanced unresectable pancreatic patients (Evens et al. 2017, Annal. Onc. 28:354). However, recently, some specialised trails that aim to selected "targeted" therapies to patients having particular cancers (including solid tumours) that express particular drug targets, may potentially test dasatinib depending on the target profile of the patients. For example (i) the "TAPUR" trial ("The Targeted Agent and

Profiling Utilization Registry", https://www.tapur.org, NCT02693535) includes dasatinib in one possible treatment arm based on one or more of the following targets: BCR-ABL, SRC, KIT, PDGFRB, EPHA2, FYN, LCK, YES1; and (ii) a Melanoma Institute Australia trial (NCT02645149) involving patients with BRAF and NRAS wild-type unresectable Stage III or Stage IV metastatic melanoma who have progressed on, or are unable to receive standard therapy (in general, immunotherapy), includes dasatinib as one possible therapy depending on KIT mutation(s) being found in the patient's cancer. Dasatinib is also one possible arm of the BMS "FRACTION-Lung" phase 2 trial (NCT02750514) where it may be tested in combination with the immune-oncology drug nivolumab in patients with advanced non-small cell lung cancer. Other arms of this trial use nivolumab in combination with other immune-oncology drugs.

[8] Accordingly, there is a particular need for new kinase inhibitors useful in the treatment of cancers - especially solid tumours – the treatment of which by dasatinib are not indicated, and/or of cancers for which dasatinib has not shown promising results. In particular, there is a need for new kinase inhibitors useful in the treatment of one or more cancers such as breast, lung (e.g., non-small cell), pancreatic or prostate (e.g., castrate or hormone resistant) cancer, as well as melanoma.

[9] There is also an especial need for new kinase inhibitors useful in the treatment of proliferative disorders - such as a mixed phenotype acute leukaemia (MPAL, also known as mixed lineage leukaemia "MLL") - that are characterised by (*inter-alia*) the presence of MEF2C protein (such as phosphorylated MEF2C protein and/or MEF2C protein as an active transcription factor), a human chromosomal translocation at 11q23, and/or a KMT2A fusion oncoprotein.

[10] Mixed phenotype acute leukaemia (MPAL) - also known as "mixed lineage leukaemia" (MLL) – is a very aggressive blood cancer that predominantly occurs in paediatric patients and, unlike other types of childhood acute leukaemias, has a dismal prognosis (reviewed by Slany 2009, Haematologica 94:984). One form of MPAL is characterised by a BCR/ABL rearrangement. MPAL with t(9;22)(q34;q11.2) (or BCR/ABL1 rearrangement) is considered as a separate entity (Arber et al 2016, Blood 127:2391). The t(9;22)(q34;q11.2 translocation results in a *BCR/ABL1* fusion gene located on the Philadelphia chromosome (Ph), causing a constitutively active BCR/ABL1 tyrosine kinase. Another form of MPAL is characterised by the presence of lysine methyltransferase 2A (KMT2A) fusion proteins (also known as MLL1 fusion proteins) that are the result of chromosomal translocations affecting the *KMT2A* gene (also known as the *MLL1* gene) at 11q23. This KMT2A/MLL rearrangement is the second most frequent genetic lesion in MPAL (MPAL MLL+). These 11q23 translation events juxtapose the amino-terminus of the histone methyltransferase KMT2A with a variety of different (translocation) fusion partners that destroy normal histone methyltransferase function of KMT2A and replace it by heterologous functions contributed by the (translocation) fusion partner. The resulting protein chimeras are transcriptional regulators that take control of other genes normally controlled by KMT2A. In particular, the transcription factor MEF2C can be controlled by KMT2A and is described as an oncogene in childhood acute leukaemias. MEF2C expression is associated with KMT2A fusion gene rearrangement in AML (Schwieger et al 2009, Blood 114:2476), and MEF2C expression defines a subset of AML patients with poor survival outcome (Lazlo et al 2015, J Hematol & Oncol 8:115).

[11] Tarumoto and co-workers (2018, Mol Cell 69:1017) showed that MEF2C activity in AML is driven by SIK3-phosphorylation of HDAC4, and that SIK3 knock-out or chemical inhibition with the small molecule tool compound HG-9-91-01 strongly decreases viability of several MPAL-associated AML cell lines (including MOLM-13 and MV4-11); because cytoplasmic retention of SIK3-phosphorylated HDAC4 regulates MEF2C activity, by preventing nuclear-located (un-phosphorylated) HDAC4 acting as a repressive cofactor of MEF2C, a transcription factor of tumour survival/maintenance genes associated with AML proliferation (Figure 19). Indeed, recent research demonstrated that SIK3 inhibition with the small molecule tool compound YKL-05-099 - administered intraperitoneally - supressed AML progression in-vivo (Tarumoto et al 2020, Blood 135:56). However further SIK3 inhibitors remain needed, in particular those with drug-like properties and especially those that can be administered orally, for use in the treatment of

proliferative disorders (such as MPAL), especially those that are associated with SIK3-driven MEF2C-controlled expression of cancer survival genes.

[12] There also remains the need for new kinase inhibitors useful in the treatment of myeloid or lymphoblastic cancers such as leukaemia, preferably, useful for the treatment of one or more Ph+ leukaemia such as CML and/or ALL.

[13] Dasatinib is described as an inhibitor of the following kinases at nanomolar concentrations: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFR-beta; where of particular relevance to dasatinib's indication for Ph+ leukaemia, is its inhibition of the hybrid protein kinase BCR-ABL.

[14] The BCR-ABL kinase is directly connected to the presence of a specific genetic abnormality in chromosome 22 of leukaemia cancer cells (particularly CML cells); known as the "Philadelphia chromosome" (or Philadelphia translocation). This reciprocal translocation of genetic material between chromosome 9 and chromosome 22, juxtaposes the ABL1 gene of chromosome 9 onto the BCR gene of chromosome 22, resulting in a coding sequence for a hybrid protein known as "BCR-ABL": a protein-tyrosine kinase that is "always on", causing the cell to divide uncontrollably. The vast majority of CML cases and 20-30% of ALL cases are Ph+. The first selective BRC-ABL inhibitor, imatinib (STI571), marketed as "GLEEVEC/GLIVEC" by Novartis, was considered a breakthrough for the treatment of Ph+ leukaemia. However, despite the increase in overall survival, drug resistance that developed during imatinib treatment led scientists to discover that most of such resistances arise due to the emergence of BCR-ABL mutations, particularly amino acid substitutions within the ABL-derived kinase domain (for review, see Rossari & Orciuolo. 2018, J. Hemat. Oncol. 11:84, incorporated herein in its entirety by reference).

[15] An analysis of BCR-ABL mutation status and the probability of survival for patients treatment with imatinib indicated that mutations within the phosphatase loop (P-loop) of the ABL-position of the BCR-ABL kinase were the most frequent, but that the (rarer) mutations outside of the P-loop (in particularly those within the kinase domain) were associated with a reduction in overall survival of imatinib-treated CML patients (Jabbour et al. 2006, Leukemia 20:1767). A number of emergent BCR-ABL mutations have since been identified and described (see, Table 1 of Manley et al. 2005, Biochem. Biophys. Acta 1754:3; and Table 1 of Rossari & Orciuolo 2018, which also describes mutations of other kinase-targets of dasatinib; both such tables specifically incorporated herein by reference). In particular the following mutations are found in the ATP-binding region of BCR-ABL (with positions indicated for the wild-type ABL protein): V299L, F311L, T315I, T315A, F317L and F317V. Indeed, dasatinib was initially developed as a "second generation" BCR-ABL inhibitor for second-line therapy for CML that had become resistant to imatinib, presumed to arise due to the emergence of one or other of these mutations. Based on modelling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase, and this is thought to explain why several conformation-altering mutations of ABL are inhibited by dasatinib, but not by imatinib. Indeed, a retrospective analysis comparing mutation development during first-line treatment with dasatinib or with imatinib revealed that fewer different mutation sites emerged with dasatinib treatment (4 different sites) compared with imatinib treatment (12 different sites) (Hughes et al. 2015, Leukemia 29:1832, in particular Figure 1 thereof). Importantly however: (i) the total proportion of patients developing any type of mutation was approximately the same (17/259 dasatinib patients and 18/260 imatinib patients); (ii) the majority of the mutation sites emerging upon dasatinib treatment were in the ATP-binding region (3/4 mutation sites); and (iii) the by far commonest mutation emerging during dasatinib treatment (11/17) was the T315I mutation at the so-called "gate-keeper" residue, which still confers resistance to dasatinib inhibition on the BCR-ABL kinase. A particular set of BCR-ABL mutants that can be tested against kinase inhibitors are provided by the ProQinase ABL1 kinase "Wildtype and Mutant Panel", and includes the ABL1 wild-type protein (amino acids P118-S525) and mutants forms that represent the most prevalent imatinib-resistant mutant forms of BCR-ABL: G250E, Q252H, Y253F, E255K, T315I, F317I, M351T and H396P (www.proqinase.com).

[16] The T315I mutation is one of the most frequently emerging BCR-ABL mutations: arising in 2 to 20% CML cases (Nicolini et al. 2009, Blood 114:5271). That such a mutation is resistant to dasatinib inhibition is one potential draw-back of dasatinib as a kinase inhibitor, which has stimulated the development of the "third generation" BCR-ABL inhibitor known as ponatinib (marketed as ICLUSIG by Incyte & Takeda). However, although ponatinib does indeed strongly inhibit the T315I mutation of the BCR-ABL kinase (*in-vitro* IC50 of 2.0nM), it is known to be a more promiscuous kinase inhibitor than dasatinib, and also inhibits a number of other kinases including with *in-vitro* IC50 concentrations between 0.1 and 20nM, for at least members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Furthermore, US sales of ponatinib were temporarily suspended in October 2013 because of "the risk of life-threatening blood clots and severe narrowing of blood vessels". This suspension was partially lifted in December 2013 with ponatinib being issued revised prescribing information, a new "Black Box Warning" and a "Risk Evaluation and Mitigation Strategy" in place to better evaluate the risks and benefits of using the drug. In addition, the price of ponatinib in the US (it can cost $138,000 a year) has been criticised. Accordingly, substantial drawbacks are shown by ponatinib, such that there still remains a need for new kinase inhibitors, in particular those with the potential to more effectively, safely, easily and/or cheaply treat Ph+ leukaemia (or other cancers); and/or that are more selective to SRC, ABL/BCR-ABL and/or LCK than other kinase inhibitors such as dasatinib or ponatinib.

[17] Compared to imatinib however, dasatinib is not particularly specific to BCR-ABL, and binds to and/or inhibits a significant number of other kinases (see: Figure 3 of Bantscheff et al. 2007, Nat. Biotech. 25:1035; supplementary Figure 2 of Anastassiadis et al. 2012, Nat. Biotech. 29:1039). In particular, compared to imatinib, dasatinib is described to more significantly bind to and/or inhibit numerous other kinases, including: BTK, CSK, EPHB2, EPHB4, FYN, GAK, KIT, LYN, QIK, QSK, RIPK2, SRC, TEC, TESK2, YES and ZAK. More specifically, dasatinib is shown to be a significant inhibitor of salt-inducible kinases with IC50 values of <3nM, <3nM and 18nM for the three family members SIK1, SIK2 and SIK3, respectively (Ozanne et al. 2015, Biochem. J. 465:271; also as described in co-pending PCT/EP2018/060172). Indeed, given that dasatinib is a less selective kinase inhibitor, is yet another potential drawback, and this reduced selectively may be causally associated with the not-insignificant toxicity challenges faced when treating patients with dasatinib, in particular with an increased occurrence of thrombocytopaenia (Wei et al. 2010, J. Hemat. Oncol. 3:47).

[18] As described above, dasatinib is a potent inhibitor of KIT, and this receptor tyrosine kinase is becoming an increasingly interesting target for the treatment of certain cancers (Babei et al. 2016, Drug Des. Dev. Thera., 10:2443), not least because mutations in the KIT gene have been detected in cancers such as leukaemia, ovarian cancer and melanoma. It is also known that dasatinib can also inhibit at least the most common KIT mutation in melanoma (Woodman et al. 2009, J. Clin. Onc. 27:9019). However, inhibition of KIT, and in particular the relative activity against FLT3 and KIT of certain tyrosine kinase inhibitors, has been associated with myelosuppression and other side effects such as hair depigmentation (Galanis and Levis 2015: Haematologica 100:e89). Indeed, treatment with dasatinib is associated with severe myelosuppression (see below).

[19] Salt-inducible kinases (SIKs) constitute a serine tyrosine kinase subfamily, belonging to the adenosine monophosphate-activated kinase (AMPK) family. Three members (SIK1, -2, and -3) have been identified so far. Amino acid homology of SIK1 with SIK2 and SIK3 is 78% and 68%, respectively, in the kinase domain. The cloning of SIK1 (also known as SIK and SNF1LK), abundantly expressed in the adrenal glands of high-salt, diet-fed rats, led to subsequent cloning of SIK2 (also known as QIK, KIAA0781 and SNF1LK2), mainly expressed in adipose tissues and the rather ubiquitous SIK3 (also known as QSK, KIAA0999 or L19) (Katoh et al. 2004, Mol. Cell. Endocrinol. 217:109). The three SIKs have a similar structure, with an N-terminal kinase domain (catalytic domain), a middle ubiquitin-associated domain (believed important for phosphorylation by LKB1) and a long C-terminal sequence (believed to be a site for further phosphorylation by PKA). However, there are very diverse roles implicated for the various SIKs. For example,

various SIKs have been implicated in biological processes as diverse as osteocyte response to parathyroid hormone (Wein et al. 2016, Nature Commun. 7:13176) to induction of SIK1 by gastrin and inhibition of migration of gastric adenocarcinoma cells (Selvik et al. 2014, PLoS ONE 9:e112485). Other potential roles of salt-inducible kinases (in particular SIK3) are described in WO2018/193084A1 (to the present applicant, and published 25-Oct-2018) furthermore that SIK3 is a gene involved in tumour cell resistance to cell-mediated immune responses, in particular tumour cell resistance to TNF. Recently, SIKs (particularly SIK3) have been demonstrated to also regulate TGFbeta-mediated transcriptional activity and apoptosis, with Hutchinson et al (2010, Cell Death and Disease 11:49) showing that SIK3 expression or activity results in resistance to TGFbeta-mediated apoptosis.

[20] In particular, as well as playing a role in various inflammatory responses (Clark et al 2014; Sundberg et al 2016) and oncology - especially the sensitisation of tumour cells to immune responses (WO2018/193084A1) – it has been known since 2011 that inhibition of SIK2 promotes melanogenesis in B16F10 melanoma cells (Kumagai et al 2011, PLoS ONE 6(10): e26148). It was subsequently described that the pigmentation pathway including in human skin explants can be efficaciously induced by (topical) treatment with SIK inhibitors, including those structurally related to YKL-05-099 (Mujahid et al 2017, Cell Reports 19:2177). Indeed, using such results, it has subsequently been sought to claim methods of increasing (the appearance of) skin pigmentation in a subject by administering topically to the subject skin an effective account of a SIK inhibitor (WO2018/160774), including using kinase inhibitors previously known to be SIK inhibitors (WO2016/023014).

[21] The kinase known as colony-stimulating factor 1 receptor (CSF1R) binds to its ligand CSF1 and the resulting downstream signalling results in differentiation and survival of myeloid cells that express CSF1R receptor. In particular, CSF1-CSF1R signalling is important for the differentiation of macrophages to the more suppressive M2 phenotype (Lenzo et al 2012, Immunol Cell Bio 90:429). Indeed, the presence of CSF1R+ macrophages in tumours correlates with poor survival in various indications including gastric cancer, breast cancer, ovarian cancer, bladder cancer etc. (Zhang et al 2012, PLoS One 7:e50946t). Therefore, targeting CSF1R with either antibodies or small molecule inhibitors has gained increasing attention in treatment of cancer by eliminating or re-educating suppressive M2 macrophages. PLX3397 is one such inhibitor targeting CSF1R and is in clinical development against melanoma, glioblastoma, AML etc. (Cannarile et al 2017, J Immunotherapy Cancer 5:53).

[22] The kinase known as haematopoietic cell kinase (HCK) is a member of the SRC family of cytoplasmic tyrosine kinases (SFKs), and is expressed in cells of the myeloid and B-lymphocyte cell lineages. Excessive HCK activation is associated with several types of leukaemia and enhances cell proliferation and survival by physical association with oncogenic fusion proteins, and with functional interactions with receptor tyrosine kinases. Elevated HCK activity is also observed in many solid malignancies, including breast and colon cancer, and correlates with decreased patient survival rates. HCK enhances the secretion of growth factors and pro-inflammatory cytokines from myeloid cells, and promotes macrophage polarization towards a wound healing and tumour-promoting alternatively activated phenotype. Within tumour associated macrophages, HCK stimulates the formation of podosomes that facilitate extracellular matrix degradation, which enhance immune and epithelial cell invasion. By virtue of functional cooperation between HCK and *bona fide* oncogenic tyrosine kinases, excessive HCK activation can also reduce drug efficacy and contribute to chemo-resistance, while genetic ablation of HCK results in minimal physiological consequences in healthy mice. Given its known crystal structure, HCK therefore provides an attractive therapeutic target to both, directly inhibit the growth of cancer cells, and indirectly curb the source of tumour- promoting changes in the tumour microenvironment (Poh et al 2015, Oncotarget 6:15742).

[23] Hence there still remains a need for new kinase inhibitors, in particular those that exhibit drug like properties (especially those suitable for oral administration) and that inhibit one or more kinases, including any of those selected from SIK3, ABL/BCR-ABL, SRC, HCK, PDGFR, KIT and/or CSF1R, and/or that exhibit a different profile of kinases to the kinases inhibited by dasatinib, in particular. For example, new kinase inhibitors which: (i) are more specific to key

disease-related kinases (e.g., ABL/BCR-ABL, SRC, LCK, HCK, PDGFR CSFR1 and/or EPHA2, EPHA4, ACK1 and/or KIT), relative to other kinases, than the specificity shown by dasatinib to one or more such other kinases; (ii) inhibit key disease- or side-effect-related kinases in a different profile than dasatinib (e.g. to KIT and/or FLT3); and/or (iii) inhibit one or more mutant of a disease-related kinase, in particular a mutant that is resistant to one or other kinase inhibitor, such as mutants of ABL/BCR-ABL or KIT.

[24] Furthermore, although dasatinib is metabolised in humans primarily by the cytochrome P450 enzyme 3A4 (CYP3A4), it is also a time-dependent inhibitor of CYP3A4. Indeed, the dosage of dasatinib must be significantly reduced (e.g., from 100mg daily to 20mg daily) if the patient is concomitantly medicated with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole), as these may increase dasatinib plasma concentrations to potentially unsafe levels. Grapefruit juice may also increase plasma concentrations of dasatinib and should also be avoided. Accordingly, there remains a need for new kinase inhibitors that show a pattern of cytochrome P450 inhibition (eg, to CYP3A4) that is different to dasatinib.

[25] Importantly, the dosage and administration of dasatinib should be stopped (or reduced) upon occurrence of myelosuppression. Indeed, myelosuppression is described as just one "Warning and Precaution" in the US Prescribing Information for dasatinib, because treatment with dasatinib is associated with *severe* (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anaemia. In addition to causing thrombocytopenia in human subjects, in all clinical studies with dasatinib: (i) severe central nervous system (CNS) haemorrhages (including fatalities) occurred in 1% of patients; (ii) severe gastrointestinal haemorrhage, including fatalities, occurred in 4% of patients and generally required treatment interruptions and transfusions; and (iii) other cases of severe haemorrhage occurred in 2% of patients.

[26] Yet further "Warning and Precautions" of dasatinib include that: (x) it is associated with fluid retention, with *severe* fluid retention reported in up to 10% of patients in clinical trials; (y) it has the potential to prolong cardiac ventricular repolarization (QT interval), and up to 1% of CML patients in clinical trials experienced a QT prolongation; and (z) cardiac adverse reactions were reported in 5.8% of 258 patients taking dasatinib, including 1.6% of patients with cardiomyopathy, heart failure congestive, diastolic dysfunction, fatal myocardial infarction, and left ventricular dysfunction. Indeed, dasatinib is known to be an inhibitor of hERG (Pharmacological/Toxicity Review and Evaluation of NDA 21-986, page 31). hERG (the human "Ether-à-go-go-Related Gene") is an ion channel that contributes to the electrical activity of the heart and coordinates the heart's beating. When this channel's ability to conduct electrical current across the cell membrane is inhibited or compromised (e.g., by administration of a drug) it can result in "long QT syndrome" which can be potentially fatal. Accordingly, there remains a need for new kinase inhibitors that show inhibition of hERG that is different to dasatinib. For example, it would be advantageous to provide new kinase inhibitors that exhibit an IC50 to hERG that is greater than that of dasatinib.

[27] Indeed, the primary metabolic pathways of dasatinib include those that follow modifications at the chloro/methyl phenyl or piperazinyl groups of dasatinib (eg, Christopher et al 2008, Drug Metab & Disp 36:1357), especially Fig 4 thereof). In particular, CYP3A4-mediated formation of reactive epoxide and quinone-imine intermediates can be formed as reactive metabolites of dasatinib that can covalently bind biomolecules such as CYP proteins (Duckett & Cameron 2010, Expert Opin Drug Metab Toxicol 6): 1175) that can contribute to the observed toxicity of dasatinib in humans and/or lead to drug-drug interactions with other CYP substrates (eg simvastin).

[28] Accordingly, there remains a need for further kinase inhibitors that exhibit a different metabolite profile to dasatinib (eg in humans), and especially further kinase inhibitors that have one or more primary metabolic pathways different to that of dasatinib (especially those of dasatinib following modifications at its chloro/methyl phenyl and/or piperazinyl groups).

[29] Compared to other BCR-ABL inhibitors, dasatinib has an extremely short half-life: with an overall mean terminal half-life of only 3-5 hours (section 12.3 "Pharmacokinetics" of the Full Prescribing Information). In stark

contrast: the elimination half-life of imatinib is approximately 18 hours; the mean terminal phase elimination half-life of bosutinib is 22.5 hours; the apparent elimination half-life for nilotinib is approximately 17 hours; and the geometric mean terminal elimination half-life of ponatinib is approximately 24 hours. Without being bound by theory, the short half-life of dasatinib – indicated for dosage once daily – may account for limited activity associated with lower *in-vivo* drug-concentrations later in the day and/or side effects associated with peak/higher *in-vivo* drug-concentrations soon after dosage. Accordingly, there remains a need for new kinase inhibitors that exhibit properties of longer half-lives (e.g., than those shown by dasatinib). For example, an advantageous kinase inhibitor may be one that is more stable than dasatinib, for example by exhibiting a longer half-life in a plasma and/or liver-microsome stability assay.

[30] Further precautions, adverse events and other prescribing information of dasatinib can be found from the respective Summary of Product Characteristics (SmPC) of Full Prescribing Information as may be found from the respective web site of the EMA and FDA (respectively shown below, accessed 20-Aug-2018, and the contents of each are incorporated by reference in their entirety herein):

(i) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000709/WC500056998.pdf; and

(ii) https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021986s7s8lbl.pdf.

[31] Numerous variants of dasatinib have been synthesised and demonstrated to have in-vitro biochemical inhibitory activity against one or more kinases and/or antiproliferative effects on cells. In particular, such variants were synthesised: (i) during the discovery phase of dasatinib to understand and describe its structure-activity relationship (SAR) (Lombardo et al 2004, J Med Chem 47:6658; Das et al 2006, J Med Chem 49:6819); and (ii) to provide alternative kinase inhibitors and/or drug candidates (eg, WO 2006/081172 and WO 2008/033746). The variants of dasatinib described therein carry a phenyl moiety at the carboxamide. These disclosures demonstrate other positions, and the substantial range of substituents that may be substituted thereat, that provide compounds that are kinase inhibitors and/or possess cellular antiproliferative activity (Figure 8).

[32] WO 2018/193084 (to the present applicant, and published 25-Oct-2018) discloses a dasatinib variant carrying a pyridinyl moiety and its uses. Co-pending application PCT/EP2019/078751 (to the present applicant) discloses further dasatinib variants carrying other heterocyclic moieties, and in particular variants that carry a thiazolyl moiety. Beutner et al (2018, Org Lett 20:4218) describes a method of forming challenging amide bonds, including those to certain pyridines pyrazines and pyrimidines. Pennington et al (2017, J Med Chem 60:3552) describes that the replacement of a CH group with a N atom in aromatic and heteroaromatic ring systems can have effects on molecular and physiological properties. However, making such a substitution has been empirically shown to result in improved potency statistically no better than mere chance: a matched molecular pair analysis (MMPA) of internal data at Abbott (Hajduk & Sauer 2008, J Med Chem 51:553) found that, as with most substituent replacements, there is an approximate equal probability of increasing or decreasing potency by exchanging CH groups and N atoms. Indeed, this analysis further revealed that the probability for realising a 10-fold increase in potency with such replacements is less than 1 in 10 and that for achieving a 100-fold is less than 1 in 100; similar to the probabilities observed when investigating the effect of such replacements to improve binding affinity (Hu et al 2014, F1000Research 3:36; de la Vega de Leon et al 2014, MedChemComm 5:64).

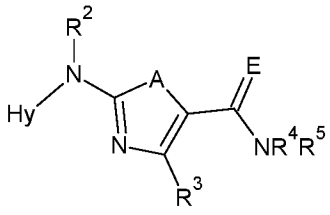
[33] Accordingly, it is one object of the present invention to provide one or more kinase inhibitors (eg, an inhibitor of SIK3, ABL/BCR-ABL, SRC, HCK, PDGFR, KIT and/or CSF1R kinases) that have one or more properties (such as those shown by *in-vitro* and/or *in-vivo* assays) that address one or more of these or other problems. In other objects, the present invention provides an alternative and/or improved kinase inhibitor to dasatinib (or one or other kinase inhibitor, such as those described herein). For example, a kinase inhibitor that can exhibit one or more functional (e.g., kinase selectivity), ADMET, PK and/or pharmacological properties that are different to, and/or are improved compared to, dasatinib (or one or other kinase inhibitor, such as those described herein), would be advantageous. In particular, it

would be advantageous to provide inhibitors of one or more SIK-family kinases that have drug-like properties and especially those that can be administered orally, for use in the treatment of a proliferative disorder (such as MPAL) characterised, *inter-alia*, by the presence of MEF2C protein (such as phosphorylated MEF2C protein and/or MEF2C protein as an active transcription factor), a human chromosomal translocation at 11q23, and/or a KMT2A fusion oncoprotein. An object underlying the present invention is solved by the subject matter as disclosed or defined anywhere herein, for example by the subject matter of the attached claims.

SUMMARY OF THE INVENTION

[34] Generally, and by way of brief description, the main aspects of the present invention can be summarised as follows:

[35] In **a first aspect**, the present invention provides **a compound** selected from the group consisting of a kinase inhibitor of the formula:



(Ia),

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; wherein Hy, R^2, R^3, R^4, R^5, A, and E are as defined herein.

[36] In **a second aspect**, the present application provides **a pharmaceutical composition** comprising a compound of the first aspect and, optionally, a pharmaceutically acceptable excipient.

[37] In **a third aspect**, the present application provides **a compound** of the first aspect **or a pharmaceutical** composition of the second aspect **for use in therapy**.

[38] In **a related aspect**, the present invention provides **a method for the treatment** of a disease, disorder or condition in a subject, comprising administering to the subject a compound of the first aspect, or a pharmaceutical composition of the second aspect, optionally wherein the disease, disorder or condition is associated with a kinase.

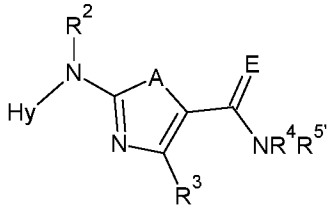
[39] In **a fourth aspect**, the present application provides **a compound** of the first aspect **for use**, **or a pharmaceutical composition** of the second aspect **for use**, in a treatment of a proliferative disorder in a subject (in particular a human patient).

[40] In **a related aspect**, the present invention **provides a method for the treatment** of a proliferative disorder in a subject, comprising administering to the subject a compound of the first aspect or a pharmaceutical composition of the second aspect.

[41] In **a fifth aspect**, the present application provides **a compound for use**, or **a pharmaceutical composition for use**, in a treatment of a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, wherein the compound is selected from the following compounds: (a) to (c), or the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient:

(a) a compound of the first aspect;

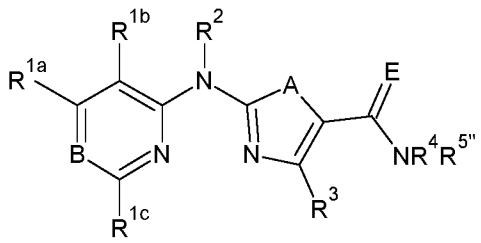
(b) a compound having the following formula:



(Ib)

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof, wherein Hy, R^2, R^3, R^4, $R^{5'}$, A, and E are as defined herein; and

(c) a compound having the following formula (Ic):



(Ic)

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined herein;

and wherein the proliferative disorder is selected from one or more of (α) to (γ):

(α) a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by) the presence of myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by the presence of phosphorylated histone deacetylase 4 (HDAC4) protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(β) a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by): (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or

(γ) a mixed phenotype acute leukaemia (MPAL).

[42] In **a related aspect**, the present invention provides **a method for the treatment** of a proliferative disorder in a subject, comprising administering to the subject a compound or pharmaceutical composition as defined in the fifth aspect, wherein the proliferative disorder is as defined in the fifth aspect.

[43] In **a further aspect**, the present application provides **a method for determining** that a subject suffering from a proliferative disorder is suitable for treatment with a compound or pharmaceutical composition as defined in the fifth aspect, the method comprising, determining in a biological sample that has been obtained from said subject:

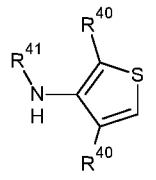
(X) the presence of MEF2C protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by the presence of phosphorylated HDAC4 protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(Y) (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the KMT2A gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the KRAS gene and/or in the RUNX1 gene, wherein, the presence of said protein, translocation, rearrangement, oncoprotein and

or mutation in the biological sample indicates that the subject is suitable for treatment with the compound or pharmaceutical composition.

[44] In **another aspect**, the invention relates to **a method of increasing skin pigmentation** (or of increasing the appearance of skin pigmentation) in a subject, the method comprising administering to the subject an (eg effective) amount of a kinase inhibitor used in the fifth aspect (or a pharmaceutical composition comprising such compound).

[45] In **a further** aspect, the present application provides **an intermediate** selected from a compound having formula (Id):



(Id)

and solvates, salts, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof, wherein R^{40} and R^{41} are as defined herein.

[46] In **a further** aspect, the present application provides **a method of manufacturing** a compound comprising an amide moiety, the method comprising the step of reacting the intermediate of the invention with a corresponding carboxylic acid, and, optionally, removing the amino protecting group.

[47] Yet **further aspects** of the invention are **disclosed** herein.

BRIEF DESCRIPTION OF THE FIGURES

[48] The figures show:

[49] **Figure 1**: depicts the chemical structures of: (A) dasatinib (compound A8), N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide; (B) the kinase inhibitor B3, N-(4-chloro-2-methylpyridin-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide; (C) certain other kinase inhibitors of formula (Ib)/(Ic) C1 to C13; (D) certain further kinase inhibitors of formula (Ib)/(Ic) D1 to D10; and (E) certain kinase inhibitors of formula (Ia) E1 to E16.

[50] **Figure 2**: depicts (in A to E) inhibitory activity of a kinase inhibitor of formula (Ib)/(Ic) (B3, left column) compared to dasatinib (A8, right column), against the kinases (A) ABL1; (B) SRC; (C) SIK1; (D) SIK2; and (E) SIK3; and depicts (in F to J) inhibitory activity of other kinase inhibitors of formula (Ib)/(Ic) (C3, left column; C12 right column), against the kinases (F) ABL1; (G) SRC; (H) SIK1; (I) SIK2; and (J) SIK3. X-axes compound concentration (M), and Y-axes kinase activity (%).

[51] **Figure 3**: depicts selectivity of kinase inhibition by % residual activity (at 1uM compound) of B3 (a kinase inhibitor of formula (Ib)/(Ic)), dasatinib (A8) and C7 (another kinase inhibitor of formula (Ib)/(Ic)): **** <25% residual activity; *** 25% to <50% residual activity; ** 50% to <75% residual activity; * >75% residual activity. Classification of protein kinase families (Manning et al. Science 6 December 2002: Vol. 298 no. 5600 pp. 1912-1934): AGC: containing PKA, PKG and PKC families; CAMK: Calcium/Calmodulin-dependent protein kinases; CK1: Casein kinase –like; CMGC: containing CDK, MAPK, GSK3 and CLK families; TK: Tyrosine Kinase; TKL: Tyrosine Kinase-like; STE: Homologs of Yeast Sterile 7, Sterile 11, Sterile 20 Kinases. ## Constitutively active kinase.

[52] **Figure 4**: depicts selectivity of kinase inhibition (by % residual activity at 1uM compound) by a kinase inhibitor of formula (Ib)/(Ic), B3 (X-axis) compared to dasatinib (A8; Y-axis): (A) axes showing the full range of residual activity; and (B) axes showing the range of 0 to 50% residual activity.

[53] **Figure 5**: depicts inhibitory activity of a kinase inhibitor of formula (Ib)/(Ic) (B3, left column) compared to dasatinib (A8, right column), against the kinases (A) FLT3; (B) SYK; (C) KIT; and (D) LCK. X-axes compound concentration (M), and Y-axes kinase activity (%).

[54] **Figure 6**: depicts sensitisation of tumour-cells to in-vitro TNF-attack by (A) the kinase inhibitor B3; and (B) A8 (dasatinib). Circles: compound (concentration as shown) plus rHuTNF (10ng/mL); squares: compound alone (concentration as shown) without rHuTNF.

[55] **Figure 7**: depicts relative tumour cell survival (Normalised RLU by cytotoxicity/viability) of certain kinase inhibitors described in PCT/EP2018/060172 in the assay using M579-A2-luc described in Example 9 at various concentrations either alone (squares) or in combination with 10ng/mL of TNF (circles). Also shown are indicative inhibitory activities of the compound for SIK-family members and for the related kinases ABL1 and SRC, shown with the indicators used for Table 3. (A) The pan-SIK and ABL1 & SRC inhibitor, compound B1; (B) The ABL1 & SRC inhibitor, compound B8. (C) The SIK1, SIK2 and ABL1 & SRC inhibitor, compound B4.

[56] **Figure 8**: depicts: (A) the cellular antiproliferative activity of dasatinib variants taken from Table 1 of Lombardo et al 2004 (J Med Chem 47:6658), showing the potency of various derivatives of dasatinib against the indicated cell lines. *a* Antiproliferative activities were determined based on tetrazolium dye conversion following 72h compound exposure. IC50 values are reported as the mean of at least three individual determinations or as individual IC50 values in the case of less than three measurements. Variability around the mean value was <50% unless otherwise indicated by an SE value in parentheses; and (B) biochemical and cellular antiproliferative activity of dasatinib variants from Table 4 of Das et al 2006 (J Med Chem 49:6819). *a* n = 3, variation in individual values, <20%. *b* n = 3, individual values, <30%.

[57] **Figure 9**: depicts selectivity of kinase inhibition (by % residual activity at 1uM compound) by a kinase inhibitor of formula (Ib)/(Ic), C7 (Y-axis) compared to: (A) dasatinib (A8; X-axis); and (B) another kinase inhibitor of formula (Ib)/(Ic), B3 (X-axis). The dashed areas highlight groups of kinases that are substantially differentially inhibited between the applicable compounds.

[58] **Figure 10**: depicts body weight of female C57Bl/6 mice after once daily (QD = A) and twice daily (BID = B) administration of different concentrations 33mg/kg (black squares) and 100mg/kg (grey diamonds) of C7 by gavage, compared to control animals (grey squares). X-axes: days after administration; Y-axes Bodyweight change (%). (C) Plasma-level of C7 measured by LC-MS/MS. A = 33mg/kg QD; B = 100mg/kg QD; C = 33mg/kg BID; D = 100mg/kg BID. Y-axis: Plasma concentration of C7 (nM).

[59] **Figure 11**: depicts (A) tumour growth kinetics in a mice implanted with MC38 cells upon treatment with vehicle (black squares), C7 100mg/kg QD (grey hexagons), C7 100mg/kg BID (grey triangles) and A8 (dasatinib) 30mg/kg QD A8 (grey circles); Y-axis = Mean tumour volume (mm3). Error bars SEM. X-axes: Days. Statistical significance was calculated with two-way ANOVA analysis including Tukey's multiple comparison analysis. ***p<0.001; (B) Body weight kinetics of the mice in (A). Y-axis: Mean body weight change (%).

[60] **Figure 12**: depicts an immuno-oncology effect of C7, a compound of formula (Ib)/(Ic), upon immune cells present in the tumour microenvironment. Intra-tumoural immune infiltrate was calculated as the percentage of intra-tumoural CD45+ cells. Statistical significance was calculated with one-way ANOVA analysis including Tukey's multiple comparison analysis. (A) Y-axis: Ratio of CTL to Treg cells. (B) Activated CTLs (CD25+CD69+); Y-axis: % of CD45+ cells. (C) Activated CTLs (granzyme B+); Y-axis: % of CD45+ cells. (D) Immunosuppressive M2-like tumour-associated macrophages (TAMs) (CD206+MHC-II+); Y-axis: % of CD45+ cells; *p<0.05; **p<0.01; ***p<0.00.

[61] **Figure 13**: depicts cell killing by TNF, sensitised by compound C7. (A) TNF-induced apoptosis of PANC-1 cells. PANC-1 cells were treated with C7 at 370nM ("diamonds"), 3333nM ("squares") and DMSO only ("stars") before addition of 100ng/ml rHuTNF for 120h (+rHuTNF = open shapes; -rHuTNF = solid shapes; open circles 10ng/mL rHuTNF control). Cell death was evaluated using real-time live cell microscopy, measuring the nuclear incorporation of YOYO-1 dye (area of YOYO-1+ cells/well). Y-axis = Tumor cell death (um2/well). X-axes = Time (h); (B) Effect of C7 on TNF-induced (100ng/ml rMuTNF) apoptosis of murine MC38 (+rMuTNF = "diamonds"; -rMuTNF = "circles"). Cell

viability was measured after 72h using a CellTiter-Glo assay. Luciferase values were normalized to cells treated with rMuTNF without inhibitor (DMSO only). Y-axis = Viability (%). X-axis = compound concentration (nM).

[62] **Figure 14**: depicts: (A) Effect of compound C7 on NFKB activity. Reporter PANC-1 cells expressing luciferase under the control of a NFKB promotor were treated with different concentrations of C7 before addition of 10ng/ml rHuTNF for 8h (+rHuTNF = "diamonds"; -rHuTNF = "circles"). Luciferase activity was normalized to PANC-1 cells treated with rHuTNF without inhibitor (DMSO only). Y-axis = NFKB activity (%). X-axis = compound concentration (nM); (B) Effect of compound C7 on HDAC4 phosphorylation. PANC-1 cells were treated with C7 at various concentrations (in the presence of 10ng/mL rHuTNF) for 3h. Whole cell lysates were analyzed in a Meso Scale Discovery (MSD) assay with anti-HDAC4 capture and anti-pHDAC4 detection antibodies. HDAC4 phosphorylation was normalized to untreated PANC-1 cells (DMSO only). Y-axis = HDAC4 phosphorylation (%). X-axis = Compound concentration (nM).

[63] **Figure 15**: depicts: growth inhibition by compound C7 of the WSU-NHL (A) and DOHH-2 (B) cell lines, showing GI50s of about 8nM and 9nM respectively. X-axes: compound concentration (M); Y-axes: Percentage Growth Inhibition (GI) at 96h.

[64] **Figure 16**: depicts selectivity of kinase inhibition (by % residual activity at 0.1uM compound) by: (A) kinase inhibitors of formula (Ia) **E9** (X-axis) compared to **E10** (Y-axis); and (B) **C7** (X-axis) compared to a kinase inhibitor of formula (Ia) **E4** (Y-axis).

[65] **Figure 17**: depicts differential inhibition of MAP3K11 and NEK11 kinases between compound **C7** (X-axis) and a kinase inhibitor of formula (Ia) **E10** (Y-axis: % residual activity) at: (A) 1uM compound concentration; and (B) 0.1uM compound concentration.

[66] **Figure 18**: depicts the activity of SIK3 inhibitors disclosed herein against MEF2C-expresing AML cell lines: (A) compound **C7** against a panel of AML cell lines, showing strong lysis of such cell lines that have phosphorylated MEF2C protein; (B) highly potent cell killing of compound **C7** against the pMEF2C-positive KASUMI-1 cell line; and (C) low cell killing of compound **C7** against the pMEF2C-negatice HEL cell line.

[67] **Figure 19**: depicts a schematic of SIK3-mediated control of the expression of survival/maintenance genes (a) by phosphorylated myocyte enhancer factor 2C (MEF2C) transcription factor. Over expression of MEF2C is associated with the presence of fusion of the lysine methyltransferase 2A (KMT2A) protein (previously known as "MLL"; (b)), typically brought about by a human chromosomal translocation at 11q23. MEF2C activity is controlled by presence in the nucleus of HDAC4 acting, as a repressive co-factor, whose retention in the cytoplasm is brought about by its phosphorylation by SIK3. Nuclear entry and presence (c) of un-phosphorylated HDAC4 (and hence reduction of expression of tumour survival/maintenance genes (a) by inhibition of the transcription-factor activity of MEF2C) can be brought about by inhibition of SIK3 by a compound disclosed herein (d).

[68] **Figure 20**: depicts (A) tumour growth kinetics in mice implanted with MC38 cells, and upon treatment with: (1) controls: ratIgG2a 10mg/kg (black filled squares), aPD-1 10mg/kg 3q7d (light grey open crossed-circles), and vehicle (light grey filled inverted triangles); and compounds **E10** 30mg/kg BID (grey open inverted triangles), **E4** 40mg/kg BID (dark grey filled circles), **E9** 25mg/kg BID (light grey filled squares), **E9** 50mg/kg BID (dark grey filled triangles) and **C7** 100mg/kg BID (light grey filled diamonds). Y-axis = Mean tumour volume (mm3). Error bars SEM Statistical significance was calculated with one-way ANOVA analysis including Tukey's multiple comparison analysis. X-axis = Days. (B) Probability of tumour volume <1000mm3 of the mice in (A). Y-axis: Probability of occurrence of tumour volumes <= 1000mm3 upon treatment. X-axis: Days. For both (A) and (B), Controls: ratIgG2a (a), aPD-1 10mg/kg (b), vehicle (c); and compounds: **C7** 100mg/kg (d) BID, **E4** 40mg/kg BID (e), **E9** 25mg/kg BID (f), **E9** 50mg/kg BID (g), and **E10** 30mg/kg BID (h). (C) to (H) Tumour growth curves of individual mice; Y-axis: Tumour volume (mm3), X-axis: Days. (C) **E9** 25mg/kg BID; (D) **E9** 50mg/kg BID; (E) **C7** 100mg/kg BID; (F) aPD-1 10mg/kg; (G) ratIgG2a 10mg/kg and (H) vehicle.

[69] **Figure 21**: depicts an immuno-oncology effect of kinase inhibitors of formula (Ia) upon immune cells present in the tumour microenvironment. Intra-tumoural immune infiltrate was calculated as the percentage of intra-tumoural CD45+ cells. Statistical significance was calculated with one-way ANOVA analysis including Tukey's multiple comparison analysis. (A) CD3+ T cells; (B) CD8+ T cells; (C) Activated CTLs (CD8+CD25+); (D) Activated CTLs (CD8+granzyme B+); (E) regulatory T cells (CD25+, FoxP3+). Y-axes: % of CD45+ cells. (F) CD11b+ Myeloid cells; (G) Anti-tumour M1 tumour-associated macrophages (TAMs) (CD206-MHC-II+); (H) Immunosuppressive M2 tumour-associated macrophages (TAMs) (CD206+MHC-II-); (I) mMDSC (Ly6C+); (J) gMDSC (Ly6G+). Y-axes: % of CD45+ cells, *p<0.05; **p<0.01; ***p<0.001. X-axes: A = ratIgG2a (10mg/kg, 3q7d); B = aPD-1 (10mg/kg, 3q7d); C = vehicle (BID); 1 = **C7** (100mg/kg, BID); 2 = **E4** (40mg/kg, BID); 3 = **E9** (25mg/kg, BID); 4 = **E9** (50mg/kg, BID); 5 = **E10** (30mg/kg, BID).

[70] **Figure 22**: depicts TNF-mediated cell killing induced by either (A) compound **E9** or (B) compound **C7** in SIK3 knockout MC38 clones (triangles) or in SIK3 wildtype MC38 clones (squares) in the presence of 5ng/ml TNF. Y-axes = viability, normalized to no TNF. X-axes = inhibitor concentration in nM.

[71] **Figure 23**: depicts a classification of all yet known *KMT2A* fusion translocation partner genes (TPGs) by disease (adapted from Figure 3 Meyer et al 2018). All TPGs are grouped by their diagnosed disease type. Such genes have been diagnosed in ALL, t-ALL, t-AML, AML, T-ALL, MLL, bilineal acute leukaemia (BAL), MDS, t-MDS, chronic myelogenous leukaemia (CML), t-CML, juvenile myelomonocytic leukaemia (JMML) and lymphoma. Genes in the intersection belong to two different groups. Bold-marked TPGs are the most frequent ones.

[72] **Figure 24**: depicts pharmacokinetic curves of compounds of formula (Ia) **E4** (circles), **E9** (inverted triangles), and **E10** (diamonds), compared to a closely related compound **C7** (squares) following 30mg/kg po administration. Y axis = Total plasma compound concentration (ng/ml); X axis = Time (h).

[73] **Figure 25**: depicts reproducibility of experiments of compounds of formula (Ia) and C7 against MC38 tumour cells plus TNF. Y axis = EC50 tumour cell lysis (nM).

[74] **Figure 26**: depicts exemplary TNF-dependent dose-response curves for compound **E9** compared to a closely related compound **C7** tested against various murine tumour cell lines at different (murine) TNF concentrations (rMuTNF concentrations: x = 0ng/ml, y = 10ng/ml and y = 100ng/ml). Vertical bars: normalised viability with no compound at the indicated concentration of rMuTNF. Left hand column compound **E9**, right hand column compound **C7**, against: MC38 (A); CT26 (B); and EMT6 (C). Y axes = Viability (normalised to no compound); X axes = compound concentration (nM).

[75] **Figure 27**: depicts superior and more uniform tumour growth inhibition in a MC38 syngeneic tumour model by compound **E9** (24mg/kg BID) (A), compared to dasatinib (30mg/kg QD) (B). Left hand column = compound treatment group; and right hand column = vehicle treatment group. Y axes = Tumour volume (mm3); X axes = Days after inoculation.

[76] **Figure 28**: depicts: (A) and (B) effect of compound **E9** on NFKB activity. Reporter PANC-1 cells (A) or MC38 cells (B) expressing luciferase under the control of a NFKB promotor were treated with different concentrations of **E9** before addition of 10ng/ml rHuTNF for 8h (+rHuTNF = "diamonds", EC50s = 405nM for PANC-1 and 389nM for MC38; -rHuTNF = "circles"). Luciferase activity was normalised to cells treated with rHuTNF without inhibitor (DMSO only). Y-axis = NFKB activity (%). X-axis = compound concentration (nM); Bar "A" viability without compound and without TNF; bar "B" viability without compound and with 10ng/ml TNF; and (C) Effect of compound **E9** on HDAC4 phosphorylation. PANC-1 cells were treated with **E9** at various concentrations (in the presence of 10ng/mL rHuTNF) for 3h. Whole cell lysates were analysed in a Meso Scale Discovery (MSD) assay with anti-HDAC4 capture and anti-pHDAC4 detection antibodies. HDAC4 phosphorylation was normalized to untreated PANC-1 cells (DMSO only). Y-axis = HDAC4 phosphorylation (%). X-axis = Compound concentration (nM).

[77] **Figure 29**: depicts the effect of compound **E9** and anti PD-1 mAB (alone or in combination) on in vivo tumour growth (mean +/- SEM) in a MC38 syngeneic tumour model. (A) Y axes = Tumour volume (mm3); X axes = Days after start of therapy. Vehicle + anti PD-1 mAB (squares), vehicle + mIgG1e ctr (circles), **E9** + anti PD-1 mAB (inverted triangles), and **E9** + mIgG1e ctr (triangles). (B) Median overall survival.) Y axes = Probability of survival (%); X axes = Days after start of therapy. Vehicle + anti PD-1 mAB (grey/dashed), vehicle + mIgG1e ctr (black/solid), **E9** + anti PD-1 mAB (grey/solid), and **E9** + mIgG1e ctr (black/dashed). (C) to (D) Tumour growth curves of individual mice; Y-axis: Tumour volume (mm3), X-axis: Days after start of therapy. (C) **E9** 25mg/kg BID; (D) aPD-1 2,5mg/kg; (E) **E9** 50mg/kg BID + aPD-1 2,5mg/kg; and (F) vehicle.

[78] **Figure 30**: depicts: (A) and (B) effect of compound **E9** on in vivo tumour growth (mean +/- SEM) in an immune-excluded tumour model (EMT6). Y axes = Tumour volume (mm3); X axes = Days after treatment start. (A) vehicle BID (squares), **E9** 25mg/kg BID (triangles), **E9** 12.5mg/kg BID (diamonds) and **E9** 5mg/kg BID (circles). (B) vehicle BID (squares), **E9** 25mg/kg BID (triangles), **E9** 25mg/kg QD (inverted triangles).

DETAILS OF THE PRESENT INVENTION

[79] The present invention, and particular non-limiting aspects and/or embodiments thereof, can be described in more detail as follows.

[80] Although the present invention may be further described in more detail, it is to be understood that this invention is not limited to the particular methodologies, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by what is described, defined or otherwise disclosed herein, in particular in any itemised embodiments or the appended claims.

[81] Herein, certain elements of the present invention are described in more detail. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description of this application should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed and/or preferred elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise. For example, if in one embodiment of the compound of the invention L is a bond and in another embodiment of the compound of the invention R^3 is H, then in a preferred embodiment of the compound of the invention, L is a bond and R^3 is H, or if in one embodiment of the use of a compound of the invention the subject is an adult human and in another embodiment of the use of a compound of the invention the proliferative disorder is prostate cancer, then in a preferred embodiment of the use of a compound of the invention, the subject is an adult human and the proliferative disorder is prostate cancer.

General definitions

[82] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[83] Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", H.G.W. Leuenberger, B. Nagel, and H. Kölbl, Eds., Helvetica Chimica Acta, CH-4010 Basel, Switzerland, (1995).

[84] The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, and recombinant DNA techniques which are explained in the literature in the field (cf., e.g., Molecular Cloning: A Laboratory Manual, 2nd Edition, J. Sambrook et al. eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor 1989).

[85] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated member, integer or step or group of members, integers or steps but not the exclusion of any other member, integer or step or group of members, integers or steps. The term "consisting essentially of" means excluding other members, integers or steps of any essential significance or group of members, integers or steps of any essential significance. For example, a pharmaceutical composition consisting essentially of the members/components as defined herein (such as a compound as defined in any of the aspects of the invention and optionally one additional therapeutic agent) would exclude further therapeutic agents (besides the compound as defined in any of the aspects of the invention and the optional one additional therapeutic agent) but would not exclude contaminants (e.g., those from the isolation and purification method) in trace amounts (e.g., the amount of the contaminant (preferably the amount of all contaminants present in the composition) is less than 5% by weight, such as less than 4% by weight, 3% by weight, 2% by weight, 1% by weight, 0.5% by weight, 0.4% by weight, 0.3% by weight, 0.2% by weight, 0.1% by weight, 0.05% by weight, with respect to the total composition) and/or pharmaceutically acceptable excipients (such as carriers, e.g., phosphate buffered saline, preservatives, and the like). The term "consisting of" means excluding all other members, integers or steps of significance or group of members, integers or steps of significance. For example, a pharmaceutical composition consisting of the members/components as defined herein (such as a compound as defined in any of the aspects of the invention, one excipient, and optionally one additional therapeutic agent) would exclude any other compound (including a second or further excipient) in an amount of more than 2% by weight (such as any other compound in an amount of more than 1% by weight, more than 0.5% by weight, more than 0.4% by weight, more than 0.3% by weight, more than 0.2% by weight, more than 0.1% by weight, more than 0.09% by weight, more than 0.08% by weight, more than 0.07% by weight, more than 0.06% by weight, more than 0.05% by weight, more than 0.04% by weight, more than 0.03% by weight, more than 0.02% by weight, more than 0.01% by weight) with respect to the total composition. The term "comprising" encompasses the term "consisting essentially of" which, in turn, encompasses the term "consisting of". Thus, at each occurrence in the present application, the term "comprising" may be replaced with the term "consisting essentially of" or "consisting of". Likewise, at each occurrence in the present application, the term "consisting essentially of" may be replaced with the term "consisting of".

[86] Where used herein, "and/or" is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example, "X and/or Y" is to be taken as specific disclosure of each of (i) X, (ii) Y, and (iii) X and Y, just as if each is set out individually herein.

[87] In the context of the present invention, the terms "about" and "approximately" are used interchangeably and denote an interval of accuracy that the person of ordinary skill will understand to still ensure the technical effect of the feature in question. The term typically indicates deviation from the indicated numerical value by ±5%, ±4%, ±3%, ±2%, ±1%, ±0.9%, ±0.8%, ±0.7%, ±0.6%, ±0.5%, ±0.4%, ±0.3%, ±0.2%, ±0.1%, ±0.05%, and for example ±0.01%. As will be appreciated by the person of ordinary skill, the specific such deviation for a numerical value for a given technical effect will depend on the nature of the technical effect. For example, a natural or biological technical effect may generally have a larger such deviation than one for a man-made or engineering technical effect.

[88] The terms "a", "an" and "the" and similar references used in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by the context.

[89] Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein.

[90] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by the context.

[91] The use of any and all examples, or exemplary language (e.g., "such as"), provided herein is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[92] Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether *supra* or *infra*, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[93] The terms "of the [present] invention", "in accordance with the [present] invention", "according to the [present] invention" and the like, as used herein are intended to refer to all aspects and embodiments of the invention described and/or claimed herein.

[94] It is to be understood that the application of the teachings of the present invention to a specific problem or environment, and the inclusion of variations of the present invention or additional features thereto (such as further aspects and embodiments), will be within the capabilities of one having ordinary skill in the art in light of the teachings contained herein.

[95] Unless context dictates otherwise, the descriptions and definitions of the features set out above or below are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments that are described.

[96] The term "alkyl" refers to a monoradical of a saturated straight or branched hydrocarbon. Preferably, the alkyl group comprises from 1 to 12 (such as 1 to 10) carbon atoms, i.e., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (such as 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), more preferably 1 to 8 carbon atoms, such as 1 to 6 or 1 to 4 carbon atoms. Exemplary alkyl groups include methyl (Me), ethyl (Et), propyl, iso-propyl (also called 2-propyl or 1-methylethyl), butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, sec-pentyl, neo-pentyl, 1,2-dimethyl-propyl, iso-amyl, n-hexyl, iso-hexyl, sec-hexyl, n-heptyl, iso-heptyl, n-octyl, 2-ethyl-hexyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, and the like. A "substituted alkyl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an alkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the alkyl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CN, -OCH_3, -OCF_3, or optionally substituted aryl. Examples of a substituted alkyl include trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trichloroethyl, 2-hydroxyethyl, 2-aminoethyl, 2-(dimethylamino)ethyl, arylalkyl (also called "aralkyl", e.g., benzyl, chloro(phenyl)methyl, 4-methylphenylmethyl, (2,4-dimethylphenyl)methyl, o-fluorophenylmethyl, 2-phenylpropyl, 2-, 3-, or 4-carboxyphenylalkyl), or heteroarylalkyl (also called "heteroaralkyl").

[97] The term "alkylene" refers to a diradical of a saturated straight or branched hydrocarbon. Preferably, the alkylene comprises from 1 to 12 (such as 1 to 10) carbon atoms, i.e., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (such as 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), more preferably 1 to 8 carbon atoms, such as 1 to 6 or 1 to 4 carbon atoms. Exemplary alkylene groups include methylene, ethylene (i.e., 1,1-ethylene, 1,2-ethylene), propylene (i.e., 1,1-propylene, 1,2-propylene (-$CH(CH_3)CH_2$-), 2,2-propylene (-$C(CH_3)_2$-), and 1,3-propylene), the butylene isomers (e.g., 1,1-butylene, 1,2-butylene, 2,2-butylene, 1,3-butylene, 2,3-butylene (cis or trans or a mixture

thereof), 1,4-butylene, 1,1-iso-butylene, 1,2-iso-butylene, and 1,3-iso-butylene), the pentylene isomers (e.g., 1,1-pentylene, 1,2-pentylene, 1,3-pentylene, 1,4-pentylene, 1,5-pentylene, 1,1-iso-pentylene, 1,1-sec-pentyl, 1,1-neo-pentyl), the hexylene isomers (e.g., 1,1-hexylene, 1,2-hexylene, 1,3-hexylene, 1,4-hexylene, 1,5-hexylene, 1,6-hexylene, and 1,1-isohexylene), the heptylene isomers (e.g., 1,1-heptylene, 1,2-heptylene, 1,3-heptylene, 1,4-heptylene, 1,5-heptylene, 1,6-heptylene, 1,7-heptylene, and 1,1-isoheptylene), the octylene isomers (e.g., 1,1-octylene, 1,2-octylene, 1,3-octylene, 1,4-octylene, 1,5-octylene, 1,6-octylene, 1,7-octylene, 1,8-octylene, and 1,1-isooctylene), and the like. The straight alkylene moieties having at least 3 carbon atoms and a free valence at each end can also be designated as a multiple of methylene (e.g., 1,4-butylene can also be called tetramethylene). Generally, instead of using the ending "ylene" for alkylene moieties as specified above, one can also use the ending "diyl" (e.g., 1,2-butylene can also be called butan-1,2-diyl). A "substituted alkylene" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an alkylene group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the alkylene group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen or optionally substituted aryl. Examples of a substituted alkylene include chloromethylene, dichloromethylene, fluoromethylene, and difluoromethylene.

[98] The term "alkenyl" refers to a monoradical of an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Generally, the maximal number of carbon-carbon double bonds in the alkenyl group can be equal to the integer which is calculated by dividing the number of carbon atoms in the alkenyl group by 2 and, if the number of carbon atoms in the alkenyl group is uneven, rounding the result of the division down to the next integer. For example, for an alkenyl group having 9 carbon atoms, the maximum number of carbon-carbon double bonds is 4. Preferably, the alkenyl group has 1 to 6 (such as 1 to 4), i.e., 1, 2, 3, 4, 5, or 6, carbon-carbon double bonds. Preferably, the alkenyl group comprises from 2 to 12 (such as 2 to 10) carbon atoms, i.e., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), more preferably 2 to 8 carbon atoms, such as 2 to 6 carbon atoms or 2 to 4 carbon atoms. Thus, in a preferred embodiment, the alkenyl group comprises from 2 to 12 (e.g., 2 to 10) carbon atoms and 1, 2, 3, 4, 5, or 6 (e.g., 1, 2, 3, 4, or 5) carbon-carbon double bonds, more preferably it comprises 2 to 8 carbon atoms and 1, 2, 3, or 4 carbon-carbon double bonds, such as 2 to 6 carbon atoms and 1, 2, or 3 carbon-carbon double bonds or 2 to 4 carbon atoms and 1 or 2 carbon-carbon double bonds. The carbon-carbon double bond(s) may be in cis (Z) or trans (E) configuration. Exemplary alkenyl groups include vinyl, 1-propenyl, 2-propenyl (i.e., allyl), 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, 11-dodecenyl, and the like. If an alkenyl group is attached to a nitrogen atom, the double bond cannot be alpha to the nitrogen atom. A "substituted alkenyl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an alkenyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the alkenyl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen or optionally substituted aryl. An example of a substituted alkenyl is styryl (i.e., 2-phenylvinyl).

[99] The term "alkenylene" refers to a diradical of an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Generally, the maximal number of carbon-carbon double bonds in the alkenylene group can be equal to the integer which is calculated by dividing the number of carbon atoms in the alkenylene group by 2 and, if the number of carbon atoms in the alkenylene group is uneven, rounding the result of the division down to the next integer. For example, for an alkenylene group having 9 carbon atoms, the maximum number of carbon-carbon double bonds is 4. Preferably, the alkenylene group has 1 to 6 (such as 1 to 4), i.e., 1, 2, 3, 4, 5, or 6, carbon-carbon double bonds. Preferably, the alkenylene group comprises from 2 to 12 (such as 2 to 10) carbon atoms, i.e., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), more preferably 2 to 8 carbon atoms, such as 2 to 6 carbon atoms or 2 to 4 carbon atoms. Thus, in a preferred embodiment, the alkenylene group comprises from 2 to 12 (such as 2 to 10 carbon) atoms and 1, 2, 3, 4, 5, or 6 (such as 1, 2, 3, 4, or 5) carbon-carbon double bonds, more preferably it comprises 2 to 8 carbon atoms and 1, 2, 3, or 4 carbon-carbon double bonds, such as 2 to 6 carbon atoms and 1, 2, or 3 carbon-carbon double bonds or 2 to 4 carbon atoms and 1 or 2 carbon-carbon double bonds. The carbon-carbon double bond(s) may be in cis (Z) or trans (E) configuration. Exemplary alkenylene groups include ethen-1,2-diyl, vinylidene (also called ethenylidene), 1-propen-1,2-diyl, 1-propen-1,3-diyl, 1-propen-2,3-diyl, allylidene, 1-buten-1,2-diyl, 1-buten-1,3-diyl, 1-buten-1,4-diyl, 1-buten-2,3-diyl, 1-buten-2,4-diyl, 1-buten-3,4-diyl, 2-buten-1,2-diyl, 2-buten-1,3-diyl, 2-buten-1,4-diyl, 2-buten-2,3-diyl, 2-buten-2,4-diyl, 2-buten-3,4-diyl, and the like. If an alkenylene group is attached to a nitrogen atom, the double bond cannot be alpha to the nitrogen atom. A "substituted alkenylene" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an alkenylene group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the alkenylene group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen or optionally substituted aryl. Examples of a substituted alkenylene are 1-phenyl-ethen-1,2-diyl and 2-phenyl-ethen-1,2-diyl.

[100] The term "alkynyl" refers to a monoradical of an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Generally, the maximal number of carbon-carbon triple bonds in the alkynyl group can be equal to the integer which is calculated by dividing the number of carbon atoms in the alkynyl group by 2 and, if the number of carbon atoms in the alkynyl group is uneven, rounding the result of the division down to the next integer. For example, for an alkynyl group having 9 carbon atoms, the maximum number of carbon-carbon triple bonds is 4. Preferably, the alkynyl group has 1 to 6 (such as 1 to 4), i.e., 1, 2, 3, 4, 5, or 6, more preferably 1 or 2 carbon-carbon triple bonds. Preferably, the alkynyl group comprises from 2 to 12 (such as 2 to 10) carbon atoms (such as 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), i.e., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms, more preferably 2 to 8 carbon atoms, such as 2 to 6 carbon atoms or 2 to 4 carbon atoms. Thus, in a preferred embodiment, the alkynyl group comprises from 2 to 12 (such as 2 to 10) carbon atoms and 1, 2, 3, 4, 5, or 6 (such as 1, 2, 3, 4, or 5 (preferably 1, 2, or 3)) carbon-carbon triple bonds, more preferably it comprises 2 to 8 carbon atoms and 1, 2, 3, or 4 (preferably 1 or 2) carbon-carbon triple bonds, such as 2 to 6 carbon atoms and 1, 2 or 3 carbon-carbon triple bonds or 2 to 4 carbon atoms and 1 or 2 carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 3-octynyl, 4-octynyl, 5-octynyl, 6-octynyl, 7-octynyl, 1-nonylyl, 2-nonynyl, 3-nonynyl, 4-nonynyl, 5-nonynyl, 6-nonynyl, 7-nonynyl, 8-nonynyl, 1-decynyl, 2-decynyl, 3-decynyl, 4-decynyl, 5-decynyl, 6-decynyl, 7-decynyl, 8-decynyl, 9-decynyl, and the like. If an alkynyl group is attached to a nitrogen atom, the triple bond cannot be alpha to the nitrogen atom. A "substituted alkynyl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an alkynyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2)

hydrogen atoms of the alkynyl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen or optionally substituted aryl.

[101] The term "alkynylene" refers to a diradical of an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Generally, the maximal number of carbon-carbon triple bonds in the alkynylene group can be equal to the integer which is calculated by dividing the number of carbon atoms in the alkynylene group by 2 and, if the number of carbon atoms in the alkynylene group is uneven, rounding the result of the division down to the next integer. For example, for an alkynylene group having 9 carbon atoms, the maximum number of carbon-carbon triple bonds is 4. Preferably, the alkynylene group has 1 to 6 (such as 1 to 4), i.e., 1, 2, 3, 4, 5, or 6 (such as 1, 2, 3, or 4), more preferably 1 or 2 carbon-carbon triple bonds. Preferably, the alkynylene group comprises from 2 to 12 (such as 2 to 10) carbon atoms, i.e., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), more preferably 2 to 8 carbon atoms, such as 2 to 6 carbon atoms or 2 to 4 carbon atoms. Thus, in a preferred embodiment, the alkynylene group comprises from 2 to 12 (such as 2 to 10) carbon atoms and 1, 2, 3, 4, 5, or 6 (such as 1, 2, 3, 4, or 5 (preferably 1, 2, or 3)) carbon-carbon triple bonds, more preferably it comprises 2 to 8 carbon atoms and 1, 2, 3, or 4 (preferably 1 or 2) carbon-carbon triple bonds, such as 2 to 6 carbon atoms and 1, 2 or 3 carbon-carbon triple bonds or 2 to 4 carbon atoms and 1 or 2 carbon-carbon triple bonds. Exemplary alkynylene groups include ethyn-1,2-diyl, 1-propyn-1,3-diyl, 1-propyn-3,3-diyl, 1-butyn-1,3-diyl, 1-butyn-1,4-diyl, 1-butyn-3,4-diyl, 2-butyn-1,4-diyl and the like. If an alkynylene group is attached to a nitrogen atom, the triple bond cannot be alpha to the nitrogen atom. A "substituted alkynylene" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an alkynylene group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the alkynylene group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen or optionally substituted aryl.

[102] The term "aryl" or "aromatic ring" refers to a monoradical of an aromatic cyclic hydrocarbon. Preferably, the aryl group contains 3 to 14 (e.g., 5, 6, 7, 8, 9, or 10, such as 5, 6, or 10) carbon atoms which can be arranged in one ring (e.g., phenyl) or two or more condensed rings (e.g., naphthyl). Exemplary aryl groups include cyclopropenylium, cyclopentadienyl, phenyl, indenyl, naphthyl, azulenyl, fluorenyl, anthryl, and phenanthryl. Preferably, "aryl" refers to a monocyclic ring containing 6 carbon atoms or an aromatic bicyclic ring system containing 10 carbon atoms. Preferred examples are phenyl and naphthyl. Aryl does not encompass fullerenes. A "substituted aryl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to an aryl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the aryl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen, -CN, nitro, $-OR^{11}$ (e.g., -OH), $-SR^{11}$ (e.g., -SH), $-N(R^{12})(R^{13})$ (e.g., $-NH_2$), alkyl (e.g., C_{1-6} alkyl), alkenyl (e.g., C_{2-6} alkenyl), and alkynyl (e.g., C_{2-6} alkynyl). Examples of a substituted aryl include biphenyl, 2-fluorophenyl, 2-chloro-6-methylphenyl, anilinyl, 3-nitrophenyl, 4-hydroxyphenyl, methoxyphenyl (i.e., 2-, 3-, or 4-methoxyphenyl), and 4-ethoxyphenyl.

[103] The term "heteroaryl" or "heteroaromatic ring" means an aryl group as defined above in which one or more carbon atoms in the aryl group are replaced by heteroatoms (such as O, S, or N). Preferably, heteroaryl refers to a five or six-membered aromatic monocyclic ring, wherein 1, 2, or 3 carbon atoms are replaced by the same or different heteroatoms of O, N, or S. Alternatively, it means an aromatic bicyclic or tricyclic ring system wherein 1, 2, 3, 4, or 5 carbon atoms are replaced with the same or different heteroatoms of O, N, or S. Preferably, in each ring of the

heteroaryl group the maximum number of O atoms is 1, the maximum number of S atoms is 1, and the maximum total number of O and S atoms is 2. For example, 3- to 14-membered heteroaryl encompasses monocyclic heteroaryl (e.g., 5- or 6-membered), bicyclic heteroaryl (e.g., 9- or 10-membered), and tricyclic heteroaryl (e.g., 13- or 14-membered). Exemplary heteroaryl groups include furanyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl (1,2,5- and 1,2,3-), pyrrolyl, imidazolyl, pyrazolyl, triazolyl (1,2,3- and 1,2,4-), tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl (1,2,3- and 1,2,5-), pyridyl (also called pyridinyl), pyrimidinyl, pyrazinyl, triazinyl (1,2,3-, 1,2,4-, and 1,3,5-), benzofuranyl (1- and 2), indolyl, isoindolyl, benzothienyl (1- and 2-), 1H-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, benzodiazinyl, quinoxalinyl, quinazolinyl, benzotriazinyl (1,2,3- and 1,2,4-benzotriazinyl), pyridazinyl, phenoxazinyl, thiazolopyridinyl, pyrrolothiazolyl, phenothiazinyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, pyrrolizinyl, indolizinyl, indazolyl, purinyl, quinolizinyl, phthalazinyl, naphthyridinyl (1,5-, 1,6-, 1,7-, 1,8-, and 2,6-), cinnolinyl, pteridinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl (1,7-, 1,8-, 1,10-, 3,8-, and 4,7-), phenazinyl, oxazolopyridinyl, isoxazolopyridinyl, pyrrolooxazolyl, and pyrrolopyrrolyl. Exemplary 5- or 6-membered heteroaryl groups include furanyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl (1,2,5- and 1,2,3-), pyrrolyl, imidazolyl, pyrazolyl, triazolyl (1,2,3- and 1,2,4-), thiazolyl, isothiazolyl, thiadiazolyl (1,2,3- and 1,2,5), pyridyl, pyrimidinyl, pyrazinyl, triazinyl (1,2,3-, 1,2,4-, and 1,3,5-), and pyridazinyl. A "substituted heteroaryl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to a heteroaryl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the heteroaryl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen, CN, nitro, $-OR^{11}$ (e.g., -OH), $-SR^{11}$ (e.g., -SH), $-N(R^{12})(R^{13})$ (e.g., $-NH_2$), alkyl (e.g., C_{1-6} alkyl), alkenyl (e.g., C_{2-6} alkenyl), and alkynyl (e.g., C_{2-6} alkynyl). Examples of a substituted heteroaryl include 2,4-dimethylpyridin-3-yl, 2-methyl-4-bromopyridin-3-yl, 3-methyl-2-pyridin-2-yl, 3-chloro-5-methylpyridin-4-yl, 4-chloro-2-methylpyridin-3-yl, 3,5-dimethylpyridin-4-yl, 2-methylpyridin-3-yl, 2-chloro-4-methyl-thien-3-yl, 1,3,5-trimethylpyrazol-4-yl, 3,5-dimethyl-1,2-dioxazol-4-yl, 1,2,4-trimethylpyrrol-3-yl, 3-phenylpyrrolyl, 2,3'-bifuryl, 4-methylpyridyl, 2-, or 3-ethylindolyl.

[104] The term "cycloalkyl" or "cycloaliphatic" represents cyclic non-aromatic versions of "alkyl" and "alkenyl" with preferably 3 to 14 carbon atoms, such as 3 to 12 or 3 to 10 carbon atoms, i.e., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms (such as 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms), more preferably 3 to 7 carbon atoms. Exemplary cycloalkyl groups include cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, cyclononyl, cyclononenyl, cylcodecyl, cylcodecenyl, and adamantyl. The term "cycloalkyl" is also meant to include bicyclic and tricyclic versions thereof. If bicyclic rings are formed it is preferred that the respective rings are connected to each other at two adjacent carbon atoms, however, alternatively the two rings are connected via the same carbon atom, i.e., they form a spiro ring system or they form "bridged" ring systems. Preferred examples of cycloalkyl include C_{3-8}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, and bicyclo[4.2.0]octyl. Cycloalkyl does not encompass fullerenes. A "substituted cycloalkyl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to a cycloalkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the cycloalkyl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen, -CN, nitro, $-OR^{11}$ (e.g., -OH), $-SR^{11}$ (e.g., -SH), $-N(R^{12})(R^{13})$ (e.g., $-NH_2$), =X (e.g., =O, =S, or =NH), alkyl (e.g., C_{1-6} alkyl), alkenyl (e.g., C_{2-6} alkenyl), and alkynyl (e.g., C_{2-6} alkynyl). Examples of a substituted cycloalkyl include oxocyclohexyl, oxocyclopentyl, fluorocyclohexyl, and oxocyclohexenyl.

[105] The term "heterocyclyl" or "heterocyclic ring" means a cycloalkyl group as defined above in which from 1, 2, 3, or 4 ring carbon atoms in the cycloalkyl group are replaced by heteroatoms (such as those selected from the group consisting of O, S, S(O), $S(O)_2$, N, B, Si, and P, preferably selected from the group consisting of O, S, $S(O)_2$, and N, more preferably selected from the group consisting of O, S, and N). If a ring of the heterocyclyl group only contains one type of heteroatom, the maximum number of said heteroatom in the ring of said heterocyclyl group may be as follows: 2 O atoms (preferably 1 O atom); 2 S atoms (preferably 1 S atom); 4 N atoms (such as 1, 2, or 3 N atoms); 2 B atoms (preferably 1 B atom); 1 Si atom; and/or 1 P atom. If a ring of the heterocyclyl group contains two or more types of heteroatoms, the maximum number of said heteroatoms in the ring of said heterocyclyl group may be as follows: 1 O atom; 1 S atom; 2 N atoms (preferably 1 N atom); 1 B atom; 1 Si atom; and/or 1 P atom, wherein the maximum total number of heteroatoms in the ring of said heterocyclyl group is 4 and the maximum total number of each heteroatom in the ring of said heterocyclyl group is as follows: 1 O atom; 1 S atom; 1 or 2 N atoms; 1 B atom (preferably 0 B atom); 1 Si atom (preferably 0 Si atom); and/or 1 P atom (preferably 0 P atom). In one embodiment, the heteroatoms of the heterocyclyl group are selected from the group consisting of O, S, and N. In this embodiment, preferably, in each ring of the heterocyclyl group the maximum number of O atoms is 1, the maximum number of S atoms is 1, and the maximum total number of O and S atoms is 2. For example, 3- to 14-membered heterocyclyl encompasses monocyclic heterocyclyl (e.g., 3-, 4-, 5-, 6-, or 7-membered, preferably 4- to 7-membered), bicyclic heterocyclyl (e.g., 8-, 9-, or 10-membered), and tricyclic heterocyclyl (e.g., 12-, 13-, or 14-membered). If a heterocyclyl group comprises two or more rings, these rings either are fused (such as in quinolinyl or purinyl), are a spiro moiety, are a bridged structure, are linked via a double bond, or are a combination thereof. In other words, an unsubstituted heterocyclyl group does not encompass two heterocyclyl groups linked via a single bond. The term "heterocyclyl" is also meant to encompass partially or completely hydrogenated forms (such as dihydro, tetrahydro, hexahydro, octahydro, decahydro, dodecahydro, etc., or perhydro forms) of the above-mentioned heteroaryl groups. Exemplary heterocyclyl groups include azetidinyl, morpholino, isochromanyl, chromanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, triazininanyl (1,2,3-, 1,2,4-, and 1,3,5-), di- and tetrahydrofuranyl, di- and tetrahydrothienyl, di- and tetrahydrooxazolyl, di- and tetrahydroisoxazolyl, di- and tetrahydrooxadiazolyl (1,2,5- and 1,2,3-), dihydropyrrolyl, dihydroimidazolyl, dihydropyrazolyl, di- and tetrahydrotriazolyl (1,2,3- and 1,2,4-), di- and tetrahydrothiazolyl, di- and tetrahydrothiazolyl, di- and tetrahydrothiadiazolyl (1,2,3- and 1,2,5-), di- and tetrahydropyridyl, di-, tetra- and hexahydropyrimidinyl, di- and tetrahydropyrazinyl, di- and tetrahydrotriazinyl (1,2,3-, 1,2,4-, and 1,3,5-), di-, tetra-, hexa- and octahydrobenzofuranyl (1- and 2-), di-, tetra-, hexa- and octahydroindolyl, di-, tetra-, hexa- and octahydroisoindolyl, di-, tetra-, hexa- and octahydrobenzothienyl (1- and 2), di-, tetra-, hexa- and octahydro-1H-indazolyl, di-, tetra-, hexa- and octahydrobenzimidazolyl, di-, tetra-, hexa- and octahydrobenzoxazolyl, di-, tetra-, hexa- and octahydroindoxazinyl, di-, tetra-, hexa- and octahydrobenzisoxazolyl, di-, tetra-, hexa- and octahydrobenzothiazolyl, di-, tetra-, hexa- and octahydrobenzisothiazolyl, di-, tetra-, hexa- and octahydrobenzotriazolyl, di-, tetra-, hexa-, octa- and decahydroquinolinyl, di-, tetra-, hexa-, octa- and decahydroisoquinolinyl, di-, tetra-, hexa-, octa- and decahydrobenzodiazinyl, di-, tetra-, hexa-, octa- and decahydroquinoxalinyl, di-, tetra-, hexa-, octa- and decahydroquinazolinyl, di-, tetra-, hexa-, octa- and decahydrobenzotriazinyl (1,2,3- and 1,2,4-), di-, tetra-, and hexahydropyridazinyl, di-, tetra-, hexa-, octa-, deca- and dodecahydrophenoxazinyl, di-, tetra-, hexa-, and octahydrothiazolopyridinyl (such as 4,5,6-7-tetrahydro[1,3]thiazolo[5,4-c]pyridinyl or 4,5,6-7-tetrahydro[1,3]thiazolo[4,5-c]pyridinyl, e.g., 4,5,6-7-tetrahydro[1,3]-thiazolo[5,4-c]pyridin-2-yl or 4,5,6-7-tetrahydro[1,3]thiazolo[4,5-c]pyridin-2-yl), di-, tetra-, and hexahydropyrrolothiazolyl, di-, tetra-, hexa-, octa- and decahydrophenothiazinyl, di-, tetra-, hexa-, and octahydroisobenzofuranyl, di-, tetra-, hexa-, and octahydrochromenyl, di-, tetra-, hexa-, octa-, deca-, and dodecahydroxanthenyl, di-, tetra-, hexa-, octa-, deca-, and dodecahydrophenoxathiinyl, di-, tetra-, and hexahydropyrrolizinyl, di-, tetra-, hexa-, and octahydroindolizinyl, di-, tetra-, hexa-, and octahydroindazolyl, di-, tetra-, hexa-, and octahydropurinyl, di-, tetra-,

hexa-, and octahydroquinolizinyl, di-, tetra-, hexa-, octa- and decahydrophthalazinyl, di-, tetra-, hexa-, octa- and decahydronaphthyridinyl (1,5-, 1,6-, 1,7-, 1,8-, and 2,6-), di-, tetra-, hexa-, octa- and decahydrocinnolinyl, di-, tetra-, hexa-, octa-, and decahydropteridinyl, di-, tetra-, hexa-, octa-, deca- and dodecahydrocarbazolyl, di-, tetra-, hexa-, octa-, deca-, dodeca-, and tetradecahydrophenanthridinyl, di-, tetra-, hexa-, octa-, deca-, dodeca-, and tetradecahydroacridinyl, di-, tetra-, hexa-, octa-, deca- and dodecahydroperimidinyl, di-, tetra-, hexa-, octa-, deca-, dodeca-, and tetradecahydrophenanthrolinyl (1,7-, 1,8-, 1,10-, 3,8-, and 4,7-), di-, tetra-, hexa-, octa-, deca-, dodeca-, and tetradecahydrophenazinyl, di-, tetra-, hexa- and octahydrooxazolopyridinyl, di-, tetra-, hexa- and octahydroisoxazolopyridinyl, di-, tetra-, hexa- and octahydrocyclopentapyrrolyl, di-, tetra-, hexa- and octahydrocyclopentpyrazolyl, di-, tetra-, hexa- and octahydrocyclopentaimidazolyl, di-, tetra-, hexa- and octahydrocyclopentathiazolyl, di-, tetra-, hexa- and octahydrocyclopentaoxazolyl, di-, tetra-, hexa- and octahydropyrrolopyrrolyl, di-, tetra-, hexa- and octahydropyrrolopyrazolyl, di-, tetra-, hexa- and octahydropyrroloimidazolyl, di-, tetra-, hexa- and octahydropyrrolothiazolyl (such as 5,6-dihydro-4H-pyrrolo[3,4-d][1,3]thiazolyl), di-, tetra-, hexa- and octahydropyrrolooxazolyl, di-, tetra-, hexa- and octahydropyrazolopyrazolyl, di-, tetra-, hexa- and octahydropyrazoloimidazolyl, di-, tetra-, hexa- and octahydropyrazolothiazolyl, di-, tetra-, hexa- and octahydropyrazolooxazolyl, di-, tetra-, hexa- and octahydroimidazoimidazolyl, di-, tetra-, hexa- and octahydroimidazothiazolyl, di-, tetra-, hexa- and octahydroimidazooxazolyl, di-, tetra-, hexa- and octahydrothiazolothiazolyl, di-, tetra-, hexa- and octahydrothiazolooxazolyl, and di-, tetra-, hexa- and octahydrooxazolooxazolyl. Exemplary 5- or 6-membered heterocyclyl groups include morpholino, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, di- and tetrahydrofuranyl, di- and tetrahydrothienyl, di- and tetrahydrooxazolyl, di- and tetrahydroisoxazolyl, di- and tetrahydrooxadiazolyl (1,2,5- and 1,2,3-), dihydropyrrolyl, dihydroimidazolyl, dihydropyrazolyl, di- and tetrahydrotriazolyl (1,2,3- and 1,2,4-), di- and tetrahydrothiazolyl, di- and tetrahydroisothiazolyl, di- and tetrahydrothiadiazolyl (1,2,3- and 1,2,5-), di- and tetrahydropyridyl, di-, tetra-, and hexahydropyrimidinyl, di- and tetrahydropyrazinyl, di- and tetrahydrotriazinyl (1,2,3-, 1,2,4-, and 1,3,5-), and triazinanyl (1,2,3-, 1,2,4-, and 1,3,5-). A "substituted heterocyclyl" means that one or more (such as 1 to the maximum number of hydrogen atoms bound to a heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atoms of the heterocyclyl group are replaced with a substituent other than hydrogen (when more than one hydrogen atom is replaced the substituents may be the same or different). Preferably, the substituent other than hydrogen is a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as halogen, -CN, nitro, $-OR^{11}$ (e.g., -OH), $-SR^{11}$ (e.g., -SH), $-N(R^{12})(R^{13})$ (e.g., $-NH_2$), =X (e.g., =O, =S, or =NH), alkyl (e.g., C_{1-6} alkyl), alkenyl (e.g., C_{2-6} alkenyl), and alkynyl (e.g., C_{2-6} alkynyl).

[106] The expression "partially hydrogenated form" of an unsaturated compound or group as used herein means that part of the unsaturation has been removed by formally adding hydrogen to the initially unsaturated compound or group without removing all unsaturated moieties. The phrase "completely hydrogenated form" of an unsaturated compound or group is used herein interchangeably with the term "perhydro" and means that all unsaturation has been removed by formally adding hydrogen to the initially unsaturated compound or group. For example, partially hydrogenated forms of a 5-membered heteroaryl group (containing 2 double bonds in the ring, such as furan) include dihydro forms of said 5-membered heteroaryl group (such as 2,3-dihydrofuran or 2,5-dihydrofuran), whereas the tetrahydro form of said 5-membered heteroaryl group (e.g., tetrahydrofuran, i.e., THF) is a completely hydrogenated (or perhydro) form of said 5-membered heteroaryl group. Likewise, for a 6-membered heteroaryl group having 3 double bonds in the ring (such as pyridyl), partially hydrogenated forms include di- and tetrahydro forms (such as di- and tetrahydropyridyl), whereas the hexahydro form (such as piperidinyl in case of the heteroaryl pyridyl) is the completely hydrogenated (or perhydro) derivative of said 6-membered heteroaryl group. Consequently, a hexahydro form of an aryl or heteroaryl can only be considered a partially hydrogenated form according to the present invention

if the aryl or heteroaryl contains at least 4 unsaturated moieties consisting of double and triple bonds between ring atoms.

[107] The term "aromatic" as used in the context of hydrocarbons means that the whole molecule has to be aromatic. For example, if a monocyclic aryl is hydrogenated (either partially or completely) the resulting hydrogenated cyclic structure is classified as cycloalkyl for the purposes of the present invention. Likewise, if a bi- or polycyclic aryl (such as naphthyl) is hydrogenated the resulting hydrogenated bi- or polycyclic structure (such as 1,2-dihydronaphthyl) is classified as cycloalkyl for the purposes of the present invention (even if one ring, such as in 1,2-dihydronaphthyl, is still aromatic). A similar distinction is made within the present application between heteroaryl and heterocyclyl. For example, indolinyl, i.e., a dihydro variant of indolyl, is classified as heterocyclyl for the purposes of the present invention, since only one ring of the bicyclic structure is aromatic and one of the ring atoms is a heteroatom.

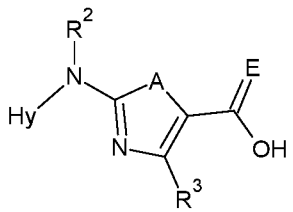
[108] The term "polycyclic" as used herein means that the structure has two or more (such as 2, 3, 4, 5, 6, 7, 8, 9, or 10), preferably, 2, 3, 4, or 5, more preferably, 2, 3, or 4, rings. Therefore, according to the invention, the term "polycyclic" does not encompass monocyclic structures, wherein the structures only contain one ring. Examples of polycyclic groups are fused structures (such as naphthyl or anthryl), spiro compounds, rings that are linked via single or double bonds (such as biphenyl), and bridged structures (such as bornyl). Exemplary polycyclic structures are those aryl, heteroaryl, cycloalkyl, and heterocyclyl groups specified above which have at least two rings.

[109] The term "halogen" or "halo" or "hal" means fluoro, chloro, bromo, or iodo.

[110] The term "azido" means $-N_3$.

[111] The term "N-oxide" means an amine oxide or amine-N-oxide which is a chemical compound containing the functional group $(R^n)_3N^+-O^-$, i.e., an N–O coordinate covalent bond, wherein R^n is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}, the R^{30} preferably being a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein.

[112] The term "carboxylic acid" as used herein refers to a compound containing at least one carboxy group (-COOH) or thiocarboxy group (-CSOH) (preferably, a compound containing at least one carboxy group (-COOH), and in the context of Examples 1.1 and 1.2, only a compound containing at least one carboxy group (-COOH)). The term "corresponding carboxylic acid" as used herein refers to a (thio)carboxylic acid which when reacted with a further compound (such as an intermediate, e.g., an intermediate of the invention) results in desired compound (e.g., a compound having an amide or a thioamide bond). For example, if it is desired to prepare a compound of formula (Ia) using an intermediate of formula (Id) the corresponding acid may have the following formula (Ie):

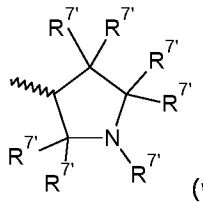
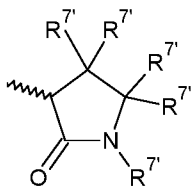
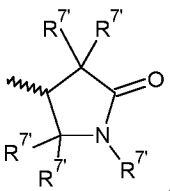
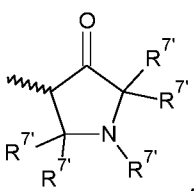
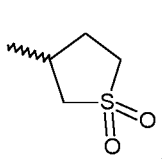
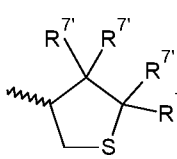
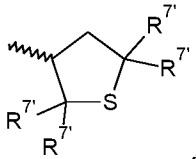


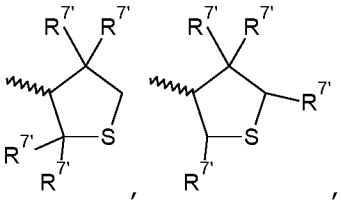
(Ie)

wherein Hy, R^2, R^3, A, and E are as defined herein (in particular with respect to formula (Ia), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)). For example, if it is desired to prepare a compound of formula (Ia), wherein E is S, it is preferred to use an intermediate of formula (Id), and the corresponding acid may have the above formula (Ie), wherein E is S. If in another embodiment, it is desired to prepare a compound of formula (Ia), wherein E is O, it is preferred to use an intermediate of formula (Id) and the corresponding acid may have the above formula (Ie), wherein E is O.

[113] The term "impurity" as used herein refers to any foreign material (in particular chemical substances) which may be present in a composition comprising a desired compound (e.g., a composition comprising a compound described herein, such a compound of formula (Ia)). Impurities may occur naturally, may be added during the synthesis and/or purification of the desired compound, or may be generated during the synthesis and/or purification of the desired compound. Exemplary impurities include one or more starting materials, one or more solvents, one or more intermediates or reactants, one or more degradation products of any of the foregoing or of the desired compound, one or more leftovers of protecting groups after deprotection, and combinations thereof.

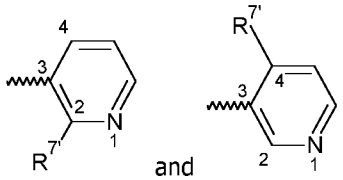
[114] The expression "at least one of R^7 is F and/or at least one of R^7 is substituted with one or more F atoms " as used herein (and similar expressions) means that R^6 is substituted with (i) at least one F atom and/or (ii) a moiety bearing one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the moiety, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) F atoms. Exemplary moieties bearing one or more F atoms include an alkyl group bearing one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2 or 3) F atoms, such as $C_{1\text{-}3}$alkyl bearing one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl group, e.g., 1, 2, 3, 4, 5, 6, or 7, or up to 6, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2 or 3) F atoms, e.g., $-CH_2F$, $-CHF_2$, or $-CF_3$. Further exemplary moieties bearing one or more F atoms include F substituted alkoxy groups (i.e., -O(alkyl), such as $-O(C_{1\text{-}3}alkyl)$) or F substituted alkyl amino groups (i.e., -NH(alkyl) or $-N(alkyl)_2$, such as $-NH(C_{1\text{-}3}alkyl)$ or $-N(C_{1\text{-}3}alkyl)_2$), wherein the alkyl (e.g., the $C_{1\text{-}3}$alkyl) portion of the alkoxy and monoalkyl amino groups and at least one of the alkyl (e.g., the $C_{1\text{-}3}$alkyl) portions of the dialkylamino groups is substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl portion, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10 or up to 7, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2 or 3) F atoms.

[115] As described elsewhere herein, for formula (Ic) $R^{5''}$ is $-L-R^{6''}$, and $R^{6''}$ is heteroaryl or heterocyclyl each of which is optionally substituted with one or more independently selected $R^{7'}$. In relation thereto, the expression "any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ may join together to form =O" as used herein means that two monoradicals (i.e., $R^{7'}$) when substituting in total 2 hydrogen atoms bound to only one ring atom of $R^{6''}$ can form the diradical =O. For example, according to the invention, $R^{6''}$ being  (wherein ~~~ represents the bond by which $R^{6''}$ is bound to the remainder of the compound) encompasses not only (1) the possibility that each of the $R^{7'}$ groups is a monoradical independently selected from the particular moieties specified herein (e.g., methyl or Cl) but also (2) the possibility that any two $R^{7'}$ groups bound to the same atom of $R^{6''}$ join together to form the diradical =O resulting in a $R^{6''}$ group having the formula  ,  , or  , wherein the remaining $R^{7'}$ groups are monoradicals. Likewise, in case $R^{6''}$ is 3-tetrahydrothienyl substituted with four $R^{7'}$, such substituted $R^{6''}$ encompasses the following formulas:  ,  ,  ,



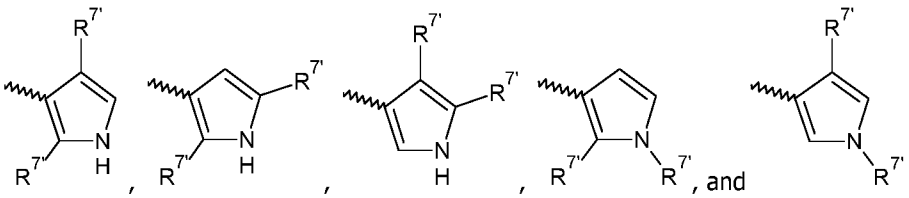
, etc. Similar terms such as "any two R^{30} which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group may join together to form $=X^1$" as used herein are to be interpreted in an analogous manner. In this respect, it is to be understood that in those embodiments, where any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ may join together to form =O, $R^{6''}$ initially (i.e., without the modification =O) has to be a heterocyclic ring (because in a heteroaromatic ring there is no carbon ring atom having two free valences). Similarly, where any two R^{30} which are bound to the same atom of a moiety may join together to form $=X^1$, this moiety initially (i.e., without the modification $=X^1$) has to be a cycloaliphatic or heterocyclic ring (because in a (hetero)aromatic ring there is no carbon ring atom having two free valences).

[116] The expression "one $R^{7'}$ group is bound to a ring atom of $R^{6'}$ at position 2 relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound" as used herein (and similar expressions) means that at least one of the two ring atoms directly adjacent to the ring atom by which $R^{6'}$ is attached to the remainder of the compound bears one $R^{7'}$ group. In other words, at least one of the ortho positions of $R^{6'}$, relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound (i.e., "yl position" of $R^{6'}$), bears a $R^{7'}$ group. For example, applying the above expression to the case where $R^{6'}$ is 3-pyridyl (thus, the yl position is the ring carbon at position 3 relative to the ring nitrogen atom) substituted with one $R^{7'}$, it follows that this $R^{7'}$ group is at position 2 or 4 of the 3-pyridyl group, as shown in the following formulas:



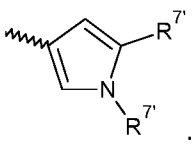
and

wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound. Furthermore, in case $R^{6'}$ is substituted with more than one (such as two or three) $R^{7'}$ groups, the expression "one $R^{7'}$ group is bound to a ring atom of $R^{6'}$ at position 2 relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound" as used herein (and similar expressions) encompasses the situation that each of the two ring atoms directly adjacent to the ring atom by which $R^{6'}$ is attached to the remainder of the compound bears one $R^{7'}$ group (i.e., $R^{6'}$ being an k-membered ring bears one $R^{7'}$ group at each of positions 2 and k, relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound, i.e., $R^{6'}$ is substituted at both of its ortho positions). For example, in case $R^{6'}$ is 3-pyrrolyl (thus, the yl position is the ring carbon at position 3 relative to the ring nitrogen atom) substituted with two $R^{7'}$ groups, the expression "one $R^{7'}$ group is bound to a ring atom of $R^{6'}$ at position 2 relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound" encompasses the following structures:



, and

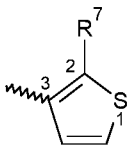
but excludes the following structure:



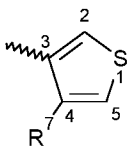
.

[117] The term "k-membered ring" as used herein means that the ring has k ring atoms. E.g., for pyrazolyl k is 5; thus, relative to the ring atom (yl position) by which the pyrazolyl group is bound to the remainder of the compound, the ortho positions are positions 2 and 5 and position k-1 is position 4. Furthermore, for pyridinyl being a 6-membered heteroaryl, the ortho positions are positions 2 and 6 and position k-1 is position 5, relative to the ring atom (yl position) by which the pyridinyl group is bound to the remainder of the compound.

[118] Regarding R^6 being a 5-membered monocyclic heteroaryl which contains at least one S ring atom, the expression "one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound" as used herein (and similar expressions) preferably means that one R^7 group is bound to the C ring atom of R^6 which (i) is directly adjacent to the ring atom by which R^6 is attached to the remainder of the compound and (ii) receives the lower number when numbering the ring atoms of R^6 (e.g., starting with number "1" for the S ring atom and continuing in such a way that the number of the ring atom by which R^6 is bound to the remainder of the compound (i.e., the "yl" position of R^6) is as low as possible). In other words, relative to the yl position of R^6, that C ring atom of the two "ortho" positions of R^6 preferably bears a R^7 group which lies between the S ring atom and the yl position of R^6 when considering the shortest path between the S ring atom and the yl position. For example, applying the above expression to the case where R^6 is 3-thienyl (thus, the yl position is the ring carbon at position 3 relative to the S ring atom) substituted with one R^7, it follows that this R^7 group is at position 2 of the 3-thienyl group, as shown in the following formula:

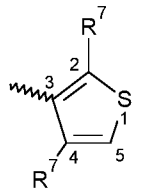


wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound. Likewise, regarding R^6 being a 5-membered monocyclic heteroaryl which contains at least one S ring atom, the expression "one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound" as used herein (and similar expressions) preferably means that one R^7 group is bound to the C ring atom of R^6 which (i) is directly adjacent to the ring atom by which R^6 is attached to the remainder of the compound and (ii) receives the higher number when numbering the ring atoms of R^6 (e.g., starting with number "1" for the S ring atom and continuing in such a way that the number of the yl position of R^6 is as low as possible). In other words, relative to the yl position of R^6, that C ring atom preferably bears a R^7 group which does not lie between the S ring atom and the yl position of R^6 when considering the shortest path between the S ring atom and the yl position. For example, applying the above expression ("one R^7 group is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound") to the case where R^6 is 3-thienyl (thus, the yl position is the ring carbon at position 3 relative to the S ring atom) substituted with one R^7, it follows that this R^7 group is at position 4 of the 3-thienyl group, as shown in the following formula:

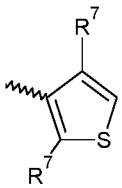


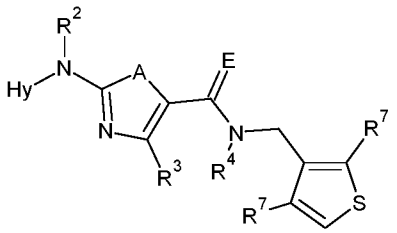
wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound. Furthermore, regarding R^6 being a 5-membered monocyclic heteroaryl which contains at least one S ring atom, the expression "one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound and one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound " as used herein (and similar expressions) preferably means that to each of the two C ring atoms of R^6 which are directly adjacent to the ring atom by which R^6 is attached to the remainder of the compound one R^7 is bound. For example, applying the above expression ("one R^7 is attached to the C ring atom at position 2

relative to the ring atom by which R^6 is bound to the remainder of the compound and one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound ") to the case where R^6 is 3-thienyl (thus, the yl position is the ring carbon at position 3 relative to the S ring atom) substituted with at least two R^7 groups, it follows that these R^7 groups are at position 2 and 4 of the 3-thienyl group, as shown in the following formula:

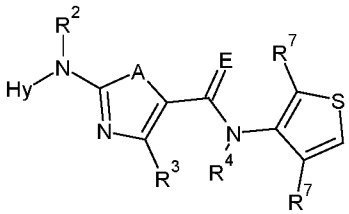


wherein ∿∿∿ represents the bond by which R^6 is bound to the remainder of the compound.

[119] The expression " ∿∿∿ represents the bond by which R^6 is bound to the remainder of the compound" as used herein refers to the bond through which R^6 is attached to the remainder of the compound (i.e., attached to either (i) L in case L is not a bond or (ii) the nitrogen atom of the carbox(thio)amide group -C(=E)N(R^4) of formula (Ia), (Ib), or (Ic) in case L is a bond). For example, in case R^6 is  and L is (i) methylene or (ii) a bond, the compound of formula (Ia) has the following structure (A1) and (A2), respectively:



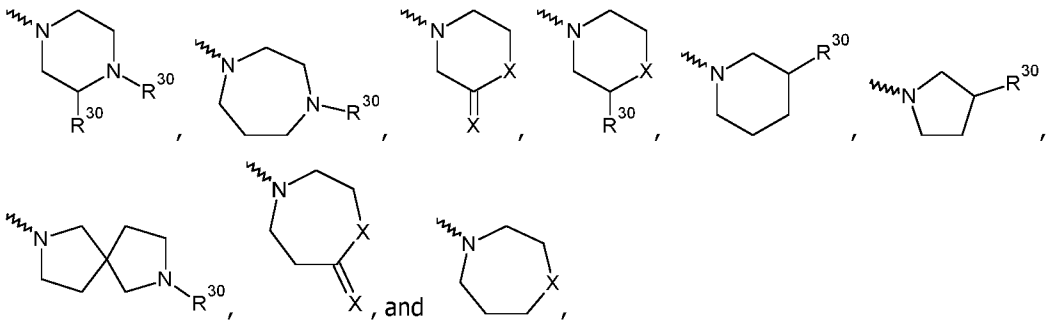
(A1)



(A2)

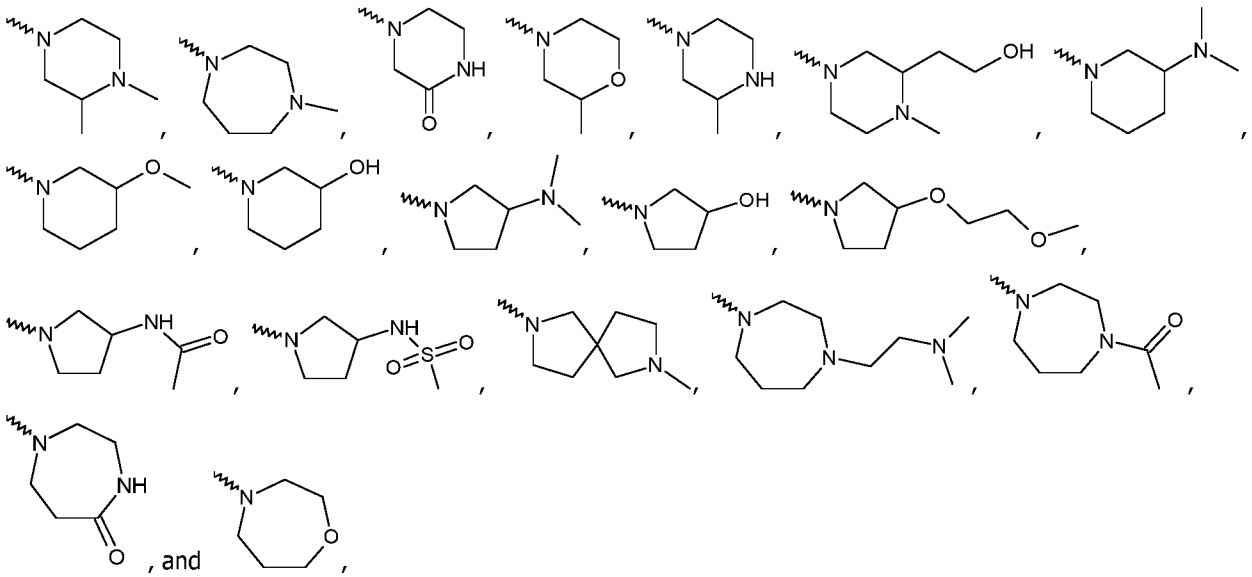
Similar terms such as " ∿∿∿ represents the bond by which Hy is bound to the remainder of the compound" or " ∿∿∿ represents the bond by which R^{1a} is bound to the remainder of the compound" as used herein are to be interpreted in an analogous manner.

[120] The term "non-symmetrical" as used herein (for example, in connection with R^{1a}) preferably means that the moiety concerned, in particular a non-symmetrical cycloalkyl or heterocyclyl group, relative to its point of attachment to the remainder of the compound, is non-symmetrical as such (e.g., 1,4-oxazepan-4-yl) and/or has a substitution pattern which is non-symmetrical (e.g., 3-oxopiperazin-1-yl or 3-methylpiperazin-1-yl). For example, relative to its point of attachment to the remainder of the compound, a symmetrical group has symmetry plane (as in 4-methylpiperazinyl), whereas a non-symmetrical group does not have a symmetry plane. A non-symmetrical group may have an asymmetric atom (e.g., a chiral C atom), such as in 2-methylmorpholin-4-yl, but does not necessarily have an asymmetric atom (such as in 3-oxopiperazin-1-yl). Exemplary groups which are non-symmetrical include the following:



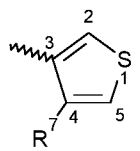
wherein R^{30} and X are as defined herein; and ~~~ represents the bond by which the non-symmetrical group is bound to the remainder of the compound.

[121] Particular groups which are non-symmetrical include the following:



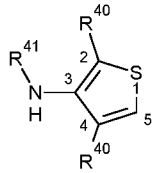
wherein R^{30} and X are as defined herein; and ~~~ represents the bond by which the non-symmetrical group is bound to the remainder of the compound.

[122] The expression "adjacent ring atoms" as used herein, like in "the C ring atom and the S ring atom are adjacent ring atoms" preferably means that these two ring atoms share a common bond and, thus, are directly bound to each other. For example, in the structure shown below (i.e., a 3-thienyl group which is substituted with R^7 at position 4), the C ring atom at position 2 and the S ring atom are adjacent ring atoms, whereas the C ring atom at position 4 and the S ring atom are separated by a C ring atom:

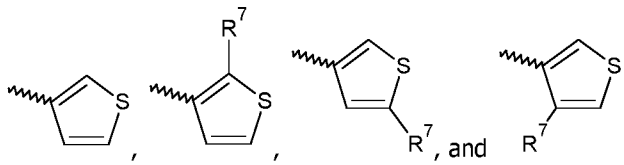


wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

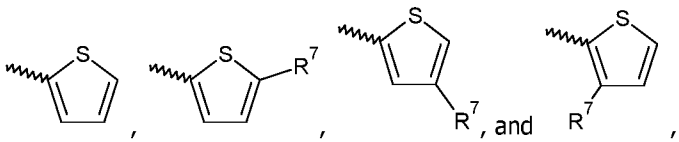
[123] Likewise, the expression "the R^{40} bound to the C ring atom adjacent to the S ring atom" as used herein preferably means that the C ring atom to which the R^{40} is attached and the S ring atom are adjacent atoms. For example, in the structure shown below, the R^{40} bound to the C ring atom adjacent to the S ring atom is the R^{40} bound to the C ring atom at position 2 (because this C ring atom is adjacent to the S ring atom), whereas the R^{40} bound to the C ring atom at position 4 is the R^{40} bound to the C ring atom separated from (or not adjacent to) the S ring atom (i.e., the C ring atom at position 4 and the S ring atom are separated by a C ring atom (at position 5)):



[124] The expression "the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound" as used herein preferably means that the S ring atom of R^6 is separated from the ring atom by which R^6 is bound to the remainder of the compound (i.e., from the yl position of R^6) by at least one ring atom. For example, in case R^6 is thienyl optionally substituted with one R^7, the expression "the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound" encompasses the following structures:

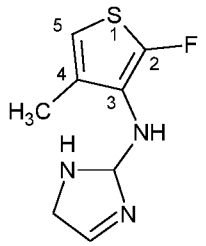


but excludes, inter alia, the following structures:



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

[125] In accordance with the IUPAC nomenclature, preferably the numbering of a substituted heterocyclyl group starts at the ring heteroatom and continues in such a way that the numbers of the substituents are as low as possible. For example, the compound shown below has the following numbering of the ring atoms and the following name:



N-(2-fluoro-4-methylthiophen-3-yl)-2,5-dihydro-1*H*-imidazol-2-amine

[126] The term "optionally substituted" indicates that one or more (such as 1 to the maximum number of hydrogen atoms bound to a group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) hydrogen atom(s) may be replaced with a group (i.e., a 1st level substituent) different from hydrogen such as alkyl (preferably, C_{1-6} alkyl), alkenyl (preferably, C_{2-6} alkenyl), alkynyl (preferably, C_{2-6} alkynyl), aryl (preferably, 6- to 14-membered aryl), heteroaryl (preferably, 3- to 14-membered heteroaryl), cycloalkyl (preferably, 3- to 14-membered cycloalkyl), heterocyclyl (preferably, 3- to 14-membered heterocyclyl), halogen, -CN, azido, $-NO_2$, $-OR^{71}$, $-N(R^{72})(R^{73})$, $-S(O)_{0-2}R^{71}$, $-S(O)_{1-2}OR^{71}$, $-OS(O)_{1-2}R^{71}$, $-OS(O)_{1-2}OR^{71}$, $-S(O)_{1-2}N(R^{72})(R^{73})$, $-OS(O)_{1-2}N(R^{72})(R^{73})$, $-N(R^{71})S(O)_{1-2}R^{71}$, $-NR^{71}S(O)_{1-2}OR^{71}$, $-NR^{71}S(O)_{1-2}N(R^{72})(R^{73})$, $-OP(O)(OR^{71})_2$, $-C(=X^1)R^{71}$, $-C(=X^1)X^1R^{71}$, $-X^1C(=X^1)R^{71}$, and $-X^1C(=X^1)X^1R^{71}$, and/or any two 1st level substituents which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group may join together to form $=X^1$, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups of the 1st level substituent may themselves be substituted by one or more (e.g., one, two or three) substituents (i.e., a 2nd level substituent) selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, $-OR^{81}$, $-N(R^{82})(R^{83})$, $-S(O)_{0-2}R^{81}$, $-S(O)_{1-2}OR^{81}$, $-OS(O)_{1-2}R^{81}$, $-OS(O)_{1-}$

$_2OR^{81}$, $-S(O)_{1-2}N(R^{82})(R^{83})$, $-OS(O)_{1-2}N(R^{82})(R^{83})$, $-N(R^{81})S(O)_{1-2}R^{81}$, $-NR^{81}S(O)_{1-2}OR^{81}$, $-NR^{81}S(O)_{1-2}N(R^{82})(R^{83})$, $-OP(O)(OR^{81})_2$, $-C(=X^2)R^{81}$, $-C(=X^2)X^2R^{81}$, $-X^2C(=X^2)R^{81}$, and $-X^2C(=X^2)X^2R^{81}$, and/or any two 2nd level substituents which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group being a 1st level substituent may join together to form $=X^2$, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl groups of the 2nd level substituent is optionally substituted with one or more (e.g., one, two or three) substituents (i.e., a 3rd level substituent) independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl, and/or any two 3rd level substituents which are bound to the same carbon atom of a 3- to 14-membered cycloalkyl or heterocyclyl group being a 2nd level substituent may join together to form =O, =S, =NH, or $=N(C_{1-3}$ alkyl);

wherein

each of R^{71}, R^{72}, and R^{73} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl;

each of R^{81}, R^{82}, and R^{83} is independently selected from the group consisting of H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl, wherein each of the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; and

each of X^1 and X^2 is independently selected from O, S, and $N(R^{84})$, wherein R^{84} is H or C_{1-3} alkyl.

[127] Typical 1st level substituents are preferably selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6- to 14-membered (such as 6- to 10-membered) aryl, 3- to 14-membered (such as 5- or 6-membered) heteroaryl, 3- to 14-membered (such as 3- to 7-membered) cycloalkyl, 3- to 14-membered (such as 3- to 7-membered) heterocyclyl, halogen, -CN, azido, $-NO_2$, $-OR^{71}$, $-N(R^{72})(R^{73})$, $-S(O)_{0-2}R^{71}$, $-S(O)_{1-2}OR^{71}$, $-OS(O)_{1-2}R^{71}$, $-OS(O)_{1-2}OR^{71}$, $-S(O)_{1-2}N(R^{72})(R^{73})$, $-OS(O)_{1-2}N(R^{72})(R^{73})$, $-N(R^{71})S(O)_{1-2}R^{71}$, $-NR^{71}S(O)_{1-2}OR^{71}$, $-C(=X^1)R^{71}$, $-C(=X^1)X^1R^{71}$, $-X^1C(=X^1)R^{71}$, and $-X^1C(=X^1)X^1R^{71}$, such as C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 6-membered aryl, 5- or 6-membered heteroaryl, 3- to 7-membered cycloalkyl, 3- to 7-membered (such as 5- or 6-membered) heterocyclyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; wherein X^1 is independently selected from O, S, NH and $N(CH_3)$; and each of R^{71},

R^{72}, and R^{73} is as defined above or, preferably, is independently selected from the group consisting of H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 5- or 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 5- or 6-membered heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl. Particular examples of 1st level substituents are independently selected from the group consisting of C_{1-3} alkyl, phenyl, imidazolyl, thiazolyl, cyclopentyl, cyclohexyl, dihydrothiazolyl, thiazolidinyl, halogen, $-CF_3$, -CN, -OH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl. Particularly preferred 1st level substituents are independently selected from the group consisting of C_{1-3} alkyl, phenyl, thiazolidinyl, halogen (such as F, Cl, or Br), $-NH_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), and $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, wherein z is 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl.

[128] Typical 2nd level substituents are preferably selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 6- or 10-membered aryl, 5- or 6-membered heteroaryl, 5- or 6-membered cycloalkyl, 5- or 6-membered heterocyclyl, halogen, =O, =S, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl. Particular examples of 2nd level substituents are independently selected from the group consisting of C_{1-3} alkyl, phenyl, 5- or 6-membered heteroaryl, 5- or 6-membered cycloalkyl, 5- or 6-membered heterocyclyl, halogen, =O, =S, $-CF_3$, -CN, -OH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl. Particularly preferred 2nd level substituents are independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, phenyl, =O, and =S.

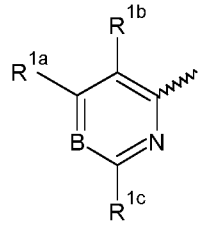
[129] Typical 3rd level substituents are preferably selected from the group consisting of C_{1-3} alkyl, phenyl, halogen, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-NH_{2-z}(CH_3)_z$, -C(=O)OH, and $-C(=O)OCH_3$, wherein z is 0, 1, or 2 and C_{1-3} alkyl is methyl, ethyl, propyl or isopropyl. Particularly preferred 3rd level substituents are selected from the group consisting of methyl, ethyl, propyl, isopropyl, halogen (such as F, Cl, or Br), and $-CF_3$, such as halogen (e.g., F, Cl, or Br), and $-CF_3$.

[130] The term "optional" or "optionally" as used herein means that the subsequently described event, circumstance or condition may or may not occur, and that the description includes instances where said event, circumstance, or condition occurs and instances in which it does not occur.

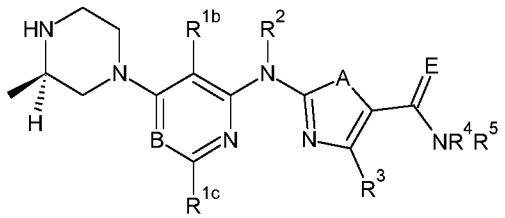
[131] "Isomers" are compounds having the same molecular formula but differ in structure ("structural isomers") or in the geometrical (spatial) positioning of the functional groups and/or atoms ("stereoisomers"). "Enantiomers" are a pair of stereoisomers which are non-superimposable mirror-images of each other. A "racemic mixture" or "racemate" contains a pair of enantiomers in equal amounts and is denoted by the prefix (±). "Diastereomers" are stereoisomers which are non-superimposable and which are not mirror-images of each other. "Tautomers" are structural isomers of the same chemical substance that spontaneously and reversibly interconvert into each other, even when pure, due to the migration of individual atoms or groups of atoms; i.e., the tautomers are in a dynamic chemical equilibrium with each other. An example of tautomers are the isomers of the keto-enol-tautomerism. "Conformers" are stereoisomers

that can be interconverted just by rotations about formally single bonds, and include - in particular - those leading to different 3-dimentional forms of (hetero)cyclic rings, such as chair, half-chair, boat, and twist-boat forms of cyclohexane.

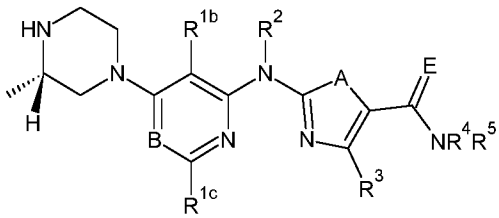
[132] In case a structural formula shown in the present application can be interpreted to encompass more than one isomer, said structural formula, unless explicitly stated otherwise, encompasses all possible isomers and, hence, each individual isomer. For example, a compound of formula (Ia), wherein Hy is:



wherein ~~~~ represents the bond by which Hy is bound to the remainder of the compound; and R^{1a} is 3-methylpiperazinyl, encompasses both isomers, e.g., the isomer having the following formula (B1) and the isomer having the following formula (B2):

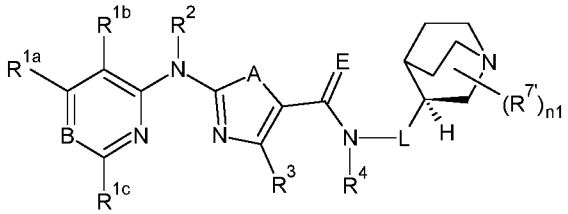


(B1)

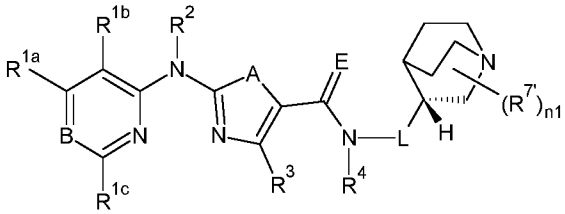


(B2)

Furthermore, a compound of formula (Ic), wherein $R^{6''}$ is 1-azabicyclo[2.2.2]oct-3-yl (optionally substituted with one or more $R^{7'}$ groups) encompasses both isomers, e.g., the isomer having the following formula (B3) and the isomer having the following formula (B4) (wherein n1 is 0, 1, 2, 3, or more):



(B3)



(B4)

[133] "Polymorphism" as referred to herein means that a solid material (such as a compound) is able to exist in more than one form or crystalline structure, i.e., "polymorphic modifications" or "polymorphic forms". The terms "polymorphic modifications", "polymorphic forms", and "polymorphs" are used interchangeable in the present invention. According to the present invention, these "polymorphic modifications" include crystalline forms, amorphous forms, solvates, and hydrates. Mainly, the reason for the existence of different polymorphic forms lies in the use of different conditions during the crystallization process, such as the following:

- solvent effects (the packing of crystal may be different in polar and nonpolar solvents);
- certain impurities inhibiting growth pattern and favor the growth of a metastable polymorphs;
- the level of supersaturation from which material is crystallized (in which generally the higher the concentration above the solubility, the more likelihood of metastable formation);
- temperature at which crystallization is carried out;
- geometry of covalent bonds (differences leading to conformational polymorphism);
- change in stirring conditions.

[134] Polymorphic forms may have different chemical, physical, and/or pharmacological properties, including but not limited to, melting point, X-ray crystal and diffraction pattern, chemical reactivity, solubility, dissolution rate, vapor pressure, density, hygroscopicity, flowability, stability, compactability, and bioavailability. Polymorphic forms may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. According to Ostwald's rule, in general it is not the most stable but the least stable polymorph that crystallizes first. Thus, quality, efficacy, safety, processability and/or manufacture of a chemical compound, such as a compound of the present invention, can be affected by polymorphism. Often, the most stable polymorph of a compound (such as a compound of the present invention) is chosen due to the minimal potential for conversion to another polymorph. However, a polymorphic form which is not the most stable polymorphic form may be chosen due to reasons other than stability, e.g. solubility, dissolution rate, and/or bioavailability.

[135] The term "crystalline form" of a material as used herein means that the smallest components (i.e., atoms, molecule or ions) of said material form crystal structures. A "crystal structure" as referred to herein means a unique three-dimensional arrangement of atoms or molecules in a crystalline liquid or solid and is characterized by a pattern, a set of atoms arranged in a particular manner, and a lattice exhibiting long-range order and symmetry. A lattice is an array of points repeating periodically in three dimensions and patterns are located upon the points of a lattice. The subunit of the lattice is the unit cell. The lattice parameters are the lengths of the edges of a unit cell and the angles between them. The symmetry properties of the crystal are embodied in its space group. In order to describe a crystal structure the following parameters are required: chemical formula, lattice parameters, space group, the coordinates of the atoms and occupation number of the point positions.

[136] The term "amorphous form" of a material as used herein means that the smallest components (i.e., atoms, molecule or ions) of said material are not arranged in a lattice but are arranged randomly. Thus, unlike crystals in which a short-range order (constant distances to the next neighbor atoms) and a long-range order (periodical repetition of a basic lattice) exist, only a short-range order exists in an amorphous form.

[137] The term "complex of a compound" as used herein refers to a compound of higher order which is generated by association of the compound with one or more other molecules. Exemplary complexes of a compound include, but are not limited to, solvates, clusters, and chelates of said compound.

[138] The term "solvate" as used herein refers to an addition complex of a dissolved material in a solvent (such as an organic solvent (e.g., an aliphatic alcohol (such as methanol, ethanol, n-propanol, isopropanol), acetone, acetonitrile, ether, and the like), water or a mixture of two or more of these liquids), wherein the addition complex exists in the form of a crystal or mixed crystal. The amount of solvent contained in the addition complex may be stoichiometric or non-stoichiometric. A "hydrate" is a solvate wherein the solvent is water.

[139] In isotopically labeled compounds one or more atoms are replaced by a corresponding atom having the same number of protons but differing in the number of neutrons. For example, a hydrogen atom may be replaced by a deuterium atom. Exemplary isotopes which can be used in the compounds of the present invention include deuterium, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{32}P, ^{32}S, ^{35}S, ^{36}Cl, and ^{125}I.

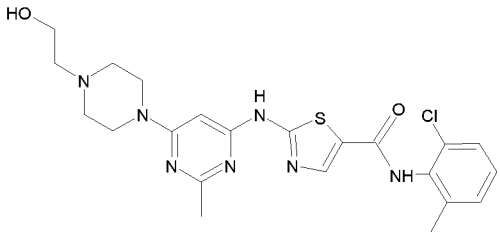
[140] The expression "amino protecting group" as used herein preferably refers to any group by which an amino group contained in a compound can be transferred into a less reactive (i.e., protected) amino group. Preferably, amino protecting groups can be incorporated into the corresponding compound under mild conditions, in a chemoselective and/or regioselective manner, and/or in good yields. Furthermore, the amino protecting groups should be stable under the conditions to which the protected compound is to be subjected (e.g., the conditions of the desired reaction and/or purification conditions). Preferably, the amino protecting groups should minimize the risk of racemization of a stereogenic center, when present in the compound. In one embodiment, the amino protecting groups should be removable from the protected compound under mild conditions and in a selective manner such that the deprotected compound is obtained in high yields. Exemplary amino protecting groups include tert-butyloxycarbonyl (BOC), 9-

fluorenylmethoxycarbonyl (FMOC), benzyloxycarbonyl (Cbz), p-methoxybenzylcarbonyl (MOZ), acetyl (Ac), trifluoroacetyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), 3,4-dimethoxyphenyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethoxycarbonyl (Troc), triphenylmethyl (trityl; Tr), toluenesulfonyl (tosyl; Ts), *para*-bromophenylsulfonyl (brosyl), 4-nitrobenzenesulfonyl (nosyl), and 2-nitrophenylsulfenyl (Nps).

[141] The term "half-life" relates to the period of time which is needed to eliminate half of the activity, amount, or number of molecules. In the context of the present invention, the half-life of a compound disclosed herein (eg a compound of formula (Ia), (Ib) or (Ic)) is indicative for the stability of said compound.

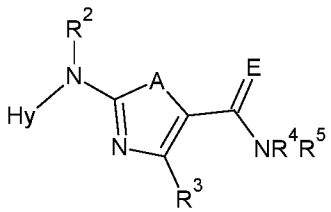
[142] The terms "subject", "patient", "individual", or "animal" relate to multicellular animals, such as vertebrates. For example, vertebrates in the context of the present invention are mammals, birds (e.g., poultry), reptiles, amphibians, bony fishes, and cartilaginous fishes, in particular domesticated animals of any of the foregoing as well as animals (in particular vertebrates) in captivity such as animals (in particular vertebrates) of zoos. Mammals in the context of the present invention include, but are not limited to, humans, non-human primates, domesticated mammals, such as dogs, cats, sheep, cattle, goats, pigs, horses etc., laboratory mammals such as mice, rats, rabbits, guinea pigs, etc. as well as mammals in captivity such as mammals of zoos. The term "animal" as used herein also includes humans. Particular non-limiting examples of birds include domesticated poultry, and include birds such as chickens, turkeys, ducks, geese, guinea fowl, pigeons, pheasants etc.; while particular non-limiting examples of bony or cartilaginous fish include those suitable for cultivation by aquiculture, and include bony fish such as salmon, trout, perch, carp, cat-fish, etc.

[143] The compound dasatinib (herein also referred to as compound A8) has the following structure:



Compounds

[144] In **a first aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the present invention provides **a compound** selected from the group consisting of a kinase inhibitor of the formula:



(Ia)

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof;

wherein:

Hy is a heteroaryl or heterocyclyl which is optionally substituted with one or more independently selected R^{1e};

each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d};

each of R^{1a} and R^{1d} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein

each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

each of R^{1b} and R^{1c} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, 3- to 7-membered heterocyclyl, $-O(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-O(CH_2)_{0-2}$(C_{6-10} aryl), $-O(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-O(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), $-NH(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-NH(CH_2)_{0-2}$(C_{6-10} aryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two, or three moieties independently selected from the group consisting of -OH, methyl, ethyl, $-OCH_3$, $-SCH_3$, and $-NH_{2-z}(CH_3)_z$;

R^2 is H;

R^3 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^4 is H;

R^5 is -L-R^6;

L is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m$-[Y-$(CH_2)_n]_o$-, wherein m is an integer between 1 and 6, n is an integer between 0 and 3, o is an integer between 1 and 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and $-N(R^{13})$-; and each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m$-, and $-(CH_2)_n$- groups is optionally substituted with one or two independently selected R^{30};

R^6 is a 5-membered monocyclic heteroaryl which contains at least one S ring atom and which is substituted with one or more independently selected R^7;

R^7 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$,
$-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}, wherein at least one of R^7 is F and/or at least one of R^7 is substituted with one or more F atoms;

A is selected from the group consisting of S, O, NR^8, and $C(R^9)_2$;

R^8 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^9 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

X is independently selected from the group consisting of O, S, and N(R^{14});

E is O or S;

R^{11} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{12} and R^{13} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, or R^{12} and R^{13} may join together with the nitrogen atom to which they are attached to form the group -N=C$R^{15}R^{16}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

R^{14} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and -OR^{11}, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{15} and R^{16} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and -$NH_yR^{20}{}_{2-y}$, or R^{15} and R^{16} may join together with the atom to which they are attached to form a ring which is optionally substituted with one or more independently selected R^{30}, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

y is an integer from 0 to 2;

R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}; and

R^{30} is a 1st level substituent and is, in each case, independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, -CN, azido, -NO_2, -OR^{71}, -N(R^{72})(R^{73}), -S(O)$_{0-2}R^{71}$, -S(O)$_{1-2}OR^{71}$, -OS(O)$_{1-2}R^{71}$, -OS(O)$_{1-2}OR^{71}$, -S(O)$_{1-2}$N(R^{72})(R^{73}), -OS(O)$_{1-2}$N(R^{72})(R^{73}), -N(R^{71})S(O)$_{1-2}R^{71}$, -NR^{71}S(O)$_{1-2}OR^{71}$, -NR^{71}S(O)$_{1-2}$N(R^{72})(R^{73}), -OP(O)(OR^{71})$_2$, -C(=X^1)R^{71}, -C(=X^1)X^1R^{71}, -X^1C(=X^1)R^{71}, and -X^1C(=X^1)X^1R^{71}, and/or any two R^{30} which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group may join together to form =X^1, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups being a 1st level substituent is optionally substituted by one or more 2nd level substituents, wherein said 2nd level substituent is, in each case, independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl, halogen, -CF_3, -CN, azido, -NO_2, -OR^{81}, -N(R^{82})(R^{83}), -S(O)$_{0-2}R^{81}$, -S(O)$_{1-2}OR^{81}$, -OS(O)$_{1-2}R^{81}$, -OS(O)$_{1-2}OR^{81}$, -S(O)$_{1-2}$N(R^{82})(R^{83}), -OS(O)$_{1-2}$N(R^{82})(R^{83}), -N(R^{81})S(O)$_{1-2}R^{81}$, -NR^{81}S(O)$_{1-2}OR^{81}$, -NR^{81}S(O)$_{1-2}$N(R^{82})(R^{83}), -OP(O)(OR^{81})$_2$, -C(=X^2)R^{81}, -C(=X^2)X^2R^{81}, -X^2C(=X^2)R^{81}, and -X^2C(=X^2)X^2R^{81}, and/or any two 2nd level substituents which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group being a 1st level substituent may join together to form =X^2, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl groups being a 2nd level substituent is optionally substituted with one or more 3rd level substituents, wherein said 3rd level substituent is, in each case, independently selected from the group consisting of C_{1-3} alkyl, halogen, -CF_3, -CN, azido, -NO_2, -OH, -O(C_{1-3} alkyl), -OCF_3, -S(C_{1-3} alkyl), -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -NHS(O)$_2$(C_{1-3} alkyl), -S(O)$_2$NH_{2-z}(C_{1-3} alkyl)$_z$, -C(=O)OH, -C(=O)O(C_{1-3} alkyl), -C(=O)NH_{2-z}(C_{1-3} alkyl)$_z$, -NHC(=O)(C_{1-3} alkyl), -NHC(=NH)NH_{2-z}(C_{1-3} alkyl)$_z$, and -N(C_{1-3} alkyl)C(=NH)NH_{2-z}(C_{1-3} alkyl)$_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl, and/or any two 3rd level substituents which are bound to the same carbon atom of a 3- to 14-membered cycloalkyl or heterocyclyl group being a 2nd level substituent may join together to form =O, =S, =NH, or =N(C_{1-3} alkyl);

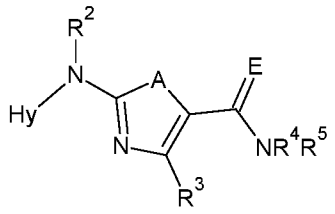
wherein

each of R^{71}, R^{72}, and R^{73} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl;

each of R^{81}, R^{82}, and R^{83} is independently selected from the group consisting of H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl, wherein each of the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and **each C_{1-3}** alkyl is independently methyl, ethyl, propyl or isopropyl; and

each of X^1 and X^2 is independently selected from O, S, and $N(R^{84})$, wherein R^{84} is H or C_{1-3} alkyl.

[145] In one embodiment, the kinase inhibitor has the formula (IIa):



(IIa)

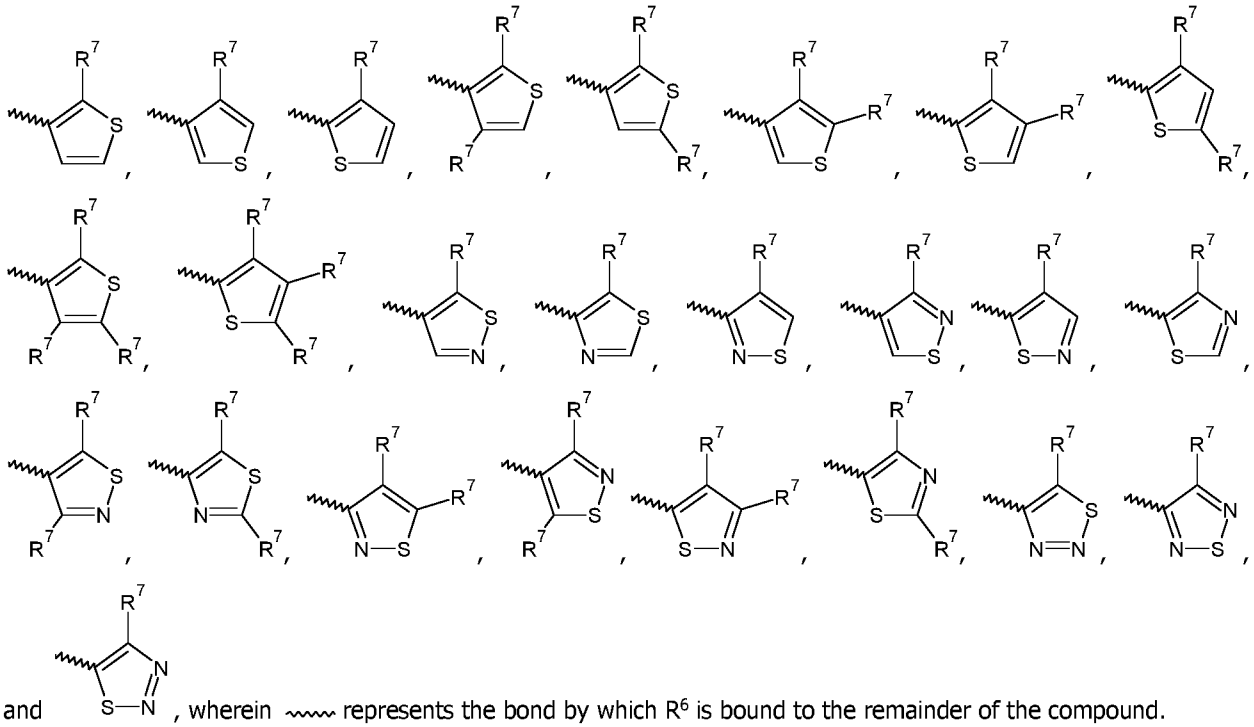
wherein Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and R^5 is -L-R^6, wherein L is as defined above (in particular with respect to formula (Ia)) or below and R^6 is a 5-membered monocyclic heteroaryl which contains at least one S ring atom and which is substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the 5-membered monocyclic heteroaryl group, e.g., 1, 2, or 3, preferably 2) independently selected R^7, wherein R^7 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}, wherein at least one of R^7 is F and/or at least one of R^7 is substituted with one or more F atoms.

[146] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^7 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and R^6 is selected from the group consisting of thienyl, thiazolyl, and thiadiazolyl, each of which is substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the 5-

membered monocyclic heteroaryl group, e.g., 1, 2, or 3) independently selected R^7. For example, R^6 may be selected from the group consisting of thienyl and thiazolyl, each of which is substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the 5-membered monocyclic heteroaryl group, e.g., 1, 2, or 3) independently selected R^7. Preferably, R^6 is thienyl which is substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the 5-membered monocyclic heteroaryl group, e.g., 1, 2, or 3, preferably 2) independently selected R^7.

[147] In any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), it is preferred that the ring atom of R^6 by which R^6 is bound to the remainder of the compound is a C atom.

[148] In any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), it is preferred that R^6 is selected from the group consisting of



and , wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

[149] In any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), it is preferred that the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound.

[150] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^7 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and R^6 is thienyl or thiazolyl, preferably thienyl, each of which is substituted with at least two R^7; in this embodiment, it is more preferred that R^6 is substituted with two R^7 which differ from each other.

[151] In any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), it is preferred that one R^7 (in particular, the R^7 which is F and/or the R^7 which is substituted with one or more F atoms) is attached to the C ring atom at position 2 or 5 relative to the ring atom by which R^6 is bound to the remainder of the compound. In those cases, where R^6 is substituted with at least two R^7 groups, it is preferred that one of the R^7 groups (in particular the R^7 which is F and/or the R^7 which is substituted with one or more F atoms) is attached to one of the C ring atoms at positions 2 and 5 relative to the ring atom by which R^6 is bound to the remainder of the compound and one of the R^7 groups is attached to the other of the C ring atoms at positions 2 and 5 relative to the ring atom by which R^6 is bound to the remainder of the compound.

[152] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^6 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa),

(Va), (VIa), (VIIa), and/or (VIIIa)), and at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, $-OR^{11}$, and $-N(R^{12})(R^{13})$, wherein each of the alkyl and R^{11} groups and at least one of the R^{12} and R^{13} groups is substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl, R^{11}, R^{12}, or R^{13} group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) F atoms.

[153] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^6 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, -O(alkyl), -NH(alkyl), and $-N(alkyl)_2$, wherein the alkyl group of alkyl, -O(alkyl) and -NH(alkyl) and at least one of the alkyl groups of $-N(alkyl)_2$ is substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) F atoms.

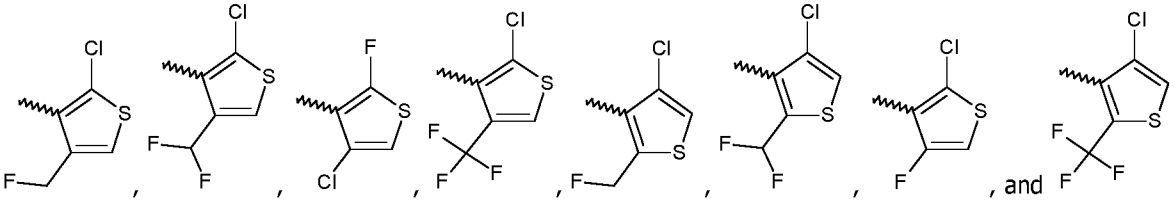
[154] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^6 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of $C_{1\text{-}3}$alkyl, $-O(C_{1\text{-}3}alkyl)$, $-NH(C_{1\text{-}3}alkyl)$ or $-N(C_{1\text{-}3}alkyl)_2$, wherein the alkyl group of $C_{1\text{-}3}$alkyl, $-NH(C_{1\text{-}3}alkyl)$, and $-O(C_{1\text{-}3}alkyl)$ and at least one of the alkyl groups of $-N(C_{1\text{-}3}alkyl)_2$ is substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the $C_{1\text{-}3}$alkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, or up to 6, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) F atoms.

[155] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^6 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and at least one of R^7 is F and/or at least one of R^7 is $C_{1\text{-}3}$alkyl, wherein the alkyl group of $C_{1\text{-}3}$alkyl is substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the $C_{1\text{-}3}$alkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, or up to 6, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) F atoms.

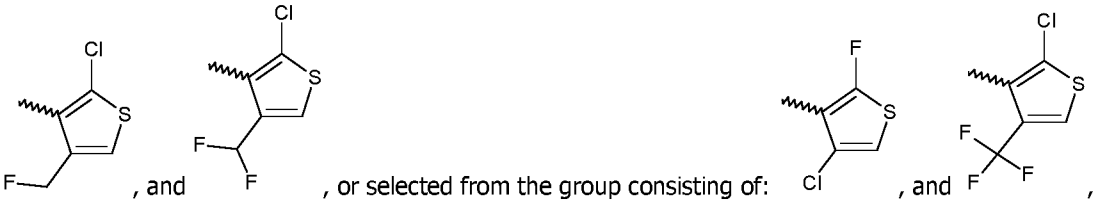
[156] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^6 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$.

[157] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, E, L, and R^6 are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and R^6 is substituted with at least two R^7, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, and one R^7 is selected from the group consisting of halogen, $-CH_3$, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, CH_3, $-CH_2F$, $-CHF_2$, and $-CF_3$. For example, in one embodiment, one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$, and one R^7 is Cl. In an alternative embodiment, one R^7 is F, and one R^7 is selected from the group consisting of halogen, CH_3, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, CH_3, $-CH_2F$, $-CHF_2$, and $-CF_3$; more preferably one R^7 is F and one R^7 is Cl. In these embodiments, it is preferred that one of these two R^7 groups is attached to one of the C ring atoms at positions 2 and 5 relative to the ring atom by which R^6 is bound to the remainder of the compound and the other of these two R^7 groups is attached to the other of the C ring atoms at positions 2 and 5 relative to the ring atom by which R^6 is bound to the remainder of the compound.

[158] In one embodiment of the kinase inhibitor of formula (IIa), Hy, R^2, R^3, R^4, A, L, and E are independently as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (IIIa), (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), and R^6 is selected from the group consisting of:



preferably selected from the group consisting of:

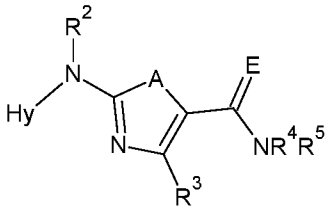


wherein in each case ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

[159] In any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), L may be selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m-[Y-(CH_2)_n]_o-$, wherein m is 1, 2, or 3, n is 0, 1, or 2, o is 1, 2, or 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and NH, wherein each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m-$, and $-(CH_2)_n-$ groups is optionally substituted with one or two independently selected R^{30}. For example, in any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), L may be selected from the group consisting of a bond; C_1 alkylene, optionally substituted with one R^{30}; C_2 alkylene (in particular 1,2-ethylene or 1,1-ethylene), optionally substituted with one R^{30}; C_3 alkylene (in particular trimethylene), optionally substituted with one R^{30}; C_4 alkylene (in particular tetramethylene or 2,4-butandiyl), optionally substituted with one R^{30}; $-(CH_2)_mO-$; and $-(CH_2)_mNH-$, wherein m is 1, 2, or 3. Particularly, in any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), L may selected from the group consisting of a bond; C_1 alkylene, optionally substituted with one R^{30}; C_2 alkylene (in particular 1,2-ethylene or 1,1-ethylene), optionally substituted with one R^{30}; $-(CH_2)O-$; and $-(CH_2)NH-$; preferably wherein L is selected from the group consisting of a bond, $-(CH_2)-$, and $-(CH_2)_2-$.

[160] Most preferably, in any of the above embodiments of the kinase inhibitor of formula (IIa) (including those of formula (Ia)), L is a bond (i.e., R^5 is R^6).

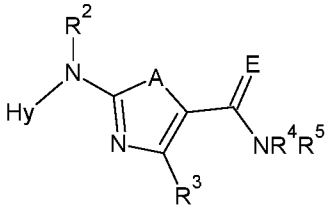
[161] In one embodiment, the kinase inhibitor has the formula (IIIa):



(IIIa)

wherein Hy, R^2, R^3, R^4, and R^5 are independently as defined above (in particular with respect to formula (Ia) and/or (IIa)) or below (in particular with respect to formula (IVa), (Va), (VIa), (VIIa), and/or (VIIIa)), E is O or S (preferably O); and A is selected from the group consisting of S, O, NH, $N(C_{1-6}$ alkyl), and $C(C_{1-6}$ alkyl$)_2$. In any of the above embodiments of the kinase inhibitor of formula (IIIa) (including those of formulas (Ia) and (IIa)), E is O or S (preferably O); and A may be S, O, or $N(CH_3)_2$. In any of the above embodiments of the kinase inhibitor of formula (IIIa) (including those of formulas (Ia) and (IIa)), it is preferred that E is O or S (preferably O); and A is S. In any of the above embodiments of the kinase inhibitor of formula (IIIa) (including those of formulas (Ia) and (IIa)), it is preferred that E is O; and A is S.

[162] In one embodiment, the kinase inhibitor has the formula (IVa):



(IVa)

wherein Hy, R^2, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa) and/or (IIIa)) or below (in particular with respect to formula (Va), (VIa), (VIIa), and/or (VIIIa)), and R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, $-NO_2$, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, or phenyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}.

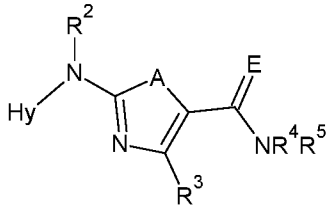
[163] In one embodiment of the kinase inhibitor of formula (IVa), Hy, R^2, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), and/or (IIIa)) or below (in particular with respect to formula (Va), (VIa), (VIIa), and/or (VIIIa)), and R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)$_2$, $-C(=O)(C_{1-4}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl)$_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl)$_z$, and $-N(C_{1-4}$ alkyl)$C(=NH)NH_{2-z}(C_{1-4}$ alkyl)$_z$, wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl)$_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl)$_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2.

[164] In one embodiment of the kinase inhibitor of formula (IVa), Hy, R^2, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), and/or (IIIa)) or below (in particular with respect to formula (Va), (VIa), (VIIa), and/or (VIIIa)), and R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)$_2$, $-C(=O)(C_{1-4}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl)$_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl)$_z$, and $-N(C_{1-4}$ alkyl)$C(=NH)NH_{2-z}(C_{1-4}$ alkyl)$_z$, wherein the phenyl group is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl)$_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl)$_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2.

[165] In one embodiment of the kinase inhibitor of formula (IVa), Hy, R^2, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), and/or (IIIa)) or below (in particular with respect to formula (Va), (VIa), (VIIa), and/or (VIIIa)), and R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen.

[166] In one embodiment of the kinase inhibitor of formula (IVa), Hy, R^2, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), and/or (IIIa)) or below (in particular with respect to formula (Va), (VIa), (VIIa), and/or (VIIIa)), and R^3 is H.

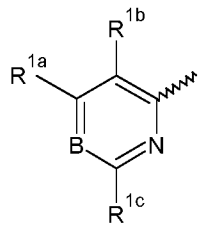
[167] In one embodiment, the kinase inhibitor has the formula (Va):



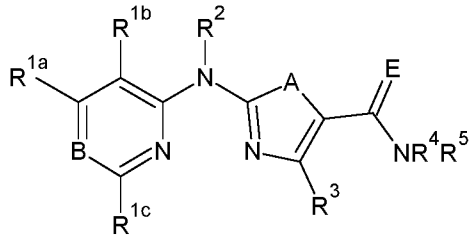
(Va)

wherein R^2, R^3, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa) and/or (IVa)) or below (in particular with respect to formula (VIa), (VIIa), and/or (VIIIa)), and Hy is a 3- to 10-membered heteroaryl or a 3- to 10-membered heterocyclyl, each of which is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the 3- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{1e}, wherein each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d}; and each of R^{1a}, R^{1b} R^{1c} and R^{1d} is independently as defined above (in particular with respect to formula (Ia)), or below (in particular with respect to formula (VIa), (VIIa), and/or (VIIIa)). For example, Hy may be selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl, a 5- to 6-membered monocyclic heterocyclyl, a 9- to 10-membered bicyclic heteroaryl, and a 8- to 10-membered bicyclic heterocyclyl, each of which is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the 5- to 6-membered monocyclic heteroaryl, 5- to 6-membered monocyclic heterocyclyl, 9- to 10-membered bicyclic heteroaryl, or 8- to 10-membered bicyclic heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{1e}, wherein each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d}; and each of R^{1a}, R^{1b} R^{1c} and R^{1d} is independently as defined above (in particular with respect to formula (Ia)), or below (in particular with respect to formula (VIa), (VIIa), and/or (VIIIa)). Preferably, Hy is a heteroaryl or heterocyclyl which contains at least one N ring atom and which is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the heteroaryl or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{1e}.

[168] In one embodiment of the kinase inhibitor of formula (Va), R^2, R^3, R^4, R^5, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa) and/or (IVa)) or below (in particular with respect to formula (VIa), (VIIa), and/or (VIIIa)), and Hy is:



wherein ~~~~ represents the bond by which Hy is bound to the remainder of the compound, such that the kinase inhibitor of formula (Va) has the formula (VIa):



(VIa)

wherein R^{1a}, R^{1b}, and R^{1c} are as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)); and B is N or CR^{1d}, wherein R^{1d} is as defined above (in particular with respect to formula (Ia)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)).

[169] In one embodiment of the kinase inhibitor of formula (VIa), R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa) and/or (Va)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)), and R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}. It is preferred that the one or more independently selected R^{30} optionally substituting R^{1a} are independently selected from a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein; more preferred the one or more independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[170] In one embodiment of the kinase inhibitor of formula (VIa), R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa) and/or (Va)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)), and R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 11-membered heterocyclyl, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein; more preferred the one or more independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

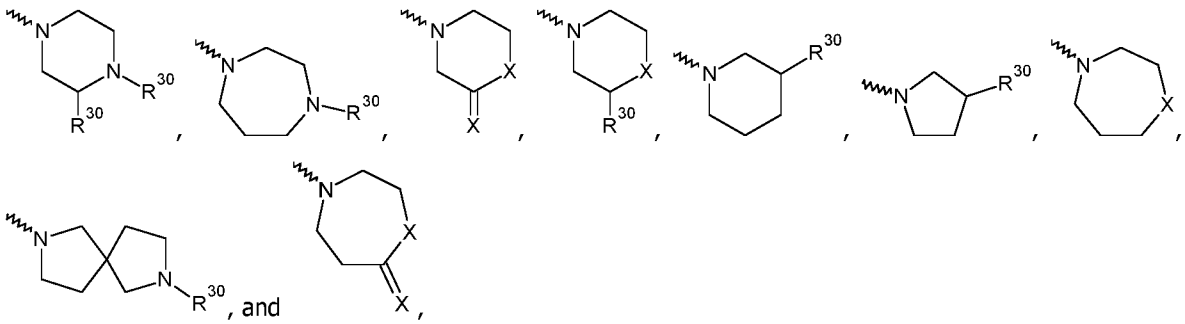
[171] In one embodiment of the kinase inhibitor of formula (VIa), R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa) and/or (Va)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)), and R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononanyl, diazaspirononanyl, azaspirodecanyl, diazaspirodecanyl, azaspiroundecanyl, and diazaspiroundecanyl, wherein each of the piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononyl, diazaspirononyl, azaspirodecyl, diazaspirodecyl, azaspiroundecyl, and diazaspiroundecyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein; more preferred the one or more independently selected R^{30} optionally substituting R^{1a} are independently selected fromthe group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-

(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[172] In one embodiment of the kinase inhibitor of formula (VIa), R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa) and/or (Va)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)), and R^{1a} is selected from the group consisting of -NH(C_{1-3} alkyl), piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl, wherein each of the piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, -OH, =O, -OCH_3, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(methoxy)ethoxy, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[173] In one embodiment of the kinase inhibitor of formula (VIa), R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa) and/or (Va)) or below (in particular with respect to formula (VIIa) and/or (VIIIa)), and R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

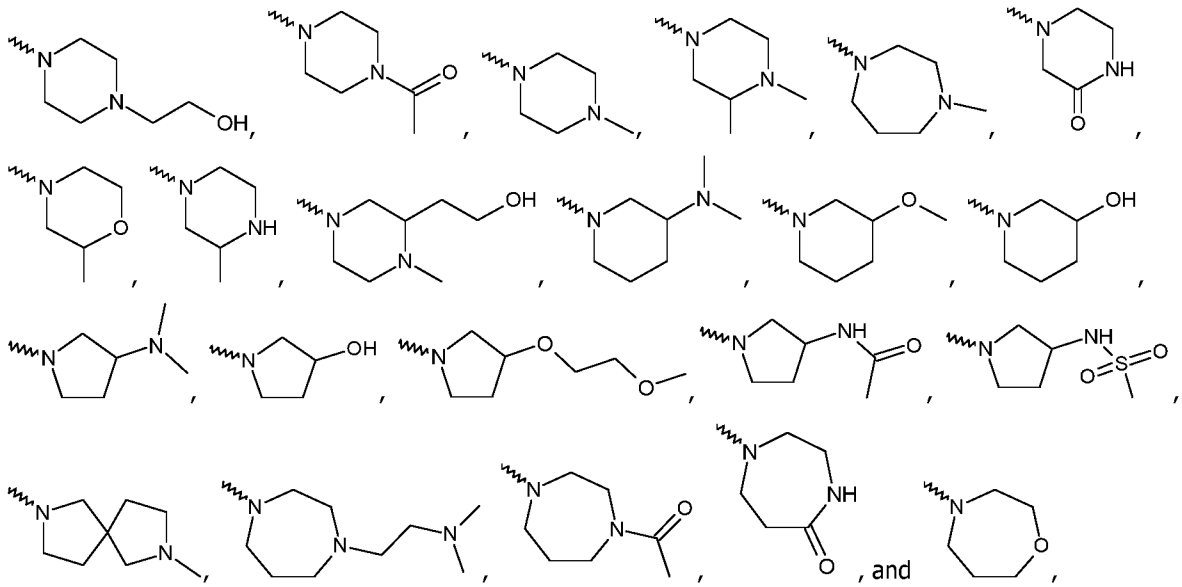
[174] In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), R^{1a} may be non-symmetrical. For example, R^{1a} may be selected from the following groups:



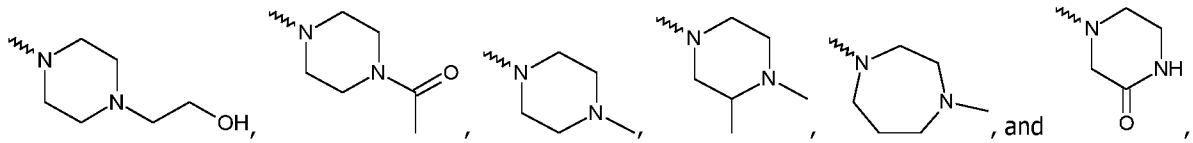
wherein R^{30} and X are as defined herein; and ~~~ represents the bond by which the R^{1a} group is bound to the remainder of the compound. In one embodiment, R^{1a} is non-symmetrical and selected from the group consisting of 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

[175] In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound may be an atom other than C; preferably, the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an N atom. In this embodiment, R^{1a} is preferably selected from the group consisting of heterocyclyl, heteroaryl, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the heterocyclyl and heteroaryl groups is bound to the remainder of the compound via an atom other than C and is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the heterocyclyl or heteroaryl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}. For example, R^{1a} may be heterocyclyl which contains at least one N ring atom and which is bound to the remainder of the compound via an N ring atom.

[176] In one embodiment of the kinase inhibitor of formula (VIa), R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa) and/or (Va)) or below, and R^{1a} is selected from the group consisting of:



wherein ~~~ represents the bond by which R^{1a} is bound to the remainder of the compound. Preferably, R^{1a} is selected from the group consisting of:



wherein ~~~ represents the bond by which R^{1a} is bound to the remainder of the compound.

[177] In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), each of R^{1b} and R^{1c} may be independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2. Preferably, at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-

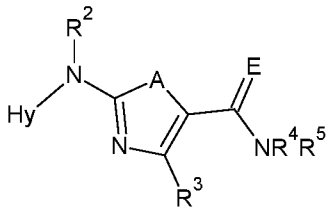
hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, -$NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2. In one embodiment, R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl. In an alternative embodiment, R^{1b} is methyl, ethyl, propyl, or isopropyl, preferably methyl; and R^{1c} is H.

[178] In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), the atom of R^{1c} by which R^{1c} is bound to the remainder of the compound may be a C atom. In this embodiment, it is preferred that R^{1c} is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CF_3, -CN, -C(=O)(C_{1-6} alkyl), -C(=O)OH, -C(=O)O(C_{1-6} alkyl), and -C(=O)NH_{2-z}(C_{1-6} alkyl)$_z$, wherein z is 0, 1, or 2 and each of the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl groups is optionally substituted with one, two, or three moieties independently selected from the group consisting of -OH, methyl, ethyl, -OCH_3, -SCH_3, and -$NH_{2-z}(CH_3)_z$.

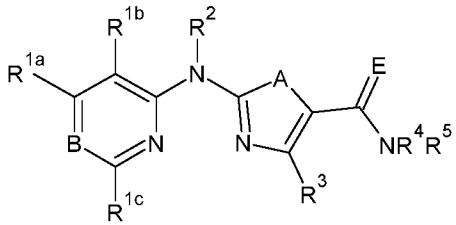
[179] In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), B is N or CR^{1d}, wherein R^{1d} may be selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, -OCH_3, -SCH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2. In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), B is N or CR^{1d}, wherein R^{1d} may be selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$.

[180] In any of the above embodiments of the kinase inhibitor of formula (VIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), and/or (Va)), it is most preferred that B is N.

[181] In one embodiment, the kinase inhibitor has the general formula (VIIa) or (VIIIa):



(VIIa)



(VIIIa)

wherein Hy, R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, R^5, A, B, and E are as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa)) or below, and is L is a bond. In preferred embodiments of the kinase inhibitor having the general formula (VIIa) or (VIIIa):

(A) R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the alkyl or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}, wherein, preferably, each R^{30} is independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and/or

(B) each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and/or

(C) R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, $-NO_2$, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), $-C(=O)OH$, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30}, preferably wherein R^3 is H; and/or

(D) at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, $-OR^{11}$, and $-N(R^{12})(R^{13})$, wherein each of the alkyl and R^{11} groups and at least one of the R^{12} and R^{13} groups is substituted with one or more F atoms; and/or

(E) A is selected from the group consisting of S, O, NH, N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$, preferably wherein A is S; and/or

(F) B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, $-OCH_3$, -SCH, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein B is N; and/or

(G) E is O or S, preferably O.

[182] In a preferred embodiment of the kinase inhibitor having the general formula (VIIa) or (VIIIa), R^{1a} is as specified above under (A); R^{1b} and R^{1c} are as defined above under (B); R^3 is as specified above under (C); R^7 is as defined above under (D), wherein R^6 is as specified above (in particular with respect to formula (IIa)); A is as specified above under (E); B is as specified above under (F); and E is as specified above under (G).

[183] In further preferred embodiments of the kinase inhibitor having the general formula (VIIa)or (VIIIa):

(A') R^{1a} is selected from the group consisting of C_{1-3} alkyl, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, and 3- to 11-membered heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$C(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$S(O)_2(C_{1-3}$ alkyl), $-(CH_2)_{1-3}COOH$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and/or

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2, and the other of R^{1b} and R^{1c} is as defined above under (B), preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and/or

(C') R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)$_2$, $-C(=O)(C_{1-4}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl)$_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl)$_z$, and $-N(C_{1-4}$ alkyl)$C(=NH)NH_{2-z}$ (C_{1-4} alkyl)$_z$, wherein the phenyl group is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl)$_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl)$_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2, preferably wherein R^3 is H; and/or

(D') at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl)$_2$ is substituted with one or more F atoms;

(E') A is S, O, or $N(CH_3)_2$, preferably wherein A is S; and/or

(F') B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl)$_2$, preferably wherein B is N; and/or

(G') E is O or S, preferably O.

[184] In a preferred embodiment of the kinase inhibitor having the general formula (VIIa) or (VIIIa), R^{1a} is as specified above under (A'); R^{1b} and R^{1c} are as defined above under (B'); R^3 is as specified above under (C'); R^7 is as defined above under (D'), wherein R^6 is as specified above (in particular with respect to formula (IIa)); A is as specified above under (E'); B is as specified above under (F'); and E is as specified above under (G').

[185] In further preferred embodiments of the kinase inhibitor having the general formula (VIIa)or (VIIIa):

(A'') R^{1a} is a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$C(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$S(O)_2(C_{1-3}$ alkyl), $-(CH_2)_{1-3}COOH$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and/or

(B'') one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and/or

(C'') R^3 is H; and/or

(D'') at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl)$_2$ is substituted with one or more F atoms;

(E'') A is S; and/or

(F'') B is N; and/or

(G'') E is O.

[186] In a preferred embodiment of the kinase inhibitor having the general formula (VIIa) or (VIIIa), R^{1a} is as specified above under (A''); R^{1b} and R^{1c} are as defined above under (B''); R^3 is as specified above under (C''); R^7 is as defined above under (D''), wherein R^6 is as specified above (in particular with respect to formula (IIa)); A is as specified above under (E''); B is as specified above under (F''); and E is as specified above under (G'').

[187] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$.

[188] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), one R^7 (preferably the R^7 which is F and/or the R^7 which is substituted with one or more F atoms) is attached to the C ring atom at position 2 or 5 relative to the ring atom by which R^6 is bound to the remainder of the compound.

[189] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), R^6 is substituted with at least two R^7. For example, R^6 may be substituted with two R^7 which differ from each other.

[190] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), R^6 is substituted with at least two R^7, wherein one R^7 (preferably the R^7 which is F and/or the R^7 which is substituted with one or more F atoms) is attached to one of the C ring atoms at positions 2 and 5 relative to the ring atom by which R^6 is bound to the remainder of the compound and one R^7 is attached to the other of the C ring atoms at positions 2 and 5 relative to the ring atom by which R^6 is bound to the remainder of the compound.

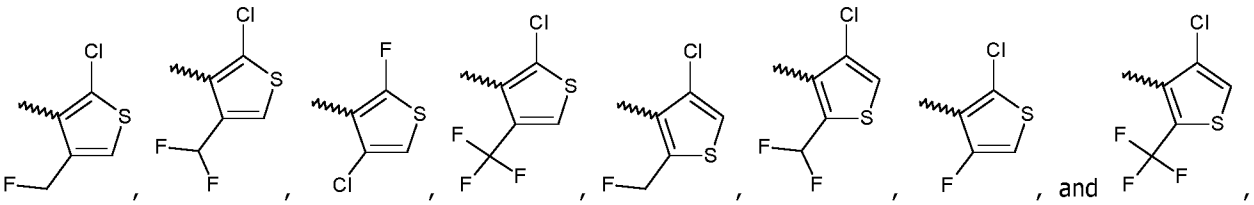
[191] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), R^6 is substituted with at least two R^7, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, and one R^7 is selected from the group consisting of halogen, $-CH_3$, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, $-CH_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In one embodiment, one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$, and one R^7 is Cl. In an alternative embodiment, one R^7 is F, and one R^7 is selected from the group consisting of halogen, CH_3, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, CH_3, $-CH_2F$, $-CHF_2$, and $-CF_3$. In this alternative embodiment, it is preferred that one R^7 is F and one R^7 is Cl.

[192] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), R^6 is selected from the group consisting of thienyl, thiazolyl, and thiadiazolyl, preferably selected from the group consisting of thienyl and thiazolyl, more preferably R^6 is thienyl, wherein each of the thienyl, thiazolyl, and thiadiazolyl groups is substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the thienyl, thiazolyl, or thiadiazolyl group, e.g., 1, 2, or 3, such as 1 or 2) independently selected R^7.

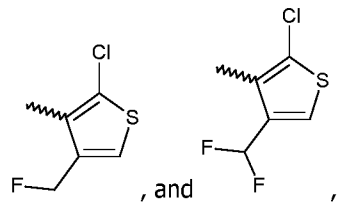
[193] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), the ring atom of R^6 by which R^6 is bound to the remainder of the compound is a C atom.

[194] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound.

[195] In further preferred embodiments of the kinase inhibitor having general formula (VIIa) or (VIIIa) (in particular when R^{1a}, R^{1b}, R^{1c}, R^3, A, B, and E are as specified above under (A), (B), (C), (E), (F), and/or (G), or under (A'), (B'), (C'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (E''), (F''), and/or (G'')), R^6 is selected from the group consisting of:



preferably selected from the group consisting of:



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

[196] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa)), R^{1a} may be selected from the group consisting of -NH(C_{1-3} alkyl), piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl, wherein each of the piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, -OH, =O, -OCH_3, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(methoxy)ethoxy, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2. For example, R^{1a} may be selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

[197] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa), in particular when R^{1a}, R^{1b}, R^{1c}, R^3, R^7, A, B, and E are as specified above under (A), (B), (C), (D), (E), (F), and/or (G), or under (A'), (B'), (C'), (D'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (D''), (E''), (F''), and/or (G'')), R^{1a} may be non-symmetrical.

[198] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa), in particular when R^{1a}, R^{1b}, R^{1c}, R^3, R^7, A, B, and E are as specified above under (A), (B), (C), (D), (E), (F), and/or (G), or under (A'), (B'), (C'), (D'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (D''), (E''), (F''), and/or (G'')), the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound may be an atom other than C; preferably, the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an N atom.

[199] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa), in particular when R^{1a}, R^{1b}, R^{1c}, R^3, R^7, A, B, and E are as specified above under (A), (B), (C), (D), (E), (F), and/or (G), or under (A'), (B'), (C'), (D'), (E'), (F'), and/or (G'), or under (A''), (B''), (C''), (D''), (E''), (F''), and/or (G'')), the atom of R^{1c} by which R^{1c} is bound to the remainder of the compound may be a C atom.

[200] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa)), it is preferred that R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl.

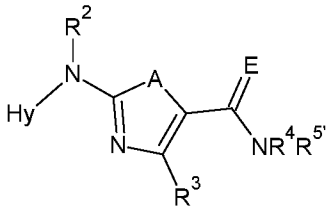
[201] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa)), it is preferred that A is S; B is N; and/or E is O.

[202] More preferably, in any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa)), A is S; B is N; and E is O.

[203] In any of the above embodiments of the kinase inhibitor of formula (VIIa) or (VIIIa) (including those of formula (Ia), (IIa), (IIIa), (IVa), (Va), and/or (VIa)), R^3 is preferably selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen; more preferably, R^3 is H.

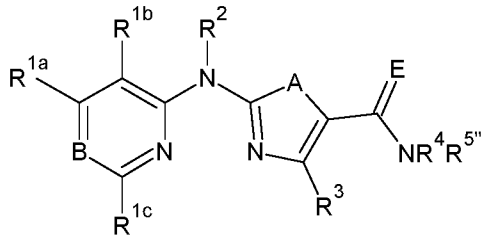
[204] In one embodiment, the compound of the invention is selected from the compounds shown in Figure 1E.

[205] In the context of the fifth aspect, the present application provides a compound for use, or a pharmaceutical composition for use, in a treatment of a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, wherein the compound is selected from (a) the compound of the first aspect; (b) a compound of the following formula (Ib); and (c) a compound of the following formula (Ic), or the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient:



(Ib)

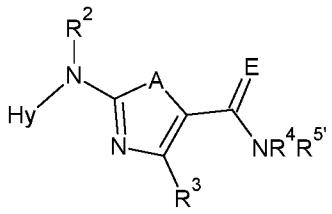
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof, wherein Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ia), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below; $R^{5'}$ is -L-$R^{6'}$; L is a bond; $R^{6'}$ is a 5- or 6-membered heteroaryl which is optionally substituted with one or more independently selected $R^{7'}$; $R^{7'}$ is independently selected from the group consisting of R^7, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, -NO_2, -OR^{11}, -$N(R^{12})(R^{13})$, -$N(R^{11})(OR^{11})$, -$S(O)_{0-2}R^{11}$, -$S(O)_{1-2}OR^{11}$, -$OS(O)_{1-2}R^{11}$, -$OS(O)_{1-2}OR^{11}$, -$S(O)_{1-2}N(R^{12})(R^{13})$, -$OS(O)_{1-2}N(R^{12})(R^{13})$, -$N(R^{11})S(O)_{1-2}R^{11}$, -$NR^{11}S(O)_{1-2}OR^{11}$, -$NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, -$P(O)(OR^{11})_2$, -$OP(O)(OR^{11})_2$, -$C(=X)R^{11}$, -$C(=X)XR^{11}$, -$XC(=X)R^{11}$, and -$XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}; and R^{11}, R^{12}, R^{13}, X, and R^{30} are independently as defined above (in particular with respect to formula (Ia));



(Ic)

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are independently as defined above (in particular with respect to formula (Ia), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below; $R^{5''}$ is -L-$R^{6''}$; L is as defined above (in particular with respect to formula (Ia) and/or (IIa)); $R^{6''}$ is heteroaryl or heterocyclyl, each of which is optionally substituted with one or more independently selected $R^{7'}$; $R^{7'}$ is independently selected from the group consisting of R^7, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0\text{-}2}R^{11}$, $-S(O)_{1\text{-}2}OR^{11}$, $-OS(O)_{1\text{-}2}R^{11}$, $-OS(O)_{1\text{-}2}OR^{11}$, $-S(O)_{1\text{-}2}N(R^{12})(R^{13})$, $-OS(O)_{1\text{-}2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1\text{-}2}R^{11}$, $-NR^{11}S(O)_{1\text{-}2}OR^{11}$, $-NR^{11}S(O)_{1\text{-}2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, and/or any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ being a heterocyclyl group may join together to form =O, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}; and R^{11}, R^{12}, R^{13}, X, and R^{30} are independently as defined above (in particular with respect to formula (Ia)).

[206] In one embodiment, the compound of formula (Ib) for use according to the fifth aspect has the general formula (IIb)



(IIb)

wherein Hy, R^2, R^3, R^4, A, and E are as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is a 5- or 6-membered heteroaryl optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the 5- or 6-membered heteroaryl group, e.g., 1, 2, 3, 4, 5, such as between 1 to 4, or 1 to 3, or 1 or 2) independently selected $R^{7'}$ (in particular as defined herein, eg with respect to formula (Vc) below).

[207] In one embodiment of the compound of formula (IIb) for use according to the fifth aspect, Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is a 5- or 6-membered heteroaryl group as defined for $R^{6''}$ below (in particular with respect to formula (Vc)).

[208] In one embodiment of the compound of formula (IIb) for use according to the fifth aspect, Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is a 5- or 6-membered heteroaryl (in particular a 5- to 6-membered monocyclic heteroaryl) containing at least one ring heteroatom selected from the group consisting of N, O, and S, wherein the 5- or 6-membered heteroaryl is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the 5- or 6-membered heteroaryl group, e.g., 1, 2, 3, 4, 5, such as between 1 to 4, or 1 to 3, or 1 or 2) independently selected $R^{7'}$ (in particular as defined herein, eg with respect to formula (Vc) below). For example, $R^{6'}$ may be a 5- or 6-membered heteroaryl containing at least one ring heteroatom selected from the group consisting of N and O (i.e., the heteroaryl does not contain S as ring heteroatom; and in some

embodiments does not contain O as ring heteroatom, i.e., $R^{6'}$ may by an N-heteroaryl), wherein the 5- or 6-membered heteroaryl group is optionally substituted with one, two, or three independently selected $R^{7'}$ (in particular as defined herein, eg with respect to formula (Vc) below).

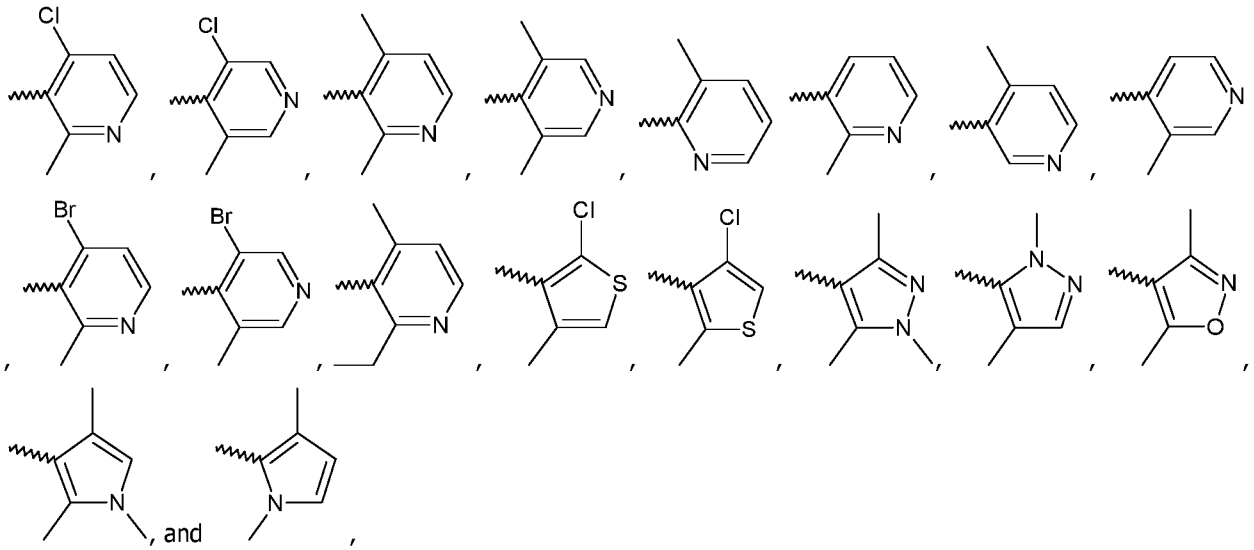
[209] In one embodiment of the compound of formula (IIb) for use according to the fifth aspect, Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is selected from the group consisting of pyridinyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, and oxadiazolyl, each of which is optionally substituted with one, two, or three independently selected $R^{7'}$ (in particular as defined herein, eg with respect to formula (Vc) below), preferably $R^{6'}$ is selected from the group consisting of pyridinyl, thienyl, pyrazolyl, isoxazolyl, and pyrrolyl, each of which is optionally substituted with one, two, or three independently selected $R^{7'}$ (in particular as defined herein, eg with respect to formula (Vc) below).

[210] In any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), $R^{7'}$ may be independently selected from the group consisting of R^7, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -NHS(O)$_{1-2}$(C_{1-6} alkyl), -NHS(O)$_{1-2}$O(C_{1-6} alkyl), -C(=O)(C_{1-6} alkyl), and -OC(=O)(C_{1-6} alkyl), wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl groups is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30} (wherein each R^{30} is preferably selected from a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein). For example, $R^{7'}$ may be independently selected from the group consisting of C_{1-3} alkyl, halogen, -CN, -O(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or more (e.g., 1 to the maximum number of hydrogen atoms bound to the C_{1-3} alkyl group, e.g., 1, 2, 3, 4, 5, 6, 7, or up to 6, such as 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30} (wherein each R^{30} is preferably selected from a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein). In any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), $R^{7'}$ may be independently selected from the group consisting of Cl, Br, methyl, and ethyl, such as from the group consisting of Cl, Br, and methyl. In another of any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), $R^{7'}$ may be independently R^7, such as any R^7 as may be defined in connection with formula (Ia).

[211] In any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), where $R^{6'}$ is substituted, it is preferred that one $R^{7'}$ group is bound to a ring atom of $R^{6'}$ at position 2 relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound (i.e., it is preferred that $R^{6'}$ bears an ortho $R^{7'}$ group). In any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), where $R^{6'}$ is substituted with two or more (such as two, three, or four) $R^{7'}$ groups, it is preferred that one of the two or more $R^{7'}$ groups is bound to a ring atom of $R^{6'}$ at position 2 relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound (i.e., $R^{6'}$ bears an ortho $R^{7'}$ group), and the remaining $R^{7'}$ group(s) is (are) attached to ring atom(s) of $R^{6'}$ at positions other than position 2. E.g., in any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), where $R^{6'}$ is an k-membered ring substituted with two or more $R^{7'}$ groups, it is preferred that one of the two or more $R^{7'}$ groups is bound to a ring atom of $R^{6'}$ at position 2 relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound (i.e., relative to the yl position) and that the remaining $R^{7'}$ group(s) is (are) bound to ring atoms of $R^{6'}$ at positions other than position 2, e.g., at position 3, 4, 5, … k. For example, in case $R^{6'}$ is a 5-membered ring, it is preferred that one of the two or more $R^{7'}$ groups is bound to a ring atom of $R^{6'}$ at position 2 (relative to the yl position) and that the remaining $R^{7'}$ group(s) is (are) bound to ring atoms of $R^{6'}$ at positions 3, 4, or 5 (relative to the yl position). Moreover, in any of the above embodiments of the compound of formula (IIb) for use

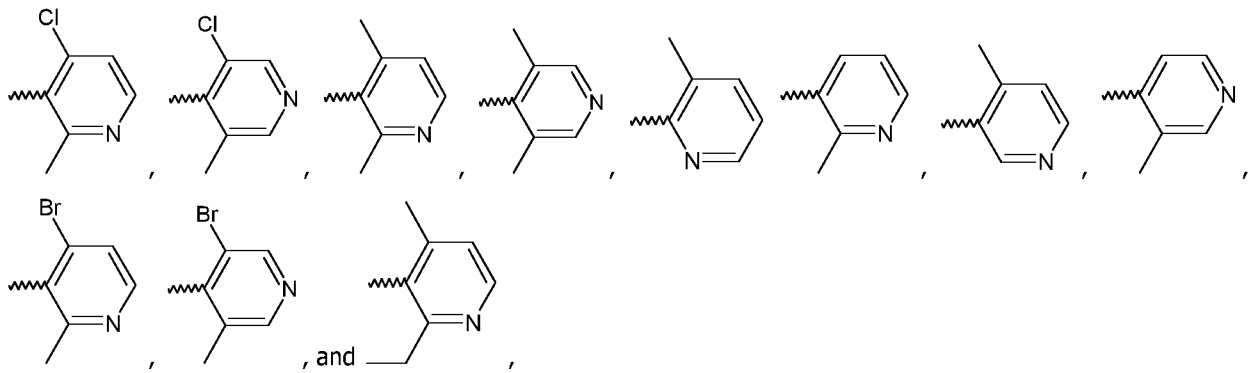
according to the fifth aspect (including those of formula (Ib)), where $R^{6'}$ is substituted with two or more (such as two, three, or four) $R^{7'}$ groups, it is preferred that each of the two ring atoms directly adjacent to the ring atom by which $R^{6'}$ is attached to the remainder of the compound bears one $R^{7'}$ group (e.g., $R^{6'}$ being an k-membered ring bears one $R^{7'}$ group at each of positions 2 and k, relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound, e.g., $R^{6'}$ is substituted at both of its ortho positions). Additionally, in any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), where $R^{6'}$ is substituted with three or more (such as three or four) $R^{7'}$ groups, it is preferred that each of the two ring atoms directly adjacent to the ring atom by which $R^{6'}$ is attached to the remainder of the compound bears one $R^{7'}$ group (e.g., $R^{6'}$ being an k-membered ring bears one $R^{7'}$ group at each of positions 2 and k, relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound, e.g., $R^{6'}$ is substituted at both of its ortho positions), and that the third $R^{7'}$ group is bound to a ring atom of $R^{6'}$ which is directly adjacent to one of the ortho ring atoms but which is not the ring atom by which $R^{6'}$ is bound to the remainder of the compound (e.g., $R^{6'}$ being an k-membered ring bears the third $R^{7'}$ group at one of positions 3 and k-1, relative to the ring atom by which $R^{6'}$ is bound to the remainder of the compound).

[212] In one embodiment of the compound of formula (IIb) for use according to the fifth aspect Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is selected from the following formulas:



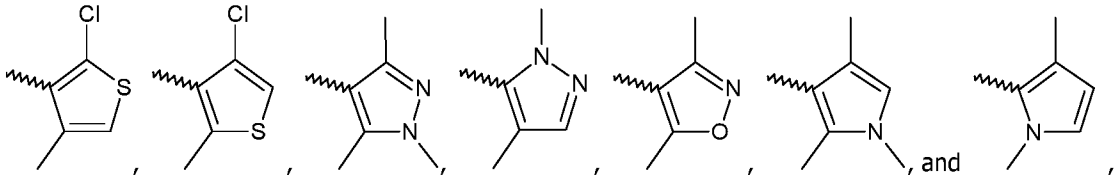
wherein ~~~ represents the bond by which $R^{6'}$ is bound to the remainder of the compound.

[213] In one embodiment of the compound of formula (IIb) for use according to the fifth aspect, Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is selected from the following formulas:



wherein ~~~ represents the bond by which $R^{6'}$ is bound to the remainder of the compound.

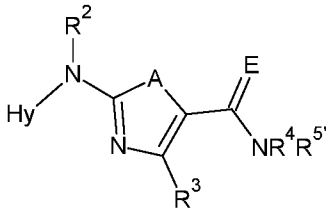
[214] In one embodiment of the compound of formula (IIb) for use according to the fifth aspect, Hy, R^2, R^3, R^4, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIb)), and $R^{6'}$ is selected from the following formulas:



wherein ~~~ represents the bond by which $R^{6'}$ is bound to the remainder of the compound.

[215] In any of the above embodiments of the compound of formula (IIb) for use according to the fifth aspect (including those of formula (Ib)), where $R^{6'}$ is a 5- or 6-membered heteroaryl containing an N atom as ring heteroatom, $R^{6'}$ may be attached to the remainder of the compound via the N ring atom of the 5- or 6-membered heteroaryl group.

[216] In one embodiment, the compound of formula (Ib) for use according to the fifth aspect has the general formula (IIIb)



(IIIb)

wherein R^2, R^3, R^4, $R^{5'}$, A, and E are as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is a heteroaryl or heterocyclyl which is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the heteroaryl or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{1e}; each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d}; and each of R^{1a}, R^{1b} R^{1c} and R^{1d} is independently as defined above (in particular with respect to formula (Ia), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIc), (IIIc), (VIIc) and/or (VIIIc)).

[217] In one embodiment of the compound of formula (IIIb), R^2, R^3, R^4, $R^{5'}$, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is as defined above (in particular with respect to formula (Va), (VIa), (VIIa) and/or (VIIIa)).

[218] In one embodiment of the compound of formula (IIIb), R^2, R^3, R^4, $R^{5'}$, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is a 3- to 10-membered heteroaryl or a 3- to 10-membered heterocyclyl, each of which is optionally substituted with one, two, three, four, five, or six independently selected R^{1e} as defined herein (in particular with respect to formula (Ib), (IIIb), (Ia), and/or (Va)).

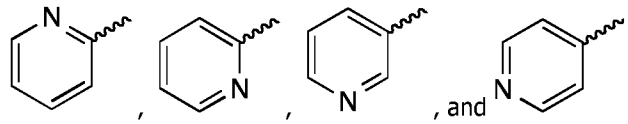
[219] In one embodiment of the compound of formula (IIIb), R^2, R^3, R^4, $R^{5'}$, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is a mono- or bicyclic heteroaryl or a mono- or bicyclic heterocyclyl, each of which is optionally substituted with one, two, three, four, five, or six independently selected R^{1e} (in particular with respect to formula (Ib), (IIIb), (Ia), and/or (Va)).

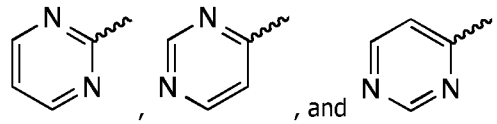
[220] In one embodiment of the compound of formula (IIIb), R^2, R^3, R^4, $R^{5'}$, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is selected from the group consisting of a 5- to 6-membered

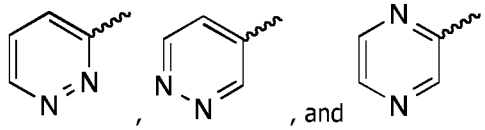
monocyclic heteroaryl, a 5- to 6-membered monocyclic heterocyclyl, a 9- to 10-membered bicyclic heteroaryl, and a 8- to 10-membered bicyclic heterocyclyl, each of which is optionally substituted with one, two, three, four, five, or six independently selected R^{1e} (in particular with respect to formula (Ib), (IIIb), (Ia), and/or (Va)).

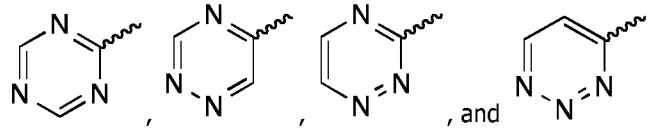
[221] In one embodiment of the compound of formula (IIIb), R^2, R^3, R^4, $R^{5'}$, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl (e.g., 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl), pyrazolyl, oxadiazolyl, thiazolyl, triazolyl, thiadiazolyl, cyclopentapyrimidinyl, dihydrocyclopentapyrimidinyl, pyrrolopyrimidinyl, indolizinyl, dihydroindolizinyl, teterahydroindolizinyl, quinazolinyl, dihydroquinazolinyl, tetrahydroquinazolinyl, pyridopyrimidinyl, pyranopyrimidinyl, dihydropyranopyrimidinyl, tetrahydropyranopyrimidinyl, piperidinyl, tetrahydropyranyl, and 1,1-dioxidotetrahydrothiopyranyl, each of which is optionally substituted with one, two, three, four, five, or six independently selected R^{1e} (in particular with respect to formula (Ib), (IIIb), (Ia), and/or (Va)).

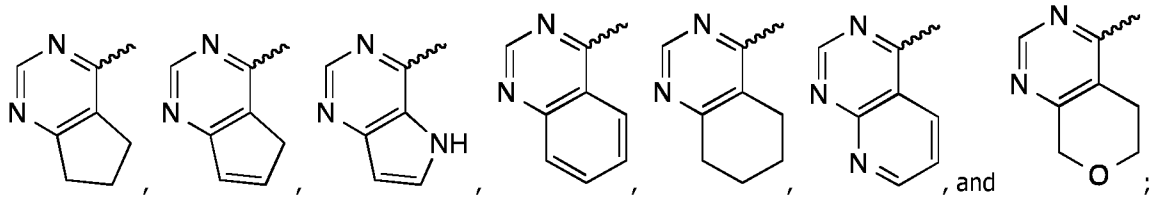
[222] In one embodiment of the compound of formula (IIIb), R^2, R^3, R^4, $R^{5'}$, A, and E are independently as defined above (in particular with respect to formula (Ib), (IIb), (IIIa), (IVa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (VIc) and/or (VIIc)), and Hy is selected from the group consisting of:

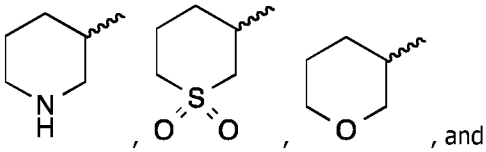
a)  ;

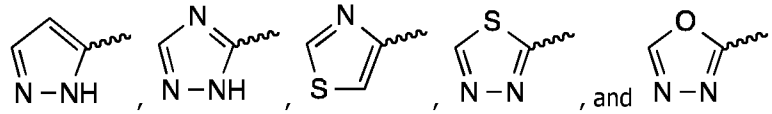
b)  ;

c)  ;

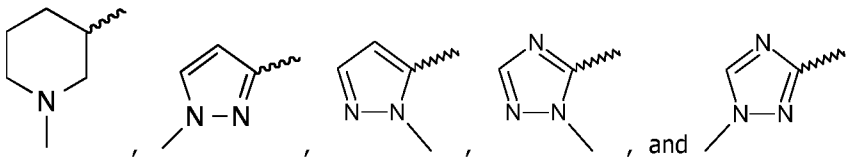
d)  ;

e)  ;

f)  ; and/or

g)  ,

wherein each of the groups specified under a), b), c), d), e), f), and g) above is optionally substituted with one, two, three, four, five, or six independently selected R^{1e} (in particular with respect to formula (Ib), (IIIb), (Ia), and/or (Va)), and wherein ∿∿∿ represents the bond by which Hy is attached to the nitrogen atom of the NR^2 moiety in formula (IIIb). In case Hy contains an NH moiety as ring member, it is preferred that the hydrogen atom is replaced with alkyl, such as C_{1-6} or C_{1-3} alkyl, more preferably methyl (resulting in an alkyl substituted N ring atom), and Hy is optionally

further substituted with one, two, three, four, or five independently selected R^{1e}. Examples of such N alkyl substituted Hy groups include  , and , wherein represents the bond by which Hy is attached to the nitrogen atom of the NR^2 moiety in formula (Ib).

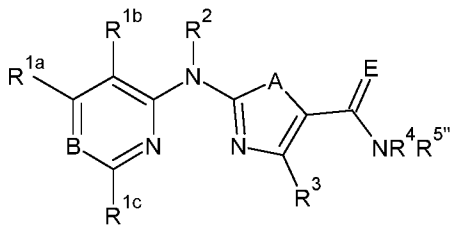
[223] In any of the above embodiments of the compound of formula (IIIb), Hy may be substituted with one R^{1b}, one R^{1c} and between 1 and 4, such as 1, 2 or 3, R^{1a} or R^{1d}; for example, Hy may be substituted with one (or two) R^{1a} and (as defined above, in particular with respect to formula (VIa), (VIIa) and/or (VIIIa), or below, in particular with respect to formula (IIc) and/or (VIIIc)), and with one (or two) of R^{1b} or R^{1c} (as defined above, in particular with respect to formula (VIa), (VIIa) and/or (VIIIa), or below, in particular with respect to formula (IIIc) and/or (VIIIc)), and all other R^{1e} are H.

[224] In any of the above embodiments of the compound of formula (Ib), (IIb), and (IIIb), it is preferred that A is S and/or E is O.

[225] In any of the above embodiments of the compound of formula (Ib), (IIb), and (IIIb), it is preferred that R^3 is H.

[226] In any of the above embodiments of the compound of formula (Ib), (IIb), and (IIIb), it is preferred that A is S and/or E is O and/or R^3 is H. For example, in one embodiment of the compound of formula (Ib), (IIb), and (IIIb), A is S; E is O; and R^3 is H.

[227] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (IIc)



(IIc)

wherein R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIc), (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more (e.g., one, two, or three) independently selected R^{30}. Preferably, each R^{30} is independently a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as alkyl (e.g., C_{1-6} alkyl), -$(CH_2)_{1-3}$OH, alkenyl (e.g., C_{2-6} alkenyl), alkynyl (e.g., C_{2-6} alkynyl), halogen, -CN, nitro, -OR^{11} (e.g., -OH), -SR^{11} (e.g., -SH), -$N(R^{12})(R^{13})$ (e.g., -NH_2), and -$C(=O)R^{11}$ (e.g., -C(=O)(C_{1-3} alkyl)).

[228] In one embodiment of the compound of formula (IIc), R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIc), (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 7-membered heterocyclyl, wherein the 3- to 7-membered heterocyclyl group is optionally substituted with one or two moieties independently selected from the group consisting of methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -

SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

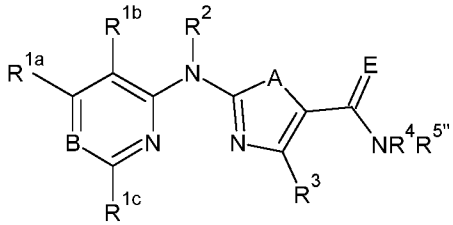
[229] In one embodiment of the compound of formula (IIc), R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIc), (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1a} is selected from the group consisting of C_{1-3} alkyl, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), piperazinyl, morpholinyl, piperidinyl, and pyrrolidinyl, wherein each of the piperazinyl, morpholinyl, piperidinyl, and pyrrolidinyl groups is optionally substituted with one or two moieties independently selected from the group consisting of methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, $-C(=O)(C_{1-3}$ alkyl), $-(CH_2)_{1-3}COOH$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[230] In one embodiment of the compound of formula (IIc), R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIc), (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1a} is selected from the group consisting of $-NH(C_{1-3}$ alkyl), piperazinyl, piperidinyl, and pyrrolidinyl, wherein the piperazinyl group is optionally substituted with one or two moieties independently selected from the group consisting of 2-hydroxyethyl, methyl, $-CH_2COOH$, and $-C(=O)CH_3$; the piperidinyl group is optionally substituted with one or two moieties independently selected from the group consisting of $-NH_2$ and 4-methylpiperazinyl; the pyrrolidinyl is optionally substituted with one or two -OH; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[231] In one embodiment of the compound of formula (IIc), R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIc), (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 4-acetylpiperazinyl, (2-hydroxyethyl)amino, 4-aminopiperidinyl, 4-(4-methylpiperazinyl)piperidinyl, (4-carboxymethylpiperazinyl), and 3-hydroxypyrrolidinyl, such as from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 4-acetylpiperazinyl, and (2-hydroxyethyl)amino.

[232] In an alternative embodiment of the compound of formula (IIc), R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IIIc), (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1a} is a leaving group (e.g., a halogen (such as Cl, Br, or F), nitro, benzotriazol-1-yloxy, C_1-C_{10} alkylsulfonate, C_1-C_{10} haloalkylsulfonate, nonaflate ($CF_3CF_2CF_2CF_2SO_3$-), $CF_3C(=O)O$-, phenylsulfonate (wherein the phenyl is optionally substituted with 1, 2, or 3 groups which are each independently selected from halogen and C_1-C_4 alkyl), or an ammonium salt of the formula $-[N(R^x)(R^y)(R^z)]^+[G]^-$, wherein R^x, R^y, and R^z are independently hydrogen or alkyl, and G is the conjugate base of a strong acid (e.g., G^- is Cl^-)).

[233] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (IIIc)



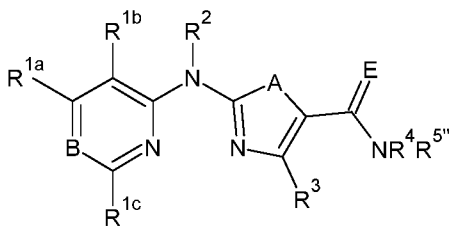
(IIIc)

wherein R^{1a}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[234] In one embodiment of the compound of formula (IIIc), R^{1a}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2. In this embodiment, the other of R^{1b} and R^{1c} may be as defined above (in particular with respect to formula (Ia), (IIa) and/or (IIIa)), e.g., the other of R^{1b} and R^{1c} may be selected from the group consisting of H, methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and wherein each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2. Alternatively, each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2.

[235] In one embodiment of the compound of formula (IIIc), R^{1a}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (IVc), (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^{1b} is methyl, ethyl, propyl, or isopropyl, preferably methyl; and R^{1c} is H. In an alternative embodiment, R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl.

[236] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (IVc)



(IVc)

wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IIIa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, $-NO_2$, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl),

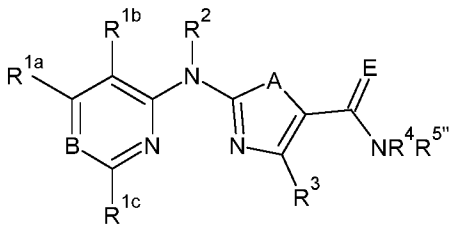
-$S(O)_2NH_{2-z}(C_{1-6}$ alkyl$)_z$, -C(=O)(C_{1-6} alkyl), -C(=O)OH, -C(=O)O(C_{1-6} alkyl), -C(=O)$NH_{2-z}(C_{1-6}$ alkyl$)_z$, -NHC(=O)(C_{1-6} alkyl), -NHC(=NH)$NH_{z-2}(C_{1-6}$ alkyl$)_z$, and -N(C_{1-6} alkyl)C(=NH)$NH_{2-z}(C_{1-6}$ alkyl$)_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30}.

[237] In one embodiment of the compound of formula (IVc), R^{1a}, R^{1b}, R^{1c}, R^2, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IIIa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, -O(C_{1-4} alkyl), -OCF_3, -S(C_{1-4} alkyl), -NH_2, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)$_2$, -C(=O)(C_{1-4} alkyl), -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)$NH_{2-z}(C_{1-4}$ alkyl$)_z$, -NHC(=O)(C_{1-4} alkyl), -NHC(=NH)$NH_{z-2}(C_{1-4}$ alkyl$)_z$, and -N(C_{1-4} alkyl)C(=NH)$NH_{2-z}(C_{1-4}$ alkyl$)_z$, wherein the phenyl group is optionally substituted with one, two or groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, -CF_3, -OCF_3, -OH, -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -NHC(=O)(C_{1-3} alkyl), -C(=O)$NH_{2-z}(C_{1-3}$ alkyl$)_z$, -$(CH_2)_{1-3}NH_2$, -$(CH_2)_{1-3}$NH(C_{1-3} alkyl), -$(CH_2)_{1-3}$N(C_{1-3} alkyl)$_2$, -$(CH_2)_{1-3}$OH, and -$(CH_2)_{1-3}$O(C_{1-3} alkyl); and wherein z is 0, 1, or 2.

[238] In one embodiment of the compound of formula (IVc), R^{1a}, R^{1b}, R^{1c}, R^2, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IIIa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen.

[239] In one embodiment of the compound of formula (IVc), R^{1a}, R^{1b}, R^{1c}, R^2, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IIIa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (Vc), (VIc), (VIIc) and/or (VIIIc)), and R^3 is H.

[240] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (Vc)



(Vc)

wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{5''}$ is -L-$R^{6''}$, wherein $R^{6''}$ is a heteroaryl containing at least one ring heteroatom selected from the group consisting of N, O, and S, or is a heterocyclyl containing at least one ring heteroatom selected from the group consisting of N, O, and S, wherein each of the heteroaryl and heterocyclyl groups is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$. For example, $R^{6''}$ may be a heteroaryl containing at least one ring heteroatom selected from the group consisting of N and O (i.e., the heteroaryl does not contain S as ring heteroatom; and in some embodiments does not contain O as ring heteroatom, i.e., $R^{6''}$ may by an N-heteroaryl), or is a heterocyclyl containing at least one ring heteroatom selected from the group consisting of N and O (i.e., the heterocyclyl does not contain S as ring heteroatom; and in some embodiments does not contain O as ring heteroatom, i.e., $R^{6''}$ may by an N-heterocyclyl), wherein each of the heteroaryl and heterocyclyl groups is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

[241] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is 3- to 10-membered heteroaryl (e.g.,

containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

[242] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is a mono- or bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a mono- or bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

[243] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), a 4- to 6-membered monocyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), a 7- to 9-membered bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), and a 7- to 9-membered bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

[244] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is a 5- to 6-membered monocyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

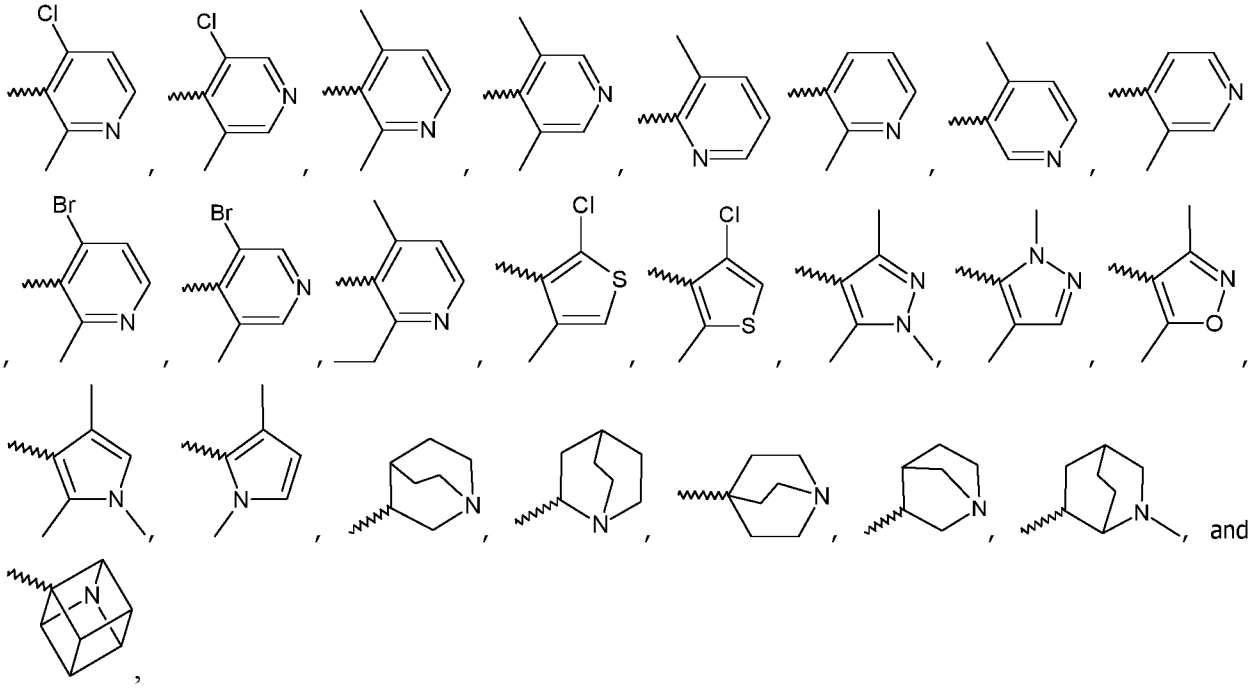
[245] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is a 7- to 9-membered bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

[246] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is selected from the group consisting of pyridinyl, thienyl, pyridazinyl, furanyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazoimidazolyl, indolyl, naphthyridinyl, thienopyridinyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, azetidinyl, azabicycloheptanyl, azabicyclooctanyl, azapentacyclooctanyl, piperazinyl, morpholinyl, and tetrahydrothiophenyl, each of which is optionally substituted with one, two, or three independently selected $R^{7'}$, preferably $R^{6''}$ is selected from the group consisting of pyridinyl, thienyl, pyrazolyl, isoxazolyl, pyrrolyl, piperidinyl, pyrrolidinyl, azetidinyl, and azabicyclooctanyl, each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$.

[247] In any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), $R^{7'}$ may be independently selected from the group consisting of R^7, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -NHS(O)$_{1-2}$(C_{1-6} alkyl), -NHS(O)$_{1-2}$O(C_{1-6} alkyl), -C(=O)(C_{1-6} alkyl), and -OC(=O)(C_{1-6} alkyl), and/or any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ being a heterocyclyl group may join together to form =O, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl groups is optionally substituted with one or more independently selected R^{30}. For example, $R^{7'}$ may be independently selected from the group consisting of R^7, C_{1-3} alkyl, halogen, -CN, -O(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, and/or any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ being a heterocyclyl group may join together to form =O, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or more independently selected R^{30}. In any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), $R^{7'}$ may be independently selected from the group consisting of Cl, Br, methyl, and ethyl, such as from the group consisting of Cl, Br, and methyl. In another of any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), $R^{7'}$ may be independently R^7, such as any R^7 as may be defined in connection with formula (Ia).

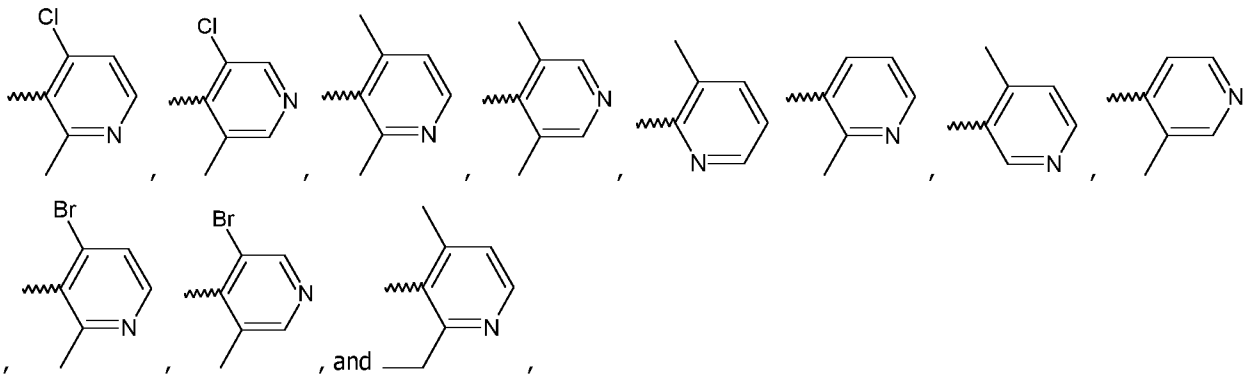
[248] In any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), where $R^{6''}$ is substituted, it is preferred that one $R^{7'}$ group is bound to a ring atom of $R^{6''}$ at position 2 relative to the ring atom by which $R^{6''}$ is bound to the remainder of the compound (i.e., it is preferred that $R^{6''}$ bears an ortho $R^{7'}$ group). In any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), where $R^{6''}$ is substituted with two or more (such as two, three, or four) $R^{7'}$ groups, it is preferred that one of the two or more $R^{7'}$ groups is bound to a ring atom of $R^{6''}$ at position 2 relative to the ring atom by which $R^{6''}$ is bound to the remainder of the compound (i.e., $R^{6''}$ bears an ortho $R^{7'}$ group), and the remaining $R^{7'}$ group(s) is (are) attached to ring atom(s) of $R^{6''}$ at positions other than position 2. E.g., in any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), where $R^{6''}$ is an k-membered ring substituted with two or more $R^{7'}$ groups, it is preferred that one of the two or more $R^{7'}$ groups is bound to a ring atom of $R^{6''}$ at position 2 relative to the ring atom by which $R^{6''}$ is bound to the remainder of the compound (i.e., relative to the yl position) and that the remaining $R^{7'}$ group(s) is (are) bound to ring atoms of $R^{6''}$ at positions other than position 2, e.g., at position 3, 4, 5, … k. For example, in case $R^{6''}$ is a 5-membered ring, it is preferred that one of the two or more $R^{7'}$ groups is bound to a ring atom of $R^{6''}$ at position 2 (relative to the yl position) and that the remaining $R^{7'}$ group(s) is (are) bound to ring atoms of $R^{6''}$ at positions 3, 4, or 5 (relative to the yl position). Moreover, in any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), where $R^{6''}$ is substituted with two or more (such as two, three, or four) $R^{7'}$ groups, it is preferred that each of the two ring atoms directly adjacent to the ring atom by which $R^{6''}$ is attached to the remainder of the compound bears one $R^{7'}$ group (e.g., $R^{6''}$ being an k-membered ring bears one $R^{7'}$ group at each of positions 2 and k, relative to the ring atom by which $R^{6''}$ is bound to the remainder of the compound, e.g., $R^{6''}$ is substituted at both of its ortho positions). Additionally, in any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), where $R^{6''}$ is substituted with three or more (such as three or four) $R^{7'}$ groups, it is preferred that each of the two ring atoms directly adjacent to the ring atom by which $R^{6''}$ is attached to the remainder of the compound bears one $R^{7'}$ group (e.g., $R^{6''}$ being an k-membered ring bears one $R^{7'}$ group at each of positions 2 and k, relative to the ring atom by which $R^{6''}$ is bound to the remainder of the compound, e.g., $R^{6''}$ is substituted at both of its ortho positions), and that the third $R^{7'}$ group is bound to a ring atom of $R^{6''}$ which is directly adjacent to one of the ortho ring atoms but which is not the ring atom by which $R^{6''}$ is bound to the remainder of the compound (e.g., $R^{6''}$ being an k-membered ring bears the third $R^{7'}$ group at one of positions 3 and k-1, relative to the ring atom by which $R^{6''}$ is bound to the remainder of the compound).

[249] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is selected from the following formulas:



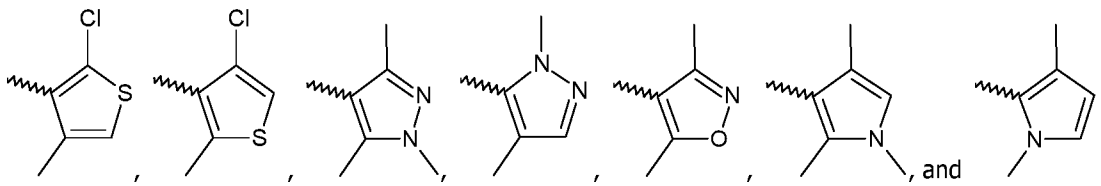
wherein ~~~ represents the bond by which $R^{6''}$ is bound to the remainder of the compound.

[250] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is selected from the following formulas:



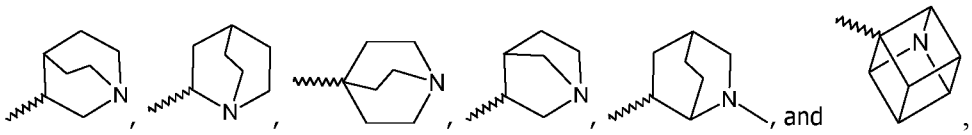
wherein ~~~ represents the bond by which $R^{6''}$ is bound to the remainder of the compound.

[251] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is selected from the following formulas:



wherein ~~~ represents the bond by which $R^{6''}$ is bound to the remainder of the compound.

[252] In one embodiment of the compound of formula (Vc), R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIc), (VIIc) and/or (VIIIc)), and $R^{6''}$ is selected from the following formulas:

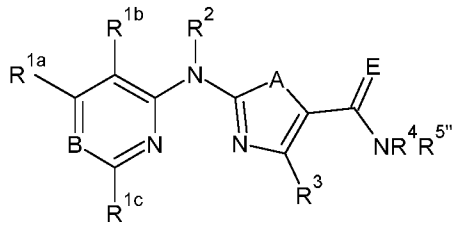


wherein ~~~ represents the bond by which $R^{6''}$ is bound to the remainder of the compound.

[253] In any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), L may be selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m-[Y-(CH_2)_n]_o-$, wherein m is 1, 2, or 3, n is 0, 1, or 2, o is 1, 2, or 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and NH, wherein each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m-$, and $-(CH_2)_n-$ groups is optionally substituted with one or more independently selected R^{30}. For example, in any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), L may be selected from the group consisting of a bond; C_1 alkylene, optionally substituted with one R^{30}; C_2 alkylene (in particular 1,2-ethylene or 1,1-ethylene), optionally substituted with one R^{30}; C_3 alkylene (in particular trimethylene), optionally substituted with one R^{30}; C_4 alkylene (in particular tetramethylene or 2,4-butandiyl), optionally substituted with one R^{30}; $-(CH_2)_mO-$; and $-(CH_2)_mNH-$, wherein m is 1, 2, or 3. Particularly, in any of the above embodiments of the compound of formula (Vc), (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), L may be a bond.

[254] In any of the above embodiments of the compound of formula (Vc) (including those of formulas (Ic), (IIc), (IIIc), and (IVc)), where $R^{6''}$ is a heterocyclyl or heteroaryl (e.g., a 5-membered heteroaryl) containing an N atom as ring heteroatom, L may be attached to $R^{6''}$ via the N ring atom of the heterocyclyl or heteroaryl group.

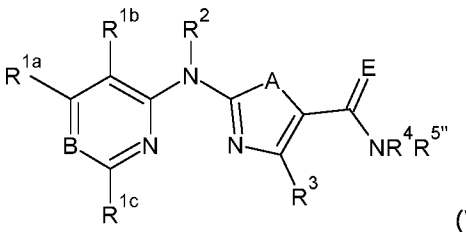
[255] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (VIc)



(VIc)

[256] wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (Vc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIIc) and/or (VIIIc)), and A is selected from the group consisting of S, O, NH, $N(C_{1-6}$ alkyl), and $C(C_{1-6}$ alkyl)$_2$. In any of the above embodiments of the compound of formula (VIc), (including those of formulas (Ic), (IIc), (IIIc), (IVc), and (Vc)), A may be S, O, or $N(CH_3)_2$. In any of the above embodiments of the compound of formula (VIc) (including those of formulas (Ic), (IIc), (IIIc), (IVc), and (Vc)), it is preferred that A is S.

[257] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (VIIc)

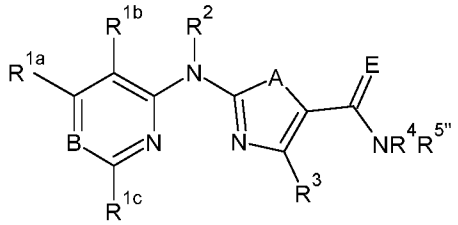


(VIIc)

[258] wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, and A are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below (in particular with respect to formula (VIIIc)), E is O or S (preferably O), and B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is

optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, $-OCH_3$, -SCH, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2. In any of the above embodiments of the compound of formula (VIIc) (including those of formulas (Ic), (IIc), (IIIc), (IVc), (Vc), and (VIc)), E is O or S (preferably O), and B is N or CR^{1d}, wherein R^{1d} may be selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), -NH (C_{1-3} alkyl), and $-N(C_{1-3}$ alkyl)$_2$. In any of the above embodiments of the compound of formula (VIIc) (including those of formulas (Ic), (IIc), (IIIc), (IVc), (Vc), and (VIc)), it is preferred that B is N, and is more preferred that E is O and B is N.

[259] In one embodiment, the compound of formula (Ic) for use according to the fifth aspect has the general formula (VIIIc)



(VIIIc)

wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, $R^{5''}$, A, B, and E are as defined above (in particular with respect to formula (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), (IIIa), (IVa), (VIa), (VIIa) and/or (VIIIa)) or below, and L is a bond. In preferred embodiments of the compound having the general formula (VIIIc):

(A) R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more (e.g., one, two, or three) independently selected R^{30}. Preferably, each R^{30} is independently a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein, such as alkyl (e.g., C_{1-6} alkyl), $-(CH_2)_{1-3}OH$, alkenyl (e.g., C_{2-6} alkenyl), alkynyl (e.g., C_{2-6} alkynyl), halogen, -CN, nitro, $-OR^{11}$ (e.g., -OH), $-SR^{11}$ (e.g., -SH), $-N(R^{12})(R^{13})$ (e.g., $-NH_2$), and $-C(=O)R^{11}$ (e.g., $-C(=O)(C_{1-3}$ alkyl));

(B) each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, propyl, or isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2;

(C) R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, $-NO_2$, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30};

(D) $R^{6''}$ is as defined above (in particular with respect to formula (Vc)), and is preferably a 3- to 10-membered heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of

N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$;

(E) A is selected from the group consisting of S, O, NH, N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$;

(F) B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, $-OCH_3$, -SCH, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and/or

(G) E is O or S, preferably O.

[260] In a preferred embodiment of the compound having the general formula (VIIIc), R^{1a} is as specified above under (A); R^{1b} and R^{1c} are as defined above under (B); R^3 is as specified above under (C); $R^{6''}$ is as defined above (in particular with respect to formula (Vc)), and is preferably a 3- to 10-membered heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$; A is as specified above under (E); B is as specified above under (F); and E is as specified above under (G).

[261] In further preferred embodiments of the compound having the general formula (VIIIc):

(A') R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 7-membered heterocyclyl, wherein the 3- to 7-membered heterocyclyl group is optionally substituted with one or two moieties independently selected from the group consisting of methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2;

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, or isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2, and the other of R^{1b} and R^{1c} is as defined above under (B);

(C') R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, -O(C_{1-4} alkyl), $-OCF_3$, -S(C_{1-4} alkyl), $-NH_2$, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)$_2$, -C(=O)(C_{1-4} alkyl), -C(=O)OH, -C(=O)O(C_{1-4} alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl)$_z$, -NHC(=O)(C_{1-4} alkyl), $-NHC(=NH)NH_{2-z}(C_{1-4}$ alkyl)$_z$, and $-N(C_{1-4}$ alkyl)$C(=NH)NH_{2-z}$ (C_{1-4} alkyl)$_z$, wherein the phenyl group is optionally substituted with one, two or groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -NHC(=O)(C_{1-3} alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl)$_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}$NH(C_{1-3} alkyl), $-(CH_2)_{1-3}$N(C_{1-3} alkyl)$_2$, $-(CH_2)_{1-3}$OH, and $-(CH_2)_{1-3}$O(C_{1-3} alkyl); and wherein z is 0, 1, or 2;

(D') $R^{6''}$ is as defined above (in particular with respect to formula (Vc)), and is preferably a 3- to 10-membered heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is a mono- or bicyclic heteroaryl or a mono- or bicyclic

heterocyclyl, each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$;

(E') A is S, O, or $N(CH_3)_2$; and/or

(F') B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl$)_2$; and/or

(G') E is O or S, preferably O.

[262] In a preferred embodiment of the compound having the general formula (VIIIc), R^{1a} is as specified above under (A'); R^{1b} and R^{1c} are as defined above under (B'); R^3 is as specified above under (C'); $R^{6''}$ is as defined above (in particular with respect to formula (Vc)), and is preferably a 3- to 10-membered heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is a mono- or bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a mono- or bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$; A is as specified above under (E'); B is as specified above under (F'); and E is as specified above under (G').

[263] In further preferred embodiments of the compound having the general formula (VIIIc):

(A'') R^{1a} is selected from the group consisting of $-NH(C_{1-3}$ alkyl), piperazinyl, piperidinyl, and pyrrolidinyl, wherein the piperazinyl group is optionally substituted with one or two moieties independently selected from the group consisting of 2-hydroxyethyl, methyl, $-CH_2COOH$, and $-C(=O)CH_3$; the piperidinyl group is optionally substituted with one or two moieties independently selected from the group consisting of $-NH_2$ and 4-methylpiperazinyl; the pyrrolidinyl is optionally substituted with one or two -OH; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of-OH, $-OCH_3$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2;

(B'') (a) R^{1b} is methyl, ethyl, propyl, or isopropyl, preferably methyl; and R^{1c} is H; or (b) R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl;

(C'') R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen;

(D'') $R^{6''}$ is as defined above (in particular with respect to formula (Vc)), and is preferably a 3- to 10-membered heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is a mono- or bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a mono- or bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), a 4- to 6-membered monocyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), a 7- to 9-membered bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting

of N, O, and S, such as from the group consisting of N and O), and a 7- to 9-membered bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is a 5- to 6-membered monocyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 7- to 9-membered bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$;

(E'') A is S;

(F'') B is N; and/or

(G'') E is O.

[264] In a preferred embodiment of the compound having the general formula (VIIIc), R^{1a} is as specified above under (A''); R^{1b} and R^{1c} are as defined above under (B''); R^3 is as specified above under (C''); $R^{6''}$ is as defined above (in particular with respect to formula (Vc)), and is preferably a 3- to 10-membered heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 3- to 10-membered heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is a mono- or bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a mono- or bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), a 4- to 6-membered monocyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), a 7- to 9-membered bicyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), and a 7- to 9-membered bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$, more preferably $R^{6''}$ is a 5- to 6-membered monocyclic heteroaryl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O) or a 7- to 9-membered bicyclic heterocyclyl (e.g., containing at least one ring heteroatom selected from the group consisting of N, O, and S, such as from the group consisting of N and O), each of which is optionally substituted with one or more, such as with one, two, or three, independently selected $R^{7'}$; A is as specified above under (E''); B is as specified above under (F''); and E is as specified above under (G'').

[265] In one embodiment, the compound of the invention is selected from the compounds shown in Table A and/or those depicted in Figure 1E.

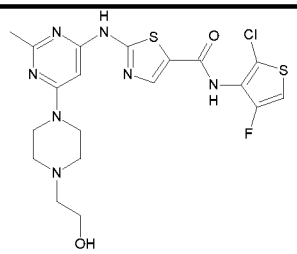
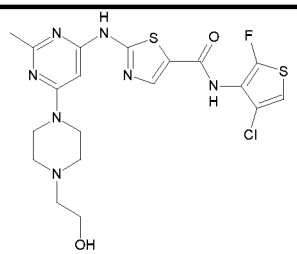
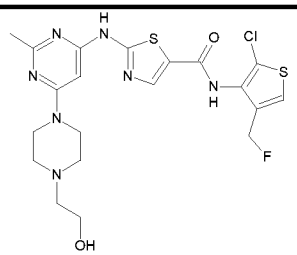
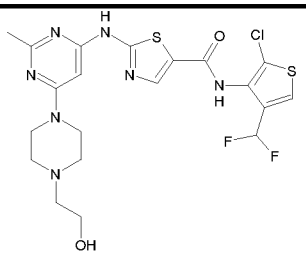
[266] In one embodiment, the compound used in the present invention (in particular, in the fifth aspect of the invention) is selected from the compounds shown in Table A (and/or those depicted in Figure 1E), and those depicted in Figure 1B, Figure 1C and/or Figure 1D.

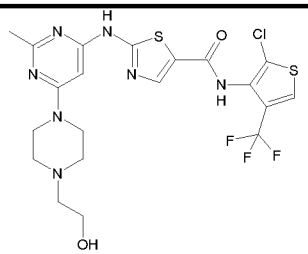
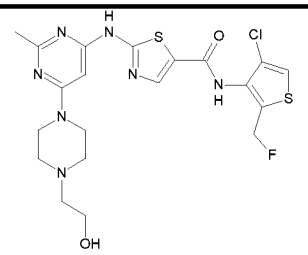
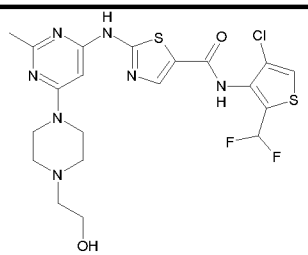
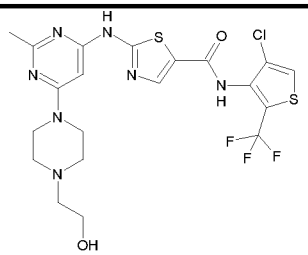
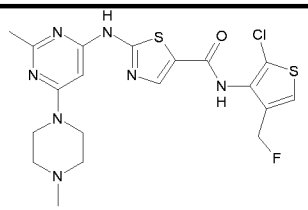
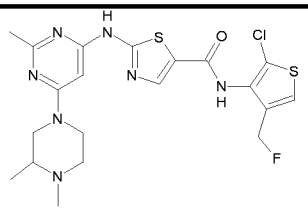
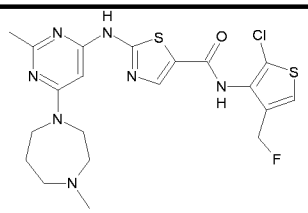
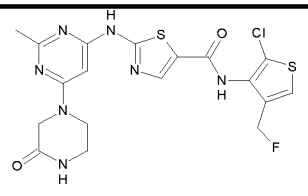
[267] It is intended that the compounds of the present invention (in particular, the compounds of any one of formulas (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa) and (VIIIa) such as those depicted in Table A, below; and/or in

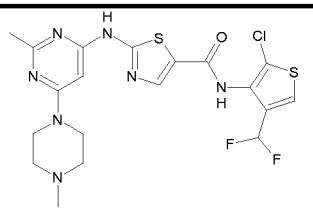
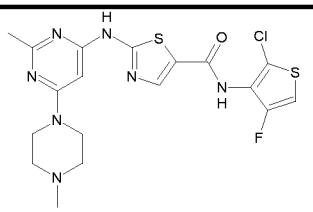
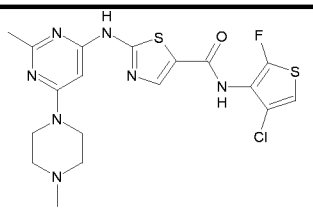
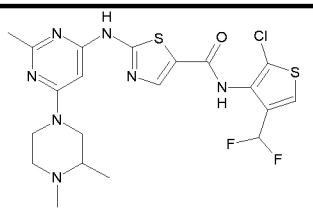
Figure 1E) and/or the compounds used in the present invention (in particular, the compounds of any one of formulas (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc) (IVc), (Vc), (VIc), (VIIc) and (VIIIc) such as those depicted in Figure 1B, Figure 1C and/or Figure 1D) encompass not only the compounds as depicted but also their solvates (e.g., hydrates), salts (in particular, pharmaceutically acceptable salts), N-oxides (in particular, N-oxides of R^{1a} and/or $R^{6''}$), complexes, polymorphs, crystalline forms, non-crystalline forms, amorphous forms, racemic mixtures, non-racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and any combinations thereof.

[268] A selection of compounds, including those which have been synthesized and tested, within the scope of, or for use within the methods of, the present invention - and/or that represent examples of various exemplary or preferred Hy substituents, R^{1a} substituents, R^{1b} substituents, R^{1c} substituents, R^{1d} substituents, R^{1e} substituents, R^2 substituents, R^3 substituents, R^4 substituents, R^5 moieties, A moieties, B moieties and/or E moieties, each individually or in any combination are useful for synthesising further compounds of the invention - is listed in the following Table A.

Table A: Kinase inhibitors of formula (Ia).

Compound Number	Structure	Name
E1		*N*-(2-chloro-4-fluorothiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E2		*N*-(4-chloro-2-fluorothiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E3		*N*-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E4		*N*-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

E5		*N*-(2-chloro-4-(trifluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E6		*N*-(4-chloro-2-(fluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E7		*N*-(4-chloro-2-(difluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E8		*N*-(4-chloro-2-(trifluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E9		*N*-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide
E10		*N*-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
E11		*N*-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide
E12		*N*-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(3-oxopiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide

E13		*N*-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methyl-pyrimidin-4-yl)amino)thiazole-5-carboxamide
E14		*N*-(2-chloro-4-fluorothiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide
E15		*N*-(4-chloro-2-fluorothiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide
E16		*N*-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide

[269] In particular embodiments, the compound of the invention is selected from the group consisting of E4, E9, E10, and E16; and also their solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labelled forms, prodrugs, and combinations thereof.

[270] In certain embodiments, the compound of the invention is E9, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, tautomer, conformer, isotopically labelled form, prodrug, or combination thereof.

[271] In another certain embodiment, the compound of the invention is E4, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, tautomer, conformer, isotopically labelled form, prodrug, or combination thereof.

[272] In another certain embodiment, the compound of the invention is E10, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, tautomer, conformer, isotopically labelled form, prodrug, or combination thereof.

[273] In another certain embodiment, the compound of the invention is E16, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labelled form, prodrug, or combination thereof.

[274] In certain embodiments, the invention may relate to a solvate, salt, N-oxide, complex, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug, or combination thereof, of any of the compounds of the invention or of any of the compounds used in the invention; such as a solvate, salt, complex, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, or combination thereof, of such compound.

[275] In one embodiment, the compounds used in the invention do not encompass compounds of one or more of the following groups (1) to (6) of formula (Ic) (in the groups (1) to (6) a moiety (such as methyl) is unsubstituted unless it is explicitly specified that said moiety is substituted):

(1) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^3 is H; A is S; and L is a bond; then $R^{6''}$ is not 4-chloro-2-methylpyridin-3-yl;

(2) when R^{1a} is methoxy; R^{1b} is H; R^{1c} is methoxy; B is N; E is O; R^3 is H; A is S; and L is a bond; then $R^{6''}$ is not 2,2-difluoro-5H-1,3-dioxolo[4,5-f]benzimidazol-6-yl;

(3) when R^3 is H; A is S; L is a bond; $R^{6''}$ is 1-methyl-4-piperidinyl; R^{1b} is H; B is N; E is O; and

(i) R^{1a} is methyl; then R^{1c} is not N-tert-butoxycarbonylpiperidin-4-yl; or

(ii) R^{1c} is methyl; then R^{1a} is not N-tert-butoxycarbonylpiperidin-4-yl or N-tert-butoxycarbonylpiperidin-3-yl;

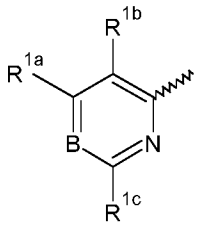
(4) when E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br, then R^{1a} is not H;

(5) when R^{1a} is methyl; each of R^{1b} and R^{1c} is H; B is CH; E is O; A is S; and R^3 is methyl; then $R^{5''}$ is not 1,3-benzodioxol-5-ylmethyl, 2-furanylmethyl, 1,3-benzodioxol-5-yl, 2-(2-thienyl)ethyl, 2-(4-morpholinyl)ethyl, 2-(2-pyridinyl)ethyl, 2-pyridinylmethyl, or tetrahydro-2-furanylmethyl; and

(6) when A is S; R^3 is H; E is O; L is a bond; $R^{6''}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; R^{1a} is H, R^{1b} is H, R^{1c} is H; and B is CR^{1d}; then R^{1d} is not H.

[276] In one embodiment, the compounds used in the invention do not encompass compounds of one or more of the following groups (7) to (10) having formula (Ib) (in the groups (7) to (10) a moiety (such as methyl) is unsubstituted unless it is explicitly specified that said moiety is substituted):

(7) when Hy is:



and

(i) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^2 is H; R^3 is H; R^4 is H; and A is S; then $R^{6'}$ is not 4-chloro-2-methylpyridin-3-yl; or

(ii) when E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br; then R^{1a} is not H;

(8) when Hy is 1-{(2E)-4-[(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}piperidine-4-yl; R^2 is H; R^3 is H; R^4 is H; A is O; E is O; then $R^{6'}$ is not 5-methyl-pyridin-2-yl;

(9) when R^2 is H; R^3 is trifluoromethyl; R^4 is H; A is O; E is O; and

(i) $R^{6'}$ is 6-{4-[(2-fluorophenyl)carbamoyl]piperazin-1-yl}pyridine-3-yl; then Hy is not 1-(phenylmethyl)-piperidine-4-yl, 1-(phenylmethyl)pyrrolidine-3-yl, or tetrahydro-2H-pyran-4-yl; or

(ii) Hy is 1-(phenylmethyl)piperidine-4-yl; then $R^{6'}$ is not 6-(3-{[(2-fluorophenyl)carbamoyl]amino}-pyrrolidin-1-yl)pyridine-3-yl or 6-({1-[(2-fluorophenyl)carbamoyl]piperidin-4-yl}amino)pyridine-3-yl; or

(iii) Hy is 1-(phenylmethyl)pyrrolidine-3-yl; then $R^{6'}$ is not 6-({(3S)-1-[(2-fluorophenyl)carbamoyl]-pyrrolidin-3-yl}amino)pyridine-3-yl or 6-({(3R)-1-[(2-fluorophenyl)carbamoyl]pyrrolidin-3-yl}-amino)pyridine-3-yl;

(10) when A is S; R^3 is H; E is O; and $R^{6'}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; then Hy is not 2-pyridyl.

[277] In certain other embodiments, the compound used in the invention is not one selected from the group consisting of:

- 5-Thiazolecarboxamide, 2-[(6-chloro-2-methyl-4-pyrimidinyl)amino]-N-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-6-methylphenyl]- (CAS Registry no: 2048106-50-7),

- 5-Thiazolecarboxamide, 2-[[7-[4-cyano-3-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]amino]-N-[(1R)-1-(1,3,4-oxadiazol-2-yl)ethyl]-4-(trifluoromethyl)- (CAS Registry no: 1831086-00-0),
- 5-Thiazolecarboxamide, 2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]-N-(2-pyrazinylmethyl)- (CAS Registry no: 385780-87-0),
- 5-Thiazolecarboxamide, 2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]-N-[2-(3-pyridinyl)ethyl]- (CAS Registry no: 385780-82-5),
- 5-Thiazolecarboxamide, N-1H-indol-5-yl-2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]- (CAS Registry no: 385780-79-0),
- 5-Thiazolecarboxamide, 2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]-N-(2-thienylmethyl)- (CAS Registry no: 385780-69-8),
- 5-Thiazolecarboxamide, N-(2-furanylmethyl)-2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]- (CAS Registry no: 385780-66-5),
- 5-Thiazolecarboxamide, 2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]-N-2-pyridinyl- (CAS Registry no: 385780-57-4), and
- 5-Thiazolecarboxamide, 2-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]-N-4-pyridinyl- (CAS Registry no: 385779-93-1).

[278] In other certain other embodiments, the compound used in the invention is not one selected from the group consisting of:

- Imidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide, N,N-dicyclopropyl-6-ethyl-1,6-dihydro-1-methyl-4-[[4-methyl-5-[[(tetrahydro-2H-pyran-4-yl)amino]carbonyl]-2-thiazolyl]amino]- (CAS Registry no: 1271022-78-6),
- Imidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide, N,N-dicyclopropyl-6-ethyl-1,6-dihydro-1-methyl-4-[[4-methyl-5-[[(tetrahydro-1,1-dioxido-3- thienyl)amino]carbonyl]-2-thiazolyl]amino]- (CAS Registry no: 1271022-57-1),
- Imidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide, N,N-dicyclopropyl-6-ethyl-1,6-dihydro-1-methyl-4-[[4-methyl-5-[[[2-(4- morpholinyl)ethyl]amino]carbonyl]-2-thiazolyl]amino]- (CAS Registry no: 1271022-45-7), and
- Imidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide, N,N-dicyclopropyl-6-ethyl-1,6-dihydro-1-methyl-4-[[5-[[methyl(tetrahydro-1,1-dioxido-3- thienyl)amino]carbonyl]-2-thiazolyl]amino]- (CAS Registry no: 1271021-43-2)
- 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}pyridin-2-yl)amino]-4-methyl-N-[1-(phenylmethyl)-1H-indazol-5-yl]-1,3-thiazole-5-carboxamide (CAS Registry no: 302963-64-0)
- 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}pyridin-2-yl)amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-1,3-thiazole-5-carboxamide (CAS Registry no: 302963-55-9)

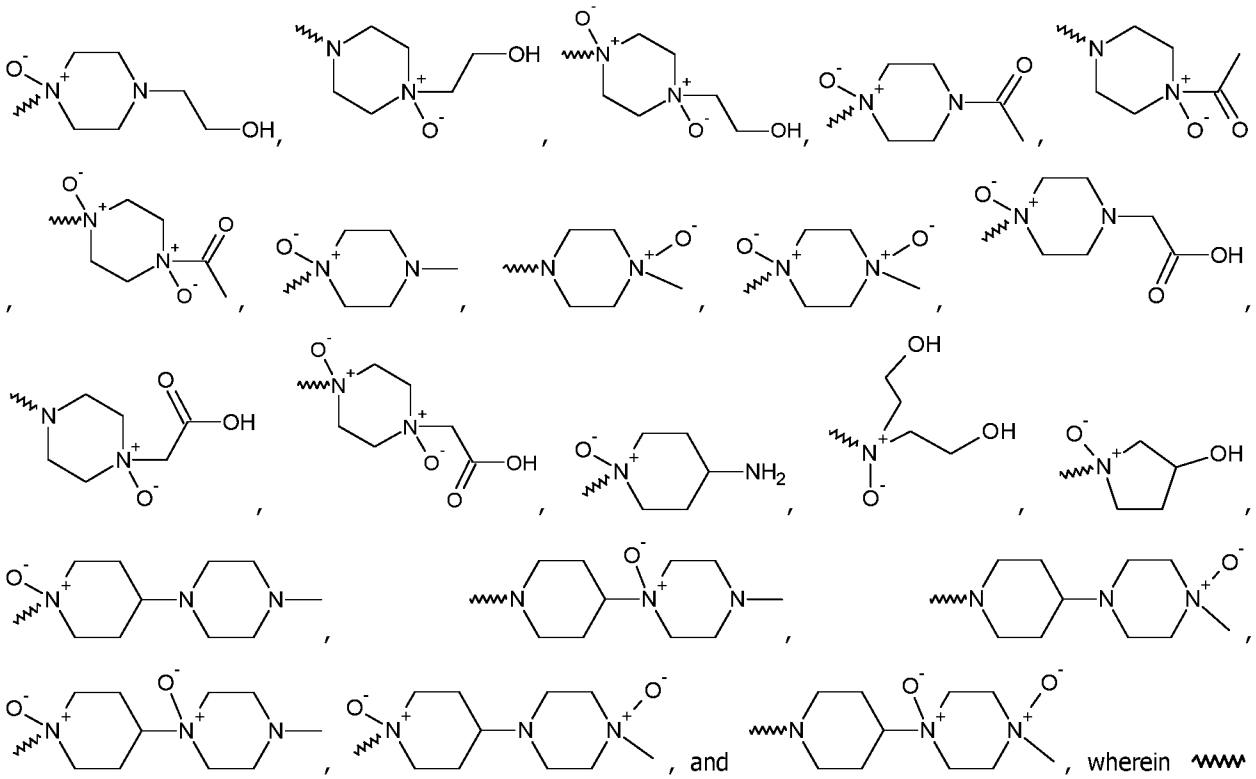
[279] In certain alternatives of one or more aspects herein (in particular, the fifth aspect of the invention), the compound is N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (A8; Figure 1A), in particular the monohydrate thereof (dasatinib).

[280] In other certain alternatives of one or more aspects herein (in particular, the fifth aspect of the invention), the compound is ARN-3261 (Vankayalapati et al 2017, AACR Cancer Res 77(13 Suppl):Abstract nr LB-296; US 9,260,426, US 9,890,153, US 9,951,062).

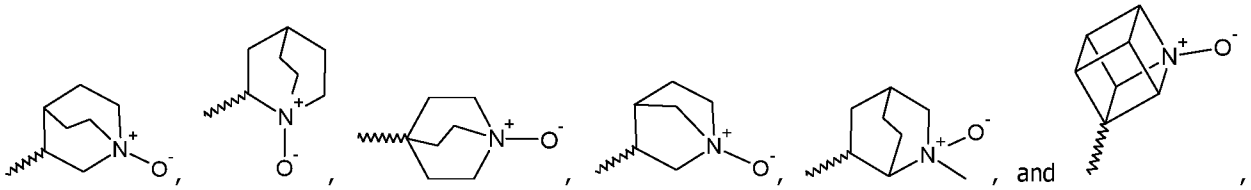
[281] The compounds of the invention (and/or the compounds used in the invention) which contain a basic functionality may form salts with a variety of inorganic or organic acids. The compounds of the invention (and/or the compounds used in the invention) which contain an acidic functionality may form salts with a variety of inorganic or organic bases. Exemplary inorganic and organic acids/bases as well as exemplary acid/base addition salts of the compounds of the present invention (or of the compounds used in the invention) are given in the definition of "pharmaceutically acceptable salt" in the section "Pharmaceutical composition", below. The compounds of the invention

(and/or the compounds used in the invention) which contain both basic and acidic functionalities may be converted into either base or acid addition salt. The neutral forms of the compounds of the invention (or of the compounds used in the invention) may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner.

[282] The compounds of the invention (and/or the compounds used in the invention) may be in the form of an N-oxide, i.e., they can contain the functional group functional group $\equiv N^+-O^-$ (e.g., $(R^n)_3N^+-O^-$, i.e., an N–O coordinate covalent bond, wherein R^n is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}, the R^{30} preferably being a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein). Particular examples of N-oxides of compounds of the invention (or of the compounds used in the invention) are those, wherein R^{1a} and/or R^6 (or $R^{6'}$ or $R^{6''}$) contains the functional group $\equiv N^+-O^-$. Non-limiting examples of R^{1a} substituents which can occur as N-oxides include the following:



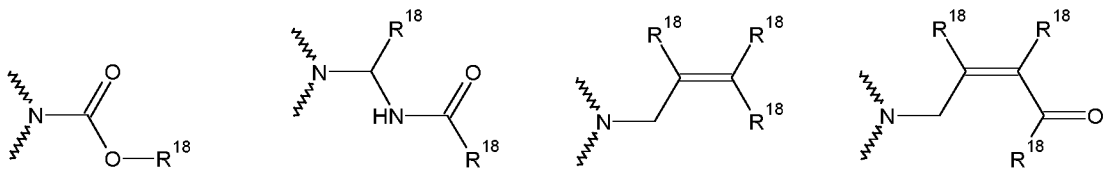
wherein represents the bond by which the R^{1a} substituent is bound to the remainder of the compound. Non-limiting examples of $R^{6''}$ substituents which can occur as N-oxides include the following:



wherein represents the bond by which the $R^{6''}$ substituent is bound to the remainder of the compound.

[283] The compounds of the invention (and/or the compounds used in the invention) may be in a prodrug form. Prodrugs of the compounds of the invention (or of the compounds used in the invention) are those compounds that upon administration to an individual undergo chemical conversion under physiological conditions to provide the

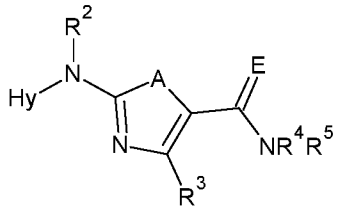
compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention (or of the compounds used in the invention) by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the invention (or to the compounds used in the invention) when, for example, placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Exemplary prodrugs are esters (using an alcohol or a carboxy group contained in the kinase inhibitor of the invention (or in the compounds used in the invention)) or amides (using an amino or a carboxy group contained in the kinase inhibitor of the invention (or in the compounds used in the invention)) which are hydrolyzable *in vivo*. Specifically, any amino group which is contained in the kinase inhibitor of the invention (or in the compounds used in the invention) and which bears at least one hydrogen atom can be converted into a prodrug form. Typical N-prodrug forms include carbamates (1), Mannich bases (2), enamines (3), and enaminones (4).



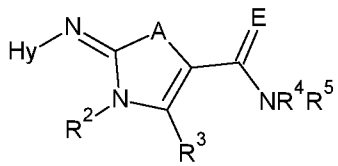
(1) (2) (3) (4)

wherein R^{18} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}, wherein R^{30} is as defined herein (preferably, each R^{30} is independently a 1st level substituent, a 2nd level substituent, or a 3rd level substituent as specified herein). The prodrug properties (such as solubility, permeability, stability, how fast cleaved, where in the body cleaved under what conditions, target specificity, etc.) can be fine-tuned via modification of R^{18}.

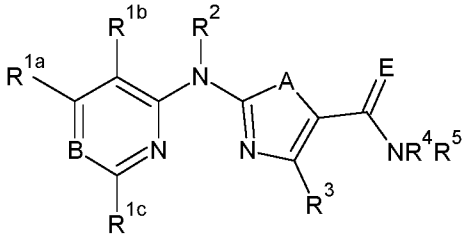
[284] Particular prodrug forms of the compounds of the invention (or of the compounds used in the invention) are those (prodrugs) having the formula (IXa), (Xa), (XIa), or (XIIa) (or (IXb), (Xb), (IXc), or (Xc)):



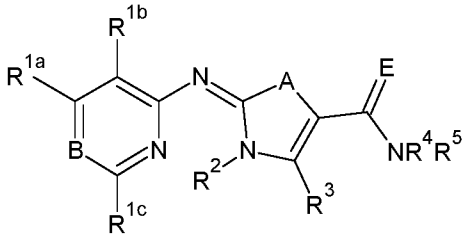
(IXa)



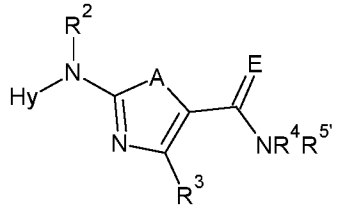
(Xa)

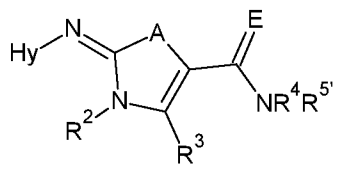


(XIa)

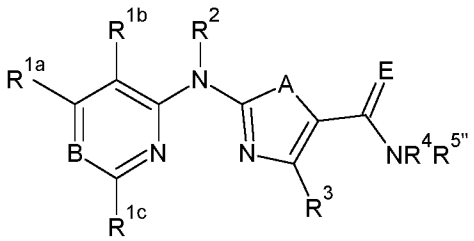


(XIIa)

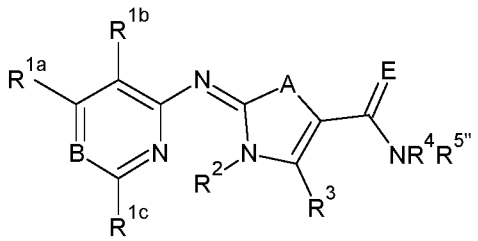




(IXb)



(Xb)



(IXc) (Xc)

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms and combinations thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^3, R^5, $R^{5'}$, $R^{5''}$, A, B, E, and Hy are as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), (VIIIa), (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), and/or (VIIIc)) or below, and each of R^2 and R^4 is independently selected from the group consisting of H, $-P(O)(OR^{11a})_2$, $-(CH_2)_{1-3}-R^{19}$, $-C(=X^a)R^{11a}$, and $-C(=X^a)X^aR^{11a}$, with the proviso that not both of R^2 and R^4 are H, wherein R^{11a} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}; R^{19} is independently selected from the group consisting of $-OP(O)(OR^{11a})_2$, $-X^aC(=X^a)R^{11a}$, $-X^aC(=X^a)X^aR^{11a}$, and 5-alkyl-2-oxo-1,3-dioxolo-4-yl; X^a is independently selected from O, S, and NH; and the $-(CH_2)_{1-3}-$ group is optionally substituted with one or two independently selected R^{30}, wherein R^{30} is as defined herein (preferably, each R^{30} is independently selected from the group consisting of a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein). In one embodiment of the prodrug form of formula (IXa), (Xa), (XIa), (XIIa), (IXb), (Xb), (IXc), or (Xc), R^{1a}, R^{1b}, R^{1c}, R^3, R^5, $R^{5'}$, $R^{5''}$, A, B, E, and Hy are as defined above (in particular with respect to formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), (VIIIa), (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), and/or (VIIIc)) or below, and each of R^2 and R^4 is independently selected from the group consisting of H, $-P(O)(OR^{11a})_2$, $-(CH_2)_{1-3}-R^{19}$, $-C(=O)R^{11a}$, and $-C(=O)OR^{11a}$, with the proviso that not both of R^2 and R^4 are H, wherein R^{11a} is independently selected from the group consisting of H and C_{1-6} alkyl (preferably C_{1-3} alkyl), wherein the alkyl group is optionally substituted with one or two substituents independently selected from halogen, -OH, $-OCH_3$, $-SCH_3$, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; R^{19} is independently selected from the group consisting of $-OP(O)(OR^{11a})_2$, $-OC(=O)R^{11a}$, $-OC(=O)OR^{11a}$, and 5-(C_{1-3} alkyl)-2-oxo-1,3-dioxolo-4-yl; and the $-(CH_2)_{1-3}-$ group is optionally substituted with one or two substituents independently selected from the group consisting of halogen, -OH, $-OCH_3$, $-SCH_3$, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[285] For those compounds of the invention having any one of formulas (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), (VIIIa), (IXa), (Xa), (XIa), and (XIIa) (or for those compounds use in the invention having any one of formulas (Ib), (IIb), (IIIb), (IXb), (Xb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), (VIIIc), (IXc) and (Xc)) and bearing one or more hydroxyl (i.e., -OH) groups, a further particular prodrug form is that wherein at least one of these two or more hydroxyl groups is derivatized to be a moiety selected from the group consisting of $-OP(O)(OR^{11a})_2$, $-O(CH_2)_{1-3}-R^{19}$, $-OC(=X^a)R^{11a}$, and $-OC(=X^a)X^aR^{11a}$, wherein R^{11a} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more (such as 1 to the maximum number of hydrogen atoms bound to the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or up to 10, such as between 1 to 5, 1 to 4, or 1 to 3, or 1 or 2) independently selected R^{30}; R^{19} is independently

selected from the group consisting of -OP(O)(OR^{11a})$_2$, -$X^aC(=X^a)R^{11a}$, -$X^aC(=X^a)X^aR^{11a}$, and 5-alkyl-2-oxo-1,3-dioxolo-4-yl; X^a is independently selected from O, S, and NH; and the -$(CH_2)_{1-3}$- group is optionally substituted with one or two independently selected R^{30}, wherein R^{30} is as defined herein (preferably, each R^{30} is independently selected from the group consisting of a 1st level substituent, a 2nd level substituent, and a 3rd level substituent as specified herein). In one embodiment of this prodrug form of the compounds of the invention (or of the compounds used in the invention), the at least one derivatized hydroxyl group is selected from the group consisting of -OP(O)(OR^{11a})$_2$, -O$(CH_2)_{1-3}$-R^{19}, -OC(=O)R^{11a}, and -OC(O)OR^{11a}, wherein R^{11a} is independently selected from the group consisting of H and C_{1-6} alkyl (preferably C_{1-3} alkyl), wherein the alkyl group is optionally substituted with one or two substituents independently selected from halogen, -OH, -OCH_3, -SCH_3, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; R^{19} is independently selected from the group consisting of -OP(O)(OR^{11a})$_2$, -OC(=O)R^{11a}, -OC(=O)OR^{11a}, and 5-(C_{1-3} alkyl)-2-oxo-1,3-dioxolo-4-yl; and the -$(CH_2)_{1-3}$- group is optionally substituted with one or two substituents independently selected from the group consisting of halogen, -OH, -OCH_3, -SCH_3, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

[286] In certain embodiments, the invention (or a compound used in the invention, such as in the fifth aspect of the invention) may relate to a solvate, salt, N-oxide, complex, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, or combination thereof, of a prodrug having the formula (IXa), (Xa), (XIa), or (XIIa) (or (IXb), (Xb), (IXc), or (Xc)); such as a solvate, salts, complex, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, or combination thereof, of such prodrug.

[287] In a one particular embodiment, a compound of the invention (or a compound used in the invention) is a hydrate, suitably a mono-hydrate or a di-hydrate of a kinase inhibitor as specified under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa) (or a compound having the general formula (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc)), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a} and/or $R^{6''}$), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug of formula (IXa), (Xa), (XIa), or (XIIa) (or (IXb), (Xb), (IXc), or (Xc)) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof). In another suitable embodiment, a compound of the invention (or a compound used in the invention) is a semi-hydrate of such a kinase inhibitor.

[288] A compound of the invention (e.g., as specified under the heading "Compounds") can, in certain embodiments, be in (e.g., provided in) a purified or (e.g., substantially) pure form. For example, the compound may be greater than about 50% pure, such as greater than about 60%, 70% or 80% pure, suitably greater than about 90% pure (in particular, greater than about 95%, 97% 98% and even 99%). That is, in certain of such embodiments such a compound is present together with only a limited amount of impurities (e.g., such as those introduced during manufacturing), such as only small amounts of impurities are present, including embodiments where the compound is present in a form where impurities are substantially absent. The purity (e.g., the absence, or degree of presence of impurities) of the compound can be determined by routine procedures e.g. by HLPC.

[289] In one embodiment, the present invention provides such a compound containing less than about 50%, 40%, 30% and suitably 10% or 5% area by HPLC, preferably less than about 3% and 2% area by HPLC, more preferably less than 1% area by HPLC, of total impurities. The term "% area by HPLC" as used herein refers to the area in an HPLC chromatogram of one or more peaks compared to the total area of all peaks in the HPLC chromatogram expressed in percent of the total area. Further, the purity of the compound may be expressed herein as "HPLC" purity. As such, "HPLC purity", is a calculation of the area under the compound peak divided by the total area under the curve in an

HPLC chromatogram. Suitably, the compound contains less than about 10% area by HPLC of total impurities. More preferably, less than about 5% area by HPLC of total impurities.

[290] In a related aspect, and as may be further described, defined, claimed or otherwise disclosed herein, the invention provides one or more containers, wherein the containers (each independently, or all collectively) contain, the kinase inhibitor of the first aspect or a compound used in the fifth aspect (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa) (or a compound having the general formula (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc)), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, an N-oxide of R^{1a} and/or $R^{6''}$), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug of formula (IXa), (Xa), (XIa), or (XIIa) (or (IXb), (Xb), (IXc), or (Xc)) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof) in an amount that is more than about 10mg; in particular, in an amount more than about 50mg or 100mg; suitably an amount that is more than about 1g, 10g, 50g or 100g; or more than about 500g or 1Kg.

[291] In a further aspect, the present invention provides a compound of the invention (in particular those specified above with respect to any of formulas (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), and (VIIIa)) for use as medicament, for example for use in therapy. In one embodiment of the fifth aspect, the compound used in the invention does not encompass compounds which have formula (Ic) and belong to one or more of the groups (1), (2), (3), (4), (5) and/or (6) (such as compounds of one or more of the groups (1) (in particular, compounds of group (1) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl), (2) and/or (4) (in particular, compounds 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}pyridin-2-yl)amino]-4-methyl-N-[1-(phenylmethyl)-1H-indazol-5-yl]-1,3-thiazole-5-carboxamide and 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}pyridin-2-yl)amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-1,3-thiazole-5-carboxamide) specified above. In one embodiment of this aspect, the compound used in the fifth aspect of the invention does not encompass compounds which have formula (Ib) and belong to one or more of the groups (7) (such as, in particular, compounds of group (7)(i) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl), (8), (9) and/or (10) as specified above.

[292] As it is evident from the examples, the inventors have found that the compounds of the invention as well as other structurally similar compounds inhibit one or more protein-tyrosine kinases, including any of those selected from the group consisting of: SIK3, ABL/BCR-ABL and CSF1R, or selected from the group consisting of SRC, HCK, PDGFR and KIT, or selected from the group consisting of ABL1/BCR-ABL, SRC, LCK, KIT, FLT3 and their mutants, and/or SIK1, SIK2 and SIK3, and/or PHA2, EPHA4, CSFR1, HCK and ACK1; and/or NEK11, WEE1, WNK2, Aurora-A, Aurora-B and TBK1. In one embodiment, the compounds of the invention exhibit pharmacological properties (selectivity, bioavailability, toxicity, side effects, dosing, patient compliance, compatibility, stability, half-life, etc.), which are in at least one aspect superior to the pharmacological properties exhibited by dasatinib.

[293] In one embodiment, the compounds of the invention exhibit a different profile of kinases to the kinases inhibited by dasatinib and/or by compound B3 (WO 2018/193084), in particular. In one embodiment, the compounds of the invention are kinase inhibitors which: (i) are more specific to one or more key disease-related kinases (e.g., ABL/BCR-ABL, SRC, HCK, PDGFR, KIT and/or CSF1R, and/or EPHA2, EPHA4, ACK1 and/or KIT, and/or LCK), relative to other kinases, than the specificity shown by dasatinib (and/or by compound B3) to one or more such other kinases; (ii) inhibit key disease- or side-effect-related kinases in a different profile than dasatinib (e.g. to KIT and/or FLT3) and/or compound B3; and/or (iii) inhibit one or more mutant of a disease-related kinase, in particular a mutant that is resistant to one or other kinase inhibitor, such as mutants of ABL/BCR-ABL or KIT.

[294] In another embodiment, the compounds of the invention exhibit one or more pharmacological properties that are different to those of dasatinib, of compound B3 (WO 2018/193084), and/or of compound C7 (PCT/EP2019/078751).

Such differences in pharmacological properties can lead to the administration of compounds of the invention in different therapeutic regimens than eg dasatinib. Such properties may be one or more improved DMPK properties such as those described in Example 5.2 (such as AUC, plasma concentration and/or free plasma concentration).

Pharmaceutical compositions

[295] The compounds described in the present invention (in particular those specified above such as those of formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), particularly those given in Table A) or the compounds used in the present invention (in particular those specified above such as those of formula (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc)) are preferably administered to a patient in need thereof via a pharmaceutical composition. Thus, in **a second aspect**, the present invention provides **a pharmaceutical composition** comprising a kinase inhibitor as specified above under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, an N-oxide of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug of formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof) and optionally one or more pharmaceutically acceptable excipients.

[296] Thus, in one embodiment the pharmaceutical composition comprises a kinase inhibitor as specified above under the heading "Compounds" (in particular a compound of the first aspect of the invention) and one or more pharmaceutically acceptable excipients. Furthermore, the pharmaceutical composition may further comprise one or more additional therapeutic agents. Thus, in particular embodiments, the pharmaceutical composition comprises (i) a kinase inhibitor as specified above under the heading "Compounds" (in particular a compound of the first aspect of the invention) and one or more additional therapeutic agents; or (ii) a kinase inhibitor as specified above under the heading "Compounds" (in particular a compound of the first aspect of the invention), one or more additional therapeutic agents, and one or more pharmaceutically acceptable excipients.

[297] The term "pharmaceutically acceptable" refers to the non-toxicity of a material which does not interact with the (e.g., therapeutic) action of the active component (e.g., a kinase inhibitor of the invention (or a compound used in the invention), either alone or in combination with one or more additional therapeutic agents) of the pharmaceutical composition.

[298] The pharmaceutical composition may be administered to an individual by any route, such as enterally or parenterally.

[299] The expressions "enteral administration" and "administered enterally" as used herein mean that the drug administered is taken up by the stomach and/or the intestine. Examples of enteral administration include oral and rectal administration. The expressions "parenteral administration" and "administered parenterally" as used herein mean modes of administration other than enteral administration, usually by injection or topical application, and include, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraosseous, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, intracerebral, intracerebroventricular, subarachnoid, intraspinal, epidural and intrasternal administration (such as by injection and/or infusion) as well as topical administration (e.g., epicutaneous, inhalational, or through mucous membranes (such as buccal, sublingual or vaginal)).

[300] Dosage forms for topical and/or transdermal administration of a compound described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active

ingredient is admixed under sterile conditions with a pharmaceutically acceptable excipient such as one or more pharmaceutical carriers) and/or any needed preservatives and/or buffers as can be required. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively, or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[301] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Alternatively, or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration. Jet injection devices which deliver liquid formulations to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form through the outer layers of the skin to the dermis are suitable.

[302] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[303] The compounds of the present invention (or the compounds used in the present invention) are generally applied in "pharmaceutically acceptable amounts" and in "pharmaceutically acceptable preparations". Such compositions may contain salts, buffers, preserving agents, carriers and optionally other therapeutic agents. "Pharmaceutically acceptable salts" comprise, for example, acid addition salts which may, for example, be formed by mixing a solution of compounds with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, acetate, adipate, alginate, arginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, galactate, galacturonate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, phthalate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, suberate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, Berge et al., "Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977)).

[304] The term "excipient" when used herein is intended to indicate all substances in a pharmaceutical composition which are not active ingredients (e.g., which are therapeutically inactive ingredients that do not exhibit any therapeutic

effect in the amount/concentration used), such as, e.g., carriers, binders, lubricants, thickeners, surface active agents, preservatives, stabilizers, emulsifiers, buffers, flavoring agents, colorants, or antioxidants.

[305] The compositions described in the present invention may comprise a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like that are physiologically compatible. The "pharmaceutically acceptable carrier" may be in the form of a solid, semisolid, liquid, or combinations thereof. Preferably, the carrier is suitable for enteral (such as oral) or parenteral administration (such as intravenous, intramuscular, subcutaneous, spinal or epidermal administration (e.g., by injection or infusion)). Depending on the route of administration, the active compound, e.g., the compound of the present invention (or the compound used in the present invention), either alone or in combination with one or more additional therapeutic agents, may be coated in a material to protect the active compound(s) from the action of acids and other natural conditions that may inactivate the active compound.

[306] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions according to the present invention include water (e.g., water for injection), ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), aqueous solutions of a salt, carbohydrate, sugar alcohol, or an amino acid (such as saline or an aqueous amino acid solution), and suitable mixtures and/or buffered forms thereof, vegetable oils (such as olive oil), and injectable organic esters (such as ethyl oleate). Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[307] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active compounds is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions according to the present invention is contemplated.

[308] Additional therapeutic agents can be administered together with, before or after the compound of the present invention or with, before or after the compound used in the invention (in particular that specified above such as those of formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), (VIIIa), (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc)) or incorporated into the compositions. In one embodiment, the pharmaceutical composition described herein comprises a kinase inhibitor of the invention as described above (or a compound as used in the present invention) (e.g. having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), (VIIIa), (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc) or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, an N-oxide of R^{1a}, $R^{6'}$ and/or $R^{6''}$), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug of formula (IXa), (Xa), (XIa), (XIIa), (IXb), (Xb), (IXc), or (Xc) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination of any of the foregoing), at least one additional therapeutic agent, and one or more pharmaceutically acceptable excipients.

[309] The "additional therapeutic agent" (which in one embodiment is not a kinase inhibitor of formula (Ia), as specified herein, or in another embodiment (i) is not a kinase inhibitor of formula (Ia), as specified herein; (ii) is not a compound of formula (Ib), as specified herein; and (iii) is not a compound of formula (IIIa), as specified herein, or in another embodiment may be a different kinase inhibitor of formula (Ia), or in another embodiment may be a different kinase inhibitor of formula or (Ia), (Ib), and/or (Ic)) may be selected from any compound which can be used in the treatment of a disorder, disease or condition being a proliferative disorder (e.g., a cancer, such as one described, defined or disclosed elsewhere herein), and/or caused by or associated with: (i) the (e.g., erroneous) expression and/or activity of kinase, such as SRC, ABL/BCR-ABL, HCK, PDGFR CSFR1, LCK, SIK1, SIK2, SIK3, FLT3 and/or KIT; and/or

PHA2, EPHA4 and ACK1; and/or NEK11, WEE1, WNK2, Aurora-A, Aurora-B and TBK1 and/or (ii) cellular resistance to an (eg a cell-mediated) immune response. Examples of suitable additional therapeutic agents are defined or disclosed elsewhere herein, and include an EGFR inhibitor, gemcitabine, docetaxel, and immune checkpoint inhibitor (such as an inhibitor of PD1, PDL1, CTLA-4, LAG3 or IDO1, and in particular an immune checkpoint inhibitor selected from the list consisting of: nivolumab, relatlimab, ipilimumab and BMS-986205), TNF or an agonist of TNFR1- or TNFR2-signalling, adoptive cellular therapy including CAR T cells directed against a tumor antigen, vaccines including dendritic cell- (DC) based vaccination, or an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to TNF or an agonist of TNFR1-signalling, is administered to the subject. The additional therapeutic agent may induce an additive or synergistic therapeutic effect.

[310] The pharmaceutical composition described herein may comprise, in addition to the kinase inhibitor of the invention (and/or the compound used in the invention), at least one, e.g., 1, 2, 3, 4, 5, 6, 7 or 8, additional therapeutic agents. According to the present teaching, the at least one additional therapeutic agent may be formulated together with the kinase inhibitor of the invention (and/or with the compound used in the invention) in a single pharmaceutical composition. Alternatively, the pharmaceutical composition may be structured as kit of parts, wherein the kinase inhibitor of the invention (or the compound used in the invention) is provided in a first formulation and the at least one additional therapeutic agent is provided in a second formulation, i.e., a second pharmaceutical composition. The first and the second pharmaceutical compositions may be combined prior to use. In other words, before administering the pharmaceutical composition, a formulation comprising the additional therapeutic agent may be added to the first pharmaceutical composition comprising the kinase inhibitor of the invention (or the compound used in the invention). Alternatively, the present teaching envisages administering the kinase inhibitor of the invention (or the compound used in the invention) formulated in a first pharmaceutical composition and administering the at least one additional therapeutic agent formulated in a second pharmaceutical composition. The pharmaceutical compositions may be administered concomitantly or in succession. For example, the first pharmaceutical composition may be administered at a first point in time and the second pharmaceutical composition may be administered at a second point in time, wherein the points in time may be separated by, for example, 0, or up to 1, 2, 3, 4, 5 or 10 min, up to 1, 2, 3, 4, 5 or 10 hours, up to 1, 2, 3, 4, 5 or 10 days, up to 1, 2, 3, 4, 5 or 10 weeks, up to 1, 2, 3, 4, 5 or 10 months or up to 1, 2, 3, 4, 5 or 10 years.

[311] The compositions may also contain adjuvants such as preservatives, stabilizers, wetting agents, emulsifying agents, pH buffering agents, and dispersing agents. Prevention of the presence of microorganisms may be ensured by sterilization procedures and/or by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[312] Regardless of the route of administration selected, the active compounds, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions according to the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art (cf., e.g., Remington, "The Science and Practice of Pharmacy" edited by Allen, Loyd V., Jr., 22nd edition, Pharmaceutical Sciences, September 2012; Ansel et al., "Pharmaceutical Dosage Forms and Drug Delivery Systems", 7th edition, Lippincott Williams & Wilkins Publishers, 1999).

[313] A pharmaceutical composition can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. The pharmaceutical compositions containing one or more active compounds can be prepared with carriers that will protect the one or more active compounds against rapid release, such as a controlled release formulation, including

implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for the preparation of such compositions are generally known to those skilled in the art. See, e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[314] To administer a compound of the present invention (or a compound used in the present invention) by certain routes of administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the compound may be administered to an individual in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., J. Neuroimmunol. 7: 27(1984)).

[315] Pharmaceutical compositions typically are sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[316] An injectable composition should be sterile and fluid to the extent that the composition is deliverable by syringe. In addition to water, the carrier can be an isotonic buffered saline solution, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration.

[317] Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[318] Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms used according to the present invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[319] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[320] For the therapeutic/pharmaceutical formulations, compositions according to the present invention include those suitable for enteral administration (such as oral or rectal) or parenteral administration (such as nasal, topical (including vaginal, buccal and sublingual)). The compositions may conveniently be presented in unit dosage form and may be prepared by any methods known in the art of pharmacy. The amount of active ingredient (in particular, the amount of a compound according to the present invention) which can be combined with a carrier material to produce a pharmaceutical composition (such as a single dosage form) will vary depending upon the individual being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect.

[321] Generally, out of 100% (for the pharmaceutical formulations/compositions), the amount of active ingredient (in particular, the amount of the compound according to the present invention (or of the compound used in the present invention), optionally together with other therapeutically active agents, if present in the pharmaceutical formulations/compositions) will range from about 0.01% to about 99%, preferably from about 0.1% to about 70%, most preferably from about 1% to about 30%, wherein the reminder is preferably composed of the one or more pharmaceutically acceptable excipients.

[322] The amount of active ingredient, e.g., a compound according to the present invention (or a compound used in the present invention), in a unit dosage form and/or when administered to an individual or used in therapy, may range from about 0.1 mg to about 1000 mg (for example, from about 1 mg to about 500 mg, such as from about 10 mg to about 200 mg) per unit, administration or therapy. In certain embodiments, a suitable amount of such active ingredient may be calculated using the mass or body surface area of the individual, including amounts of between about 1 mg/kg and 10 mg/kg (such as between about 2 mg/kg and 5 mg/kg), or between about 1 mg/m^2 and about 400 mg/m^2 (such as between about 3 mg/m^2 and about 350 mg/m^2 or between about 10 mg/m^2 and about 200 mg/m^2).

[323] Actual dosage levels of the active ingredients in the pharmaceutical compositions according to the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[324] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the (e.g., therapeutically) effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start with doses of the compounds according to the present invention (or of the compounds used in the present invention) at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable daily dose of a composition according to the present invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. It is preferred that administration be oral, intravenous, intramuscular, intraperitoneal, or subcutaneous, preferably administered proximal to the site of the target. If desired, the (e.g., therapeutically) effective daily dose of a pharmaceutical composition may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. While it is possible for a compound according to the present invention (or for the compound used in the present invention) to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation/composition.

[325] For oral administration, the pharmaceutical composition according to the present invention can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutical acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone, hydroxypropyl methylcellulose), fillers (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate), lubricants (e.g., magnesium stearate, talc, silica), disintegrants (e.g., potato starch, sodium starch glycolate), or wetting agents (e.g., sodium lauryl sulphate). Liquid preparations for oral administration can be in the form of, for example, solutions, syrups, or suspensions, or can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparation can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol, syrup, cellulose derivatives, hydrogenated edible fats), emulsifying agents (e.g., lecithin, acacia), non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol, fractionated vegetable oils), preservatives (e.g., methyl or propyl-p-hydroxycarbonates, sorbic acids). The preparations can also contain buffer salts, flavouring, coloring and sweetening agents as deemed appropriate. Preparations for oral administration can be suitably formulated to give controlled release of the pharmaceutical composition of the invention.

[326] In one embodiment, the compound is orally administered in a concentration of, for example, at most 100 mg/kg body weight (such as at most 50 mg/kg body weight, at most 40 mg/kg body weight, at most 30 mg/kg body weight, at most 20 mg/kg body weight, at most 10 mg/kg body weight, at most 5 mg/kg body weight, at most 4 mg/kg body weight, at most 3 mg/kg body weight, at most 2 mg/kg body weight, at most 1 mg/kg body weight).

[327] In one embodiment, the compound is parenterally administered (e.g., intravenously, intramuscularly, or subcutaneously), in a concentration of, for example, at most 10 mg/kg body weight (such as at most 5 mg/kg body weight, at most 4 mg/kg body weight, at most 3 mg/kg body weight, at most 2 mg/kg body weight, at most 1 mg/kg body weight, at most 0.5 mg/kg body weight, at most 0.4 mg/kg body weight, at most 0.3 mg/kg body weight, at most 0.2 mg/kg body weight, at most 0.1 mg/kg body weight).

[328] The pharmaceutical composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc.

[329] For administration by inhalation, the pharmaceutical composition according to the present invention is conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer, with the use of a suitable propellant (e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, nitrogen, or other suitable gas). In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatine, for use in an inhaler or insufflator can be formulated containing a powder mix of the pharmaceutical composition according to the present invention and a suitable powder base such as lactose or starch.

[330] The pharmaceutical composition according to the present invention can be formulated for parenteral administration by injection, for example, by bolus injection or continuous infusion. In one embodiment, the compounds or compositions according to the present invention may be administered by slow continuous infusion over a long period, such as more than 24 hours, in order to reduce toxic side effects. The administration may also be performed by continuous infusion over a period of from 2 to 24 hours, such as of from 2 to 12 hours. Such regimen may be repeated one or more times as necessary, for example, after 6 months or 12 months.

[331] In yet another embodiment, the compounds or compositions according to the present invention are administered by maintenance therapy, such as, e.g., once a week for a period of 6 months or more.

[332] Formulations for injection can be presented in units dosage form (e.g., in phial, in multi-dose container), and with an added preservative. The pharmaceutical composition according to the present invention can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, or dispersing agents. Alternatively, the agent can be in powder form for constitution with a

suitable vehicle (e.g., sterile pyrogen-free water) before use. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition can also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[333] Compositions according to the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate. Dosage forms for the topical or transdermal administration of compositions according to the present invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[334] Therapeutic/pharmaceutical compositions can be administered with medical devices known in the art. For example, in a preferred embodiment, a therapeutic/pharmaceutical composition according to the present invention can be administered with a needleless hypodermic injection device, such as the devices disclosed in US 5,399,163; US 5,383,851; US 5,312,335; US 5,064,413; US 4,941,880; US 4,790,824; or US 4,596,556. Examples of well-known implants and modules useful in the present invention include those described in: US 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; US 4,486,194, which discloses a therapeutic device for administering medicaments through the skin; US 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; US 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; US 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and US 4,475,916, which discloses an osmotic drug delivery system.

[335] Many other such implants, delivery systems, and modules are known to those skilled in the art. In certain embodiments, the compounds according to the present invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the compounds according to the present invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., US 4,522,811; US 5,374,548; and US 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, and thus enhance targeted drug delivery (see, e.g., V.V. Ranade (1989) J. Clin. Pharmacol. 29: 685). Exemplary targeting moieties include folate or biotin (see, e.g., US 5,416,016 to Low et al.); mannosides (Umezawa et al., (1988) Biochem. Biophys. Res. Commun. 153: 1038); antibodies (P.G. Bloeman et al. (1995) FEBS Lett. 357: 140; M. Owais et al. (1995) Antimicrob. Agents Chemother. 39: 180); and surfactant protein A receptor (Briscoe et al. (1995) Am. J. Physiol. 1233: 134).

[336] In one embodiment, the compounds according to the present invention (or the compounds used in the present invention) are formulated in liposomes. In a more preferred embodiment, the liposomes include a targeting moiety. In a most preferred embodiment, the compounds in the liposomes are delivered by bolus injection to a site proximal to the desired area. Such liposome-based composition should be fluid to the extent that easy syringability exists, should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

[337] A "therapeutically effective dosage" for therapy/treatment can be measured by objective responses which can either be complete or partial. A complete response (CR) is defined as no clinical, radiological or other evidence of a

condition, disorder or disease. A partial response (PR) results from a reduction in disease of greater than 50%. Median time to progression is a measure that characterizes the durability of the objective tumor response.

[338] A "therapeutically effective dosage" for therapy/treatment can also be measured by its ability to stabilize the progression of a condition, disorder or disease. The ability of a compound to inhibit one or more protein kinases or to reduce the viability of cells associated with a proliferative disorder, such as cancer cells can be evaluated by using appropriate *in-vitro* assays known to the skilled practitioner, such as those described herein (in particular in the Examples below). Alternatively, the properties of a compound described in the present invention can be evaluated by examining the ability of the compound in appropriate animal model systems known to the skilled practitioner such as those described herein (in particular in the Examples below). A therapeutically effective amount of a compound according to the present invention can cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the condition, disorder or disease or the symptoms of the condition, disorder or disease or the predisposition toward the condition, disorder or disease in an individual. One of ordinary skill in the art would be able to determine such amounts based on such factors as the individual's size, the severity of the individual's symptoms, and the particular composition or route of administration selected.

[339] The pharmaceutical composition according to the invention can also, if desired, be presented in a pack, or dispenser device which can contain one or more (e.g., unit) dosage forms containing the active compound. The pack can for example comprise metal or plastic foil, such as blister pack. The pack or dispenser device can be accompanied with a leaflet or other information; in particular, that describing (either to the patient and/or the administering physician) salient information or details on the pharmaceutical composition contained in the package, such as how to administer, recommended dosages, safety and/or side-effect information.

[340] In a particular embodiment, a pharmaceutical composition of the invention is formulated for oral administration, and in an alternative particular embodiment, a pharmaceutical composition of the invention is formulated for intravenous administration.

[341] In one embodiment, a pharmaceutical composition of the invention is in unit dose form, and in particular may be in a unit dose form that is formulated for oral administration.

[342] Each of such a unit dose form may comprise (e.g., it may contain) between 1 and 950mg of the compound, such as the kinase inhibitor of the first aspect or a compound used in the fifth aspect (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa) (or a compound having the general formula (Ib), (IIb), (IIIb), (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc)), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, an N-oxide of R^{1a}, $R^{6'}$ and/or $R^{6''}$), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug of formula (IXa), (Xa), (XIa), or (XIIa) (or (IXb), (Xb), (IXc), or (Xc)) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof). In particular, (e.g., each of) such a unit dose form may comprise (e.g., it may contain) between 2 and 150mg of such compound; and suitably, between 10 and 150mg of such compound.

[343] In particular of such embodiments, a pharmaceutical composition of the invention that is in unit dose form (and in particular one be in a unit dose form that is formulated for oral administration) may comprise (e.g., it may contain) - for each unit dose form - about an amount of such compound selected from the list of amounts consisting of: 2mg, 5mg, 15mg, 20mg, 50mg, 70mg, 80mg, 100mg and 140mg; in particular, comprising (e.g., containing) an amount of about 20mg, 50mg, 70mg or 100mg of a compound of the invention (or of a compound used in the invention).

[344] In one particular embodiment, the pharmaceutical composition of the invention is (e.g., is formed as) a tablet, caplet or capsule; suitably the pharmaceutical composition of the invention (e.g., a unit dose form thereof) is a caplet. Methods to form (e.g., manufacture) tablets and caplets are, for example, described elsewhere herein.

[345] Suitable excipients for the pharmaceutical compositions of the invention, in particular when formed as a tablet or caplet, include, and particular embodiments of such a pharmaceutical composition of the invention include those that further comprise one or more (e.g., all of) the excipients selected from the list consisting of: lactose (e.g., lactose monohydrate), microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose and magnesium stearate.

Therapeutic and other applications

[346] In **a third aspect**, the present application provides **a compound** as specified above under the heading "Compounds" **or a pharmaceutical composition** as specified above under the heading "Pharmaceutical compositions" **for use as a medicament**, for example for use in therapy.

[347] It is contemplated that a compound as specified above under the heading "Compounds" may be used for the inhibition of: (i) a kinase, such as one described herein, in particular SRC, ABL/BCR-ABL, SRC, HCK, PDGFR, CSFR1, LCK, SIK1, SIK2, SIK3, FLT3 and/or KIT, and/or PHA2, EPHA4 and ACK1, and/or NEK11, WEE1, WNK2, Aurora-A, Aurora-B and TBK1, such as SIK3, ABL/BCR-ABL, SRC, HCK, PDGFR and/or CSF1R; and/or (ii) cellular resistance to an (e.g., a cell-mediated) immune response. For example, in a related aspect the compound (especially, where the compound is one of the first aspect of the invention) can be used in a method for the treatment of a disease, disorder or condition in a subject (in particular a human patient), comprising administering to the subject the compound, wherein the disease or condition is associated with such kinase.

[348] In particular (and as further described in the fifth aspect below), it is contemplated that a compound as specified above under the heading "Compounds" may be used for the treatment of a proliferative disorder (such as MPAL) characterised by (or cells involved with the proliferative disorder characterised by), *inter-alia*, the presence of MEF2C protein (such as phosphorylated MEF2C protein and/or MEF2C protein as an active transcription factor), a human chromosomal translocation at 11q23, and/or a KMT2A fusion oncoprotein.

[349] The compounds of the invention (or the compounds used in the fifth aspect of the invention) may be used for treatment alone or in conjunction with one or more additional therapeutic agents, for example in combination with those that are defined or disclosed elsewhere herein, and that include an EGFR inhibitor, gemcitabine, docetaxel, and immune checkpoint inhibitor (such as an inhibitor of PD1, PDLL, CTLA-4, LAG3 or IDO1, and in particular an immune checkpoint inhibitor selected from the list consisting of: nivolumab, relatlimab, ipilimumab and BMS-986205), TNF or an agonist of TNFR1- or TNFR2-signalling, adoptive cellular therapy including CAR T cells directed against a tumor antigen, vaccines including dendritic cell- (DC) based vaccination, or an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to TNF or an agonist of TNFR1-signalling, is administered to the subject.

[350] Treatment including or utilising such compounds may be provided at home, the doctor's office, a clinic, a hospital's outpatient department, or a hospital. Treatment generally begins under medical supervision so that medical personnel can observe the treatment's effects closely and make any adjustments that are needed. The duration of the treatment depends on the age and condition of the patient, as well as how the patient responds to the treatment.

[351] A person having a greater risk of developing a condition, disorder or disease may receive prophylactic treatment to inhibit or delay symptoms of the condition, disorder or disease.

[352] The term "treatment" is known to the person of ordinary skill, and includes the application or administration of a therapeutic agent (e.g., a pharmaceutical composition containing said agent) or procedure to a patient or application or administration of a therapeutic agent (e.g., a pharmaceutical composition containing said agent) or

procedure to a cell, cell culture, cell line, sample, tissue or organ isolated from a patient, who has a condition, disorder or disease, a symptom of the condition, disorder or disease or a predisposition toward a condition, disorder or disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, affect or prevent the condition, disorder or disease, the symptoms of the condition, disorder or disease or the predisposition toward the condition, disorder or disease. Hence, the term "treatment" can include prophylactic treatment of a condition, disorder or disease, or the symptom of a condition, disorder or disease. A therapeutic agent, when used in treatment, includes the kinase inhibitors of the invention (or the compounds used in the fifth aspect of the present invention) and includes, but is not limited to, additional therapeutic agents that may be small molecules, peptides, peptidomimetics, polypeptides/proteins, antibodies, nucleotides such as DNA or RNA, cells, viruses, ribozymes, siRNA, and antisense oligonucleotides.

[353] Accordingly, in **one fourth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the present invention relates to **a compound** as specified under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof) **for use in a treatment of a proliferative disorder** in a subject.

[354] In **another fourth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the present invention relates to **a pharmaceutical composition** as described above (e.g., one comprising a compound as specified under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof)) **for use in a treatment of a proliferative disorder** in a subject.

[355] In **a related fourth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the present invention relates to **a method for the treatment of a proliferative disorder** in a subject, comprising administering to the subject (e.g., a therapeutically effective amount of): (X) a compound as specified under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof); or (Y) a pharmaceutical composition as described above (e.g., one comprising a compound as specified under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex,

polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof)).

[356] In **another related fourth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the present invention relates to **a use of a compound** as specified under the heading "Compounds" (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof) **for the manufacture of a medicament for the treatment of a proliferative disorder** in a subject.

[357] In such fourth aspects, the treatment of such use or method comprises administering to the subject (e.g., a therapeutically effective amount of) a compound or pharmaceutical composition of the invention.

[358] Furthermore, in **a fifth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the present invention relates to **a compound for use, or a pharmaceutical composition for use, in a treatment of a proliferative disorder** in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, wherein the compound is selected from (a) a compound of the first aspect (e.g., a kinase inhibitor having the general formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa), or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa), (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof); (b) a compound of formula (Ib), as defined herein (e.g., a compound having the general formula (Ib), (IIb), or (IIIb), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a} and/or $R^{6'}$), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXb) or (Xb) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof); and (c) a compound of formula (Ic), as defined herein (e.g., a compound having the general formula (Ic), (IIc), (IIIc), (IVc), (Vc), (VIc), (VIIc), or (VIIIc), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, N-oxides of R^{1a} and/or $R^{6''}$), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXc) or (Xc) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof), or the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient; wherein the proliferative disorder is selected from one or more of (α) to (γ): (α) a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by) the presence of (or an amount of) myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by (or cells involved with the proliferative disorder are further characterised by) the presence of (or an amount of phosphorylated histone deacetylase 4 (HDAC4) protein, such as of HDAC4 protein phosphorylated by SIK3; and/or (β) a proliferative disorder characterised by: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A

(*KMT2A*) gene; (iii) the presence of (or an amount of) an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or (γ) a mixed phenotype acute leukaemia (MPAL). In a related aspect, the present invention provides a method for the treatment of a proliferative disorder in a subject, comprising administering to the subject a compound or pharmaceutical composition as defined in the fifth aspect, wherein the proliferative disorder is as defined in the fifth aspect. In one embodiment of the fifth aspect, the compound of formula (Ic) does not encompass compounds which belong to one or more of the groups (1), (2), (3), (4), (5) and/or (6) (such as compounds of one or more of the groups (1) (in particular, compounds of group (1) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl), (2) and/or (4) (in particular, compounds in particular, compounds 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}pyridin-2-yl)amino]-4-methyl-N-[1-(phenylmethyl)-1H-indazol-5-yl]-1,3-thiazole-5-carboxamide and 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}pyridin-2-yl)amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-1,3-thiazole-5-carboxamide) specified above under the heading "Compounds". In one embodiment of the fifth aspect, the compound of formula (Ib) does not encompass compounds which belong to one or more of the groups (7) (such as, in particular, compounds of group (7)(i) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl), (8), (9) and/or (10) as specified above under the heading "Compounds".

[359] In one particular embodiment of such aspects, the subject is a human, suitably an adult human. For example, a human that is 18 (or 16) years or older, such as a human between the ages of about 18 (or 16) and 90, or between 18 (or 16) and 80. In certain of such embodiments, the adult human is about 20 or older, 30 or older, 35 or older, 40 or older, 45 or older, 50 or older or 55 or older. In more particular of such embodiments, the adult human is a young adult (such as between about 18 (or 16) and 45 (or 40), or between about 30 and 45 (or 40)), is middle aged (such as between about 45 (or 40) and 65 (or 60), or between about 45 (or 40)) and 55 (or 50), or between about 55 (or 50) and 65 (or 60), or is elderly (such as being between about 60 and 90 (or older, such as 92, 95 or 98), between about 65 and 85 or between about 70 and 88).

[360] As an alternative to such embodiments, the subject treated is a paediatric human such as being younger than about 18 (or 16). For example, such a human may be between about 3 and 18 (or 16), such as between about 5 and 16 or between about 10 and 16 or 12 and 17. The paediatric human may be an infant (such as between about two months of age to about 2 years or age), a toddler (such as between about 2 years to about 4 years), an early child (such as between about 4 years and about 9 years), a preadolescent (such as between about 9 years and about 12 or 13 (or 11 or 14) years) or an adolescent (such as between about 12 or 13 (or 11 or 14) years) years and about 15 (or 16 or 17)).

[361] In one embodiment of such aspects, the treatment comprises administering to an adult human subject in need thereof an amount of a compound of the invention (for example, as comprised in a pharmaceutical composition) of less than about 140mg daily. For example, optionally, where the proliferative disorder is not (e.g., the subject suffers from a proliferative disorder that is not) chronic phase Ph+ CML. In an alternative embodiment of such aspects, the treatment comprises administering to an adult human subject in need thereof an amount of such compound (for example, as comprised in a pharmaceutical composition) of more than about 140mg daily, such as more than 150mg daily.

[362] In another embodiment of such aspects, the treatment comprises administering to an adult human subject in need thereof an amount of a compound of the invention, or of a compound used in the invention, (for example, as comprised in a pharmaceutical composition) of less than about 100mg daily. For example, optionally, where the proliferative disorder is (e.g., the subject suffers from) chronic phase Ph+ CML. In an alternative embodiment of such aspects, the treatment comprises administering to an adult human subject in need thereof an amount of such compound, or of a compound used in the invention, (for example, as comprised in a pharmaceutical composition) of more than about 100mg daily, such as more than 120mg daily.

[363] In one alternative embodiment, the treatment comprises administering to a paediatric human subject in need thereof an amount of a compound of the invention (or of a compound used in the invention) of:

- less than about 40mg daily for paediatric patients with a body weight of 10kg to less than 20kg;
- less than about 60mg daily for paediatric patients with a body weight of 20kg to less than 30kg;
- less than about 70mg daily for paediatric patients with a body weight of 30kg to less than 45kg; or
- less than about 100mg daily for paediatric patients with a body weight of at least 45kg.

[364] In one further alternative embodiment, the treatment comprises administering to a paediatric human subject in need thereof an amount of a compound of the invention (or of a compound used in the invention) of:

- greater than about 40mg daily for paediatric patients with a body weight of 10kg to less than 20kg;
- greater than about 60mg daily for paediatric patients with a body weight of 20kg to less than 30kg;
- greater than about 70mg daily for paediatric patients with a body weight of 30kg to less than 45kg; or
- greater than about 100mg daily for paediatric patients with a body weight of at least 45kg.

[365] In respect of those embodiments where an amount of such compound is (e.g. to be) administered to the human subject, such amount may be administered less frequently than daily. For example, a given amount of "less than 40mg daily", may be achieved by administering, for example, 35, 30 or 20mg each day, or 75, 65, or 40mg once every two days (or less frequently).

[366] In a particular embodiment, upon (or after) such administration of the (eg therapeutically effective) amount of a compound of the invention (or of a compound used in the invention) the subject is less likely to (eg, does not) have (or suffer from) an adverse reaction, such myelosuppression.

[367] In one of such particular embodiments, upon (or after) such administration of the (eg therapeutically effective) amount of the compound to the subject is less likely to (eg, does not) have (or suffer from) a non-haematological adverse reaction, such as a cardiological adverse reaction.

[368] In more particular of such embodiments, upon (or after) such administration of the (eg therapeutically effective) amount of the compound, to the subject is less likely to (eg, does not) have (or suffer) QT-prolongation.

[369] In one embodiment, the subject is characterised by not concomitantly using a strong CYP3A4 inhibitor. For example, is not concomitantly using ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, or ingests grapefruit juice.

[370] The disease, disorder or a condition, in the context of the herein described invention, is, in certain embodiments, a proliferative disorder (including a condition or symptom associated with such disorder).

[371] A "proliferative disorder" refers to a disorder characterised by abnormal proliferation of cells. A proliferative disorder does not imply any limitation with respect to the rate of cell growth, but merely indicates loss of normal controls that affect growth and cell division. Thus, in some embodiments, cells of a proliferative disorder can have the same cell division rates as normal cells but do not respond to signals that limit such growth. Within the ambit of "proliferative disorder" is neoplasm or tumour, which is an abnormal growth of tissue or cells. Cancer is art understood, and includes any of various malignant neoplasms characterised by the proliferation of cells that have the capability to invade surrounding tissue and/or metastasise to new colonisation sites. Proliferative disorders include cancer, atherosclerosis, rheumatoid arthritis, idiopathic pulmonary fibrosis and cirrhosis of the liver. Non-cancerous proliferative disorders also include hyperproliferation of cells in the skin such as psoriasis and its varied clinical forms, Reiter's syndrome, pityriasis rubra pilaris, and hyperproliferative variants of disorders of keratinisation (e.g., actinic keratosis, senile keratosis), scleroderma, and the like.

[372] In more particular embodiments, the proliferative disorder is a cancer or tumour, in particular a solid tumour (including a condition or symptom associated with such cancer or tumour). Such proliferative disorders including but not limited to head and neck cancer, squamous cell carcinoma, multiple myeloma, solitary plasmacytoma, renal cell cancer, retinoblastoma, germ cell tumours, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumour of

the kidney, Ewing Sarcoma, chondrosarcoma, any haemotological malignancy (e.g., chronic lymphoblastic leukemia, chronic myelomonocytic leukemia, acute lymphoblastic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, acute myeloblasts leukemia, chronic myeloblastic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, hairy cell leukemia, mast cell leukemia, mast cell neoplasm, follicular lymphoma, diffuse large cell lymphoma, mantle cell lymphoma, marginal zone lymphoma, Burkitt Lymphoma, mycosis fungoides, seary syndrome, cutaneous T-cell lymphoma, peripheral T cell lymphoma, chronic myeloproliferative disorders, myelofibrosis, myeloid metaplasia, systemic mastocytosis), and central nervous system tumours (eg, brain cancer, glioblastoma, non- glioblastoma brain cancer, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumour, medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma and choroid plexus papilloma), myeloproliferative disorders (eg, polycythemia vera, thrombocythemia, idiopathic myelfibrosis), soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer, or liver cancer.

[373] In a particular embodiment, the various aspects of the invention relate to (for example the compounds or the pharmaceutical compositions of the invention are used in) treatments for proliferative disorders that include those described herein. Accordingly, in such embodiments the proliferative disorder may be a cancer or tumour.

[374] In certain embodiments of the various aspects of the invention, the proliferative disorder is selected from one or more of:

- a mixed phenotype acute leukaemia (MPAL), especially MPAL with MLL (KMT2A) rearrangement; and/or
- a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by): (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of a KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or
- a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by) the presence of myocyte enhancer factor 2C (MEF2C) protein.

[375] In particular embodiments, the proliferative disorder may be mixed phenotype acute leukaemia (MPAL); also known as "mixed lineage leukaemia" (MLL). MPAL is a very aggressive blood cancer that predominantly occurs in paediatric patients and, unlike other types of childhood acute leukaemias, has a dismal prognosis (reviewed by Slany 2009, Haematologica 94:984). One form of MPAL is characterised by the presence of lysine methyltransferase 2A (KMT2A) fusion proteins (also known as MLL fusion proteins) that are the result of chromosomal translocations affecting the *KMT2A* gene (also known as the *MLL1* gene) at 11q23. This KMT2A/MLL rearrangement is the second most frequent genetic lesion in MPAL (MPAL MLL+). These 11q23 translation events juxtapose the amino-terminus of the histone methyltransferase KMT2A with a variety of different (translocation) fusion partners that destroy normal histone methyltransferase function of KMT2A and replace it by heterologous functions contributed by the (translocation) fusion partner. The resulting protein chimeras are transcriptional regulators that take control of targets normally controlled by KMT2A. In particular, the transcription factor MEF2C can be controlled by KMT2A and is described as an oncogene in childhood acute leukaemias. MEF2C expression is associated with KMT2A fusion gene rearrangement in AML (Schwieger et al 2009, Blood 114:2476), and MEF2C expression defines a subset of AML patients with poor survival outcome (Lazlo et al 2015, J Hematol & Oncol 8:115). In one of such embodiments, the proliferative disorder is MPAL with MLL (KMT2A) rearrangement.

[376] In particular embodiments, the proliferative disorder may be characterised by (or cells involved with the proliferative disorder may be characterised by) the presence of a human chromosomal translocation at 11q23, such as a human chromosome translocation selected from the group consisting of: t(4,11), t(9,11), t(11,19), t(10,11) and t(6,11), in particular t(4;11)(q21;q23) [TPG: *AF4*], t(9;11)(p22;q23) [TPG: *AF9*], t(11;19)(q23;p13.3) [TPG: *ENL*],

ins(10;11)(p12;q23q13) [TPG: *AF10*], t(11;19)(q23;p13.1) [TPG: *ELL*] and t(6;11)(q27;q23) [TPG: *AF6*]. In other embodiments, the human chromosomal translocation may be any of those identified in Table 2 of Meyer et al 2018.

[377] The lysine methyltransferase 2A (*KMT2A*) gene on human chromosome 11q23 (previously now as mix-lineage leukaemia 1 gene, *MLL1*) can be disrupted by such translocations; producing a fusion with one of more than 90 (known) translocation partner genes (Meyer et al 2018, Leukemia 32:273). The majority of leukaemias result from *KMT2A* fusions with one of about six common (translocation) partner genes (as reviewed by Winters & Bernt 2017, Front Ped 5:4), with nine specific gene fusions accounting for more than 90% of all illegitimate recombinations of the *KMT2A* fusions (Meyer et al 2018). Approximately 10% or all leukaemias harbour such translocations (and hence, *KMT2A*-fusion genes).

[378] In certain embodiments, the proliferative disorder may be characterised by (or cells involved with the proliferative disorder may be characterised by) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene, and/or the presence of a KMT2A fusion oncoprotein. For example, the KMT2A fusion oncoprotein may be present at an amount (eg a quantitative amount), such as an amount that is in excess of physiological amount (eg, for that cell type and/or that time/stage), including from expression or over-expression of the protein. In another embodiment, such protein may be present at an amount (eg a quantitative amount) that is in excess of a threshold amount or is an outlier from a reference distribution of amounts of such protein. In particular of such embodiments, the rearrangement of the *KMT2A* gene comprises, or the KMT2A fusion oncoprotein is expressed from a rearrangement that comprises, a fusion of the *KMT2A* gene with a translocation partner gene (TPG) selected from the group consisting of: *AF4*, *AF9*, *ENL*, *AF10*, *ELL* and *AF6*, in particular selected from the group consisting of *AF4*, *AF9* and *ENL*. Other TPGs can include *EPS15* or *AF1Q*, or any other any of those TPGs identified in lines 10 to 20, 21 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, 71 to 80, 81, 82 and/or 83 or Table 1 of Meyer et al 2018.

[379] Certain TPGs can be associated with certain proliferative disorders, and in particular embodiments herein, the proliferative disorder and TPG of the *KMT2A* gene is one selected from the group shown in Figure 23 (from Meyer et al 2018).

[380] Tarumoto and co-workers (2018, Mol Cell 69:1017) showed that MEF2C activity in AML is driven by SIK3-phosphorylation of HDAC4, and that SIK3 knock-out or chemical inhibition with the small molecule tool compound HG-9-91-01 strongly decreases viability of several MPAL-associated AML cell lines (including MOLM-13 and MV4-11): because cytoplasmic retention of SIK3-phosphorylated HDAC4 regulates MEF2C activity, by preventing nuclear-located (un-phosphorylated) HDAC4 acting as a repressive cofactor of MEF2C, a transaction factor of tumour survival/maintenance genes associated with AML proliferation (Figure 19).

[381] Accordingly, in certain embodiments, a proliferative disorder may be one (or more) characterised by (or cells involved with the proliferative disorder may be characterised by) the presence of myocyte enhancer factor 2C (MEF2C) protein. For example, the MEF2C protein may be present at an amount (eg a quantitative amount), such as an amount that is in excess of physiological amount (eg, for that cell type and/or that time/stage), including from expression or over-expression of the protein. In another embodiment, such protein may be present at an amount (eg a quantitative amount) that is in excess of a threshold amount or is an outlier from a reference distribution of amounts of such protein. In particular of such embodiments, the MEF2C protein is a phosphorylated MEF2C protein, such as one phosphorylated by a MARK kinase (Vakoc & Kentis 2018, Oncotarget 9:32276), such as MEF2C protein phosphorylated at S222. The MEF2C protein may be one that acts as (eg, is) an active transcription factor. In particular embodiments, the proliferative disorder may be further characterised by (or cells involved with the proliferative disorder may be further characterised by) the presence of histone deacetylase 4 (HDAC4) protein, preferably in the nucleus of a cell and/or of phosphorylated HDAC4 protein (eg, HDAC4 protein phosphorylated by SIK3). Any of such HDAC4 proteins may be present at an amount (eg a quantitative amount), such as an amount that is in excess of physiological amount (eg, for that cell type and/or that time/stage), including from expression or over-expression of the protein. In another

embodiment, such protein may be present at an amount (eg a quantitative amount) that is in excess of a threshold amount or is an outlier from a reference distribution of amounts of such protein.

[382] Furthermore, Tarumoto and co-workers (2020, Blood 135:56) noted that multiple myeloma and AML cell lines express the highest levels of MEF2C and SIK3 when compared to other cancer cell lines. In their analysis of 162 genomically characterised human AML samples in TCGA1, they found that MEF2C expression was correlated, not only with the presence of MLL (11q23) translocations, but was also correlated with K-RAS proto-oncogene GTPase (*KRAS*) mutations and RUNX family transcription factor 1 (*RUNX1*) mutations.

[383] Therefore, in certain embodiments the proliferative disorder may be characterised by (or cells involved with the proliferative disorder may be characterised by) the presence of a mutation in the *KRAS* gene and/or in the *RUNX1* gene.

[384] Another form of of MPAL is characterised by a BCR/ABL rearrangement. MPAL with t(9;22)(q34;q11.2) (or BCR/ABL1 rearrangement) is considered as a separate entity (Arber et al 2016, Blood 127:2391). The t(9;22)(q34;q11.2 translocation results in a *BCR/ABL1* fusion gene located on the Philadelphia chromosome (Ph), causing a constitutively active BCR/ABL1 tyrosine kinase.

[385] Hence, in another certain embodiments of the various aspects of the invention, the proliferative disorder is selected from one or more of:

- a mixed phenotype acute leukaemia (MPAL), in particular MPAL with BCR/ABL1 fusion gene; and/or
- a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by): (i) the presence of a human chromosomal translocation t(9;22)(q34;q11.2); (ii) the presence of a BCR/ABL1 rearrangement gene; (iii) the presence of a BCR/ABL1 fusion oncoprotein.

[386] Accordingly, and in **a further aspect**, the invention relates to **a compound or a pharmaceutical composition for use in a treatment of a proliferative disorder** in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, wherein the compound is selected from the following compounds (a) to (c), or (d) or (e), or the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient: (a) a compound of formula (Ia), such as any embodiment thereof as described above; (b) a compound of formula (Ib), such as any embodiment thereof as described above; and (c) a compound of formula (Ic), such as any embodiment thereof as described above, and in each case , salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or (d) dasatinib, in particular N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate (Figure 1A); or (e) ARN-3261 (Vankayalapati et al 2017, AACR Cancer Res 77(13 Suppl):Abstract nr LB-296; US 9,260,426, US 9,890,153, US 9,951,062).

[387] In **a related aspect**, the invention relates to **a method for the treatment of a proliferative disorder** in a subject, comprising administering to the subject such a compound or pharmaceutical composition.

[388] In one particular embodiments of such further and related aspects, the proliferative disorder is selected from one or more of (X) to (Z):

(X) a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by) the presence of (and/or an amount of) myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by (or cells involved with the proliferative disorder are further characterised by) the presence of (and/or an amount of) phosphorylated histone deacetylase 4 (HDAC4) protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(Y) a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by): (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine

methyltransferase 2A (*KMT2A*) gene; (iii) the presence of (and/or an amount of) a KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or

(Z) a mixed phenotype acute leukaemia (MPAL), especially MPAL with MLL (KMT2A) rearrangement.

[389] In another particular embodiments of such further and related aspects, the proliferative disorder is selected from one or more of (X') an (Y'):

(X') a mixed phenotype acute leukaemia (MPAL), especially MPAL with BCR/ABL1 fusion gene; and/or

(Y') a proliferative disorder characterised by (or cells involved with the proliferative disorder characterised by): (i) the presence of a human chromosomal translocation t(9;22)(q34;q11.2); (ii) the presence of a BCR/ABL1 rearrangement gene; (iii) the presence of a BCR/ABL1 fusion oncoprotein.

[390] In further embodiments of such aspects, the compound is one having a formula of (Ib) or of (Ic), wherein L is a bond and R^6 is a 5-membered heteroaryl which is optionally substituted with one or more independently selected R^7. In certain of such embodiments, the compound is not 5-thiazolecarboxamide, *N*-[1-[[2,4-bis(trifluoromethyl)phenyl]methyl]-1*H*-pyrazol-4-yl]-2-(2-pyridinylamino)- (CAS 2377755-04-7).

[391] In further embodiments of such aspects, the compound is one having a formula of (Ib) or of (Ic), wherein L is a bond and R^6 is a 5 or 6-membered monocyclic heteroaryl which contains at least one S ring atom and which is optionally substituted with one, two or three independently selected R^7, in particular those embodiments where R^6 is thienyl optionally substituted with one, two or three independently selected R^7.

[392] In particular of such embodiments, such R^6 is substituted with one, two or three independently selected R^7, including those embodiments wherein R^7 is independently selected from the group consisting of halogen and C_{1-2} alkyl, wherein the C_{1-2} alkyl is optionally substituted with one, two or three independently selected R^{30}.

[393] In certain of embodiments of such aspects, the compound is of formula (Ia), such as one selected from the group consisting of those shown in Table A (or depicted in Figure 1E). In other aspects, the compound can be one selected from the group consisting of **C7**, **E4**, **E9**, **E10** and **E16**, such as selected from compound **E4** , **E9** or **E10**. In yet other aspects, the compound can be **A8** (dasatinib), or can be ARN-3261 (Vankayalapati et al 2017, AACR Cancer Res 77(13 Suppl):Abstract nr LB-296; US 9,260,426, US 9,890,153, US 9,951,062).

[394] In any of such aspects, the proliferative disorder is, for example, a cancer of a tumour, such as a cancer or tumour described elsewhere herein. In particular embodiments, the proliferative disorder is a haematopoietic malignancy. The proliferative disorder may be a lymphoid malignancy.

[395] In particular of such embodiments, the proliferative disorder may be: (i) a myeloma, preferably multiple myeloma; or (ii) a leukaemia, preferably an acute myeloid leukaemia (AML) or an acute lymphoblastic leukaemia (ALL), more preferably T cell acute lymphoblastic leukaemia (T-ALL), an MLL-AML or an MLL-ALL. In other embodiments, the the proliferative disorder may be one selected from the group set out in Figure 23.

[396] A subject for treatment in connection with such aspects may, suitably, be a human paediatric patient; for example, a human individual of less than about 18 years of age (or 16 years or age). For example, such a human may be between about 3 and 18 (or 16), such as between about 5 and 16 or between about 10 and 16 or 12 and 17. The paediatric human may be an infant (such as between about two months of age to about 2 years or age), a toddler (such as between about 2 years to about 4 years), an early child (such as between about 4 years and about 9 years), a preadolescent (such as between about 9 years and about 12 or 13 (or 11 or 14) years) or an adolescent (such as between about 12 or 13 (or 11 or 14) years) years and about 15 (or 16 or 17)).

[397] In further embodiments, the subject carries a *KMT2A* rearrangement (*KMT2A-r*). For example, the subject may be a patient suffering from a *KMT2A-r* leukaemia, especially a (eg, paediatric) human patient as described elsewhere herein.

[398] In one particular embodiment, the cancer is a hematopoietic or lymphoid cancer, and in one such embodiment, the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) a Philadelphia chromosome-positive leukaemia; for example, Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) or Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL).

[399] In a certain embodiment, the proliferative disorder is (eg, the subject (eg an adult human subject) suffers from, or is suspected of suffering from):

- newly diagnosed (Ph+ CML) in the chronic phase;
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib (eg, imatinib mesilate); or
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

[400] In another certain embodiment, the subject is a paediatric human and proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from):

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.

[401] In another particular embodiment, the cancer is a solid tumour, and in one such embodiment, the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) a solid tumour being one of those described elsewhere herein, such as pancreatic cancer, breast cancer, lung, prostate, melanoma, ovarian cancer, oesophageal cancer, sarcoma and colorectal cancer. In a certain of such embodiments, the proliferative disorder is (eg, the subject suffers from. or is suspected of suffering from) pancreatic cancer; in another of such embodiments, the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) prostate cancer; and in yet another of such embodiments, the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) lung cancer (eg, non-small cell lung cancer).

[402] As described elsewhere, a compound (or pharmaceutical composition) of the invention (or a compound used in the invention) may be administered to the subject (eg, as a combination therapy or regimen) with another medical procedure (eg, an additional therapeutic agent, such as described elsewhere herein, surgery or radiotherapy). Then such combination treatment regimen may comprise embodiments where such exposures/administrations are concomitant. In alternative embodiments such administrations may be sequential; in particular those embodiments where a compound (or pharmaceutical composition) of the invention (or a compound used in the invention) is administered before such other procedure. For example the compound (or pharmaceutical composition) may be sequentially administered within about 14 days of (eg before) the other procedure, such as within about 10 days, 7 days, 5 days, 2 days or 1 day of (eg before) the other procedure; and further including where the compound (or pharmaceutical composition) may be sequentially administered within about 48 hours, 24 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 1 hours, 30 mins, 15 mins or 5 mins of (eg before) the other procedure.

[403] Such combination regimens can include the (eg further) administration to the subject of:

- an EGFR inhibitor and/or gemcitabine - in particular when the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) pancreatic cancer;
- docetaxel - in particular when the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) prostate cancer; and/or
- an immune checkpoint inhibitor - in particular when the proliferative disorder is (eg, the subject suffers from, or is suspected of suffering from) lung cancer, such as non-small cell lung cancer.

[404] Exemplary immune checkpoint inhibitor that may be comprise such combination therapy or regimen are described elsewhere, and include an antibody or small-molecule inhibitor of PD1, PDL1, CTLA-4, LAG3 or IDO1, and in

particular such an immune checkpoint inhibitor may be one selected from the list consisting of: nivolumab, relatlimab, ipilimumab and BMS-986205, in particular nivolumab.

[405] In other embodiments, the combination regimens can include the (eg further) administration to the subject of:

- an immune-activator (eg, agonist) antibody, such as an antibody against OX40 (eg, Yang et al 2012, Blood 120:4533), 41BB, CD40 or ICOS (eg, Deng et al 2004, Hybrid Hybridomics 23:176), in particular those that increase TNF levels by stimulated/stimulating T cells; and/or
- dendritic cell- (DC) based vaccination (eg, Lowe et al 2014, Oncoimmunology 3:e27589).

[406] In one particular embodiment, the proliferative disorder (eg, in the subject) has progressed on (eg despite) standard therapy, or in anther embodiment, the subject may be unable to receive standard therapy, for example as the subject is intolerant thereto. In either of such embodiments, the subject may be so characterised (eg, stratified) as having progressed on standard therapy or being unable to receive (eg, is intolerant to) standard therapy.

[407] As examples of standard therapy, may be imatinib (eg, for CML or ALL), docetaxel (eg for prostate cancer) or immunotherapy such as an immune checkpoint inhibitor described herein (eg, for melanoma or lung cancer).

Sensitisation to immune responses and inhibition of kinases

[408] The compounds of the invention can sensitise cells involved with a proliferative disorder to a cell-mediated immune response.

[409] Accordingly, in one embodiment, a treatment comprising administering a compound (or a pharmaceutical composition) of the invention to the subject involves (eg, is mediated, is or supported) sensitising cells involved with the proliferative disorder (in the subject) to a cell-mediated immune response.

[410] In an alternative embodiment, a treatment comprising administering a compound (or a pharmaceutical composition) of the invention to the subject involves (eg, is mediated, is or supported by) inhibiting a kinase involved in resistance to a cell-mediated immune response, such as inhibiting SIK3 (in the subject).

[411] In a related embodiment, a treatment comprising administering a compound (or a pharmaceutical composition) of the invention to the subject involves (eg, is mediated, is or supported by) inhibiting a kinase involved in resistance to a cell-mediated immune response, such as inhibiting SIK3, and (for example, thereby) sensitising cells involved with the proliferative disorder (in the subject) to a cell-mediated immune response.

[412] In **a further aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a method for the sensitisation of cells** involved with a proliferative disorder to a cell-mediated immune response in the treatment of the proliferative disorder in a subject, the method comprising administering a compound (or a pharmaceutical composition) of the invention to the subject; and in another further aspect, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to a method for the inhibition of a kinase (in the subject) involved in resistance to a cell-mediated immune response, such as inhibiting, in the treatment of a proliferative disorder in a subject, the method comprising administering a compound (or a pharmaceutical composition) of the invention to the subject.

[413] In a **related further aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a compound (or a pharmaceutical composition)** of the invention **for use as a medicament** for: (i) sensitising cells involved with a proliferative disorder (in the subject) to a cell-mediated immune response; and/or (ii) inhibiting a kinase involved in resistance to a cell-mediated immune response, such as inhibiting SIK (in the subject).

[414] In yet **a related further aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a compound (or a pharmaceutical composition)** of the invention **for use as a**

medicament (eg an immuno-oncology medicament) sensitising cells involved with a proliferative disorder (such as a tumour or cancer) to a cell-mediated immune response, for example sensitising cells involved with a proliferative disorder (in the subject) to killing (cell-death) that may be induced by the cell-mediated immune response. An "immune-oncology" medicament is one that would be recognised by the person of ordinary skill, and includes a medicament that is intended to (eg, specifically designed to) enhance one or more components of the immune system of an organism (such as a human) towards cancerous or tumourous cells present in such organism. An immune-oncology medicament may be one (eg an antibody) that binds to an extrinsic immune (inhibitory) checkpoint molecule (such as one described elsewhere herein) and that (eg directly) suppresses T cell function against the cancerous or tumourous cells, or an immune-oncology medicament may be one that inhibits an immune regulator (such as SIK3, as in the present invention) that is intrinsic to the cancerous or tumourous cells where such intrinsic immune regulator does not actively (eg directly) suppress T cells but rather protects the tumour or cancer cells from an immune response via a resistance mechanism.

[415] In particular embodiments of such aspects, the cells involved with a proliferative disorder (in the subject) may be sensitised to killing (cell-death) by (such as induced by) the cell-mediated immune response.

[416] "Salt-inducible kinase 3" or "SIK3" (synonyms QSK and KIAA0999) is a member of a subfamily of serine/threonine protein kinases including SIK1, SIK2, and SIK3 that belong to an AMP-activated protein kinase (AMPK) family. A SIK3 protein in context of the invention is, typically, a protein kinase. Pertinent information on the human SIK3 protein is accessible on UniProt: Q9Y2K2 (Entry version 138 of 15-Mar-2017) and a SIK3 protein in context of the invention has, preferably, an amino acid sequence shown in SIK3, Entry version 138 of 15-Mar-2017 or Entry version 144 of 28-Mar-2018, which sequences are incorporated herein by reference. SIK3 is a cytoplasmatic protein with serine/threonine kinase activity which is regulated through phosphorylation of a conserved threonine residue (position 163) in the T-loop of the kinase domain by the LKB1 complex; a phosphorylation which is reported as essential for catalytic activity of SIK3 (Lizcano, J. M. et al.; EMBO J. 23, 833–843 (2004)). For the purposes of the herein disclosed invention the term "phosphorylated SIK3" shall denote a SIK3 protein that is phosphorylated substantially as SIK3 protein can be (eg is) phosphorylated by LKB1, wherein preferably such phosphorylated SIK3 comprising a phosphor-threonine at amino acid position 163. A phosphorylated SIK3 in context of the invention is an SIK3 protein that is activated in its cell-biological context. At least four protein isoforms (SIK3-001 to SIK3-004) generated by alternative splicing of the SIK3 gene product are known. The human SIK3 gene is located at chromosomal position 11q23.3 (HGNC gene Symbol Acc: HGNC:29165), and is conserved in many species such as in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and frog. The term SIK3 in some embodiments of the invention may also pertain to variants of the human SIK3 protein having an amino acid sequence that is substantially identical to, or of at least 80%, preferably 85%, more preferably 90, 95, 96, 97, 98, 99, or 100% sequence identity to, the amino acid sequence of SIK3 as described above, as determined using, e.g., the "Blast 2 sequences" algorithm described by Tatusova & Madden 1999 (FEMS Microbiol Lett 174: 247-250), and which (preferably) retain biological activity identical or substantially identical to the respective reference SIK3 (eg to phosphorylate one or more class II (eg IIa) HDACs, such as HDAC4). Preferred variants of SIK3 protein comprise sequence variants thereof due to sequence polymorphism between and within populations of the respective species, as well as mutations compared to the wild-type sequence of SIK3 which are located in or in close proximity to the activity loop or activation loop (T-loop) of SIK3. A preferred variant of SIK3 protein is a SIK3 T163 mutation, such as a mutation affecting the activation of SIK3. In preferred embodiments a SIK3 protein of the invention is not a SIK1 (synonyms: SIK and SNF1LK) protein and/or is not a SIK2 (synonyms: QIK, KIAA0781 and SNF1LK2) protein. The amino acid sequence of human SIK1 (UniProt: P57059; entry version 168 of 15-Mar-2017) and human SIK2 (UniProt: Q9H0K1; entry version 153 of 15-Mar-2017) are incorporated herein by reference. The term SIK3 can mean, as applicable to the context (if not more specifically indicated), a SIK3 protein

(such as one described above) or an mRNA molecule encoding such a SIK3 protein. The analogous meaning with respect of "SIK1" and "SIK2" is to be understood.

[417] A compound being an "inhibitor of SIK3" (or "SIK3 inhibitor") is any moiety that inhibits SIK3, which can mean inhibition of the activity of SIK3, especially of protein of SIK3, and in particular of phosphorylated SIK3. A SIK3 inhibitor may impair (eg, induces a decrease or reduction in) the efficiency, effectiveness, amount or rate of one or more activities of SIK3, such as one or more of those activities described herein, for example, the activity of SIK3 to phosphorylate class II (eg IIa) HDACs (eg HDAC4) and/or to sensitise a cell involved with a proliferative disorder to a cell-mediated immune response.

[418] Such a SIK3 inhibiting moiety can act directly, for example, by binding to SIK3 and decreasing the amount or rate of one or more of the properties of SIK3 such as its function, in particular its ability to act as a kinase (eg to phosphorylate HDAC4), for example by reducing the activity of phosphorylated SIK3 in the cell.

[419] Compounds being SIK3 inhibitors are described elsewhere herein, including those as may be characterised by the applicable functional and/or structural features set out herein.

[420] In preferred embodiments, a "subject", in particular, is also meant to include all mammals, including without limitation humans, but also non-human primates such as cynomolgus monkeys. It also includes dogs, cats, horses, sheep, goats, cows, rabbits, pigs and rodents (such as mice and rats). It will be appreciated that a particularly preferred subject according to the invention is a human subject, such as a human suffering from (or at risk of suffering from) a disorder, disease or condition, for example a human patient.

[421] As used herein, "therapy" is synonymous with treating a disease, disorder or condition, which includes reducing symptoms of the disease, disorder or condition, inhibiting progression of the disease, disorder or condition, causing regression of the disease, disorder or condition and/or curing the disease, disorder or condition.

[422] In preferred embodiments, a "treatment" in the present invention, and in particular, is also meant to include therapy, e.g. therapeutic treatment, as well as prophylactic or suppressive measures for a disease (or disorder or condition). Thus, for example, successful administration of a compound (or pharmaceutical composition) of the invention prior to onset of the disease results in treatment of the disease. "Treatment" also encompasses administration of a compound (or pharmaceutical composition) of the invention after the appearance of the disease in order to ameliorate or eradicate the disease (or symptoms thereof). Administration of a compound (or pharmaceutical composition) of the invention after onset and after clinical symptoms, with possible abatement of clinical symptoms and perhaps amelioration of the disease, also comprises treatment of the disease. Those "in need of treatment" include subjects (such as a human subject) already having the disease, disorder or condition, as well as those prone to or suspected of having the disease, disorder or condition, including those in which the disease, disorder or condition is to be prevented.

[423] The cell that is sensitised to the cell-mediated immune response is, suitably, one involved with the proliferative disorder (eg, a cell associated with the proliferative disorder) (in the subject), which in certain embodiments such cell is one involved in the proliferative disorder (eg, a cell that is abnormally proliferating, such as one that is over-proliferating). For example, such cell may be a cell characterised by loss of normal controls that affect its growth and cell division, such as a cell of a neoplasm or tumour. In particular embodiments, such cell may be a cancerous cell or one that is derived form or is a cell of a cancer or tumour. In other embodiments, such cell may be skin cell, such as one showing hyperproliferation such as one involved in psoriasis, Reiter's syndrome, pityriasis rubra pilaris or scleroderma.

[424] A cell may be "involved with a proliferative disorder" if, for example, it is associated therewith, such as it being a causative factor in such proliferative disorder or if it is affected by such proliferative disorder. In particular a cell is "involved with a proliferative disorder" if the cell is characterised by an abnormal proliferation such as abnormal cell growth or cell division, and if the abnormal cell growth or cell division is part of the pathology of, or causative for,

the proliferative disease. A cell "involved with a proliferative disorder", in those embodiments wherein the proliferative disorder is a tumour or cancer, can as a non-limiting example, be a tumour (or cancer) cell, or a cell of derived from (tissue) of such tumour or cancer; in particular of a solid tumour.

[425] In certain embodiments, a compound of the invention may inhibit SIK3 in the cell involved with the proliferative disorder (eg the tumour cell). In particular of such embodiments, the compound may inhibit SIK3 in such cell preferentially to inhibiting SIK1 and/or SIK2 in such cell; and/or may inhibit SIK3 in such cell preferentially to inhibiting SIK1 and/or SIK2 and/or SIK3 in one or more types of immune cells. For example, a compound of the invention may inhibit SIK3 in the cell involved with the proliferative disorder (eg the tumour cell) preferentially to inhibiting SIK1 and/or SIK2 and/or SIK3 in macrophages and/or dendritic cells (in particular, those capable of or producing IL-10).

[426] A compound (or pharmaceutical composition) of the invention (or a compound used in the invention) may be administered to the subject, in particular in an amount (such as a dose) that is effective to, inhibit SIK3 and/or that is effective to sensitise the cells involved with the proliferative disorder to the cell-mediated immune response. Suitable amounts, formulations and means for such administration are described elsewhere herein.

[427] In particular embodiments, a compound (or pharmaceutical composition) of the invention (or a compound used in the invention) is administered in an amount (such as a therapeutically effective amount) that is effective to reduce activity of SIK3, preferably of SIK3 in (of) the cells involved with the proliferative disorder. In such embodiments, a "therapeutically effective amount" of the compound (or pharmaceutical composition) can be an amount that is capable to reduce the activity of the SIK3 to an applicable level, but that does not lead to significant (eg intolerable) side effects or over-dosage in respect of other activities of the compound (or pharmaceutical composition).

[428] Preferably, the activity of SIK3 is effectively inhibited (reduced), preferably referring to the SIK3 kinase in (of) the cells involved with a proliferative disorder. For example, an "effective" inhibition (or reduction) may include one where the activity is lowered by a degree (or to a level) that has a physiological effect (eg to a therapeutically effective level), such as a reduction by about 10%, 20%, 50%, or more than 50% such as 70% or 90% of activity of the respective kinase. In respect of SIK3, one of such reductions may be desirable to elicit a therapeutic response.

[429] The term "immune cell" is art recognised to describe any cell of an organism involved in the immune system of such organism, in particular of a mammal such as a human. Leukocytes (white blood cells) are immune cells that are involved in the innate immune system, and the cells of the adaptive immune system are special types of leukocytes, known as lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow. B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response. In preferred embodiments of the invention, the immune cell can be a myeloid cell eg a T cell, and in particular (such as when an increase in cell-mediated immune response is required, such as to treat a cancer) the T cell can be a cytotoxic T cell (also known as TC, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, CD8+ T-cell or killer T cell). A CTL is a T-cell that is involved in the killing of cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways. Other preferred immune cells for such embodiments can include Tumour-Infiltrating Lymphocytes (TILs). TILs are white blood cells that have left the bloodstream and migrated into a tumour. Typically, TILs are a mix of different types of cells (eg, T cells, B cells, NK cells, macrophages) in variable proportions, T cells being the most abundant cells. TILs can often be found in the stroma and within the tumour itself, and are implicated in killing tumour cells. The presence of lymphocytes in tumours is often associated with better clinical outcomes.

[430] The term "cell-mediated immune response", as used herein, may include, but is not limited to, a response in a host organism involving, utilising, and/or promoting any one or combinations of T cell maturation, proliferation, activation, migration, infiltration and/or differentiation, and/or the activation/modulation/migration/infiltration of a macrophage, a natural killer cell, a T lymphocyte (or T cell), a helper T lymphocyte, a memory T lymphocyte, a

suppressor T lymphocyte, a regulator T lymphocyte, and/or a cytotoxic T lymphocyte (CTL), and/or the production, release, and/or effect of one or more cell–secretable or cell-secreted factor such as a cytokine or autocoid (in particular a pro-inflammatory cytokine such as TNF), and/or one or more components of any of such processes (such as a cytokine or autocoid, particular a pro-inflammatory cytokine such as TNF). The term "cell-mediated immune response," as used herein, may include a cellular response involving a genetically engineered, *in-vitro* cultured, autologous, heterologous, modified, and/or transferred T lymphocyte, or it may include a cell–secretable or cell-secreted factor (such as a cytokine or autocoid, in particular a pro-inflammatory cytokine such as TNF) produced by genetic engineering. A cell-mediated immune response is preferably not a humoral immune response, such as an immune response involving the release of antibodies. In certain embodiments, in particular when the proliferative disorder is a cancer or tumour, the cell-mediated immune response is an anti-tumour cell-mediated immune response. For example, one that leads to a reduction in tumour (cell) growth, such as a cytotoxic cell-mediated immune response (such as a cytotoxic T cell and/or TNF exposure) that kills cells of the cancer or tumour.

[431] In certain embodiments, the cell-mediated immune response may be mediated by a cell, such as an immune cell, capable of secreting (eg secreting) pro-inflammatory cytokine, such as one selected from the group consisting of: interleukin-1 (IL-1), IL-8 and IL-12, tumour necrosis factor (TNF), interferon gamma (IFN-gamma), and granulocyte-macrophage colony stimulating factor. In particular of such embodiments, the pro-inflammatory cytokine is tumour necrosis factor (TNF) [alpha].

[432] In other embodiments, the cell-mediated immune response may a cell–secretable or cell-secreted factor (such as a cytokine or autocoid), in particular one secretable or secreted by an immune cell. In particular of such embodiments, the cell-mediated immune response is a pro-inflammatory cytokine, in particular tumour necrosis factor (TNF).

[433] The terms "sensitising", "sensitisation" and "to sensitise" (and the like), as used herein in the context of cell(s) being sensitised to a cell-mediated immune response, will be understood by the person of ordinary skill, and include the meaning that such cells can exhibit an increased susceptibility to one or more effect (eg a treatment effect) that the cell-mediated immune response may have on such cells. In particular, cells that are so sensitised may, when in the presence of (eg exposed to) a cell-mediated immune response, be killed more easily (such as more rapidly, a greater proportion of cells dying or being killed and/or upon a lower amount or exposure of the cell-mediated immune response) than analogous cells that have not been so "sensitised". For example, cell(s) so sensitised may be induced into cell-death (eg apoptosis) upon exposure to a lower number of T cells or to a lower concentration of TNF (such as about 10%, 20%, 30% 40%, 50% or more than 50% fewer T cells or lower concentration of TNF). Methods to determine whether such cells have been sensitised (and by which degree) to cell-mediated immune responses are described herein, such as in the examples. Accordingly, in certain embodiments of the present invention, cells involved with the proliferative disorder may be sensitised to cell-death/killing (eg by entry into apoptosis) by a cell-mediated immune response (such as CTL or a proinflammatory cytokine eg TNF).

[434] The terms "tumour necrosis factor" and "TNF" (previously and hence alternatively known as tumour necrosis factor alpha and TNF-alpha) shall, in the context of the herein disclosed invention, be understood to refer to any proteins know under these denotations in the art. In particular, the term TNF encompasses endogenous TNF of any organism where such is present, and preferably of animals or mammals, such as humans. By means of example and not limitation, human TNF may encompass endogenous proteins as disclosed in inter alia Pennica et al. 1984 (Nature 312: 724-9) and in the UniProtKB/Swiss-Prot database with the entry No P01375 (for example, entry version 224 of 15-Mar-2017), as well as any sequence variants thereof due to normal sequence polymorphism between and within human populations. By means of further non-limiting examples, the term may encompass endogenous TNF proteins as annotated in the UniProtKB/Swiss-Prot database for bovine (Q06599), dog (P51742), goat (P13296), guinea pig (P51435), cat (P19101), horse (P29553), mouse (P06804), chimp (Q8HZD9), pig (P23563), rabbit (P04924), rat

(P16599) and others, as well as any sequence variants thereof due to sequence polymorphism between and within populations of each respective species. Further, the term TNF particularly encompasses the soluble, secreted cytokine form of TNF, including monomeric as well as, preferably, the typically more active trimeric forms thereof (see, e.g., Smith & Baglioni 1987. J Biol Chem 262: 6951-4). The primary amino acid sequences of soluble forms of endogenous TNF are indicated in the above mentioned UniProtKB/Swiss-Prot database entries for the respective exemplified organisms. In addition, the term TNF may also encompass membrane-bound forms of TNF expressed on the surface of some cell types (see, e.g., Kriegler et al. 1988. Cell 53: 45-53). Further, the term TNF may also encompass synthetic or recombinant proteins whose primary amino acid sequence is identical or substantially identical ("substantially identical", as used throughout this specification, generally refers to ≧80%, e.g., ≧85%, preferably ≧90%, more preferably ≧95%, even more preferably ≧98% or ≧99% sequence identity) to the sequence of an endogenous TNF, as determined using, e.g., the "Blast 2 sequences" algorithm described by Tatusova & Madden 1999 (FEMS Microbiol Lett 174: 247-250), and which (preferably) retain biological activity identical or substantially identical to the respective endogenous TNF, as determined using, e.g., the cytotoxicity tests described by Flick & Gifford 1984 (J Immunol Methods 68: 167-75). As will appear from the context of aspects and embodiments of the present invention, the term TNF may, in particular, refer herein to endogenous TNF, soluble and/or membrane bound, preferably soluble, produced by cells, tissues, organs or organisms, preferably human. Nevertheless, also envisioned by the term "TNF" are exogenous forms of tumour necrosis factor, in particular those produced by recombinant technologies and, in certain embodiments, may be administered to subjects, or exposed to or contacted with cells in various aspects and embodiments of the invention. In certain of such embodiments, the TNF may be a recombinant TNF used as a therapeutic, such as tasonermin (BEROMUN).

[435] In certain embodiments, the cell-mediated immune response can be mediated by a pro-inflammatory cytokine-secreting cell, such as a lymphocyte (eg a T cell), in particular a cytotoxic T lymphocyte (CTL).

[436] In particular embodiments, the cell-mediated immune response may induce killing (eg cell-death, such via apoptosis) of cells involved with the proliferative disorder. For example, the treatment (method) may comprise (eg may involve) that (or be mediated by) the cell-mediated immune response induces such killing of cells involved with the proliferative disorder.

[437] The cells involved with the proliferative disorder may be killed (eg induced into cell death) by one or more cytotoxic processes, in particular those that are endogenous to such cell such as programmed cell death (PCD). Cell death processes may include, but are not limited to, necrosis (in particular necroptosis), apoptosis, anoikis, autophagy, ferroptosis, mitotic catastrophe and activation-induced cell death. In certain preferred embodiments, the cells involved with the proliferative disorder (eg the tumour cells) are induced into apoptosis by the cell-mediated immune response (eg by TNF). In a further embodiment, a compound (or pharmaceutical composition) of the invention is administered to not kill such cells in the absence of the cell-mediated immune response (eg in the absence of TNF). In particular of such further embodiments, the compound (or pharmaceutical composition) may be administered in an amount (eg in a dose) that is not effective to kill such cells in the absence of the cell-mediated immune response. The examples herein, describe various assays by which an amount of a compound (or pharmaceutical composition) of the invention may be determined that is effective to kill such cells only, or preferentially, in the presence of the cell-mediated immune response.

[438] In other particular embodiments, the cell-mediated immune response may involve at least one immune cell effector molecule, in particular an effector molecule that is secretable or secreted by an immune cell. In particular of such embodiments, the effector molecule can be a pro-inflammatory cytokine, preferably tumour necrosis factor (TNF).

[439] In certain embodiments, the effector molecule is not a cell effector molecule selected from Fas ligand (FasL or CD95L) and TNF-related apoptosis-inducing ligand (TRAIL, CD253 or TNFSF10).

[440] In particular embodiments of the invention, a compound (or pharmaceutical composition) of the invention may be administered to the subject (eg in an amount or dose effective) with the intent to (or so as to) (effectively) sensitise cells involved with the proliferative disorder to killing induced by TNF. For example, the compound (or pharmaceutical composition) may be administered in a therapeutically effective amount, such as an amount effective to sensitise the cells involved with the proliferative disorder to killing (cell-death) induced by TNF.

[441] For example, a compound (or pharmaceutical composition) of the invention may be administered to the subject (for example, in an amount or dose effective) to induce apoptosis of such cells mediated by TNF, such as when such cells are in the presence of or contacted with TNF. In further embodiments, the a compound (or pharmaceutical composition) of the invention may be administered to the subject (eg in an amount or dose effective) to induce a reduced amount of cytotoxicity (eg apoptosis) – such as to not induce killing (eg apoptosis) of such cells - in the absence of TNF; for example the compound (or pharmaceutical composition) may be administered in an amount or dose that is - not as effective in cytotoxicity (eg apoptosis) – such as being not effective to induce such killing - in the absence of TNF.

[442] TNF can induce pro-apoptotic processes via binding to and/or signalling via tumour necrosis factor receptor 1 (TNFR1) and or tumour necrosis factor receptor 2 (TNFR2). Accordingly, in certain embodiments a compound (or pharmaceutical composition) of the invention may be administered to the subject (eg in an amount or dose effective) to (effectively) sensitise cells involved with the proliferative disorder to apoptosis mediated by tumour necrosis factor receptor 1 (TNFR1) signalling and/or tumour necrosis factor receptor 2 (TNFR2) signalling. Preferably, the compound (or pharmaceutical composition) can be administered to the subject (eg in an amount or dose effective) to (effectively) sensitise cells involved with the proliferative disorder to apoptosis mediated thereby in particular mediated by TNFR1. For example, the compound (or pharmaceutical composition) may be administered in a therapeutically effective amount that is effective to mediate TNFR1- and/or TNFR2-signalling, and/or apoptosis mediated thereby.

[443] For example in certain embodiments, a compound (or pharmaceutical composition) of the invention may be administered (eg in an amount or dose effective) to induce apoptosis of such cells by TNFR1 and/or TNFR2 signalling, such as upon active TNFR1 signalling. In particular of such embodiments, the compound (or pharmaceutical composition) may be administered to the subject (eg in an amount or dose, such as a therapeutically effective amount) to (effectively) induce a reduced amount of cytotoxicity (eg apoptosis) – such as to not induce apoptosis of such cells - in the absence of TNFR1 and/or TNFR2 signalling, such as in the absence of active TNFR1 signalling. For example, the compound (or pharmaceutical composition) may be administered in an amount or does that is not as effective in cytotoxicity (eg apoptosis) – such as being not effective to induce such apoptosis - in the absence of such signalling.

[444] Therefore, in certain embodiments, a compound (or pharmaceutical composition) of the invention may be administered to the subject (eg in an amount or dose) to induce a reduced amount of cytotoxicity (eg apoptosis) – such as to not be cytotoxic - to cells involved with the proliferative disorder in the absence of the cell-mediated immune response.

[445] In particular embodiments, a compound (or pharmaceutical composition) of the invention may be continued to be administered to the subject even if the tumour of the subject is increased in size during treatment. Without being bound to theory, even if an increase in tumour size is observed during such treatment, this may indicate an (enhanced) immune reaction against cells of the tumour (eg, the cells have become sensitised to the cell-mediated immune response; and the tumour is increasing in size because of such immune response), and hence the administration of the compound (or pharmaceutical composition) can, in such embodiments, continued to be administered so as to maintain such sensitivity and associated (enhanced) immune reaction.

[446] As described in PCT/EP2018/060172 (WO 2018/193084), the inhibition of SIK3 is associated with a number of key biological processes or phenotypes, including those surprisingly involved in the control and/or triggering of cytotoxic process innate to cells, such as apoptosis. For example, tumour cells can be sensitised to the

apoptotic/cytotoxic effects of TNF by the inhibition of SIK3, acting through pathways and components thereof including liver kinase B1 (LKB1, STK11 or NY-REN-19), histone deacetylase 4 (HDAC4), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB), and pro-apoptotic genes regulated by NF-kappaB such as Caspase 8 and Caspase 9. Also c-Jun N-terminal kinase (JNK) is a signalling component associated with sensitisation to the apoptotic/cytotoxic effects of TNF by the inhibition of SIK3.

[447] The term "associated with", in the context of this embodiment (and other embodiments, where applicable) can mean that two components, variables, effects or phenotypes are interrelated with each other, and/or that they are related to (eg correlated to) each other, and/or that there is a causative link between a first and a second component, variable, effect or phenotype (such as the second is in response to the first, the second is a consequence of the first, or the second is caused by the first).

[448] Accordingly, in one such embodiment, administration of a compound (or pharmaceutical composition) of the invention can associate with impairment of NF-kappaB activity (eg, by an enhancement or increase in translocation of NF-kappaB out of the nucleus) in cells involved with the proliferative disorder.

[449] In particular of such embodiments, such impairment of NF-kappaB activity (eg, by an enhancement or translocation of NF-kappaB out of the nucleus) may be associated with (activated) TNF- and/or TNFR1-mediated signalling (or TNFR2-mediated signalling) in such cells.

[450] In certain embodiments, a compound (or pharmaceutical composition) of the invention may be administered to the subject (eg in an amount or dose effective) to impair or inhibit NF-kappaB activity in the cells involved with the proliferative disorder, for example to enhance or increase translocation of NF-kappaB out of the nucleus of such cells. For example, the compound (or pharmaceutical composition) may be administered to the subject in a (eg, therapeutically effective) amount being effective to (effectively) impair NF-kappaB activity in cells involved with the proliferative disorder, in particular in an amount effective to (effectively) enhance or increase translocation of NF-kappaB out of the nucleus of the cells involved with the proliferative disorder.

[451] In alternative or further embodiments, administration of a compound (or pharmaceutical composition) of the invention may be associated with an increase in (eg, the compound (or pharmaceutical composition) is administered, such as in an amount or dose effective, to increase) activity of class II (eg IIa) HDACs, eg HDAC4, in the cells involved with the proliferative disorder, for example its translocation or localisation to or its activity in the nucleus of such cells; and in particular upon TNF- and/or TNFR1-mediated signalling (or TNFR2-mediated signalling) in such cells.

[452] In other alternative or further embodiments, administration of a compound (or pharmaceutical composition) of the invention may be associated with de-acylation of nuclear NF-kappaB (eg de-acylation at its p65 subunit) and/or decreased transactivation of one or more anti-apoptotic factors, in particular upon TNF- and/or TNFR1-mediated signalling (or TNFR2-mediated signalling) in the cells involved with the proliferative disorder. For example, the compound (or pharmaceutical composition) may be administered (such as in an amount or dose effective) to cause de-acylation of nuclear NF-kappaB (eg at its p65 subunit) and/or decreased transactivation of one or more anti-apoptotic factors.

[453] In another alternative or further embodiment, administration of a compound (or pharmaceutical composition) of the invention may be associated with an increase in (eg the compound (or pharmaceutical composition) is administered, such as in an amount or dose effective, to increase) cleavage of Caspase 8 and/or Caspase 9 in the cells involved with the proliferative disorder, in particular upon TNF- and/or TNFR1-mediated (or TNFR2-mediated signalling) signalling in such cells.

[454] In yet other alternative or further embodiments, administration of a compound (or pharmaceutical composition) of the invention may be associated with a reduction in the transcription of one or more anti-apoptotic factors, in particular upon TNF- and/or TNFR1-mediated signalling (or TNFR2-mediated signalling) in the cells involved with the proliferative disorder, for example the reduction of the transcription of one or more NF-kappaB target genes

in such cells. In particular, the compound (or pharmaceutical composition) may be administered (eg in an amount dose effective) to reduce the transcription of one or more such anti-apoptotic factors, in particular upon TNF- and/or TNFR1-mediated signalling (or TNFR2-mediated signalling) in the cells involved with the proliferative disorder.

[455] In one embodiment the administration of a compound (or pharmaceutical composition) of the invention may be associated with an increase in (eg the compound (or pharmaceutical composition) is administered, such as in an amount or dose effective, to increase) JNK activation (such as by phosphorylation) in the cells involved with the proliferative disorder, in particular upon TNF- and/or TNFR1-mediated signalling (or TNFR2-mediated signalling) in such cells.

[456] In another embodiment, administration of a compound (or pharmaceutical composition) of the invention may not be associated with a significant change in CREB-pathways signalling and/or a significant change gene expression mediated by CREB and/or CREB-regulation.

[457] In a particular embodiment, the TNF- (TNFR2-) and/or TNFR1-mediated signalling in the cells involved with the proliferative disorder may be associated with increased levels of pLKB1 in such cells.

[458] As will now be apparent to the person of ordinary skill given knowledge of the present invention, the treatment aspects of the invention may further comprise a step of administering one or more other moieties that appropriately modify the expression, activity, function or stability of one or more these other pathway components described above, so as to additively or synergistically contribute to the treatment effect. For example, in one such embodiment, a treatment aspect of the invention may further comprise a step of administering an inhibitor of LKB1.–In another of such embodiments, a treatment aspect of the invention may further comprise a step of administering a compound of the invention that promotes, enhances or increases one or more class II (eg IIa) HDACs (histone deacetylases), such as HDAC4, in the nucleus of the cells involved with the proliferative disorder. In yet another of such embodiments, a treatment aspect of the invention may further comprise a step of administering an inhibitor of NF-kappaB (activation). The invention also envisions that combinations of two or more such other moieties may be used in a treatment together with a compound (or pharmaceutical composition) of the invention and/or using other (eg anti-cancer) therapeutically active agents (such as an additional therapeutic agent as described elsewhere herein) together with the compound (or pharmaceutical composition).

[459] In **a further aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a method for the sensitisation of cells** involved with a proliferative disorder to a cell-mediated immune response, the method comprising exposing (eg contacting) the cells involved with a proliferative disorder to a compound (or pharmaceutical composition) of the invention. Such a method may, typically, be practiced as an in-vitro and/or ex-vivo method.

[460] In a particular embodiment, the cell-mediated immune response comprises killing the cells involved with a proliferative disorder, such as where said killing involves (eg, is mediated, is or supported by) TNF, TNFR2- and/or TNFR1-mediated signalling. For example, the killing of such cells may involve apoptosis of such cells induced by TNF, TNFR2- and/or TNFR1-mediated signalling. Within this and the other applicable embodiments of the various aspects of the invention, TNFR2- and/or TNFR1-mediated signalling may be triggered (eg activated) by any appropriate triggering molecule, such as TNF, a variant of TNF and or a TNFR2 or TNFR1 agonist; in particular by exposing (eg by contacting) the cells associated with the proliferative disorder to the triggering molecule (eg TNF, TNF variant or TNFR1 agonist). Such exposure can lead to the triggering molecule (eg TNF, TNF variant or TNFR1 agonist) binding to TNFR2 and/or TNFR1 and, in particular the triggering (eg activation) of TNFR1 signalling.

[461] In **a yet further aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a method for the killing of cells** involved with a proliferative disorder, the method comprising exposing (eg contacting) the cell involved with the proliferative disorder to: (i) TNF, a TNF variant and/or an agonist of TNFR1- or TNFR2-signalling (preferably, TNFR1-signalling); and exposing (eg contacting) the cells

involved with the proliferative disorder to (ii) a compound (or pharmaceutical composition) of the invention. As will be appreciated by the person or ordinary skill, such a method may, typically, be practiced as an in-vitro and/or ex-vivo method.

[462] In **a related aspect**, the invention relates to **a compound (or pharmaceutical composition)** of the invention **for use in the treatment of a proliferative disease** involving the killing of a cell involved with the proliferative disorder, the treatment comprising exposing such cell to: (i) TNF, a TNF variant and/or a TNFR1 or TNFR2 agonist; and (ii) a compound (or pharmaceutical composition) of the invention.

[463] In particular embodiments of such aspects, the killing of the cell involved with the proliferative disorder is mediated by sensitising such cell to a cell-mediated immune response, in particular by inducing sensitivity to apoptosis of such cell that involves (eg, is mediated, is or supported by) TNF, TNFR2 and/or TNFR1-mediated signalling.

[464] The cell(s) involved with the proliferative disorder may be exposed to the TNF, a TNF variant and/or a TNFR1 or TNFR2 agonist by contacting the cell to such triggering molecule; and/or such cell(s) may be exposed to a compound (or pharmaceutical composition) of the invention by contacting (or introducing into) such cell(s) with a compound (or pharmaceutical composition) of the invention. The amounts (or dose) of (i) TNF, a TNF variant and/or a TNFR1 or TNFR2 agonist; and/or (ii) a compound (or pharmaceutical composition) of the invention are, typically, effective amounts; that is amounts (or doses) that are effective in, for example, sensitising the cell(s) to (such as killing such cell(s) by) apoptosis induced by TNF, TNFR2 and/or TNFR1-mediated signalling. Elsewhere are disclosed suitable amounts of these active agents (or ways to determine them) that may be incorporated in these aspects of the invention; as are further particular characteristics of the compound (or pharmaceutical composition) of the invention. Accordingly, in certain embodiments: (i) TNF, a TNF variant and/or a TNFR1 or TNFR2 agonist; and (ii) a compound (or pharmaceutical composition) of the invention, can be administered to a subject suffering from the proliferative disorder (eg, the treatment can comprise the administration of: (i) TNF, a TNF variant and/or a TNFR1 or TNFR2 agonist; and (ii) a compound (or pharmaceutical composition) of the invention, can be administered to the subject).

[465] The cell(s) involved with the proliferative disorder may be one as described elsewhere herein, and in particular such cell(s) may be cancerous or tumour cell. For example, such cell(s) may be one that is of, or derived from, a solid tumour.

[466] In certain embodiments of these aspects, the method is an in vitro (and/or ex-vivo) method. In alternative embodiments of such methods, the cell(s) involved with the proliferative disorder (such as tumour cells) is present in such subject, in particular in a subject in need of treatment thereof.

[467] In further embodiments of the methods of these aspects, the (treatment) effect of such method (eg, on the cell(s) involved with the proliferative disorder) can be mediated by (eg, the treatment may comprise, involve or be mediated by) inhibiting SIK3; in particular, by inhibiting the function and/or activity of SIK3 ~~mRNA or~~ protein (eg, of phosphorylated SIK3 protein, and/or as described elsewhere herein). In particular, in such embodiments, the SIK3 activity is (eg, effectively) reduced, such as reduced to a therapeutically effective level.

[468] In certain embodiments of such methods, in the absence of (eg such effective amount or dose of) a compound (or pharmaceutical composition) of the invention, the cell(s) involved with the proliferative disorder (such as the tumour cell(s)) are not killed or induced to enter apoptosis (for example, they proliferate) upon TNF, TNFR2- and/or TNFR1-mediated signalling and/or exposure to (eg, the effective amount or dose of) TNF, TNF variant, TNFR2 or TNFR1 agonist.

[469] As described above, in certain embodiments of these methods, a compound (or pharmaceutical composition) of the invention may inhibit SIK3 in (of) the cell(s) involved with the proliferative disorder (eg tumour cells). In particular of such embodiments, the compound (or pharmaceutical composition) may inhibit SIK3 in (of) such cell(s) preferentially to inhibiting SIK1 and/or SIK2 in (of) such cell; and/or may inhibit SIK3 in such cell preferentially to inhibiting SIK1 and/or SIK2 and/or SIK3 in (of) one or more types of immune cells. For example, a compound (or pharmaceutical

composition) of the invention may inhibit SIK3 in (of) the cell(s) involved with the proliferative disorder (eg tumour cells) preferentially to inhibiting SIK1 and/or SIK2 and/or SIK3 in (of) macrophages and/or dendritic cells (in particular, those capable of or producing IL-10). In particular embodiments, the (treatment) effect is mediated by (eg, the treatment comprises, involves, is by or is mediated by) inhibition of SIK3 in (of) the cell(s) involved with the proliferative disorder (eg a tumour cell); and in further of such embodiments, the (treatment) effect is not mediated by (or the effect is mediated by not) (eg, the treatment does not comprise, involve or is not mediated by) inhibiting SIK2, in particular SIK2 in/of other cells (such as those involved with the proliferative disorder or immune cells), and/or the (treatment) effect is not mediated by (or the effect is mediated by not) inhibiting SIK1 (eg, the treatment does not comprise, involve or is not mediated by inhibiting SIK1), in particular SIK1 in/of other cells (such as those involved with the proliferative disorder or immune cells).

[470] Accordingly, in one embodiment, the SIK3 of (eg, in) the cell(s) involved with the proliferative disorder is inhibited (eg, by a compound or pharmaceutical composition of the invention). In another (or further) embodiment, another kinase (eg SIK2, in particular SIK2) of (eg in) immune cells - such as CTLs - is inhibited to a lesser extent than SIK3 (eg in the cell(s) involved with the proliferative disorder). In yet another (or further) embodiment SIK1, in particular SIK1 of (eg in) immune cells - such as CTLs - is inhibited to a lesser extent than such SIK3.

[471] In certain of such embodiments, one or more of the kinases selected from the list consisting of: SIK3, SIK1, SIK2, JAK1, RET, ERBB4 PDGFR-alpha, and EPHB2, is inhibited (eg, by a compound or pharmaceutical composition of the invention) to a lesser extent than one or more of the kinases selected from the list consisting of: ABL1, SRC, BCR-ABL, LCK, LYN, YES, FYN, KIT and FLT3.

[472] In certain of such embodiments, one or more of the kinases selected from the list consisting of: PDGFR-alpha, TGFB-R1, B-RA, p38-beta, ACV-R1, BMPR1A and RET, is inhibited (eg, by a compound or pharmaceutical composition of the invention) to a lesser extent than one or more of the kinases selected from the list consisting of: EPHA2, EPHA4, CSF1R, HCK and ACK1.

[473] In certain of such embodiments, one or more of the kinases selected from the list consisting of: NEK11, WEE1, WNK2, Aurora-A, Aurora-B and TBK1, is inhibited (eg, by a compound or pharmaceutical composition of the invention) to a lesser extent than one or more of the kinases selected from the list consisting of: ABL1, SRC, BCR-ABL, LCK, LYN, YES, FYN and KIT.

[474] A given kinase (such as SIK1 or SIK2) may be inhibited to a "lesser extent" than another kinase (such as SIK3) if, for example, the other kinase (such as SIK3) is inhibited by an amount greater than about 2 fold more than the given kinase, such as by an amount greater than about 5, 10, 20, 50, 75 or 100-fold more than the given kinase. In particular, the other kinase (such as SIK3) may be inhibited by an amount between about 5 and 20 fold, 20 and 50 or 50 and 100 fold more than the given kinase. For example, the SIK3 (ie, the other kinase) may be inhibited between about 20 and 50 fold more than SIK1 and/or SIK2 (ie, a given kinase). By way of example, a compound (or pharmaceutical composition) of the invention may inhibit the other kinase (eg SIK3) by 80% (ie, to have only 20% of its uninhibited activity) but inhibit the given kinase (eg SIK1) by only 4% and SIK2 by only 8%. Accordingly, the other kinase (eg SIK3) is inhibited about 20-fold more than the given kinase (eg SIK1) and 10-fold more than another given kinase (eg SIK2). In particular embodiments, the other kinase (eg SIK3) may be inhibited to about the same extent as eg SIK1 (eg between about 2 to 53 fold of each other), and eg SIK2 is inhibited to a lesser extent that either (or both) of eg SIK3 and SIK1: For example, in such embodiments, eg SIK3 and SIK1 are inhibited by between about a 20 and 50 fold more than eg SIK2 (eg in immune cells) is inhibited.

[475] The compounds of the invention (in particular those of formula (Ia)) and/or compounds used in the invention (in particular those of formula (Ib) or (Ic)) are shown to be potent inhibitors of one or more kinases (as shown in the Examples, and in particular by Figure 16, Figure 17 and Figure 3). In particular, any of (or any combination of) those kinases in Figure 16, Figure 17 and/or Figure 3 having a residual activity of between about 50% and about 25%, or

less than about 25% residual activity (and particular, those having a residual activity of less than about 10%), are considered, in certain embodiments to be "key-kinases" that are inhibited by the respective compounds of the invention. Mutants of such kinases are also considered therein. As particular examples, the key-kinases include one or more kinases selected from the list consisting of: SIK1, SIK2, SIK3, ABL1/BCR-ABL, SRC, FLT3, KIT, YES, LYN and FYN; and/or EPHA2, EPHA4, CSF1R, HCK, ACK1; and/or PDGFR-alpha, TGFB-R1, B-RAF and/or p38-beta; and/or ACV-R1 and/or BMPR1A; and/or RET; and/or NEK11, WEE1 and/or WNK2; and/or Aurora-A and/or Aurora-B; and/or TBK1; in particular, SIK3, ABL1/BCR-ABL, SRC, HCK, PDGFR, KIT and CSF1R, such as SIK3, SRC, HCK and CSF1R.

[476] The inventors find that, despite the significant structural differences compared to dasatinib (**A8**) and compound **B3** (WO2018/193084A1) the compounds of the invention are potent inhibitors of various disease related kinases such as one selected from the group consisting of: SIK3, ABL/BCR-ABL SRC, HCK, PDGFR, KIT and CSF1R. Accordingly, in one embodiment a compound of (or for use in a method of) the invention is an inhibitor of one or more of the kinases SIK3, ABL/BCR-ABL, SRC, HCK, PDGFR, KIT and/or CSF1R. In one particular embodiment, such a compound may be an inhibitor of SIK3 kinase. In one further (or alternative) particular embodiment, such a compound may be an inhibitor of CSF1R kinase, and/or for example is a compound that is capable of depleting (eg depletes) M2-like tumour associated macrophages (TAMs) in an MC38 syngeneic mouse tumour model such as one analogous to that described in Example 8 herein. In another further (or alternative) particular embodiment, such a compound may be an inhibitor of HCK kinase, and/or for example is a compound that is capable of inhibiting the formation of podosomes within TAMs (such as TAMs in an MC38 syngeneic mouse tumour model analogous to one described in Example 8 herein).

[477] The inventors find that compounds disclosed herein inhibit a different set of kinases and/or each to a different degree compared to other kinase inhibitors. For example, compounds B3 and A8 are equivalent inhibitors of ABL1 and SRC (and of mutants of ABL1). However, as shown in the Examples, they inhibit SIK1, SIK2, SIK3, and in particular FLT3, KIT and SYK to different degrees.

[478] Also shown in the examples, are that compounds disclosed herein are more selective for ABL1 and (in particular) for SRC kinases than dasatinib, and that this selectivity also applies within the class of protein-tyrosine kinases.

[479] In particular, and as shown in the examples, the compounds of the invention appear to inhibit MAP3K11 less strongly than compound **C7**, and to inhibit NEK11 more strongly than compound **C7**.

[480] Compounds that inhibit different kinases and/or kinases to different degrees will have different properties in vivo, and can be used for different medical indications, or for the same medical indications but showing different properties in terms of efficacy and side-effects. As will be appreciated, compounds with different specificity to kinases can have surprisingly different properties and applications.

[481] Accordingly, in one embodiment, the treatment comprises (eg, involves, is by or is mediated by) inhibition of one or more of the key-kinases (eg of ABL1/BCR-ABL and/or SRC kinase and/or HCK and/or PDGFR and/or KIT and/or CSF1R). In particular of such embodiments, the treatment comprises (eg, involves, is by or is mediated by) inhibition of such key-kinase(s) more than comprising (eg, involving, is or is mediated by) inhibition of one or more of the other key-kinases (eg SIK3 and/or SIK1 and/or SIK2). For example, the treatment can involve inhibiting SIK3, r SRC, HCK, PDGFR, KIT and/or CSF1R kinase, and/or one or more kinases selected from the list consisting of: BCR-ABL, LCK, LYN, YES, FYN and KIT.

[482] In a particular (alternative or additional) embodiment, the treatment does not comprise (eg, does not involve, is not or is not mediated by) inhibition of one or more of the key-kinases. In particular of such embodiments, the treatment does not comprise (eg, does not involve, is not or is not mediated by) inhibition of SIK3, and/or the treatment does not comprise (eg, does not involve, is not or is not mediated by) inhibition of SIK1 and/or SIK2.

[483] In further embodiments, the treatment may not comprise (eg, may not involve, is not or is not mediated by) inhibition of one or more of following kinases: JAK1, RET, ERBB4, PDGFR-alpha or EPHB2, or MAP3K11.

[484] In another particular (alternative or additional) embodiment, the treatment does not comprise (eg, does not involve, is not or is not mediated by) inhibition of SYK. For example, compound B3 inhibits SYK with an IC50 of over 25uM, while compound A8 has an IC50 for SYK of less than 5uM.

[485] In yet another particular (alternative or additional) embodiment, the treatment comprises (eg, involves, is by or is mediated by) inhibition of KIT. For example, compound B3 inhibits KIT with an IC50 of less than 50nM, and compound A8 has an IC50 for KIT also of less than 50nM.

[486] In one further particular (alternative or additional) embodiment, the treatment comprises (eg, involves, is by or is mediated by) inhibition of FLT3. For example, compound B3 inhibits FLT3 with an IC50 of less than 10uM, while compound A8 has an IC50 for FLT3 of greater than 25uM.

[487] In yet another particular (alternative or additional) embodiment, the treatment comprises (eg, involves, is by or is mediated by) inhibition of NEK11. For example, compounds of Formula (Ia) appear to inhibit NEK11 more strongly than compound **C7**.

[488] Indeed, in a certain particular (alternative or additional) embodiment, the treatment comprises (eg, involves, is by or is mediated by) inhibition of both KIT and FLT3; for example, by administration of compound B3 to the subject, and for example, the treatment comprises (eg, involves, is by or is mediated by) inhibition of ABL1, SRC and/or SIK3.

[489] In one further embodiment, the treatment comprises (eg, involves, is by or is mediated by) inhibition of a mutant of either ABL1 or KIT kinase; such as the inhibition of BCR-ABL, or another mutant of ABL1, such as one selected from the list consisting of: G250E, Q252H, Y253F, E255K, F317I, M351T and H396P.

[490] As described elsewhere herein, in one (alternative or additional) embodiment, compounds of the invention sensitise (eg, the treatment comprises, involves, is by or is mediated by sensitisation of) cells involved with a proliferative disorder to a cell-mediated immune response (such as TNF). However, in an alternative (alternative or additional) embodiment, the compounds do not sensitise (eg, the treatment does not comprise, involve, is not by or is not mediated by sensitisation of) cells involved with a proliferative disorder to a cell-mediated immune response (such as TNF).

[491] In contrast to other studies using kinase (eg SIK) inhibitors, treatment with a compound (or pharmaceutical composition) of the invention in accordance with the present invention, in certain embodiments, may not be associated with an (effective) increase in the production of one or more anti-inflammatory cytokines (for example the anti-inflammatory cytokine may be one selected from the list consisting of: IL-1ra, IL-4, IL-10, IL-11, IL-13 and TGF-beta), and in particular may not be associated with an (effective) increase in the production of IL-10. Correspondingly, in other or further embodiments, treatment with a compound (or pharmaceutical composition) of the invention in accordance with the present invention may not be associated with an (effective) decrease in the production of one or more pro-inflammatory cytokines; for example, one selected from the list consisting of: IL-1-beta, IL-6, IL-12 and TNF, IFN-gamma and granulocyte-macrophage colony stimulating factor, and in particular embodiments may not be associated with an (effective) decrease in the production of TNF. Accordingly, in certain embodiments, a compound (or pharmaceutical composition) of the invention may be administered to a subject in: (i) a (therapeutically effective) amount NOT effective to (effectively) increase the production of one or more (eg such) anti-inflammatory cytokines; and/or (ii) in a (therapeutically effective) amount NOT effective to (effectively) decrease the production of one or more (eg such) pro-inflammatory cytokines.

[492] Certain cells involved with the proliferative disorder (eg tumour cells) may, in certain embodiments, be expected to be more susceptible to the sensitising effects of a compound (or pharmaceutical composition) of the invention in the various aspects of the invention. For example, such cells may be those that exhibit (eg are subject to) activation of TNFR2 and/or TNFR1 signalling, in particular an activated TNFR1. In certain embodiments, such cells are

those that express TNFR2 and/or TNFR1, in particular tumour cells that express TNFR1. Accordingly, in certain embodiments, such cells are distinguished or characterised by activated TNFR1- and/or TNFR2-signalling (or the subject is distinguished or characterised by having cells involved with the proliferative disorder - eg tumour cells – that are so distinguished or characterised). The person of ordinary skill will know techniques for determining the status of TNFR1- and/or TNFR2-activation in such cells (such as of the subject). For example, by detecting or monitoring one or more down-stream protein in the TNFR1- and/or TNFR2-signalling pathways. Such proteins are described elsewhere herein, and include NF-kappaB and/or HDAC4.

[493] In **one related aspect**, the invention relates to **a method for the treatment of a proliferative disorder** (such as a tumour) in a subject, the (treatment) method comprising administering a compound (or pharmaceutical composition) of the invention to the subject, by inhibiting a kinase/key-kinase (eg SIK3), wherein cells involved with the proliferative disorder are characterised by (eg exhibit or are subject to) activated TNFR2 and/or TNFR1 signalling (eg activated TNFR1 signalling). In another related aspect, the invention relates to a compound (or pharmaceutical composition) of the invention for use in the treatment of a proliferative disorder, wherein cells involved with the proliferative disorder are distinguished or characterised by (eg exhibit or are subject to) activated TNFR2 and/or TNFR1 signalling (eg activated TNFR1 signalling).

[494] In certain embodiments of the various aspects of the invention, cells involved with the proliferative disorder are those exposed to an appropriate triggering or activating molecule, such as TNF, a variant of TNF and or an agonist of TNFR2- or TNFR1-signalling (preferably, an agonist of TNFR1-signalling), in particular are exposed to an effective amount of such triggering or activating molecule.

[495] In particular embodiments, when the triggering or activating molecule is TNF, it is human TNF. In certain of such embodiments, the TNF is recombinant human TNF (rHuTNF). However, in other embodiments the TNF is endogenous TNF, such as that is produced by or otherwise present in the subject (eg the human patient).

[496] Studies have shown that plasma TNF levels are elevated in numerous types of cancers, including in ovarian cancer (Dobrzycka et al 2009, Eur Cytokine Netw 20:131), and that for example, the upper normal limit of total TNF in healthy subjects is 1.8 pg/mL, as measured using a Quantikine human TNF-alpha Immunoassay PDTA00C. In other cancers and assays (eg, TNF-alpha-EASIA Kit, DIAsource), the TNF plasma levels of oesophageal cancer patients and the control group were 12.35 ± 9.69 and 4.62 ± 3.06 pg/ mL, respectively (Aydin et al 2012, Turk J Med Sci 42:762). Accordingly, in other embodiments the cells involved with the proliferative disorder are (for example a tumour is) one present in a subject having a plasma concentration of TNF greater than about 1.5, 2.5 or 4 pg/mL, such as greater than about 5 pg/mL, and in particular greater than about 10 pg/mL (for example, as measured by a Quantikine human TNF-alpha Immunoassay PDTA00C or a TNF-alpha-ELISA Kit, DIAsource).

[497] Accordingly, in one particular embodiment, the subject involved in the treatment methods of the invention may have (that is, such a subject can be distinguished by, such as distinguished as one suitable for the therapeutic methods of the present invention, by showing, possessing or displaying) a plasma concentration of TNF greater than about 2 pg/mL or greater than about 5 pg/mL (eg, the cells involved with the proliferative disorder are one present in a subject having a plasma concentration of TNF greater than about 2 pg/mL or 5 pg/mL).

[498] Indeed, in those embodiments where the proliferative disorder is a tumour, then the intratumoural concentration of TNF may be a characterisation of the tumour, such as when the tumour is a solid tumour and accessible for biopsy (Reissfelder et al 2015, J Clin Inv 125:739). For example, a tumour (such as a solid tumour eg colorectal cancer) can, in some embodiments of the invention, have an intratumoural concentration (eg, within the tumour tissue) of TNF that is greater than about 0.2, 0.5 or 1 pg/mL, such as greater than about 2 pg/mL, and in particular greater than about 5 pg/mL (for example, as measured by a Quantikine human TNF-alpha Immunoassay).

[499] Accordingly, in such embodiments when the proliferative disorder is a tumour (eg a solid tumour), then the solid tumour (eg, within the subject) may have (that is, such a subject can be distinguished by, such as distinguished

as one suitable for the therapeutic methods of the present invention, by showing, possessing or displaying) an intratumoural concentration of TNF greater than (about) 0.5 pg/mL or greater than about 1 pg/mL.

[500] Accordingly, **in a related aspect**, the invention can relate to **a method for the treatment of a proliferative disorder** (or a compound (or pharmaceutical composition) of the invention for use in such a treatment) in a subject distinguished by having: (i) a plasma concentration of TNF greater than about 2 pg/mL (preferably greater than about 5 pg/mL); and/or (ii) an intratumoural concentration of TNF greater than about 0.5 pg/mL preferably greater than about 1 pg/mL), the treatment method comprising administering a compound (or pharmaceutical composition) of the invention to the subject, wherein the compound (or pharmaceutical composition): (a) inhibits a kinase/key-kinase (eg SIK3) in cells involved with the proliferative disorder; and/or (b) sensitises cells in the subject involved with the proliferative disorder to a cell-mediated immune response.

[501] In particular of such embodiments, the amount (or dose) of a compound (or pharmaceutical composition) of the invention that is exposed to cells involved with the proliferative disorder, or that is administered to the subject, is related to (eg correlated to) the plasma or intratumoural concentration of TNF, wherein a greater amount (or dose) of the compound (or pharmaceutical composition) is exposed to such cells (or administered to such subject) in those cases of a greater plasma or intratumoural concentration of TNF.

[502] In other or further embodiments, the tumour may be present in a subject having tumour-reactive T-cells in peripheral blood or bone marrow, for example as may be determined by IFN-gamma ELISPOT. In yet other or further embodiments, the tumour shows infiltration by Tregs, CD4+ Tconv and/or CD8+ T cells.

[503] In other embodiments, the cells involved with the proliferative disorder comprises a single nucleotide polymorphism (SNP) in the promoter region of TNF associated with increased expression of TNF and cancer sensitivity, for example with an AA or GA genotype at the -308G/A SNP in the promoter region of TNF; and in alternative embodiments the tumour does not comprise a SNP associated with decreased expression of TNF and reduced cancer risk, such as does not comprise an AA or GA genotype at the -238G/A SNP or a -857T allele, in each case in the promoter region of TNF (Wang and Lin 2008, Acta Pharmacol Sin 28:1275).

[504] The invention hereby provides alternative combination treatment regimens based on the surprising finding of the inventors that inhibition of one or more kinase, such a one or more key-kinases, (eg SIK3) by compounds of the invention can influence the sensitivity of a cell towards the apoptotic/cytotoxic effects of TNF. Accordingly, in a further aspect, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to a method for the treatment of a proliferative disorder in a subject, the method comprising exposing (eg contacting) cells involved with the proliferative disorder in the subject to: (i) TNF, a TNF variant and/or an agonist of TNFR2- or TNFR1-signalling; and exposing (eg contacting) the cells involved with the proliferative disorder in the subject to (ii) a compound (or pharmaceutical composition) of the invention. In certain embodiments, step (i) of such method does not comprise exposing (eg contacting) cells involved with the proliferative disorder in the subject to a TNF variant.

[505] In certain embodiments, the proliferative disorder and/or such cells are those of the tumour, and in other embodiments, component (i) is TNF, in particular human TNF (such as rHuTNF); and/or component (i) is an agonist of TNFR1-signalling.

[506] In particular embodiments, the method comprises (eg the treatment comprises, involves, is by or is mediated by) increasing the amount of TNF exposed to the cells involved with the proliferative disorder in the subject.

[507] In certain embodiments of such aspects, the treatment may comprise (eg, involves, is by or is mediated by) increasing TNFR1- and/or TNFR2-signalling in (of) the cells involved with the proliferative disorder in the subject. Accordingly, in a related aspect the invention relates to a method for the treatment of a proliferative disorder in a subject, the method comprising: (i) increasing TNFR1- and/or TNFR2-signalling in (of) the cells involved with the proliferative disorder; and (ii) exposing (eg contacting) the cells involved with the proliferative disorder in the subject to a compound (or pharmaceutical composition) of the invention.

[508] In particular the method can, for example, be effected though the consequence(s) of inhibition of a kinase (eg a key-kinase such as SIK3) (such as inhibition of the function and/or activity of phosphorylated SIK3), in particular in combination with the consequence(s) of activation of TNFR1- and/or TNFR2-signalling, such as upon binding of the TNF, TNF variant and/or TNFR1 agonist to TNFR1 or TNFR2.

[509] Accordingly, the treatment effect can, in certain embodiments, involve, or be mediated (eg, caused) by, inhibiting a kinase (eg a key-kinase, such as SIK3), and/or by sensitising the cells involved with the proliferative disorder to the cytotoxic (eg apoptotic) effects of TNFR1- or TNFR2-signalling. In particular of such embodiments, the kinase/key-kinase activity may be (effectively) reduced, such as to a therapeutically effective level.

[510] As described above, herein are also envisioned embodiments wherein a kinase, such as a key-kinase (eg SIK3) in the tumour cells is inhibited and, optionally, where one or more other kinase/key-kinase (eg SIK2 and/or SIK1) are inhibited to a lesser extent, such as such other kinase (eg SIK2 or SIK1) of immune cells.

[511] Also as described above, herein are also envisioned embodiments wherein the treatment comprises, involves, is by or is mediated by (eg, a compound (or pharmaceutical composition) of the invention is administered in an amount, such as a therapeutically effective amount that is effective to) inhibition of a kinase/key-kinase activity such that it is (eg, effectively) reduced, such as reduced to a therapeutically effective level.

[512] In certain embodiments of such aspect, the subject can be administered a compound (or pharmaceutical composition) of the invention and/or can be administered (the) TNF, an (the) TNF variant or an (the) agonist of TNFR1- or TNFR2-signalling.

[513] In such embodiments, a compound (or pharmaceutical composition) of the invention and the TNF, TNF variant or TNFR1 or TNFR2 agonist can be exposed to (for example administered in) an effective amount (or dose), including in formulations or administrative routes as described elsewhere herein. In particular are envisioned embodiments where the TNF, TNF variant or TNFR1 or TNFR2 agonist is encapsulated as a liposomal or other nanoparticle formulation.

[514] When the TNF, TNF variant or TNFR1 or TNFR2 agonist is exposed/administered and a compound (or pharmaceutical composition) of the invention is exposed/administered, then such combination treatment regimen may comprise embodiments where such exposures/administrations are concomitant. In alternative embodiments such exposures/administrations may be sequential; in particular those embodiments where a compound (or pharmaceutical composition) of the invention is exposed/administered before the TNF, TNF variant or TNFR1 or TNFR2 agonist is exposed/administered. For example a compound (or pharmaceutical composition) of the invention may be sequentially exposed/administered within about 14 days of (eg before) the other component, such as within about 10 days, 7 days, 5 days, 2 days or 1 day of (eg before) the other component; and further including where the compound (or pharmaceutical composition) may be sequentially exposed/administered within about 48 hours, 24 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 1 hours, 30 mins, 15 mins or 5 mins of (eg before) the other component.

[515] The TNF or the TNF variant or TNFR1 or TNFR2 agonist may be administered via conventional routes, such as s.c., i.v. or i.m., and on certain embodiments may be administered intratumourally or by isolated limb perfusion (ILP), such as isolated hepatic perfusion (IHP); and/or may be so administered (in particular, rHuTNF may be so administered) at a dose of between about 5 and 500 $\mu g/m^2$/day. For example, TNF may be administered between about 25 and 250 $\mu g/m^2$/day, such as between about 50 and 150 $\mu g/m^2$/day or between about 75 and 100 $\mu g/m^2$/day; or wherein TNF is administered up to a MTD of about 50 and 75 $\mu g/m^2$/day when administered s.c. or up to a MTD of about 150 and 200 $\mu g/m^2$/day when administered i.v. or i.m. Accordingly, in particular of such embodiments, TNF can be administered to the subject at a dose of between about 5 and 500 $\mu g/m^2$/day, in particular between about 20 and 200 $\mu g/m^2$/day.

[516] In particular embodiments a variant of TNF, such as a TNF variant having higher anti-tumour activity and lower systemic toxicity that rHuTNF may be exposed/administered. For example, the TNF variant may be one selected

from the group consisting of: (i) a –K90R variant of TNF; (ii) a tumour-homing peptide conjugated to TNF; and (iii) a TNF-antibody conjugate.

[517] In those embodiments of the invention involving a TNF variant, it may be a variant form of TNF having higher cytotoxic activity and lower systemic toxicity.

[518] In other embodiments a TNFR1 or TNFR2 agonist, such as the anti-TNFR1 monoclonal antibody htr-9 (Ferrero et al 2001, Am J Physiol Cell Physiol 281:C1173) may be exposed/administered, and in other embodiments lymphotoxin-alpha (Etemadi et al 2013, FEBS J 280:5283) or a variant thereof may be exposed/administered.

[519] In alternative embodiments, cells involved with the proliferative disorder (eg tumour cells) may be exposed to TNF (or increased TNFR1- and/or TNFR2-signalling) through the administration of an agent (eg to a subject harbouring such cell) that can lead to the exposure of such cells to (eg endogenous) TNF, or to another triggering molecule such as a variant of TNF or a TNFR1 or TNFR2 agonist. Such an agent may, for example, be one that is capable of inducing (eg induces) the exposure of such cells to (eg an elevated level of) TNF, in particular an agent that induces the exposure of such cells to TNF levels, such as to an effective amount of (eg endogenous) TNF, for example levels of plasma or intratumoural TNF that are greater than one or those levels described elsewhere herein.

[520] Accordingly, the invention includes those embodiments wherein the subject is administered an agent that is capable of inducing (eg induces) the exposure of the cells involved with the proliferative disorder to (the) TNF, an (the) TNF variant or an (the) agonist of TNFR1- or TNFR2-signalling. The invention also includes those embodiments wherein the subject gets administered an agent that is capable of increasing TNFR1-signalling (and/or TNFR2-signalling) of, and/or increasing the amount of TNF exposed to, cells involved with the proliferative disorder in the subject.

[521] In certain of such embodiments, the agent is a virus, in particular one that has been engineered to produce a triggering molecule being TNF, a TNF variant or the TNFR1 or TNFR2 agonist (especially, a virus engineered to produce human TNF). Further of such embodiments include those where such virus preferentially infects the cell(s) involved with the proliferative disorder (eg tumour cells) and/or preferentially produces the triggering molecule in the context of (eg when it infects) such cells. As will now be apparent, the administration of such a virus can lead to the exposure of the cell(s) involved with the proliferative disorder to such triggering molecule, and in particular to an effective amount of such a triggering molecule such as TNF.

[522] Accordingly, in certain of such methods, the agent may be a virus that is capable of inducing (eg induces) the exposure of the cell(s) involved with the proliferative disorder the TNF, TNF variant or agonist of TNFR1- or TNFR2-signalling.

[523] Such a virus may be any that is suitable for inducing the exposure of the triggering molecule, and in particular may be a recombinant virus; for example one engineered to infect tumour cells and/or to express TNF (eg after infecting a tumour cell). Examples of virus that may be so engineered include oncolytic viruses (eg, those based on an adenovirus, HSV, vaccinia virus, vesicular stomatitis virus or Newcastle disease virus), such as intratumoural injection of adenovirus vectors to increase plasma levels of pro-inflammatory cytokines and chemokines, including TNF (Bernt et al 2005, Cancer Res 65:4343). In particular of such embodiments, the oncolytic virus may be one based on a DNA virus described in Table 1 of Kaufman et al 2015 (Nature Rev Drug Disc 14:642), one based on an RNA virus described in Table 2 of Kaufman et al 2015, preferably, is an oncolytic virus described in Table 3 of Kaufman et al 2015 as being in clinical trials.

[524] In other of such embodiments, the agent that is administered (and that consequentially leads to exposure of the cells involved with the proliferative disorder to a triggering molecule being TNF, a TNF variant or a TNFR1 or TNFR2 agonist) is an immune cell. In certain of such embodiments, the immune cell may not be an IL10-producing macrophage, for example the immune cells can be a pro-inflammatory immune cell. In particular of such embodiments, the immune cell that is administered may be a lymphoid cell, eg a T cell or a natural killer (NK) cell, for example such a cell that produces TNF.

[525] When administered as an agent in such embodiments of the invention, the immune cell may be administered via adoptive cell transfer (ACT); meaning the transfer of the immune cell into the subject (eg, by infusion or other delivery techniques). Such process is, typically, conducted with the goal of improving immune functionality and characteristics in the subject, and while conventionally the transferred immune cells will have originated from the same subject, they may alternatively have been derived from another (suitable) individual.

[526] When used in this embodiment of the invention, the immune cells may be T cells extracted from the subject, genetically modified and cultured in vitro and returned to the same subject, such as in a therapeutic method of the invention. Such genetic modification can include those that enhance the specificity or targeting of the immune cell, such as the targeting of the immune cell (eg increasing its specificity) to the cell(s) involved with the proliferative disorder (eg a tumour cell). For example, a T cell that is used in such embodiments may be modified to alter the specificity of the T cell receptor (TCR) or to introduce antibody-like recognition in chimeric antigen receptors (CARs). CAR immune cells, in particular, are envisioned for use in such embodiments. CAR immune cells are immune cells displaying engineered receptors, which graft an arbitrary specificity (eg to a tumour cell) onto an immune effector cell (eg a T cell). Typically, these receptors are used to graft the specificity of a monoclonal antibody onto a T cell; with transfer of their coding sequence facilitated by retroviral vectors. CAR T cells are a promising therapy for cancer (Song et al 2015, Oncotarget. 6:21533): using ACT, T cells are removed from an individual (typically the subject) and modified so that they express receptors specific to the patient's particular cancer. These T cells, which can then recognise the subject's cancer cells, are (re)introduced into the subject, leading to exposure of TNF (eg produced by the CAR T cells) to the tumour cells and hence killing of such cells, in particular such cells that are sensitised to such TNF-mediate cytotoxicity by exposure to (eg following administration to the subject of) a compound (or pharmaceutical composition) of the invention. Accordingly, in particular of such embodiments, the immune cells can be a CAR T cell, such as one engineered to have increased specificity to the subject's cells that are involved with the proliferative disorder (such as tumour cells).

[527] In alternative embodiments, the exposure of the cells involved with the proliferative disorder to TNF (eg endogenous TNF) may be induced by other means or procedures. Accordingly, in such embodiments, the exposure of the cells involved with the proliferative disorder to (eg an effective amount of) TNF can be induced by (and/or the increase in TNFR1-signalling (and/or TNFR2-signalling) in/of the cells involved with the proliferative disorder is induced by) a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

[528] In certain embodiments, such induced exposure to TNF may be brought about by the administration of a cancer immunotherapy.

[529] In one example, such induced exposure to TNF is brought about by an anti-tumour vaccine (eg, a cancer vaccine). Such cancer vaccines include those whereby antigens (eg, those specific to or preferentially expressed by cancer cells) are directly or indirectly introduced into the subject so as to raise or increase an immune response (typically, an adaptive immune response) in the subject that is envisioned to be (more) specific to the cancer cell. Cancer vaccine may comprise, for example, attenuated viruses, in particular for use against cancers such as cervical or liver cancers that are caused by such virus (eg HPV or HBV). Cancer vaccines can alternatively represent individual (or combinations) of particular tumour antigens (eg, those specific to or preferentially expressed by cancer cells), such as tumour-associated antigens (TAAs) that are used to immunise the subject so as to also raise or increase the immune response in the subject. The cancer vaccine may comprise recombinant protein representing (eg a peptide from) the TAA(s), or may be a tumour specific carbohydrate antigen, and hence are directly introduced into the subject upon administration. The cancer vaccine may, alternatively, comprise a nucleic acid (such as DNA or mRNA) than encodes the protein (or peptide) TAA, and upon administration of the nucleic acid vaccine into the subject, the encoded TAA is expressed by cellular targets in the subject, and hence are indirectly introduced into the subject. TAAs may be divided

into two categories: shared tumour antigens; and unique tumour antigens. Shared antigens are expressed by many tumours. Unique tumour antigens result from mutations induced through physical or chemical carcinogens (also known as neoantigens); they are therefore expressed only by individual tumours. The person of ordinary skill will be aware of examples of cancer vaccines in clinical trials, or approved for use, and include PROSTVAC (Bavarian Nordic), PROVENGE (Dendreon) and CV9104 (CureVac), as well as being aware of various TAAs (including neoantigens) and approaches by such tumour antigens may be utilised in cancer vaccines. As further examples: (1) immunisation with recipient-derived clonal myeloma immunoglobulin, idiotype (Id), as a tumour antigen, conjugated with keyhole limpet hemocyanin (KLH) has been shown to produce substantial amount or pro-inflammatory cytokines including TNF (Foglietta et al 2013, Bone Marrow Transplant 48: 269); and (2) a synthetic micro-consensus SynCon DNA vaccine of WT1 antigens induced new, neo-antigen-like responses that were superior to those induced by native WT1 DNA immunogens, such as strong CD4 and CD8 T cell responses (including IFN-gamma, CD107a, and TNF responses).

[530] In another example, such induced exposure to TNF may be brought about by the administration of a ligand (such as an antibody, eg, a monoclonal antibody), for example one that binds to the surface of the cell(s) involved with the proliferative disorder (such as a tumour cell), for example by binding to a TAA or a receptor on the surface of such cell. Cell surface receptors are common targets for such ligand (antibody) therapies and include CD52 and CD20. Once bound to such a cancer antigen, the eg antibodies can induce antibody-dependent cell-mediated cytotoxicity, activate the complement system, or prevent a receptor from interacting with its ligand, all of which can lead to cell death. Approved such ligands that are antibodies include alemtuzumab, ofatumumab and rituximab. In certain embodiments, such ligands used in combination with a compound (or pharmaceutical composition) of the invention can include those that activate T cells or other cell-mediated immune response. For example: (1) anti-CD137 monoclonal antibodies can dramatically promote proliferation of cytokine-induced killer (CIK) cells and expression of TNF (Zhu et al 2009, Biomed Pharmacother 63:509); (2) an agonist anti-OX40 monoclonal antibody can enhance antitumour immune response by augmenting T-cell differentiation (Redmond et al 2014, Cancer Immunol Res. 2014, 2:142); and (3) an anti-ICOS antibody that activates T cells (eg Deng et al 2004, Hybrid Hybridomics 23:176).

[531] In yet another example, the ligand that is administered to the subject is one that binds to an immune (inhibitory) checkpoint molecule. For example, such checkpoint molecule may be one selected from the group consisting of: A2AR, B7-H3, B7-H4, CTLA-4, IDO, KIR, LAG3, PD-1 (or one of its ligands PD-L1 and PD-L2), TIM-3 (or its ligand galectin-9), TIGIT and VISTA. In particular of such embodiments, the ligand binds to a checkpoint molecule selected from: CTLA-4, PD-1 and PD-L1. In other more particular embodiments, the ligand is an antibody selected from the group consisting of: ipilimumab, nivolumab, pembrolizumab, BGB-A317, atezolizumab, avelumab and durvaluma; in particular an antibody selected from the group consisting of: ipilimumab (YERVOY), nivolumab (OPDIVO), pembrolizumab (KEYTRUDA) and atezolizumab (TECENTRIQ). In other embodiments, the ligand that binds to a immune (inhibitory) checkpoint molecule may be a non-antibody peptide, such as a high-affinity PD-1 variant (eg, Maute et al, 2015; PNAS 112:E6506), a peptide targeting the immune checkpoint molecule (such as AUNP-12 of Aurigene Discovery Technologies, US 2011/0318373) or a D peptide blocking an interaction between immune checkpoint molecule (such as the PDL1-PD1 interaction and (D) PPA-1, Chang et al, 2015; Anyeg Chem Int 54:11760). In yet other embodiments, the ligand that binds to an immune (inhibitory) checkpoint molecule may be a small molecule, such as the PDL1-targeting BMS-202 or BMS-8 (Zak et al 2016; Oncotarget 7:30323), the inhibitors of PDL1/D1 known as BMS-1001 or BMS-1166 (Skalniak et al, 2017; Oncotarget 8:72167), the PDL1 and VISTA antagonist CA-170 of Curis/Aurigen undergoing phase 1 trials (Powderly et al, Ann Onc 28: Issue suppl 5, mdx376.007) or CA-327 of Curis/Aurigen which targets PDL1 and TIM3.

[532] In yet another particular embodiments, such induced exposure to TNF may be brought about by radiotherapy.

[533] Radiotherapy is a method of locoregional treatment of cancers or tumours, using radiation to destroy the cancer cells by blocking their ability to multiply and/or to stimulate an immune reaction against them (such one raised

as a response to the presence of dead or dying cancer cells). Radiotherapy, in the context of the present invention, consists - in particular - of the therapeutic use of ionising radiation. Said radiotherapy and the associated ionising radiation are those commonly used and known to those skilled in the art. Radiotherapy includes in particular the use of ionizing radiation, for example gamma-rays, X-rays and/or radiation emanating from radioisotopes. In the context of the present invention, it is more particularly X-ray radiation. The radiotherapy may be administered in fractionated form during one or more cycles, such as a cycle that can range from 1 to 4 weeks, more particularly 3 weeks. The cycle defines the interval between the beginning and the end of an administration scheme. When the cycle takes three weeks, radiotherapy can be administered over three weeks, with one week between. The radiotherapy may in particular be administered at a rate of one daily irradiation, 5 days out of 7, for the desired number of weeks. The amount of radiation used in (photon) radiation therapy is measured in gray (Gy), and varies depending on the type and stage of cancer being treated. For curative cases, the typical dose for a solid epithelial tumour ranges from 60 to 80 Gy, while lymphomas are treated with 20 to 40 Gy.

[534] When a compound (or pharmaceutical composition) of the invention (or a compound used in the fifth aspect of the invention) is used in combinations treatments together with any of such other procedures (eg, the other agent, the cancer immunotherapy, the cancer vaccine, the antibody or the radiotherapy, in each case as described herein), then such combination treatment regimen may comprise embodiments where such exposures/administrations are concomitant. In alternative embodiments such administrations may be sequential; in particular those embodiments where the compound (or pharmaceutical composition) is administered before such other procedure. For example a compound (or pharmaceutical composition) of the invention (or a compound used in the invention) may be sequentially administered within about 14 days of (eg before) the other procedure, such as within about 10 days, 7 days, 5 days, 2 days or 1 day of (eg before) the other procedure; and further including where the compound (or pharmaceutical composition) may be sequentially administered within about 48 hours, 24 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 1 hours, 30 mins, 15 mins or 5 mins of (eg before) the other procedure.

[535] Without being bound to theory, administration of a compound (or pharmaceutical composition) of the invention (and hence inhibition of the expression, amount, function, activity or stability of a kinase /key-kinase such as SIK3, eg in a tumour cell) prior to administration of the TNF, TNF variant or TNFR1 or TNFR2 agonist, or prior to administration of such other procedures (eg, the other agent, the cancer immunotherapy, the cancer vaccine, the antibody or the radiotherapy, is foreseen to be particularly effective in sensitising the cells involved with the proliferative disorder to the cytotoxic effects of the cell-mediated immune response.

[536] As described above, existing therapies (or those under clinical trials) involving administration of TNF and/or use of anti-TNF molecules suffer certain known disadvantages; and particular side effects. The present invention provides methods that may be used to mitigate (or reduce) such disadvantages and/or particular side effects.

[537] In **a sixth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a method for the increase of the therapeutic index of treatment with TN**F in a subject being treated therewith for a proliferative disorder (eg a cancer disease or a tumour), the method comprising administering a compound (or pharmaceutical composition) of the invention to the subject.

[538] In **a related aspect**, the invention relates to **a method for supporting TNF therapy** in a subject suffering from a proliferative disorder (eg a cancer disease or a tumour), the method comprising administering a compound (or pharmaceutical composition) of the invention to the subject.

[539] In **a seventh aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a method for the sensitisation** of a subject suffering from a proliferative disorder (eg a cancer disease or tumour) to a therapy involving the administration of TNF to the subject, the method comprising administering a compound (or pharmaceutical composition) of the invention to the subject.

[540] The term "sensitisation" (and the like), as used herein in the context of a subject being sensitised to a therapy (eg one involving the administration of TNF), will be understood by the person of ordinary skill, and includes the meaning that the subject increases susceptibility to one or more (treatment) effect – in particular an efficacy effect - that such therapy may have on the subject. In particular, a subject that is so sensitised may, when undergoing such therapy, show an increased response (such as more rapidly, a greater degree of response and/or upon a lower amount or exposure of such therapy) than an analogous subject that have not been so "sensitised".

[541] In **an eighth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **a method for the reduction in risk of (developing) a haematological proliferative disorder** (eg, as a secondary disorder) in a subject being treated with an anti-TNF agent, the method comprising administering a compound (or pharmaceutical composition) of the invention to the subject. For example, such aspect may alternatively, be considered as a method for the prevention of a haematological proliferative disorder (as a secondary disorder) in a subject being treated with an anti-TNF agent, the method comprising administering a compound (or pharmaceutical composition) of the invention to the subject.

[542] This aspect of the invention is based on the observation as described above, that there are reports of patients receiving anti-TNF biologics developing lymphomas and other haematological malignancies. Indeed, such disorders are typically described in package leaflets/prescribing information as possible (but rare) side-effects of treatment with anti-TNF agents. As a direct consequence of the perceived increase in haematological malignancy and widespread use of these and other immunosuppressive agents, the WHO classification of tumours now includes the category "iatrogenic immunodeficiency-associated lymphoproliferative disease".

[543] Therefore, typically in such aspects, the subject is being treated with the anti-TNF agent for an indication other than a proliferative disorder, and in particular of such embodiments the subject does not – upon commencement of the anti-TNF treatment - suffer from a haematological proliferative disorder. Indeed, typically the subject would suffer from, and/or is being treated with the anti-TNF agent for an autoimmune disorder; preferably an autoimmune disorder selected from the group consisting of: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's Disease, psoriasis, hidradenitis suppurativa and refractory asthma; such as one selected from the group consisting of: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis and Crohn's Disease; and in particular rheumatoid arthritis.

[544] In certain embodiments, the anti-TNF agent is one selected from a list consisting of: infliximab, adalimumab, golimumab, humicade, etanercept, onercept and certolizumab pegol, in particular infliximab or humicade.

[545] In certain embodiments, the haematological malignancies proliferative disorder may be a lymphoproliferative disease, in particular an iatrogenic immunodeficiency-associated lymphoproliferative disease.

[546] In certain embodiments of such sixth to eighth aspects, the (treatment) effect (eg the increase in therapeutic index, sensitisation of a subject or reduction in risk) is mediated by (eg, the treatment comprises, is by, is mediated by or involves): (i) inhibiting a kinase (eg a key-kinase such as SIK3) (such as by the inhibition of the function and/or activity of phosphorylated SIK3), in particular by inhibiting such a kinase (eg a key-kinase) in cells involved with the proliferative disorder; and/or (ii) sensitising such cells to the killing (apoptotic/cytotoxic) effects of TNF. In further embodiments, the (treatment) effect may not be mediated by (eg, the treatment may not comprise or involve) inhibiting one or more other key-kinases (eg, ABL1 and/or SRC, or SIK2 and/or SIK1), in particular not mediated by (eg, the treatment does not comprise or involve) inhibiting or more other key-kinases (eg SIK2 and/or SIK1 (and/or SIK3) in immune cells.

Pre-clinical and clinical testing

[547] In certain embodiments, the subject is a human volunteer; for example one that has chosen (eg consented) to be administered a compound (or pharmaceutical composition) of the invention for a clinical trial or other experimental use of the compound. Such a human volunteer may be a healthy human (eg, a healthy volunteer) or may be suffering from a disorder such as a proliferative disorder (eg, a cancer patient). In another embodiment, the subject is a laboratory animal, in particular an animal selected from the group consisting of: mouse, rat, rabbit, pig and monkey.

[548] In such (eg experimental treatment) embodiments, a plurality of such subjects can be treated; in particular 5 or more subjects, such as between about 5 and 20, 10 and 50, 25 and 200, or 75 and 250 subjects, or more than about 250 subjects.

[549] Such experimental (or clinical trial) treatments may comprise: (i) the administration to at least one of such subjects of one dosage of a compound of the invention and/or one formulation of a pharmaceutical composition of the invention; and (ii) the administration to at least one other of such subjects of a different dosage of the compound and/or a different formulation of the pharmaceutical composition.

[550] In further of such embodiments, such experimental (or clinical trial) treatments may comprise: (i) the administration to at least one of such subjects of one dosage of a compound of the invention and/or one formulation of the pharmaceutical composition of the invention; and (ii) the administration to at least one other of such subjects of either: (a) a placebo; or (b) the dosage of the compound and/or the formulation of the pharmaceutical composition of the subject(s) of (i) as well as an additional pharmaceutical, therapeutic or other procedure.

[551] The term "placebo" will be art recognised, and includes a substance or treatment of no intended therapeutic value. In such embodiments, the placebo can be made to resemble the other administration so that it functions as a control, such as in a blinded trial.

[552] In certain of such embodiments, such experimental (or clinical trial) treatment is specifically designed for the investigation and/or determination of a therapeutically effective dosage of a compound of the invention and/or the identification of a therapeutically effective formulation of a pharmaceutical composition of the invention.

Diagnosis

[553] In **a ninth aspect**, the invention relates to **a method of diagnosing and treating** a disease, disorder or condition characterised by the presence of or an amount of, and/or characterised by (eg aberrant) expression or activity of, one or more applicable biomarkers (such as a kinase) in a subject, such as a human patient, comprising:

- detecting one or more such applicable biomarkers in a biological sample from said subject, thereby diagnosing if the subject is suffering (or is likely to suffer) from such a disease, disorder or condition; and
- administering an effective amount of a compound of the invention (and/or a pharmaceutical composition comprising such compound) to the so diagnosed subject, in particular practicing a treatment method of the invention on the subject.

[554] In one of such embodiments, the disease, disorder or condition is a proliferative disorder, such as one disclosed elsewhere herein (eg a tumour or cancer).

[555] The term "applicable biomarker" means any one (or more) of the genes expressed by the cell involved with the proliferative disorder that are involved in the (eg kinase/key-kinase mediated) cellular resistance against an immune response (eg a cell-mediated immune response such as TNF). Such genes include: (X) one or more kinase, in particular one or more key-kinase as described herein, such as one selected from the group consisting of: SIK1, SIK2, SIK3, ABL1 (BCR-ABL), SRC, HCK, PDGFR, FLT3, KIT, YES, LYN and FYN (and LCK); in particular, CSF1R, ABL1 (BCR-ABL), HCK, PDGFR and FLT3 and, in particular, phosphorylated SIK3; (Y) a mutant of a kinase, such as a mutant ABL1 kinase (eg BCR-ABL) or a mutant of KIT kinase; and/or (Z) one or more of (a) to (f) below):

(a) TNFR1 (or TNFR2), such as the presence of (or an amount of) or expression and/or activity of TNFR1 (or TNFR2), in particular TNFR1;

(b) LKB1, such as the presence of (or an amount of) or expression and/or activity of LKB1, in particular increased amount or activity of LKB1 or pLKB1;

(c) one or more class II (eg IIa) HDACs, eg HDAC4, such as the presence of (or an amount of) or expression and/or activity of such HDAC, in particular increased amount or activity of such HDAC or pHDAC, especially in the cytoplasm of cells of the tumour;

(d) Expression of NF-kappa-B, in particular, constitutive expression of NF-kappa-B;

(e) NF-kappa-B, such as the presence of (or an amount of) or expression and/or activity of NF-kappa-B, in particular increased amount or activity of NF-kappa-B or acetylated NF-kappa-B, especially in the nucleus of cells of the tumour; and/or

(f) one or more anti-apoptotic genes, such as the presence of (or an amount of) or expression and/or activity of one or more anti-apoptotic genes, in particular one or more of such genes under transcriptional control by NF-kappa-B.

[556] In certain embodiments, the applicable biomarker is one or more key-kinases selected from the list consisting of: EPHA2, EPHA4, CSF1R, HCK, ACK1 (in particular, CSF1R); and/or PDGFR-alpha, TGFB-R1, B-RAF and/or p38-beta; and/or ACV-R1 and/or BMPR1A; and/or RET; and/or NEK11, WEE1 and/or WNK2; and/or Aurora-A and/or Aurora-B; and/or TBK1; and also in particular NEK11.

[557] In a certain of such embodiments, the applicable biomarker is CSF1R or NEK11.

[558] In another embodiment of the above method of diagnosing and treating, the "applicable biomarker" is, alternatively, TGFbeta. In particular, those subjects having tumour types with high TGFbeta content (Hsing et al 1996, Cancer Res 56:5146) such as breast, lung, prostate, liver cancer, or a lymphoma, may be suitable for treatment with a compound disclosed herein (eg a compound of any of Formulae (Ia), (Ib) or (Ic)), for example by the compound inhibiting SIK3 and rendering sensitive to apoptosis the tumour cells. Recently, SIKs (particularly SIK3) have been demonstrated to also regulate TGFbeta-mediated transcriptional activity and apoptosis, with Hutchinson et al (2010, Cell Death and Disease 11:49) showing that SIK3 expression or activity results in resistance to TGFbeta-mediated apoptosis. TGFbeta is a member of the cytokine family that binds to its cognate receptors on cells and mediates multiple cellular processes ranging from proliferation, differentiation, migration, apoptosis to epithelial-mesenchymal transition (Massagué et al 2012, Nat Rev Mol Cell Biol 13:616). In a tumour setting, the TGFbeta axis can be mis-regulated; leading to oncogenic processes (Drabsch & ten Dijke 2012, Cancer Metastasis Rev 31:553). The TGFbeta axis can serve to limit immune responses by inhibiting the expression of pro-apoptotic and cytolytic factors such as granzymes, perforins, IFNgamma in T cells or NK cells. Therefore, targeting TGFbeta in oncology has recently gained prominence. However, TGFbeta can also induce apoptosis in tumour cells via the caspase pathway. Indeed, tumour cell lines from lymphoma (Inman & Allday 2000, J Immunol 165:2500), liver cancer (Kim et al 2002, Mol Cell Biol 22:1369) and prostate cancer (http Hsing et al 1996, Cancer Res 56:5146) have been shown to be sensitive to TGFbeta-mediated apoptosis.

[559] In **one aspect**, the invention relates to **a method for determining** that a subject suffering from a proliferative disorder is suitable for treatment with a compound or pharmaceutical composition as defined elsewhere herein, in particular wherein the compound is selected from the following compounds (a) to (c), or (d) or (e), or the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient: (a) a compound of formula (Ia), such as any embodiment thereof as described above; (b) a compound of formula (Ib), such as any embodiment thereof as described above; and (c) a compound of formula (Ic), such as any embodiment thereof as described above, and in each case , salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations

thereof; or (d) dasatinib, in particular N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate (Figure 1A); or (e) ARN-3261 (Vankayalapati et al 2017, AACR Cancer Res 77(13 Suppl):Abstract nr LB-296; US 9,260,426, US 9,890,153, US 9,951,062).

[560] Such a determining method can comprise, determining in a biological sample that has been (previously) obtained from said subject, (X) the presence of (and/or an amount of) MEF2C protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by the presence of (and/or an amount of) phosphorylated HDAC4 protein, such as of HDAC4 protein phosphorylated by SIK3; and/or (Y) (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; (iii) the presence of (and/or an amount of) a KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the *KRAS* gene and/or in the *RUNX1* gene. For example, the protein or oncoprotein may be present at an amount (eg a quantitative amount), such as an amount that is in excess of physiological amount (eg, for that cell type and/or that time/stage), including from expression or over-expression of the protein. In another embodiment, such protein may be present at an amount (eg a quantitative amount) that is in excess of a threshold amount or is an outlier from a reference distribution of amounts of such protein/oncoprotein.

[561] In one embodiment of such method, the biological sample that had (previously) been obtained from the subject comprises cells that are involved with the proliferative disorder (eg, cancer or tumour cells).

[562] Such a method is, for example, conducted as an in-vitro method; such as a method that is not practiced on the human or animal body (eg, is not practiced on the body of such subject).

[563] The presence of (and/or the amount of) said protein, translocation, rearrangement, oncoprotein and or mutation (as applicable) in the biological sample can indicate that the subject is suitable for treatment with the compound or pharmaceutical composition.

[564] Certain embodiments of such determining methods comprise those embodiments of said protein, translocation, rearrangement, oncoprotein and or mutation as are described elsewhere herein.

[565] In other embodiments (and as may be further specified elsewhere herein), the proliferative disorder may be a cancer or a tumour, for example a haematopoietic malignancy and/or a lymphoid malignancy. In particular, the proliferative disorder may be: (i) a myeloma, preferably multiple myeloma; or (ii) a leukaemia, preferably an acute myeloid leukaemia (AML) or an acute lymphoblastic leukaemia (ALL), more preferably T cell acute lymphoblastic leukaemia (T-ALL), an MLL-AML or an MLL-ALL. The proliferative disorder may be one set forth in Figure 23.

[566] The subject in such determining methods may be, for example, a human paediatric patient and/or may be a subject carrying a *KMT2A* rearrangement (*KMT2A-r*); In particular embodiments, the subject may be a patient suffering from a *KMT2A-r* leukaemia, especially a (eg, paediatric) human patient as described elsewhere herein.

[567] In certain embodiments, such determining method can further comprise administering the compound (eg, a compound selected from the compounds (a) to (c), or (d) or (e)) to the subject, in particular when the presence of (and/or the amount of) said protein, translocation, oncoprotein and or mutation is determined in a biological sample that had been obtained from said subject. Such embodiment may, alternatively, be described as an additional aspect of the invention that provides a method of determining (the suitability for) and treating the subject, such method comprising the steps of such embodiment.

[568] Further embodiments of the administering (or treatment) step of this method of diagnosis and treatment are described in more details elsewhere; as are particular embodiments of the methods of the detection, determination or diagnostic method step of this method. Particular of such embodiments include those where the amount of a compound (and/or pharmaceutical composition) of the invention administered to the subject is correlated to the plasma or intratumoural concentration of TNF (in the subject), wherein a greater amount (or dose) of the compound (and/or pharmaceutical composition) administered to such subject in those cases of a greater plasma or intratumoural concentration of TNF.

[569] In certain embodiments, a biological sample will (preferably) comprise cells or tissue of the subject, or an extract of such cells or tissue, in particular where such cells are those (usually, typically; or in the case or a specific subject as suspected to be) involved with the proliferative disorder (eg tumour cells such as cells of a solid tumour). The tumour or cell thereof, may be one of, or derived from, one of the tumours described elsewhere herein.

[570] In particular embodiments of such aspect, the method will also comprise a step of:

- providing (such as by obtaining) the biological sample from the subject, in particular where such step is conducted prior to the detection step.

[571] In particular embodiments, such detection and/or determination methods can be practiced as a method of diagnosis, such as a method of diagnosis whether a mammalian subject (such as a human subject or patient) has a disease, disorder or condition, in particular (the presence of) a proliferative disorder such as a cancer or tumour (or has a risk of developing such a disease, disorder or condition) that is associated with cellular resistance against a cell-mediated immune response and/or that is associated with (eg aberrant) expression or activity of the applicable biomarker (eg SIK3); in particular a (solid) tumour, such as one having cellular resistance against a cell-mediated immune response.

[572] In certain embodiments of these detection, determination and/or diagnostic methods, the cellular resistance against a cell-mediated immune response is cellular resistance against a T cell-mediated immune response, in particular cellular resistance to the killing (apoptotic/cytotoxic) effect of TNF and/or of TNFR1 or TNFR2 signalling.

[573] Accordingly, particular embodiments of these detection and/or diagnostic methods may also comprise a step of determining the presence or amount of TNF in the sample, wherein the presence of (or an amount of) TNF in the sample indicates a/the proliferative disorder (or a/the risk of developing a proliferative disorder) that is associated with cellular resistance against the cell-mediated immune response, and/or associated with (aberrant) expression or activity of the kinase (eg SIK3), in the subject. In particular of such embodiments, amount of TNF in the sample is determined qualitatively. Preferably, the subject is distinguished as having: (i) a plasma concentration of TNF greater than about 2 pg/mL or 5 pg/mL in a plasma sample from the subject; and/or (ii) an intratumoural concentration of TNF greater than about 0.5 pg/mL or 1 pg/mL from a tissue sample from the subject, indicates the (presence of the proliferative disorder or a risk of developing the proliferative disorder that is associated with cellular resistance against the cell-mediated immune response, and/or associated with expression or activity of the kinase (eg SIK3), in the subject.

[574] Methodologies to determine the presence or amount of TNF in a sample are described elsewhere herein (in particular, quantitative detection of TNF using ELISA assays such as a Quantitkine TNF-alpha Immunoassay; as are amounts of TNF that, if are exceeded by the TNF present in the sample, indicate that a proliferative disorder associated with cellular resistance against the cell-mediated immune response, and/or associated with (aberrant) expression or activity of the kinase (eg SIK3), in the subject.

[575] In certain embodiments, the biological sample is one obtained from a mammalian subject like a human patient. The term "biological sample" is used in its broadest sense and can refer to a bodily sample obtained from the subject (eg, a human patient). For example, the biological sample can include a clinical sample, ie, a sample derived from a subject. Such samples can include, but are not limited to: peripheral bodily fluids, which may or may not contain cells, eg, blood, urine, plasma, mucous, bile pancreatic juice, supernatant fluid, and serum; tissue or fine needle biopsy samples; tumour biopsy samples or sections (or cells thereof), and archival samples with known diagnosis, treatment and/or outcome history. Biological samples may also include sections of tissues, such as frozen sections taken for histological purposes. The term "biological sample" can also encompass any material derived by processing the sample. Derived materials can include, but are not limited to, cells (or their progeny) isolated from the biological sample, nucleic acids and/or proteins extracted from the sample. Processing of the biological sample may involve one or more of: filtration, distillation, extraction, amplification, concentration, fixation, inactivation of interfering components, addition

of reagents, and the like. In certain embodiments, the biological sample may comprise cells that are involved with a disorder (eg, a proliferative disorder) such as cancer or tumour cells).

[576] In some embodiments, these detection, determination and/or diagnostic methods may be a computer-implemented method, or one that is assisted or supported by a computer. In some embodiments, information reflecting the presence or an amount of the applicable biomarker (eg, a key-kinase such as ABL1/BCR-ABL, SRC and/or SIK3) to be determined (or activity thereof) in a sample is obtained by at least one processor, and/or information reflecting the presence or an amount of such marker (or activity thereof) in a sample is provided in user readable format by another processor. The one or more processors may be coupled to random access memory operating under control of or in conjunction with a computer operating system. The processors may be included in one or more servers, clusters, or other computers or hardware resources, or may be implemented using cloud-based resources. The operating system may be, for example, a distribution of the Linux™ operating system, the Unix™ operating system, or other open-source or proprietary operating system or platform. Processors may communicate with data storage devices, such as a database stored on a hard drive or drive array, to access or store program instructions other data. Processors may further communicate via a network interface, which in turn may communicate via the one or more networks, such as the Internet or other public or private networks, such that a query or other request may be received from a client, or other device or service. In some embodiments, the computer-implemented method of detecting the presence or an amount of the applicable biomarker (or activity thereof) in a sample is provided as a kit.

[577] Such detection, determination and/or diagnosis methods can be conducted as an in-vitro (eg ex-vivo) method, and can be, for example, practiced using the kit of the present invention (or components thereof). An in-vitro method may use, involve or be practised on immortalised cell lines (such as those replicated, cultured or indefinitely maintained outside of the body of an animal or human), or it may be use, involve or be practised in-vitro using cells (such as primary cells) directly or freshly obtained from the body of an animal of human (eg, practised as a so-called "ex-vivo" method).

[578] In some embodiments of these detection, determination and/or diagnosis methods, the biological sample is a tissue sample from the subject, such as a sample of a tumour or a cancer from the subject. As described above, such tissue sample may be a biopsy sample of the tumour or a cancer such as a needle biopsy sample, or a tumour biopsy section or an archival sample thereof. Such a tissue sample may comprise living, dead or fixed cells, such as from the tumour or a cancer, and such cells may be suspected of expressing (e.g. aberrantly or localised) the applicable biomarker to be determined.

[579] In some embodiments, determination and/or diagnosis method of the invention can comprise, such as in a further step, comparing the detected amount (or activity of) of (eg protein or mRNA of) the applicable biomarker (eg the kinase/key-kinase such as SIK3, and in particular phosphorylated SIK3) with a standard or cut-off value; wherein a detected amount greater than the standard or cut-off value indicates a phenotype (or a risk of developing a phenotype) that is associated with cellular resistance against the cell-mediated immune response in the subject and/or is associated with is associated with (aberrant) expression or activity of the kinase/key-kinase (eg SIK3) in the subject. Such a standard or cut-off value may be determined from the use of a control assay, or may be pre-determined from one or more values obtained from a study or a plurality of samples having known phenotypes. For example, a cut-off value for a diagnostic test may be determined by the analysis of samples taken from patients in the context of a controlled clinical study, and determination of a cut-off depending on the desired (or obtained) sensitivity and/or specificity of the test.

[580] The applicable biomarker can, in certain embodiments, be detected by detecting protein of the applicable biomarker, or by detecting mRNA that encodes protein of the applicable biomarker. Methods to detect proteins (eg antibody detection, in particular by immunohistochemistry) and mRNA (eg by hybridisation, qPCR or sequencing) are well known.

[581] Examples of methods useful in the detection of (such as the presence or absence of, or an amount of) the applicable biomarker (such as the kinase/key-kinase eg SIK3, and in particular phosphorylated SIK3) include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA), which employ an antigen binding protein ("ABP") such as an antibody or an antigen-binding fragment thereof, that specifically binds to such applicable biomarker.

Skin pigmentation and related aspects

[582] The role of salt inducible kinase 2 (SIK2) as an inhibitor of melanogenesis via the suppression of the cAMP-response element binding protein (CREB)-specific coactivator 1 (TORC1) is described by Kumagai et al (2011), and that a potent inhibitor of SIK2 was able to promote melanogenesis in B16F10 Melanoma Cells. Mujahid et al (2017) was able to confirm that topical treatment of human skin explants with the SIK2 inhibitor HG-9-91-01 (and other SIK2 inhibitors structurally related to those of the present invention) was able to induce eumelanisation in such human skin. Example 12 herein describes analogous investigations into the promotion of melanogenesis in (human) skin cells by compounds of formulae (Ia), (Ib) and (Ic).

[583] Accordingly, in **another aspect**, the invention relates to **a method of increasing skin pigmentation** (or of increasing the appearance of skin pigmentation) in a subject, the method comprising administering to the subject an (eg effective) amount of a kinase inhibitor as specified under the heading "Compounds", or a pharmaceutical composition thereof. An amount (such as an effective amount) of the compound (or pharmaceutical composition), in this context, is one that refers to an amount sufficient to elicit the desired biological response (eg, the degree of skin pigmentation, or the appearance of skin pigmentation).

[584] In one embodiment of such aspect, this method is not practiced as a method for treatment of the human or animal body by surgery or therapy (or a diagnostic method) practised on the human or animal body. For example, the method is practised for cosmetic purposes, such as to increase the production of melanin in the skin (and hence the skin colour) of the subject for aesthetic reasons.

[585] In another embodiment of such aspect, it is practiced as a method of increasing skin pigmentation (or of increasing the appearance of skin pigmentation) in a subject for medical purposes (eg for treatment, including to prevent). For example, the method may be practiced to increase skin pigmentation (eg, without a requirement for UV irradiation), to improve UV protection and for example to reduce the risk of skin cancer. For example, in such contexts term "prevent" can refer to a prophylactic treatment of a subject who is not and did not have a disease but is at risk of developing the disease or who had a disease, does not have the disease, but is at risk of regression of the disease. In certain of such embodiments, the administered amount of the compound or pharmaceutical composition may be one that is "prophylactically effective". A "prophylactically effective amount" of a compound (or pharmaceutical composition) described herein can be an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. For example, a prophylactically effective amount in this context can mean an amount of a therapeutic agent, alone or in combination with other agents, (or those present in one or more pharmaceutical compositions) which provides a prophylactic benefit in the prevention of skin cancer. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[586] Accordingly, in **a related aspect** the invention relates to **a compound for use, or a pharmaceutical composition for use, in a treatment of increasing skin pigmentation** (or of increasing the appearance of skin pigmentation) in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, wherein the compound is selected from a a kinase inhibitor as specified under the heading "Compounds".

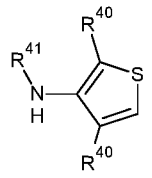
[587] In certain embodiments of such aspects, the compound is any compound of formula (Ia), or of formula (Ib) or of formula (Ic), and any embodiment thereof as specified under the heading "Compounds".

[588] In certain embodiments of such another and related aspects, the compound (or the pharmaceutical composition comprising the compound) can be topical (or transdermal) administration to the subject. The term "topical" is art-recognised in this context and its meaning includes the local application of the compounds described herein to a body surface of a human or non-human animal. In certain embodiments, the body surface is skin. In certain embodiments, the skin is on a body part. In certain embodiments, the skin is on the face. In certain embodiments, the skin is on the neck. In certain embodiments, the skin is on the torso. In certain embodiments, the skin is on the chest. In certain embodiments, the skin is on the back. In certain embodiments, the skin is on the arms. In certain embodiments, the skin is on the legs.

Intermediates, synthesis, manufacturing and other aspects

[589] The compounds disclosed herein can be prepared as described below or prepared by methods analogous thereto, which are readily known and available to one of ordinary skill in the art of organic synthesis.

[590] In **a tenth aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to **an intermediate** selected from a compound having formula (Id):



(Id)

and solvates, salts, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof, wherein:

one of R^{40} is F or is selected from the group consisting of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), -NH($C_{1\text{-}2}$alkyl) and -N($C_{1\text{-}2}$alkyl)$_2$, wherein the alkyl group of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), and -NH($C_{1\text{-}2}$alkyl) and at least one of the alkyl groups of -N($C_{1\text{-}2}$alkyl)$_2$ is substituted with one, two, or three F atoms, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt; and

R^{41} is selected from the group consisting of H and an amino protecting group.

[591] In one embodiment of the intermediate of the tenth aspect, the two R^{40} differ from each other.

[592] In one embodiment of the intermediate of the tenth aspect, one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt, preferably the other R^{40} is selected from the group consisting of Cl, Br, F, and -Me. For example, one R^{40} may be selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, preferably selected from the group consisting of -CH_2F and -CHF_2, and the other R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, may be Cl.

[593] In another embodiment of the intermediate of the tenth aspect, one R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, is F, and the other R^{40} is selected from the group consisting of halogen, -Me, and -Et, preferably the other R^{40} is selected from the group consisting of Cl, Br, F, -Me, and -Et, more preferably selected from the group consisting of Cl, -Me, and -Et. For example, one R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, may be F and the other R^{40} may be Cl.

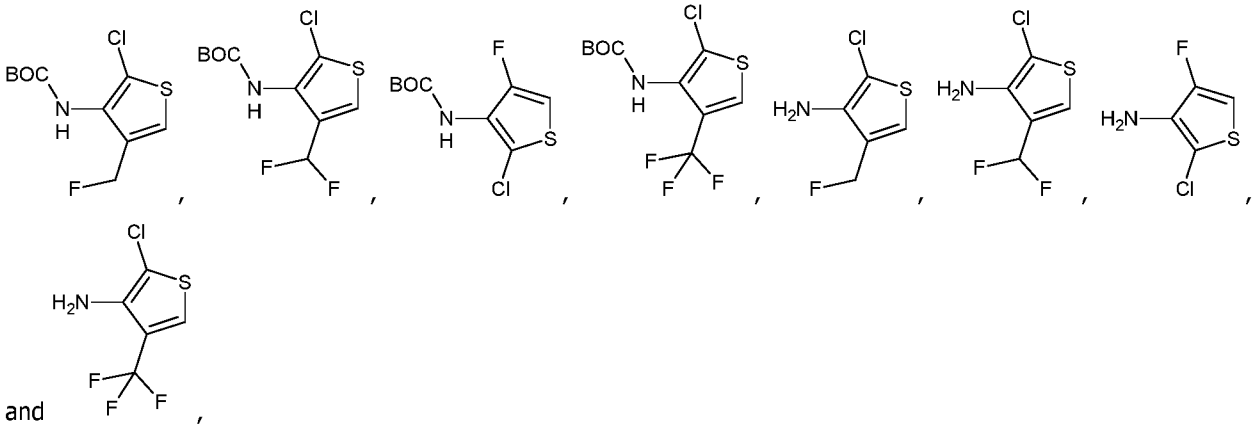
[594] In one embodiment of the intermediate of the tenth aspect, the C ring atom to which R^{40} being F or being selected from the group consisting of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), -NH($C_{1\text{-}2}$alkyl) and -N($C_{1\text{-}2}$alkyl)$_2$, wherein the alkyl group of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), and -NH($C_{1\text{-}2}$alkyl) and at least one of the alkyl groups of -N($C_{1\text{-}2}$alkyl)$_2$ is substituted with one, two, or three F atoms, is bound and the S ring atom are adjacent ring atoms.

[595] In an alternative embodiment of the intermediate of the tenth aspect, the C ring atom to which R^{40} being F or being selected from the group consisting of C_{1-3}alkyl, -O(C_{1-2}alkyl), -NH(C_{1-2}alkyl) and -N(C_{1-2}alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, -O(C_{1-2}alkyl), and -NH(C_{1-2}alkyl) and at least one of the alkyl groups of -N(C_{1-2}alkyl)$_2$ is substituted with one, two, or three F atoms, is bound and the S ring atom are separated by a C ring atom.

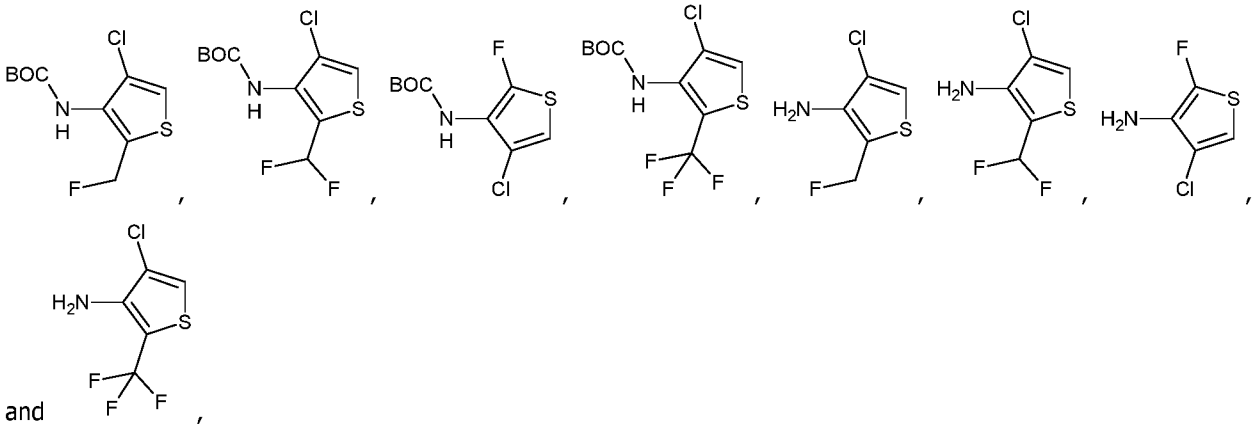
[596] In one embodiment of the intermediate of the tenth aspect, R^{41} is an amino protecting group. For example, the amino protecting group may be selected from the group consisting of tert-butyloxycarbonyl (BOC), 9-fluorenylmethoxycarbonyl (FMOC), benzyloxycarbonyl (Cbz), p-methoxybenzylcarbonyl (MOZ), acetyl (Ac), trifluoroacetyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), 3,4-dimethoxyphenyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethoxycarbonyl (Troc), triphenylmethyl (trityl; Tr), toluenesulfonyl (tosyl; Ts), *para*-bromophenylsulfonyl (brosyl), 4-nitrobenzenesulfonyl (nosyl), and 2-nitrophenylsulfenyl (Nps).

[597] In an alternative embodiment of the intermediate of the tenth aspect, R^{41} is H.

[598] In one embodiment of the intermediate of the tenth aspect, the intermediate is selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof. For example, the intermediate may be selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

[599] In one embodiment, the intermediates of the invention do not encompass compounds of one or more of the following groups (1) to (3) (in the groups (1) to (3) a moiety (such as methyl) is unsubstituted unless it is explicitly specified that said moiety is substituted):

(1) the intermediate is not 2-bromo-4-(trifluoromethyl)thiophen-3-amine; *[CAS 1369240-59-4]*

(2) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is -CHF_2, then R^{41} is not (1-propylpiperidin-2-yl)carbonyl; and *[CAS 2099704-46-6, 2099704-17-1, 2099703-62-3, 2099703-17-8]*

(3) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is F, then R^{41} is not 4,5-dihydro-1*H*-imidazol-2-yl. *[CAS 1369494-03-0]*

[600] In **an eleventh aspect**, and as may be further described, defined, claimed or otherwise disclosed herein, the invention relates to the **use of an intermediate** of formula (Id) to prepare a compound comprising an amide moiety (in particular a kinase inhibitor, especially an inhibitor of one or more protein kinases selected from the list consisting of: SIK (preferably SIK3), CSFR1, ABL/BCR-ABL, HCK, PDGRF, LCK, SRC, and KIT; preferably one or more protein kinases selected from the list consisting of: SIK3, ABL/BCR-ABL, HCK, and CSF1R kinases, such as a compound of the invention (eg, a compound of formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa) or (VIIIa), or a solvate, salt (in particular a pharmaceutically acceptable salt), N-oxide (in particular, an N-oxide of R^{1a}), complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form, prodrug (in particular a prodrug having formula (IXa), (Xa) (XIa), or (XIIa) and/or having at least one derivatized hydroxyl group, as specified above, or a solvate, salt, N-oxide, complex, polymorph, crystalline form, racemic mixture, diastereomer, enantiomer, tautomer, conformer, isotopically labeled form or combination thereof), or combination thereof)), wherein the method comprises reacting the intermediate of formula (Id) with a corresponding carboxylic acid, and, optionally, removing the amino protecting group.

[601] In one embodiment of the method of the eleventh aspect, the step of reacting the intermediate with the corresponding carboxylic acid is conducted in the presence of (i) a base and/or (ii) a coupling agent.

[602] In one embodiment of the method of the eleventh aspect, the reaction of the intermediate with the corresponding carboxylic acid takes place in a solvent, such as an aprotic solvent, e.g., acetonitrile. Thus, in a preferred embodiment of the eleventh aspect, the method comprises reacting the intermediate of formula (Id) with a corresponding carboxylic acid in a solvent in the presence of (i) a base and/or (ii) a coupling agent.

[603] It is within the skills of a skilled person to determine suitable reaction parameters (eg amounts of the intermediate and the corresponding carboxylic acid, optionally, the amounts of base, coupling agent, and/or solvent; reaction temperature; reaction time; etc.) in order to obtain the desired product. Preferably, an excess of base relative to the molar amount of carboxylic acid is used (eg the base is used in at least about 1.5-fold, such as at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5.fold, or at least about 4-fold, and up to about 5-fold, the molar amount of the carboxylic acid). Furthermore, the intermediate and the carboxylic acid may be reacted in a molar ratio of intermediate to carboxylic acid of about 0.8:1 to about 1:1.2, such as about 0.9:1 to about 1:1.1, or in about equimolar amounts. The amount of coupling agent when used is preferably about at least about 1.0-fold, such as at least about 1.1-fold, at least about 1.2-fold, at least about 1.3-fold, and up to about 2-fold, the molar amount of the carboxylic acid.

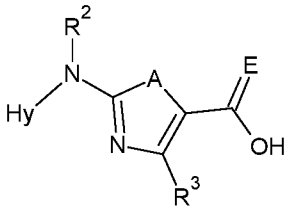
[604] In one embodiment of the method of the eleventh aspect, the base is a non-nucleophilic base, preferably selected from the group consisting of *N,N*-diisopropylethylamine (DIPEA), 2,2,6,6-tetramethylpiperidine, triethylamine, tributylamine, 1,8-diazabicycloundec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,4-diazabicyclo[2.2.2]octane (TED), collidine, 1,1,3,3-tetramethylguanidine (TMG), quinuclidine, 2,2,6,6-tetramethylpiperidine (TMP), pempidine (PMP), 2,6-di-tert-butylpyridine, 2,6-lutidine, phosphazene bases (eg t-Bu-P_4), lithium diisopropylamide (LDA), sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS), sodium *tert*-butoxide, and potassium *tert*-butoxide.

[605] In one embodiment of the method of the eleventh aspect, the coupling agent is selected from the group consisting of N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (TCFH), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-

tetramethylaminium tetrafluoroborate (TBTU), 1-propanephosphonic anhydride (T3P), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP), and (6-chlorobenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (TPTDP).

[606] In those embodiments where the carboxylic acid is a thiocarboxylic acid (eg, when E is S in formula (Ie)), then the reaction with an intermediate of formula (Id) may proceed under suitable conditions (such as Mitsunobu conditions) to favour the formation of a resulting thioamide compound.

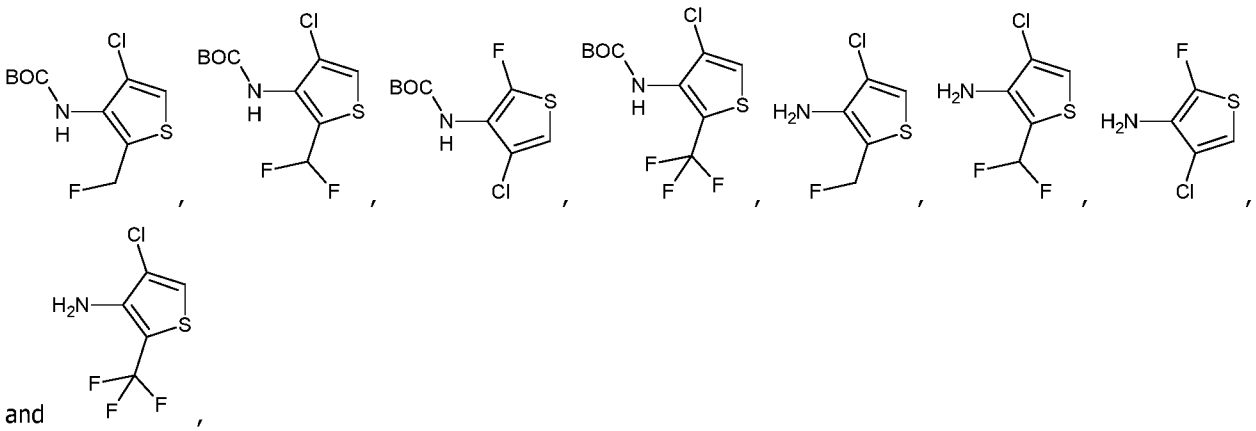
[607] In one embodiment of the method of the eleventh aspect, the corresponding carboxylic acid has the general formula (Ie):



(Ie)

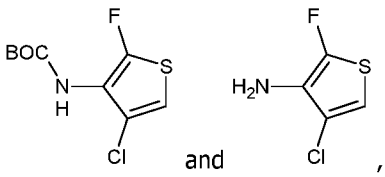
wherein Hy, R^2, R^3, A, and E are as defined herein (in particular with respect to formula (Ia), (IIIa), (IVa), (Va), (VIa), (VIIa) and/or (VIIIa)). Preferably in such an embodiment, E is O.

[608] In a related aspect, the invention also relates to (the composition of matter of) a compound (eg an intermediate) selected from the group consisting of:



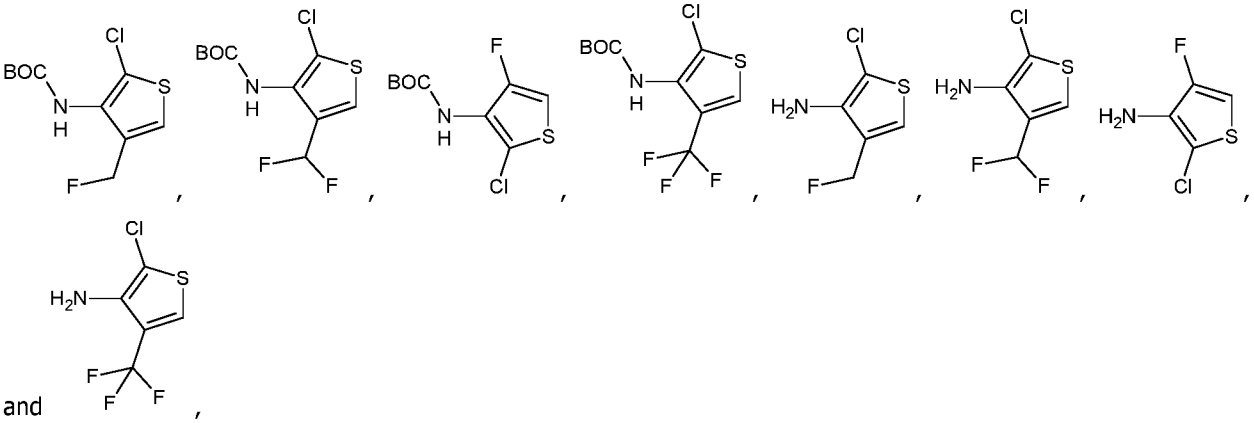
and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof, in particular wherein such compound (eg the intermediate) is in an amount of greater than about 1g or 10g, such as greater than about 100g, and/or is in purified form (eg, as defined elsewhere herein).

[609] In one embodiment of such related aspect, the compound (eg the intermediate) is selected from the group consisting of:



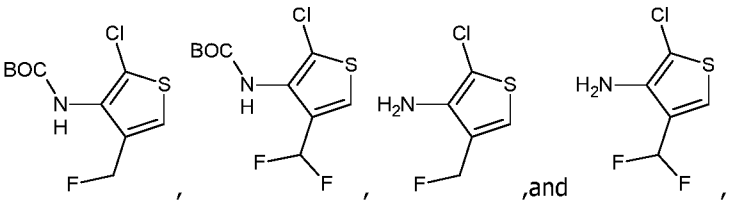
and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof, in particular wherein such compound (eg the intermediate) is in an amount of greater than about 1g or 10g, such as greater than about 100g, and/or is in purified form (eg, as defined elsewhere herein).

[610] In another related aspect, the invention also relates to (the composition of matter of) a compound (eg an intermediate) is selected from the group consisting of:

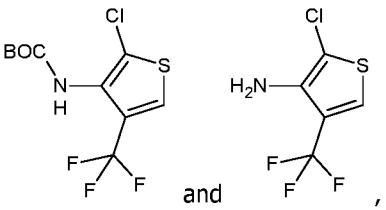


and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof, in particular wherein such compound (eg the intermediate) is in an amount of greater than about 1g or 10g, such as greater than about 100g, and/or is in purified form (eg, as defined elsewhere herein).

[611] In one embodiment of such related aspect, the compound (eg the intermediate) is selected from the group consisting of:



[612] and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof, in particular wherein such compound (eg the intermediate) is in an amount of greater than about 1g or 10g, such as greater than about 100g, and/or is in purified form (eg, as defined elsewhere herein).In another embodiment of such related aspect, the compound (eg the intermediate) is selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof, in particular wherein such compound (eg the intermediate) is in an amount of greater than about 1g or 10g, such as greater than about 100g, and/or is in purified form (eg, as defined elsewhere herein).

[613] In **a twelfth aspect**, the invention relates to **a method for preparing a compound** of the invention (eg, a compound of formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa) or (VIIIa)) that is in a (eg substantially) purified form, the method comprising the steps:

- providing the compound (eg E4, E9, E10 or E16) in admixture with one or more impurities; and
- removing at least a fraction of the impurities from the admixture.

[614] In certain embodiments of such aspect, suitable methods to remove a fraction of the impurities are well known and include eg column chromatography, selective precipitation, trituration and elution of impurities with a suitable solvent in which the desired compound is not soluble, etc.

[615] The fraction of impurities removed may be such that the compound is prepared in substantially pure form; that is, for example, in a percentage purity as described above.

[616] In other embodiments, the admixture of provided by synthesising an impure form of the compound.

[617] In **a thirteenth aspect**, the invention also relates to **a method for manufacturing a pharmaceutical composition** comprising the step of formulating a compound of the invention (eg a compound of formula (Ia), (IIa), (IIIa), (IVa), (Va), (VIa), (VIIa) or (VIIIa)) together with a pharmaceutically acceptable excipient (such as one described elsewhere herein, such as a pharmaceutically acceptable stabiliser of carrier).

[618] In a particular of such embodiments, the pharmaceutical composition is manufactured in an amount that is greater than about 10g; such as greater than about 100g, and suitably greater than about 1Kg (or greater than 10Kg).

[619] In one embodiment of such aspect, the pharmaceutical composition is manufactured in unit dose form.

[620] In certain of such embodiments, the pharmaceutical composition is formed as a tablet, caplet or capsule; in particular as a tablet or capsule.

[621] In a further of such embodiments, the pharmaceutical composition is formed as a film-coated tablet, or as a film-coated caplet. For example, the method may comprise a further step of coating a tablet or caplet with a film, in particular with a pharmaceutical effective film-coating.

[622] In **a fourteenth aspect**, the invention also relates to **a method of preparing a pharmaceutical package**, comprising the steps:

- inserting into packaging a pharmaceutical composition of the invention, thereby forming a package containing the pharmaceutical composition; and optionally,
- inserting into the package a leaflet describing prescribing information for the pharmaceutical composition.

[623] In one of such embodiments, the pharmaceutical composition is in finished pharmaceutical form; for example, that is in the form that would be administered (or finally prepared to be administered) to a subject.

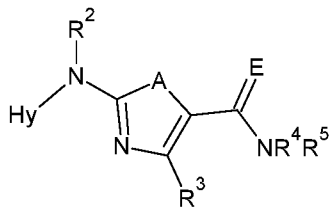
[624] The packaging can be primary and/or secondary packaging. For example, the primary packaging may be a glass vial or a blister strip. Typical (but non-limiting) secondary packaging can be a box or carton, which in certain embodiments may be marked with the name, strength and/or brand of the pharmaceutical composition it contains.

[625] The packaging may further comprise a leaflet or other information. In particular, that describing (either to the patient and/or the administering physician) salient information or details on the pharmaceutical composition contained in the package, such as how to administer, recommended dosages, safety and/or side-effect information.

[626] In **a fifteenth aspect**, the invention also relates to **a pharmaceutical package** containing a pharmaceutical composition of the invention; preferably, wherein the pharmaceutical composition is in finished pharmaceutical form. In certain embodiments of such aspect, the pharmaceutical package may further containing a leaflet describing prescribing information for the pharmaceutical composition.

[627] In view of the above, it will be appreciated that the present invention also relates to the following itemised embodiments:

ITEM 1. **A compound** selected from the group consisting of a kinase inhibitor of the formula:



(Ia),

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof;

wherein:

Hy is a heteroaryl or heterocyclyl which is optionally substituted with one or more independently selected R^{1e};

each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d};

each of R^{1a} and R^{1d} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

each of R^{1b} and R^{1c} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, 3- to 7-membered heterocyclyl, $-O(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-O(CH_2)_{0-2}$(C_{6-10} aryl), $-O(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-O(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), $-NH(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-NH(CH_2)_{0-2}$(C_{6-10} aryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two, or three moieties independently selected from the group consisting of -OH, methyl, ethyl, $-OCH_3$, $-SCH_3$, and $-NH_{2-z}(CH_3)_z$;

R^2 is H;

R^3 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^4 is H;

R^5 is $-L-R^6$;

L is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m-[Y-(CH_2)_n]_o-$, wherein m is an integer between 1 and 6, n is an integer between 0 and 3, o is an integer between 1 and 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and $-N(R^{13})-$; and each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m-$, and $-(CH_2)_n-$ groups is optionally substituted with one or two independently selected R^{30};

R^6 is a 5-membered monocyclic heteroaryl which contains at least one S ring atom and which is substituted with one or more independently selected R^7;

R^7 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}, wherein at least one of R^7 is F and/or at least one of R^7 is substituted with one or more F atoms;

A is selected from the group consisting of S, O, NR^8, and $C(R^9)_2$;

R^8 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^9 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

X is independently selected from the group consisting of O, S, and $N(R^{14})$;

E is O or S;

R^{11} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{12} and R^{13} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, or R^{12} and R^{13} may join together with the nitrogen atom to which they are attached to form the group $-N=CR^{15}R^{16}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

R^{14} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and $-OR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{15} and R^{16} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and $-NH_yR^{20}{}_{2-y}$, or R^{15} and R^{16} may join together with the atom to which they are attached to form a ring which is optionally substituted with one or more independently selected R^{30}, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

y is an integer from 0 to 2;

R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}; and

R^{30} is a 1st level substituent and is, in each case, independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, -CN, azido, $-NO_2$, $-OR^{71}$, $-N(R^{72})(R^{73})$, $-S(O)_{0-2}R^{71}$, $-S(O)_{1-2}OR^{71}$, $-OS(O)_{1-2}R^{71}$, $-OS(O)_{1-2}OR^{71}$, $-S(O)_{1-2}N(R^{72})(R^{73})$, $-OS(O)_{1-2}N(R^{72})(R^{73})$, $-N(R^{71})S(O)_{1-2}R^{71}$, $-NR^{71}S(O)_{1-2}OR^{71}$, $-NR^{71}S(O)_{1-2}N(R^{72})(R^{73})$, $-OP(O)(OR^{71})_2$, $-C(=X^1)R^{71}$, $-C(=X^1)X^1R^{71}$, $-X^1C(=X^1)R^{71}$, and $-X^1C(=X^1)X^1R^{71}$, and/or any two R^{30} which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group may join together to form $=X^1$, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups being a 1st level substituent is optionally substituted by one or more 2nd level substituents, wherein said 2nd level substituent is, in each case, independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, $-OR^{81}$, $-N(R^{82})(R^{83})$, $-S(O)_{0-2}R^{81}$, $-S(O)_{1-2}OR^{81}$, $-OS(O)_{1-2}R^{81}$, $-OS(O)_{1-2}OR^{81}$, $-S(O)_{1-2}N(R^{82})(R^{83})$, $-OS(O)_{1-2}N(R^{82})(R^{83})$, $-N(R^{81})S(O)_{1-2}R^{81}$, $-NR^{81}S(O)_{1-2}OR^{81}$, $-NR^{81}S(O)_{1-2}N(R^{82})(R^{83})$, $-OP(O)(OR^{81})_2$, $-C(=X^2)R^{81}$, $-C(=X^2)X^2R^{81}$, $-X^2C(=X^2)R^{81}$, and $-X^2C(=X^2)X^2R^{81}$, and/or any two 2nd level substituents which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group being a 1st level substituent may join together to form $=X^2$, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl groups being a 2nd level substituent is optionally substituted with one or more 3rd level substituents, wherein said 3rd level substituent is, in each case, independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-NHS(O)_2(C_{1-3}$ alkyl),

$-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)OH$, $-C(=O)O(C_{1-3}$ alkyl$)$, $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl$)$, $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl, and/or any two 3rd level substituents which are bound to the same carbon atom of a 3- to 14-membered cycloalkyl or heterocyclyl group being a 2nd level substituent may join together to form =O, =S, =NH, or $=N(C_{1-3}$ alkyl$)$;

wherein

each of R^{71}, R^{72}, and R^{73} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl$)$, $-OCF_3$, =O, $-S(C_{1-3}$ alkyl$)$, $-NH_2$, $-NH(C_{1-3}$ alkyl$)$, $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl$)$, $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl$)$, $-C(=O)OH$, $-C(=O)O(C_{1-3}$ alkyl$)$, $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl$)$, $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl;

each of R^{81}, R^{82}, and R^{83} is independently selected from the group consisting of H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl, wherein each of the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl$)$, $-OCF_3$, =O, $-S(C_{1-3}$ alkyl$)$, $-NH_2$, $-NH(C_{1-3}$ alkyl$)$, $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl$)$, $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl$)$, $-C(=O)OH$, $-C(=O)O(C_{1-3}$ alkyl$)$, $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl$)$, $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; and

each of X^1 and X^2 is independently selected from O, S, and $N(R^{84})$, wherein R^{84} is H or C_{1-3} alkyl.

ITEM 2. The compound of item 1, wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, $-OR^{11}$, and $-N(R^{12})(R^{13})$, wherein each of the alkyl and R^{11} groups and at least one of the R^{12} and R^{13} groups is substituted with one or more F atoms.

ITEM 3. The compound of item 1 or 2, wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, -O(alkyl), -NH(alkyl), and $-N(alkyl)_2$, wherein the alkyl group of alkyl, -O(alkyl) and -NH(alkyl) and at least one of the alkyl groups of $-N(alkyl)_2$ is substituted with one or more F atoms.

ITEM 4. The compound of any one of items 1 to 3, wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl$)$, $-NH(C_{1-3}$alkyl$)$ or $-N(C_{1-3}$alkyl$)_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl$)$, and $-O(C_{1-3}$alkyl$)$ and at least one of the alkyl groups of $-N(C_{1-3}$alkyl$)_2$ is substituted with one or more F atoms.

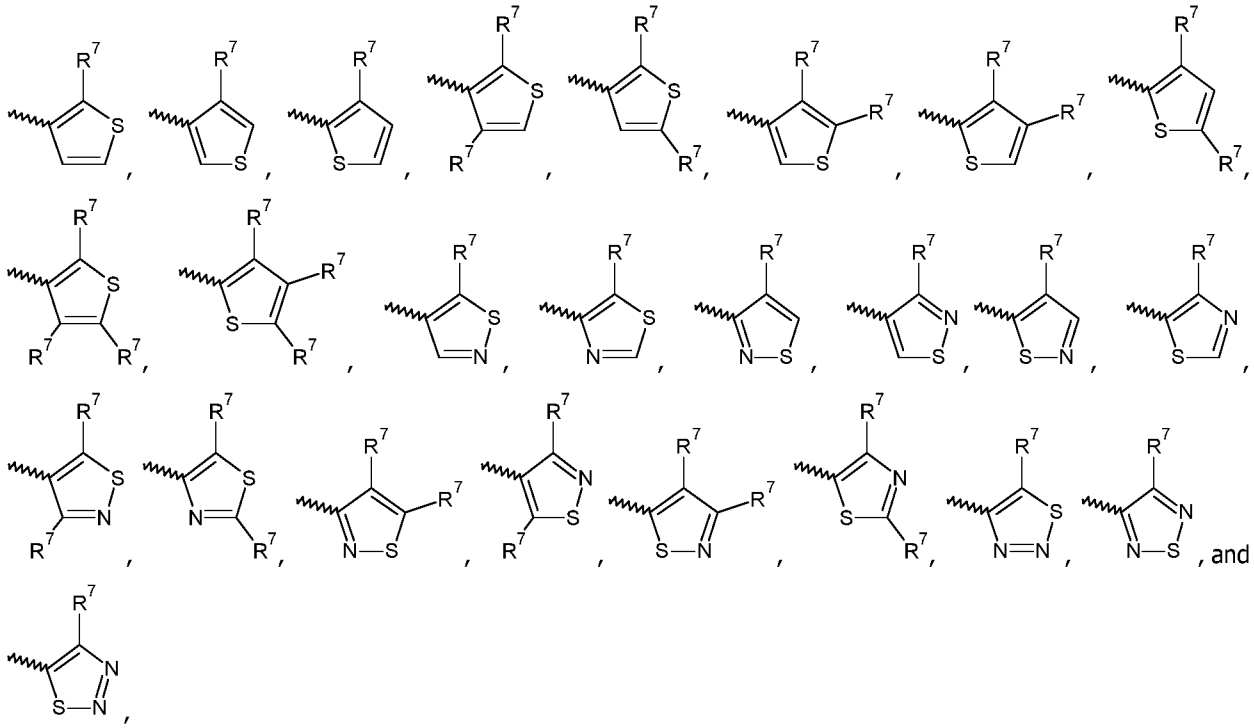
ITEM 5. The compound of any one of items 1 to 4, wherein at least one of R^7 is F and/or at least one of R^7 is C_{1-3}alkyl, wherein the alkyl group of C_{1-3}alkyl is substituted with one or more F atoms.

ITEM 6. The compound of any one of items 1 to 5, wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$.

ITEM 7. The compound of any one of items 1 to 6, wherein one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms.

ITEM 8. The compound of any one of items 1 to 7, wherein one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms.

ITEM 9. The compound of any one of items 1 to 8, wherein R^6 is selected from the group consisting of



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

ITEM 10. The compound of any one of items 1 to 9, wherein R^6 is substituted with at least two R^7.

ITEM 11. The compound of any one of items 1 to 10, wherein R^6 is substituted with two R^7 which differ from each other.

ITEM 12. The compound of any one of items 1 to 11, wherein one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound and one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein at least one of said R^7 is F and/or at least one of R^7 is substituted with one or more F atoms.

ITEM 13. The compound of any one of items 1 to 12, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, and one R^7 is selected from the group consisting of halogen, $-CH_3$, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, CH_3, $-CH_2F$, $-CHF_2$, and $-CF_3$.

ITEM 14. The compound of any one of items 1 to 13, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$, and one R^7 is Cl.

ITEM 15. The compound of any one of items 1 to 12, wherein one R^7 is F, and one R^7 is selected from the group consisting of halogen, CH_3, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, CH_3, $-CH_2F$, $-CHF_2$, and $-CF_3$.

ITEM 16. The compound of any one of items 1 to 12 and 15, wherein one R^7 is F and one R^7 is Cl.

ITEM 17. The compound of any one of items 1 to 16, wherein R^6 is selected from the group consisting of thienyl, thiazolyl, and thiadiazolyl, each of which is substituted with one or more independently selected R^7.

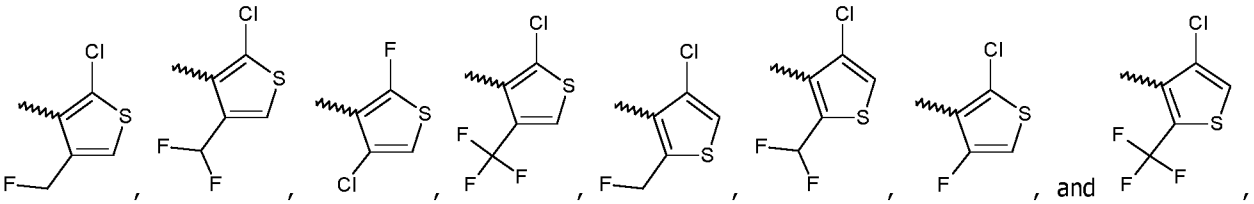
ITEM 18. The compound of any one of items 1 to 17, wherein R^6 is selected from the group consisting of thienyl and thiazolyl, each of which is substituted with one or more independently selected R^7.

ITEM 19. The compound of any one of items 1 to 18, wherein R^6 is thienyl which is substituted with one or more independently selected R^7.

ITEM 20. The compound of any one of items 1 to 19, wherein the ring atom of R^6 by which R^6 is bound to the remainder of the compound is a C atom.

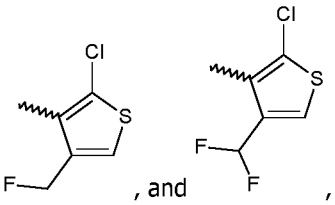
ITEM 21. The compound of any one of items 1 to 20, wherein the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound.

ITEM 22. The compound of any one of items 1 to 21, wherein R^6 is selected from the group consisting of



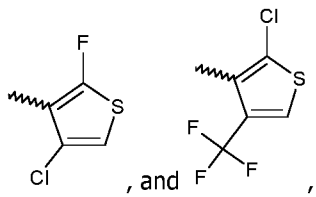
wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

ITEM 23. The compound of any one of items 1 to 22, wherein R^6 is selected from the group consisting of



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

ITEM 23a. The compound of any one of items 1 to 22, wherein R^6 is selected from the group consisting of



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

ITEM 24. The compound of any one of items 1 to 23a, wherein L is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m-[Y-(CH_2)_n]_o-$, wherein m is 1, 2, or 3, n is 0, 1, or 2, o is 1, 2, or 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and NH, wherein each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m-$, and $-(CH_2)_n-$ groups is optionally substituted with one or two independently selected R^{30}.

ITEM 25. The compound of any one of items 1 to 24, wherein L is selected from the group consisting of a bond; C_1 alkylene, optionally substituted with one R^{30}; C_2 alkylene (in particular 1,2-ethylene or 1,1-ethylene), optionally substituted with one R^{30}; C_3 alkylene (in particular trimethylene), optionally substituted with one R^{30}; C_4 alkylene (in particular tetramethylene or 2,4-butandiyl), optionally substituted with one R^{30}; $-(CH_2)_mO-$; and $-(CH_2)_mNH-$, wherein m is 1, 2, or 3.

ITEM 26. The compound of any one of items 1 to 25, wherein L is selected from the group consisting of a bond; C_1 alkylene, optionally substituted with one R^{30}; C_2 alkylene (in particular 1,2-ethylene or 1,1-ethylene),

optionally substituted with one R^{30}; -(CH_2)O-; and -(CH_2)NH-; preferably wherein L is selected from the group consisting of a bond, -(CH_2)-, and -$(CH_2)_2$-.

ITEM 27. The compound of any one of items 1 to 26, wherein L is a bond.

ITEM 28. The compound of any one of items 1 to 27, wherein E is O.

ITEM 29. The compound of any one of items 1 to 28, wherein A is selected from the group consisting of S, O, NH,
N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$.

ITEM 30. The compound of any one of items 1 to 29, wherein A is S, O, or N$(CH_3)_2$.

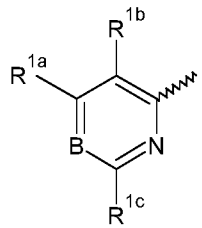
ITEM 31. The compound of any one of items 1 to 30, wherein A is S.

ITEM 32. The compound of any one of items 1 to 31, wherein Hy is a 3- to 10-membered heteroaryl or a 3- to 10-membered heterocyclyl, each of which is optionally substituted with one or more independently selected R^{1e}.

ITEM 33. The compound of any one of items 1 to 32, wherein Hy is selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl, a 5- to 6-membered monocyclic heterocyclyl, a 9- to 10-membered bicyclic heteroaryl, and a 8- to 10-membered bicyclic heterocyclyl, each of which is optionally substituted with one or more independently selected R^{1e}.

ITEM 34. The compound of any one of items 1 to 33, wherein Hy is heteroaryl or heterocyclyl which contains at least one N ring atom and which is optionally substituted with one or more independently selected R^{1e}.

ITEM 35. The compound of any one of items 1 to 34, wherein Hy is:



wherein ~~~~ represents the bond by which Hy is bound to the remainder of the compound; R^{1a}, R^{1b}, and R^{1c} are as defined in item 1; and B is N or CR^{1d}.

ITEM 36. The compound of any one of items 1 to 35, wherein R^{1a} is selected from the group consisting of alkyl,
-O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}.

ITEM 37. The compound of item 36, wherein the one or more independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 38. The compound of any one of items 1 to 37, wherein R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 11-membered heterocyclyl, wherein the

3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)C(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)S(O)_2(C_{1-3}$ alkyl), $-(CH_2)_{1-3}COOH$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 39. The compound of any one of items 1 to 38, wherein R^{1a} is selected from the group consisting of C_{1-3} alkyl, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononanyl, diazaspirononanyl, azaspirodecanyl, diazaspirodecanyl, azaspiroundecanyl, and diazaspiroundecanyl, wherein each of the piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononyl, diazaspirononyl, azaspirodecyl, diazaspirodecyl, azaspiroundecyl, and diazaspiroundecyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)C(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)S(O)_2(C_{1-3}$ alkyl), $-(CH_2)_{1-3}COOH$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 40. The compound of any one of items 1 to 39, wherein R^{1a} is selected from the group consisting of $-NH(C_{1-3}$ alkyl), piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl, wherein each of the piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, -OH, =O, $-OCH_3$, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(methoxy)ethoxy, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 41. The compound of any one of items 1 to 40, wherein R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

ITEM 42. The compound of any one of items 1 to 41, wherein R^{1a} is non-symmetrical.

ITEM 43. The compound of item 42, wherein R^{1a} is selected from the group consisting of 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl,

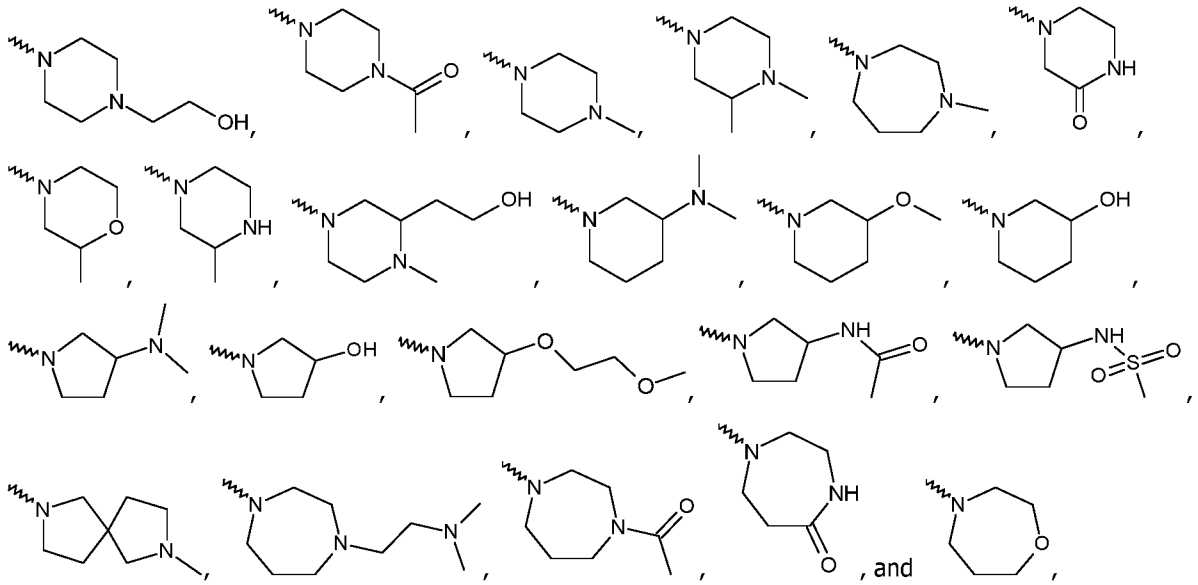
3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

ITEM 44. The compound of any one of items 1 to 43, wherein the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an atom other than C, preferably is an N atom.

ITEM 45. The compound of item 44, wherein R^{1a} is selected from the group consisting of heterocyclyl, heteroaryl,
$-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the heterocyclyl and heteroaryl groups is bound to the remainder of the compound via an atom other than C and is optionally substituted with one or more independently selected R^{30}.

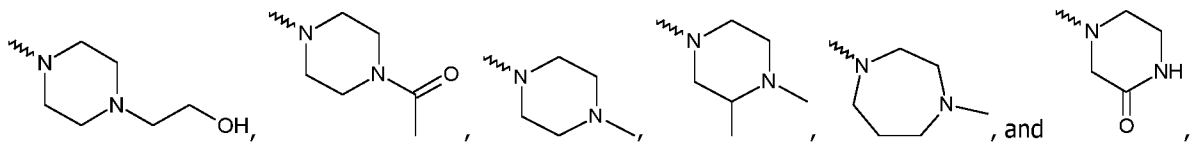
ITEM 46. The compound of item 44 or 45, wherein R^{1a} is heterocyclyl which contains at least one N ring atom and which is bound to the remainder of the compound via an N ring atom.

ITEM 47. The compound of any one of items 44 to 46, wherein R^{1a} is selected from the group consisting of:



wherein ~~~ represents the bond by which R^{1a} is bound to the remainder of the compound.

ITEM 48. The compound of items 47, wherein R^{1a} is selected from the group consisting of:



wherein ~~~ represents the bond by which R^{1a} is bound to the remainder of the compound.

ITEM 49. The compound of any one of items 1 to 48, wherein each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy,

wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 50. The compound of any one of items 1 to 49, wherein at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2.

ITEM 51. The compound of any one of items 1 to 50, wherein R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl.

ITEM 52. The compound of any one of items 1 to 51, wherein the atom of R^{1c} by which R^{1c} is bound to the remainder of the compound is a C atom.

ITEM 53. The compound of item 52, wherein R^{1c} is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-CF_3$, -CN, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), and $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and each of the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl groups is optionally substituted with one, two, or three moieties independently selected from the group consisting of -OH, methyl, ethyl, $-OCH_3$, $-SCH_3$, and $-NH_{2-z}(CH_3)_z$.

ITEM 54. The compound of any one of items 1 to 50, wherein R^{1b} is methyl, ethyl, propyl, or isopropyl, preferably methyl; and R^{1c} is H.

ITEM 55. The compound of any one of items 1 to 54, wherein B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, $-OCH_3$, -SCH, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 56. The compound of any one of items 1 to 55, wherein B is N.

ITEM 57. The compound of any one of items 1 to 56, wherein R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, $-NO_2$, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30}.

ITEM 58. The compound of any one of items 1 to 57, wherein R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)$_2$, $-C(=O)(C_{1-4}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl)$_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl)$_z$, and $-N(C_{1-4}$ alkyl)$C(=NH)NH_{2-z}(C_{1-4}$ alkyl)$_z$, wherein the phenyl group is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl)$_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl)$_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2.

ITEM 59. The compound of any one of items 1 to 58, wherein R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen.

ITEM 60. The compound of any one of items 1 to 59, wherein R^3 is H.

ITEM 61. The compound of item 1 or 35, wherein:

L is a bond; and

(A) R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}, wherein, preferably, each R^{30} is independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and/or

(B) each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, -$NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and/or

(C) R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, -NO_2, -O(C_{1-6} alkyl), -OCF_3, -S(C_{1-6} alkyl), -NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -NHS(O)$_2$(C_{1-6} alkyl), -S(O)$_2$$NH_{2-z}$($C_{1-6}$ alkyl)$_z$, -C(=O)(C_{1-6} alkyl), -C(=O)OH, -C(=O)O(C_{1-6} alkyl), -C(=O)NH_{2-z}(C_{1-6} alkyl)$_z$, -NHC(=O)(C_{1-6} alkyl), -NHC(=NH)NH_{z-2}(C_{1-6} alkyl)$_z$, and -N(C_{1-6} alkyl)C(=NH)NH_{2-z}(C_{1-6} alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30}, preferably wherein R^3 is H; and/or

(D) at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, -OR^{11}, and

-N(R^{12})(R^{13}), wherein each of the alkyl and R^{11} groups and at least one of the R^{12} and R^{13} groups is substituted with one or more F atoms; and/or

(E) A is selected from the group consisting of S, O, NH, N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$, preferably wherein A is S; and/or

(F) B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally

substituted with one or two moieties independently selected from the group consisting of halogen, -OH, -OCH_3, -SCH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein B is N; and/or

(G) E is O or S, preferably O.

ITEM 62. The compound of item 1 or 35, wherein:

L is a bond; and

(A) R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}, wherein, preferably, each R^{30} is independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and

(B) each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, -$NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and

(C) R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, -NO_2, -O(C_{1-6} alkyl), -OCF_3, -S(C_{1-6} alkyl), -NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -NHS(O)$_2$(C_{1-6} alkyl), -S(O)$_2$$NH_{2-z}$($C_{1-6}$ alkyl)$_z$, -C(=O)(C_{1-6} alkyl), -C(=O)OH, -C(=O)O(C_{1-6} alkyl), -C(=O)NH_{2-z}(C_{1-6} alkyl)$_z$, -NHC(=O)(C_{1-6} alkyl), -NHC(=NH)NH_{z-2}(C_{1-6} alkyl)$_z$, and -N(C_{1-6} alkyl)C(=NH)NH_{2-z}(C_{1-6} alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30}, preferably wherein R^3 is H; and

(D) at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of alkyl, -OR^{11}, and

-N(R^{12})(R^{13}), wherein each of the alkyl and R^{11} groups and at least one of the R^{12} and R^{13} groups is substituted with one or more F atoms; and

(E) A is selected from the group consisting of S, O, NH, N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$, preferably wherein A is S; and

(F) B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally

substituted with one or two moieties independently selected from the group consisting of halogen, -OH, $-OCH_3$, -SCH, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein B is N; and

(G) E is O or S, preferably O.

ITEM 63. The compound of item 1 or 35, wherein:

L is a bond; and

(A') R^{1a} is selected from the group consisting of C_{1-3} alkyl, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and 3- to 11-membered heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)C(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)S(O)_2(C_{1-3}$ alkyl), $-(CH_2)_{1-3}COOH$, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and/or

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2, and the other of R^{1b} and R^{1c} is as defined above under (B) in item 61, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and/or

(C') R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl$)_2$, $-C(=O)(C_{1-4}$ alkyl), $-C(=O)OH$, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl$)_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl$)_z$, and $-N(C_{1-4}$ alkyl$)C(=NH)NH_{2-z}(C_{1-4}$ alkyl$)_z$, wherein the phenyl group is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl$)_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2, preferably wherein R^3 is H; and/or

(D') at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl$)_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl$)_2$ is substituted with one or more F atoms;

(E') A is S, O, or $N(CH_3)_2$, preferably wherein A is S; and/or

(F') B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl$)_2$, preferably wherein B is N; and/or

(G') E is O or S, preferably O.

ITEM 64. The compound of item 1 or 35, wherein:

L is a bond; and

(A') R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 11-membered heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, -$NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2, and the other of R^{1b} and R^{1c} is as defined above under (B) in item 61, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and

(C') R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, -O(C_{1-4} alkyl), -OCF_3, -S(C_{1-4} alkyl), -NH_2, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)$_2$, -C(=O)(C_{1-4} alkyl), -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)NH_{2-z}(C_{1-4} alkyl)$_z$, -NHC(=O)(C_{1-4} alkyl), -NHC(=NH)NH_{z-2}(C_{1-4} alkyl)$_z$, and -N(C_{1-4} alkyl)C(=NH)NH_{2-z}(C_{1-4} alkyl)$_z$, wherein the phenyl group is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, -CF_3, -OCF_3, -OH, -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -NHC(=O)(C_{1-3} alkyl), -C(=O)NH_{2-z}(C_{1-3} alkyl)$_z$, -$(CH_2)_{1-3}NH_2$, -$(CH_2)_{1-3}$NH(C_{1-3} alkyl), -$(CH_2)_{1-3}$N(C_{1-3} alkyl)$_2$, -$(CH_2)_{1-3}$OH, and -$(CH_2)_{1-3}$O(C_{1-3} alkyl); and wherein z is 0, 1, or 2, preferably wherein R^3 is H; and

(D') at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, -O(C_{1-3}alkyl), -NH(C_{1-3}alkyl) or -N(C_{1-3}alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, -NH(C_{1-3}alkyl), and -O(C_{1-3}alkyl) and at least one of the alkyl groups of -N(C_{1-3}alkyl)$_2$ is substituted with one or more F atoms;

(E') A is S, O, or N(CH_3)$_2$, preferably wherein A is S; and

(F') B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, preferably wherein B is N; and

(G') E is O or S, preferably O.

ITEM 65. The compound of any one of items 61 to 64, wherein one R^7 is selected from the group consisting of -CH_2F, -CHF_2, and -CF_3, preferably selected from the group consisting of -CH_2F and -CHF_2.

ITEM 66. The compound of any one of items 61 to 65, wherein one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms.

ITEM 67. The compound of any one of items 61 to 66, wherein one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms.

ITEM 68. The compound of any one of items 61 to 67, wherein R^6 is substituted with at least two R^7.

ITEM 69. The compound of any one of items 61 to 68, wherein R^6 is substituted with two R^7 which differ from each other.

ITEM 70. The compound of any one of items 61 to 69, wherein one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound and one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein at least one of said R^7 is F and/or at least one of said R^7 is substituted with one or more F atoms.

ITEM 71. The compound of any one of items 61 to 70, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, and one R^7 is selected from the group consisting of halogen, $-CH_3$, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, $-CH_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$.

ITEM 72. The compound of any one of items 61 to 71, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$, and one R^7 is Cl.

ITEM 73. The compound of any one of items 61 to 70, wherein one R^7 is F, and one R^7 is selected from the group consisting of halogen, CH_3, $-CH_2(hal)$, $-CH(hal)_2$, and $-C(hal)_3$, more preferably selected from the group consisting of Cl, Br, F, CH_3, $-CH_2F$, $-CHF_2$, and $-CF_3$.

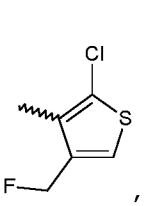
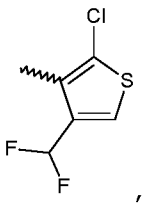
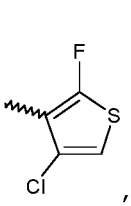
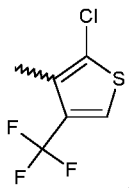
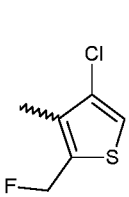
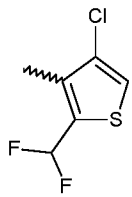
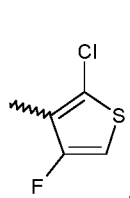
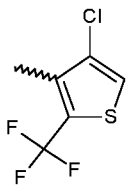
ITEM 74. The compound of any one of items 61 to 70 and 73, wherein one R^7 is F and one R^7 is Cl.

ITEM 75. The compound of any one of items 61 to 74, wherein R^6 is selected from the group consisting of thienyl, thiazolyl, and thiadiazolyl, preferably selected from the group consisting of thienyl and thiazolyl, more preferably R^6 is thienyl, wherein each of the thienyl, thiazolyl, and thiadiazolyl groups is substituted with one or more independently selected R^7.

ITEM 76. The compound of any one of items 61 to 75, wherein the ring atom of R^6 by which R^6 is bound to the remainder of the compound is a C atom.

ITEM 77. The compound of any one of items 61 to 76, wherein the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound.

ITEM 78. The compound of any one of items 61 to 64, wherein R^6 is selected from the group consisting of


, 
, 
, 
, 
, 
, 
, and 
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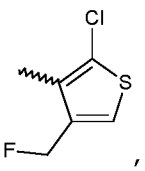
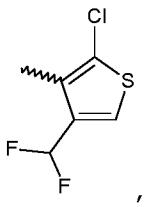
wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

ITEM 79. The compound of any one of items 61 to 64, wherein R^6 is selected from the group consisting of


, and 
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wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

ITEM 80. The compound of any one of items 61 to 79, wherein R^{1a} is selected from the group consisting of -NH(C_{1-3} alkyl), piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl, wherein each of the piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, -OH, =O, $-OCH_3$, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(methoxy)ethoxy, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), $-NHS(O)_2$(C_{1-3} alkyl), and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

ITEM 81. The compound of any one of items 61 to 80, wherein R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

ITEM 82. The compound of any one of items 61 to 81, wherein R^{1a} is non-symmetrical.

ITEM 83. The compound of item 61 to 82, wherein the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an atom other than C, preferably is an N atom.

ITEM 84. The compound of any one of items 61 to 83, wherein the atom of R^{1c} by which R^{1c} is bound to the remainder of the compound is a C atom.

ITEM 85. The compound of any one of items 61 to 84, wherein R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl.

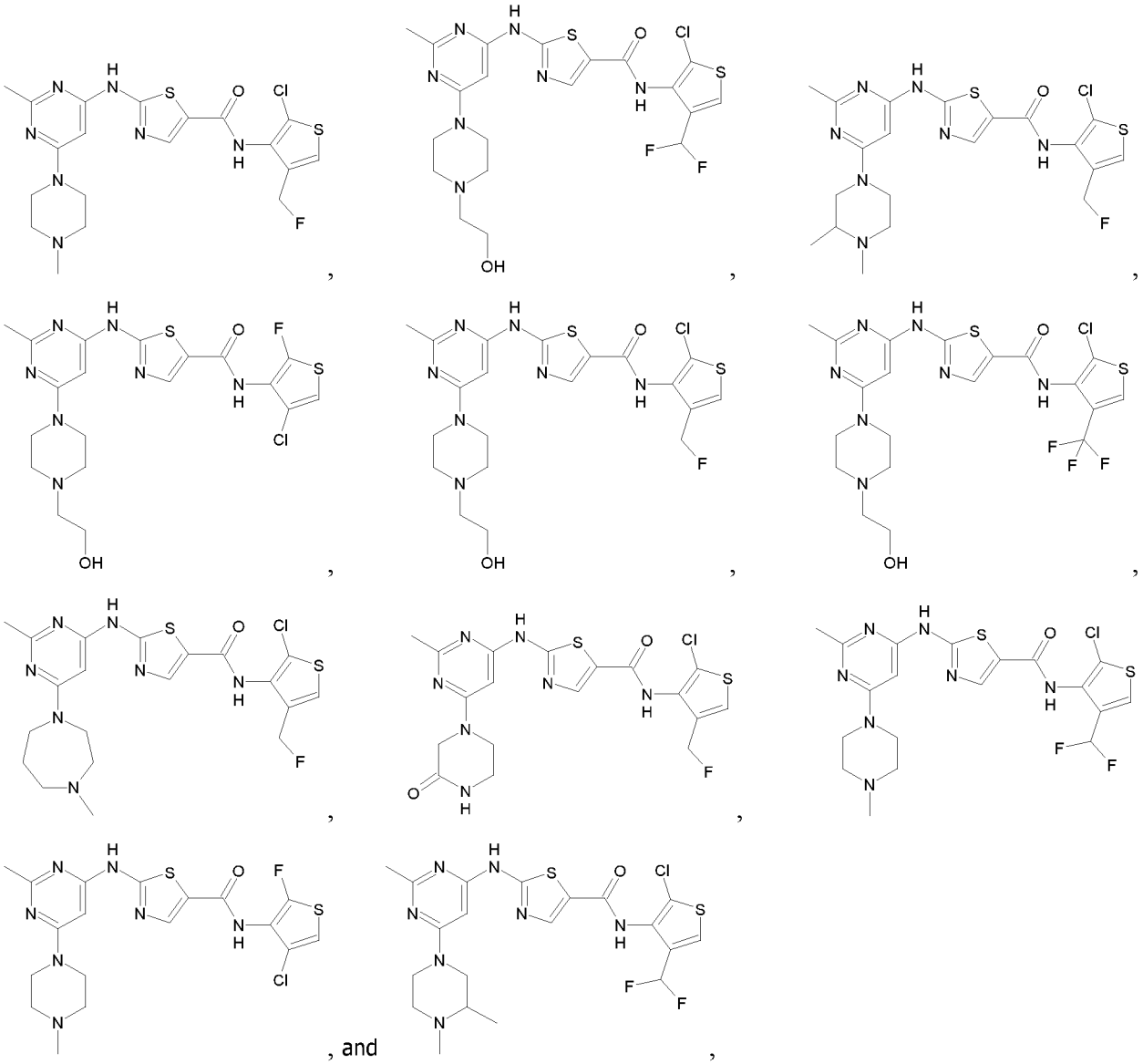
ITEM 86. The compound of any one of items 61 to 85, wherein A is S; B is N; and/or E is O.

ITEM 87. The compound of any one of items 61 to 86, wherein A is S; B is N; and E is O.

ITEM 88. The compound of any one of items 61 to 87, wherein R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen, preferably H.

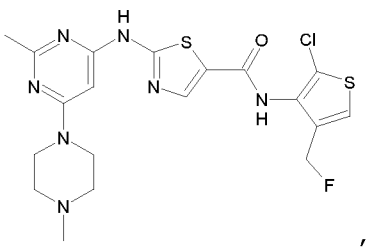
ITEM 89. The compound of any one of items 61 to 88, wherein R^3 is H.

ITEM 90. The compound of any one of items 1 to 89, wherein the compound is selected from the group consisting of:



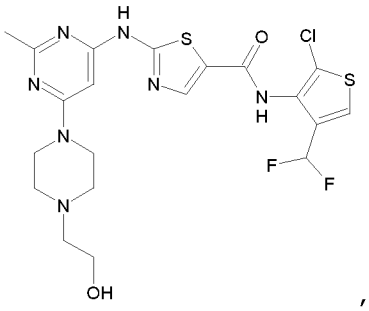
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 91. The compound of any one of items 1 to 90, wherein the compound is selected from the group consisting of:



and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 92. The compound of any one of items 1 to 90, wherein the compound is selected from the group consisting of:



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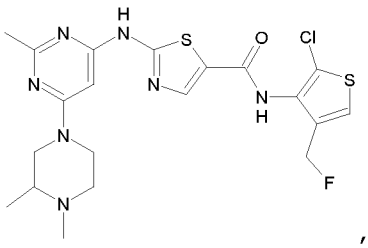
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 93. The compound of any one of items 1 to 90, wherein the compound is selected from the group consisting of:



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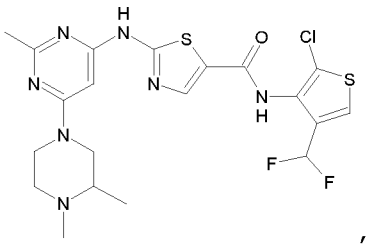
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 94. The compound of any one of items 1 to 90, wherein the compound is selected from the group consisting of:



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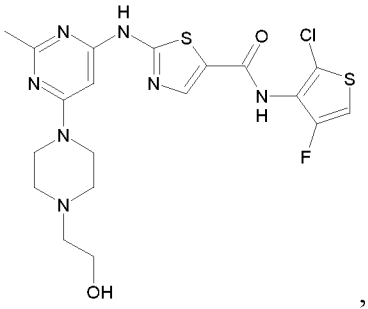
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 95. The compound of any one of items 1 to 89, wherein the compound is selected from the group consisting of: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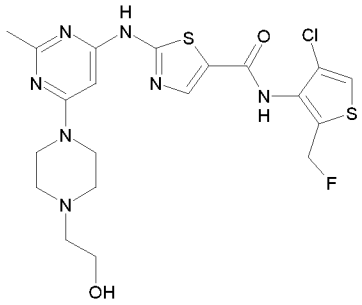
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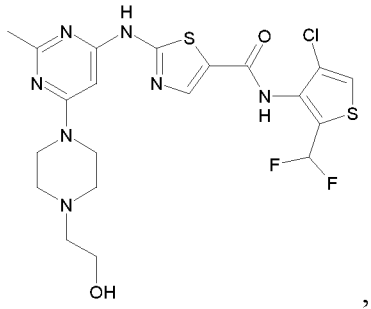
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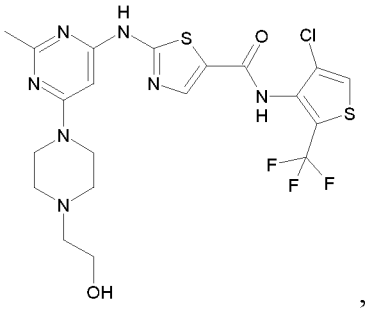
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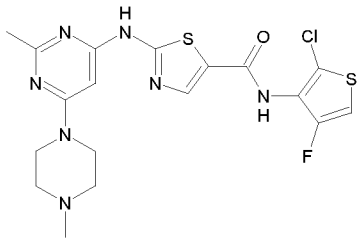
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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 96. The compound of any one of items 1 to 95, wherein the compound is in substantially pure form, in particular in greater than about 90%, 95%, 98% or 99% pure form.

ITEM 97. **A pharmaceutical composition** comprising the compound of any one of items 1 to 96, and optionally further comprising a pharmaceutically acceptable excipient.

ITEM 98. The pharmaceutical composition of item 97 formulated for oral administration.

ITEM 99. The pharmaceutical composition of item 97 or 98 in unit dose form.

ITEM 100. The compound of any one of items 1 to 96, or the pharmaceutical composition of any one of items 97 to 99, for use in therapy.

ITEM 101. **A method for the treatment** of a disease, disorder or condition in a subject, comprising administering to the subject a compound of any one of items 1 to 96, or a pharmaceutical composition of any one of items 97 to 99, optionally wherein the disease, disorder or condition is associated with a kinase.

ITEM 102. **A method for the treatment** of a proliferative disorder in a subject, comprising administering to the subject a compound of any one of items 1 to 96, or a pharmaceutical composition of any one of items 97 to 99.

ITEM 103. **A compound for use, or a pharmaceutical composition for use**, in a treatment of a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, wherein, the compound is a compound of any one of items 1 to 96, and the pharmaceutical composition is a pharmaceutical composition of any one of items 97 to 99.

ITEM 104. The compound for use, or the pharmaceutical composition for use, of item 103, wherein the proliferative disorder is a cancer or tumour.

ITEM 105. The compound for use, or the pharmaceutical composition for use, of item 104, wherein the cancer is a solid tumour.

ITEM 106. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 105, wherein treatment further comprises administration of an immune checkpoint inhibitor to the subject.

ITEM 107. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 106, wherein: (i) the proliferative disorder has progressed on standard therapy in the subject; or (ii) the subject is unable to receive standard therapy.

ITEM 108. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 107, wherein the treatment involves inhibiting SIK3 in the subject.

ITEM 109. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 108, wherein the treatment involves sensitising cells involved with the proliferative disorder in the subject to a cell-mediated immune response.

ITEM 110. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 109, wherein the compound or pharmaceutical composition is administered to the subject to sensitise cells involved with the proliferative disorder to killing induced by TNF.

ITEM 111. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 110, the treatment comprising exposing cells involved with the proliferative disorder in the subject to: (i) TNF, a TNF variant, and/or an agonist of TNFR12 or TNFR1-signalling; and (ii) the compound or pharmaceutical composition.

ITEM 112. The compound for use, or the pharmaceutical composition for use, of item 111, wherein the amount of TNF exposed to cells involved with the proliferative disorder in the subject is increased.

ITEM 113. The compound for use, or the pharmaceutical composition for use of item 111 or 112, wherein: (i) TNF, a TNF variant or an agonist of TNFR1 or TNFR2-signalling is administered to the subject; (ii) an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to TNF, a TNF variant or an agonist of TNFR1- or TNFR2-signalling, is administered to the subject; or (iii) the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

ITEM 114. The compound for use, or the pharmaceutical composition for use, of any one of items 111 to 113, wherein the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

ITEM 114a. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 114, wherein the treatment comprises administering the compound or the pharmaceutical composition once or more than once in a given twenty-four hour period, such as once or more than once a day.

ITEM 114b. The compound for use, or the pharmaceutical composition for use, of item 114a, wherein the treatment comprises administering the compound or the pharmaceutical composition twice or more than twice in a given twenty-four hour period, such as twice or more than twice a day.

ITEM 114c. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 114b, wherein the treatment comprises administering the compound or the pharmaceutical composition two times daily (*bis in die*; BID).

ITEM 114d. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 114, wherein the treatment comprises administering the compound or the pharmaceutical composition once or more than once each twenty-four hour period for two or more than two sequential twenty-four hour periods, such as once or more than once each day for two or more than two sequential days, and optionally up to about twenty eight, such as up to about eighteen or about fourteen, sequential twenty-four hour periods or sequential days.

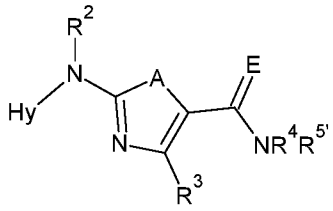
ITEM 114e. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 114d, wherein the treatment comprises administering the compound or the pharmaceutical composition once or more than once each twenty-four hour period for about 28, 21, 18, 14, 7, 5 or 3 or less sequential twenty-four hour period, such as once or more than once each day for about 28, 21, 18, 14, 7, 5 or 3 or less sequential two sequential days.

ITEM 114f. The compound for use, or the pharmaceutical composition for use, of any one of items 100 and 103 to 114e, wherein the treatment comprises administering the compound or the pharmaceutical composition two times daily (*bis in die*; BID) each day for about eighteen or for about fourteen or for about seven (or, in each case, for more) sequential twenty-four hour period, such as two times daily (*bis in die*; *bid*) each day for about eighteen or for about fourteen or for about seven sequential (or, in each case, for more) days.

ITEM 115. **A compound for use, or a pharmaceutical composition for use**, in a treatment of a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, **wherein the compound is selected from the following compounds (a) to (c)**, and the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient:

(a) a compound of any one of items 1 to 96;

(b) a compound having the following formula:



(Ib),

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof,

wherein:

Hy, R^2, R^3, A, E, and R^4 are as defined in item 1;

$R^{5'}$ is -L-$R^{6'}$;

L is a bond;

$R^{6'}$ is a 5- or 6-membered heteroaryl which is optionally substituted with one or more independently selected $R^{7'}$;

$R^{7'}$ is independently selected from the group consisting of R^7, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, -NO_2, -OR^{11}, -$N(R^{12})(R^{13})$, -$N(R^{11})(OR^{11})$, -$S(O)_{0\text{-}2}R^{11}$, -$S(O)_{1\text{-}2}OR^{11}$, -$OS(O)_{1\text{-}2}R^{11}$, -$OS(O)_{1\text{-}2}OR^{11}$, -$S(O)_{1\text{-}2}N(R^{12})(R^{13})$, -$OS(O)_{1\text{-}2}N(R^{12})(R^{13})$, -$N(R^{11})S(O)_{1\text{-}2}R^{11}$, -$NR^{11}S(O)_{1\text{-}2}OR^{11}$, -$NR^{11}S(O)_{1\text{-}2}N(R^{12})(R^{13})$, -$P(O)(OR^{11})_2$, -$OP(O)(OR^{11})_2$, -$C(=X)R^{11}$, -$C(=X)XR^{11}$, -$XC(=X)R^{11}$, and -$XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}; and

R^{11}, R^{12}, R^{13}, X, and R^{30} are as defined in item 1,

optionally, with the proviso that

(I) when A is S; R^3 is H; E is O; and $R^{6'}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; then Hy is not 2-pyridyl;

(II) when Hy is 1-{(2E)-4-[(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}piperidine-4-yl; R^3 is H; A is O; E is O; then $R^{6'}$ is not 5-methyl-pyridin-2-yl;

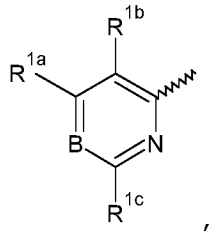
(III) when R^3 is trifluoromethyl; A is O; E is O; and

(i) $R^{6'}$ is 6-{4-[(2-fluorophenyl)carbamoyl]piperazin-1-yl}pyridine-3-yl; then Hy is not 1-(phenylmethyl)-piperidine-4-yl, 1-(phenylmethyl)pyrrolidine-3-yl, or tetrahydro-2H-pyran-4-yl; or

(ii) Hy is 1-(phenylmethyl)piperidine-4-yl; then $R^{6'}$ is not 6-(3-{[(2-fluorophenyl)carbamoyl]amino}-pyrrolidin-1-yl)pyridine-3-yl or 6-({1-[(2-fluorophenyl)carbamoyl]piperidin-4-yl}amino)pyridine-3-yl; or

(iii) Hy is 1-(phenylmethyl)pyrrolidine-3-yl; then $R^{6'}$ is not 6-({(3S)-1-[(2-fluorophenyl)carbamoyl]-pyrrolidin-3-yl}amino)pyridine-3-yl or 6-({(3R)-1-[(2-fluorophenyl)carbamoyl]pyrrolidin-3-yl}-amino)pyridine-3-yl; and/or

(IV) when Hy is



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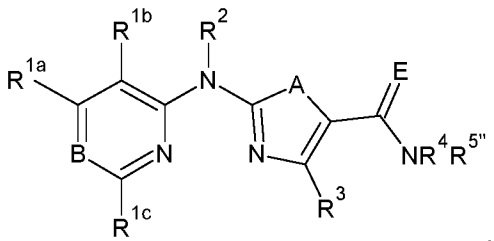
and

(1) R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^3 is H; and A is S; then $R^{6'}$ is not 4-chloro-2-methylpyridin-3-yl;

(2) E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br, then R^{1a} is not H;

(c) a compound having the following formula (Ic):



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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof,

wherein:

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, A, E, and R^4 are as defined in item 1;

B is N or CR^{1d}, wherein R^{1d} is as defined in item 1;

$R^{5''}$ is -L-$R^{6''}$;

L is as defined in item 1;

$R^{6''}$ is heteroaryl or heterocyclyl, each of which is optionally substituted with one or more independently selected $R^{7'}$;

$R^{7'}$ is independently selected from the group consisting of R^7, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, and/or any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ being a heterocyclyl group may join together to form =O, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}; and

R^{11}, R^{12}, R^{13}, X, and R^{30} are as defined in item 1,

optionally, with the proviso

(1) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^3 is H; A is S; and L is a bond; then $R^{6''}$ is not 4-chloro-2-methylpyridin-3-yl;

(2) when R^{1a} is methoxy; R^{1b} is H; R^{1c} is methoxy; B is N; E is O; R^3 is H; A is S; and L is a bond; then $R^{6''}$ is not 2,2-difluoro-5H-1,3-dioxolo[4,5-f]benzimidazol-6-yl;

(3) when R^3 is H; A is S; L is a bond; $R^{6''}$ is 1-methyl-4-piperidinyl; R^{1b} is H; B is N; E is O; and

(i) R^{1a} is methyl; then R^{1c} is not N-tert-butoxycarbonylpiperidin-4-yl; or

(ii) R^{1c} is methyl; then R^{1a} is not N-tert-butoxycarbonylpiperidin-4-yl or N-tert-butoxycarbonylpiperidin-3-yl;

(4) when E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br, then R^{1a} is not H; and/or

(5) when R^{1a} is methyl; each of R^{1b} and R^{1c} is H; B is CH; E is O; A is S; and R^3 is methyl; then $R^{5''}$ is not 1,3-benzodioxol-5-ylmethyl, 2-furanylmethyl, 1,3-benzodioxol-5-yl, 2-(2-thienyl)ethyl, 2-(4-morpholinyl)ethyl, 2-(2-pyridinyl)ethyl, 2-pyridinylmethyl, or tetrahydro-2-furanylmethyl;

(6) when A is S; R^3 is H; E is O; L is a bond; $R^{6''}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; R^{1a} is H, R^{1b} is H, R^{1c} is H; and B is CR^{1d}; then R^{1d} is not H; and

wherein the proliferative disorder is selected from one or more of (α) to (γ):

(α) a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by, the presence of myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by, or cells involved with the proliferative disorder characterised by, the presence of phosphorylated histone deacetylase 4 (HDAC4) protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(β) a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by,: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or

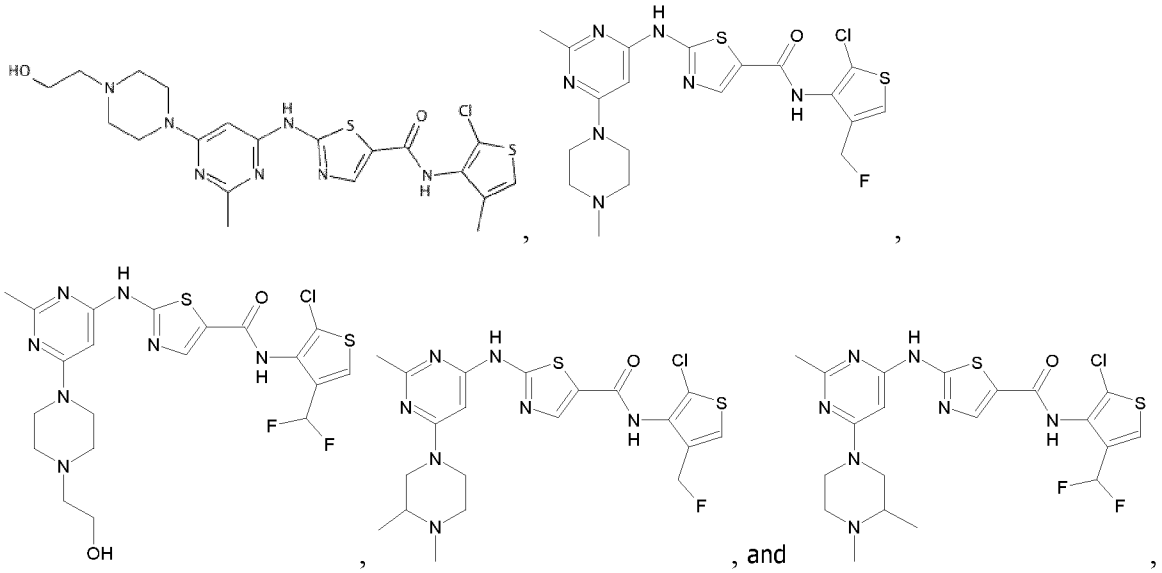
(γ) a mixed phenotype acute leukaemia (MPAL).

ITEM 115a. The compound or a pharmaceutical composition for use of item 115, wherein the compound is a compound as defined in (a) of item 115.

ITEM 115b. The compound or a pharmaceutical composition for use of item 115, wherein the compound is a compound as defined in (b) of item 115 and $R^{6'}$ is a 5-membered monocyclic heteroaryl contains at least one ring heteroatom selected from the group consisting of N, O, and S, and which is optionally substituted with one, two or three independently selected $R^{7'}$.

ITEM 115c. The compound or a pharmaceutical composition for use of item 115, wherein the compound is a compound as defined in (c) of item 115 and $R^{6''}$ is a 5- or 6-membered heteroaryl which contains at least one S ring atom and which is optionally substituted with one two or three independently selected $R^{7'}$.

ITEM 116. The compound or a pharmaceutical composition for use of any one of items 115 to 115c, wherein the compound is selected from the group consisting of:



and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

ITEM 117. **A method for the treatment of a proliferative disorder** in a subject, comprising administering to the subject a compound or pharmaceutical composition as defined in any one of items 115 to 115c, wherein the proliferative disorder is as defined in item 115.

ITEM 118. The compound or pharmaceutical composition for use of item any one of items 115 to 115c or the method of item 117, wherein the proliferative disorder is characterised by, or cells involved with the proliferative disorder characterised by,: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; and/or (iii) the presence of an KMT2A fusion oncoprotein, preferably wherein:

(a) the human chromosome translocation is one selected from the group consisting of: t(4,11), t(9,11), t(11,19), t(10,11) and t(6,11); and/or

(b) the rearrangement of the *KMT2A* gene comprises, or the KMT2A fusion oncoprotein is expressed from a rearrangement that comprises, a fusion of the *KMT2A* gene with a translocation partner gene selected from the group consisting of: *AF4*, *AF9*, *ENL*, *AF10*, *ELL* and *AF6*.

ITEM 119. The compound or pharmaceutical composition for use of any one of items 115 to 116 and 118 or the method of item 117 or 118, wherein the proliferative disorder is a cancer or a tumour, preferably a haematopoietic malignancy and/or a lymphoid malignancy.

ITEM 120. The compound or pharmaceutical composition for use of any one of items 115 to 116, 118 and 119, or the method of any one of items 117 to 119, wherein the proliferative disorder is: (i) a myeloma, preferably multiple myeloma; or (ii) a leukaemia, preferably an acute myeloid leukaemia (AML) or an acute lymphoblastic leukaemia (ALL), more preferably T cell acute lymphoblastic leukaemia (T-ALL), an MLL-AML or an MLL-ALL.

ITEM 121. The compound or pharmaceutical composition for use of any one of items 115 to 116 and 118 to 120, or the method of any one of items 117 to 120, wherein the subject is a human paediatric patient and/or is a subject carrying a *KMT2A* rearrangement (*KMT2A-r*); preferably wherein the subject is a patient suffering from a *KMT2A-r* leukaemia.

ITEM 122. **A method for determining** that a subject suffering from a proliferative disorder is suitable for treatment with a compound or pharmaceutical composition as defined in any one of items 115 to 115c, the method

comprising, determining in a biological sample that has been obtained from said subject, and preferable that comprises cells involved with the proliferative disorder:

(X) the presence of MEF2C protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by the presence of phosphorylated HDAC4 protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(Y) (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the *KRAS* gene and/or in the *RUNX1* gene,

wherein, the presence of said protein, translocation, rearrangement, oncoprotein and or mutation in the biological sample indicates that the subject is suitable for treatment with the compound or pharmaceutical composition.

ITEM 123. The method of item 122, comprising determining in a biological sample that has been obtained from said subject: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; and/or (iii) the presence of an KMT2A fusion oncoprotein, preferably wherein:

(a) the human chromosome translocation is one selected from the group consisting of: t(4,11), t(9,11), t(11,19), t(10,11), and t(6,11); and/or

(b) the rearrangement of the *KMT2A* gene comprises, or the KMT2A fusion oncoprotein is expressed from a rearrangement that comprises, a fusion of the *KMT2A* gene with a translocation partner gene selected from the group consisting of: *AF4*, *AF9*, *ENL*, *AF10*, *ELL* and *AF6*.

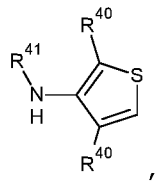
ITEM 124. The method of item 122 or 123, wherein the proliferative disorder is a cancer or a tumour, preferably a haematopoietic malignancy and/or a lymphoid malignancy.

ITEM 125. The method of any one of items 122 to 124, wherein the proliferative disorder is: (i) a myeloma, preferably multiple myeloma; or (ii) a leukaemia, preferably an acute myeloid leukaemia (AML) or an acute lymphoblastic leukaemia (ALL), more preferably T cell acute lymphoblastic leukaemia (T-ALL), an MLL-AML or an MLL-ALL.

ITEM 126. The method of any one of items 122 to 125, wherein the subject is a human paediatric patient and/or is a subject carrying a *KMT2A* rearrangement (*KMT2A-r*); preferably wherein such subject is a patient suffering from a *KMT2A-r* leukaemia.

ITEM 127. The method of any one of items 122 to 126, further comprising a step of administering a compound or pharmaceutical composition as defined in item 115 or 116 to a subject where the presence of, or an amount of, said protein, translocation, oncoprotein and or mutation is determined in a biological sample that had been obtained from said subject.

ITEM 128. **An intermediate** selected from a compound having formula (Id):



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and solvates, salts, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof,

wherein:

one of R^{40} is F or is selected from the group consisting of C_{1-3}alkyl, -O(C_{1-2}alkyl), -NH(C_{1-2}alkyl) and -N(C_{1-2}alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, -O(C_{1-2}alkyl), and -NH(C_{1-2}alkyl) and at least one of the alkyl groups of -N(C_{1-2}alkyl)$_2$ is substituted with one, two, or three F atoms, **and the other R^{40}** is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt; and

R^{41} is selected from the group consisting of H and an amino protecting group,

with the proviso that

(1) the intermediate is not 2-bromo-4-(trifluoromethyl)thiophen-3-amine;

(2) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is -CHF_2, then R^{41} is not (1-propylpiperidin-2-yl)carbonyl; and

(3) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is F, then R^{41} is not 4,5-dihydro-1*H*-imidazol-2-yl.

ITEM 129. The intermediate of item 128, wherein the two R^{40} differ from each other.

ITEM 130. The intermediate of item 128 or 129, wherein one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt, more preferably selected from the group consisting of Cl, Br, F, and -Me.

ITEM 131. The intermediate of any one of items 128 to 130, wherein one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, preferably selected from the group consisting of -CH_2F and -CHF_2, and the other R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, is Cl.

ITEM 132. The intermediate of any one of items 128 to 130, wherein one R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, is F, and the other R^{40} is selected from the group consisting of halogen, -Me, and -Et, preferably selected from the group consisting of Cl, Br, F, -Me, and -Et, and more preferably selected from the group consisting of Cl, -Me, and -Et.

ITEM 133. The intermediate of any one of items 128 to 130 and 132, wherein one R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, is F and the other R^{40} is Cl.

ITEM 134. The intermediate of any one of items 128 to 133, wherein the C ring atom to which R^{40} being F or being selected from the group consisting of C_{1-3}alkyl, -O(C_{1-2}alkyl), -NH(C_{1-2}alkyl) and -N(C_{1-2}alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, -O(C_{1-2}alkyl), and -NH(C_{1-2}alkyl) and at least one of the alkyl groups of -N(C_{1-2}alkyl)$_2$ is substituted with one, two, or three F atoms, is bound and the S ring atom are adjacent ring atoms.

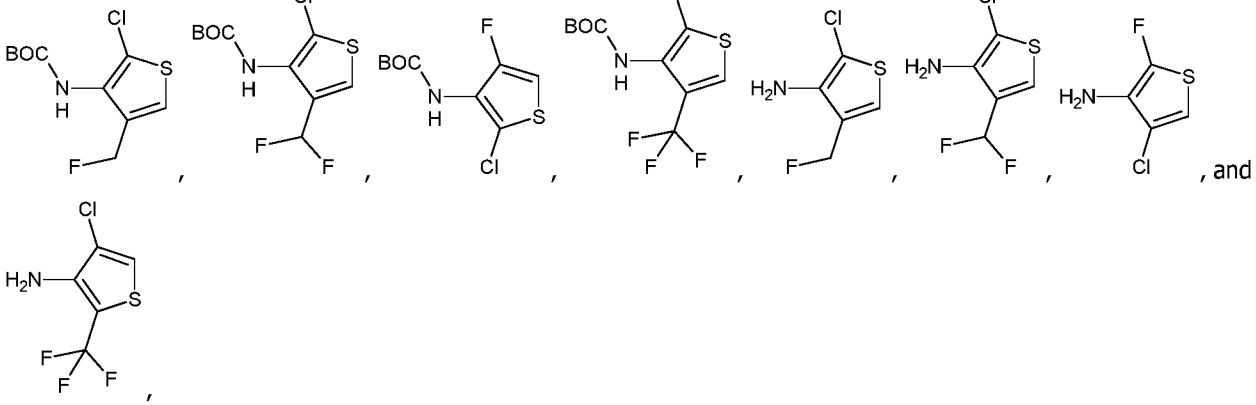
ITEM 135. The intermediate of any one of items 128 to 133, wherein the C ring atom to which R^{40} being F or being selected from the group consisting of C_{1-3}alkyl, -O(C_{1-2}alkyl), -NH(C_{1-2}alkyl) and -N(C_{1-2}alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, -O(C_{1-2}alkyl), and -NH(C_{1-2}alkyl) and at least one of the alkyl groups of -N(C_{1-2}alkyl)$_2$ is substituted with one, two, or three F atoms, is bound and the S ring atom are separated by a C ring atom.

ITEM 136. The intermediate of any one of items 128 to 135, wherein R^{41} is an amino protecting group.

ITEM 137. The intermediate of any one of items 128 to 136, wherein the amino protecting group is selected from the group consisting of tert-butyloxycarbonyl (BOC), 9-fluorenylmethoxycarbonyl (FMOC), benzyloxycarbonyl (Cbz), p-methoxybenzylcarbonyl (MOZ), acetyl (Ac), trifluoroacetyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), 3,4-dimethoxyphenyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethoxycarbonyl (Troc), triphenylmethyl (trityl; Tr), toluenesulfonyl (tosyl; Ts), *para*-bromophenylsulfonyl (brosyl), 4-nitrobenzenesulfonyl (nosyl), and 2-nitrophenylsulfenyl (Nps).

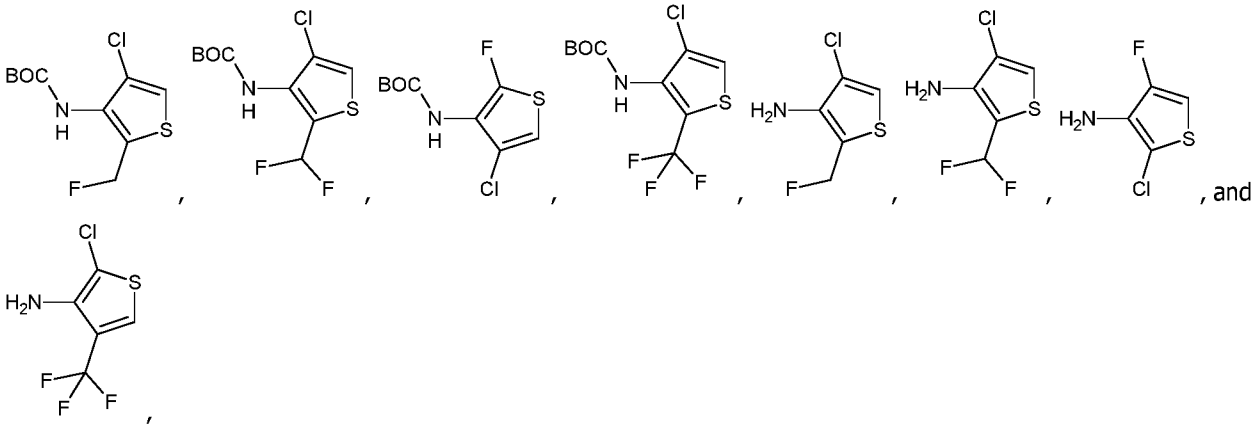
ITEM 138. The intermediate of any one of items 128 to 135, wherein R^{41} is H.

ITEM 139. The intermediate of item 128, selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

ITEM 140. The intermediate of item 128, selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

ITEM 141. **A method of manufacturing a compound** comprising an amide moiety, the method comprising the step of reacting the intermediate of any one of items 128 to 140 with a corresponding carboxylic acid, and, optionally, removing the amino protecting group.

ITEM 142. The method of item 141, wherein the compound is a kinase inhibitor, in particular an inhibitor of one or more protein kinases selected from the list consisting of: SIK (preferably SIK3), CSFR1, ABL, SRC, HCK, PDGFR and KIT; preferably selected from the list consisting of: SIK3, ABL/BCR-ABL, HCK and CSF1R kinases.

ITEM 143. The method of item 141 or 142, wherein the step of reacting the intermediate with the corresponding carboxylic acid is conducted in the presence of (i) a base and/or (ii) a coupling agent.

ITEM 144. The method of item 143, wherein the base is a non-nucleophilic base, preferably selected from the group consisting of *N,N*-diisopropylethylamine (DIPEA), 2,2,6,6-tetramethylpiperidine, triethylamine, tributylamine, 1,8-diazabicycloundec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,4-diazabicyclo[2.2.2]octane (TED), collidine, 1,1,3,3-tetramethylguanidine (TMG), quinuclidine, 2,2,6,6-tetramethylpiperidine (TMP), pempidine (PMP), 2,6-di-tert-butylpyridine, 2,6-lutidine, phosphazene bases (eg t-Bu-P_4), lithium diisopropylamide (LDA), sodium

bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS), sodium *tert*-butoxide, and potassium *tert*-butoxide.

ITEM 145. The method of item 143 or 144, wherein the coupling agent is selected from the group consisting of N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (TCFH), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU), 1-propanephosphonic anhydride (T3P), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP), and (6-chlorobenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (TPTDP).

ITEM 146. **A method of preparing a compound** of item 96, comprising the steps:

- providing a compound of any one of items 1 to 95 in admixture with one or more impurities; and
- removing at least a fraction of the impurities from the admixture.

ITEM 147. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of items 1 to 96 together with a pharmaceutically acceptable excipient.

ITEM 148. **A method of manufacturing a pharmaceutical composition** comprising:

- practicing, or having practiced, the method of any one of items 141 to 145 to manufacture a compound; and
- formulating the manufactured compound together with a pharmaceutically acceptable excipient.

ITEM 149. **A method of preparing a pharmaceutical package**, comprising the steps:

- inserting into packaging a pharmaceutical composition of any one of items 97to 99 (preferably in finished pharmaceutical form), thereby forming a package containing the pharmaceutical composition; and optionally,
- inserting into the package a leaflet describing prescribing information for the pharmaceutical composition.

ITEM 150. **A pharmaceutical package** containing a pharmaceutical composition of any one of items 97 to 99; preferably, wherein the pharmaceutical composition is in finished pharmaceutical form.

EXAMPLES

[417] A selection of compounds within the scope of, or for use within the methods of, the present invention - and/or that represent examples of various exemplary or preferred Hy substituents, R^{1a} substituents, R^{1b} substituents, R^{1c} substituents, R^{1d} substituents, R^{1e} substituents, R^2 substituents, R^3 substituents, R^4 substituents, R^5 moieties, A moieties, B moieties and/or E moieties, each individually or in any combination are useful for synthesising further compounds of the invention - is listed in Table A (and/or depicted in Figure 1E). The compounds in Table A (and/or those depicted in Figure 1E) and/or those depicted in Figure 1B, Figure 1C and/or Figure 1D are synthesised and tested as described herein.

[628] The examples show:

Example 1.1: Synthesis of the kinase inhibitors, including kinase inhibitors of formulae (Ia), and compound **C7**

Synthesis of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

General methods and materials:

[629] MPLC purification was performed using a Biotage Isolera Four system, using KP-Sil cartridges with technical grade organic solvents, *i.e.* dichloromethane and methanol, 3-4 N NH_3 in MeOH. A gradient of DCM to 3 N NH_3 (in MeOH) from 0 % to 25 % over 10 CV was used for the purification of the final compounds.

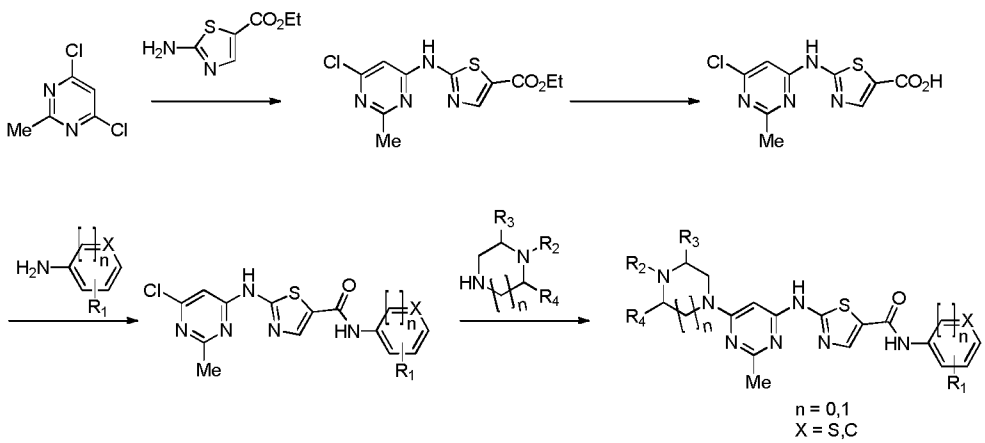
[630] ^1H NMR spectra were recorded on Bruker DPX 400 MHz spectrometers and are reported in ppm with the solvent resonance employed as the internal standard [$CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm]. Peaks are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad signal, coupling constant(s) in Hz, integration).

[631] Reverse phase HPLC was performed on a Shimadzu HPLC system using following system [solvent A: acetonitrile, solvent B: 0.1% formic acid in water]. Formic acid was used as HPLC grade. All the separations were performed at ambient temperatures. For analytical RP-HPLC analysis [Interchim: Uptisphere Strategy 100Å, 5 µm, 100x4.6 mm], the flow rate was 1.0 ml.min^{-1}; injection volume: 20 µL, detection wavelengths: 220 nm and 254 nm. The following gradient was used: 2.0 min 100 % B, over 8 min to 10 % B, 5 min 10 % B.

[632] LC-MS spectra were recorded on a Dionex Ultimate 3000 system using the following system [solvent A: acetonitrile, solvent B: 0.1% formic in water]. Formic acid was used as HPLC grade. All the separations were performed at ambient temperatures. For analytical RP-HPLC analysis [Interchim: Uptisphere Strategy C18, 2.6 µm, 50x4.6 mm], the flow rate was 1.0 ml.min^{-1}; detection wavelengths: 220 nm and 254 nm. The following gradient was used: 90 % B, over 5 min to 5 % B. The MS was recorded with the following settings: Dionex Surveyor MSQ plus, ESI+, Probe T(°C) 350, Cone 30 (v), Needle (KV) 3.0.

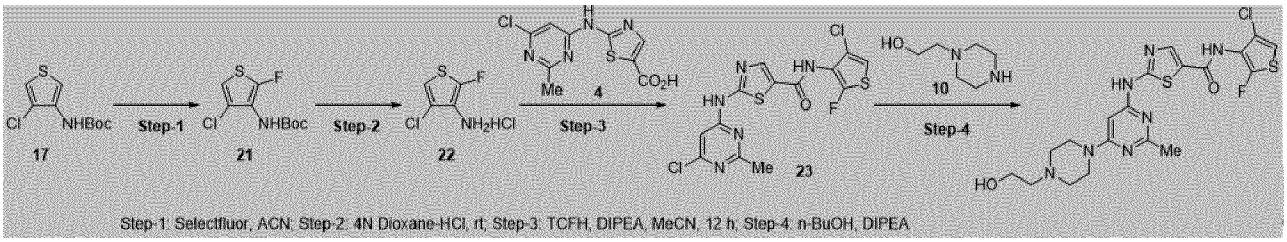
[633] Abbreviations: Boc_2O: di-tert-butyl decarbonate; 1-BuOH: 1-butanol; cHex: cyclohexane; CV: column value; d: doublet (NMR); d: days; dd: doublet of doublets; DCM = CH_2Cl_2: dichloromethane; DIPEA: *N,N*-diethylisopropyl amine; DMF: *N,N*-dimethylformamide; DMSO: dimethyl sulphoxide; EDC HCl: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; equiv.: equivalents; Et_2O: diethyl ether; EtOAc: ethyl acetate; g: gram; h: hours; H: proton; HCl: hydrochloric acid; H_2O: water; HOBT: 1-hydroxybenzotriazol; Hz: Hertz; IPA: iso-propanol; *J*: scalar ^1H-^1H coupling constant; K_2CO_3: potassium carbonate; KOH: potassium hydroxide; LC-MS: liquid chromatography – mass spectrometry; m: multiplet; M: molar; mAU: milliabsorption units; Me: methyl; MeCN: acetonitrile; MeOH: methanol; mg: milligram; MHz: mega Hertz; min: minutes; µw: microwave; N_2: nitrogen; NaH: sodium hydride; $NaHCO_3$: sodium bicarbonate; NaOH: sodium hydroxide; Na_2SO_4: sodium sulphate; NBS: *N*-bromo succinimide; NCS: *N*-chloro succinimide; NMR: nuclear magnetic resonance; $PdCl_2$(dppf): [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II); Pd_2dba_3: Tris(dibenzylideneacetone)dipalladium(0); quant.: quantitative; R_f: retention factor (TLC); rt: room temperature; s: singlet; SiO_2: silica; TCFH: tetramethylchloroformamidinium hexafluorophosphate; TFA: trifluoro acetic acid; THF: tetrahydrofuran; TLC: thin layer chromatography; XantPhos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

General scheme:



Compound E2:

*Synthesis of N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E2**)*



Step-1: tert-butyl (4-chloro-2-fluorothiophen-3-yl)carbamate

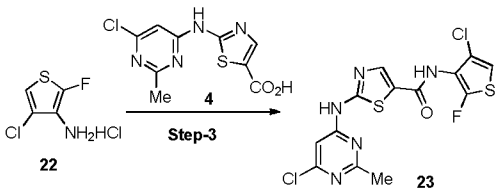
[634] Selectfluor™ (1.51 g, 4.3 mmol) was dissolved in CH_3CN (30 mL) at 70 °C. This solution was treated with tert-butyl (4-chlorothiophen-3-yl)carbamate **17** (1.0 g, 4.3 mmol) under nitrogen atmosphere at room temperature and stirred for 1h. The reaction mixture was diluted with ethyl ether, washed with water, then with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, concentrated and purified by column chromatography to afford tert-butyl (4-chloro-2-fluorothiophen-3-yl)carbamate **21** (0.59 g, yield 55%) as a white solid.

[635] LCMS: m/z = 152.07 $[M-100]^+$, 83.74 % (3.70 min).

Step-2: 4-chloro-2-fluorothiophen-3-amine hydrochloride

[636] To a solution of tert-butyl (4-chloro-2-fluorothiophen-3-yl)carbamate **21** (252 mg, 1.0 mmol, 1.0 eq.) in anhydrous dioxane (1.0 mL) was added 4.0 N HCl in dioxane (2.5 mL, 10.0 mmol, 10.0 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. Solid precipitated was filtered and washed with hexane to afford 4-chloro-2-fluorothiophen-3-amine hydrochloride **22** (141 mg, 75 %) as an off-white solid.

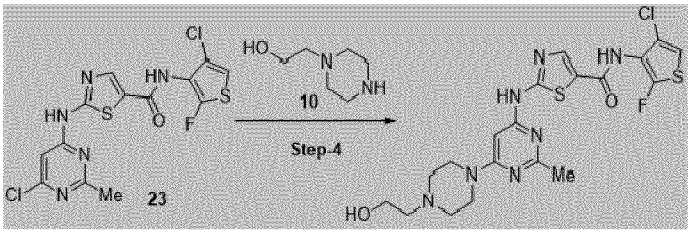
Step-3: N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



[637] To a suspension of 4-chloro-2-fluorothiophen-3-amine hydrochloride **22** (100 mg, 0.53 mmol, 1.0 eq.) and 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid **4** (187 mg, 0.69 mmol, 1.3 equiv) in acetonitrile (3 mL) was added DIPEA (240 mg 1.86 mmol, 3.5 eq.) and TCFH (171 mg, 0.61 mmol, 1.15 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hr. Reaction was monitored by LCMS. The reaction mixture was concentrated under vacuum and obtained residue was passed through column to afford crude N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide **23** (230 mg, purity ca. 74 %) as a yellow solid.

[638] LCMS: m/z = 403.99 $[M-100]^+$, (3.29 min).

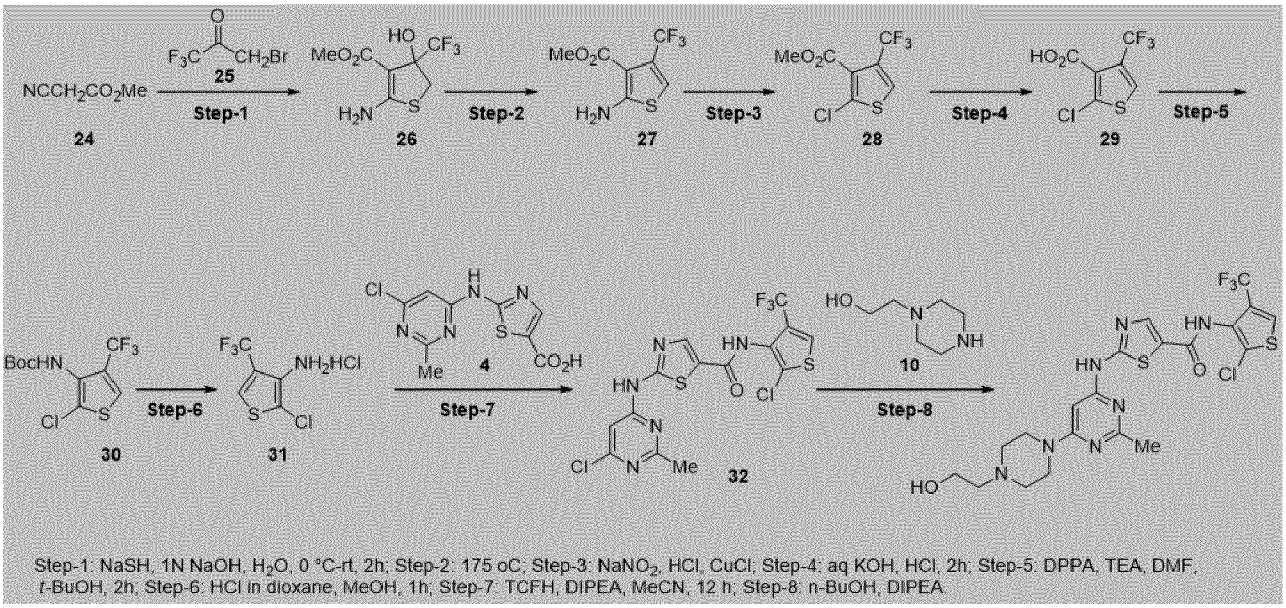
*Step-4: N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methyl pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E2**)*



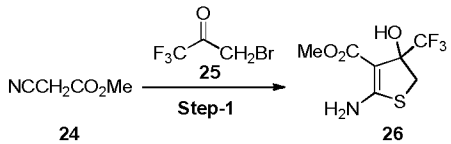
[639] 2-(piperazin-1-yl)ethanol **10** (370 mg, 2.84 mmol, 5.0 eq.) and DIPEA (30 mg, 0.23 mmol, 0.4 eq.) were added to the well stirred solution of N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide **23** (230 mg, 0.57 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methyl pyrimidin-4-yl)amino) thiazole-5-carboxamide (**E2**, Figure 1E) (69 mg, 26% yield over two steps) as a white solid. Analytical data for this synthesised compound **E2** is shown in Table 1.1.

Compound E5:

*Synthesis of N-(2-chloro-4-(trifluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E5**)*



Step-1: methyl 2-amino-4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiophene-3-carboxylate

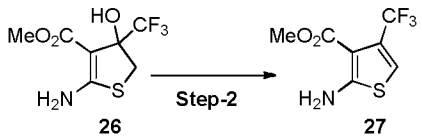


[640] Aqueous NaOH solution (1M, 20 mL) was added slowly to a solution of sodium hydrogensulphide hydrate (4.1 g, 73 mmol, 1.4 eq.) in water (16 mL) at 0°C. The reaction mixture was degassed and flushed with nitrogen before the addition of 1-bromo-3,3,3-trifluoroacetone **25** (10 g, 52 mmol, 1.0 eq.). After stirring at 0°C for 50 minutes, methyl cyanoacetate **24** (3.8 mL, 54 mmol, 1.04 eq.) was added, followed by triethylamine (7.6 mL, 54 mmol, 1.04 eq.), and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 1.5 hours, then filtered and the solid that was collected by filtration was washed with water and dried in vacuum

to afford methyl 2-amino-4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiophene-3-carboxylate **26** (4.12 g, 32 % yield) as an off-white solid.

[641] ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.01 (bs, 2H), 6.19 (s, 1H), 3.59 (s, 3H), 3.48 (d, J = 12.6 Hz, 1H), 3.17 (d, J = 12.6 Hz, 1H). LCMS: m/z = 244.18 $[M+H]^+$, 99.02 (2.73 min).

Step-2: methyl 2-amino-4-(trifluoromethyl)thiophene-3-carboxylate

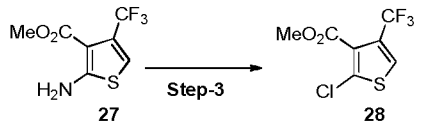


26 27

[642] Methyl 2-amino-4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiophene-3-carboxylate **26** (4 g) was heated to 175°C until melted and stirred for 10 minutes before cooling. EtOAc was added and the organics were washed with brine, dried and concentrated in vacuo to give the methyl 2-amino-4-(trifluoromethyl)thiophene-3-carboxylate **27** (3.7 g, yield 99%) as a brown solid.

[643] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (s, 1H), 3.84 (s, 3H). LCMS: m/z = 226.05 $[M+H]^+$, 98.85 (3.37 min).

Step-3: methyl 2-chloro-4-(trifluoromethyl)thiophene-3-carboxylate



27 28

[644] $NaNO_2$ solution (0.20 g in 1 ml water, 2.68 mmol, 1.4 eq.) was added to the mixture of methyl 2-amino-4-(trifluoromethyl)thiophene-3-carboxylate **27** (0.5 g, 1.92 mmol, 1.0 eq.), water (7 ml) and conc. HCl (3 ml) at 0 °C during 20 min. After 30 more minutes in an ice bath the mixture was filtered and the diazonium-salt solution was added dropwise to CuCl-solution (0.80 g, 8.08 mmol, 4.2 eq.) in conc. HCl (20 ml) at 0 °C. The reaction mixture was stirred for 30 min, extracted with Et_2O, dried (Na_2SO_4) and evaporated. The crude residue was purified by column chromatography to afford methyl 2-chloro-4-(trifluoromethyl)thiophene-3-carboxylate **28** (201 mg, yield 37%).

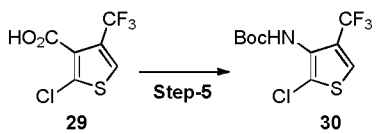
[645] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (s, 1H), 3.92 (s, 3H).

Step-4: 2-chloro-4-(trifluoromethyl)thiophene-3-carboxylic acid

28 29

[646] KOH (413 mg, 7.37 mmol, 3.0 eq.) was added to the suspension of methyl 2-chloro-4-(trifluoromethyl)thiophene-3-carboxylate **28** (600 mg, 2.46 mmol, 1.0 eq.) in water (12 ml) and the resultant reaction mixture was refluxed for one hour. The reaction mixture was cooled to 0 °C and acidified to pH 2 by the addition of con. HCl. The precipitate formed was filtered under vacuum to afford 2-chloro-4-(trifluoromethyl)thiophene-3-carboxylic acid **29** (550 mg, yield 97%) as a white solid.

Step-5: tert-butyl (2-chloro-4-(trifluoromethyl)thiophen-3-yl)carbamate



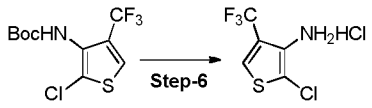
29 30

[647] To a solution of 2-chloro-4-(trifluoromethyl)thiophene-3-carboxylic acid **29** (1.00 g, 4.35 mmol, 1.0 eq.) in dry dimethylformamide (25 mL) at 0 °C was added diphenylphosphoryl azide (1.19 g, 4.35 mmol, 1.0 eq.) and the mixture was stirred at room temperature for 2 hours. After disappearance of the starting material, tert-butanol was added (4.2 mL, 43.5 mmol, 10.0 eq.) and the mixture was stirred at reflux for 17 hours. The reaction mixture was

concentrated and the crude residue was purified by silica gel flash column chromatography to yield tert-butyl (2-chloro-4-(trifluoromethyl)thiophen-3-yl)carbamate **30** (0.65 g, 50%).

[648] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (s, 1H), 5.83 (bs, 1H), 1.48 (s, 9H).

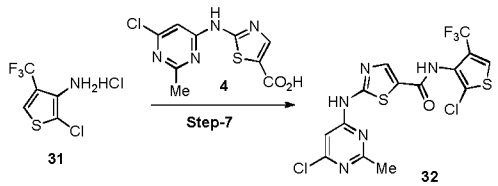
Step-6: 2-chloro-4-(trifluoromethyl)thiophen-3-amine hydrochloride



30 31

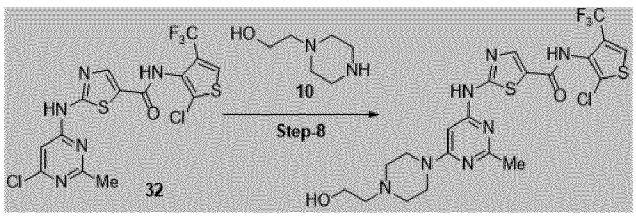
[649] To a solution of tert-butyl (2-chloro-4-(trifluoromethyl)thiophen-3-yl)carbamate **30** (302 mg, 1.0 mmol, 1.0 eq.) in anhydrous dioxane (1.0 mL) was added 4.0 N HCl in dioxane (2.5 mL, 10.0 mmol, 10.0 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. Solid precipitated was filtered and washed with hexane to afford 2-chloro-4-(trifluoromethyl)thiophen-3-amine hydrochloride **31** (181 mg, 76 %) as an off-white solid.

Step-7: 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(trifluoromethyl)thiophen-3-yl) thiazole-5-carboxamide



[650] To a suspension of 2-chloro-4-(trifluoromethyl)thiophen-3-amine hydrochloride **31** (114 mg, 0.48 mmol, 1.0 eq.) and 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid **4** (170 mg, 0.63 mmol, 1.3 equiv) in acetonitrile (3 mL) was added DIPEA (217 mg 1.68 mmol, 3.5 eq.) and TCFH (154 mg, 0.55 mmol, 1.15 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hr. Reaction was monitored by LCMS. The reaction mixture was concentrated under vacuum and obtained residue was passed through column to afford crude 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(trifluoromethyl) thiophen-3-yl) thiazole-5-carboxamide **32** (230 mg, purity ca. 73 %) as a yellow solid.

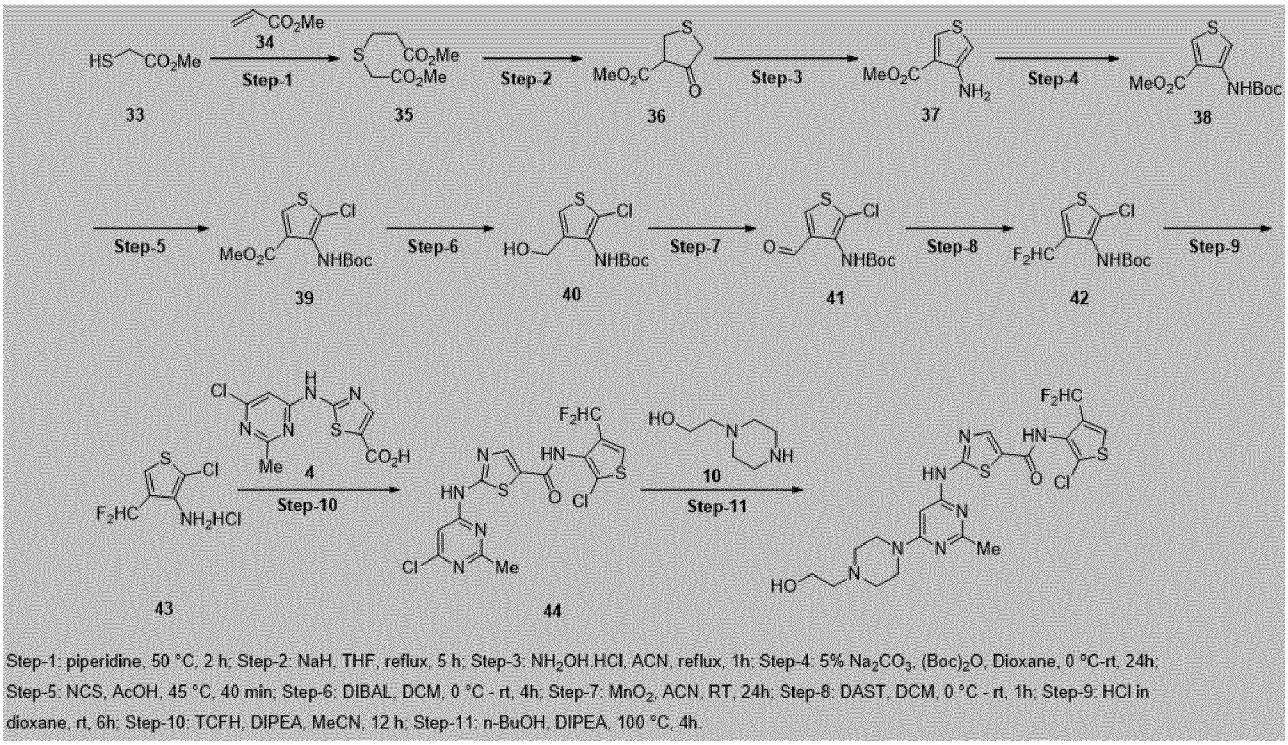
*Step-8: N-(2-chloro-4-(trifluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E5**)*



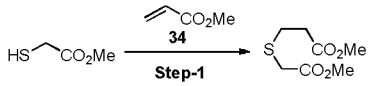
[651] 2-(piperazin-1-yl)ethanol **10** (329 mg, 2.53 mmol, 5.0 eq.) and DIPEA (26 mg, 0.20 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(trifluoromethyl)thiophen-3-yl) thiazole-5-carboxamide (230 mg, 0.51 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(trifluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl) amino)thiazole-5-carboxamide (**E5**, Figure 1E) (52 mg, 20% yield over two steps) as a white solid. Analytical data for this synthesised compound **E5** is shown in Table 1.1.

Compound E4:

*Synthesis of N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E4**)*



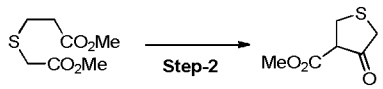
Step-1: methyl 3-((2-methoxy-2-oxoethyl)thio)propanoate



[652] Methyl acrylate **34** (99.16 mL, 1.1 mol) was slowly added to a solution of methyl 2-mercaptoacetate **33** (91 mL, 1 mol) and piperidine (2 mL) and stirred the reaction mixture at temperature 50 °C for 2 h. After complete disappearance of starting material by TLC, excess methyl acrylate and piperidine were distilled under high vacuum to give methyl 3-((2-methoxy-2-oxoethyl)thio)propanoate **35** (190 g, 99% yield) as a colorless viscous liquid oil.

[653] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.69 (s, 3H), 3.25 (s, 2H), 2.9 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H).

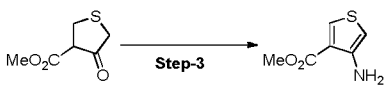
Step-2: methyl 4-oxotetrahydrothiophene-3-carboxylate



[654] To a solution of 60% NaH (13.2 g, 330 mmol, 1.1 eq.) in THF, methyl 3-((2-methoxy-2-oxoethyl) thio)propanoate **35** (58 g, 300 mmol, 1.0 eq.) in dry THF (800 mL) was added slowly within 2 h, and the reaction mixture was refluxed for 5 h. Then, the solvent was concentrated under reduced pressure, and H_2O (300 mL) was added to the residue. The pH value of the solution was adjusted to 1 by cold 1M HCl solution and extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography to yield methyl 4-oxotetrahydrothiophene-3-carboxylate **36** (17 g, 35%) as colorless viscous oil.

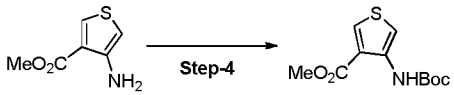
[655] ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.94 (s, 1H), 3.75-3.82 (m, 7H).

Step-3: methyl 4-aminothiophene-3-carboxylate



[656] The mixture of methyl 4-oxotetrahydrothiophene-3-carboxylate **36** (3.9g, 24.4 mmol, 1.0 eq.), hydroxylamine hydrochloride (1.69 g, 24.4 mmol, 1.0 eq.) and acetonitrile (20 mL) was stirred under reflux temperature for 1 h. The reaction mixture was then cooled and the solid which separated was filtered off and washed with dry ether to afford the methyl 4-aminothiophene-3-carboxylate **37** (2.9 g, 75%) as colorless viscous liquid oil.

Step-4: methyl 4-((tert-butoxycarbonyl)amino)thiophene-3-carboxylate

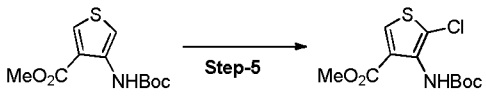


37 38

[657] To a solution of methyl 4-aminothiophene-3-carboxylate **37** (6.57 g, 41.8 mmol, 1.0 eq.) in 1,4-dioxane (25 mL) at 0 °C was added 5% aqueous Na_2CO_3 solution, followed by a solution of di-tert-butyl dicarbonate (18.26 g, 83.7 mmol, 2.0 eq.) in dioxane (25 mL). The cold bath was removed and the reaction mixture was allowed to room temperature and stirred for 24 hours, then diluted with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue obtained was purified using column chromatography to provide methyl 4-((tert-butoxycarbonyl)amino)thiophene-3-carboxylate **38** (6.45 g, 60% yield).

[658] ^{1}H NMR (400 MHz, DMSO-d6): δ 9.06 (s, 1H), 8.34 (d, *J*= 3.6 Hz, 1H), 7.58 (s, 1H), 3.83 (s, 3H), 1.47 (s, 9H).

Step-5: methyl 4-((tert-butoxycarbonyl)amino)-5-chlorothiophene-3-carboxylate



38 39

[659] To a solution of methyl 4-((tert-butoxycarbonyl)amino)thiophene-3-carboxylate **38** (16 g 62.2 mmol, 1.0 eq.) in glacial acetic acid (80 mL) was added N-chlorosuccinimide (8.3 g 62.2 mmol, 1.0 eq.) and the resultant reaction mixture was stirred at 50 °C for 45 minutes. Acetic acid was distilled under reduced pressure and the residue obtained was treated with water. The mixture was made alkaline with sodium hydroxide solution and then extracted with ethyl acetate. Organic extracts were combined, washed with water, dried over Na_2SO_4, concentrated and purified by column chromatography to offered methyl 4-((tert-butoxycarbonyl)amino)-5-chlorothiophene-3-carboxylate **39** (14.4 g, 80% yield) as colourless liquid.

[660] ^{1}H NMR (300 MHz, DMSO-d6): δ 8.78 (s, 1H), 8.13 (s, 1H), 3.73 (s, 3H), 1.41 (s, 9H). LCMS: *m/z*: 192.16 $[M-100]^+$, 99.40% (3.71 min).

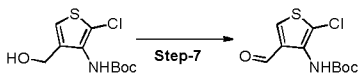
Step-6: tert-butyl (2-chloro-4-(hydroxymethyl)thiophen-3-yl)carbamate

39 40

[661] 1M DIBAL in toluene (51.4 ml, 51.4 mmol, 3.0 eq.) was added slowly to the solution of methyl 4-((tert-butoxycarbonyl) amino)-5-chlorothiophene-3-carboxylate **39** (5 g, 17.14 mmol, 1.0 eq.) in DCM at 0 °C and the reaction mixture was stirred at room temperature for 4h. The reaction mixture was diluted with 2N NaOH solution and extracted with DCM. The combined organic layers were concentrated and purified by column chromatography to give tert-butyl (2-chloro-4-(hydroxymethyl)thiophen-3-yl)carbamate **40** (4 g, 88% yield).

[662] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (s, 1H), 6.18 (s, 1H), 4.43 (s, 2H), 1.51 (s, 9H). LCMS: *m/z*: 190.13 $[M-56-18]^+$, (3.14 min).

Step-7: tert-butyl (2-chloro-4-formylthiophen-3-yl)carbamate

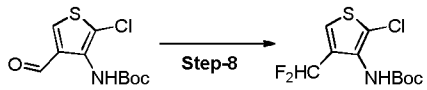


40 41

[663] MnO_2 (3.69 g, 42.4 mmol, 8.0 eq.) was added to a solution of tert-butyl (2-chloro-4-(hydroxymethyl) thiophen-3-yl)carbamate **40** (1.4 g, 5.3 mmol, 1.0 eq.) in ACN. The reaction mixture was stirred at rt for 24 h, after complete disappearance of starting material by TLC, the reaction mixture was then filtered and the filtrate was distilled under reduced pressure to obtain tert-butyl (2-chloro-4-formyl thiophen-3-yl)carbamate **41** (1.32 g, 95% yield) as colorless liquid.

[664] LCMS: m/z: 162.06 $[M+H-100]^+$, 96.53 % (3.45 min).

Step-8: tert-butyl (2-chloro-4-(difluoromethyl)thiophen-3-yl)carbamate

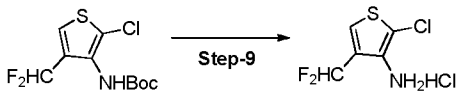


41 42

[665] Diethylaminosulfur trifluoride (0.9 ml, 6.88 mmol, 2.0 eq.) was added dropwise into a round-bottom flask under an inert atmosphere containing tert-butyl (2-chloro-4-formyl thiophen-3-yl)carbamate **41** (0.9 g, 3.44 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C. The mixture was stirred for 3 h at ambient temperature and then cooled to 0 °C, before adding a saturated aqueous sodium bicarbonate solution until the neutral state was reached. The mixture was then extracted with dichloromethane. The organic phase was distilled under low pressure and the obtained residue was purified by column chromatography that offered the tert-butyl (2-chloro-4-(difluoromethyl) thiophen-3-yl)carbamate **42** (432 mg, 44% yield) as a colorless liquid.

[666] ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 1H), 6.78 (t, J = 56.4 Hz 1H), 6.14 (bs, 1H), 1.41 (s, 9H). LCMS: *m/z*: 282.13 $[M-H]^+$, 82.84 % (3.87 min).

Step-9: 2-chloro-4-(difluoromethyl)thiophen-3-amine hydrochloride

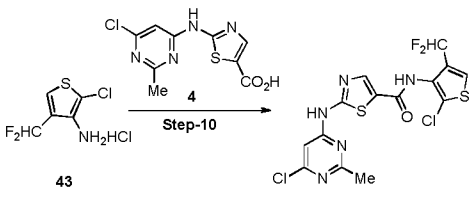


42 43

[667] To a solution of tert-butyl (2-chloro-4-(difluoromethyl)thiophen-3-yl)carbamate **42** (284 mg, 1.0 mmol, 1.0 eq.) in anhydrous dioxane (1.0 mL) was added 4.0 N HCl in dioxane (2.5 mL, 10.0 mmol, 10.0 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. Solid precipitated was filtered and washed with hexane to afford 2-chloro-4-(difluoromethyl)thiophen-3-amine hydrochloride as white solid **43** (165 mg, 75 %) as an off-white solid.

[668] LCMS: *m/z*: 164.16 $[M-19]^+$, 95.36 % (2.88 min).

Step-10: 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)thiazole-5-carboxamide



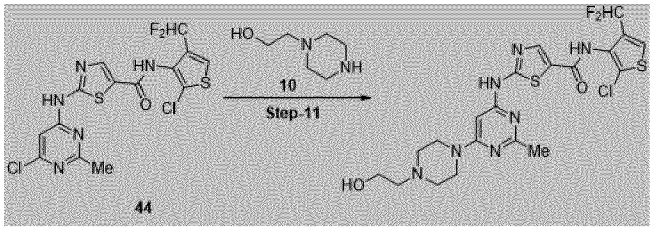
43 44

[669] To a suspension of 2-chloro-4-(difluoromethyl)thiophen-3-amine hydrochloride **43** (106 mg, 0.48 mmol, 1.0 eq.) and 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid **4** (170 mg, 0.63 mmol, 1.3 equiv) in acetonitrile (3 mL) was added DIPEA (217 mg 1.68 mmol, 3.5 eq.) and TCFH (154 mg, 0.55 mmol, 1.15 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hr. Reaction

was monitored by LCMS. The reaction mixture was concentrated under vacuum and obtained residue was passed through column to afford crude 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(difluoromethyl) thiophen-3-yl)thiazole-5-carboxamide **44** (225 mg, purity ca. 74 %) as a yellow solid.

[670] LC-MS: *m/z*: 436.05 $[M+H]^+$, (3.46 min).

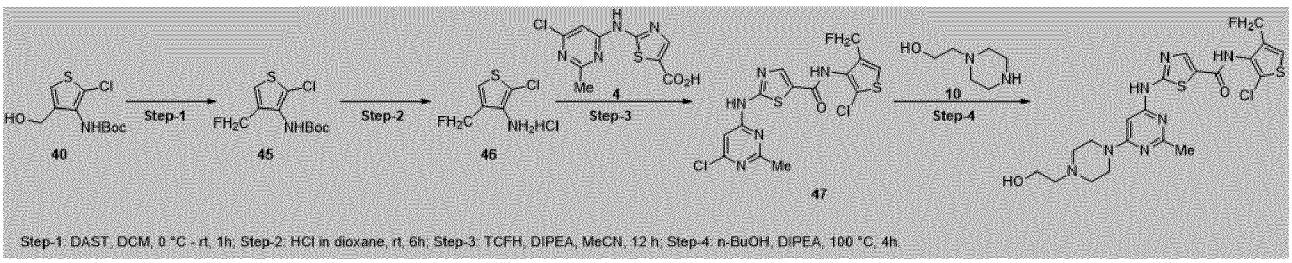
*Step-11: N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E4**)*



[671] 2-(piperazin-1-yl)ethanol **10** (329 mg, 2.53 mmol, 5.0 eq.) and DIPEA (26 mg, 0.20 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)thiazole-5-carboxamide **44** (225 mg, 0.51 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E4**, Figure 1E) (51 mg, 20% yield over two steps) as a white solid. Analytical data for this synthesised compound **E4** is shown in Table 1.1.

Compound E3:

*Synthesis of N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E3**)*

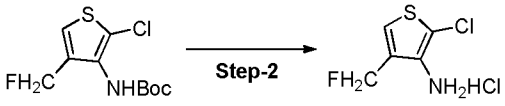


Step-1: tert-butyl (2-chloro-4-(fluoromethyl)thiophen-3-yl)carbamate

[672] Diethylaminosulfur trifluoride (DAST) (0.9 ml, 6.82 mmol, 2.0 eq.) was added drop-wise to the solution of tert-butyl (2-chloro-4-(hydroxymethyl)thiophen-3-yl)carbamate **40** (0.9 g, 3.41 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C . The reaction mixture was stirred for 3 h at ambient temperature and then cooled to 0°C, before adding a saturated aqueous sodium bicarbonate solution until the neutral state was reached. The mixture was then extracted with dichloromethane. The organic phase was distilled under low pressure and the obtained residue was purified by column chromatography that offered the tert-butyl (2-chloro-4-(fluoromethyl)thiophen-3-yl)carbamate **45** (408 mg, 45% yield) as a colorless liquid.

[673] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, *J* = 2.7 Hz, 1H), 6.09 (bs, 1H), 5.27 (d, *J* = 47.7 Hz, 2H), 1.49 (s, 9H). LCMS: *m/z*: 264.19 $[M+H]^+$, 98.14% (3.75 min).

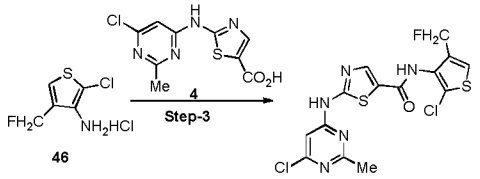
Step-2: 2-chloro-4-(fluoromethyl)thiophen-3-amine hydrochloride



45 46

[674] To a solution of tert-butyl (2-chloro-4-(fluoromethyl)thiophen-3-yl)carbamate **45** (266 mg, 1.0 mmol, 1.0 eq.) in anhydrous dioxane (1.0 mL) was added 4.0 N HCl in dioxane (2.5 mL, 10.0 mmol, 10.0 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. Solid precipitated was filtered and washed with hexane to afford 2-chloro-4-(fluoromethyl)thiophen-3-amine hydrochloride **46** (157 mg, 78 %) as an off-white solid.

Step-3: 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl)thiophen-3-yl) thiazole-5-carboxamide

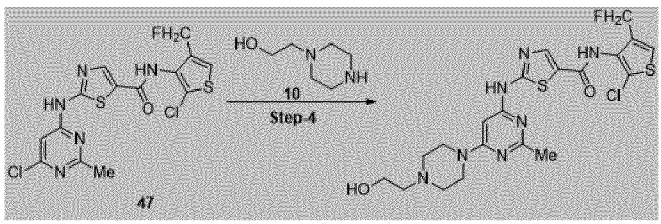


46 47

[675] To a suspension of 2-chloro-4-(fluoromethyl)thiophen-3-amine hydrochloride **46** (100 mg, 0.49 mmol, 1.0 eq.) and 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid **4** (173 mg, 0.64 mmol, 1.3 equiv) in acetonitrile (3 mL) was added DIPEA (224 mg 1.73 mmol, 3.5 eq.) and TCFH (160 mg, 0.57 mmol, 1.15 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hr. Reaction was monitored by LCMS. The reaction mixture was concentrated under vacuum and obtained residue was passed through column to afford crude 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl) thiophen-3-yl) thiazole-5-carboxamide **47** (220 mg, purity ca. 72 %) as a yellow solid.

[676] LCMS: *m/z*: 418.07 $[M+H]^+$, (3.33 min).

*Step-4: N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E3**)*

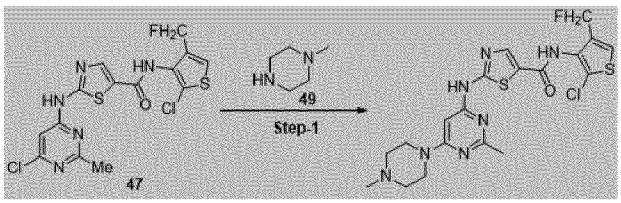


47

[677] 2-(piperazin-1-yl)ethanol **10** (343 mg, 2.63 mmol, 5.0 eq.) and DIPEA (27 mg, 0.21 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl)thiophen-3-yl) thiazole-5-carboxamide **47** (220 mg, 0.52 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl) amino)thiazole-5-carboxamide (**E3**, Figure 1E). (55 mg, 22% yield over two steps) as a white solid. Analytical data for this synthesised compound **E3** is shown in Table 1.1.

Compound E9:

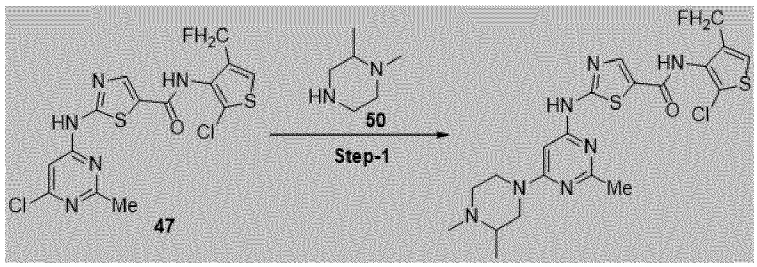
*Synthesis of N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E9**)*



[678] 1-methylpiperazine **49** (263 mg, 2.63 mmol, 5.0 eq.) and DIPEA (27 mg, 0.21 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl)thiophen-3-yl) thiazole-5-carboxamide **47** (220 mg, 0.52 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino) thiazole-5-carboxamide (**E9**, Figure 1E) (55 mg) as a white solid. Analytical data for this synthesised compound **E9** is shown in Table 1.1.

Compound E10 (racemic):

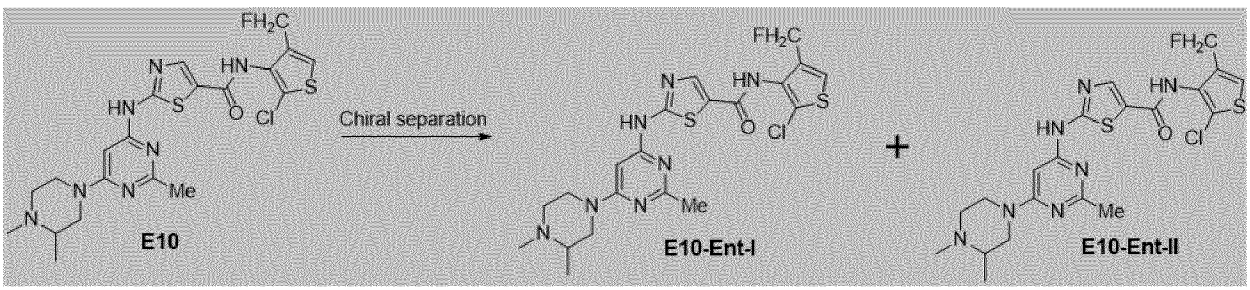
*Synthesis of N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E10**)*



[679] 1,2-dimethylpiperazine **50** (300 mg, 2.63 mmol, 5.0 eq.) and DIPEA (27 mg, 0.21 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl)thiophen-3-yl) thiazole-5-carboxamide **47** (220 mg, 0.52 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methylpyrimidin-4-yl)amino) thiazole-5-carboxamide (**E10**, Figure 1E) (50 mg) as a white solid. Analytical data for this synthesised compound **E10** is shown in Table 1.1.

Enantiomers of compound E10:

*Chiral separation of N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E10**)*



[680] *Analytical Chiral HPLC method of racemic **E10**:*

Column: CHIRAL PAK IG, 250 x 4.6 mm, 20 µm

Mobile phase: n-Hexane:DCM:MtOH:IPAm (35:60:5:0.10)

Flow rate: 2.0 mL/min.

Column Temp: 40 °C

Retention time: 5.067 min and 6.445 min

[681] *Analytical details of racemic **E10***:

LCMS: *m/z*: 496.24 $[M+H]^+$, 97.75% (13.73 min).

Column: LUNA 5µ C18 (4.6 x 100 mm),

Mobile Phase: A-0.1% NH3 solution in water; B-ACN, (T/%B: 0.01/10,2/10, 20/90, 30/90),

Flow Rate: 0.8 mL/min.

^{1}H NMR (400 MHz, DMSO-d6): δ 11.62 (s, 1H), 9.99 (s, 1H), 8.24 (s, 1H), 7.67 (d, J = 2.8 Hz, 1H), 6.15 (s, 1H), 5.25 (d, J = 47.6 Hz, 2H), 4.34 (bs, 2H), 3.08 (bs, 2H), 2.80 (bs, 2H), 2.45 (s, 6H), 1.34 (bs, 3H).

[682] *Chiral Prep-HPLC method of racemic **E10***:

Column: CHIRAL PAK IG, 250 x 50 mm, 20 µm

Mobile phase: n-Hexane:DCM:MtOH:IPAm (35:60:5:0.10)

Flow rate: 50 mL/min

[683] *Chiral HPLC of **E10**-Enatiomer-I (1st eluted enantiomer)*:

Column: CHIRAL PAK IG, 250 x 4.6 mm, 20 µm

Mobile phase: n-Hexane:DCM:MtOH:IPAm (35:60:5:0.10)

Flow rate: 2.0 mL/min.

Column Temp: 40 °C

Retention time: 5.067 min

Chiral Purity: 98.77%

[684] *Analytical details of **E10**-Enatiomer-I (1st eluted enantiomer)*:

LCMS: *m/z*: 496.28 $[M+H]^+$, 99.53% (8.08 min).

Column: LUNA 5µ C18 (4.6 x 100 mm),

Mobile Phase: A-0.1% FA in water; B-ACN,

(T/%B: 0.01/10,2/10, 20/90, 30/90),

Flow Rate: 0.8 mL/min

^{1}H NMR (400 MHz, DMSO-d6): δ 11.46 (s, 1H), 9.95 (s, 1H), 8.21 (s, 1H), 7.67 (d, J = 3.2 Hz, 1H), 6.06 (s, 1H), 5.25 (d, J = 47.6 Hz, 2H), 4.01 (m, 2H), 3.01 (bs, 1H), 2.82 (bs, 1H), 2.67 – 2.64 (m, 1H), 2.41 (s, 3H), 2.22 (bs, 3H), 2.1- 2.07 (m, 2H), 1.05 (d, J = 4Hz, 3H).

[685] *Chiral HPLC of **E10**-Enatiomer-II (2nd eluted enantiomer)*:

Column: CHIRAL PAK IG, 250 x 4.6 mm, 20 µm

Mobile phase: n-Hexane:DCM:MtOH:IPAm (35:60:5:0.10)

Flow rate: 2.0 mL/min.

Column Temp: 40 °C

Retention time: 6.445 min

Chiral Purity: 99.70%

[686] *Analytical details of **E10**-Enatiomer-II (2nd eluted enantiomer)*:

LCMS: *m/z*: 496.24 $[M+H]^+$, 99.62% (8.10 min).

Column: LUNA 5µ C18 (4.6 x 100 mm),

Mobile Phase: A-0.1% FA in water; B-ACN, (T/%B: 0.01/10,2/10, 20/90, 30/90),

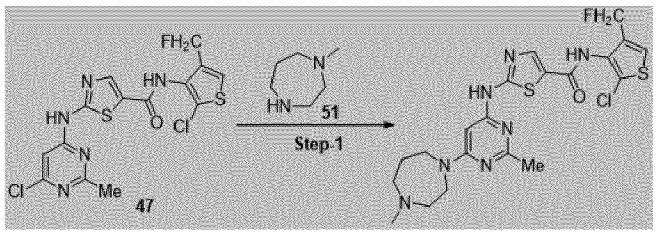
Flow Rate: 0.8 mL/min

^{1}H NMR (400 MHz, DMSO-d6): δ 11.46 (s, 1H), 9.94 (s, 1H), 8.21 (s, 1H), 7.67 (d, J = 2.8 Hz, 1H), 6.06 (s, 1H), 5.25 (d, J = 48 Hz, 2H), 4.02 (bs, 2H), 3.02 (bs, 1H), 2.82 (bs, 1H), 2.66 – 2.64 (m, 1H), 2.41 (s, 3H), 2.22 (bs, 3H), 2.1- 2.07 (m, 2H), 1.06 (s, 3H).

[687] Analytical data for these isolated enantiomers of compound **E10** is shown in Table 1.1.

Compound E11:

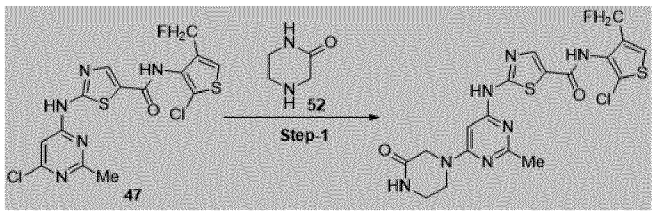
*Synthesis of N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E11**)*



[688] 1-methyl-1,4-diazepane **51** (300 mg, 2.63 mmol, 5.0 eq.) and DIPEA (27 mg, 0.21 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl)thiophen-3-yl) thiazole-5-carboxamide **47** (220 mg, 0.52 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E11**, Figure 1E) (54 mg) as a white solid. Analytical data for this synthesised compound **E11** is shown in Table 1.1.

Compound E12:

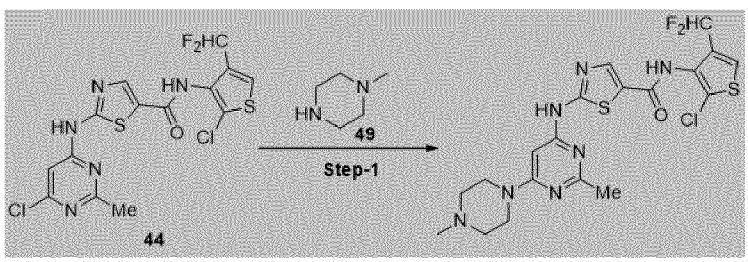
*Synthesis of N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(3-oxopiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E12**)*



[689] piperazin-2-one **52** (263 mg, 2.63 mmol, 5.0 eq.) and DIPEA (27 mg, 0.21 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(fluoromethyl)thiophen-3-yl) thiazole-5-carboxamide **10** (220 mg, 0.52 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield N-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(3-oxopiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E12**, Figure 1E) (50 mg) as a white solid. Analytical data for this synthesised compound **E12** is shown in Table 1.1.

Compound E13:

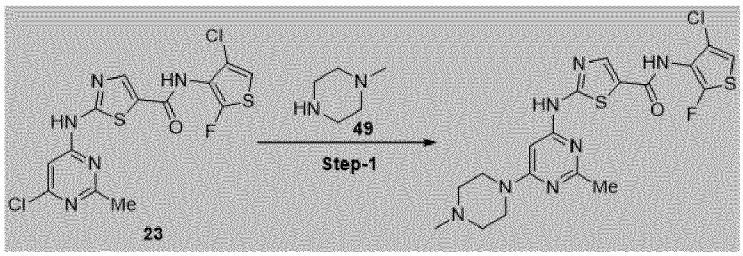
*Synthesis of N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E13**)*



[690] 1-methylpiperazine **49** (253 mg, 2.53 mmol, 5.0 eq.) and DIPEA (26 mg, 0.20 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)thiazole-5-carboxamide **44** (225 mg, 0.51 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield 50 mg of N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E13**, Figure 1E) as a white solid. Analytical data for this synthesised compound **E13** is shown in Table 1.1.

Compound E15:

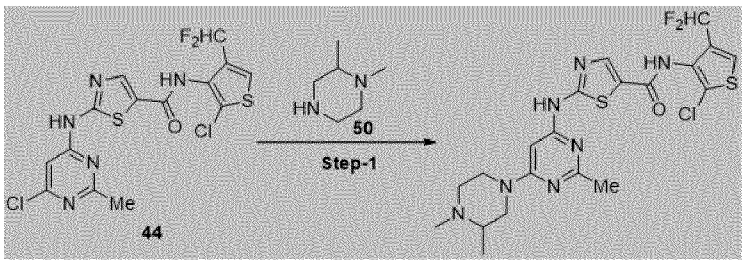
*Synthesis of N-(4-chloro-2-fluorothiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl) pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E15**)*



[691] 1-methylpiperazine **49** (284 mg, 2.84 mmol, 5.0 eq.) and DIPEA (30 mg, 0.23 mmol, 0.4 eq.) were added to the well stirred solution of N-(4-chloro-2-fluorothiophen-3-yl)-2-((6-chloro-2-methyl pyrimidin-4-yl)amino)thiazole-5-carboxamide **23** (230 mg, 0.57 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield 60 mg of N-(4-chloro-2-fluorothiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl) pyrimidin-4-yl)amino)thiazole-5-carboxamide (**E15**, Figure 1E) as a white solid. Analytical data for this synthesised compound **E15** is shown in Table 1.1.

Compound E16:

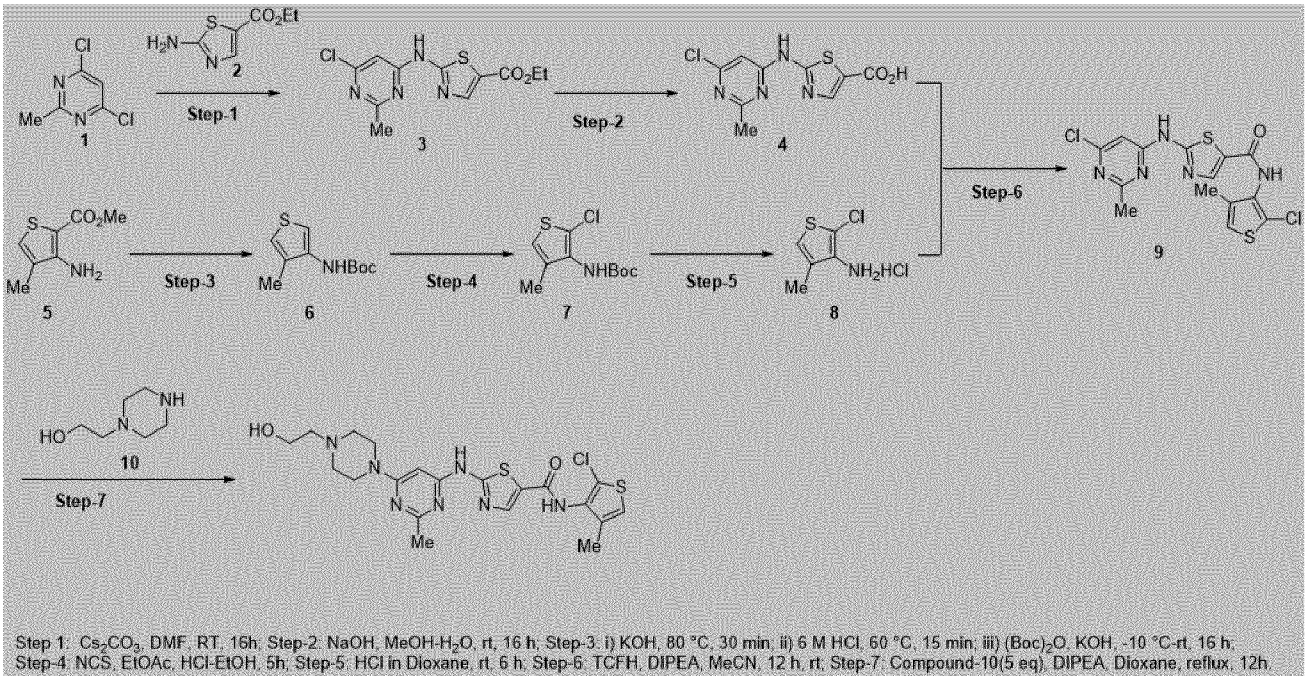
*Synthesis of N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E16**)*



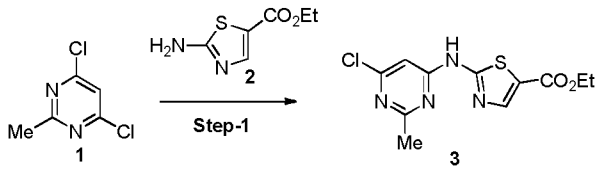
[692] 1,2-dimethylpiperazine **50** (291 mg, 2.55 mmol, 5.0 eq.) and DIPEA (26 mg, 0.20 mmol, 0.4 eq.) were added to a well stirred solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)thiazole-5-carboxamide **44** (225 mg, 0.51 mmol, 1.0 eq.) in n-BuOH. The reaction temperature was then raised to 100 °C for 3h. The reaction mixture was concentrated under vacuum and the obtained residue was purified by RP C18 to yield 40 mg of N-(2-chloro-4-(difluoromethyl)thiophen-3-yl)-2-((6-(3,4-dimethylpiperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**E16**, Figure 1E) as a white solid. Analytical data for this synthesised compound **E16** is shown in Table 1.1.

Compound C7:

*N-(2-chloro-4-methylthiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (**C7**)*



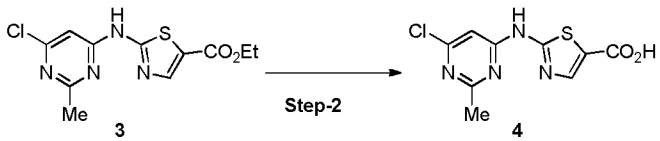
*Step-1: ethyl 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylate (**3**)*



[693] To a solution of 4,6-dichloro-2-methylpyrimidine **1** (10 g, 61.4 mmol, 1.0 eq.) and ethyl 2-aminothiazole-5-carboxylate **2** (10.6 g, 61.4 mmol, 1.0 eq.) in DMF (210 ml) at 0°C under inert atmosphere was added 60% sodium hydride (4.9 g, 122.8 mmol, 2.0 eq.) in portions and the reaction mixture was slowly warmed to room temperature and stirred for 3 days. Excess of NaH was quenched by the addition of saturated ammonium chloride solution and the reaction mixture was diluted with water (3000 ml) and stirred for 1h at room temperature. Obtained precipitate was filtered off and air dried to get ethyl 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylate **3** (18 g, 98% yield) as a beige solid.

[694] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 – 1.51 (t, 3H), 2.75 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.73 (s, 1H), 8.14 (s, 1H). LCMS: m/z = 299.17 $[M+H]^+$, (3.45 min).

*Step-2: 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid (**4**)*



[695] To a suspension of ethyl 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylate **3** (36.0 g, 120.5 mmol, 1.0 eq.) in methanol (350 ml) and water (150 ml) was added sodium hydroxide (38.6 g, 964 mmol, 8.0 eq.) at room temperature and the mixture was stirred for 16hrs. LCMS analysis showed complete conversion of starting material to product. The reaction mixture was concentrated to remove most of the solvent and then the aqueous layer was acidified using 6M aqueous HCl. The obtained precipitate was filtered off, washed with water and dried under high vacuum for 3 days to afford 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid **4** (27.0 g, 83 % yield) as a beige colored powder.

[696] ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.57 (s, 3H), 6.93 (s, 1H), 8.04 (s, 1H), 12.46 (bs. 1H). LCMS: m/z = 271.05 $[M+H]^+$, 99.19 % (2.51 min).

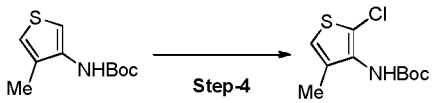
*Step-3: tert-butyl (4-methylthiophen-3-yl)carbamate (**6**)*

5 6

[697] To a solution of methyl 3-amino-4-methylthiophene-2-carboxylate **5** (1.71 g, 10.0 mmol, 1.0 eq.) in H_2O (5.1 mL) was added KOH solution (45 %, 1.75 mL, 14.0 mmol, 1.4 eq.) at room temperature. The reaction mixture was stirred at 80 °C for 30 min and afterwards cooled to room temperature. This solution was slowly added to a 6 M HCl solution (5.50 mL, 33.0 mmol, 3.3 eq.) at 50 °C and the resultant reaction mixture was stirred at 60 °C for 15 min (gas evolution, clear solution was obtained). The reaction was diluted with hexane (3.5 mL) and cooled to -10 °C, KOH solution (45 %, 3.4 mL, 27.0 mmol, 2.7 eq.) and di-*tert*-butyl dicarbonate (2.40 mL, 10.5 mmol, 1.05 eq.) were added and stirred overnight at this temperature. The reaction mixture was warmed to room temperature and was extracted with EtOAc. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated to obtain *tert*-butyl (4-methylthiophen-3-yl)carbamate **6** (2.32 g, quantitative yield) as an orange solid and used without further purification.

[698] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (s, 1H), 6.86 (dq, *J* = 3.3 Hz, *J* = 1.1 Hz, 1H), 6.36 (s, 1H), 2.14 (d, *J* = 1.1 Hz, 3H), 1.53 (s, 9H). LCMS: m/z = 158.16 $[M+H-56]^+$, 97.82 % (3.85 min).

*Step-4: tert-butyl (2-chloro-4-methylthiophen-3-yl)carbamate (**7**)*

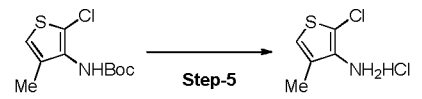


6 7

[699] To a solution of (4-methyl-thiophen-3-yl)carbamic acid *tert*-butyl ester **6** (1.07 g, 5.00 mmol, 1.0 eq.) in anhydrous EtOAc (8 mL) was added NCS (0.70 g, 5.25 mmol, 1.05 eq.) and a hydrochloric acid solution in EtOH (1.25 N, 200 µL, 0.25 mmol, 0.05 eq) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 5h and quenched by the addition of 1.0 N sodium hydroxide solution (5.50 mL, 5.50 mmol, 1.1 eq) and sodium hydrogensulfite (40 %, 0.065 mL, 0.25 mmol, 0.05 eq). The lower aqueous layer was discarded. The organic phase was washed with water (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to obtain *tert*-butyl (2-chloro-4-methylthiophen-3-yl)carbamate **7** (734 mg, 2.96 mmol, 59 %) as an orange solid.

[700] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.71 (s, 1H), 5.83 (s, 1H), 2.14 (s, 3H), 1.49 (s, 9H). LCMS: m/z = 233.11 $[M+H-56]^+$, 98.14 % (3.88 min).

*Step-5: 2-chloro-4-methylthiophen-3-amine hydrochloride (**8**)*

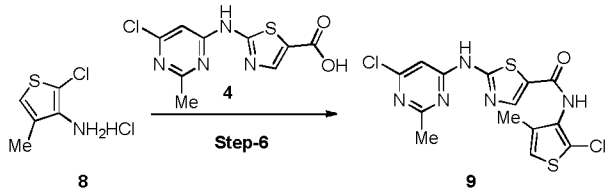


7 8

[701] To a solution of *tert*-butyl (2-chloro-4-methylthiophen-3-yl)carbamate **7** (567 mg, 2.29 mmol, 1.0 eq.) in anhydrous dioxane (2.0 mL) was added 4.0 N HCl in dioxane (5.70 mL, 22.9 mmol, 10.0 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. Solid precipitated was filtered and washed with hexane to afford 2-chloro-4-methylthiophen-3-amine hydrochloride **8** (360 mg, 86 %) as an off-white solid.

[702] ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.06 (s, 1H), 5.54 (s, 3H), 2.14 (d, *J* = 1.2 Hz, 3H). LCMS: m/z = 148.18 $[M+H]^+$, (3.18 min).

*Step-6: 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-methylthiophen-3-yl)thiazole-5-carboxamide (**9**)*

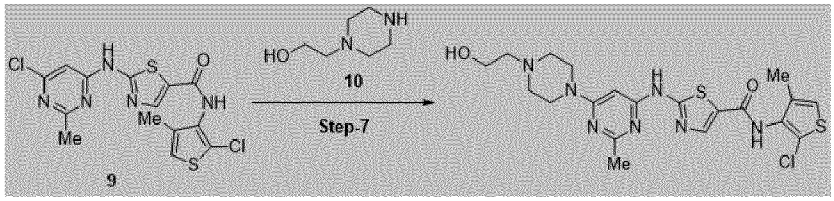


8 9

[703] To a suspension of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid **4** (367 mg, 1.36 mmol, 1.0 eq.) and 2-chloro-4-methylthiophen-3-amine hydrochloride **8** (275 mg, 1.5 mmol, 1.1 eq.) in acetonitrile (0.2 M) was added DIPEA (703 mg, 5.44 mmol, 4.0 eq.) and TCFH (457 mg, 1.63 mmol, 1.2 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. Acetonitrile was removed under vacuum and then reaction was poured into water. The resulting precipitate was filtered off, washed with water, air-dried to afford 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-4-methylthiophen-3-yl)thiazole-5-carboxamide **9** as a yellow powder, which was directly used in the next step without further purification (462 mg, purity ca. 70%).

[704] LCMS: m/z = 400.05 $[M+H]^+$, (3.41 min).

*Step-7: N-(2-chloro-4-methylthiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methyl pyrimidin-4-yl)amino)thiazole-5-carboxamide (**C7**)*



[705] To a suspension of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-4-methylthiophen-3-yl)thiazole-5-carboxamide **9** (230 mg, 0.575 mmol, 1.0 eq.) in *n*-butanol (2 ml) was added 2-(piperazin-1-yl)ethan-1-ol **10** (374 mg, 2.87 mmol, 5.0 eq.) and DIPEA (30 mg, 0.23 mmol, 0.4 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed for 12 h. After cooling to room temperature, the reaction mixture was poured in water and stirred for 30 min. The resulting precipitate was filtered off, washed with water, passed through column and trituration in Et_2O afforded N-(2-chloro-4-methylthiophen-3-yl)-2-((6-(4-(2-hydroxyethyl) piperazin-1-yl)-2-methyl pyrimidin-4-yl)amino)thiazole-5-carboxamide (**C7**, Figure 1C) as an off-white solid (92 mg, 33 % yield over 2 steps).

[706] Those compounds synthesised from **E1** to **E16** and compound **C7** were characterised as set forth below in Table 1.1.

Table 1.1: Synthesis of compounds of formula (Ia) and compound C7.

Compound Number	Mol. Wt. LCMS: m/z $[M+H]^+$	^1H NMR
E2	498.20 95.91% (7.49 min)	^1H NMR (400 MHz, DMSO-d_6): δ 11.51 (s, 1H), 9.92 (s, 1H), 8.19 (s, 1H), 7.22 (d, J = 4.8 Hz, 1H), 6.05 (s, 1H), 4.46 (t, J = 5.1 Hz, 1H), 3.53 – 3.50 (m, 6H), 2.43-2.40 (m, 9H).
E3	512.11 [96.70% (9.95 min)	^1H NMR (300 MHz, DMSO-d6): δ 11.49 (bs, 1H), 9.94 (s, 1H), 8.21 (s, 1H), 7.67 (d, J = 3 Hz, 1H), 6.04 (s, 1H), 5.25(d, J = 47.7 Hz, 2H), 4.40(t, J = 5.1 Hz, 1H), 3.53-3.50 (m, 6H), 2.44-2.40 (m, 9H).

E4	530.09 96.90% (8.26 min)	^{1}H NMR (300 MHz, DMSO-d6): δ 11.49 (bs, 1H), 10.0 (s, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 6.84 (t, J = 55.2 Hz, 1H), 6.05 (s, 1H), 4.42(bs, 1H), 3.51-3.53 (m, 6H), 2.40-2.44 (m, 9H).
E5	548.28 98.14% (2.96 min)	^{1}H NMR (300 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.93 (s, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 6.04 (s, 1H), 4.43 (bs, 1H), 3.53 – 3.50 (m, 6H), 2.43-2.40 (m, 9H).
E9	482.18 99.57% (4.25 min)	^{1}H NMR (300 MHz, DMSO-d6): δ 11.49 (s, 1H), 9.94 (s, 1H), 8.21 (s, 1H), 7.67 (d, J = 3.3 Hz, 1H), 6.05 (s, 1H), 5.25(d, J = 47.7 Hz, 2H), 3.51 (bs, 4H), 2.41 (s, 3H), 2.37 (bs, 4H), 2.21 (s, 3H).
E10	496.16 97.22% (15.70 min)	^{1}H NMR (300 MHz, DMSO-d6): δ 11.52 (s, 1H), 9.95 (s, 1H), 8.21 (s, 1H), 7.67 (s, 1H), 6.09 (s, 1H), 5.22 (d, J = 47.7 Hz, 2H), 4.10 (m, 2H), 3.09 (m, 2H), 2.80 – 2.73 (m, 1H), 2.50 (m, 2H), 2.40 (s, 6H), 1.13 (s, 3H).
E10 (Ent-I)	496.28 99.53% (8.08 min)	^{1}H NMR (400 MHz, DMSO-d6): δ 11.46 (s, 1H), 9.95 (s, 1H), 8.21 (s, 1H), 7.67 (d, J = 3.2 Hz, 1H), 6.06 (s, 1H), 5.25 (d, J = 47.6 Hz, 2H), 4.01 (m, 2H), 3.01 (bs, 1H), 2.82 (bs, 1H), 2.67 – 2.64 (m, 1H), 2.41 (s, 3H), 2.22 (bs, 3H), 2.1- 2.07 (m, 2H), 1.05 (d, J = 4Hz, 3H).
E10 (Ent-II)	496.24 99.62% (8.10 min)	^{1}H NMR (400 MHz, DMSO-d6): δ 11.46 (s, 1H), 9.94 (s, 1H), 8.21 (s, 1H), 7.67 (d, J = 2.8 Hz, 1H), 6.06 (s, 1H), 5.25 (d, J = 48 Hz, 2H), 4.02 (bs, 2H), 3.02 (bs, 1H), 2.82 (bs, 1H), 2.66 – 2.64 (m, 1H), 2.41 (s, 3H), 2.22 (bs, 3H), 2.1- 2.07 (m, 2H), 1.06 (s, 3H).
E11	496.20 96.73% (3.31 min)	^{1}H NMR (300 MHz, DMSO-d6): δ 11.40 (s, 1H), 9.93 (s, 1H), 8.20 (s, 1H), 7.67 (d, J = 3.3 Hz, 1H), 5.94 (s, 1H), 5.25 (d, J = 47.7 Hz, 2H), 3.72 – 3.44 (m, 4H), 2.26 – 2.55 (m, 4H), 2.39 (s, 3H), 2.25 (s, 3H), 1.90 (bs, 2H).
E12	482.14 96.26% (2.60 min)	^{1}H NMR (300 MHz, DMSO-d6): δ 11.55 (s, 1H), 9.96 (s, 1H), 8.21 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 3.3 Hz, 1H), 5.99 (s, 1H), 5.25 (d, J = 47.7 Hz, 2H), 3.98 (s, 2H), 3.51 (m, 2H), 2.43 (m, 5H).
E13	500.20 98.82% (14.03 min)	^{1}H NMR (300 MHz, DMSO-d6): δ 11.54 (s, 1H), 10.02 (s, 1H), 8.22 (s, 1H), 7.89 (s, 1H), 6.85 (t, J = 55.2 Hz, 1H), 6.01 (s, 1H), 3.51 (bs, 4H), 2.42 (s, 3H), 2.33 (bs, 4H).
E15	468.27 99.19 (13.26 min)	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.88 (s, 1H), 8.19 (s, 1H), 7.21 (d, J = 4.8 Hz, 1H), 6.05 (s, 1H), 3.52 (bs, 4H), 2.41 (s, 3H), 2.38 (bs, 4H), 2.22 (s, 3H).
E16	514.23 98.12% (16.34 min)	^{1}H NMR (400 MHz, DMSO-d6): δ 11.46 (s, 1H), 10.01 (s, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 6.85 (t, J = 55.6 Hz, 1H), 6.05 (s, 1H), 4.01 (d, J = 12.4 Hz, 2H), 3.00 (t, J = 11.6 Hz, 1H), 2.8 (d, J = 11.2 Hz, 1H), 2.6 (d, J = 10 Hz, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.13 – 2.00 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H).
C7	494.21 99.16% (12.62 min)	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 9.77 (s, 1H), 8.19 (s, 1H), 7.17 (s, 1H), 6.05 (s, 1H), 4.43 (s, 1H), 3.55 – 3.51 (m, 6H), 2.44-2.40 (m, 9H), 2.05 (s, 3H).

Example 1.2 [comparative]: Synthesis of the kinase inhibitors, including kinase inhibitors of formulae (Ib) and (Ic), and other compounds.

Synthesis of other compounds disclosed herein:

General methods and materials:

[707] MPLC purification was performed using a Biotage Isolera Four system, using KP-Sil cartridges with technical grade organic solvents, *i.e.* dichloromethane and methanol, 3-4 N NH_3 in MeOH. A gradient of DCM to 3 N NH_3 (in MeOH) from 0 % to 25 % over 10 CV was used for the purification of the final compounds.

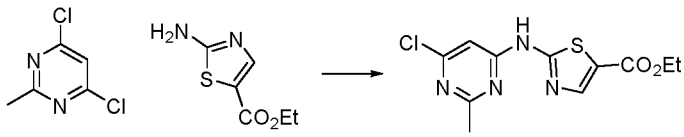
[708] ^1H NMR spectra were recorded on Bruker DPX 400 MHz spectrometers and are reported in ppm with the solvent resonance employed as the internal standard [$CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm]. Peaks are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad signal, coupling constant(s) in Hz, integration).

[709] Reverse phase HPLC was performed on a Shimadzu HPLC system using following system [solvent A: acetonitrile, solvent B: 0.1% formic acid in water]. Formic acid was used as HPLC grade. All the separations were performed at ambient temperatures. For analytical RP-HPLC analysis [Interchim: Uptisphere Strategy 100Å, 5 µm, 100x4.6 mm], the flow rate was 1.0 ml.min^{-1}; injection volume: 20 µL, detection wavelengths: 220 nm and 254 nm. The following gradient was used: 2.0 min 100 % B, over 8 min to 10 % B, 5 min 10 % B.

[710] LC-MS spectra were recorded on a Dionex Ultimate 3000 system using the following system [solvent A: acetonitrile, solvent B: 0.1% formic acid in water]. Formic acid was used as HPLC grade. All the separations were performed at ambient temperatures. For analytical RP-HPLC analysis [Interchim: Uptisphere Strategy C18, 2.6 µm, 50x4.6 mm], the flow rate was 1.0 ml.min^{-1}; detection wavelengths: 220 nm and 254 nm. The following gradient was used: 90 % B, over 5 min to 5 % B. The MS was recorded with the following settings: Dionex Surveyor MSQ plus, ESI+, Probe T(°C) 350, Cone 30 (v), Needle (KV) 3.0.

Procedures:

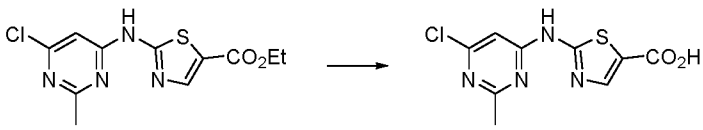
I. Ethyl 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylate:



[711] To a solution of 4,6-dichloro-2-methylpyrimidine (10 g, 61.4 mmol, 1.0 eq.) and ethyl 2-aminothiazole-5-carboxylate (10.6 g, 61.4 mmol, 1.0 eq.) in DMF (210 ml) at 0°C under inert atmosphere was added sodium hydride (5.40 g, 135 mmol, 2.0 eq.) in portions and the reaction mixture was slowly warmed to room temperature and stirred for 3d. Excess of the NaH was quenched by addition of saturated solution of ammonium chloride and the reaction mixture was poured on water (3000 ml) and stirred for 1h at room temperature. Obtained precipitate was filtered off and air dried to get ethyl 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylate (18 g, 60.0 mmol, 98 % yield) as a beige solid.

[712] ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 – 1.51 (t, 3H), 2.75 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.73 (s, 1H), 8.14 (s, 1H). LCMS: m/z = 297.1 [M-H]$^-$.

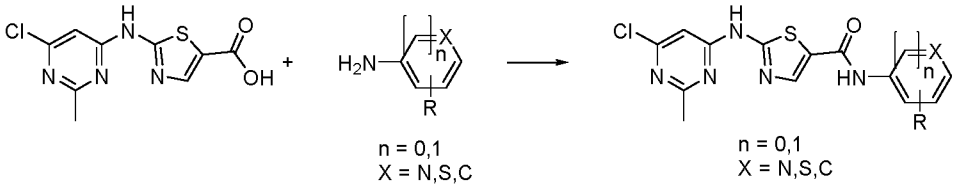
II. 2-((6-Chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid:



[713] To a suspension of ethyl 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylate (36.0 g, 121 mmol, 1.0 eq.) in methanol (350 ml) and water (150 ml) was added sodium hydroxide (38.6 g, 964 mmol, 8.0 eq.) at room temperature and the mixture was stirred at room temperature for 16hrs. LCMS analysis showed complete conversion of starting material to product. The reaction mixture was concentrated to remove most of the solvent and then the aqueous layer was acidified using 6 M aqueous HCl. The obtained precipitate was filtered off and washed with water, dried under high vacuum for 3 d to afford 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid (27.0 g, 99.7 mmol, 83 % yield) as a beige colored powder.

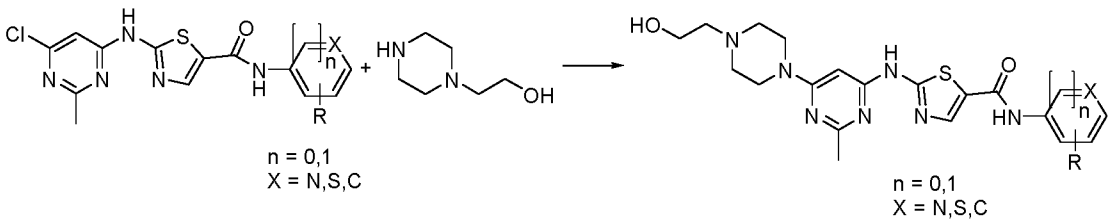
[714] ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.57 (s, 3H), 6.93 (s, 1H), 8.04 (s, 1H), 12.46 (bs. 1H). LCMS: m/z = 269.0 $[M-H]^-$.

General procedure A1 – GP A1 - amide formation:



[715] To a suspension of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxylic acid (1.0 equiv.) and aniline (1.1 equiv.) in acetonitrile (0.2 M) was added *N,N*-diisopropylethylamine (3.5 equiv.) and tetramethylchloroformamidinium hexafluorophosphate (1.2eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. Acetonitrile was removed under vacuum and then reaction was poured into water (100 mL/mmol). The resulting precipitate was filtered off, washed with water [5x], air-dried and dried under high vacuum to afford the respective amide as a yellow powder, which was directly used in the next step without further purification. All substances were confirmed by ^{1}H NMR analysis.

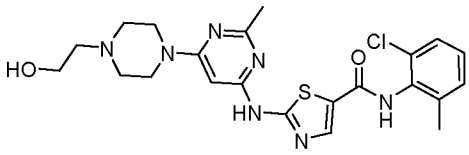
General procedure B - GP B:



[716] To a suspension of chloropyrimidine derivative (1.0 equiv.) in *n*-butanol (2 ml) was added 2-(piperazin-1-yl)ethan-1-ol (5.0 equiv.) and *N,N*-diisopropylethylamine (0.4 equiv.) at room temperature under a nitrogen atmosphere. The tube was sealed and irradiated under microwave conditions (Biotage Initiator$^+$) at 120°C for 30 min. After cooling to room temperature, the reaction mixture was poured in water (200 ml/mmol) and stirred for minimum 30 min. The resulting precipitate was filtered off, washed with water [5x], air-dried to afford to afford the respective target. If no or < 10 % precipitate resulted, the aqueous layer was extracted with DCM/IPA (2:1, 3*). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product or a crude product with a purity of < 95 % was purified by flash chromatography (Biotage cartridge, DCM 100 % 1 CV to 80 % DCM/3 N NH_3 in MeOH over 10 CV, 80 % DCM/3 N NH_3). For some substances with purities < 95 %, a trituration in Et_2O was done and all substances were dried under high vacuum (up to 65 °C, if necessary) until purities > 95 % was obtained, unless otherwise stated. All substances were confirmed by ^{1}H NMR and LC-MS analysis.

Compound A8:

N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

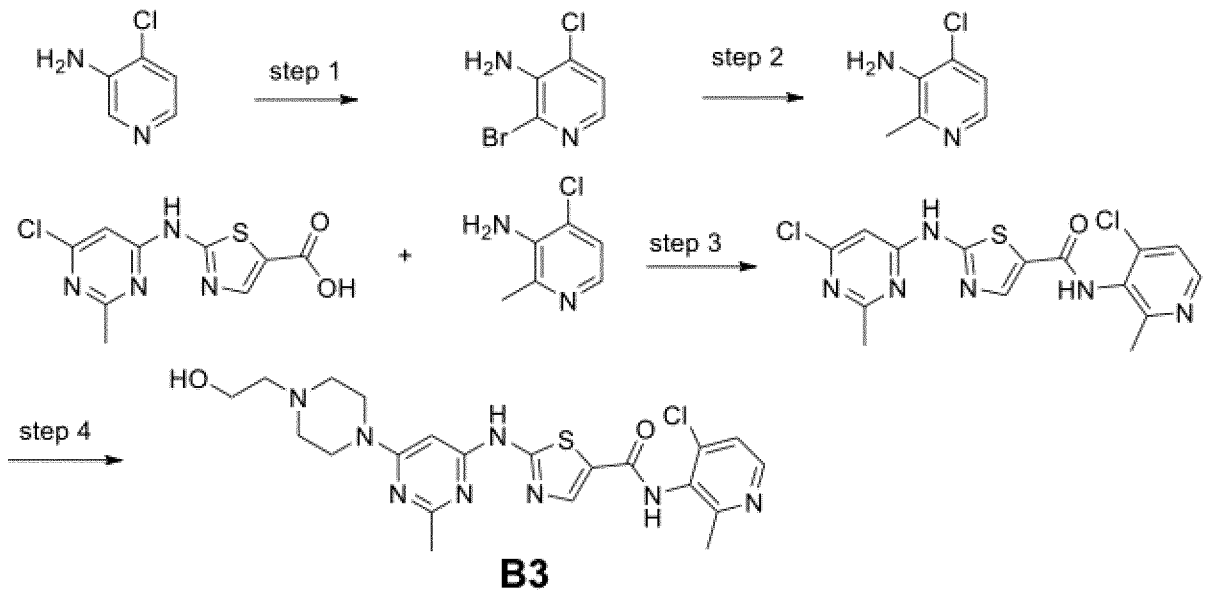


[717] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (750 mg, 2.77 mmol), 2-chloro-6-methylaniline (959 mg, 6.77 mmol), tetramethylchloroformamidinium hexafluorophosphate (959 mg, 3.42 mmol), *N,N*-diisopropylethylamine (1.25 g, 9.70 mmol) and acetonitrile (6.0 mL, 0.42 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (480 mg, 1.22 mmol) was obtained after precipitation from H_2O as a yellow solid and used without further purification in the next step.

[718] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (250 mg, 0.634 mmol), 2-(piperazin-1-yl)ethan-1-ol (413 mg, 3.17 mmol), *N,N*-diisopropylethylamine (33 mg, 0.25 mmol) and 1-butanol (2.0 mL, 0.3 M). **A8** (Figure 1A)

Compound B3:

N-(4-chloro-2-methylpyridin-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



Scheme 1: Synthesis of B3

[719] Step 1: 2-bromo-4-chloropyridin-3-amine (Compound **IaB3**):

[720] To a solution of 4-chloropyridin-3-amine (7.00 g, 54.0 mmol, 1.0 eq.) in anhydrous TFA (200 mL, 0.27 M) was added NBS (10.7 g, 60.1 mmol, 1.1 eq.) under a nitrogen atmosphere at room temperature. and the solution was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 2 N NaOH (200 mL). The aqueous layer was extracted with EtOAc (3* 200 mL). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (340 g biotage cartridge, cHex 100 % 1 CV to 40 % EtOAc over 10 CV, 2 CV 40 % EtOAc) affording 2-bromo-4-chloropyridin-3-amine (3.07 g, 14.8 mmol, 27 %) as a beige solid. **IaB3**

[721] R_f = 0.82 (cHex/EtOAc 1:1, UV 254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.70 (s, 2H), 7.35 (d, J = 5.0 Hz, 1H), 7.56 (d, J = 5.0 Hz, 1H).

[722] Step 2: 4-chloro-2-methylpyridin-3-amine (Compound **IbB3**):

[723] In a 10-mL microwave vial was a mixture of 2-bromo-4-chloropyridin-3-amine (200 mg, 0.96 mmol, 1.0 eq.), trimethylboroxine (141 µL, 1.01 mmol, 1.05 eq.), K_2CO_3 (466 mg, 3.37 mmol, 3.5 eq.) and PdCl2(dppf)-CH_2Cl_2 adduct (79 mg, 0.096 mmol, 0.1 eq.) in 1,4-dioxane:H2O (10:1, 3.3 mL, 0.28M) evacuated and back-filled with nitrogen three times and sealed with an aluminum/Teflon crimp top. The reaction mixture was then irradiated for 45 min at 120 °C. After completion of the reaction, the vial was cooled to room temperature and opened. The reaction mixture was diluted with EtOAc, silica was added (2 g) and the reaction mixture concentrated under reduced pressure. The crude product was purified by flash chromatography (25 g biotage cartridge 100 % cHex 1 CV to 100 % EtOAc over 10 CV, 5 CV 100 % EtOAc) affording 4-chloro-2-methylpyridin-3-amine (58 mg, 0.041 mmol, 42 %) as violet oil. **IbB3**.

[724] R_f = 0.24 (UV 254 nm, cHex/EtOAc 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 5.28 (s, 2H), 7.11 (d, J = 5.2 Hz, 1H), 7.61 (d, J = 5.2 Hz, 1H).

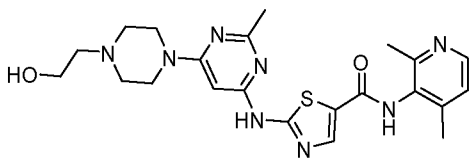
[725] Steps 3 and 4: *N*-(4-chloro-2-methylpyridin-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (Compound **B3**, Figure 1B):

[726] Step 3 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (530 mg, 1.96 mmol), 4-chloro-2-methylpyridin-3-amine (363 mg, 2.55 mmol), tetramethylchloroformamidinium hexafluorophosphate (659 mg, 2.35 mmol), *N,N*-diisopropylethylamine (886 mg, 6.85 mmol) and acetonitrile (5.8 mL, 0.3 M). *N*-(4-chloro-2-methylpyridin-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (Compound **IcB3**) (326 mg, 0.825 mmol) was obtained after precipitation from H_2O as a yellow solid and used without further purification in the next step. **IcB3**

[727] Step 4 was run according to GP B using *N*-(4-chloro-2-methylpyridin-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (320 mg, 0.810 mmol), 2-(piperazin-1-yl)ethan-1-ol (527 mg, 4.05 mmol), *N,N*-diisopropylethylamine (42 mg, 0.32 mmol) and 1-butanol (2.5 mL, 0.3 M). **B3** (90 mg, 0.18 mmol, 10 % yield over 2 steps) was obtained as a white solid after extraction with EtOAc, flash purification (100 % DCM to 85 % DCM/3 N NH_3 in MeOH over 10 CV) and trituration in Et_2O.

Compound C1:

N-(2,4-dimethylpyridin-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



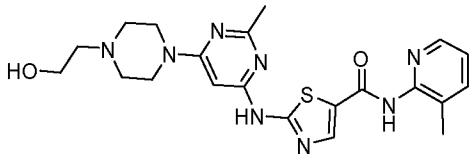
[728] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (266 mg, 0.982 mmol), 2,4-dimethylpyridin-3-amine (120 mg, 0.982 mmol, 1.0 eq.), tetramethylchloroformamidinium hexafluorophosphate (331 mg, 1.18 mmol), *N,N*-diisopropylethylamine (444 mg, 3.44 mmol) and acetonitrile (5.0 mL, 0.2 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2,4-dimethylpyridin-3-yl)thiazole-5-carboxamide (123 mg, 0.328 mmol, 33 %) was obtained after flash purification (100 % DCM to 75 % DCM/MeOH over 10 CV) as a yellow solid.

[729] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2,4-dimethylpyridin-3-yl)thiazole-5-carboxamide (118 mg, 0.315 mmol), 2-(piperazin-1-yl)ethan-1-ol (0.205 g, 1.57 mmol), *N,N*-diisopropylethylamine (16 mg, 0.13 mmol) and 1-butanol (2.5 mL, 0.1 M). **C1** (Figure 1C, 133 mg, 0.284 mmol, 21 % yield over 2 steps) was obtained as a beige solid after flash purification (100 % DCM to 75 % DCM/MeOH over 10 CV).

[730] Purity (HPLC, 254 nm): 90 % (couldn't be removed by trituration, 2nd silica column or RP column).

Compound C2:

N-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-N-(3-methylpyridin-2-yl)thiazole-5-carboxamide

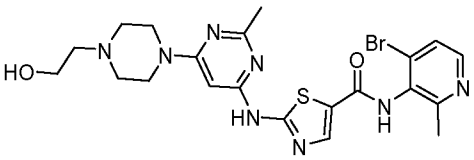


[731] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (530 mg, 1.96 mmol), 3-methylpyridin-2-amine (275 mg, 2.55 mmol), tetramethylchloroformamidinium hexafluorophosphate (659 mg, 2.35 mmol), *N,N*-diisopropylethylamine (886 mg, 6.85 mmol) and acetonitrile (5.8 mL, 0.3 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3-methylpyridin-2-yl)thiazole-5-carboxamide (326 mg, 0.903 mmol) was obtained after extraction with EtOAc as a yellow solid and used without further purification in the next step.

[732] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3-methylpyridin-2-yl)thiazole-5-carboxamide (510 mg, 1.41 mmol), 2-(piperazin-1-yl)ethan-1-ol (920 mg, 7.07 mmol), *N,N*-diisopropylethylamine (73 mg, 0.57 mmol) and 1-butanol (4.3 mL, 0.3 M). **C2** (Figure 1C, 105 mg, 0.231 mmol, 8 % yield over 2 steps) was obtained as an off-white solid after flash purification (100 % DCM to 85 % DCM/3 N NH_3 in MeOH over 10 CV).

Compound C3:

N-(4-bromo-2-methylpyridin-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

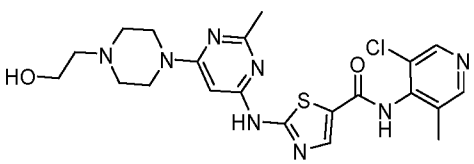


[733] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (145 mg, 0.535 mmol), 4-bromo-2-methylpyridin-3-amine (100 mg, 0.535 mmol), tetramethylchloroformamidinium hexafluorophosphate (180 mg, 0.642 mmol), *N,N*-diisopropylethylamine (242 mg, 1.87 mmol) and acetonitrile (2.7 mL, 0.2 M). *N*-(4-bromo-2-methylpyridin-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (67 mg, 0.15 mmol) was obtained after extraction with EtOAc as a yellow solid and used without further purification in the next step.

[734] Step 2 was run according to GP B using *N*-(4-bromo-2-methylpyridin-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (65 mg, 0.15 mmol), 2-(piperazin-1-yl)ethan-1-ol (96 mg, 0.74 mmol), *N,N*-diisopropylethylamine (7.6 mg, 0.059 mmol) and 1-butanol (0.50 mL, 0.3 M). **C3** (Figure 1C, 68 mg, 0.13 mmol, 24 % yield over 2 steps) was obtained as a slight yellow solid after flash purification (100 % DCM to 85 % DCM/3 N NH_3 in MeOH over 10 CV) and trituration in Et_2O.

Compound C4:

N-(3-chloro-5-methylpyridin-4-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



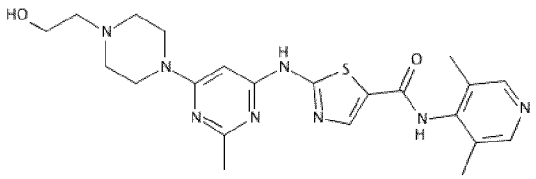
[735] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (530 mg, 1.96 mmol), 3-chloro-5-methylpyridin-4-amine (363 mg, 2.55 mmol), tetramethylchloroformamidinium hexafluorophosphate (659 mg, 2.35 mmol), *N,N*-diisopropylethylamine (886 mg, 6.85 mmol) and acetonitrile (5.8 mL, 0.3 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3-chloro-5-methylpyridin-4-yl)thiazole-5-carboxamide (113 mg, purity ca. 60 %) was obtained after extraction with EtOAc as a yellow solid and used without further purification in the next step.

[736] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3-chloro-5-methylpyridin-4-yl)thiazole-5-carboxamide (110 mg, 0.278 mmol), 2-(piperazin-1-yl)ethan-1-ol

[737] (181 mg, 1.39 mmol), *N,N*-diisopropylethylamine (14 mg, 0.11 mmol) and 1-butanol (0.84 mL, 0.3 M). **C4** (Figure 1C, 28 mg, 0.058 mmol, 12 % yield over 2 steps, 88 % purity) was obtained as a yellow solid after flash purification (100 % DCM to 80 % DCM/MeOH over 10 CV) and trituration in Et_2O.

Compound C5:

N-(3,5-dimethylpyridin-4-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

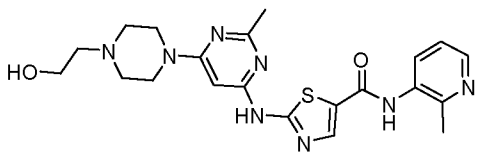


[738] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (500 mg, 1.85 mmol), 3,5-dimethylpyridin-4-amine (271 mg, 2.22 mmol), tetramethylchloroformamidinium hexafluorophosphate (622 mg, 2.22 mmol), *N,N*-diisopropylethylamine (836 mg, 6.46 mmol) and acetonitrile (10 mL, 0.2 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3,5-dimethylpyridin-4-yl)thiazole-5-carboxamide (273 mg) was obtained after precipitation from H_2O as a green solid and used without further purification in the next step.

[739] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3,5-dimethylpyridin-4-yl)thiazole-5-carboxamide (270 mg, 0.720 mmol), 2-(piperazin-1-yl)ethan-1-ol (469 mg, 3.60 mmol), *N,N*-diisopropylethylamine (37 mg, 0.29 mmol) and 1-butanol (2.5 mL, 0.3 M). **C5** (Figure 1C, 110 mg, 0.235 mmol, 12 % yield over 2 steps) was obtained as a slight yellow solid after flash purification (100 % DCM to 80 % DCM/MeOH over 10 CV) and trituration in Et_2O.

Compound C6:

2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-N-(2-methylpyridin-3-yl)thiazole-5-carboxamide

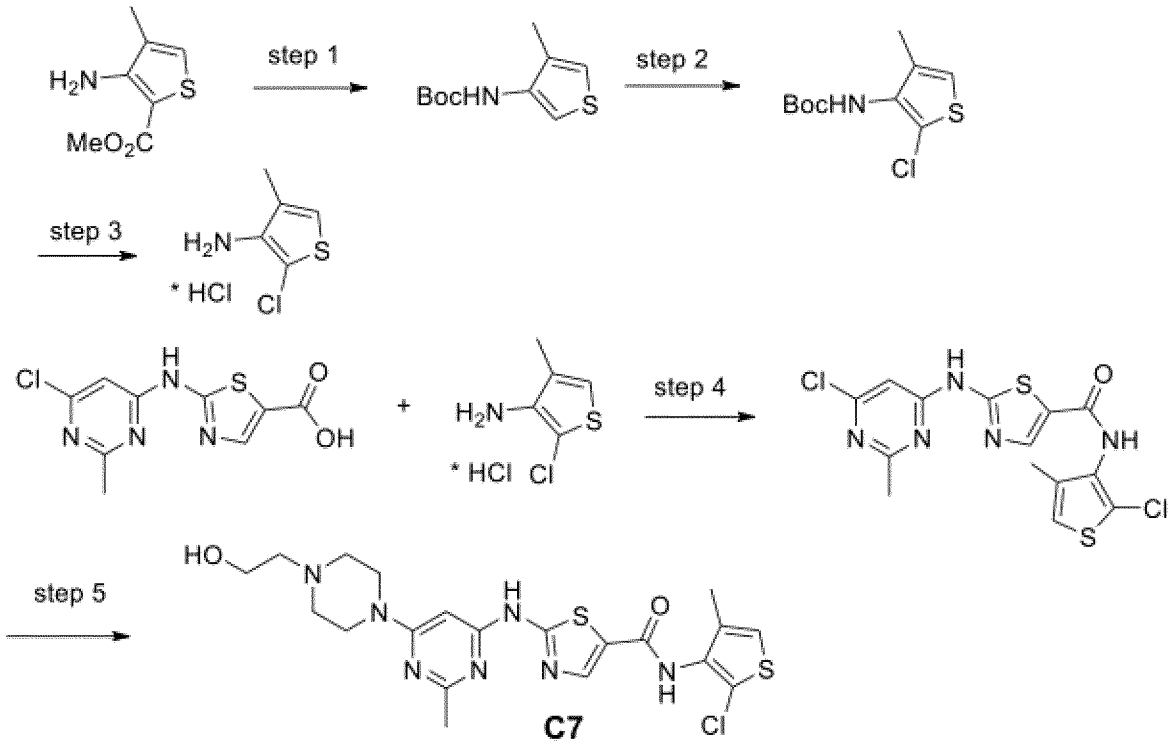


[740] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (530 mg, 1.96 mmol), 2-methylpyridin-3-amine (275 mg, 2.55 mmol), tetramethylchloroformamidinium hexafluorophosphate (659 mg, 2.35 mmol), *N,N*-diisopropylethylamine (886 mg, 6.85 mmol) and acetonitrile (5.8 mL, 0.3 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-methylpyridin-3-yl)thiazole-5-carboxamide (442 mg, 1.22 mmol) was obtained after precipitation from H_2O as a yellow solid and used without further purification in the next step.

[741] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-methylpyridin-3-yl)thiazole-5-carboxamide (440 mg, 1.41 mmol), 2-(piperazin-1-yl)ethan-1-ol (920 mg, 7.07 mmol), *N,N*-diisopropylethylamine (73 mg, 0.57 mmol) and 1-butanol (4.3 mL, 0.3 M). **C6** (Figure 1C, 355 mg, 0.781 mmol, 40 % yield over 2 steps) was obtained as an off-white solid after precipitation from H_2O.

Compound C7:

N-(2-chloro-4-methylthiophen-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



Scheme 2: Synthesis of C7

[742] Step 1: *tert*-butyl (4-methylthiophen-3-yl)carbamate:

[743] To a solution of methyl 3-amino-4-methylthiophene-2-carboxylate (1.71 g, 10.0 mmol) in H_2O (5.1 mL) was added KOH solution (45 %, 1.90 mL, 14.0 mmol, 1.4 eq.) at room temperature. The reaction was stirred at 80 °C for 30 min and afterwards cooled to room temperature. This solution was slowly added to a 6 M HCl solution (5.50 mL, 33.0 mmol, 3.3 eq) at 50 °C. After completion of the addition, the reaction was stirred at 60 °C for 15 min (gas evolution, clear solution was obtained). The solution was cooled to 5 °C (ice bath), hexanes (3.5 mL) was added, and the solution cooled to -10 °C (acetone, dry ice). A solution of KOH (45 %, 3.70 mL, 27.0 mmol, 2.7 eq.) and di-*tert*-butyl dicarbonate (2.40 mL, 10.5 mmol, 1.05 eq.) were added at -10 °C. The reaction solution was stirred overnight and slowly warmed to room temperature. The formed suspension was extracted with EtOAc (3*15 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1*25 mL), dried over Na_2SO_4, concentrated and filtered. *tert*-butyl (4-methylthiophen-3-yl)carbamate (2.32 g, quantitative yield) was obtained as an orange solid and used without further purification.

[744] R_f = 0.68 (cHex/EtOAc 9:1, UV 254 nm). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (s, 1H), 6.86 (dq, *J* = 3.3 Hz, J = 1.1 Hz, 1H), 6.36 (s, 1H), 2.14 (d, *J* = 1.1 Hz, 3H), 1.53 (s, 9H).

[745] Step 2: *tert*-butyl (2-chloro-4-methylthiophen-3-yl)carbamate:

[746] To a solution of (4-methyl-thiophen-3-yl)-carbamic acid *tert*-butyl ester (1.07 g, 5.00 mmol, 1.0 eq.) in anhydrous EtOAc (8 mL) was added N-chlorosuccinimide (0.700 g, 5.25 mmol, 1.05 eq.) and a hydrochloric acid

solution in EtOH (1.25 N, 200 uL, 0.05 eq) at room temperature under a nitrogen atmosphere. After 5 h, TLC indicated starting material still present (cHex/EtOAc 9:1: slightly more polar spot: 0.76 starting material, product: 0.68, longer reaction times didn't result in better conversions). The reaction was quenched by addition of a solution of 1.0 N sodium hydroxide (5.50 mL, 5.50 mmol, 1.1 eq) and sodium hydrogensulfite (40 %, 0.05 eq). The lower aqueous layer was discarded. The organic phase was washed with water (10 mL). The organic layer was dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (100 g biotage cartridge, cHex 100 % 1 CV, to 15 % EtOAc over 10 CV, to 100 % EtOAc over 5 CV) to obtain *tert*-butyl (2-chloro-4-methylthiophen-3-yl)carbamate (734 mg, 2.96 mmol, 59 %) as an orange solid.

[747] R_f = 0.76 (cHex/EtOAc 9:1, UV 254 nm). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (s, 1H), 5.91 (s, 1H), 2.13 (d, *J* = 1.2 Hz, 3H), 1.49 (s, 9H).

[748] Step 3: 2-chloro-4-methylthiophen-3-amine hydrochloride:

[749] To a solution of *tert*-butyl (2-chloro-4-methylthiophen-3-yl)carbamate (567 mg, 2.29 mmol, 1.0 eq.) in anhydrous dioxane (4.6 mL) was added a HCl solution (4.0 N in dioxane, 1.70 mL, 6.80 mmol, 3.0 eq.) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h. TLC (cHex/EtOAc 9:1, UV 254 nm) showed still starting material present. A HCl solution (4.0 N in dioxane, 1.20 mL, 4.80 mmol, 2.1 eq.) and the suspension was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the crude product was triturated in Et_2O (5 mL) with 5 min ultrasound sonication and 3 h stirring at room temperature. 2-chloro-4-methylthiophen-3-amine hydrochloride (360 mg, 1.89 mmol, 86 %) was obtained as a grey solid after filtration and drying under high vacuum.

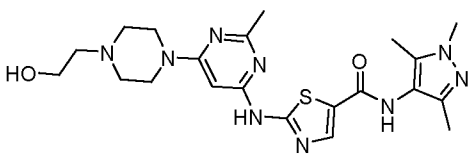
[750] R_f = 0.00 (cHex/EtOAc 9:1, UV 254 nm). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.06 (s, 1H), 5.54 (s, 3H), 2.14 (d, *J* = 1.2 Hz, 3H).

[751] Step 4 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (367 mg, 1.35 mmol), 2-chloro-4-methylthiophen-3-amine hydrochloride (200 mg, 1.16 mmol), tetramethylchloroformamidinium hexafluorophosphate (456 mg, 1.63 mmol), *N,N*-diisopropylethylamine (700 mg, 5.42 mmol, 4.0 eq.) and acetonitrile (6.9 mL, 0.3 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-4-methylthiophen-3-yl)thiazole-5-carboxamide (462 mg, 1.15 mmol, purity ca. 70 %) was obtained after extraction with EtOAc as a yellow solid and used without further purification in the next step.

[752] Step 5 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-4-methylthiophen-3-yl)thiazole-5-carboxamide (230 mg, 0.575 mmol), 2-(piperazin-1-yl)ethan-1-ol (374 mg, 2.87 mmol), *N,N*-diisopropylethylamine (30 mg, 0.23 mmol) and 1-butanol (2.0 mL, 0.3 M). **C7** (Figure 1C, 92 mg, 0.19 mmol, 33 % yield over 2 steps) was obtained as an off-white solid after flash purification (100 % DCM to 25 % DCM/MeOH over 10 CV) and trituration in Et_2O.R_f = 0.15 (DCM/MeOH 9:1, UV 254 nm).

Compound C8:

2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)thiazole-5-carboxamide



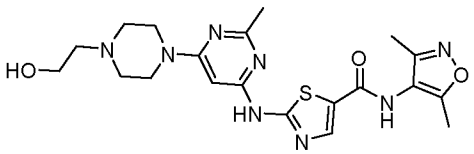
[753] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (530 mg, 1.96 mmol), 1,3,5-trimethyl-1*H*-pyrazol-4-amine (319 mg, 2.55 mmol), tetramethylchloroformamidinium hexafluorophosphate (659 mg, 2.35 mmol), *N,N*-diisopropylethylamine (886 mg, 6.85 mmol) and acetonitrile (5.8 mL, 0.3 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(1,3,5-trimethyl-1*H*-

pyrazol-4-yl)thiazole-5-carboxamide (177 mg, 0.468 mmol) was obtained after precipitation from H_2O as a yellow solid and used without further purification in the next step.

[754] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)thiazole-5-carboxamide (175 mg, 0.463 mmol), 2-(piperazin-1-yl)ethan-1-ol (301 mg, 2.32 mmol), *N,N*-diisopropylethylamine (24 mg, 0.19 mmol) and 1-butanol (1.4 mL, 0.3 M). **C8** (Figure 1C, 142 mg, 0.301 mmol, 16 % yield over 2 steps) was obtained as an off-white solid after flash purification (100 % DCM to 85 % DCM/3 N NH_3 in MeOH over 10 CV, 85 % DCM/3 N NH_3 in MeOH 10 CV) and trituration in Et_2O.

Compound C9:

N-(3,5-dimethyl-1,2-isoxazolyl)-3-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

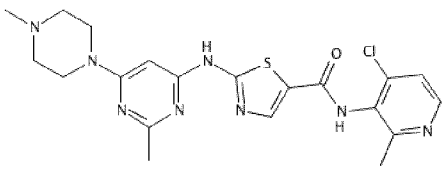


[755] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (530 mg, 1.96 mmol), 3,5-dimethylisoxazol-4-amine (285 mg, 2.55 mmol), tetramethylchloroformamidinium hexafluorophosphate (659 mg, 2.35 mmol), *N,N*-diisopropylethylamine (886 mg, 6.85 mmol) and acetonitrile (5.8 mL, 0.3 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3,5-dimethylisoxazol-4-yl)thiazole-5-carboxamide (525 mg, 1.44 mmol) was obtained after precipitation from H_2O and washing with Et_2O as a yellow solid and used without further purification in the next step.

[756] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(3,5-dimethylisoxazol-4-yl)thiazole-5-carboxamide (530 mg, 1.45 mmol), 2-(piperazin-1-yl)ethan-1-ol (946 mg, 7.26 mmol), *N,N*-diisopropylethylamine (75 mg, 0.58 mmol) and 1-butanol (4.4 mL, 0.3 M). **C9** (Figure 1C, 280 mg, 0.611 mmol, 31 % yield over 2 steps) was obtained as an off-white solid after flash purification (100 % DCM to 75 % DCM/MeOH over 10 CV, 75 % DCM/MeOH 5 CV).

Compound C10:

N-(4-chloro-2-methylpyridin-3-yl)-2-((2-methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide

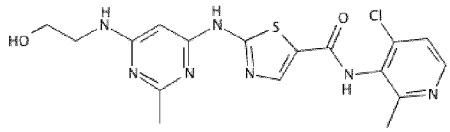


[757] Step 1-3 was run according to the procedure for **B3**.

[758] Step 4 was run according to GP B using *N*-(4-chloro-2-methylpyridin-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (206 mg, 0.521 mmol), 1-methylpiperazine (261 mg, 2.61 mmol), *N,N*-diisopropylethylamine (27 mg, 0.21 mmol) and 1-butanol (1.5 mL, 0.3 M). **C10** (Figure 1C, 50 mg, 0.11 mmol, 6 % yield over 2 steps) was obtained as a white solid after extraction with EtOAc, flash purification (100 % DCM to 80 % DCM/3 N NH_3 in MeOH over 10 CV).

Compound C11:

N-(4-chloro-2-methylpyridin-3-yl)-2-((6-((2-hydroxyethyl)amino)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

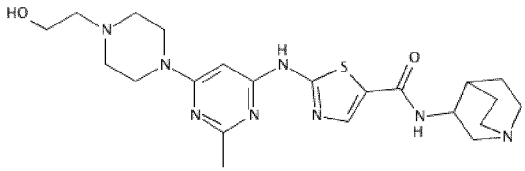


[759] Step 1-3 was run according to the procedure for **B3**.

[760] Step 4 was run according to GP B using *N*-(4-chloro-2-methylpyridin-3-yl)-2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (200 mg, 0.506 mmol), 2-aminoethan-1-ol (155 mg, 2.30 mmol), *N,N*-diisopropylethylamine (26 mg, 0.20 mmol) and 1-butanol (1.5 mL, 0.3 M). **C11** (Figure 1C, 15 mg, 0.036 mmol, 1 % yield over 2 steps) was obtained as a grey solid after extraction with EtOAc, flash purification (100 % DCM to 80 % DCM/3 N NH_3 in MeOH over 10 CV) and trituration in DCM/MeOH (96/4).

Compound C12:

(R)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)-N-(quinuclidine-3-yl)thiazole-5-carboxamide

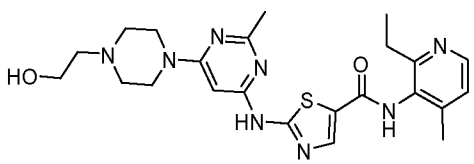


[761] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (500 mg, 1.85 mmol), (*R*)-quinuclidine-3-amine dihydrochloride (441 mg, 2.22 mmol), tetramethylchloroformamidinium hexafluorophosphate (622 mg, 2.22 mmol), *N,N*-diisopropylethylamine (1.31 g, 10.2 mmol, 5.5 eq.) and acetonitrile (10 mL, 0.2 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(quinuclidine-3-yl)thiazole-5-carboxamide (250 mg, 0.491 mmol) was obtained after precipitation from H_2O as a yellow solid and used without further purification in the next step.

[762] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(quinuclidine- 3-yl)thiazole-5-carboxamide (222 mg, 0.540 mmol), 2-(piperazin-1-yl)ethan-1-ol (553 mg, 4.25 mmol), *N,N*-diisopropylethylamine (44 mg, 0.34 mmol) and 1-butanol (2.5 mL, 0.3 M). **C12** (Figure 1C, 30 mg, 0.063 mmol, 3 % yield over 2 steps) was obtained as a white solid after preparative TLC (DCM/MeOH 4:1, R_f = 0.00, UV 254 nm).

Compound C13:

N-(2-ethyl-4-methylpyridin-3-yl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



[763] Step 1 was run according to GP A1 using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxoxylic acid (170 mg, 0.628 mmol), 2-ethyl-4-methylpyridin-3-amine (103 mg, 0.754 mmol), tetramethylchloroformamidinium hexafluorophosphate (211 mg, 0.754 mmol), *N,N*-diisopropylethylamine (284 mg, 2.20 mmol) and acetonitrile (5.0 mL, 0.1 M). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-ethyl-4-methylpyridin-3-yl)thiazole-5-carboxamide

(90 mg, 0.23 mmol) was obtained after extraction with EtOAc as a green solid and used without further purification in the next step.

[764] Step 2 was run according to GP B using 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-ethyl-4-methylpyridin-3-yl)thiazole-5-carboxamide (87 mg, 0.22 mmol), 2-(piperazin-1-yl)ethan-1-ol (150 mg, 1.10 mmol), *N,N*-diisopropylethylamine (12 mg, 0.089 mmol) and 1-butanol (0.7 mL, 0.3 M). **C13** (Figure 1C, 48 mg, 0.099 mmol, 16 % yield over 2 steps) was obtained as an off-white solid after flash purification (100 % DCM to 75 % DCM/MeOH over 10 CV).

[765] The compounds C1 to C15, B3 and compound A8 (dasatinib) were characterised as set forth below in Table 1A.

Table 1A: Synthesis of kinase inhibitors.

Compound Number	Mol. Wt. LCMS: m/z $[M+H]^+$	^{1}H NMR
B3	489.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H), 2.43-2.50 (m, 9H), 3.44 – 3.68 (m, 6H), 4.46 (s, 1H), 6.06 (s, 1H), 7.53 (d, J = 5.3 Hz, 1H), 8.25 (s, 1H), 8.37 (d, J = 5.3 Hz, 1H), 10.10 (s, 1H), 11.52 (s, 1H).
A8 (dasatinib)	488.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H), 2.38-2.50 (m, 9H), 3.38 – 3.62 (m, 6H), 4.45 (t, J = 5.3 Hz, 1H), 6.04 (s, 1H), 7.23 – 7.32 (m, 2H), 7.37 – 7.43 (m, 1H), 8.21 (s, 1H), 9.87 (s, 1H), 11.47 (s, 1H).
C1	469.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.21 (s, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 2.42-2.50 (m, 6H), 3.49 – 3.56 (m, 6H), 4.46 (t, J = 5.3 Hz, 1H), 6.06 (s, 1H), 7.18 (d, J = 4.8 Hz, 1H), 8.17 – 8.28 (m, 2H), 9.82 (s, 1H), 11.48 (s, 1H).
C2	455.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.21 (s, 3H), 2.38-2.51 (m, 9H), 3.49 – 3.57 (m, 6H), 4.48 (s, 1H), 6.08 (s, 1H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 7.72 (dd, J = 7.7, 1.7 Hz, 1H), 8.26 (s, 1H), 8.31 (dd, J = 4.8, 1.8 Hz, 1H), 10.44 (s, 1H), 11.47 (s, 1H).
C3	533.1 (^{81}Br: 535.1)	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26-2.56 (m, 12H), 3.41 – 3.73 (m, 6H), 4.45 (s, 1H), 6.06 (s, 1H), 7.36 (s, 1H), 7.82 (s, 1H), 8.24 (s, 1H), 9.96 (s, 1H), 11.48 (s, 1H).
C4	489.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.40-2.50 (m, 9H), 3.43 – 3.67 (m, 6H), 4.47 (s, 1H), 6.08 (s, 1H), 8.28 (s, 1H), 8.48 (s, 1H), 8.57 (s, 1H), 10.19 (s, 1H), 11.56 (s, 1H).
C5	469.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 6H), 2.34-2.49 (m, 9H), 3.49 – 3.58 (m, 6H), 4.46 (s, 1H), 6.05 (s, 1H), 8.23 (s, 1H), 8.33 (s, 2H), 9.86 (s, 1H), 11.50 (s, 1H).
C6	455.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37-2.50 (m, 12H), 3.48 – 3.61 (m, 6H), 4.46 (t, J = 5.6 Hz, 1H), 6.06 (s, 1H), 7.27 (dd, J = 7.9, 4.7 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 8.22 (s, 1H), 8.33 (d, J = 4.8 Hz, 1H), 9.87 (s, 1H), 11.49 (s, 1H).

C7	494.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 3H), 2.35-2.50 (m, 9H), 3.47 – 3.58 (m, 6H), 4.46 (s, 1H), 6.05 (s, 1H), 7.23 – 7.32 (m, 2H), 7.18 (m, 1H), 8.20 (s, 1H), 9.79 (s, 1H), 11.48 (s, 1H).
C8	472.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 2.09 (s, 3H), 2.35-2.51 (m, 9H), 3.40 – 3.60 (m, 6H), 3.66 (s, 3H), 4.45 (s, 1H), 6.04 (s, 1H), 8.15 (s, 1H), 9.36 (s, 1H), 11.39 (s, 1H).
C9	459.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 3H), 2.31 (s, 3H), 2.41 (s, 3H), 2.43-2.50 (m, 6H), 3.48 – 3.59 (m, 6H), 4.46 (t, J = 5.3 Hz, 1H), 6.05 (s, 1H), 8.18 (s, 1H), 9.66 (s, 1H), 11.48 (s, 1H).
C10	459.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.32-2.47 (m, 10H), 3.47 – 3.58 (m, 4H), 6.06 (s, 1H), 7.53 (d, J = 5.3 Hz, 1H), 8.24 (s, 1H), 8.37 (d, J =5.3 Hz, 1H), 10.09 (s, 1H), 11.53 (s, 1H).
C11	420.0	^{1}H NMR (400 MHz, CD_3OD) δ 2.48 (s, 3H), 2.54 (s, 3H), 3.44 (s, 2H), 3.72 (s, 2H), 5.95 (s, 1H), 7.49 (d, J = 5.0 Hz, 1H), 8.17 (s, 1H), 8.33 (d, J = 5.1 Hz, 1H).
C12	473.2	^{1}H NMR (400 MHz, DMSO-d_6 + 1 drop D_2O) δ 1.45-1.55 (m, 1H), 1.68-1.73 (m, 1H), 1.83-2.01 (m, 2H), 2.38-2.48 (m, 7H), 2.55-2.58 (m, 2H), 2.77-3.15 (m, 7H), 3.33 (t, J = 11.7 Hz, 1H), 3.47-3.54 (m, 6H), 4.06 (t, J = 7.4 Hz, 1H), 6.02 (s, 1H), 8.10 (s, 1H).
C13	483.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, J = 7.5 Hz, 3H), 2.21 (s, 3H), 2.38-2.50 (m, 9H), 2.73 (q, J = 7.5 Hz, 2H), 3.47 – 3.59 (m, 6H), 4.43 (s, 1H), 6.06 (s, 1H), 7.19 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.31 (d, J = 4.9 Hz, 1H), 9.79 (s, 1H), 11.49 (s, 1H).

Compounds D1 to D10:

[766] The compounds D1 to D10 (Figure 1D) are made analogously to compound C7 via Scheme 2, except that the applicable amine is used at step 4 (GP A1) and the applicable piperazinyl derivative is used at step 5 (GP B).

[767] Compounds synthesised from Table B were characterised as set forth below in Table 1B.

Table 1B: Synthesis of further kinase inhibitors.

Compound Number	Mol. Wt. LCMS: m/z $[M+H]^+$	^{1}H NMR*
D1	494.23	1H NMR (300 MHz, DMSO-d6): δ 11.45 (s, 1H), 9.71 (s, 1H), 8.19 (s, 1H), 7.43 (s, 1H), 6.04 (s, 1H), 4.43 (t, J = 5.1 Hz, 1H), 3.54-3.50 (m, 6H), 2.45-2.42 (m, 6H), 2.40 (s, 3H), 2.29 (s, 3H)
D7	514.11	1H NMR [300 MHz, DMSO-d6]: δ 11.51 (s, 1H), 9.98 (s, 1H), 8.20 (s, 1H), 7.66 (s, 1H), 6.04 (s, 1H), 4.45 (t, J = 5.1 Hz, 1H), 3.55-3.51 (m, 6H), 2.45-2.42 (m, 6H), 2.40 (s, 3H).
D8	492.17	1H NMR [300 MHz, DMSO-d6]: δ 11.53 (s, 1H), 9.80 (s, 1H), 8.20 (s, 1H), 7.17 (s, 1H), 6.05 (s, 1H), 3.57-3.53 (m, 8H), 2.49 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H).

D9	464.19	1H NMR [300 MHz, DMSO-d6]: δ 11.46 (s, 1H), 9.76 (s, 1H), 8.19 (s, 1H), 7.16 (s, 1H), 6.05 (s, 1H), 3.52 - 3.49 (m, 4H), 2.4 (s, 3H), 2.38 - 2.36 (m, 4H), 2.21 (s, 3H), 2.05 (s, 3H).

* Determined at 300MHz using a Bruker AV300 machine.

Example 1.3 [prophetic]: Synthesis of further kinase inhibitors of formulae (Ia), (Ib) and (Ic).

***Additional kinase inhibitors based on the structure-activity relationship (SAR) of dasatinib (A8)*:**

[768] Additional kinase inhibitors are synthesised, in particular those of formulae (Ia), (Ib) and/or (Ic), to exemplify that a yet further diverse set of substitutions (in particular, at Hy, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^2, R^3, R^4, R^5, R^6, R^7, E and B) of formulae (Ia), (Ib) and (Ic) (as applicable)provide compounds that are kinase inhibitors and/or possess cellular antiproliferative activity.

[769] For example: (i) by reference to Figure 8A (from Table 1 of Lombardo et al 2004, J Med Chem 47:6658), compounds of formulae (Ia), (Ib) and/or (Ic) are made with substituents at R^{1a}, R^{1c} and B analogous to those independently selected from R_2, R_1 and X (respectively), as shown in Figure 8A; and/or (ii) by reference to Figure 8B (from Table 4 of Das et al 2006, J Med Chem 49:6819), compounds of formulae (Ia), (Ib) and (Ic) are made with substituents at B/R^{1a}/R^{1c} and R^7 analogous to those independently selected from R_1 and R (respectively), as shown in Figure 8B.

Example 2.1: Inhibition of SIK3, SIK2, CSF1R and other kinases by kinase inhibitors of formula (Ia).

SIK 2/3 inhibitory activity of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

[770] Compounds of formula (Ia), fluorinated variants of compound C7, were synthesised, and using assays such as those described herein the inventors showed that despite the significant structural changes, fluorinated **C7** variants of the invention (eg **E4, E9** and **E10**) also potently inhibit SIK kinases, with many compounds inhibiting SIK3 and/or SIK2 with low double-digit nM IC50s, and some compounds even inhibiting SIK2 with low single-digit nM IC50s. The inventors were surprised to observe that the kinase inhibitor **E4** was comparable to dasatinib and **C7** in inhibiting SIK2 and SIK3, and that the fluorinated-compound **E9** was even superior in inhibiting SIK3 than both dasatinib and **C7** (Table 2.1).

Table 2.1: Biological activity of kinase inhibitors of formula (Ia) compared to other compounds disclosed herein

Compound	Kinase: IC50 (nM)	
	SIK2	SIK3
A8	<20	20-50
B3	50-100	200-500
C7	<20	20-50
E2	<10	50-100
E3	<10	20-50
E4	<20	<20
E5	20-50	50-100
E9	<10	<20
E10	<20	20-50

(racemic)		
E11	<10	20-50
E12	<20	50-100
E13	<10	<20
E15	<20	20-50
E16 (racemic)	<20	20-50

[771] Each of the two separated enantiomers of compound **E10** were also tested for their inhibitory activity against SIK2 and SIK3. Enantiomers **E10-Ent-I** and **E10-Ent-II** exhibited similar IC50s against SIK2 as that of the racemic **E10**, but with an indication that **E10-Ent-I** may be a moderately more potent inhibitor against SIK2 compared to **E10-Ent-II**. In contrast, and surprisingly, it was demonstrated that the IC50 of **E10-Ent-II** against SIK3 was approximately half that of the IC50 of **E10-Ent-I** against SIK3 (and with the IC50 of racemic **E10** being approximately mid-way between those of its two enantiomers.

Selectivity of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

[772] Further compounds described herein are also tested in a single-point (0.1uM or 1uM) inhibition assay over a diverse set of 335 wild-type protein (ProQinase "Kinase Profiler"; ProQinase, Freiburg, Germany).

[773] Except for their R^{1a} moieties (which are believed to be solvent exposed and hence expected to have little effect on kinase selectively), compounds **E9** and **E10**, have an identical structure - in particular at their R^6 having fluorinated substituents – and these compounds showed a virtually identical kinome profile (Figure 16A). In contrast, compound **C7** (which has no fluorinated substituents of R^6) showed a significantly different profile of the kinases it inhibits compared to those of compound **E4** which is structurally identical to **C7** *except for* **E4**'s di-fluorinated -CHF_2 substituent at R^6 compared to **C7**'s -CH_3 (Figure 16B). Furthermore, there is an indication that fluorinated substituents of R^6 may affect certain kinases more than others. For example, the kinase MAP3K11 appeared to be inhibited less by compounds of formula (Ia) having fluorinated substituents of R^6 than by the highly similar compound **C7** not having fluorinated substituents of R^6, and in contrast the kinase NEK11 appeared to be more strongly inhibited by compounds of formula (Ia) having fluorinated substituents of R^6 than by **C7**. This was seen at compound concentrations of both 1uM (Figure 17A) and 0.1M (Figure 17B). This indication is further supported from analogous comparison of kinase profiles for other compounds disclosed herein (data not shown). Subsequent IC50 testing is conducted to further investigate these differences, especially for compounds **E4**, **E9**, **E10** and/or **E16** having fluorinated substituents of R^6 compared to eg compound **C7** not having fluorinated substituents of R^6, and in particular kinases such as MAP311, NEK11 and/or one or more other kinases as disclosed herein (such as below in this Example 3).

Inhibition of CSF1R by compounds disclosed herein, including those with fluorinated substituents of R^6 of compounds of formula (Ia):

[774] The compounds disclosed herein (including, those of formula (Ia), and formulae (Ib) and (Ic)) are also potent inhibitors of colony-stimulating factor 1 receptor (CSF1R). In particular, when tested against CSF1R kinase as part of the "Kinase Profiler assays described herein, compounds **E4**, **E9** and **E10**, as well as compounds **C7**, **A8** (dasatinib) and **B3**, each resulted in less than 1% residual activity of the kinase CSF1R (and similarly, HCK). The inventors thereby demonstrate the utility of the compounds herein (including, those of formula (Ia), and formulae (Ib) and (Ic)) to be inhibitors of this disease-relevant kinase. Compounds disclosed herein (especially compounds **E4**, **E9** and **E10**, as well as compounds **C7** and **B3**) are further shown to be potent inhibitors of CSF1R (and similarly, HCK) by determination

of their IC50 against CSF1R (and/or HCK) in assays analogous to those described in connection with Table 3E, except using CSF1R (and/or HCK) enzyme and its (respective) applicable peptide substrate.

[775] CSF1R binds to its ligand CSF1 and the resulting downstream signalling results in differentiation and survival of myeloid cells that express CSF1R receptor. In particular, CSF1-CSF1R signalling is important for the differentiation of macrophages to the more suppressive M2 phenotype (Lenzo et al 2012, Immunol Cell Bio 90:429). Indeed, the presence of CSF1R+ macrophages in tumours correlates with poor survival in various indications including gastric cancer, breast cancer, ovarian cancer, bladder cancer etc. (Zhang et al 2012, PLoS One 7:e50946).

[776] Without being bound by theory, the specific depletion of (suppressive) M2 tumour associated macrophages (TAMs) by compound **E9** in the MC38 syngeneic mouse tumour model described in Example 8.1 (especially Figure 21H) may result from CSF1R inhibition by compound **E9.**

[777] Within TAMs, HCK stimulates the formation of podosomes that facilitate extracellular matrix degradation, which enhance immune and epithelial cell invasion (Poh et al 2015, Oncotarget 6:15742). The formation of podosomes within TAMs are investigated in animal models such as those described herein, upon treatment with the compounds of formula (Ia), and formulae (Ib) and (Ic).

Example 2.2 [comparative]: Inhibition of SIK; Abl and Src kinases by other kinase inhibitors disclosed herein.

[778] It was demonstrated that kinase inhibitors of formula (Ib)/(Ic) (eg C1 to C12 and B3, and compounds from Table B, D1 to D10) potently inhibit SIK, ABL1 and/or SRC kinases (Table 3A and Table 3A1), with many compounds inhibiting SRC with low single-digit nM IC50s, and inhibiting SIK (esp SIK3 and/or SIK2) and/or ABL1 with low double-digit nM IC50s. Compound C13 is similarly tested.

[779] The IC50 for the inhibition of ABL1 by dasatinib, by C7 and by B3 is approximately 1.5nM, 5.1nM and 1.6nM, and of SRC is 1.5nM, 1.5nM and 1.5nM; each, respectively for dasatinib, C7 and by B3 (Table 3A). The compound C12 is also a strong inhibitor of SRC (<100nM IC50), and is selective to SRC over ABL1.

[780] Briefly, a radiometric protein kinase assay (33PanQinase® Activity Assay) was used for measuring the kinase activity of the five protein kinases. All kinase assays were performed in 96-well FlashPlatesTM from PerkinElmer (Boston, MA, USA) in a 50uL reaction volume. The reaction cocktail was pipetted in four steps in the following order:

- 25uL of assay buffer (standard buffer/[gamma-33P]-ATP)
- 10uL of ATP solution (in water)
- 5uL of test compound (in 10% DMSO)
- 20uL enzyme/substrate mix

[781] The assay for all protein kinases contained 70 mM HEPES-NaOH pH7.5, 3mM $MgCl_2$, 3 mM $MnCl_2$, 3µM Na-orthovanadate, 1.2mM DTT, ATP (variable concentrations, corresponding to the apparent ATP-Km of the respective kinase, see Table 2A), [gamma-33P]-ATP (approx. 8 x 10^5 cpm per well), protein kinase (variable amount, see Table 2A), and substrate (variable amounts, see Table 2A).

[782] The following amounts of enzyme and applicable substrate were used per well:

Table 2A: Assay parameters for the tested protein kinases.

Kinase Name	Kinase Conc. (ng/50µL)	Kinase Conc. (nM*)	ATP Conc. (µM)	Substrate	Substrate Conc. (µg/50µL)
ABL1 wt	5	1.3	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125
SRC (GST-HIS-tag)	5	1.1	0.3	Poly(Glu,Tyr)4:1	0.125
SIK1	50	14.6	3.0	RBER-CHKtide	2
SIK2	3	1	1.0	RBER-CHKtide	2
SIK3	50	15.9	1.0	RBER-CHKtide	2

* Maximal molar enzyme assay concentrations, implying enzyme preparations exclusively containing 100% active enzyme

[783] The reaction cocktails were incubated at 30oC for 60 minutes. The reaction was stopped with 50uL of 2% (v/v) H3PO4, plates were aspirated and washed two times with 200µL 0.9% (w/v) NaCl. Incorporation of 33Pi was determined with a microplate scintillation counter (Microbeta, Wallac). All assays were performed with a BeckmanCoulter/SAGIAN(TM) Core System.

Example 3 [comparative]: Improved kinase selectively of kinase inhibitors of formula (Ib)/(Ic).

[784] It was demonstrated that kinase inhibitors of formula (Ib)/(Ic) (eg C1 to C12 and B3, and compounds from Table B, D1 to D10) appeared to be selective (especially, SRC-selective) protein-tyrosine kinase inhibitors (favouring the inhibition of, eg ABL1, and particularly SRC kinase) than the kinase inhibitor dasatinib. Compound C13 is similarly tested.

[785] In particular, although many of these kinase inhibitors inhibited each (or one or more) of the SIK family of kinases (SIK1, SIK2 and SIK3), some even at sub-micromolar concentrations, they were less potent inhibitors of these protein-serine/threonine kinases than dasatinib (Table 3A and Table 3A1).

[786] In particular, and by way of example, compounds C3, C8 and C12 are significantly less active inhibitor of at least SIK1, SIK2, and SIK3 than dasatinib, yet remain strong inhibitors of both SRC and ABL1, especially SRC (IC50s: <2nM, <25nM, and <100nM, respectively).

Table 3A: Biological activity of kinase inhibitors of formula (Ib)/(Ic)

Kinase Name	Compound: IC50 (nM)							
	C1	C2	C3	C4	C5	C6	C7	C8
ABL1	13.0	14.4	39.7	17.7	28.2	14.7	5.02	296
SRC	<1.50	<1.50	1.59	<1.50	<1.50	<1.50	<1.50	22.8
SIK1	132	177	571	32.7	30.6	336	13.4	2,800
SIK2	641	427	1,540	130	119	385	17.7	4,440
SIK3	867	1100	2,780	677	340	987	52.3	9,730

Kinase Name	Compound: IC50 (nM)					
	C9	C10	C11	C12	B3	A8
ABL1	27.4	4.30	4.43	391	~1 to 2	~1 to 2
SRC	6.44	<1.5	<1.5	73.7	~1 to 2	~1 to 2
SIK1	169	302	302	1,710	~30	~1 to 2
SIK2	232	138	470	1,940	~60	~3 to 4
SIK3	800	493	1,510	8,850	~250	~5 to 7

Table 3A1: Biological activity of further kinase inhibitors of formula (Ib)/(Ic).

Compound	Kinase: IC50 (nM)		
	SIK1	SIK2	SIK3
D1	NT	~10 to 15	~40 to 45
D7	NT	~2 to 5	~15 to 20
D8	~20 to 25	~25 to 30	~150
D9	~10 to 15	~10 to 15	~60

[787] The IC50s of the compounds against the SIK family of protein-serine/threonine kinases (SIK1, SIK2 and SIK3) were determined as described in Example 2 (in particular, see Table 2A), with the inhibition curves for B3 and A8 shown in Figure 2 (A to E) and for C3 and C12 in Figure 2 (F to J). For example (Figure 2 F to J), compounds C3 and C12 retain potent inhibitory activity against SRC (IC50s: <2nM and <100nM, respectively), but compared to dasatinib (see Figure 2 A to E, right column) are significantly less active inhibitors against ABL1, and especially less active against SIK1, SIK2 and SIK3.

[788] Furthermore, conducting a single-point (1uM) inhibition assay (in duplicate) over a diverse set of 320 wild-type protein (ProQinase "Kinase Profiler"; ProQinase, Freiburg, Germany) shows that compounds of formula (Ib)/(Ic) are more selective than dasatinib (Figures 3 and 4, Table 3AA). Other compounds of formula (Ib)/(Ic) are similarly tested (for example, one or more of compounds D1 to D10). Indeed, overall (and for one example compound of formula (Ib)/(Ic)) kinase inhibitor B3 is numerically more selective than dasatinib (A8), with B3 having a selectivity score of 0.163 compared to 0.188 for dasatinib. The selectivity score, according to Karaman et al (2008; Nat Biotech 26:127), is a compound concentration-dependent parameter describing the portion of kinases, which are inhibited to more than a predefined degree (eg, more than 50 %), in relation to all tested kinases of the particular project.

Table 3AA: Selectivity score across 320 kinases for compounds of formula (Ib)/(Ic) and dasatinib (A8).

Kinase Family*	Number	Compound Selectivity score at 1uM						
		C2	C4	C7	C8	C9	B3	A8
All tested	320	0.144	0.169	0.234	0.940	0.172	0.163	0.188
TK	77	0.468	0.506	0.558	0.377	0.442	0.481	0.532
TKL	19	0.263	0.421	0.632	0.053	0.579	0.474	0.579
CAMK	45	0.067	0.067	0.067	0.067	0.000	0.067	0.089

* TK: Tyrosine Kinase; TKL: Tyrosine Kinase-like; CAMK: Calcium/Calmodulin-dependent protein kinases.

[789] The selectivity score of the compounds at the tested concentration was calculated for a residual activity <50%; ie, an inhibition of >50%. The selectivity score for a particular compound at a particular concentration was calculated by using the following formula:

Selectivity Score = (count of data points < 50 %)/(total number of data points)

[790] Indeed, virtually all tested compounds of formula (Ib)/(Ic) showed a significantly enhanced selectively score (ie, they inhibited a smaller number of kinases by more than 50%) than dasatinib. This selectivity was shown not just across all 320 kinases, but also by kinase family-specific selectively scores; and, for example, virtually all tested compounds of formula (Ib)/(Ic) were more selective even within the protein-tyrosine and protein-tyrosine-like families of kinases than dasatinib, and all (including C7) were more selective to the CAMK family of kinases than dasatinib. Indeed, compound C9 was shown to not inhibit any CAMK kinase (even SIK1, SIK2 or SIK3) by more than 50%.

[791] By way of further example for one particular kinase inhibitor of formula (Ib)/(Ic), compound B3, in particular, with a few exceptions (eg, FLT3, showing only 32% residual activity after treatment with 1μM of compound B3, yet over 80% of its activity remains on treatment with 1uM dasatinib), unlike the kinases such as ABL1 and SRC that are equivalently inhibited by both compounds, this kinase inhibitor of formula (Ib)/(Ic) was a less potent inhibitor of most of these kinases tested (Figures 3 and 4). For example, WNK2 is not inhibited by B3 (100% residual activity at 1μM B3), yet only 62% of WNK2 activity remains after treatment with 1μM dasatinib; likewise, JAK1 is not inhibited by 1μM B3, yet only 41% of activity remains after treatment with 1μM dasatinib; almost 100% of RET activity remains after treatment with 1μM B3, yet under 40% of its activity remains on treatment with 1μM dasatinib. Also, treatment of the serine/threonine kinase MAP4K5 with 1μM dasatinib shows a residual activity of only 3%, while treatment with 1μM

B3 shows 28% residual activity. Indeed, many kinases have less than 20% residual activity after inhibition with 1μM dasatinib, yet retain almost 50% of their activity when inhibited with 1μM B3. For example, B-RAF retains almost 50% activity when inhibited with 1μM B3, yet retains only 15% when inhibited with 1μM dasatinib.

[792] Kinase inhibitors of formula (Ib)/(Ic) show differential inhibition of a number of other kinases and kinase-family members that are inhibited by dasatinib; for example, and in particular, inhibition of KIT and certain members of the EphA/B subfamilies by a kinase inhibitor of formula (Ib)/(Ic), compound B3, (Table 3B).

Table 3B: Certain kinases/kinase subfamilies showing differential inhibition between a compound of formula (Ib)/(Ic) and dasatinib (A8).

Kinase Name	Kinase Family*	Compound Residual activity (%) at 1μM	
		B3	A8
NIK	STE	100	82
EPH-A1	TK	3	1
EPH-A2	TK	0	0
EPH-A3	TK	0	0
EPH-A4	TK	10	8
EPH-A5	TK	1	0
EPH-A6	TK	86	50
EPH-A7	TK	88	88
EPH-A8	TK	3	0
EPH-B1	TK	0	0
EPH-B2	TK	15	1
EPH-B3	TK	3	1
EPH-B4	TK	1	0
KIT	TK	5	1
PDGFR-alpha	TK	18	3
PDGFR-beta	TK	6	2

* TK: Tyrosine Kinase; STE: Homologs of Yeast Sterile 7, Sterile 11, Sterile 20 Kinases

[793] Overall, 1μM dasatinib inhibits 23 of these kinases to less than 1% or residual activity, while 1μM B3 inhibits only 13 kinases to less than 1% residual activity. Similarly, given a threshold of <5% residual activity, dasatinib inhibits 38 kinases and 1μM B3 inhibits only 30 kinases; and a threshold of <10% residual activity, dasatinib inhibits 43 kinases and 1μM B3 inhibits only 34 kinases.

[794] Table 3C shows those kinases retaining an activity of *greater* than 50% when treated with one compound and which show a residual activity of 50% *or less* when treated with the other compound. Compound A8 (dasatinib) inhibits 9 kinases by greater than 50%, where such kinases retain more than 50% of their activity when treated with compound B3, a kinase inhibitor of formula (Ib)/(Ic). In contrast, of all the kinases tested, the kinase inhibitor of formula (Ib)/(Ic) (B3) inhibited by greater than 50% only one kinase (FLT3) that was not also inhibited by dasatinib by greater than 50%.

Table 3C: Kinases showing differential inhibition (residual activity of 50%) between B3, a compound of formula (Ib/)(Ic), and dasatinib (A8).

Kinase Name	Kinase Family*	Compound Residual activity (%) at 1µM	
		B3	A8
ACV-R2B	TKL	57	15
BMPR1A	TKL	83	42
EPHA6	TK	86	50
ERBB2	TK	84	47
FGF-R2	TK	74	30
FLT3	TK	32	84
JAK1 aa583-1154 wt	TK	104	41
MAP3K11	STE	61	50
p38-beta	CMGC	63	25
RET	TK	98	39

* TK: Tyrosine Kinase; STE: Homologs of Yeast Sterile 7, Sterile 11, Sterile 20 Kinases; TKL: Tyrosine Kinase-like; CMGC: containing CDK, MAPK, GSK3 and CLK families.

[795] Indeed, in comparison to dasatinib (A8), kinase inhibitors of formula (Ib)/(Ic) (eg C2, C4, C7, C8, and C9, and B3) are confirmed to show differential biological inhibitory activity against one or more of the above kinases, when tested in a biochemical assay to determine IC50s (Table 3D), and the corresponding IC50 curves are shown in Figure 5A to D (other compounds of formula (Ib)/(Ic) are similarly tested). Indeed, although both compounds B3 and A8 are (also) strong inhibitors of the kinases LCK and KIT, in contrast to dasatinib (A8) compound B3 inhibits FLT3 far more strongly than it does SYK (IC50s 6.9µM and 26.0µM, respectively, for B3; and 25.7µM and 4.8µM, respectively, for A8).

[796] Accordingly, although B3 (a kinase inhibitor of formula (Ib)/(Ic)) is generally more selective than the kinase inhibitor A8 (dasatinib), B3 is shown to inhibit FLT3 more potently than compound A8 (and as reflected by the single outlying point in Figure 4A, which represents FLT3).

Table 3D: Biological activity of a compound of formula (Ib)/(Ic) compared to dasatinib (A8) tested against further kinases

Kinase Name	Kinase Family*	Compound: IC50 (nM)	
		B3	A8
FLT3	TK	6,900	25,700
SYK	TK	26,000	4,820
KIT	TK	40.4	10.4
LCK	TK	<1.5	<1.5

[797] The IC50 of each compound against these kinases was tested analogously to the IC50 assay described in Example 2 above, except that the following amounts of enzyme and applicable substrate were used per well (Table 3E):

Table 3E: Assay parameters for the additional tested protein kinases.

Kinase Name	Kinase Conc. (ng/50µl)	Kinase Conc. (nM*)	ATP Conc. (µM)	Substrate	Substrate Conc. (µg/50µL)
FLT3	20	5.2	1	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125

SYK	50	9.6	1	Poly(Glu,Tyr)4:1	0.125
KIT	100	25.8	3	Poly(Glu,Tyr)4:1	0.125
LCK	20	4.3	0.3	Poly(Glu,Tyr)4:1	0.125

* Maximal molar enzyme assay concentrations, implying enzyme preparations exclusively containing 100 % active enzyme

[798] Indeed, one compound disclosed herein (C7) had a yet other profile of kinase inhibition (Figure 3); exhibiting a profile being different to both of compound A8 and compound B3. Figure 9 shows scatter plots of the % residual activity (mean, of duplicate 1uM single-point inhibition assays) of a diverse set of 320 wild-type protein kinases (ProQuinase "Kinase Profiler", as described above), with the % residual activity of compound C7 shown on each Y axis, and the % residual activity of compound A8 and B3 shown on the X axis of Figure 9A and 9B, respectively.

[799] Furthermore, compound C7 was significantly more potent at inhibiting a number of kinases than both compounds A8 (dasatinib) and B3 (Tables 3F.1 and 3F.2, respectively), for example for those kinases included in the dashed-groups identified in Figures 9A and 9B. In addition, compound C7 was notably different to compound B3 by C7's relative inactivity in inhibiting FLT3 (60% residual activity for C7 compared to 32% residual activity for B3).

Table 3F.1: Certain kinases/kinase subfamilies showing differential inhibition between a compound C7 and dasatinib (A8).

Kinase Name	Kinase Family	Compound Residual activity (%) at 1μM	
		C7	A8
Aurora A	Other	37	67
Aurora B	Other	49	90
MAP3K9	STE	43	64
MAP3K10	STE	41	69
MAP3K11	STE	16	49
MST4	STE	41	79
MYLK2	CAMK	51	91
NEK11	Other	10	54
RPS6KA6	AGC	49	95
TBK1	Other	49	86
TRKA	TK	29	60
TRKB	TK	52	100
TRKC	TK	29	75
VEGF-R1	TK	50	92
WEE1	Other	33	61

Table 3F.2: Certain kinases/kinase subfamilies showing differential inhibition between a compound C7 and compound B3.

Kinase Name	Kinase Family	Compound Residual activity (%) at 1μM	
		C7	B3
FLT3	TK	60	32
JAK1	TK	30	104
MST4	STE	41	107
NEK11	Other	10	89
RET	TK	23	98

[800] Indeed, of particular significance is the differential pattern of inhibition shown by compound C7 compared to both of compounds A8 and B3 for the following kinases (Table 3G). Compound C7 is demonstrated to be more potent than the prior art compound A8 (dasatinib) to a number of key kinases listed in Table 3G, in particular such kinases that are TKLs (eg the ACV-family of kinases, RAF1 and BRAF and TBFB-R1), and to the CMGC kinases p38-alpha and -beta. Furthermore, compound C7 (a compound of formula (Ib)/(Ic) is significantly more potent as an inhibitor for such kinases than the compound B3 (also, a compound of formula (Ib)/(Ic)). Of particular note, is also that compound C7 is a very potent inhibitor of NEK11 (only 10% residual activity), while such kinase is only moderately inhibited by dasatinib (over 50% residual activity), and is hardly inhibited at all by compound B3 (almost 90% residual activity).

Table 3G: Differential pattern of inhibition shown by compound C7 compared to dasatinib (A8) and compound B3

Kinase Name	Kinase Family	Compound Residual activity (%) at 1μM		
		C7	A8	B3
ACV-R1	TKL	12	22	48
ACV-R1B	TKL	1 to 2	10	41
ACV-R2A	TKL	2 to 3	7 to 8	34
BRAF	TKL	8 to 9	15	46
JAK1	TK	30	41	107
MAP3K11	STE	16	49	61
NEK11	Other	10	54	89
p38-alpha	CMGC	3 to 4	12	38
p38-beta	CMGC	13	25	63
RAF1	TKL	4 to 5	14	46
RET	TK	23	39	98
TGFB-R1	TKL	1 to 2	5 to 6	28

[801] IC50 testing reflects one or more of these (or other) differences, and confirms that, in comparison to compound A8 (dasatinb) [and/or to compound B3], compound C7 of formula (Ib)/(Ic) shows a differential profile of inhibitory activity against a number of the above kinases. For example, the IC50 of compound C7 to the kinase TGFB-R1 was determined to be about 490nM for C7 and 880nM for A8 (International Centre for Kinase Profiling, Dundee).

Example 4 [comparative]: Inhibition of Abl1 kinase mutants by the kinase inhibitors of formula (Ib)/(Ic) and by dasatinib.

[802] It was demonstrated that kinase inhibitors of formula (Ib)/(Ic) (eg C3, C4 and C7, and B3) are also able to inhibit clinically relevant ABL1 mutants, eg, that are associated with CLL resistance to imatinib, a standard of care for CLL (Table 4A). For example, not only are the inhibitors of formula (Ib)/(Ic) more potent inhibitors of ABL1 wild-type (wt) than imatinib (2.60μM vs 1,060 nM), they are also potent inhibitors of all these relevant mutants of ABL (other than T315I), and showing IC50s comparable to A8. Other compounds of formula (Ib)/(Ic) are similarly tested.

Table 4A: Inhibition of Abl 1kinase mutants.

ABL1 kinase wt/mutant	Kinase Region	Compound: IC50 (μM)					
		C3	C4	C7	B3	imatinib	A8 (dasatinib)
wt	N/A	18.3	9.20	2.13	2.60	1,060	1.70

G250E	P-loop	101	45.6	9.16	10.2	10,600	5.78
Q252H		29.7	15.2	3.17	3.70	1,670	2.47
Y253F		16.1	11.0	2.81	4.00	7,910	2.45
E255K		111	51.6	12.5	15.3	14,500	8.88
T315I	ATP binding site	43,800	23,400	1,990	33,100	>100,000	5,230
F317I		823	189	9.83	12.8	3,440	4.21
M351T	SH2 contact	37.0	19.4	2.99	4.12	3,550	3.19
H396P	A-loop	32.5	13.2	2.87	3.70	1,410	2.48

[803] Briefly, the ABL1 radiometric protein kinase assay as described in Example 1 was conducted, except that the [gamma-33P]-ATP activity was approx. 7 x 10^5 cpm per well, and the amount and substrate for each form of the ABL1 kinase was as shown in Table 4B.

Table 4B: Assay parameters for the ABL1 mutant protein kinases.

Kinase Name	Kinase Conc. (ng/50µL)	Kinase Conc. (nM*)	ATP Conc. (µM)	Substrate	Substrate Conc. (µg/50µL)
ABL1 wt	5	1.3	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125
ABL1 G250E	10	2.6	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.25
ABL1 Q252H	10	2.6	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125
ABL1 Y253F	5	1.3	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.25
ABL1 E255K	10	2.6	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.25
ABL1 T315I	10	2.6	0.1	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125
ABL1 F317I	10	2.6	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125
ABL1 M351T	10	2.6	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125
ABL1 H396P	10	2.6	0.3	Poly(Ala,Glu,Lys,Tyr)6:2:5:1	0.125

* Maximal molar enzyme assay concentrations, implying enzyme preparations exclusively containing 100% active enzyme

Example 5.1: Improved ADMET properties of kinase inhibitors of formula (Ia).

ADMET properties of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

[804] Using assays such as those described elsewhere herein (such as below in Example 5.1, for example in connection with the data presented in Table 5A), the inventors demonstrated that kinase inhibitors of formula (Ia) (fluorinated C7-like compounds, eg **E4, E9** and **E10**) showed comparable, and in some aspects even improved, drug-like properties in a number of in-vitro ADMET assays, including plasma-protein binding, stability, and cell permeation, (Tables 5.1A and 5.1B).

[805] Overall, they showed that the fluorinated C7 series compounds exhibited high human and mouse plasma protein binding (> 95%). However, **C7** and all fluorinated C7-like compounds, as well as dasatinib, showed excellent plasma stability in human and mouse plasma with T1/2 >150min.

[806] Accordingly, fluorinated C7-like kinase inhibitors (eg **E4, E9** and **E10**), were unstable in human and mouse liver microsomes (half-lives in the range of 10-20min, intrinsic clearance between 70-250µL/min/mg; Table 5.1A). Those microsomal stabilities classified the compounds as high clearance drugs.

[807] Indeed, in the presence of human hepatocytes, **E9** and **E10** exhibited half-lives in the range of 21-30min, therefore confirming them to be high clearance drugs. However, **C7** and **E4** displayed improved stability with half-lives of approx. 1h, classifying them rather as medium-to-high clearance drugs (Table 5.1A).

[808] Fluorinated C7-like derivatives showed improved stability in the presence of mouse hepatocytes and can be classified as medium clearance drugs, with a typic half-life in the range of 50-78min (Table 5.1A).

Table 5.1A: Comparable stability and solubility of kinase inhibitors of formula (Ia) compared to C7.

Assay	Parameter	Compound							
		A8	B3	C7	E3	E4	E9	E10	E11
Human Liver microsomal stability	Half-life (min)	10	58	10	16	22	11	12	19
	Intrinsic clearance (uL/min/mg)	141	24	142	86	65	131	120	72
Mouse liver microsomal stability	Half-life (min)	18	62	13	18	20	9	14	21
	Intrinsic clearance (uL/min/mg)	72	22	110	76	70	158	99	66
Human hepatocyte stability	Half-life (min)	NT	NT	54	34	64	24	21	26
	Intrinsic clearance (uL/min/mg)	NT	NT	26	41	22	58	67	55
Mouse hepatocyte stability	Half-life (min)	NT	NT	50	63	78	65	78	56
	Intrinsic clearance (uL/min/mg)	NT	NT	28	22	18	21	18	25
Human plasma-protein binding	Percentage unbound (%)	2	7	2	2	<1	1	1	3
	Recovery at 4h (%)	NT	NT	75	76	77	92	74	77
Murine plasma protein binding	Percentage unbound (%)	3	11	3	4	2	1	1	1
	Recovery at 4h (%)	93	NT	87	89	80	88	101	98

NT = not tested

[809] By testing in the same, similar or analogous assays for MDR1-MDCK efflux ratio as described below (eg, in connection with the data show in Table 5D), the investigators showed that the efflux ratios (MDCK-wild type) of kinase inhibitors of formula (Ia) (fluorinated **C7** like derivatives) were in the range of 2–4, whereas the MDCK-MDR1 efflux ratios for **E9** and **E10** were in a lower range of 20–30, and for **C7** and E4 in the range of 40–50. As all those compounds exhibited effective MDCK-MDR1 efflux ratios of > 10, they are most likely P-gp substrates (Table 5.1B).

Table 5.1B: Mean efflux ratios of C7 and kinase inhibitors of formula (Ia) in MDCK wild type and MDCK-MDR1 cells.

Assay	Parameter	Compound					
		C7	E3	E4	E9	E10	E11
MDCK-wild type cells	Mean Papp A>B (10^{-6} cm/s)	9	7	5	10	10	8
	Mean Efflux Ratio (wt)	4.0	4.3	4.1	1.0	1.6	2.6
MDCK-MDR1 cells	Mean Papp A>B (10^{-6} cm/s)	2	2	3	5	4	3
	Mean Efflux Ratio (MDR1)	52	53	43	26	31	61
P-gP driven efflux ratio (MDR1/wt)		13	12	11	27	19	24

[810] Further fluorinated C7-like kinase inhibitors of formula (Ia) are tested in the same, similar or analogous assays.

ADMET properties of other compounds disclosed herein, including of formula (Ib)/(Ic): [comparative]

[811] It was demonstrated that kinase inhibitors of formula (Ib)/(Ic) (eg C2, C4, C8, C9 and C12, and B3) showed improved drug-like properties in a number of in-vitro ADMET (absorption, distribution, metabolism, excretion, toxicity) assays, including solubility, stability, plasma-protein binding, CYP450 inhibition and hERG inhibition assays (Tables 5A, 5B, 5C, and 5D). Other compounds of formula (Ib)/(Ic) are similarly tested

[812] For an orally administered drug, dasatinib is a poorly soluble compound, with a measured kinetic solubility of even less than 5μM. However, kinase inhibitor B3 shows a significantly improved solubility of 82μM.

[813] In a separate experiment, compounds C2, C4, C7, C8, C9 and C12 of formula (Ib)/(Ic) were similarly tested, and all (except C7) showed a yet further enhanced kinetic solubility, of between 128 to even 195μM (for compound C12).

[814] Furthermore, and as described above, dasatinib has an extremely short half-life in humans (an overall mean terminal half-life of only 3-5 hours; section 12.3 "Pharmacokinetics" of the Full Prescribing Information for SPRYCEL). This is reflected in it showing a very short half-life when tested in human (h) and mouse (m) live microsomal (LM) stability assays. In contrast, the kinase inhibitor B3 shows a significantly improved stability in both the hLM and mLM assays, with significantly improved half-life, intrinsic clearance and % of compound remaining after 40min incubation, with almost a 6-times longer half-life and 10 times more drug remaining at 40min than dasatinib in the hLM assay.

[815] In a separate experiment, compounds C2, C4, C7, C8, C9 and C12 were similarly tested, and all (except C7) showed improved stability in both human and mouse liver microsomes, with compounds C8, C9 and C12 having a half-life of over 100min.

[816] Both dasatinib and kinase inhibitors of formula (Ib)/(Ic) (eg, C2, C4, C8 and C9, and B3) were shown to bind moderately to both human and murine plasma-proteins with certain of the kinase inhibitors of formula (Ib)/(Ic) (eg, C2, C8 and C9, and B3) showed a marked increase (up to 2 to 5 times) in the amount of free-drug in human plasma (ie, unbound to plasma-proteins, and potentially available for pharmacological activity), than that of unbound dasatinib, and this effect was even more pronounced in murine plasma. Indeed, certain compounds of formula (Ib)/(Ic) showed very low plasma-protein binding: compound C12 remained over 90% unbound in both human and murine plasma.

[817] Accordingly, kinase inhibitors of formula (Ib)/(Ic) show, in some cases (eg C2, C8, C9 and C12, and B3), highly improved drug-like properties over dasatinib for these in-vitro ADMET parameters (Table 5A). Other compounds of formula (Ib)/(Ic), eg one or more of compound D1 to D10, are similarly investigated,

Table 5A: Improved solubility and stability of kinase inhibitors, including those of formula (Ib)/(Ic).

Assay	Parameter	Compound	
		B3	A8
Solubility	Kinetic solubility (μM)	82	<5
Human liver microsomal stability	Half-life (min)	58	10
	Intrinsic clearance (L/min/mg)	24	141
	% Remaining at 40min (%)	60	6
Mouse liver microsomal stability	Half-life (min)	62	18
	Intrinsic clearance (L/min/mg)	22	77
	% Remaining at 40min (%)	63	22
Human plasma-protein binding	Percentage unbound (%)	7	2
Murine plasma protein binding	Percentage unbound (%)	11	3

Assay	Parameter	Compound					
		C2	C4	C7	C8	C9	C12
Solubility	Kinetic solubility (μM)	160	128	13	189	174	195
Human liver microsomal stability	Half-life (min)	>86	12	5	>100	>100	>100
	Intrinsic clearance (L/min/mg)	<17	115	253	<14	<14	<14
	% Remaining at 40min (%)	69	10	1	81	89	91
Mouse liver microsomal stability	Half-life (min)	40	37	12	>100	>100	>100
	Intrinsic clearance (L/min/mg)	35	38	111	<14	<14	<14
	% Remaining at 40min (%)	48	45	10	86	83	105
Human plasma-protein binding	Percentage unbound (%)	9	2	<1	5	6	>90
Murine plasma protein binding	Percentage unbound (%)	30	14	5	62	44	>90

[818] Solubility and stability testing was conducted by Charles River Inc., at their UK Discovery site (Cambridge, UK), according to their applicable standard operating procedures (ADME-SOP-01 for solubility; AMDE-SOP-100 for microsome stability; AMDE-SOP-90 for plasma-protein binding).

[819] Dasatinib is known to inhibit certain cytochrome P450 (CYP450) enzymes; including those that are involved in its metabolism. Indeed, although dasatinib is metabolised in humans primarily by the cytochrome P450 enzyme 3A4 (CYP3A4), it is also a time-dependent inhibitor of CYP3A4. Indeed, the dosage of dasatinib must be significantly reduced (eg from 100mg daily to 20mg daily) if the patient is concomitantly medicated with a strong CYP3A4 inhibitor (see above). However, kinase inhibitor B3 was shown not to significantly inhibit any of the CYP450 enzymes tested, importantly B3 was not an inhibitor of CYP3A4 or of CYP2C8 that is also known to be inhibited by dasatinib (Table 5B).

[820] Other kinase inhibitors of formula (Ib)/(Ic) (eg, one or more of C1 to C13, and/or of D1 to D10) are tested in the same, similar or analogous assays for CYP450 inhibition.

Table 5B: Kinase inhibitor B3 does not inhibit the CYP450 enzymes 2C8 and 3A4.

CYP450 Enzyme	Compound: IC50 (μM)	
	B3	A8 (dasatinib)*
1A2	>30	>50
2A6	NT	35
2B6	>30	>50
2C8	>30	12
2C9	>30	50
2C19	>30	>50
2D6	>30	>50
3A4 (M)	>30	18
3A4 (T)	>30	17

* Values obtained from page 33, NDA 21-986 Pre-clinical Review for SPRYCEL (dasatinib)

[821] CYP450 inhibition assays (not for A8) were conducted by Charles River Inc, at their UK Discovery site (Cambridge, UK), according to their applicable standard operating procedures (ADME-SOP-97). CYP450 inhibition values for dasatinib are taken from page 33 of the Pre-clinical Review of NDA 21-986 for SPRYCEL (dasatinib).

[822] One "Warning and Precaution" of dasatinib (Full Prescribing Information for SPRYCEL) is that it has the potential to prolong cardiac ventricular repolarization (QT interval). Indeed, it is reported therein: that up to 1% of CML patients in clinical trials experienced a QT prolongation, and cardiac adverse reactions were reported in 5.8% of 258 patients taking dasatinib, including 1.6% of patients with cardiomyopathy, heart failure congestive, diastolic dysfunction, fatal myocardial infarction, and left ventricular dysfunction.

[823] The potential cardiac risks of dasatinib was already recognised during the NDA process, with the Pharmacological/Toxicity Review and Evaluation of NDA 21-986 summarised on page 3 thereof: "Based on the in vitro hERG and rabbit Purkinje fibre assays, dasatinib has the potential to cause QT prolongation", and dasatinib was reported on page 31 therein as inhibiting hERG currents by about 6%, 36% and 77% at 3, 10 and 3uM respectively, and a calculated IC50 of 14.3uM.

[824] In stark contrast, as shown in Table 5C, kinase inhibitor B3 essentially shows *no* hERG liability, generating an IC50 value of greater than or equal to the top concentration tested (30uM), and at 30uM inhibited hERG by only 7.7% (+/-1.0%) compared to the reported 76.8% (+/-4.5%) inhibition of hERG at 30uM dasatinib.

[825] Other kinase inhibitors of formula (Ib)/(Ic) (eg, one or more of C1 to C13, and/or of D1 to D10) are tested in the same, similar or analogous assays for hERG inhibition.

Table 5C: Kinase inhibitor B3 does not inhibit hERFG.

hERG Assay parameter	Compound	
	B3	A8 (dasatinib)*
IC50 (μM)	>30	14.3
Top concentration tested (μM)	30	30
Inhibition at 30μM (%)	7.7 +/- 1.0%	76.8 +/- 4.5%

* Values obtained from page 31, NDA 21-986 Pharmacological/Toxicity Review and Evaluation for SPRYCEL

[826] hERG inhibition assays (not for A8) were conducted by Charles River Inc., at their UK Discovery site (Cambridge, UK). Briefly, the potential for test compound to inhibit the hERG potassium channel was determined using the Charles River ChanTest® hERG-HEK stably transfected cell line on the Sophion Qube automated electrophysiology platform. The assay was performed at room temperature and recordings of the hERG tail current from individual cells were made using single-hole QChips. The cells were held at a voltage of -80 mV and then stepped to +40 mV for 2 seconds before stepping to -40 mV for a further 2 seconds, this represents 1 experimental sweep. This voltage protocol was applied every 15 seconds for the duration of the experiment. Both the vehicle and 2nd compound addition periods were applied for 20 sweeps. The 1st compound addition period was applied for 10 sweeps. The potency (IC50) of the test compound to inhibit the hERG channel was determined from a concentration- response curve generated from up to 8 test compound concentrations with up to 4 replicates per concentration. The compound concentration was added to the test well twice to assure complete exchange of the external buffer with the test compound. In total, compound was applied to the well for 450 seconds. Quality control filters used were: whole-cell membrane resistance ≥200MOhm, and vehicle current amplitude ≥400pA. The analysis methodology comprised: The peak tail currents evoked by the step to -40mV were measured for the analysis of the percentage inhibition by test compounds. The peak tail currents were first normalised to the vehicle addition (0.3% DMSO) in the same well. The percent inhibition versus Log10 compound concentration data was plotted and the IC50 determined using a sigmoidal dose response equation. The hERG inhibition values for dasatinib are taken from page 31 of Pharmacological/Toxicity Review and Evaluation of NDA 21-986 for SPRYCEL (dasatinib).

[827] Assays to determine the MDR1-MDCK effective efflux ratio suggested that dasatinib is a substrate for the MDR1 pump and actively from cells that express this efflux pump (effective efflux ratio of 18.3). Although no definitive conclusion can be made on the relative efflux of B3, the compound of formula (Ib)/(Ic) (effective efflux ratio of >9.6) because of the limit of detection of the compound in the A>B direction in the MDCK-MDR1 cells, there is an indication that kinase inhibitor B3 shows significantly different parameters in this assay compared to dasatinib (Table 5D).

[828] Other kinase inhibitors of formula (Ib)/(Ic) (eg, one or more of C1 to C13, and/or of D1 to D10) are tested in the same, similar or analogous assays for MDR1-MDCK effective efflux ratio.

Table 5D: Mean efflux ratios in MDCK wild type and MDCK-MDR1 cells.

Assay	Parameter	Compound	
		B3	A8 (dasatinib)
MDCK-wild type cells	Mean Papp A>B (10^{-6} cm/s)	6.8	21
	Mean Papp B>B (10^{-6} cm/s)	20	49
	Mean recovery A>B (%)	103	100
	Mean recovery B>A (%)	120	107
	Mean Efflux Ratio (wt)	2.9	2.4
MDCK-MDR1 cells	Mean Papp A>B (10^{-6} cm/s)	<0.8	2.4
	Mean Papp B>B (10^{-6} cm/s)	20	105
	Mean recovery A>B (%)	93	94
	Mean recovery B>A (%)	103	117
	Mean Efflux Ratio (MDR1)	>27	43.4
Effective efflux ratio (MDR1/wt)		>9.6	18.3

[829] The MDR1-MDCK effective efflux assay was (or is) conducted by Charles River Inc, at their UK Discovery site (Cambridge, UK), according to their applicable standard operating procedures (ADME-SOP-56).

Example 5.2: Pharmacokinetic and tolerability studies of kinase inhibitors disclosed herein.

Pharmacokinetic and tolerability studies of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

[830] Screening PK properties of kinase inhibitors of formula (Ia) (fluorinated C7-like compounds, eg, **E4, E9** and **E10**) were tested (such as by using assays described in connection with Table 5.2B below), and can be compared to those of **C7** and **A8** (dasatinib).

[831] Following an oral dose of 30mg/Kg (*po*, per os), the investigators demonstrated, surprisingly, an improved exposure of kinase inhibitors of formula (Ia) (eg **E4** and **E9**) in mice compared to **C7**, **B3** and dasatinib (**C8**). Both, **E4** and **E9**, showed reduced drug clearance and therefore PK properties superior to those of **C7** (Table 5.2C).

[832] Accordingly, **E4** showed reduced drug clearance compared to **C7**. Serum levels at 6h timepoint indicated 9.6-fold and 5-fold improvement for total and free serum concentrations, respectively, over **C7**. Additionally, the concentration of **E4** at 6h was increased 3-fold compared to dasatinib.

[833] On the other hand, **E9** and **E11** showed slightly improved drug clearance compared to **C7**. **E9** showed a 4.5-fold and 2-fold improvement for total and free serum concentrations over **C7**, respectively, and **E11** showed a 3.1-fold and 2-fold improvement for total and free serum concentrations over **C7**, respectively. However, serum concentrations of **E9** and **E11** were comparable to dasatininb.

[834] **E4**, and also to an extent **E3**, showed a slightly increased C_{max} compared to **A8** (dasatinib) and **C7**, while no increase in C_{max} for **E9, E10** and **E11** could be shown. Screening PK characteristics of **E9** seemed not to be superior to **E4**.

Table 5.2C: Screening PK properties of kinase inhibitors of formula (Ia) in mice compared to dasatinib and to C7

Compounds	Plasma concentration at timepoint after 30mg/kg po		
	Plasma concentration after 6 h (nM)	Free plasma concentration after 6 h (nM)	C_{max} after 2 h (ng/ml)
A8	243	6	550
B3	29	3	56
C7	69	3.7	347
E3	73	3,7	889
E4	662	17.9	1,212
E9	309	7.7	426
E10	157	3.3	374
E11	219	7.7	487

[835] Screening PK properties of other kinase inhibitors of formula (Ia) are similarly tested and can be compared to those of other compounds disclosed herein such as **C7**, **A8** (dasatinib) and **B3**.

[836] To further investigate these advantageous PK properties of kinase inhibitors of formula (Ia) (fluorinated C7-like variants), compounds **E4, E9** and **E10**) were tested in a full pharmacokinetic study with oral administration (*per os*, po).

[837] The experimental procedure and the determination of the pharmacokinetic parameters was done using assays as described below (in connection with the data presented in Table 5.2A below).

[838] The inventors were particularly surprised that, when administered orally, the tested kinase inhibitors of formula (Ia) exhibited improved *in vivo drug* exposure and potency (Table 5.2D).

[839] Surprisingly indeed, the inventors observed that the Cmax for free compounds of formula (Ia) are significantly higher than those for dasatinib (**A8**), as well especially higher than the prior art heterocycle compound B2, as well as for the structural related compound **C7**. Further surprisingly, the PK parameters of the tested compounds appeared to exhibit two shapes of PK curves: with compound **E4** showing a similar shaped curve to **C7** (but overall improved level of free compound), while compounds E9 and E10 exhibited a shorter half-life, but with Cmax of for free compound in plasma (Figure 24). These different shapes of PK curves provides opportunities for different dosage and treatment regimens to be developed for these compounds of formula (Ia) as drug candidates having otherwise the same mechanism of action.

[840] In particular, a significantly improved AUC of total and free plasma levels for **E4, E9** and **E10** was exhibited compared to **C7**, upon oral administration of these compounds. However, the differences in the free plasma levels are not as prominent as in the total plasma levels (Table 5.2D), because the plasma protein binding is higher for **E4, E9** and **E10** (see Table 5.1A). Additionally, absorption and/or clearance of **E9** and **E10** was different compared to **E4** and **C7**. In general, the inventors were surprised to observe that compound **E9**, in particular, displayed significantly improved DMPK properties compared to **C7**.

Table 5.2D: DMPK properties of kinase inhibitors of formula (Ia) (**E4**, **E9** and **E10**) in comparison to **C7**, **B3** and **A8** (dasatinib)

	Compound

DMPK Parameter	E4		E9		E10	
Dose:	30mg/kg po		30mg/kg po		30mg/kg po	
Plasma Concentration	Total	Free	Total	Free	Total	Free
C_{max} (ng/ml):	1,237.07	33.40	2,688.72	66,92	2,040.24	42.36
T_{max} (h):	2.00	2.00	0.25	0.25	0.25	0.25
$t_{1/2}$ (h):	4.49	4.49	2.76	2.76	4.35	4.35
AUC_{last} (nM*h):	5,479.99	147.93	9,584.81	238.75	5,917.81	122.87
AUC_{inf} (nM*h):	5,495.75	148.39	9,631.95	239.92	6,168.06	128.06
% AUC_{extrap}:	0.31	0.31	0.49	0.49	4.05	4.05
MRT_{last} (h) :	5.88	5.88	3.38	3.38	4.10	4.10
Rsq	0.90	0.90	0.84	0.84	0.81	0.81

DMPK Parameter	Compound					
	C7		A8 (dasa)		B3	
Dose:	30mg/kg po		30mg/kg po		30mg/kg po	
Plasma Concentration	Total	Free	Total	Free	Total	Free
C_{max} (ng/ml):	474.16	21.34	550	14.4	99	10.7
T_{max} (h):	2.00	2.00	2.00	2.00	0.5	0.5
$t_{1/2}$ (h):	1.42	1.42	3.0	3.0	2.4	2.4
AUC_{last} (nM*h):	1,157.10	52.07	6,465	NC	589	NC
AUC_{inf} (nM*h):	1,306.48	58.79	6,487	NC	697	NC
% AUC_{extrap}:	11.24	11.24	0.3	NC	14	NC
MRT_{last} (h) :	2.75	2.75	NC	NC	NC	NC
Rsq	0.99	0.99	NC	NC	NC	NC

NC = not calculated

[841] The maximal tolerable dose (MTD) of kinase inhibitors of formula (Ia) (eg **E4, E9** and **E10**) was investigated in C57BL/6 mice (such as, by using assays described in connection with Figures 10A, B and C), and are shown in Table 5.2E. The doses investigated were determined, *inter alia*, by the solubility of the particular compounds. Upon considering the results obtained, each compound's observed DMPK properties and SIK3 IC50 value, a BID dose for a murine in vivo efficacy study (using MC38 tuomurs) was proposed.

Table 5.2E: DLT on administration of kinase inhibitors of formula (Ia) compared to C7

Compounds	DLT@QD dosing	DLT@BID dosing	HRD in vivo @QD	HRD in vivo @BID	Proposed BID dose(s) for in vivo study
C7	n.d. @100 mg/kg	n.d. @100 mg/kg	100 mg/kg	100 mg/kg	100 mg/kg
E4	n.d. @80 mg/kg	60 -80 mg/kg	80 mg/kg	33 mg/kg	40 mg/kg
E9	n.d. @50 mg/kg	n.d. @50 mg/kg	50 mg/kg	50 mg/kg	25 & 50 mg/kg
E10	n.d. @30 mg/kg	n.d. @30 mg/kg	30 mg/kg	30 mg/kg	30 mg/kg

n.d. = not detected; DLT = dose-limiting toxicity; HRD = highest recommended dose

Pharmacokinetic and tolerability studies of other compounds disclosed herein, including of formula (Ib)/(Ic): [comparative]

[842] It was observed that although compound C7 (a compound of formula (Ib)/(Ic)) exhibited less favourable in-vitro ADMET properties compared to dasatinib or compound B3 (also a compound of formula (Ib)/(Ic)), when tested in-vivo, compound C7 showed substantially improved pharmacokinetic properties compared to compound B3 (and also a suitable pharmacokinetic profile with reference to dasatinib). For example, Table 5A (Example 5.1) shows that compound C7 had decreased metabolic stability when tested in-vitro with human or mouse liver microsomes, and higher binding to human and mouse plasma proteins, in each case compared to dasatinib (and also to compound B3). Yet, when tested in-vivo, compound C7 exhibited drug metabolism and pharmacokinetic (DMPK) properties that were significantly improved over the structurally related compound B3 (Table 5.2A).

[843] It was also observed that the suitable pharmacokinetic properties of compound C7 were yet distinct compared to dasatinib (A8), and this provides new opportunities to dose this active compound C7 compared to those opportunities using dasatinib. For example, after oral administration compound C7 showed similar half-life and bioavailability as dasatinib, yet displayed a higher clearance and about 1/3 of the AUC of dasatinib (Table 5.2A).

[844] It is well known that dosage regimens, especially in combination (order and timing thereof) with other therapeutics, form the basis of many important and successful anti-cancer therapies. Accordingly, to have a compound such as C7 – having similar kinase activity to dasatinib, yet a different pharmacokinetic profile – enables the design, research and (clinical) testing of new and (potentially) therapeutically effective treatment regimens for the treatment of cancer.

[845] In particular, it has recently been shown that dasatinib can act as a pharmacological on/off switch for CAR T cells (Mestermann et al 2019, Sci Transl Med 11: eaau5907). CAR T cells are administered as a single-shot "living drug" treatment. They are able to persist in patients for several years and to undergo sequential expansion, contraction, and re-expansion in vivo upon (re-)exposure to antigen, and as a consequence, CAR T cell therapy has been associated with substantial acute and chronic side effects that have restricted clinical utilisation to medically fit patients at highly specialised cancer center. The most common acute toxicity associated with CAR T cell therapy is cytokine release syndrome (CRS), which is triggered by release of inflammatory cytokines from CAR T cells and, subsequently, from innate immune cells that produce the key CRS cytokine interleukin 6 (IL-6). Mestermann showed that treatment with dasatinib halted cytolytic activity, cytokine production, and proliferation of CAR T cells in vitro and in vivo. The dose of dasatinib could be titrated to achieve partial or complete inhibition of CAR T cell function. Upon discontinuation of dasatinib, the inhibitory effect was rapidly and completely reversed, and CAR T cells resumed their antitumor function. As a kinase inhibitor with an analogous inhibitory profile yet different pharmacodynamic attributes to dasatinib, compound C7 could be exploited to steer the activity of CAR T cells in "function-on-off-on" sequences in real time, and at a different resolution of timing than that for dasatinib. By further (pre- and clinical) testing, it would be determined which dosage of compound C7 would be efficacious for such CAR T cell "function switching" effect; and this dosage

could be very different (eg lower) than the dosage required for C7 for tumour growth inhibition in a monotherapy setting (and associated modification of the immune response) such as that shown by Example 8.

Table 5.2A: DMPK properties of compound C7 compared to dasatinib and B3.

DMPK Parameter	Compound					
	C7		A8 (dasatinib)		B3	
Dose:	1mg/kg iv	30mg/kg po	1mg/kg iv	30mg/kg po	1mg/kg iv	30mg/kg po
C_{max} (nM):	603	702	1,285	1,127	1,234	202
T_{max} (h):	0.08	2.0	0.08	2.0	0.083	0.5
$t_{1/2}$ (h):	1.2	3.3	1.9	3.0	0.2	2.4
AUC_{last} (nM*h):	340	2,328	1,020	6,465	437	589
AUC_{inf} (nM*h):	360	2,337	1,065	6,487	450	687
% AUC_{extrap}:	5.81	0.45	4	0.3	3	14
MRT_{last} (h) :	0.7		1.3		0.25	
MRT_{inf} (h) :	1.0		1.6		0.29	
Vss (L/kg) :	5.4		3.1		1.31	
CL (mL/min/kg) :	94		32		75	
F (%):	23		21		4	

[846] Pharmacokinetic characteristics of C7, B3 and A8 were investigated after single administration of each compound per gavage in male CD1 mice (Charles River Inc, UK Discovery site). The compounds were diluted in a propylene glycol : water 1:1 mixture (v:v). Plasma level (sampling 0,25h; 0,5h; 1h; 1,5h; 2h; 4h; 7h; 24h after drug administration) of C7, A8 and B3 were analysed by LC-MS/MS and pharmacokinetic parameters were determined using non-compartmental analysis and nominal dose levels of 30mg/kg. Three animals were analysed per time point and each mouse was used for three plasma samplings in total.

[847] Screening PK properties of other kinase inhibitors disclosed herein (eg, those from Table B, D1 to D10) are similarly tested, and can be compared to those of C7, A8 (dasatinib) and B3. For example, the free concentration of compound after a dose of 30mg/kg po (per os) administered mice can be determined for certain time points after administrations (Table 5.2B).

Table 5.2B: Screening PK-properties of certain kinase inhibitors of formula (Ib)/(Ic) compared to dasatinib and B3.

Compound	Free concentration (nM) at timepoint after 30mg/kg po				
	2 hours	6 hours	7 hours	12 hours	24 hours
C7	32	NT	3	NT	0.10
A8 (dasatinib)	30	NT	60	NT	0.14
B3	13	NT	3	NT	ND
D1	80	4	NT	2.14	NT
D7	43	5	NT	1.10	NT
D9	44	8	NT	2.71	NT

ND = not determinable

NT = not tested

[848] Maximal tolerable dose (MTD) of compound C7 was investigated by once (QD) or twice daily (BID) administration of different concentrations (33 and 100mg/kg) of C7 by gavage in female C57Bl/6 mice for 7 consecutive days. Compound C7 was diluted in 4% (v/v) DMSO, 72% (v/v) propylene glycol + 24%(v/v) dd-water. Compound C7

was tolerable up to 100mg/kg BID in female C57BL/6 animals for seven days. Compound C7 was safe and did not show any signs of intolerance (posture, vocalization, ease of handling, lacrimation, chromodacryorrhea, salivation, intact fur/coat, rearing, arousal, piloerection, normal motor movements, tail pinch, diarrhoea). A minor reduction in body weight was observed in all dosing groups compared to non-treated control animals, which was caused by the plasma sampling on day 2 (Figures 10A and B). Plasma-level of C7 were measured by LC-MS/MS and showed a dose-dependent increase in plasma concentration (Figure 10C).

Example 5.3 [prophetic]: Metabolism profiles of kinase inhibitors disclosed herein.

[849] The inventors investigate the metabolism profile of compounds disclosed herein (in particular, those of formulae (Ia), (Ib) and (Ic) and compare such profile (and individual metabolites) to those known for dasatinib (eg Christopher et al 2008, Drug Metab & Disp 36:1357). For example, the modifications seen at the chloro/methly phenyl or piperazinyl groups of dasatinib are not observed during metabolism of the corresponding heterocycle of the compounds of formulae (Ia), (Ib) and (Ic), in particular such as during metabolism of compounds **C7**, **E4**, **E9**, **E10** and **E17** (eg, **E4** or **E9**). For example, the quinone-imine reactive metabolite of dasatinib (**A8**) (Duckett & Cameron 2010) is not observed for the (thiophene-based) compounds such as **C7**, **E4**, **E9**, **E10** and **E17**.

[850] Metabolite profiles of compounds of formulae (Ia), (Ib) and (Ic) (eg, **E4** and **E9**) ae compared to that of dasatinib (**A8**) briefly as follows. For in-vitro analysis, compounds are incubated (37oC) with hepatocytes sourced from, different species (eg mouse, rate, dog, minipig, cynomolgus monkey and/or human) at two different concentrations (eg, 2uM for clearance studies and 10uM for metabolite generation). % parent compound remaining (relative to t_0) is determined for multiple timepoints from the 2uM incubation, and single time points are selected for metabolite profiling/identification from samples taken from the 10uM incubation. Metabolites are identified using high-resolution mass spectrometry. For in-vivo analysis, methods described by Christopher et al (2008) may be used to follow metabolite studies in humans, or analogously in animal species such as one or more of those described above.

Example 6: In-vitro cell-based anti-cancer and anti-leukaemia efficacy of kinase inhibitors, especially anti-MPAL activity of SIK3 inhibitors.

Activity of kinase inhibitors described herein against mixed phenotype acute leukaemia (MPAL)-associated cell lines:

[851] The inventors demonstrate that compounds disclosed herein (in particular, those of formulae (Ia), (Ib) and (Ic) show significant anticancer activity against a particular subset of acute myeloid leukaemia (AML) cell lines. In particular in this subset of cell lines are those that are described by other to be positive for phosphorylated myocyte enhancer factor 2C (MEF2C) protein such as KASUMI-1, MOLM-13 and MV4-11 (eg, Brown et al 2018, Cancer Discov 8:478, esp Supp Fg S6a thereof; Tarumoto et al 2020, esp Fig 2 D thereof); or in contrast to be pMEF2C-negative cell lines such as HL-60 and HEL, or control PBMCs (Figure 18A). In particular, compound **C7** showed a highly potent GI50 of about 2nM against the pMEF2C-positive KASUMI-1 cell line, yet a GI50 as high as about 5uM against the pMEF2C-negative HEL cell line (Figure 18B and C). Indeed, compound **A8** (dasatinib) also shows a potent GI50 against this pMEF2C-positive KASUMI-1 cell line almost as potently as compound **C7** (compound **C7** 1.6nM and **A8** 2.8nM), and also against the pMEF2C-positive MV4-11 cell line (compound **C7** 480nM and **A8** 325nM).

[852] Expression of the transcription factor MEF2C is one characteristic of mixed phenotype acute leukaemia (MPAL) (also known as "mixed lineage leukaemia", MLL). Other characteristics of MPAL include: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of (or an amount of) a KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in

the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene (Slany 2009; Schwieger et al 2009; Laszlo et al 2015; Meyer et al 2018; Tarumoto et al 2020), and in particular the expression of MEF2C is controlled by HDAC4 as a cofactor, which in turn can be retained in the cytoplasm when phosphorylated by the kinase SIK3 (Tarumoto et al 2018; Figure 19).

[853] Compounds disclosed herein, especially those of formulae (Ia), (Ib) and (Ic) (such as compounds **E4**, **E9**, **E10** and/or **E16**) are inhibitors of SIK3 (and SIK2), and hence the inventors show that such compounds are suitable for use in treatments for proliferative disorders (such as MPAL) characterised by expression of the transcription factor MEF2C, and/or is characterised by: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of (or an amount of) a KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene.

[854] Other compounds disclosed herein are also tested for their potency against cancer cell lines that overexpress MEF2C. For example, the potent SIK3 inhibitors **E4**, **E9**, **E10** and/or **E16** are tested for anti-cancer against pMEF2C-positive cell lines, such as KASUMI-1 and MV4-11 cell lines. Indeed, the GI50 of compound **E4** against KASUMI-1 cells was determined as less than 7.5nM, and its GI50 against MV4-11 cells was determined as less than 750nM.

Activity of other kinase inhibitors described herein against other cancer and leukaemia-associated cell lines: [comparative]

[855] Kinase inhibitors of formula (Ib)/(Ic) (eg, one or more of C1 to C13, or B3, and/or of D1 to D10) are tested for anti-cancer activity in one or more cell-based assays, and their activity in such assay(s) and compared to dasatinib (A8) to determine its differentiation and/or superiority.

[856] In one method, the direct cytotoxic effects of one or more of such compounds is tested on solid tumour cell lines in vitro using with the CellTiter-Glo® (CTG) Luminescent Cell Viability Assay (Promega, Cat. G7570). Tumour cells such as MDA-MB-231 (breast cancer), M579 primary melanoma cultures (as described in Khandelwal et al, 2015, EMBO Mol Med 7:540), PANC-1 (pancreatic cancer), SW480 (colorectal cancer), DMS273 (lung cancer) or murine tumour cell lines such as B16.ova, MC38, 4T1, and 1956 etc. are incubated (37oC/5% CO2) in wells of a microtitre plate with dasatinib (A8) or a kinase inhibitor of formula (Ib)/(Ic) (eg, C2, C8, C9 or C12, or B3, and/or one or more of D1 to D10) in a concentration series (eg, at 0, 1, 10, 100, 1,000, and 10,000 nM) for 48 hours. The protein-tyrosine kinase inhibitor (TKI)-susceptible K562 cell line is used as a control with 100 nM dasatinib. Viable cells are determined by adding 100uL of CTG reagent to the wells and incubating at room temperature for 10 min before luminescence readout using a Tecan Spark 10M luminometer.

[857] Indeed compound C7 was tested for its anticancer activity across a cell-panel representing a large number of haematological cancers and cell-lines (Oncolead, Karlsfeld Germany), and was found to inhibit the growth of numerous of such cell lines; showing a, sub-nanomolar GI50 activity on about 5 such cell lines and a GI50 activity of less than 10nM on about an further 10 such cell lines. For example, after 96 hours compound C7 showed a GI50 of about 8nM on the growth of the WSU-NKL B cell lymphoma cell line (Figure 15A), and a GI50 of about 9nM on the growth of the DIHH-2 B cell lymphoma cell line (Figure 15B). Other kinase inhibitors of formula (Ib)/(Ic) (eg, one or more of C1 to C13, or B3, and/or of D1 to D10) are similarly investigated.

[858] In an additional or alternative method, the anti-leukaemia activity of one or more of such compounds is tested, in particular in one or more cell-line(s) driven by BCR-ABL or mutants thereof (such as described by Gibbons et al 2014, PNAS 111:3550). Gene constructs for wild-type (wt) and T315I mutant Bcr-Abl (C-terminally tagged with eGFP) are constructed as previously described (Donato et al 2004, Cancer Res 64:672). The wt or T351I single mutant pMX/eGFP-Bcr-Abl template is used to generate templates for further or double mutants of BCR-ABL that are also associated with resistance to drug therapy with various TKIs of leukaemia (for example, T315I/V299L, T315I/F317L,

T315I/F359V, or other mutations listed in Table 6A) by site-directed mutagenesis (Stratagene). Following mutagenesis, the 4-kb XhoI/SgrAI sequence carrying the mutant (or double mutant) is sequenced and subcloned into the pMX/eGFP-BcrAbl template (at XhoI/SgrAI sites) to ensure that no other mutations are introduced during mutagenesis.

Table 6A:* BCR-ABL mutations associated with resistance to TKIs and therapeutic options. Compiled from studies reporting IC50 values derived using cell-line models.

BCR-ABL mutation	Drug resistance	Therapeutic options
Wild type M244V Q252H M315T F311L L387M H396P	-	imatinib dasatinib nilotinib bosutinib
G250E F311I H396R	imatinib	dasatinib nilotinib bosutinib
V299L T315A F317L/V/I/C	dasatinib bosutinib	nilotinib imatinib
Y253H/F E255K/V E355G V279I F359V/C/I	imatinib nilotinib	dasatinib
T315I	imatinib dasatinib nilotinib bosutinib	ponatinib
T315M	All TKIs	-

* Taken from Pophali & Patnik 2016, Canc J 22:40

[859] Parental Ba/F3 cells (murine IL-3 dependent murine pro B cell line) are maintained in RPMI medium with 10% FBS and 1 ng/mL mouse IL-3. Parental Ba/F3 cells at 2.5×10^6 are electroporated with 2.5 µg plasmid using the Amaxa Nucleofector system. After electroporation, Ba/F3 cells are rested overnight, and puromycin then added to the medium at a final concentration of 1 µg/mL. Transfected Ba/F3 cells are cultured in the RPMI medium/IL-3/puromycin media for more than a week. To ensure equivalent expression of BCR-ABL1 between wild-type and mutant cells, Ba/F3 cells are sorted by flow cytometry for eGFP positivity. Sorted eGFP-positive Ba/F3 cells are further selected in medium without IL-3. Cell growth rates are confirmed to be equivalent in all BCR-ABL1–transformed cells. Cells maintained in the absence of IL-3 for more than 1 week are used to examine inhibitor activity. For this, cells are incubated for 72h with the applicable TKIs to determine their effect on growth and survival of BaF3 cells as previously described (Wu et al 2010, Leukemia 24:869); for example by using a concentration series of a kinase inhibitor of formula (Ib)/(Ic) or dasatinib as described above.

[860] Analogously, the effect of kinase inhibitors of formula (Ib)/(Ic) (eg, one or more of C1 to C13, or B3, and/or D1 to D10) or dasatinib in leukaemia cell models carrying KIT mutations can be tested. For example, vectors carrying KIT wt or mutations (eg, those associated with drug resistance) can be transfected into transfect FDC-P1 murine bone-marrow cells and the effect of the compounds investigated on proliferation and clonogenic activity of FDC-P1/KIT (wt or mutant) cells, such as based on that described by Liu et al (2010, Cancer Cell 17:333).

Example 7 [prophetic]: In-vivo anti-leukemic efficacy of kinase inhibitors of formulae (Ia), (Ib) and (Ic) and of dasatinib.

[861] The in-vivo pharmacological activity of dasatinib, and the experiments used to show it are described in the EMEA's Committee for Medicinal Products for Human Use (CMHP) Scientific Discussion on dasatinib in 2006. In particular, as follows:

[862] The tumour inhibiting activity of dasatinib was evaluated in human CML xenograft models grown subcutaneously (SC) in SCID mice. Cures were defined as the absence of detectable tumour at a time greater than ten times the tumour volume doubling time after the cessation of treatment.

[863] Dasatinib was curative in mice bearing K562 human CML tumours over a range of dose levels (8-50mg/kg) when administered PO once a day for 10 days using a "5-days-on and 2-days off" treatment regimen. Treatment was initiated when the tumours reached a size of 200 to 500mg. High doses of imatinib failed to produce a comparative response. The minimum effective dose for dasatinib was determined as 2.5 mg/kg. In addition, dasatinib was highly efficient in this model when administered IV. Dasatinib was curative in mice bearing large KU812 tumours (up to > 1g tumour) when treated with 50mg/kg/day for 5 days.

[864] The SRC phosphorylation was investigated in peripheral mononuclear cell (PBMCs) collected from human prostate cancer cell (PC-3) bearing mice administered 1, 5, 15 or 50mg/kg dasatinib. Dasatinib treatment resulted in a dose-dependent inhibition of SRC phosphorylation with an almost complete inhibition within 5 hours following administration of 15 and 50mg/kg. Administration of 5mg/kg resulted in 44% inhibition of SRC phosphorylation whereas 1mg/kg was almost inactive. Based on AUC 0-24h values, the animal:human plasma exposure ratios were 0.8 and 1.9 for the 5mg/kg and 15mg/kg dose groups, respectively. Based on pharmacokinetic data it was estimated that the dasatinib plasma concentration required to inhibit 50% of phospho-SRC was 91nM in PBMCs.

[865] Dasatinib treatment (10mg/kg/day) increased survival in mice inoculated intracranially with K562 CML cells and the survival efficacy was superior to what was observed with imatinib (300 mg/kg/day). In a similar study, increased survival was observed following treatment with 10 and 30mg/kg/day dasatinib whereas 200mg/kg/day imatinib failed to inhibit intracranial tumour growth. Thus dasatinib appears to have a therapeutic advantage over imatinib in the treatment of intracranial CML.

[866] Dasatinib was active against a human CML model in mice whether treatment was administered daily for ten consecutive days or if a short treatment break (5-days-on and 2-days off) was introduced into the dosing regimen. Moreover, a twice-daily dosing regimen produced efficacy that was superior to the once daily dosing regimen. Consequently, in mice bearing K562 human CML tumours, a superior anti-tumour activity (cure) was observed in the twice-daily 1.25mg/kg dose group when compared to the dose group administered 2.5mg/kg dasatinib on a once-daily schedule (growth inhibition).

[867] One or more kinase inhibitor of formulae (Ia) (Ib) and (Ic) (eg, E1 to E16, C1 to C13, or B3, and/or D1 to D10) is tested in one or more of such investigations (for example, at doses of 1, 1.25, 2.5, 5, 10, 25, 30 or 50mg/Kg/day) to determine its differentiation and/or superiority in comparison to dasatinib (A8); in particular, one or more of **C7**, **E9**, **E10** and/or **E16**, or of C2, C8, C9 or C12, or B3 are so tested.

[868] In addition, or alternatively, one or more of such compounds are compared in the animal model described by Puttini et al (2006, Cancer Res 66: 11314), briefly as follows:

[869] Five- to 7-week-old female CD1 nu/nu mice are purchased from Charles River Breeding Laboratories and kept under standard laboratory conditions. Human KU812Bcr-Abl+ cells are suspended at 50 million cells in 0.5mL PBS and this cell suspension injected s.c. in the left flank of each animal. In another group of mice, murine Ba/F3 pro-B cells expressing Bcr-Abl WT or imatinib-resistant point mutants (Y253F, E255K, D276G, and T315I) are suspended at 10 million cells in 0.4mL PBS and injected s.c. to syngeneic nude mice. Tumour weight and body weight are monitored twice or thrice weekly. Tumour weight is calculated by the formula tumour weight (mg) = (d2 D / 2), where d and D are the shortest and longest diameters of the tumour, respectively, measured in millimetres. Tumour weight is calculated considering tumour-bearing animals only. Dasatinib (A8), or a kinase inhibitor of formulae (Ia), (Ib) and (Ic)

(eg, **C7**, **E9**, **E10** and/or **E16**, or C2, C8, C9 or C12, or B3), is given by oral gavage from day after cell infusion (for example, at doses of 1.25, 2.5, 5, 10, 30 or 50mg/Kg/day), at 8 days after cell injection when tumours entered growth phase or at 15 days to mice bearing measurable tumours. Placebo-treated animals received the same regimen with vehicle alone.

[870] As a further additional or alternative method, one or more of such compounds are compared in the animal model described by Fauvel et al (2013, Am J Can Sci 2:28), briefly as follows:

[871] A xenograft mouse model of imatinib-resistant leukemia is prepared by subcutaneously injecting Ba/F3 BCR-ABLT315I ($1x10^8$cell/mL sterile PBS) into the right flank of athymic nude male mice (HSD, 6-7 weeks old). When the tumour volume reaches approximately 50mm3, mice are assigned randomly to vehicle alone or treatment (dasatinib or compound B3) groups (five mice per group). Mice are treated with either vehicle (eg., DMSO or propylene glycol : water 1:1) or compounds (eg, 5, 10 or 40mg/kg q.d.; per os for 11 consecutive days) in vehicle. Tumour volumes in mm^3 are determined three times a week with a digital calliper and calculated using the following formula: Tumour Volume (mm^3) = length (mm) x width (mm) x width (mm) x ½. Body weight is measured three times a week, and mice observed daily for monitoring signs of stress to detect possible toxicities. One-way ANOVA is used for statistical comparisons using Prism 5.0b (GraphPad Software) by one-way ANOVA with Bonferroni post hoc.

Example 8.1: In-vivo anti-cancer (solid tumour) efficacy of kinase inhibitors of formula (Ia) and of other compounds disclosed herein, including compound **C7** and dasatinib

In-vivo anti-cancer (solid tumour) efficacy of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

[872] Using assays such as those described elsewhere herein (such as described below in Example 8.2), the inventors found that kinase inhibitors of formula (Ia) (fluorinated C7-like variants, eg **E4, E9 and E10**) showed surprisingly significant in-vivo anti-cancer efficacy.

[873] Similar as described in Table 8A (see Example 8.2) the following study outline was used (Table 8.1A). Dosage and administration regimens for the tested kinase inhibitors of formula (Ia) are adapted according to their respective SIK3 kinase inhibition and DMPK properties (see previous examples), such that their plasma free-drug concentration in relation to their SIK3 IC50 value was comparable to that for **C7**.

Table 8.1A: Example treatment groups.

Group	Treatment	Single dose (mg/kg)	Dosing	Route	Cumulated doses	Vehicle	Number of mice
1	Rat IgG2a isotyp control (clone 2A3)	10mg/Kg	3q7d	i.p.	6	Vehicle	6
2	Anti-mPD-1 (clone RMP1-14)	10mg/Kg	3q7d	i.p.	6	Vehicle	6
3	Vehicle*	10mg/Kg	BIDx14	po	28	-	6
4	C7	100mg/Kg	BIDx14	po	28	Vehicle	6
5	E4	40mg/Kg	BIDx14	po	28	Vehicle	6
6	E9	25mg/Kg	BIDx14	po	28	Vehicle	6
7	E9	50mg/Kg	BIDx14	po	28	Vehicle	6

8	E10	30mg/Kg	BIDx14	po	28	Vehicle	6
9	Rat IgG2a isotyp control (clone 2A3)	10mg/Kg	3q7d	i.p.	12	Vehicle	10
10	Anti-mPD-1 (clone RMP1-14)	10mg/Kg	3q7d	i.p.	12	Vehicle	10
11	Vehicle	10mg/Kg	BIDx28	po	56		10
12	C7	100mg/Kg	BIDx28	po	56	Vehicle	10
13	E4	40mg/Kg	BIDx28	po	56	Vehicle	10
14	E9	25mg/Kg	BIDx28	po	56	Vehicle	10
15	E9	50mg/Kg	BIDx28	po	56	Vehicle	10
16	E10	30mg/Kg	BIDx28	po	56	Vehicle	10

* = 10% DMSO + 5% Solutol +40% PEG + 45% water

[874] Additionally, tumour and blood samples were used to analyse various immune-response markers, for example those set forth in Table 8.1B below (and as described below in connection with Table 8D in Example 8.2).

Table 8.1B: Example immune-phenotype markers.

T cell panel		Myeloid cell panel	
Target	Clone	Target	Clone
CD45	30-F11	CD45	30-F11
CD3e	145-2C11	CD3e	145-2C11
CD4	RM4-5	CD11b	M1/70
CD8	53-6.7	F4/80	BM8
CD25	PC61	Ly6C	AL-21
FoxP3	FJK-16s	Ly6G	1A8
IFNy	XMG1.2	CD206	C068C2
GrzB	NGZB	MHC-II	10-3.6
CD69	H1.2F3	CD49b	DX5
CD107a	1D4B	CD335	29A1.4
Live/dead	(Zombie Dye)	Live/dead	(Zombie Dye)

[875] The inventors were surprised to observe that twice daily application of all tested kinase inhibitors of formula (Ia) induced strong tumour growth inhibition. Indeed, compound **E10** showed 46% TGI, whereas **C7, E9** and **E10** showed even 60 to 80% TGI (Table 8.1C). The inventors also observed the very surprising result that the anti-cancer efficacy of those compounds was even superior to anti-PD-1 therapy, which only resulted in 4% TGI (Figures 20 A and B, and Table 8.1C). Indeed, a tumour growth inhibition effect with the inhibitors was seen in almost all of the treated mice of the compound treated cohortss (Figures 20C to E), in comparison to only few responding animals in the anti-PD1 treated and control groups (Figures 20F to H).

[876] Indeed, a compound of formula (Ia) (**E9**, dosed at 25mg/kg BID) consistency shows tumour growth inhibition across all individual mice in the treatment group (average TGI = 72%), compared to increased variability in a

comparative study with dasatinib (**A8**, dosed at 30mg/kg QD), where in some cases individual mice in the dasatinib treatment (average TGI = 56%) grew significant tumours (Figure 27).

[877] Furthermore, and providing further evidence that kinase inhibitors of formulae (Ia) (especially **E4, E9** and **E10**) exhibit drug-like properties when administered orally, no direct treatment related side effects and clinical signs, such as loss of body weight were observed.

Table 8.1C: In-vivo data of kinase inhibitors of formula (Ia) compared to PD-1.

Treatment	Tumour growth inhibition (%)	Body weight increase (%)	Non-treatment related death
Rat IgG2a isotyp control (10mg/Kg)	0	25.4	2/16
Anti-mPD-1, (10mg/Kg)	4	30.6	1/16
Vehicle (10mg/Kg)	0	24.0	2/16
C7 (100mg/Kg, BID)	78	1.0	3/16
E4 (40mg/Kg, BID)	64	12.0	3/16
E9 (25mg/Kg, BID)	74	16.8	2/16
E9 (50mg/Kg, BID)	69	18.7	3/16
E10 (30mg/Kg, BID)	46	19.8	0/16

[878] In addition, these kinase inhibitors of formula (Ia) demonstrated a surprisingly significant effect on the immune cells present in the tumour microenvironment (Figure 21). Twice daily treatment with the fluorinated C7-like kinase inhibitors induced a prominent anti-tumour immune-phenotype. A significant increase (Figures 21 A and B) of activated cytotoxic T lymphocytes (CD3+CD8+), as well as increased activation of cytotoxic T lymphocytes indicated by CD25 and granzyme B (Figures 21 C and D) and CD69 and CD107 (data not shown) could be demonstrated, even compared to anti-PD-1 treatment.

[879] It was particularly surprising to observe the increase in granzyme B (increase in CTLs), and a decrease on immunosuppressive cells (Tregs and M1 TAM) when animals are treated with compound E9.

[880] Accordingly, a reduction of immunosuppressive regulatory T cells (CD3+CD4+CD25+FoxP3+) was also induced for **E4** and **E9**, and also for **C7** (Figure 21 E).

[881] In addition, a surprising reduction of the immunosuppressive myeloid immune compartment could be observed by the inventors (Figures 21 F to H). A depletion of myeloid cells could be detected after treatment with **E4** and **E9** (at 25mg/kg), and also for **C7** (Figure 21 F). Indeed, immunosuppressive M2 macrophages (CD206+MHC-II-) were demonstrated by the inventors to be significantly reduced by twice daily treatment with kinase inhibitors of formula (Ia), again even compared to anti-PD-1 (Figure 21 H). Maintenance of anti-tumour M1 macrophages (CD206-MHC-II+) was also demonstrated (Figure 21 G).

[882] Furthermore, a moderate increase of mMDSC's could be demonstrated by the inventors after treatment with **E4** and **E9**, and **E10**, and also with **C7**, although a moderate decrease on gMDSCs was observed (Figures 21 I and J).

[883] Compounds of formula (Ia) (for example, **E9**) are analogously tested in other syngeneic murine tumour models, including those with tumours generated from cells lines selected from the group consisting of: CT26, RENCA; EMT6 and 4T1.

Example 8.2 [comparative]: In-vivo anti-cancer (solid tumour) efficacy of kinase inhibitors of formula (Ib)/(Ic) and of dasatinib.

In-vivo anti-cancer (solid tumour) efficacy of other compounds disclosed herein, including of compounds of formula (Ib)/(Ic): [comparative]

[884] The anti-cancer activity of kinase inhibitors of formula (Ib)/(Ic) (eg, C1 to C13, or B3) and of dasatinib (A8) against solid tumours are investigated in an in vivo syngeneic mouse model, whereby murine colorectal carcinoma cells MC38 are implanted subcutaneously in the flanks of C57Bl/6N mice and treated with the test compound (eg, C2, C8, C9 or C12, or B3 or A8, at doses of between eg 2.5mg/mL/day up to 50, 60 or 100mg/Kg/day*). In detail, female C57Bl/6N mice (4-6 weeks old), are implanted with of $1x10^6$ MC38 colorectal carcinoma cells (100µl in PBS). Mice are randomised into treatment groups after reaching $150mm^3$ tumour volume, and treatment groups may, for example, comprise those as set forth in Table 8A, with treatment starting within 24h of randomisation.

Table 8A: Example treatment groups.

Group	Treatment	Total daily dose [mg/kg/d]	Dosing days	Route**	Vehicle	Number of mice
1	Vehicle	-	daily	po	-	15
2	B3	60mg/Kg*#	daily#	po	Vehicle**	15
2	B3	30mg/Kg*	daily	po	Vehicle**	15
3	A8 (dasatinib)	30mg/Kg*	daily	po	Vehicle**	15

* Based on last bodyweight measurement; ** po = per os, oral administration via gavage

For at least 3 weeks, up to about 5-8 weeks. Lower dosage (eg, 10, 15 or 20mg/Kg) for C2, C8, C9 and C12 can be adapted according to their ADMET/PK properties.

** Propylene glycol : water 1:1

[885] Mice are measured for body weight and tumour volume (mm^3) by calliper measurement twice weekly for up to 8 weeks until termination criteria (tumour volume> 2000 mm^3) is reached.

[886] Additionally, 5 mice per group are sacrificed after day 9 of first treatment to analyse tumour and blood samples for various immune-response markers, for example those set forth in Table 8B below, (as well as using Aqua Zombie (BioLegend) to determine live/dead cells).

[887] Briefly, peripheral blood samples are collected (however, the day before sacrifice) from these mice into heparin-precoated tubes by making an incision in the tail of the mice. After treating the blood samples with ammonium–chloride–potassium (ACK) lysing buffer (Life Technologies, Cat. A10492-01), the cells are stained with fluorochrome-conjugated mAbs to one or more of the example immune-phenotyping markers (eg, Table 8B).

[888] For immune-phenotyping of the tumours, tumours are surgically removed on the day of sacrifice with a scalpel and then divided in half. One part of the tumour is fixed in 4% paraformaldehyde (PFA) for immunohistochemistry for one or more of the example immune-phenotype markers. For IHC, PFA-fixed tumor tissues are embedded into paraffin blocks and cut at 4 mm thickness. After fixing on glass slides and antigen-retrieval step, the sections are stained with anti-CD8 antibody and counterstained with Mayer-Hematoxylin. The counting of the tumour infiltrating CD8 T cells is done at 50x magnification starting from capsule area and counting 3 fields toward to the core of the tissue. The same process was repeated 3 times. All counts were summed, and the median calculated (as described in Hekim et al 2017, Can Imm Res 5:157).

[889] The other half of the tumour is transferred into 1.5-mL tubes containing RPMI 1640 medium and then homogenized manually using micro tube pellet pestle. After centrifugation at 300xg, the supernatant was discarded, and cells were resuspended in RPMI medium equal to the tumour weight. Tumour homogenate is diluted 1:1 in PBS

and stained with fluorochrome-labelled antibodies for one or more of the example immune-phenotype markers. For all Foxp3-specific staining (peripheral or intra-tumoural), cells are first labelled with the anti-CD4 antibody before incubation with the anti-Foxp3 antibody using an Intracellular Fixation and Permeabilization Kit as recommended by the manufacturer (eBioscience)

Table 8B: Example immune-phenotype markers.

Marker	Antibody clone	Supplier
Populations: T-cells, CD4+ T cells, CD8+ T-cells, Tregs:		
CD45	30-F11	Biolegend
CD3e	145-2C11	BD Biosciences
CD4	RM4-5	BD Biosciences
CD8	53-6.7	BD Biosciences
CD25	PC61	BD Biosciences
FOXP3	FJK-16s	Thermo Fisher (eBioscience)
IFN-g	XMG1.2	Biolegend
Granzyme B	NGZB	Thermo Fisher (eBioscience)
CD107a	1D4B	Biolegend
CD69	H1.2F3	BD Biosciences
Populations: M1 macrophages, M2 macrophages, monocytic MDSC's, granulocytic MDSC's, NK cells:		
CD45	30-F11	Biolegend
CD3e	500A2	BD Biosciences
CD11b	M1/70	BD Biosciences
F4/80	BM8	ThermoFisher
CD206	MR6F3	ThermoFisher
LY6G	M1/70	BD Biosciences
LY6C	AL-21	BD Biosciences
CD49b	DX5	BD Biosciences
CD335	29A1.4	BD Biosciences

[890] It was demonstrated both the anti-cancer activity of kinase inhibitor C7, compared to dasatinib (A8), against solid tumours in an in vivo syngeneic mouse model, as well as the immune-oncology effect of this compound of formula (Ib)/(Ic). Dosage and administration regimens for the compounds of formula (Ib)/(Ic) (eg, C7) are adapted according to their respective SIK3 kinase inhibition and DMPK properties (see previous examples), such that their plasma free-drug concentration in relation to their SIK3 IC50 value was comparable to that for dasatinib. Compound A8 (dasatinib) was treated as previously described (Hekim et al 2017). One or more other kinase inhibitor of formula (Ib)/(Ic) (eg, C1 to C13, or B3, and/or D1 to D10) are analogously investigated.

[891] Twice daily treatment with C7 (100mg/kg) demonstrated significant tumour growth retardation (44% TGI) whereas once daily C7 treatment showed 29% tumour growth inhibition compared to vehicle control (Figure 11A). In comparison, daily treatment with A8 (30mg/kg) demonstrated a tumour growth inhibition of 38%. Animals were weighed at least twice per week until completion of the study. No treatment related side effects and clinical signs, such as loss of body weight were observed (Figure 11B).

[892] In addition, compound C7 was demonstrated to have a significant effect on the immune cells present in the tumour microenvironment (Figure 12). Twice daily treatment with C7 induced a prominent anti-tumour immune-phenotype; with significantly increased ratio (Figure 12A) of cytotoxic T lymphocytes (CD3+CD8+) to regulatory T cells (CD3+CD4+CD25+FoxP3+), as well as increased activation of cytotoxic T lymphocytes indicated by CD25+CD69+ (Figure 12B) and granzyme B (Figure 12C) expression. In addition, immunosuppressive M2 macrophages (CD206+MHC-II+) were significantly reduced by once and twice daily treatment with C7 as well as A8 (Figure 12D).

[893] The in vivo syngeneic mouse model was conducted as follows: female C57Bl/6N mice (4-6 weeks old), were implanted with of 5x10e5 MC38 colorectal carcinoma cells (100ul in PBS). Mice were distributed into treatment groups (Table 8C) to reach an average tumour volume of 100mm^3, and per-oral treatment by gavage was started within 24h of randomisation.

Table 8C: Treatment groups.

Group	Treatment	Dose*	Dosing	Route	Number doses	Animals
1	PBS	10ml/kg	QD x 18	**p.o	18	10
2	vehicle#	10ml/kg	QD x 18	p.o	18	10
3	Dasatinib	30mg/kg	QD x 18	p.o	18	10
4	C7	100mg/kg	QD x 18	p.o	18	10
5	C7	100mg/kg	BID x 18	p.o	36	10

* Based on last bodyweight measurement; ** p.o. = per os, oral administration via gavage; # 4%(v/v) DMSO, 72%(v/v) propylene glycol and 24%(v/v) dd-water

[894] On Day 18, two hours after the last dose, at least 100uL of whole blood, as well as tumour tissue, of six animals in each group were analysed by flow cytometry for CD4+ and CD8+ T cells, Tregs, granulocytic and monocytic MDSCs, M1 and M2 macrophages and NK cells. Immediately following blood collection, tumours were excised and processed for analysis by flow cytometry. Tumour and blood samples were analysed for various immune-response markers (Table 8D), as well as using a Zombie dye (BioLegend) to determine live/dead cells. Intracellular cytokines within the lymphoid panel were detected after ex vivo stimulation of T cells with PMA/ionomycin/Brefeldin A.

Table 8D: Immune-phenotype markers.

T cell panel		Myeloid cell panel	
Target	Clone	Target	Clone
CD45	30-F11	CD45	30-F11
CD3e	145-2C11	CD3e	145-2C11
CD4	RM4-5	CD11b	M1/70
CD8	53-6.7	F4/80	BM8
CD25	PC61	Ly6C	AL-21
FoxP3	FJK-16s	Ly6G	1A8
IFNy	XMG1.2	CD206	C068C2
GrzB	NGZB	MHC-II	10-3.6
CD69	H1.2F3	CD49b	DX5
CD107a	1D4B	CD335	29A1.4
Live/dead	(Zombie Dye)	Live/dead	(Zombie Dye)

[895] Sample preparation for flow cytometry was conducted as follows: whole blood samples were processed by adding a ten-fold volume of ammonium-chloridepotassium (ACK) buffer at ambient temperature, mixed gently and incubated for 3-5 minutes at room temperature. Immediately after incubation, a ten-fold volume of cold PBS was added to stop the lysis reaction, and cells were pelleted at 400g for five minutes and washed again in PBS. Mouse tumour samples were dissociated according to the manufacturer's instructions using the gentleMACS(TM) protocol "Tumor Dissociation Kit". Briefly, tumours were excised, cut into small pieces (2-4 mm), placed into an enzymatic buffer and processed on a gentleMACS Dissociator, incubated for 20 minutes at 37°C with continuous rotation. Samples were filtered through a 70um cell strainer and rinsed twice in PBS/2.5% FBS buffer to remove enzymatic buffer. All single cell suspensions were prepared at ~1x10e7 cells/mL in PBS and kept on ice. Ex vivo stimulation of samples was performed for T-cell marker-panel populations with PMA/ionomycin/Brefeldin A. 100uL of single cell suspensions were added into 96-well plates, stained, and analysed with an LSRFortessaTM (BD) and analysed with FlowJo software (Tree Star, Inc.; version 10.0.7r2).

Example 9.1: Sensitisation of tumour cells to in-vitro TNF attack by the kinase inhibitor of formulae (Ia) and (Ib)/(Ic), and of dasatinib

Sensitisation of tumour cells to in-vitro TNF attack by of compounds with fluorinated substituents of R^6 of compounds of formula (Ia):

[896] Using assays such as those described in connection with Table 9B (see Example 9.2), the inventors used kinase inhibitors of formula (Ia) (fluorinated C7-like variants, eg **E4, E9** and **E10**) to demonstrate a surprising sensitisation of tumour cells to the cytotoxic effects of recombinant mouse TNF. That was done in a TNF-sensitised (100ng/mL) cell viability assay using the MC38 murine tumour cell line described below (Table 9B). The compounds were analogously tested against the human cancer cell line HCT116 and PANC1. Indeed, MC38 tumour cells as well as HCT116 and PANC1 tumour cells were surprisingly sensitised to the cytotoxic effect of TNF by the kinase inhibitors of formula (Ia) **E4, E9**, **E10** and **E16**, comparably to **A8** (dasatinib) and C7 (Table 9.1A). TNF-induced cell killing in HCT116 and PANC1 cells was measured analogously to the assay in MC38 cells (described in Example 9.2), except that 10ng/ml and 100ng/ml human TNF was used, respectively.

Table 9.1A: Sensitisation to TNF-mediated killing of MC38 and HCT116 cells by fluorinated C7-like compounds compared to C7 and dasatinib

Compound	MC38 IC50 (at 100ng/mL rMuTNF)	HCT116 IC50 (at 10ng/ml rHuTNF)	PANC IC50 (at 100ng/ml rHuNF)
A8	++	++	NT
C7	+	++	NT
E4	++	++	NT
E9	++	++	++
E10	++	++	NT
E10 Ent-I	++	++	+
E10 Ent-II	+	++	++
E16	++	++	++

++ = <100nM; + = <200nM;

NT = not tested

[897] The investigators also demonstrated that the compounds **E4, E9** and **E10** exhibited a surprisingly increased inhibition of TNF-induced activity of NFkB in MC38 and PANC1 cells, compared to **A8** and **C7** (Table 9.1C and Figure

14A and Figure 28 A and B). Indeed, Figure 25 shows that kinase inhibitors of formula (Ia) **E4, E9** and **E10** are consistently more potent at sensitising MC38 tumour cells to TNF-mediated killing, with mean EC50s of well under 100nM compared to almost 150nM for the structurally similar compound **C7**.

[898] A compound of formula (Ia) (**E9**) was also potent at sensitising different murine tumour cells to TNF-mediated killing, typically more potently than the structurally similar compound **C7** (Figure 25). Other compounds of formula (Ia) are similarly tested.

[899] Taking into consideration biochemical and key pharmacokinetic properties, it can be clearly seen from Table 9.1B that compounds of formula (Ia) exhibit relatively superior drug-like properties in comparison to the structurally similar compound **C7**, which (by comparison to the above) is itself superior to the prior art heterocyclic compound **B3**. Indeed, compound **E9** is surprisingly potent as a SIK3 inhibitor, and shows surprisingly superior PK properties compared to the other tested compounds (and also to dasatinib, A8)

Table 9.1B: Relative superiority of compounds of formula (Ia) over compound **C7**

Parameter	C7	E4	E9	E10
SIK3 IC50 (nM)	1x	0.6x	0.3x	0.7x
Total plasma concentration at 30 mg/kg p.o dose				
C max (ng/ml)	1x	2.6x	5.6x	1.7x
$t_{1/2}$ (h)	1x	3.2x	2x	14.5x
$AUC_{0\text{-last}}$ (nM*h)	1x	4.7x	8.2x	2x
$MRT_{0\text{-last}}$ (h)	1x	2x	1.2x	2.8x

[900] Additionally, the compounds also surprisingly showed increased inhibition of phosphorylation of HDAC4, the direct substrate of SIK3 kinase and the key mediator of NFkB activity (Table 9.1C, Figure 14 B and Figure 28 C). TNF-induced NFKB activity in MC38 cells was measured analogously to the assay in PANC-1 cells described in connection with Table 9C (Example 9.2), except that 10ng/ml rMuTNF was used.

[901] Overall, the investigators demonstrate that compounds of the formula (Ia), and in particular compound **E9**, show enhanced biochemical inhibition of SIK3 kinase (Table 9.1B) resulting in more potent inhibition of TNF-induced phosphorylation of HDAC4 and NFkB activity in diverse cells than the structurally related compound **C7** (Table 9.1C). Furthermore, compounds **E4** and **E10** exhibit, and especially compound **E9** exhibits, superior drug-like pharmacokinetic profile in vivo than the compound **C7** as summarised in Table 9.1B.

Table 9.1C: Increased inhibition of NFKB activity and HDAC4 phosphorylation by kinase inhibitors of formula (Ia) compared to **C7** and dasatinib

Compound	Inhibition of NFKB activity (MC38)	Inhibition of NFKB activity (PANC-1)	Inhibition of HDAC4 phosphorylation
A8	+	+	++
C7	+	+	+
E4	++	++	++
E9	++	++	++
E10	++	++	++

+ = Significant inhibition; ++ = Strong and significant inhibition

[902] On-target SIK3 inhibition was demonstrated for **C7** and the kinase inhibitor of formula (Ia) **E9**. Wildtype (WT) and SIK3 knockout (KO) MC38 clones were treated with sub-optimal concentration of TNF (i.e. <10ng/ml to allow sufficient assay window with SIK3 KO cells which would be fully sensitive to higher doses of TNF regardless of inhibitor

titration) and the SIK3 inhibitors **C7**, **E4**, **E9** and **E10**, and viability of the cells was subsequently determined. The inventors thereby showed these compounds induced TNF-mediated killing only in SIK3 WT clones, but not in the KO clones (Figure 22 for **C7** and **E9**), thereby demonstrating SIK3-dependent effect of inhibitors in mediating TNF-induced killing.

[903] The assay was performed as follows: MC38 SIK3 KO clones were generated using CRISPR. Cells were transfected with RNP complexes (Cas9 + gRNA) containing gRNAS targeting SIK3 or non-targeting sequences (control). SIK3 expression in the bulk was validated using qPCR 72h after transfection. Subsequently, single cell clones were generated by limiting dilution. CRISPR-derived mutations in single clones were detected by next-generation sequencing and analysed using CRISPResso. Knockout and wildtype clones were selected and plated overnight. KO and WT cells were treated with rMuTNF and different concentrations of inhibitor for 72h. Cells treated with different concentrations of inhibitor but without TNF served as no TNF control. Cell viability was measured by CTG assay.

Example 9.2 [comparative]: Sensitisation of tumour cells to in-vitro TNF attack by the kinase inhibitor of formula (Ib)/(Ic), and of dasatinib

Sensitisation of tumour cells to in-vitro TNF attack by other compounds described herein, including compounds of formula (Ib)/(Ic):

[904] Investigated was the effect of the kinase inhibitors of formula (Ib)/(Ic) (eg C2, C8, C9 or C12, or C4, or C7 or B3; or in particular, C7; and/or one or more of D1 to D10), and dasatinib (A8) in comparison, on the killing (apoptotic/cytoxic) effect of TNF to tumour cells in vitro, and determined the sensitisation - by the kinase inhibitor of formula (Ib)/(Ic) - of a modified PANC1 or M579-A2 cell-line to TNF attack. Other compounds of formula (Ib)/(Ic), such as C5, are similarly tested.

[905] Treatment with the kinase inhibitor (eg, C7 or B3) (tested at one or more concentrations of, for example, between about 1nM to 10,000nM, such as about 10nM, 25nM, 50nM, 100nM, 150nM, 500nM, 1,000nM, 2,500nM and/or 5,000nM in DMSO) is used to investigate sensitisation of PANC-1-luc or M579-A2-luc tumour cells to the cytotoxic effects of recombinant human TNF (rHuTNF; R&D Systems), and also the speed of onset of this effect. PANC1-luc is an HLA-A2.1+ luciferase-expressing pancreatic adenocarcinoma (PDAC) tumour cell line, and M579-A2-luc is an HLA-A2.1+ luciferase-expressing melanoma tumour cell line.

[906] The dose-response effect of rHuTNF treatment on the viability of the indicated PANC-1-luc cells is shown as a graph (Figure 6) of the relative (cytotoxicity/viability) of tumour cells after treatment with rHuTNF at the respective concentration with the respective test compound (eg, B3 or A8) or control (eg, DMSO), and Y-axis is the normalised RLU (as a measure of cytoxicity) of +TNF (cytotoxicity)/relative to without TNF (viability) measured using a luciferase-based killing assay: cells, test compound and then rHuTNF (10ng/mL) are incubated for 24h at 37oC, 5% CO2, supernatant removed after culture and the remaining PANC-1-Luc cells lysed with luciferase cell lysis reagent (0.3% Triton-X in water) for 10min. After lysis, luciferase assay buffer is added and immediately the luciferase intensity was measured by using the TECAN-Spark microplate reader.

[907] To determine speed of onset of cell death, tumour cells are pre-labelled with nuclear incorporation of YOYO-1 dye and treated with inhibitors and TNF as indicated above. Tumour death kinetics is evaluated using real-time live cell microscopy with IncuCyte Zoom (Essen BioScience) by a graph showing the area of YOYO-1+ cells/well (μm^2/well) (ie, apoptotic cell area) of images after 6h stimulation, with cumulative data of (eg 5 – 10) different pictures from the same experiment. Indeed, compound C7 is shown to sensitise PANC-1 cells to the effect of rHuTNF in such real-time live cell assay (Figure 13A), and also in the luciferase-based tumour cell viability readout described above (data not shown).

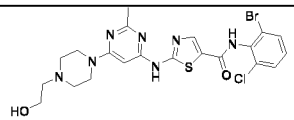
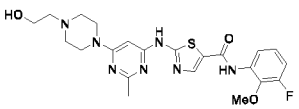
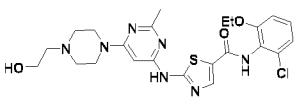
[908] The PANC1-luc cell line is constructed as follows: PANC-1 cells acquired from the American Type Cell Culture (ATCC). Tumour cells are transfected with a pEGFP-Luc plasmid, using TransIT-LT1 (Mirus) as transfection reagent. Transfected cells are selected with 1mg/mL of G418/Geneticin, and 14 days after selection EGFP+ cells are sorted using, eg a BD FACSARIA II cell sorter.

[909] The tumour immuno-oncology effect is demonstrated to be mediated by SIK family members, and by SIK3 in particular. Using the luciferase-based tumor cell viability readout described above, tumour cells show increased cytotoxicity in the presence of TNF (10ng/mL) and a pan-SIK and ABL1 & SRC inhibitor (compound B1) at a concentration of between about 10 and 100 nM (circles), compared to in the presence of inhibitor alone (squares) (Figure 7A). In contrast however, compound B8 which is a potent ABL1 & SRC inhibitor but with low inhibitory activity against SIK family members (in particular SIK3), in combination with TNF (circles) fails to exhibit cytotoxicity of M579 A2 cells at such concentration range, compared to inhibitor alone (squares) (Figure 7B). Indeed, in combination with TNF compound B4 (circles) also fails to exhibit cytotoxicity of M579 A2 cells at such concentration range, compared to inhibitor alone (squares) (Figure 7C), despite compound B4 being not only a potent inhibitor of ABL1 & SRC but also a strong inhibitor or SIK1 and SIK2, but only a weak inhibitor of SIK3.

[910] Taken together, these data implicate SIK family members, and in particular SIK3, as being the mediator of the anti-tumour immuno-oncology effect and not the other kinase ABL1 or SRC.

[911] Compounds B1, B4 and B8 are as described, including their synthesis, in PCT/EP2018/060172, and are shown in Table 9A.

Table 9A: Compounds B1, B4 and B8

Compound Number	Structure	Name
B1		N-(2-bromo-6-chlorophenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
B4		N-(3-fluoro-2-methoxyphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide
B8		N-(2-chloro-6-ethoxyphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

[912] Other kinase inhibitors of formula (Ib)/(Ic) (e.g., one or more of C1 to C13, such as C7, and/or one or more compounds from Table B, D1 to D10) are used to investigate sensitisation of tumour cells to the cytotoxic effects of recombinant human TNF, including in a TNF-sensitised (100ng/mL) cell viability assay using the MC38 murine tumour cell line (Table 9B). Indeed, MC38 tumour cells are sensitised to the cytotoxic effect of TNF by compound C7 (Figure 13B).

Table 9B: Sensitisation to TNF-mediated killing of MC38 cells by compounds of formula (Ib)/(Ic)

Compound	MC38 IC50 (nM at 100ng/mL TNF)
A8 (dasatinib)	++
C7	++
D1	+

D7	+
D8	/
D9	++

++ = <100nM; + = <200nM; / = >200nM

[913] The assay demonstrating that compounds of formula (Ib)/(Ic) sensitise MC38 cells to TNF-mediated killing is conducted as follows. Cell viability of MC38 tumour cells was measured using the CellTiter-Glo (CTG) luminescent cell viability assay (Promega, Madison, USA) according to the manufacturer's protocol. In short, $1x10^3$ MC38 cells were seeded in a 384-well plate for 24h and subsequently treated with different concentrations of compounds of formula (Ib)/(Ic) / C7 and 100ng/ml rMuTNF for 72h at 37°C and 5% CO_2. After incubation, CTG reagent was added to the wells and cells were lysed for 10min. Read-out was performed using the Tecan reader with 0.1sec counting time.

[914] Compound C7 is also shown to inhibit TNF-induced activity of NFkB in a dose-dependent manner (Figure 14A), and also to inhibit the phosphorylation of HDAC4, the key mediator of NFkB activity (Figure 14B). Other compounds disclosed herein, such as dasatinib (A8), and/or those selected from compounds C2 to C12 and/or D1 to D10 are investigated for analogous activities (Table 9C).

Table 9C: Inhibition of NFKB activity and HDAC4 phosphorylation by compounds of formula (Ib)/(Ic)

Compound	Inhibition of NFKB activity	Inhibition of HDAC4 phosphorylation
A8 (dasatinib)	+	++
C7	+	+
D9	+	+

+ = Significant inhibition; ++ = Strong and significant inhibition

[915] TNF-induced NFKB activity in PANC-1 cells was measured using NFKB-dependent luciferase activity. PANC-1 clones were generated to express luciferase under the control of a NFKB promotor. NFKB reporter PANC-1 cells (1,250 per well) were seeded in 384-well plates for 24h. Afterwards, cells were treated with different concentrations compounds of formula (Ib)/(Ic) / C7 / fluorinated C7-like variants (formula (Ia)) for one hour at 37°C and 5%CO_2 before addition of 10ng/ml rHuTNF. After 7h incubation, cells were lysed, and luciferase activity was measured as before.

[916] HDAC4 phosphorylation levels in PANC-1 cells were measured using a Meso Scale Discovery (MSD) assay. PANC-1 cells ($6x10^4$) were seeded in a 96-well plate overnight and subsequently treated with different concentrations of compounds of formula (Ib)/(Ic) / C7 / fluorinated C7-like variants (in the presence of 10ng/mL rHuTNF) for 3h at 37°C and 5%CO_2. Whole cell lysates were generated using RIPA lysis buffer (Thermo Scientific) and incubated on GAM plates coated with anti-total HDAC4 antibody (Abcam ab12171) overnight at 4°C. Afterwards, phosphorylated HDAC4 was detected using the pHDAC4 antibody (CST#3443). ECL signal was measured using an MSD reader.

Example 10: In-vivo immune-oncology activity of kinase inhibitors of formulae (Ia) and(Ib)/(Ic)

[917] The anti-cancer activity of kinase inhibitor E9 and anti-PD-1 mAb (murine anti-PD1-mIgGe3, clone: RMP1-14, Invivogen; Cat No: mpd1-mab15) against solid tumours – alone and in combination - were investigated in an in vivo syngeneic mouse model, essentially as describe in Example 8.2, whereby murine colorectal carcinoma cells MC38 were implanted subcutaneously in the flanks of C57Bl/6N mice and treated with the test compound **E9** at dosage 25 mg/Kg twice daily. In this study, however, at an average tumour volume of 100 mm3 MC38 tumour-bearing animals were

block-randomised into 4 groups of 18 animals each, as summarised in Table 10(a). For block-randomisation, a robust automated random number generation within individual blocks was used (MS-Excel 2016). During the course of the study 8 animals per group were terminated after 21 days of treatment for ImmunoPD analysis (PD study), similar to as described above, and a necropsy was performed. For overall survival analysis of study animals were euthanised individually, after they had reached ethical abortion criteria. All animals were euthanised by cervical dislocation without performing a necropsy.

Table 10(a): Treatment groups.

Group	Treatment	Single dose [mg/kg]*	Dosing	Route	No. of mice
1	Vehicle#	10ml/kg	BID; 7q7d##	p.o.**	18
	mIgG1e (isotype Ctrl)###	2.5mg/kg	2q7d	i.p.***	
2	Vehicle#	10ml/kg	BID; 7q7d	p.o.	18
	anti-mPD-1 (clone: RMP1-14)	2.5mg/kg	2q7d	i.p.	
3	E9	25mg/kg	BID; 7q7d	p.o.	18
	mIgG1e	2.5mg/kg	2q7d	i.p.	
4	E9	25mg/kg	BID; 7q7d	p.o.	18
	anti-mPD-1	2.5mg/kg	2q7d	i.p.	

* Based on last bodyweight measurement; ** p.o. = per os, oral administration via gavage; *** i.p. intraperitoneal # vehicle = 10% DMSO + 5% Solutol +40% PEG + 45% water; ## For at least 3 weeks, up to about 5-8 weeks; ### murine anti-beta-Gal-mIgG1e3, Invivogen; Cat No: bgal-mab15.

[918] Twice daily application of compound **E9** induced strong tumour growth inhibition (Table 10(b) and Figure 29A) and significant prolonged median overall survival (Table 10(b) and Figure 29B) compared to vehicle treated animals. Compound **E9** showed 73% TGI and a homogenous response in all treated animals (Figure 29C), whereas treatment with the immune checkpoint inhibitor anti-PD-1 reached only 59% TGI (Table 10(b) and Figure 29A) with a diverse anti-tumour efficacy in different animals (Figure 29D). The combination of **E9** and anti-PD-1 demonstrated 81% TGI, 50 days overall survival. Although it is not significantly superior compared to **E9** monotherapy ($p=0.0905$) it could significantly improve TGI compared to that if the anti-PD-1 therapy ($p<0.0001$), as well as showing a homogenous response in all treated animals (Figure 29E).

Table 10(b): Tukey's multiple comparisons test.

Comparison	Significance summary	Adjusted P Value
Vehicle + mIgG1e ctrl. vs. vehicle + αPD-1	****	<0.0001
Vehicle + mIgG1e ctrl. vs. E9	****	<0.0001
Vehicle + mIgG1e ctrl. vs. E9 + αPD-1	****	<0.0001
Vehicle + αPD-1 vs. E9	****	0.0003
Vehicle + αPD-1 vs. E9 + αPD-1	****	<0.0001
E9 vs. E9 + αPD-1	ns	0.0905

ns = not significant

[919] To investigate the synergistic effect of TNF-inducing therapy (eg, an anti-PD1 antibody, such as murine anti-PD1 clone: RMP1-14, BioLegend or Invivogen) with another kinase inhibitor of formulae (Ia) and (Ib)/(Ic) (eg, **E10** or **E16**, or C2, C7, C8, C9 or C12, or B3; and/or one or more of compounds D1 to D10), and **E9** and/or dasatinib (A8) in

comparison (at doses of between eg 2.5mg/Km/day up to 50, 60 or 100mg/Kg/day*), a further in vivo syngeneic mouse model as described in Example 8.2 is conducted, but with treatment groups addressing applicable combinations (and controls), for example treatment groups which may, for example, comprise those as set forth in Table 10A, below.

Table 10A: Example treatment groups.

Group	Treatment	Total daily dose [mg/kg/d]	Dosing days	Route**	Vehicle	Number of mice
5	Vehicle** + ratIgG2a (control)	10mg/Kg*	2x weekly	ip	- + PBS	15
6	Vehicle** + anti-PD-1	- 10mg/Kg*	daily + 2x weekly	po + ip	- + PBS	15
7a	B3 + anti-PD-1	60mg/Kg*# 10mg/Kg*	daily# + 2x weekly	po + ip	Vehicle** + PBS	15
7b	B3 + anti-PD-1	30mg/Kg* 10mg/Kg*	daily# + 2x weekly	po + ip	Vehicle** + PBS	15
8	A8 (dasatinib) + anti-PD-1	30mg/Kg* 10mg/Kg*	daily# + 2x weekly	po + ip	Vehicle** + PBS	15

* Based on last bodyweight measurement;

** po = per os, oral administration via gavage, ip = intra-peritoneal

Compound dosed for at least 3 weeks, up to between 5 and 8 weeks. Anti-PD-1 and vehicle treatment for duration. Lower dosage (eg, 10, 15 or 20mg/Kg) or higher dosage (eg, 50, 75 or 100mg/Kg) for C2, C7, C8, C9 and C12 can be adapted according to their ADMET/PK properties.

** Propylene glycol : water 1:1

[920] As described in Example 8.2: (i) mice are measured for body weight and tumour volume (mm^3) by calliper measurement twice weekly for up to 8 weeks until termination criteria (tumour volume> 2000 mm^3) is reached; and (ii) 5 mice per group are sacrificed after day 9 of first treatment to analyse tumour and blood samples for various immune response markers (eg, as described in Example 8.2).

Example 10.1: In-vivo anti-tumour activity of kinase inhibitors of formulae (Ia) and(Ib)/(Ic) in an immune-excluded tumour model

[921] The investigated the compounds disclosed herein (eg compound **E9**) for in vivo anti-tumour activity against an immune-excluded ("cold") tumour model. Such "cold" tumours are characterised by lack or paucity of tumour T cell infiltration, and pose a particular therapeutic challenge for immunotherapy (Bonaventura et al 1019, Frontiers in Immunology 10: article 168; doi: 10.3389/fimmu.2019.00168). Compound **E9** exhibited significant antitumour activity against a EMT6 "cold" tumour in vivo model (Figures 30A and B; Table 10.1B): indeed, even resulting in 24% tumour growth inhibition when administered to mice at only 5mg/kg two times daily (DIB).

[922] The anti-cancer activity of kinase inhibitor **E9** against a solid "cold" tumour was investigated in an in vivo syngeneic mouse model, whereby murine breast cancer cells EMT6 were implanted into the left mammary fat pad in BALB/c mice and treated with the test compound **E9** at dosages 25mg/kg, 12.5mg/kg, 5mg/kg twice daily as well as 25mg/kg once daily. Female BALB/c mice (5-6 weeks old), were implanted with of 1x10^6 EMT6 breast cancer cells (100ul in PBS). Mice were randomised into treatment groups after reaching 100mm3 tumour volume, and treatment groups comprised those as set forth in Table 10.1A with treatment starting within 24h of randomisation.

[923] Compound **E9** demonstrated significant dose dependent, anti-tumour efficacy compared to vehicle control animals at three different dose levels (5 mg/kg, 12.5mg/kg and 25mg/kg) in the generally known immune-excluded tumour model EMT6 (Figure 30A). Interestingly, administration of compound **E9** at 12.5mg/kg showed essentially the same efficacy (tumour growth inhibition; TGI) as 25mg/kg (40% vs 37% TGI; each, twice daily dosing; BID), and even

administration of compound **E9** at only 5mg/kg BID showed a surprising 25% TGI. Furthermore, administration of compound E9 at 25mg/kg was substantially more efficacious when administered two times daily (BID) than once administered once daily (QD), showing TGIs of 37% and 9% respectively (Figure 30B).

Table 10.1A: Treatment groups.

Group	Test specimen	Dose (mg/kg)*	Dose volume (ml/kg)	Route	Scheme	No. of animals
1	Vehicle#	-	10.0	p.o.**	BID, 7q7d##	16
2	E9	25.0	10.0	p.o.**	QD, 7q7d##	16
3	E9	25.0	10.0	p.o.**	BID, 7q7d##	16
4	E9	12.5	10.0	p.o.**	BID, 7q7d##	16
5	E9	5.0	10.0	p.o.**	BID, 7q7d##	16

* Based on last bodyweight measurement; ** p.o. = per os, oral administration via gavage; ##For at least 3 weeks, up to about 5-8 weeks; # vehicle = 10% DMSO + 5% Solutol +40% PEG + 45% water

Table 10.1B: Tukey's multiple comparisons test.

Comparison	Significance summary	Adjusted P Value
Vehicle vs. E9 25mg/kg bid	****	<0.0001
Vehicle vs. E9 25mg/kg qd	ns	0.6366
Vehicle vs. E9 12.5mg/kg bid	****	<0.0001
Vehicle vs. E9 5mg/kg bid	**	0.008
E9 25mg/kg bid vs. E9 25mg/kg qd	****	<0.0001
E9 25mg/kg bid vs. E9 12.5mg/kg bid	ns	0.9811
E9 25mg/kg bid vs. E9 5mg/kg bid	*	0.0291
E9 25mg/kg qd vs. E9 12.5mg/kg bid	****	<0.0001
E9 25mg/kg qd vs. E9 5mg/kg bid	ns	0.2782
E9 12.5mg/kg bid vs. E9 5mg/kg bid	**	0.0048

ns = not significant

Example 11 [prophetic]: Formulation for and preparation of unit dose form of kinase inhibitors of formulae (Ia) and (Ib)/(Ic) for oral administration.

[924] A caplet unit dose form of a pharmaceutical composition is made, briefly as follows.

[925] First, a tableting blend comprising the kinase inhibitor of formula (Ia) or (Ib)/(Ic) (eg, **E4**, **E9**, **E10** or **E16**, or C7, C8 or B3) is prepared by dry granulation of an amount of **E4**, **E9**, **E10** or **E16**, or C7 or C8 (or B3) together with one or more excipients. Example excipients in the tableting blend can include a binder, such as lactose (monohydrate), microcrystalline cellulose and/ hydroxypropyl cellulose, and optionally with a disintegrant such as starch. The blend may also include a lubricant such as magnesium stearate. Alternatively, the tableting blend is prepared by wet granulation followed by drying.

[926] Second, using a rotary tablet press, the blend is filled into a suitably shaped die from above, and compressed to a porosity of between about 5% and 20% by lowering an upper punch into the die. Compression can take pace in in one or two stages (main compression, and optionally pre-compression or tamping), with compression occurring rapidly for scaled manufacturing (eg within 500ms per caplet). The upper punch is pulled up and out of the die (decompression), and the caplet is ejected from the die.

[927] Third, the caplet is coated using an automatic coater. The coating can comprise hypromellose, titanium dioxide, polyethylene glycol and purified water.

[928] The tableting blend comprises an amount of the kinase inhibitor (**E4**, **E9**, **E10** or **E16**, or C7, C8 or B3, as used) such that each caplet is made to include a therapeutically effective amount of C7 or C8 (or B3), and caplets of different dosages may be made to aid the administration of the correct overall dose of **E4**, **E9**, **E10** or **E16**, or C7 or C8 (or B3). For example, each caplet may include about 20mg, 50mg or 70 mg of **E4**, **E9**, **E10** or **E16**, or C7 or C8 (or B3, as applicable), or may include less than these amounts such as about 5mg, 10mg or 40mg of **E4**, **E9**, **E10** or **E16**, or C7 or C8 (or B3, as applicable).

Example 12 [prophetic]: Production of melanin in human skin by compounds of formula (Ia) and/or (Ib)/(Ic).

[929] Following the methodology described by Kumagai et al (2011, PLoS ONE 6(10): e26148), compounds of formula (Ia) and/or (Ib)/(Ic) are tested first for their ability to induce melanogenesis in B16F10 melanoma cells.

[930] B16F10 murine melanoma cells and HEK293 cells are obtained from the American Type Culture Collection (Manassas, VA, USA). B16F10 cells are growth at 37oC under 5% CO2 in Dulbecco's modified Eagle's medium (DMEM; high glucose) (Wako) supplemented with 10% foetal bovine serum (FBS), penicillin (100U/mL), and streptomycin (50mg/mL). B16F10 are seeded in 6-well plates at a density of 3.4x10**5 cells/well. After 24h, the culture medium is replaced with fresh medium supplemented with test compound, and, after 48h, the medium is changed again with fresh medium containing the same compound. After an additional 24h, the cells ae harvested for a melanin or mRNA/protein assay. To measure melanin, the cells are washed twice with phosphate-buffered saline (PBS), suspended in PBS, and recovered by centrifugation at 8,000 rpm for 1.5min. The cell pellet is suspended in 300mL of 1N NaOH and incubated at 45oC for 2h, and, then, melanin extracted with a chloroform-methanol mixture (2:1). Melanin is detected with a spectrophotometer (BIO-RAD Model 680 MICRO PLATE READER; Bio-Rad, Hercules, CA, USA) at 405 nm. A standard curve is obtained by using purified melanin (0–1,000mg/mL). The protein concentration of the cell pellets was determined using the Bradford reagent (Bio-Rad) and used for normalisation of the melanin content.

[931] Compounds of formula (Ia) and/or (Ib)/(Ic) are secondly tested for their ability to recue melanogenesis I mice with an inactive melanocortin 1 receptor, using the methodology described in Mujahid et al (2017, Cell Reports 19:2177).

[932] Briefly, a previously described mouse "red hair" model is utilised that carries the inactivating *Mc1r*$^{e/e}$ mutant allele and a transgene, K14-SCF, in which stem cell factor expression is driven by the keratin-14 promoter, allowing for epidermal homing of melanocytes (D'Orazio et al 2006, Nature 443:430; Kunisada et al 1998, J Exp Med 187:1565). Albino mice harbouring a mutation in the tyrosinase gene are combined with the K14-SCF transgene (*Tyr*$^{c/c}$;K14-SCF mice) and serve as controls to evaluate whether the pigmentation afforded by topical SIK inhibitor is dependent upon the canonical tyrosinase-melanin pathway. Daily application of the SIK inhibitors of formula (Ia) and/or (Ib)/(Ic)) for 7 days can cause darkening in *Mc1r*$^{e/e}$;K14-SCF mice. No visible change in skin pigmentation is observed in *Mc1r*$^{e/e}$;K14-SCF mice treated with vehicle or in *Tyr*$^{c/c}$;K14-SCF mice treated with vehicle or SIK inhibitors of formula (Ia) and/or (Ib)/(Ic).

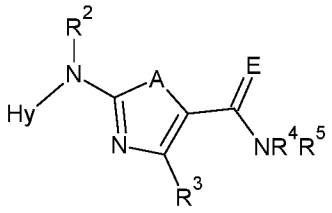
[933] In a third investigation, compounds of formula (Ia) and/or (Ib)/(Ic) are studied for their ability to induce human skin eumelanisation, using the methodology described in WO2018/160774.

[934] Full thickness human breast skin explants are cultured in petri dishes with a solid phase and liquid phase phenol red free DMEM medium with 20% penicillin streptomycin, 5% fungizone (Gibco®), and 10% FBS. Explants are treated daily with vehicle, HG 9-91-01 (obtained from MedChemExpress LLC, Monmouth Junction, NJ, USA) or SIK inhibitor of formula (Ia) and/or (Ib)/(Ic). Passive application refers to simply applying the treatment to skin without further rubbing or manipulation. Mechanical application refers to application of agents to skin with further rubbing of

treatment with 10 clockwise turns of a gloved cotton swab applicator. Skin is harvested, fixed, and processed for paraffin embedding. Sections are cut from paraffin blocks, and sections stained utilising haematoxylin and eosin (morphology) and Fontana-Masson (for melanin). Treatment of human skin explants with passive topical application of SIK inhibitors of formula (Ia) and/or (Ib)/(Ic) can induce significant pigmentation without any additional treatments after 8 days (1x/day) of treatment, but no significant gross pigmentation is observed in skin treated with HG 9-91-01. Fontanna Mason staining reveals increased melanin content in skin treated with SIK inhibitors of formula (Ia) and/or (Ib)/(Ic) and marginally increased melanin in skin treated with HG 9-91-01 as compared to control. Mechanical application of the HG 9-91-01 (by rubbing via an applicator) induces significant gross pigmentation, and increased melanin content is observed upon Fontana Masson staining of skin sections. HG 9-91-01's human skin limited penetration can thereby be at least partially overcome through mechanical application. SIK inhibitors of formula (Ia) and/or (Ib)/(Ic) may not require mechanical application (rubbing) to induce significant human epidermal darkening after 8 days (1x/day) of treatment. Fontanna Mason staining for melanin further illustrates whether exemplary SIK inhibitors of formula (Ia) and/or (Ib)/(Ic) induce pigmentation in the human skin explants.

CLAIMS

1. **A compound** selected from the group consisting of a kinase inhibitor of the formula:



(Ia),

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof;

wherein:

Hy is a heteroaryl or heterocyclyl which is optionally substituted with one or more independently selected R^{1e};

each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d};

each of R^{1a} and R^{1d} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

each of R^{1b} and R^{1c} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, 3- to 7-membered heterocyclyl, $-O(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-O(CH_2)_{0-2}$(C_{6-10} aryl), $-O(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-O(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), $-NH(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-NH(CH_2)_{0-2}$(C_{6-10} aryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two, or three moieties independently selected from the group consisting of -OH, methyl, ethyl, $-OCH_3$, $-SCH_3$, and $-NH_{2-z}(CH_3)_z$;

R^2 is H;

R^3 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^4 is H;

R^5 is -L-R^6;

L is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m-[Y-(CH_2)_n]_o-$, wherein m is an integer between 1 and 6, n is an integer between 0 and 3, o is an integer between 1 and 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and $-N(R^{13})-$; and each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m-$, and $-(CH_2)_n-$ groups is optionally substituted with one or two independently selected R^{30};

R^6 is a 5-membered monocyclic heteroaryl which contains at least one S ring atom and which is substituted with one or more independently selected R^7;

R^7 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}, wherein at least one of R^7 is F and/or at least one of R^7 is substituted with one or more F atoms;

A is selected from the group consisting of S, O, NR^8, and $C(R^9)_2$;

R^8 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^9 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

X is independently selected from the group consisting of O, S, and $N(R^{14})$;

E is O or S;

R^{11} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{12} and R^{13} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, or R^{12} and R^{13} may join together with the nitrogen atom to which they are attached to form the group $-N=CR^{15}R^{16}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

R^{14} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and $-OR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{15} and R^{16} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and $-NH_yR^{20}{}_{2-y}$, or R^{15} and R^{16} may join together with the atom to which they are attached to form a ring which is optionally substituted with one or more independently selected R^{30}, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

y is an integer from 0 to 2;

R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}; and

R^{30} is a 1st level substituent and is, in each case, independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, -CN, azido, $-NO_2$, $-OR^{71}$, $-N(R^{72})(R^{73})$, $-S(O)_{0-2}R^{71}$, $-S(O)_{1-2}OR^{71}$, $-OS(O)_{1-2}R^{71}$, $-OS(O)_{1-2}OR^{71}$, $-S(O)_{1-2}N(R^{72})(R^{73})$, $-OS(O)_{1-2}N(R^{72})(R^{73})$, $-N(R^{71})S(O)_{1-2}R^{71}$, $-NR^{71}S(O)_{1-2}OR^{71}$, $-NR^{71}S(O)_{1-2}N(R^{72})(R^{73})$, $-OP(O)(OR^{71})_2$, $-C(=X^1)R^{71}$, $-C(=X^1)X^1R^{71}$, $-X^1C(=X^1)R^{71}$, and $-X^1C(=X^1)X^1R^{71}$, and/or any two R^{30} which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group

may join together to form $=X^1$, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups being a 1st level substituent is optionally substituted by one or more 2nd level substituents, wherein said 2nd level substituent is, in each case, independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, $-OR^{81}$, $-N(R^{82})(R^{83})$, $-S(O)_{0-2}R^{81}$, $-S(O)_{1-2}OR^{81}$, $-OS(O)_{1-2}R^{81}$, $-OS(O)_{1-2}OR^{81}$, $-S(O)_{1-2}N(R^{82})(R^{83})$, $-OS(O)_{1-2}N(R^{82})(R^{83})$, $-N(R^{81})S(O)_{1-2}R^{81}$, $-NR^{81}S(O)_{1-2}OR^{81}$, $-NR^{81}S(O)_{1-2}N(R^{82})(R^{83})$, $-OP(O)(OR^{81})_2$, $-C(=X^2)R^{81}$, $-C(=X^2)X^2R^{81}$, $-X^2C(=X^2)R^{81}$, and $-X^2C(=X^2)X^2R^{81}$, and/or any two 2nd level substituents which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group being a 1st level substituent may join together to form $=X^2$, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl groups being a 2nd level substituent is optionally substituted with one or more 3rd level substituents, wherein said 3rd level substituent is, in each case, independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)OH$, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl, and/or any two 3rd level substituents which are bound to the same carbon atom of a 3- to 14-membered cycloalkyl or heterocyclyl group being a 2nd level substituent may join together to form =O, =S, =NH, or $=N(C_{1-3}$ alkyl);

wherein

each of R^{71}, R^{72}, and R^{73} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), $-C(=O)OH$, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl;

each of R^{81}, R^{82}, and R^{83} is independently selected from the group consisting of H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl, wherein each of the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), $-C(=O)OH$, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; and

each of X^1 and X^2 is independently selected from O, S, and $N(R^{84})$, wherein R^{84} is H or C_{1-3} alkyl.

2. The compound of claim 1, wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl$)_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl$)_2$ is substituted with one or more F atoms.

3. The compound of claim 1 or 2, wherein at least one of R^7 is F and/or at least one of R^7 is $C_{1\text{-}3}$alkyl, wherein the alkyl group of $C_{1\text{-}3}$alkyl is substituted with one or more F atoms; and/or,

wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$; and/or

wherein one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms; and/or

wherein one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms.

4. The compound of any one of claims 1 to 3, wherein R^6 is selected from the group consisting of thienyl, thiazolyl, and thiadiazolyl, each of which is substituted with one or more independently selected R^7; and/or,

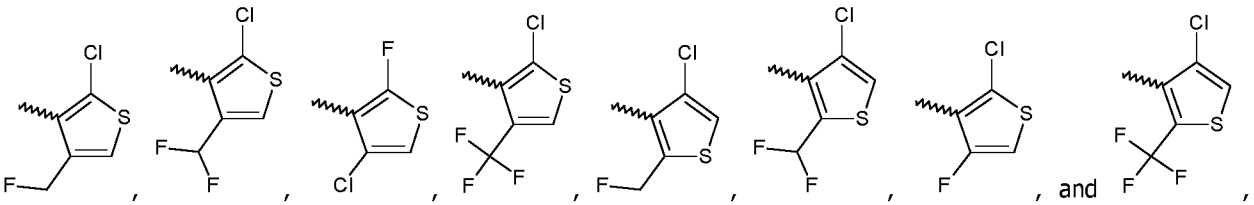
wherein R^6 is selected from the group consisting of thienyl and thiazolyl, each of which is substituted with one or more independently selected R^7

5. The compound of any one of claims 1 to 4, wherein R^6 is thienyl which is substituted with one or more independently selected R^7.

6. The compound of any one of claims 1 to 5, wherein the ring atom of R^6 by which R^6 is bound to the remainder of the compound is a C atom; and/or

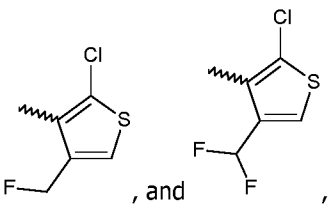
wherein the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound.

7. The compound of any one of claims 1 to 6, wherein R^6 is selected from the group consisting of



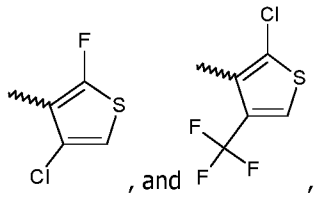
wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound; and/or,

wherein R^6 is selected from the group consisting of



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound; or

wherein R^6 is selected from the group consisting of



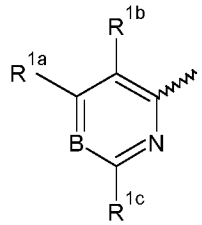
wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

8. The compound of any one of claims 1 to 7, wherein L is a bond; E is O; and/or A is selected from the group consisting of S, O, NH, N($C_{1\text{-}6}$ alkyl), and C($C_{1\text{-}6}$ alkyl)$_2$.

9. The compound of any one of claims 1 to 8, wherein L is a bond; E is O; and A is S.

10. The compound of any one of claims 1 to 9, wherein Hy is selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl, a 5- to 6-membered monocyclic heterocyclyl, a 9- to 10-membered bicyclic heteroaryl, and a 8- to 10-membered bicyclic heterocyclyl, each of which is optionally substituted with one or more independently selected R^{1e}.

11. The compound of any one of claims 1 to 10, wherein Hy is:



wherein ~~~~ represents the bond by which Hy is bound to the remainder of the compound; R^{1a}, R^{1b}, and R^{1c} are as defined inclaim 1; and B is N or CR^{1d}.

12. The compound of any one of claims 1 to 11, wherein R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononanyl, diazaspirononanyl, azaspirodecanyl, diazaspirodecanyl, azaspiroundecanyl, and diazaspiroundecanyl, wherein each of the piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononyl, diazaspirononyl, azaspirodecyl, diazaspirodecyl, azaspiroundecyl, and diazaspiroundecyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

13. The compound of any one of claims 1 to 12, wherein R^{1a} is non-symmetrical; optionally,

wherein R^{1a} is selected from the group consisting of 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

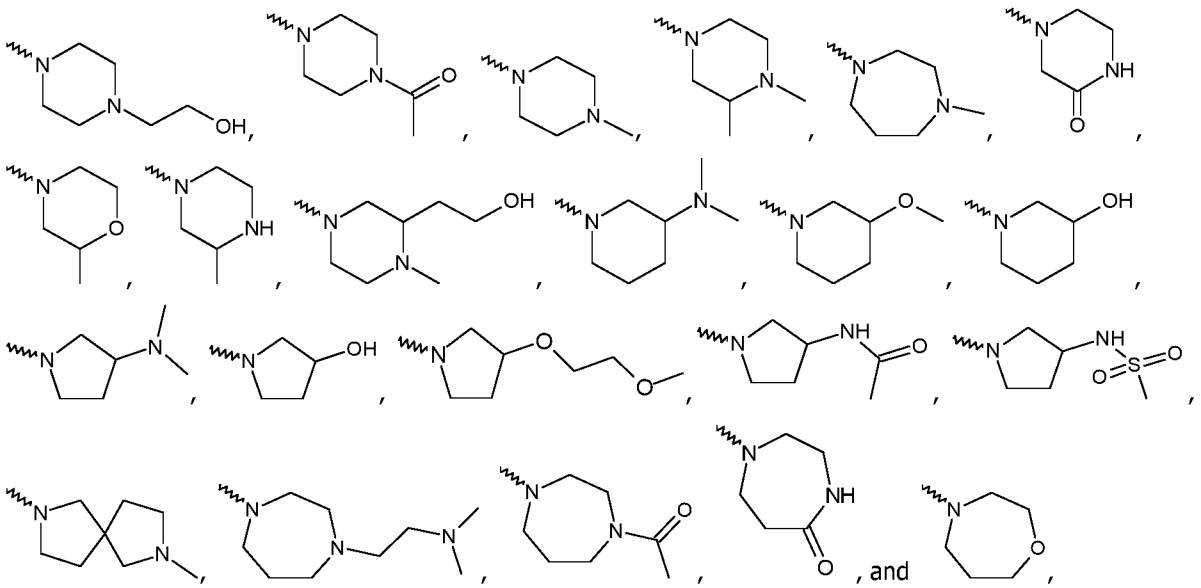
14. The compound of any one of claims 1 to 13, wherein the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an atom other than C, preferably is an N atom; optionally,

wherein R^{1a} is selected from the group consisting of heterocyclyl, heteroaryl, -OR^{11}, -N(R^{12})(R^{13}), -N(R^{11})(OR^{11}), -S(O)$_{0-2}R^{11}$, -S(O)$_{1-2}OR^{11}$, -OS(O)$_{1-2}R^{11}$, -OS(O)$_{1-2}OR^{11}$, -S(O)$_{1-2}$N(R^{12})(R^{13}), -OS(O)$_{1-2}$N(R^{12})(R^{13}), -N(R^{11})S(O)$_{1-2}R^{11}$, -NR^{11}S(O)$_{1-2}OR^{11}$, -NR^{11}S(O)$_{1-2}$N(R^{12})(R^{13}), -P(O)(OR^{11})$_2$, -OP(O)(OR^{11})$_2$,

-XC(=X)R^{11}, and -XC(=X)XR^{11}, wherein each of the heterocyclyl and heteroaryl groups is bound to the remainder of the compound via an atom other than C and is optionally substituted with one or more independently selected R^{30}; and/or

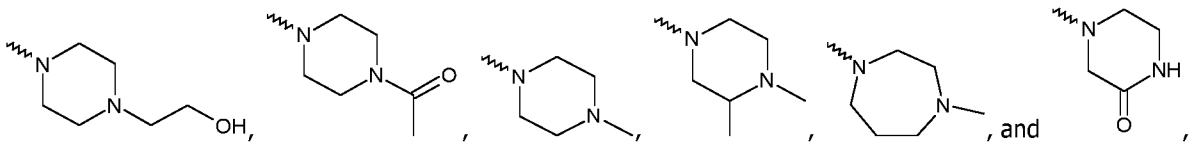
wherein R^{1a} is heterocyclyl which contains at least one N ring atom and which is bound to the remainder of the compound via an N ring atom.

15. The compound of claim 14, wherein R^{1a} is selected from the group consisting of:



wherein ~~~~ represents the bond by which R^{1a} is bound to the remainder of the compound; optionally,

wherein R^{1a} is selected from the group consisting of:



wherein ~~~~ represents the bond by which R^{1a} is bound to the remainder of the compound.

16. The compound of any one of claims 1 to 15, wherein R^{1b} is methyl, ethyl, propyl, or isopropyl, preferably methyl; and R^{1c} is H.

17. The compound of any one of claims 1 to 16, wherein B is N.

18. The compound of any one of claims 1 to 17, wherein R^{1b} is H; R^{1c} is methyl; B is N; and R^3 is H.

19. The compound of claim 11, wherein:

L is a bond; and

(A') R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 11-membered heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and

$-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2, and the other of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and

(C') R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)$_2$, $-C(=O)(C_{1-4}$ alkyl), $-C(=O)OH$, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl)$_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl)$_z$, and $-N(C_{1-4}$ alkyl)$C(=NH)NH_{2-z}(C_{1-4}$ alkyl)$_z$, wherein the phenyl group is optionally substituted with one, two or three groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl)$_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl)$_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2, preferably wherein R^3 is H; and

(D') at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl)$_2$ is substituted with one or more F atoms;

(E') A is S, O, or $N(CH_3)_2$, preferably wherein A is S; and

(F') B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl)$_2$, preferably wherein B is N; and

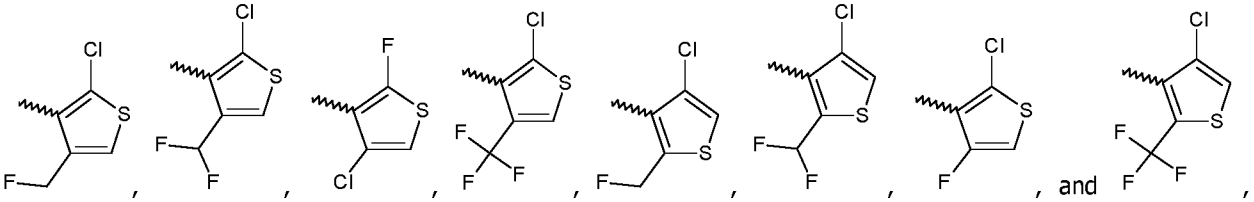
(G') E is O or S, preferably O.

20. The compound of claim 19, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$.

21. The compound of claim 19 or 20, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$, and one R^7 is Cl.

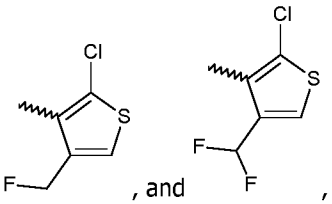
22. The compound of claim 19, wherein one R^7 is F and one R^7 is Cl.

23. The compound of claim 19, wherein R^6 is selected from the group consisting of



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound; or

wherein R^6 is selected from the group consisting of



wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound.

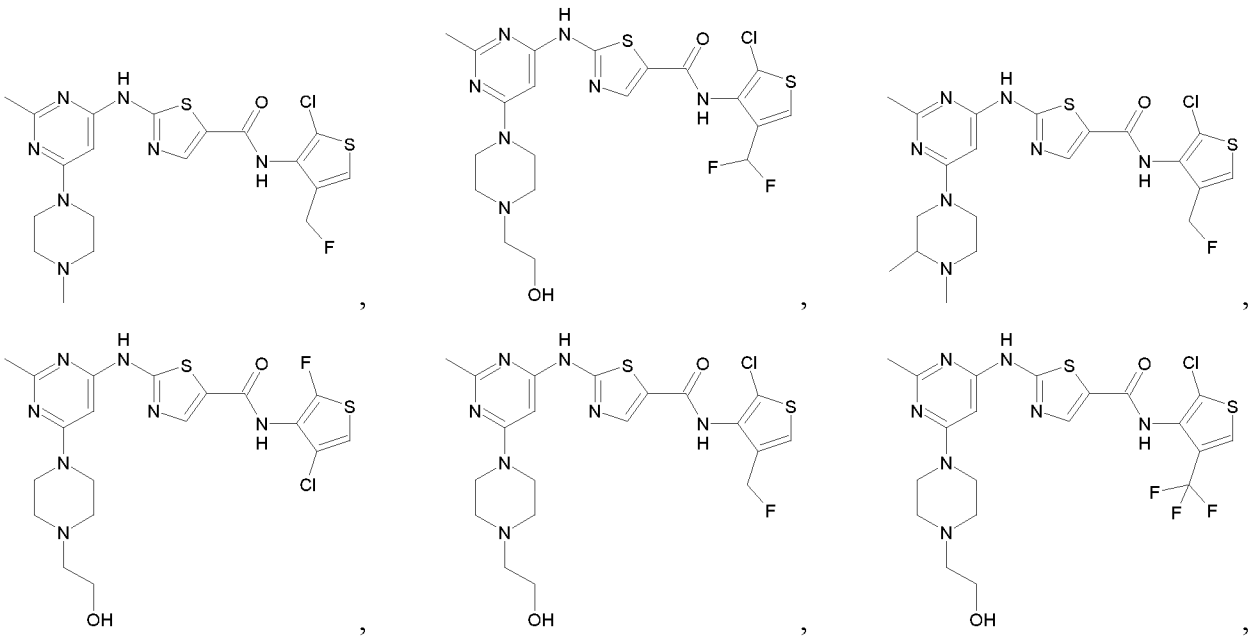
24. The compound of any one of claims 19 to 23, wherein R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

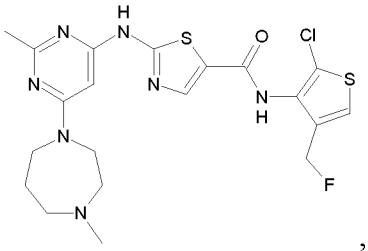
25. The compound of any one of claims 19 to 24, wherein R^{1a} is non-symmetrical.

26. The compound of any one of claims 19 to 25, wherein the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an atom other than C, preferably is an N atom.

27. The compound of any one of claims 19 to 26, wherein R^{1b} is H; R^{1c} is methyl; A is S; B is N; E is O; and R^3 is H.

28. The compound of any one of claims 1 to 27, wherein the compound is selected from the group consisting of:

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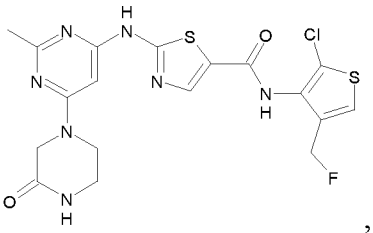
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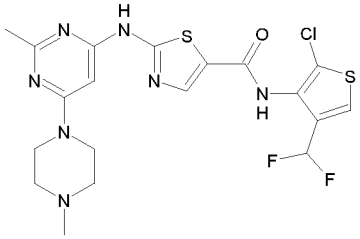
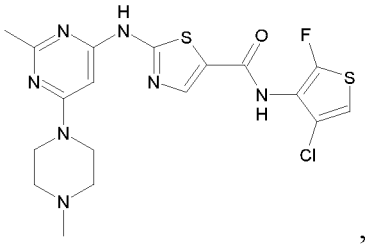
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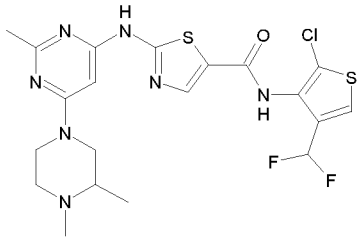
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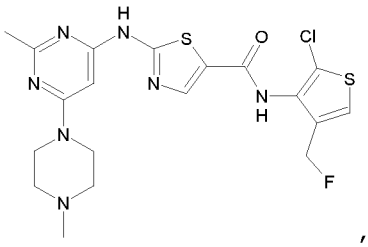
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

29. The compound of any one of claims 1 to 28, wherein the compound is selected from the group consisting of: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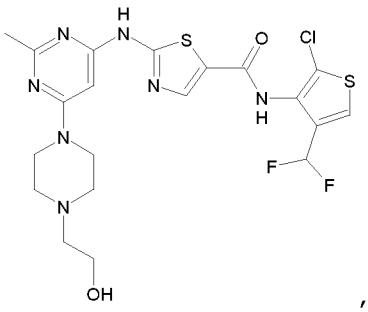
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or

wherein the compound is selected from the group consisting of: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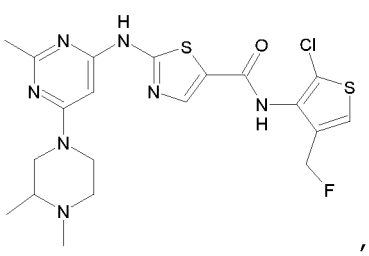
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or

wherein the compound is selected from the group consisting of: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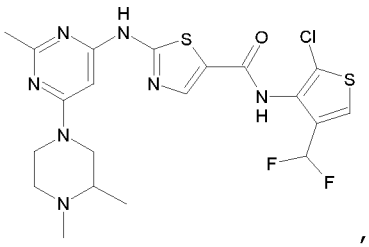
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or

wherein the compound is selected from the group consisting of:



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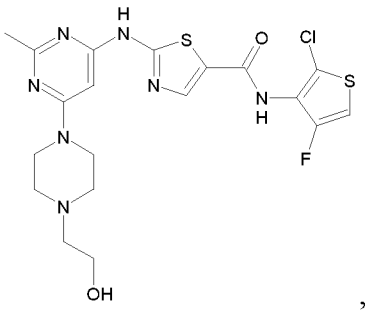
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

30. The compound of any one of claims 1 to 27, wherein the compound is selected from the group consisting of:



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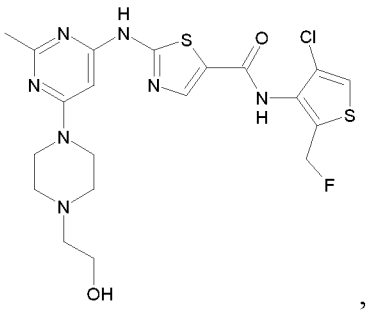

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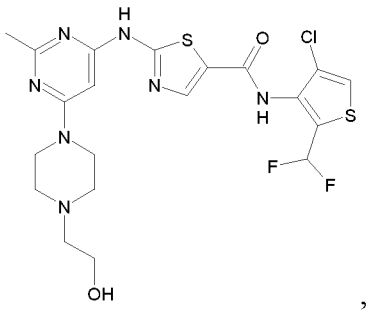

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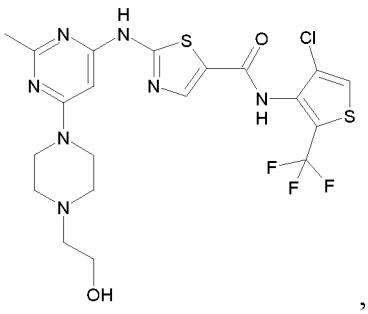

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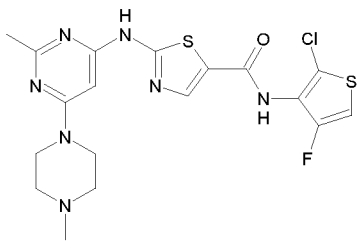

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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

31. The compound of any one of claims 1 to 30, wherein the compound is in substantially pure form, in particular in greater than about 90%, 95%, 98% or 99% pure form.

32. **A pharmaceutical composition** comprising the compound of any one of claims 1 to 31, and optionally further comprising a pharmaceutically acceptable excipient; optionally,

wherein the pharmaceutical composition is formulated for oral administration; and/or

wherein the pharmaceutical composition is in unit dose form.

33. The compound of any one of claims 1 to 31, or the pharmaceutical composition of claim 32, for use in therapy.

34. **A method for the treatment** of a disease, disorder or condition in a subject, comprising administering to the subject a compound of any one of claims 1 to 31, or a pharmaceutical composition of claim 32, optionally wherein the disease, disorder or condition is associated with a kinase.

35. **A compound for use, or a pharmaceutical composition for use**, in a treatment of a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject,

wherein, the compound is a compound of any one of claims 1 to 31, and the pharmaceutical composition is a pharmaceutical composition of claim 32.

36. The compound for use, or the pharmaceutical composition for use, of claim 35, wherein the proliferative disorder is a cancer or tumour; optionally, where the cancer is a solid tumour.

37. The compound for use, or the pharmaceutical composition for use, of claim 35 or 36, wherein treatment further comprises administration of an immune checkpoint inhibitor to the subject.

38. The compound for use, or the pharmaceutical composition for use, of any one of claims 35 to 37, the treatment comprising exposing cells involved with the proliferative disorder in the subject to: (i) TNF, a TNF variant, and/or an agonist of TNFR12 or TNFR1-signalling; and (ii) the compound or pharmaceutical composition; optionally:

wherein the amount of TNF exposed to cells involved with the proliferative disorder in the subject is increased; and/or

wherein: (i) TNF, a TNF variant or an agonist of TNFR1 or TNFR2-signalling is administered to the subject; (ii) an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to TNF, a TNF variant or an agonist of TNFR1- or TNFR2-signalling, is administered to the subject; or (iii) the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells; and/or

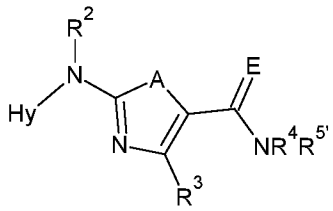
wherein the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

39. The compound for use, or the pharmaceutical composition for use, of any one of claims 35 to 38, wherein the treatment comprises administering the compound or the pharmaceutical composition two times daily (*bis in die*; BID).

40. **A compound for use, or a pharmaceutical composition for use**, in a treatment of a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject, **wherein the compound is selected from the following compounds (a) to (c)**, and the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient:

(a) a compound of any one of claims 1 to 31; and

(b) a compound having the following formula:



(Ib),

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof,

wherein:

Hy, R^2, R^3, A, E, and R^4 are as defined in claim 1;

$R^{5'}$ is -L-$R^{6'}$;

L is a bond;

$R^{6'}$ is a 5- or 6-membered heteroaryl which is optionally substituted with one or more independently selected $R^{7'}$;

$R^{7'}$ is independently selected from the group consisting of R^7, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}; and

R^{11}, R^{12}, R^{13}, X, and R^{30} are as defined in claim 1,

optionally, with the proviso that

(I) when A is S; R^3 is H; E is O; and $R^{6'}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; then Hy is not 2-pyridyl;

(II) when Hy is 1-{(2E)-4-[(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}piperidine-4-yl; R^3 is H; A is O; E is O; then $R^{6'}$ is not 5-methyl-pyridin-2-yl;

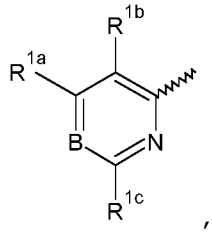
(III) when R^3 is trifluoromethyl; A is O; E is O; and

(i) $R^{6'}$ is 6-{4-[(2-fluorophenyl)carbamoyl]piperazin-1-yl}pyridine-3-yl; then Hy is not 1-(phenylmethyl)-piperidine-4-yl, 1-(phenylmethyl)pyrrolidine-3-yl, or tetrahydro-2H-pyran-4-yl; or

(ii) Hy is 1-(phenylmethyl)piperidine-4-yl; then $R^{6'}$ is not 6-(3-{[(2-fluorophenyl)carbamoyl]amino}-pyrrolidin-1-yl)pyridine-3-yl or 6-({1-[(2-fluorophenyl)carbamoyl]piperidin-4-yl}amino)pyridine-3-yl; or

(iii) Hy is 1-(phenylmethyl)pyrrolidine-3-yl; then $R^{6'}$ is not 6-({(3S)-1-[(2-fluorophenyl)carbamoyl]-pyrrolidin-3-yl}amino)pyridine-3-yl or 6-({(3R)-1-[(2-fluorophenyl)carbamoyl]pyrrolidin-3-yl}-amino)pyridine-3-yl; and/or

(IV) when Hy is



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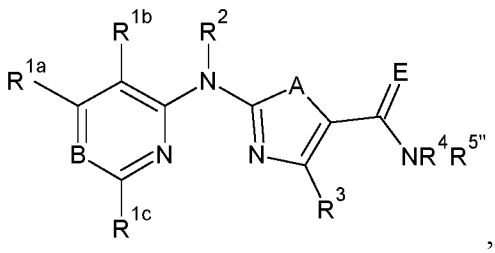
and

(1) R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^3 is H; and A is S; then $R^{6'}$ is not 4-chloro-2-methylpyridin-3-yl;

(2) E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br, then R^{1a} is not H;

(c) a compound having the following formula (Ic):



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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof,

wherein:

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, A, E, and R^4 are as defined in claim 1;

B is N or CR^{1d}, wherein R^{1d} is as defined in claim 1;

$R^{5''}$ is -L-$R^{6''}$;

L is as defined in claim 1;

$R^{6''}$ is heteroaryl or heterocyclyl, each of which is optionally substituted with one or more independently selected $R^{7'}$;

$R^{7'}$ is independently selected from the group consisting of R^7, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, -NO_2, -OR^{11}, -$N(R^{12})(R^{13})$, -$N(R^{11})(OR^{11})$, -$S(O)_{0-2}R^{11}$, -$S(O)_{1-2}OR^{11}$, -$OS(O)_{1-2}R^{11}$, -$OS(O)_{1-2}OR^{11}$, -$S(O)_{1-2}N(R^{12})(R^{13})$, -$OS(O)_{1-2}N(R^{12})(R^{13})$, -$N(R^{11})S(O)_{1-2}R^{11}$, -$NR^{11}S(O)_{1-2}OR^{11}$, -$NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, -$P(O)(OR^{11})_2$, -$OP(O)(OR^{11})_2$, -$C(=X)R^{11}$, -$C(=X)XR^{11}$, -$XC(=X)R^{11}$, and -$XC(=X)XR^{11}$, and/or any two $R^{7'}$ which are bound to the same atom of $R^{6''}$ being a heterocyclyl group may join together to form =O, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}; and

R^{11}, R^{12}, R^{13}, X, and R^{30} are as defined in claim 1,

optionally, with the proviso

(1) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^3 is H; A is S; and L is a bond; then $R^{6''}$ is not 4-chloro-2-methylpyridin-3-yl;

(2) when R^{1a} is methoxy; R^{1b} is H; R^{1c} is methoxy; B is N; E is O; R^3 is H; A is S; and L is a bond; then $R^{6''}$ is not 2,2-difluoro-5H-1,3-dioxolo[4,5-f]benzimidazol-6-yl;

(3) when R^3 is H; A is S; L is a bond; $R^{6''}$ is 1-methyl-4-piperidinyl; R^{1b} is H; B is N; E is O; and

(i) R^{1a} is methyl; then R^{1c} is not N-tert-butoxycarbonylpiperidin-4-yl; or

(ii) R^{1c} is methyl; then R^{1a} is not N-tert-butoxycarbonylpiperidin-4-yl or N-tert-butoxycarbonylpiperidin-3-yl;

(4) when E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br, then R^{1a} is not H; and/or

(5) when R^{1a} is methyl; each of R^{1b} and R^{1c} is H; B is CH; E is O; A is S; and R^3 is methyl; then $R^{5''}$ is not 1,3-benzodioxol-5-ylmethyl, 2-furanylmethyl, 1,3-benzodioxol-5-yl, 2-(2-thienyl)ethyl, 2-(4-morpholinyl)ethyl, 2-(2-pyridinyl)ethyl, 2-pyridinylmethyl, or tetrahydro-2-furanylmethyl;

(6) when A is S; R^3 is H; E is O; L is a bond; $R^{6''}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; R^{1a} is H, R^{1b} is H, R^{1c} is H; and B is CR^{1d}; then R^{1d} is not H; and

wherein the proliferative disorder is selected from one or more of (α) to (γ):

(α) a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by, the presence of myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by, or cells involved with the proliferative disorder characterised by, the presence of phosphorylated histone deacetylase 4 (HDAC4) protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(β) a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by,: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or

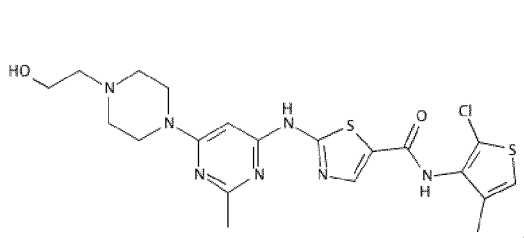
(γ) a mixed phenotype acute leukaemia (MPAL).

41. The compound or a pharmaceutical composition for use of claim 40:

wherein the compound is a compound as defined in (b) of claim 19 and $R^{6'}$ is a 5-membered monocyclic heteroaryl contains at least one ring heteroatom selected from the group consisting of N, O, and S, and which is optionally substituted with one, two or three independently selected $R^{7'}$; or

wherein the compound is a compound as defined in (c) of claim 19 and $R^{6''}$ is a 5- or 6-membered heteroaryl which contains at least one S ring atom and which is optionally substituted with one two or three independently selected $R^{7'}$.

42. The compound or a pharmaceutical composition for use of claim 40 or 41, wherein the compound is selected from the group consisting of: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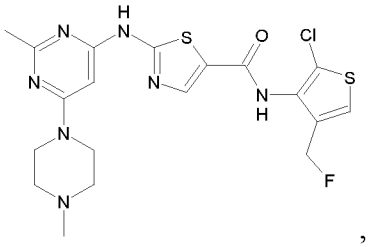
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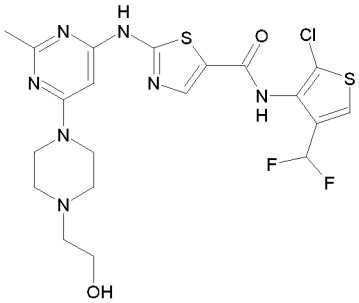
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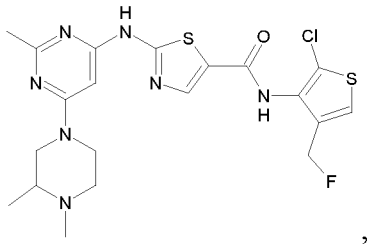
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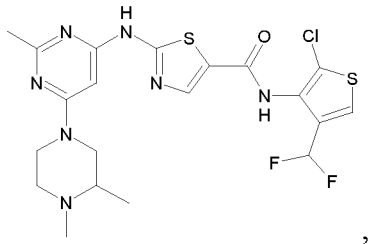
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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

43. **A method for determining** that a subject suffering from a proliferative disorder is suitable for treatment with a compound or pharmaceutical composition as defined in any one of claims 40 to 42, the method comprising, determining in a biological sample that has been obtained from said subject, and preferable that comprises cells involved with the proliferative disorder:

(X) the presence of MEF2C protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by the presence of phosphorylated HDAC4 protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(Y) (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the *KRAS* gene and/or in the *RUNX1* gene,

wherein, the presence of said protein, translocation, rearrangement, oncoprotein and or mutation in the biological sample indicates that the subject is suitable for treatment with the compound or pharmaceutical composition.

44. The compound or pharmaceutical composition for use of any one of claims 40 to 42, or the method of claim 43, wherein the proliferative disorder is characterised by, or cells involved with the proliferative disorder characterised by,: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; and/or (iii) the presence of an KMT2A fusion oncoprotein, preferably wherein:

(a) the human chromosome translocation is one selected from the group consisting of: t(4,11), t(9,11), t(11,19), t(10,11) and t(6,11); and/or

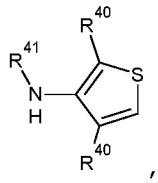
(b) the rearrangement of the *KMT2A* gene comprises, or the KMT2A fusion oncoprotein is expressed from a rearrangement that comprises, a fusion of the *KMT2A* gene with a translocation partner gene selected from the group consisting of: *AF4*, *AF9*, *ENL*, *AF10*, *ELL* and *AF6*.

45. The compound or pharmaceutical composition for use of any one of claims 40 to 42 and 44, or the method of claim 43 or 44, wherein the proliferative disorder is: (i) a myeloma, preferably multiple myeloma; or (ii) a leukaemia, preferably an acute myeloid leukaemia (AML) or an acute lymphoblastic leukaemia (ALL), more preferably T cell acute lymphoblastic leukaemia (T-ALL), an MLL-AML or an MLL-ALL.

46. The compound or pharmaceutical composition for use of any one of claims 40 to 42, 44 and 45, or the method of any one of claims 43 to 45, wherein the subject is a subject carrying a *KMT2A* rearrangement (*KMT2A-r*); preferably wherein such subject is a patient suffering from a *KMT2A-r* leukaemia.

47. The method of claim 43, further comprising a step of administering a compound or pharmaceutical composition as defined in any one of claims 40 to 42 to a subject where the presence of, or an amount of, said protein, translocation, oncoprotein and or mutation is determined in a biological sample that had been obtained from said subject.

48. **An intermediate** selected from a compound having formula (Id):



,

and solvates, salts, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof,

wherein:

one of R^{40} is F or is selected from the group consisting of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), -NH($C_{1\text{-}2}$alkyl) and -N($C_{1\text{-}2}$alkyl)$_2$, wherein the alkyl group of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), and -NH($C_{1\text{-}2}$alkyl) and at least one of the alkyl groups of -N($C_{1\text{-}2}$alkyl)$_2$ is substituted with one, two, or three F atoms, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt; and

R^{41} is selected from the group consisting of H and an amino protecting group,

with the proviso that

(1) the intermediate is not 2-bromo-4-(trifluoromethyl)thiophen-3-amine;

(2) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is -CHF_2, then R^{41} is not (1-propylpiperidin-2-yl)carbonyl; and

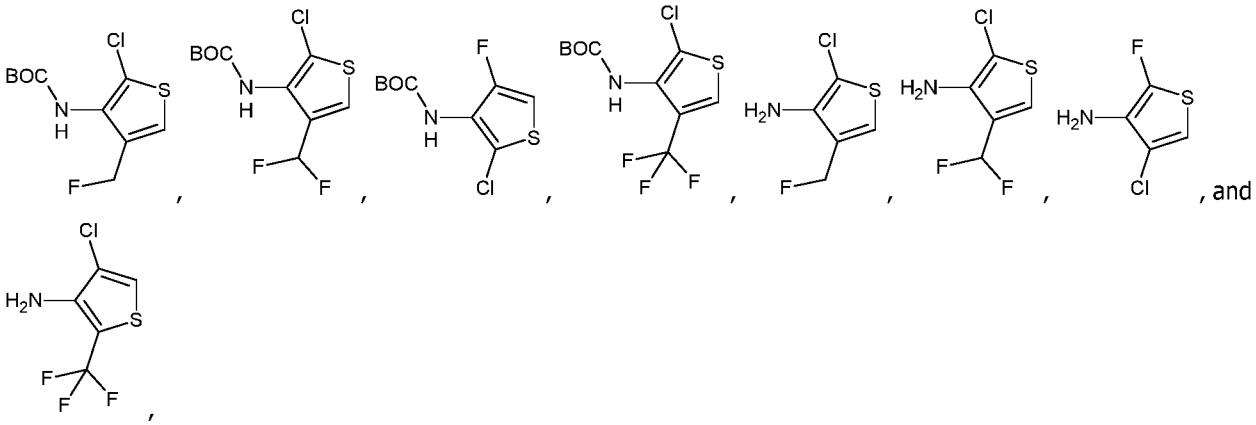
(3) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is F, then R^{41} is not 4,5-dihydro-1*H*-imidazol-2-yl.

49. The intermediate of claim 48, wherein one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt, more preferably selected from the group consisting of Cl, Br, F, and -Me; and/or

wherein one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, preferably selected from the group consisting of -CH_2F and -CHF_2, and the other R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, is Cl.

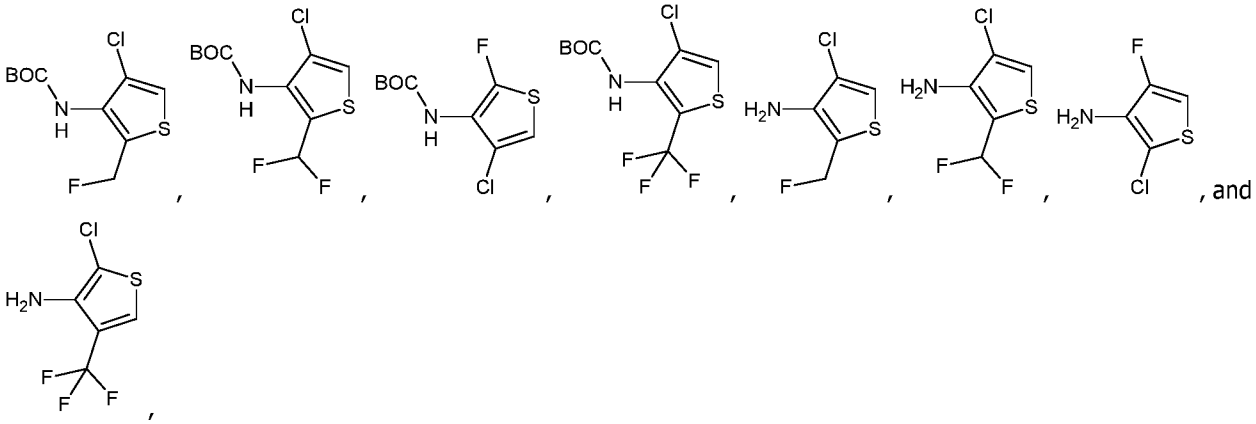
50. The intermediate of claim 48 or 49, wherein the amino protecting group is selected from the group consisting of tert-butyloxycarbonyl (BOC), 9-fluorenylmethoxycarbonyl (FMOC), benzyloxycarbonyl (Cbz), p-methoxybenzylcarbonyl (MOZ), acetyl (Ac), trifluoroacetyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), 3,4-dimethoxyphenyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethoxycarbonyl (Troc), triphenylmethyl (trityl; Tr), toluenesulfonyl (tosyl; Ts), *para*-bromophenylsulfonyl (brosyl), 4-nitrobenzenesulfonyl (nosyl), and 2-nitrophenylsulfenyl (Nps).

51. The intermediate of any one of claims 48 to 50, wherein the intermediate is selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof; or

wherein the intermediate is selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

52. **A method of manufacturing a compound** comprising an amide moiety, the method comprising the step of reacting the intermediate of claim 48 or 49 with a corresponding carboxylic acid, and, optionally, removing the amino protecting group; optionally,

wherein the compound is a kinase inhibitor, in particular an inhibitor of one or more protein kinases selected from the list consisting of: SIK (preferably SIK3), CSFR1, ABL, SRC, HCK, PDGFR and KIT; preferably selected from the list consisting of: SIK3, ABL/BCR-ABL, HCK and CSF1R kinases.

53. **A method of preparing a compound** of claim 31, comprising the steps:

- providing a compound of any one of claims 1 to 30 in admixture with one or more impurities; and
- removing at least a fraction of the impurities from the admixture.

54. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of claims 1 to 31 together with a pharmaceutically acceptable excipient.

55. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of claims 1 to 29 together with a pharmaceutically acceptable excipient; or

comprising:

- practicing, or having practiced, the method of claim 52 to manufacture a compound; and
- formulating the manufactured compound together with a pharmaceutically acceptable excipient.

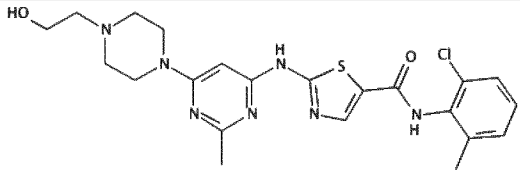
56. **A method of preparing a pharmaceutical package**, comprising the steps:

- inserting into packaging a pharmaceutical composition of claim 32 (preferably in finished pharmaceutical form), thereby forming a package containing the pharmaceutical composition; and optionally,
- inserting into the package a leaflet describing prescribing information for the pharmaceutical composition.

57. **A pharmaceutical package** containing a pharmaceutical composition of claim 32; preferably, wherein the pharmaceutical composition is in finished pharmaceutical form.

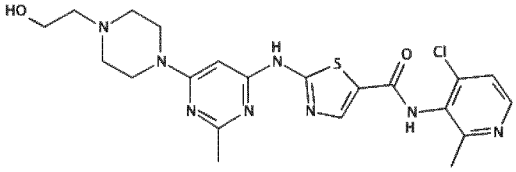
FIGURE 1

A



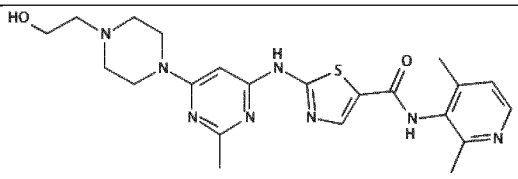
(**A8**)

B



(**B3**)

C



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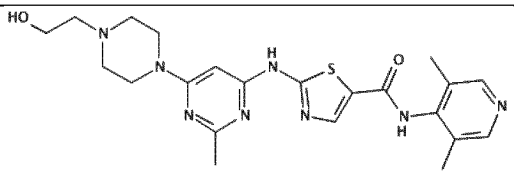

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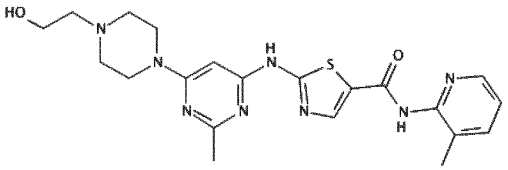

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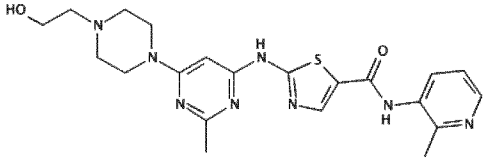

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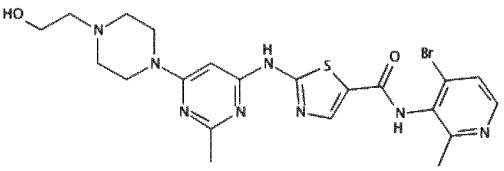

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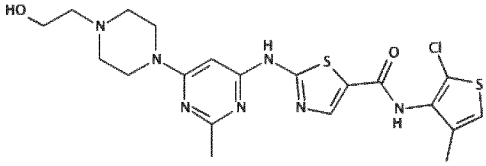

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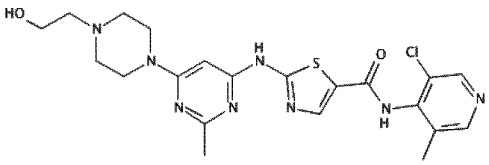

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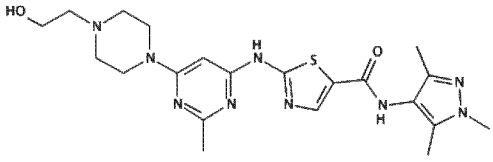

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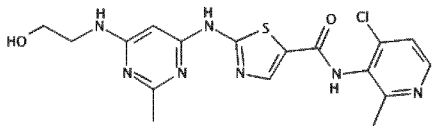

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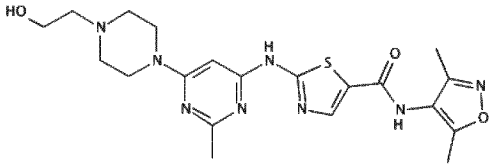

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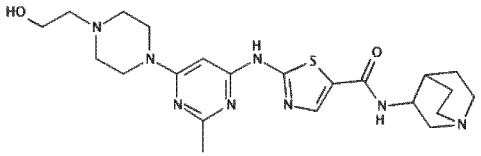

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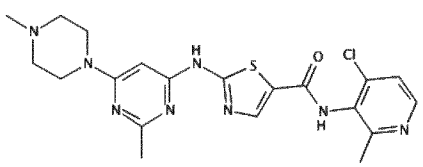

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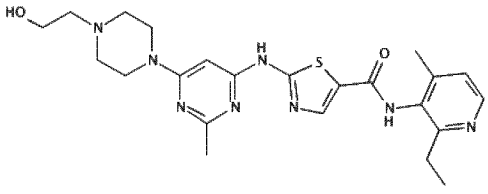
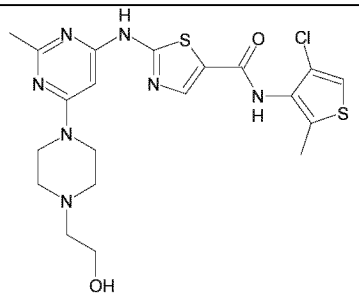


(**C13**)

FIGURE 1 (CONT)

D



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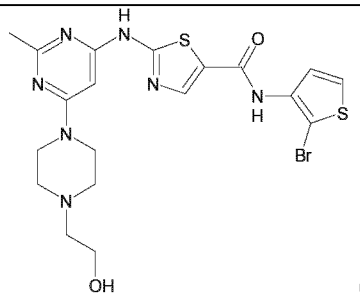

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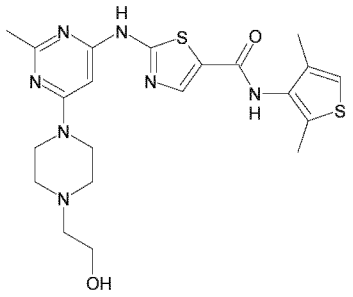

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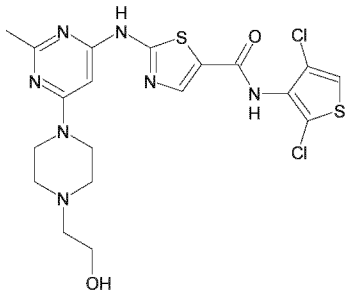

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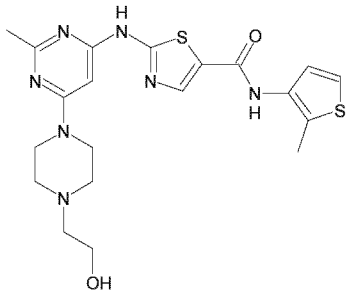

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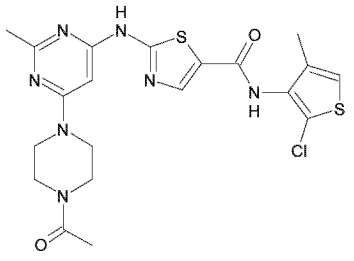

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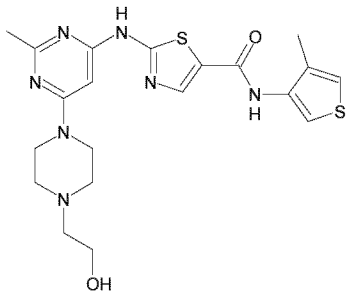

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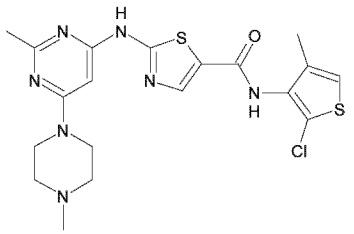

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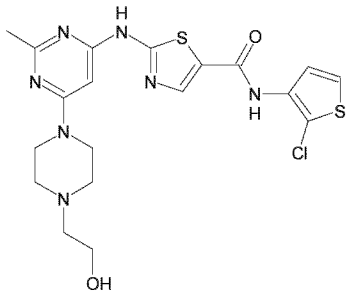

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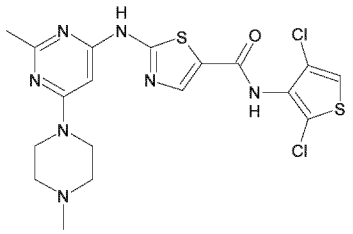
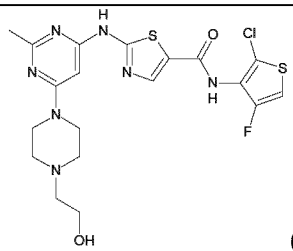


(D10)

FIGURE 1 (CONT)

E



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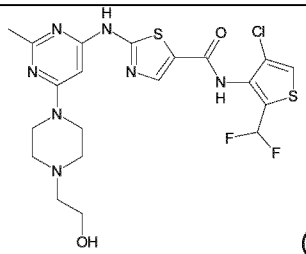

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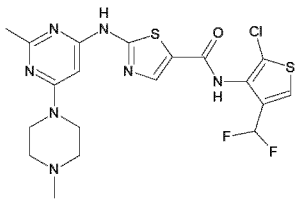

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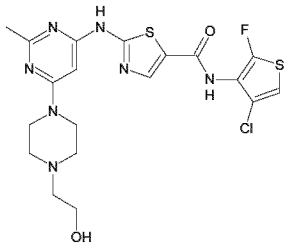

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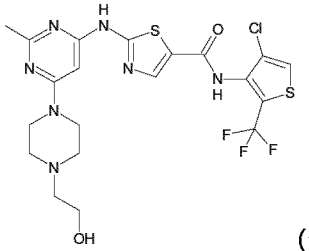

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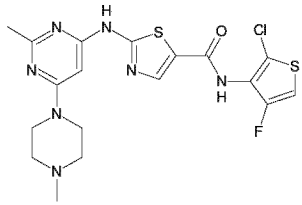

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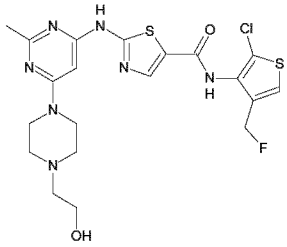

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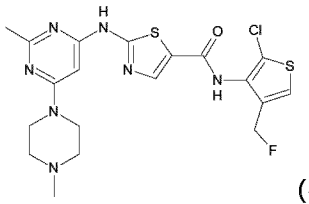

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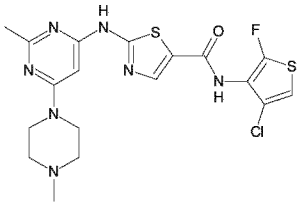

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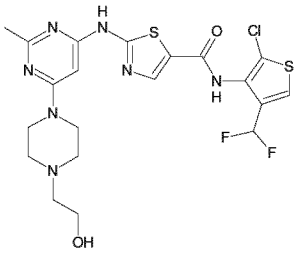

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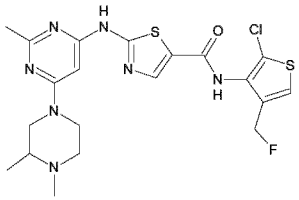

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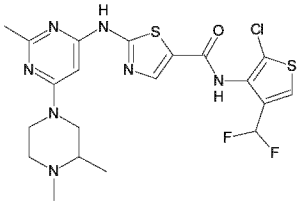

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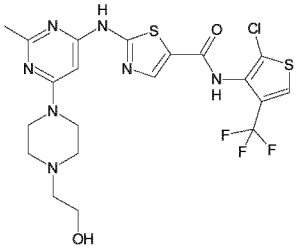
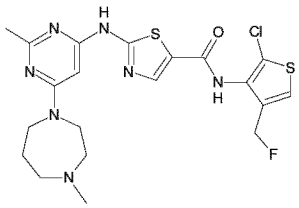
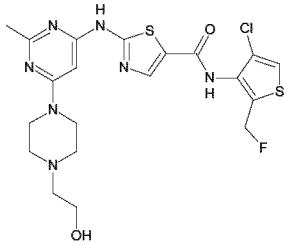


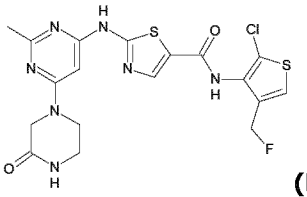
(E5)



(E11)



(E6)



(E12)

FIGURE 2

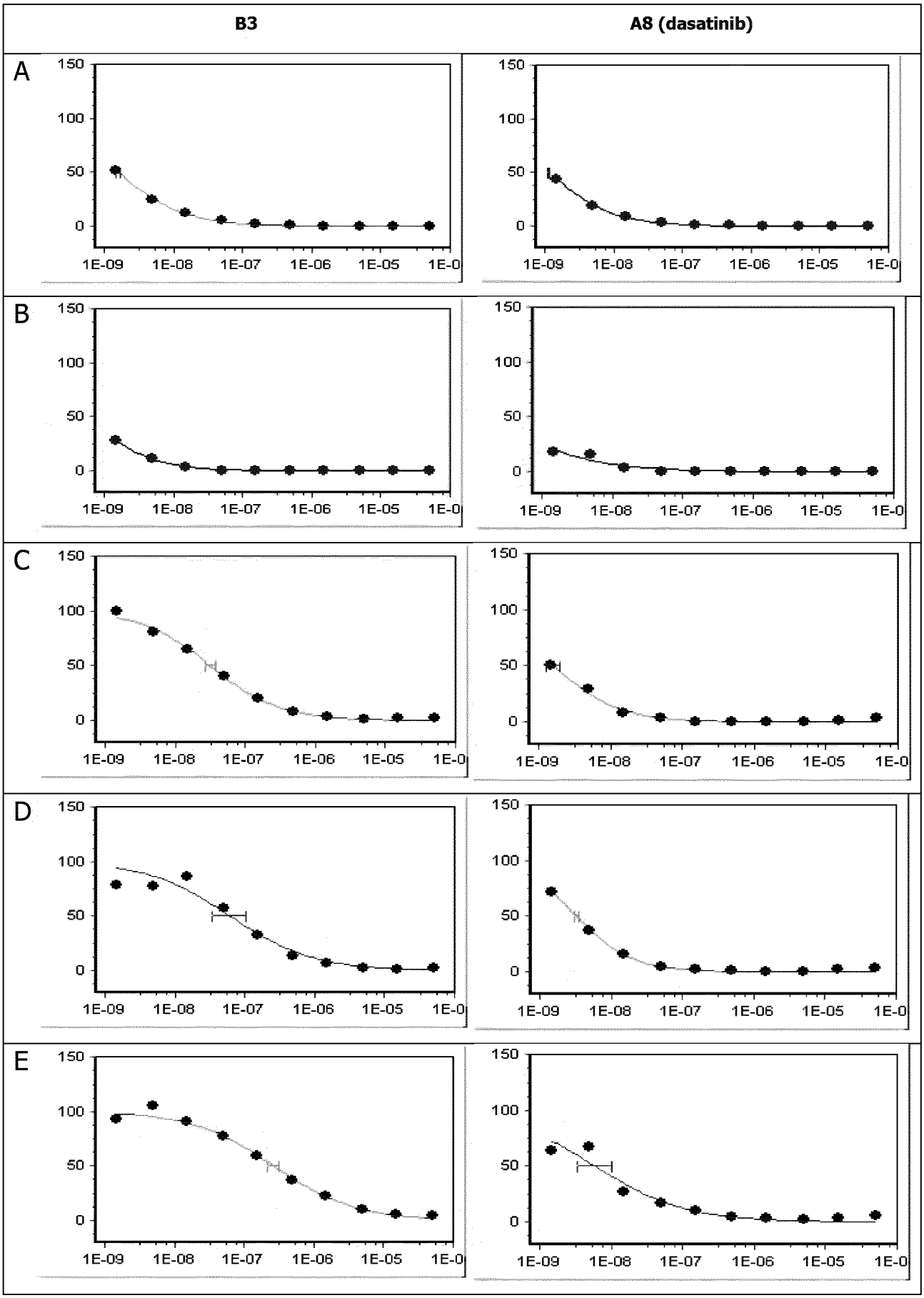

B3
A8 (dasatinib)
A
B
C
D
E
150
100
50
0
1E-09
1E-08
1E-07
1E-06
1E-05
1E-0

FIGURE 2 (Cont)

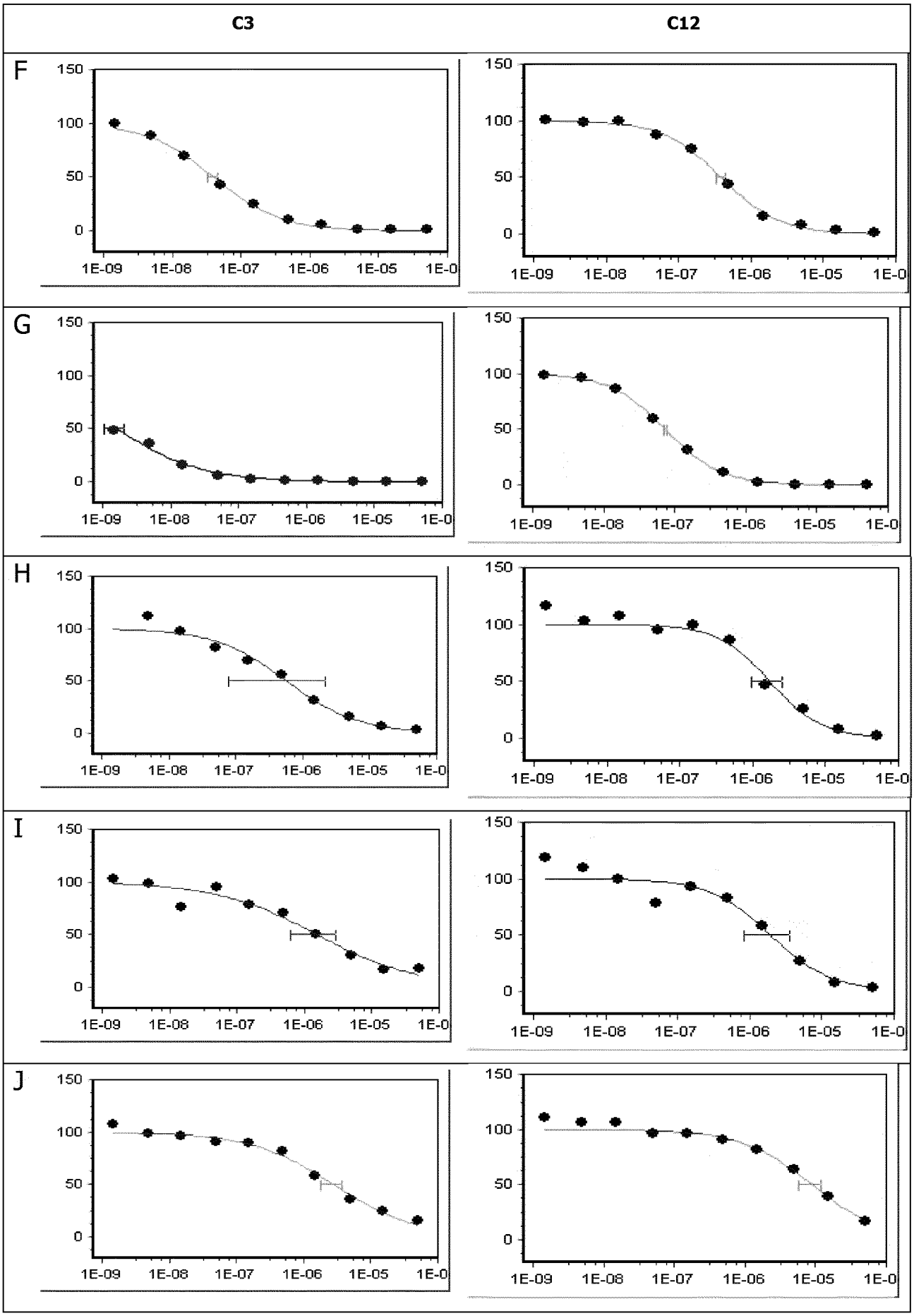


FIGURE 3

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
ABL1	TK	****	****	****
ABL2	TK	****	****	****
ACK1	TK	****	****	****
ACV-R1	TKL	***	****	****
ACV-R1B	TKL	***	****	****
ACV-R2A	TKL	***	****	****
ACV-R2B	TKL	**	****	****
ACV-RL1	TKL	***	****	****
AKT1 aa106-480	AGC	*	*	*
AKT2 aa107-481	AGC	*	*	*
AKT3 aa106-479	AGC	*	*	*
ALK (GST-HIS-tag)	TK	*	*	*
AMPK-alpha1 aa1-550	CAMK	*	*	*
ARK5	CAMK	*	*	*
ASK1	STE	*	*	*
Aurora-A	OTHER	*	**	***
Aurora-B	OTHER	*	*	***
Aurora-C	OTHER	*	*	*
AXL	TK	**	*	*
BLK	TK	****	****	****
BMPR1A	TKL	*	***	***
BMX	TK	****	****	****
B-RAF	TKL	***	****	****
BRK	TK	****	****	****
BRSK1	CAMK	*	*	*
BRSK2	CAMK	*	*	*
BTK	TK	****	****	****
BUB1B	OTHER	*	*	*
CAMK1D	CAMK	*	*	*
CAMK2A	CAMK	*	*	*
CAMK2B	CAMK	*	*	*
CAMK2D	CAMK	*	*	*
CAMK2G	CAMK	*	*	*
CAMK4	CAMK	*	*	*
CAMKK1	OTHER	*	*	*
CAMKK2	OTHER	*	*	*
CDC42BPA	AGC	*	*	**
CDC42BPB	AGC	*	*	*
CDC7/DBF4	OTHER	*	*	*
CDK1/CycA2	CMGC	*	*	*
CDK1/CycB1	CMGC	*	*	*
CDK1/CycE1	CMGC	*	*	*

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
CDK16/CycY	CMGC	*	*	*
CDK19/CycC	CMGC	*	*	*
CDK2/CycA2	CMGC	*	*	*
CDK2/CycE1	CMGC	*	*	*
CDK3/CycC	CMGC	*	*	*
CDK3/CycE1	CMGC	*	*	*
CDK4/CycD1	CMGC	*	*	*
CDK4/CycD3	CMGC	*	*	*
CDK5/p25NCK	CMGC	*	*	*
CDK5/p35NCK	CMGC	*	*	*
CDK6/CycD1	CMGC	*	*	*
CDK6/CycD3	CMGC	*	*	*
CDK7/CycH/MAT1	CMGC	*	*	*
CDK8/CycC	CMGC	*	*	*
CDK9/CycK	CMGC	*	*	*
CDK9/CycT1	CMGC	*	*	*
CHK1	CAMK	*	*	*
CHK2	CAMK	*	*	*
CK1-alpha1	CK1	*	*	*
CK1-delta	CK1	*	*	*
CK1-epsilon	CK1	*	*	*
CK1-gamma1	CK1	*	*	*
CK1-gamma2	CK1	*	*	*
CK1-gamma3	CK1	*	*	*
CK2-alpha1	OTHER	*	*	*
CK2-alpha2	OTHER	*	*	*
CLK1	CMGC	*	*	*
CLK2	CMGC	*	*	*
CLK3	CMGC	*	*	*
CLK4	CMGC	*	*	*
COT	STE	*	*	*
CSF1R	TK	****	****	****
CSK	TK	****	****	****
DAPK1	CAMK	*	*	*
DAPK2	CAMK	*	*	*
DAPK3	CAMK	*	*	*
DCAMKL2	CAMK	*	*	*
DDR2	TK	****	****	****
DMPK	AGC	*	*	**
DNA-PK	ATYPICAL	*	*	*
DYRK1A	CMGC	*	*	*
DYRK1B	CMGC	*	*	*

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
DYRK2	CMGC	*	*	*
DYRK3	CMGC	*	*	*
DYRK4	CMGC	*	*	*
EEF2K	ATYPICAL	*	*	*
EGF-R	TK	***	****	****
EIF2AK2	OTHER	*	*	*
EIF2AK3	OTHER	*	*	*
EPHA1	TK	****	****	****
EPHA2	TK	****	****	****
EPHA3	TK	****	****	****
EPHA4	TK	****	****	****
EPHA5	TK	****	****	****
EPHA6	TK	*	***	***
EPHA7	TK	*	*	*
EPHA8	TK	****	****	****
EPHB1	TK	****	****	****
EPHB2	TK	****	****	****
EPHB3	TK	****	****	****
EPHB4	TK	****	****	****
ERBB2	TK	*	***	***
ERBB4	TK	****	****	****
ERK1	CMGC	*	*	*
ERK2	CMGC	*	*	*
ERK5	CMGC	*	*	*
ERK7	CMGC	*	*	*
FAK aa2-1052	TK	*	*	*
FER	TK	*	*	*
FES	TK	*	*	*
FGF-R1	TK	*	**	**
FGF-R2	TK	**	***	****
FGF-R3	TK	*	*	**
FGF-R4	TK	*	*	*
FGR	TK	****	****	****
FLT3	TK	***	*	**
FRK	TK	****	****	****
FYN	TK	****	****	****
GRK2	AGC	*	*	*
GRK3	AGC	*	*	*
GRK4	AGC	*	*	*
GRK5	AGC	*	*	*
GRK6	AGC	*	*	*
GRK7	AGC	*	*	*

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
GSG2	OTHER	*	*	*
GSK3-alpha	CMGC	*	*	*
GSK3-beta	CMGC	*	*	*
HCK	TK	****	****	****
HIPK1	CMGC	*	*	*
HIPK2	CMGC	*	*	*
HIPK3	CMGC	*	*	*
HIPK4	CMGC	*	*	*
HRI	OTHER	*	*	*
IGF1-R	TK	*	*	*
IKK-alpha	OTHER	*	*	*
IKK-beta	OTHER	*	*	*
IKK-epsilon	OTHER	*	*	**
INS-R	TK	*	*	*
INSR-R	TK	*	*	*
IRAK1	TKL	*	*	*
IRAK4 (untagged)	TKL	*	*	**
ITK	TK	*	*	*
JAK1 aa583-1154 wt	TK	*	***	***
JAK2	TK	**	**	**
JAK3	TK	*	*	**
JNK1	CMGC	*	*	*
JNK2	CMGC	*	*	*
JNK3	CMGC	*	*	*
KIT	TK	****	****	****
LCK	TK	****	****	****
LIMK1	TKL	*	*	*
LIMK2	TKL	*	*	*
LRRK2	TKL	*	*	**
LTK	TK	*	*	*
LYN	TK	****	****	****
MAP3K1	STE	*	*	*
MAP3K10	STE	*	**	***
MAP3K11	STE	**	***	****
MAP3K7/MAP3K7IP1	STE	*	*	*
MAP3K9	STE	*	**	***
MAP4K2	STE	*	*	*
MAP4K4	STE	*	*	*
MAP4K5	STE	***	****	****
MAPKAPK2	CAMK	*	*	*
MAPKAPK3	CAMK	*	*	*
MAPKAPK5	CAMK	*	*	*

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
MARK1	CAMK	*	*	*
MARK2	CAMK	*	*	*
MARK3	CAMK	*	*	*
MARK4	CAMK	*	*	*
MATK	TK	*	*	*
MEK1	STE	*	*	*
MEK2	STE	*	*	*
MEK5	STE	*	*	*
MEKK2	STE	*	**	***
MEKK3	STE	*	**	***
MELK	CAMK	*	*	*
MERTK	TK	*	*	*
MET	TK	*	*	*
MINK1	STE	*	**	**
MKK4	STE	*	*	*
MKK6 S207D/T211D##	STE	*	*	*
MKK7	STE	*	*	*
MKNK1	CAMK	**	*	*
MKNK2	CAMK	*	*	*
MLK4	TKL	*	*	*
MST1	STE	*	*	*
MST2	STE	*	*	*
MST3	STE	*	*	*
MST4	STE	*	*	***
mTOR	ATYPICAL	*	*	*
MUSK	TK	*	*	*
MYLK	CAMK	*	*	*
MYLK2	CAMK	*	*	**
MYLK3	CAMK	*	*	*
NEK1	OTHER	*	*	*
NEK11	OTHER	*	**	****
NEK2	OTHER	*	*	*
NEK3	OTHER	*	*	*
NEK4	OTHER	*	*	*
NEK6	OTHER	*	*	*
NEK7	OTHER	*	*	*
NEK9	OTHER	*	*	*
NIK	STE	*	*	*
NLK	CMGC	***	****	****
p38-alpha	CMGC	***	****	****
p38-beta	CMGC	**	****	****
p38-delta	CMGC	*	*	*

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
p38-gamma	CMGC	*	*	*
PAK1	STE	*	*	*
PAK2	STE	*	*	*
PAK3	STE	*	*	*
PAK4	STE	*	*	*
PAK6	STE	*	*	*
PAK7	STE	*	*	*
PASK	CAMK	*	*	*
PBK	OTHER	*	*	*
PDGFR-alpha	TK	****	****	****
PDGFR-beta	TK	****	****	****
PDK1	AGC	*	*	*
PHKG1	CAMK	*	*	*
PHKG2	CAMK	*	*	*
PIM1	CAMK	*	*	*
PIM2	CAMK	*	*	*
PIM3	CAMK	*	*	*
PKA	AGC	*	**	*
PKC-alpha	AGC	*	*	*
PKC-beta1	AGC	*	*	*
PKC-beta2	AGC	*	*	*
PKC-delta	AGC	*	*	*
PKC-epsilon	AGC	*	*	*
PKC-eta	AGC	*	*	*
PKC-gamma	AGC	*	*	*
PKC-iota	AGC	*	*	*
PKC-mu	AGC	*	*	*
PKC-nu	AGC	*	*	*
PKC-theta	AGC	*	*	**
PKC-zeta	AGC	*	*	*
PKMYT1	OTHER	*	*	*
PLK1	OTHER	*	*	*
PLK3	OTHER	*	*	*
PRK1	AGC	*	*	*
PRK2	AGC	*	*	*
PRKD2	CAMK	*	*	*
PRKG1	AGC	*	*	*
PRKG2	AGC	*	*	*
PRKX	AGC	*	*	**
PYK2	TK	*	*	*
RAF1 Y340D/Y341D (untagged)##	TKL	***	****	****
RET	TK	*	***	****

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
RIPK2	TKL	****	****	****
RIPK5	TKL	*	*	*
ROCK1	AGC	*	*	*
ROCK2	AGC	*	*	*
RON	TK	*	*	*
ROS	TK	*	*	*
RPS6KA1	AGC	*	*	*
RPS6KA2	AGC	*	*	**
RPS6KA3	AGC	*	*	*
RPS6KA4	AGC	*	*	*
RPS6KA5	AGC	*	*	*
RPS6KA6	AGC	*	*	***
S6K	AGC	*	*	*
S6K-beta	AGC	*	*	*
SAK	OTHER	*	*	*
SGK1	AGC	*	*	*
SGK2	AGC	*	*	*
SGK3	AGC	*	*	*
SIK1	CAMK	****	****	****
SIK2	CAMK	****	****	****
SIK3	CAMK	****	****	****
SLK	STE	*	**	**
SNARK	CAMK	*	*	*
SNK	OTHER	*	*	*
SRC (GST-HIS-tag)	TK	****	****	****
SRMS	TK	***	****	****
SRPK1	CMGC	*	*	*
SRPK2	CMGC	*	*	*
STK17A	CAMK	*	*	*
STK23	CAMK	*	*	*
STK25	STE	*	*	**
STK33	CAMK	*	*	*
STK39	STE	*	*	*
SYK aa1-635	TK	*	**	**
TAOK2	STE	*	*	*
TAOK3	STE	*	*	*
TBK1	OTHER	*	*	***
TEC	TK	****	****	****
TGFB-R1	TKL	***	****	****
TGFB-R2	TKL	*	**	***
TIE2	TK	*	*	**
TLK1	AGC	*	*	*

FIGURE 3 (cont)

Kinase Name	Kinase Family	B3 (1μM)	A8 (1μM)	C7 (1μM)
TLK2	AGC	*	*	*
TNK1	TK	*	*	**
TRK-A	TK	**	**	***
TRK-B	TK	*	*	**
TRK-C	TK	**	**	***
TSF1	OTHER	*	*	*
TSK2	CAMK	*	*	*
TSSK1	CAMK	*	*	*
TTBK1	CK1	*	*	*
TTBK2	CK1	*	*	*
TTK	OTHER	*	*	*
TXK	TK	****	****	****
TYK2	TK	*	*	*
TYRO3	TK	*	*	*
VEGF-R1	TK	*	*	**
VEGF-R2	TK	*	**	**
VEGF-R3	TK	*	*	**
VRK1	CK1	*	*	*
VRK2	CK1	*	*	**
WEE1	OTHER	*	**	***
WNK1	OTHER	*	*	*
WNK2	OTHER	*	**	***
WNK3	OTHER	*	*	**
YES	TK	****	****	****
ZAK	TKL	****	****	****
ZAP70	TK	*	*	*
Selectivity Score	< 50 % residual activity	0.163	0.188	0.234

FIGURE 4

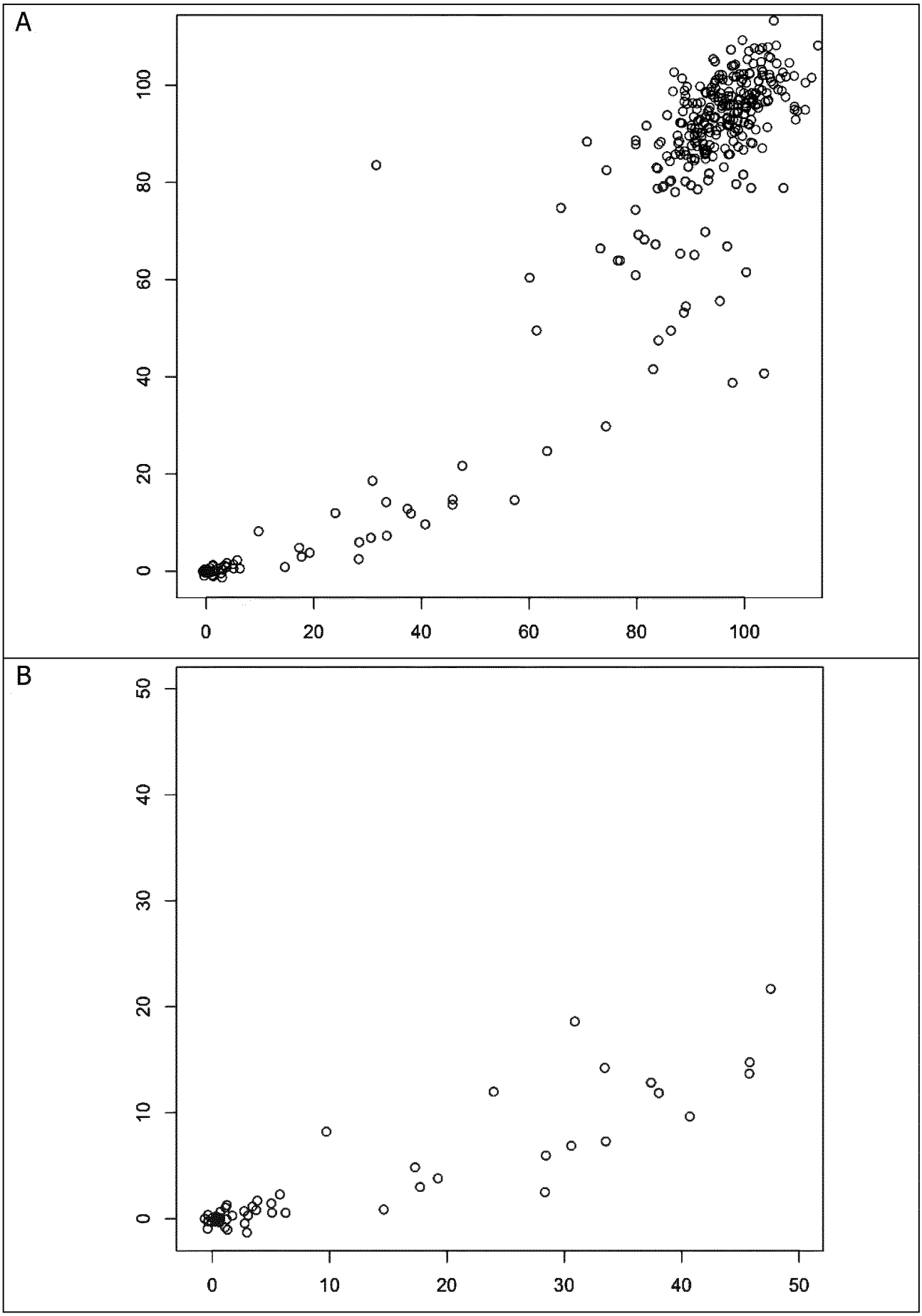


FIGURE 5

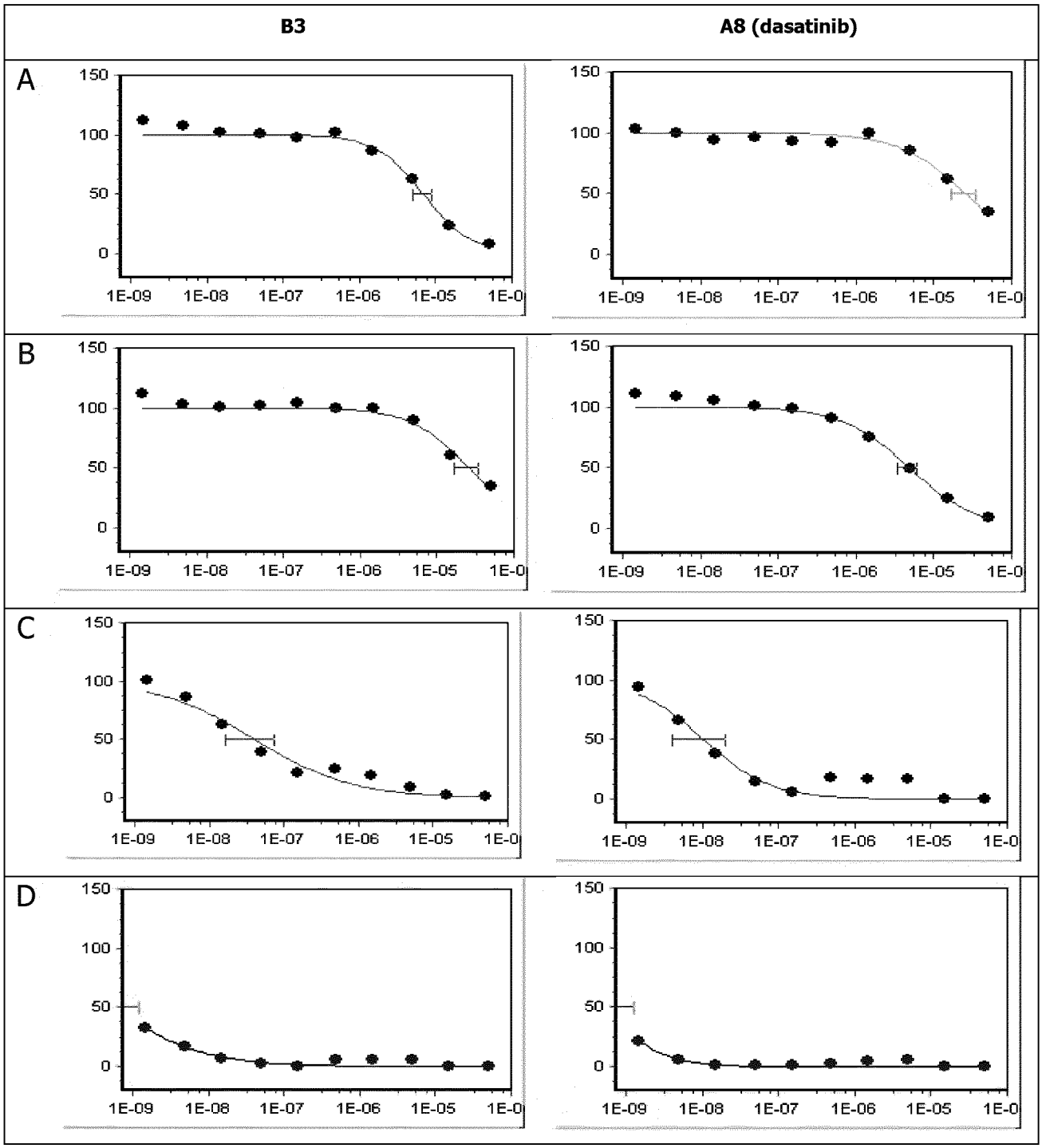


FIGURE 6

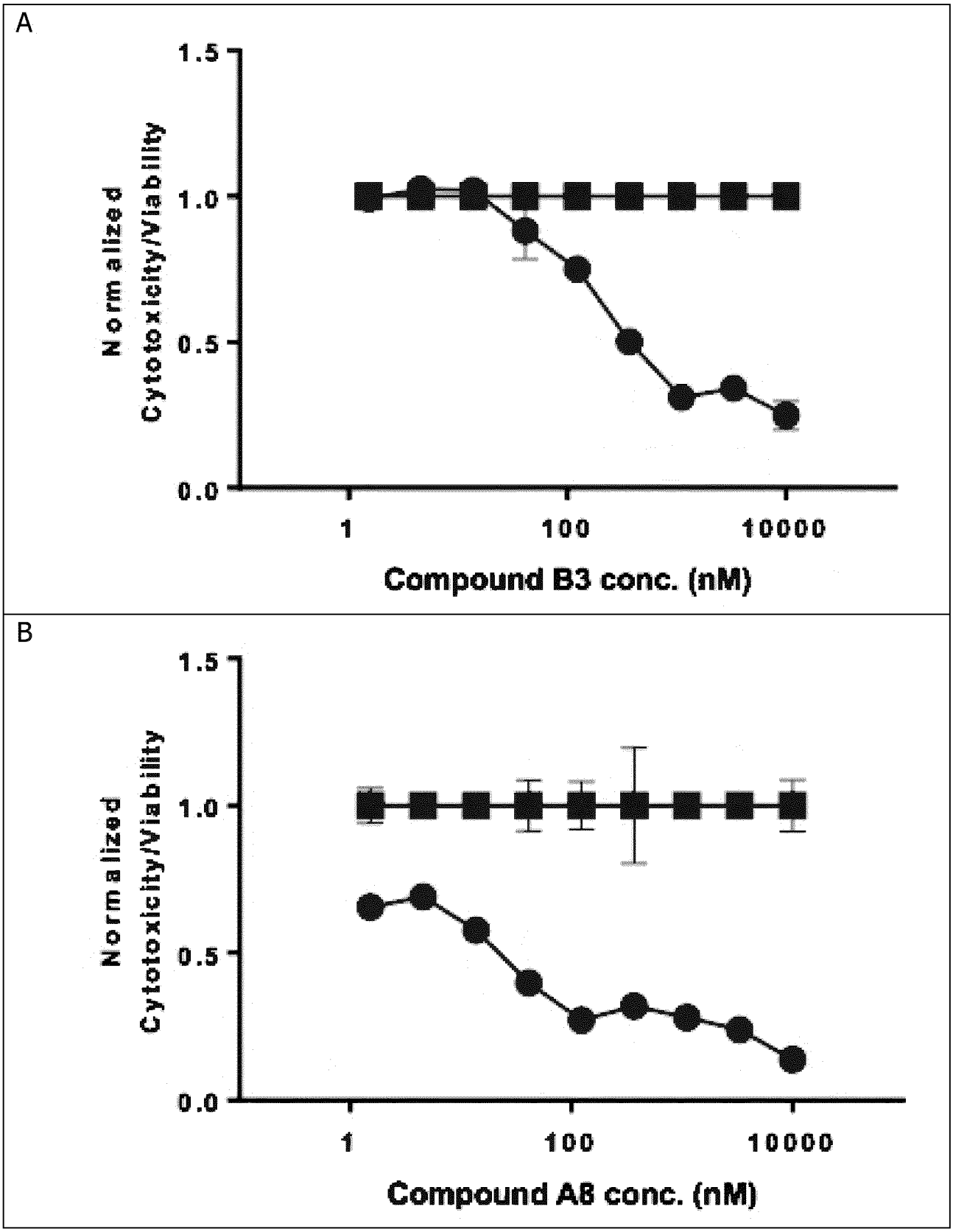

A
Normalized Cytotoxicity/Viability
1.5
1.0
0.5
0.0
1
100
10000
Compound B3 conc. (nM)
B
Normalized Cytotoxicity/Viability
1.5
1.0
0.5
0.0
1
100
10000
Compound A8 conc. (nM)

FIGURE 7

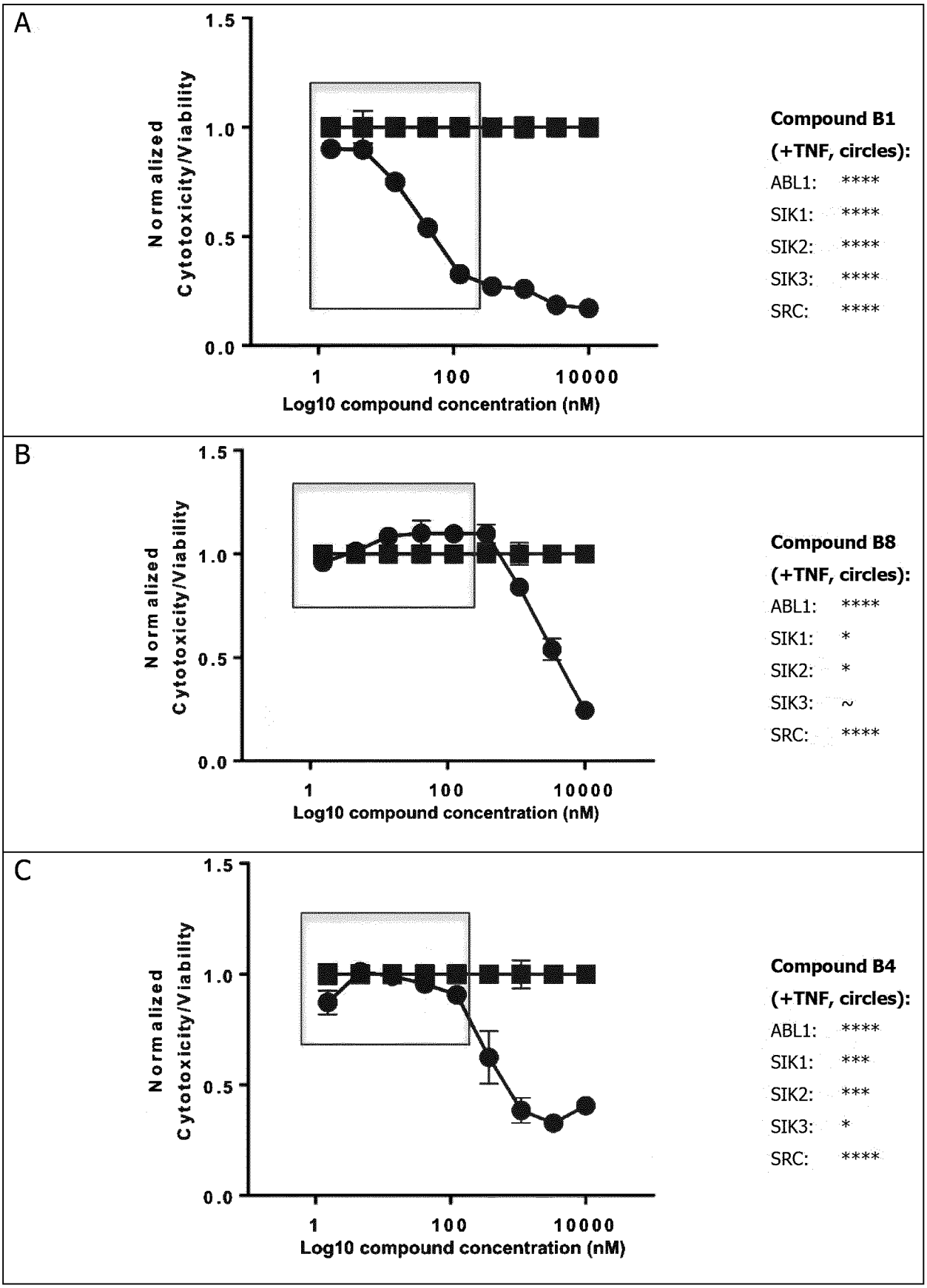
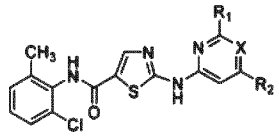
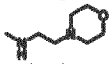
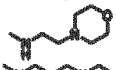

A
Normalized Cytotoxicity/Viability
1.5
1.0
0.5
0.0
1
100
10000
Log10 compound concentration (nM)
Compound B1
(+TNF, circles):
ABL1: ****
SIK1: ****
SIK2: ****
SIK3: ****
SRC: ****
B
Normalized Cytotoxicity/Viability
1.5
1.0
0.5
0.0
1
100
10000
Log10 compound concentration (nM)
Compound B8
(+TNF, circles):
ABL1: ****
SIK1: *
SIK2: *
SIK3: ~
SRC: ****
C
Normalized Cytotoxicity/Viability
1.5
1.0
0.5
0.0
1
100
10000
Log10 compound concentration (nM)
Compound B4
(+TNF, circles):
ABL1: ****
SIK1: ***
SIK2: ***
SIK3: *
SRC: ****

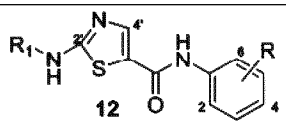
FIGURE 8

A



cmpd	X	R_1	R_2	IC_{50}*, nM K562	PC3	MDA-MB-231	WiDr
1	N	CH_3	CH_3	1.6, 2.1	67		
2	CH		H	<3.0	2.8	<3.0	4.1
3	CH		H	<2.0	3.6 (2.1)	6.2	23
4	CH		H	<3.0	13 (8)	3.1, 5.4	7.9, 47
5	CH		H	<2.0	10	42, 34	32, 67
6	N	H		<3.0	24 (16)	45 (25)	270 (170)
7	N	H		<2.0	82	170	270
8	N	CH_3		<3.0	3.6 (2.3)	16	27
9	N	CH_3		<1.0	25	47	180
10	N	CH_3		<2.0	14	23, 28	92, 27
11	N	CH_3		<4.0	27 (25)	140	210 (120)
12	N	CH_3		<1.0	11 (8)	9.0 (5.1)	41
13	N	CH_3		<1.0	9.4 (5.6)	12 (10)	52 (38)

B



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compd	R	R_1	hLck IC_{50}[a] (nM)	T-cell IC_{50}[b] (nM)
12a	2-Cl, 6-Me	2″-pyridyl	1.2	140
12b	2-Cl, 6-Me	3″-pyridyl	6.7	870
12c	2-Cl, 6-Me	4″-pyridyl	9.4	270
12d	2,6-*di*-Me	2″-pyridyl	1.2	180
12e	2,4,6-*tri*-Me	2″-pyridyl	5	510
12f	2-Cl, 6-Me	3″-pyridazinyl	4	350
12g	2,6-*di*-Me	3″-pyridazinyl	0.3	350
12h	2-Cl, 6-Me	3″,5″-*di*-Me-2″-pyrazinyl	6.3	570
12i	2,4,6-*tri*-Me	2″-pyrazinyl	4.9	500
12j	2-Cl, 6-Me	6″-Me-2″-pyridinyl	0.6	110
12k	2-Cl, 6-Me	4″-Me-2″-pyridinyl	0.5	80
12l	2-Cl, 6-Me	4″,6″-di-Me-2″-pyridinyl	4	140
12m	2-Cl, 6-Me	2″,6″-di-Me-4″-pyrimidinyl	1	80
12n	2-Cl, 6-Me	4″,6″-di-Me-2″-pyrimidinyl	50	
12o	2,4,6-*tri*-Me	2″,6″-di-Me-4″-pyrimidinyl	3	140

[a] $n = 3$, variation in individual values, <20%. [b] $n = 3$, variation in individual values, <30%.

FIGURE 9

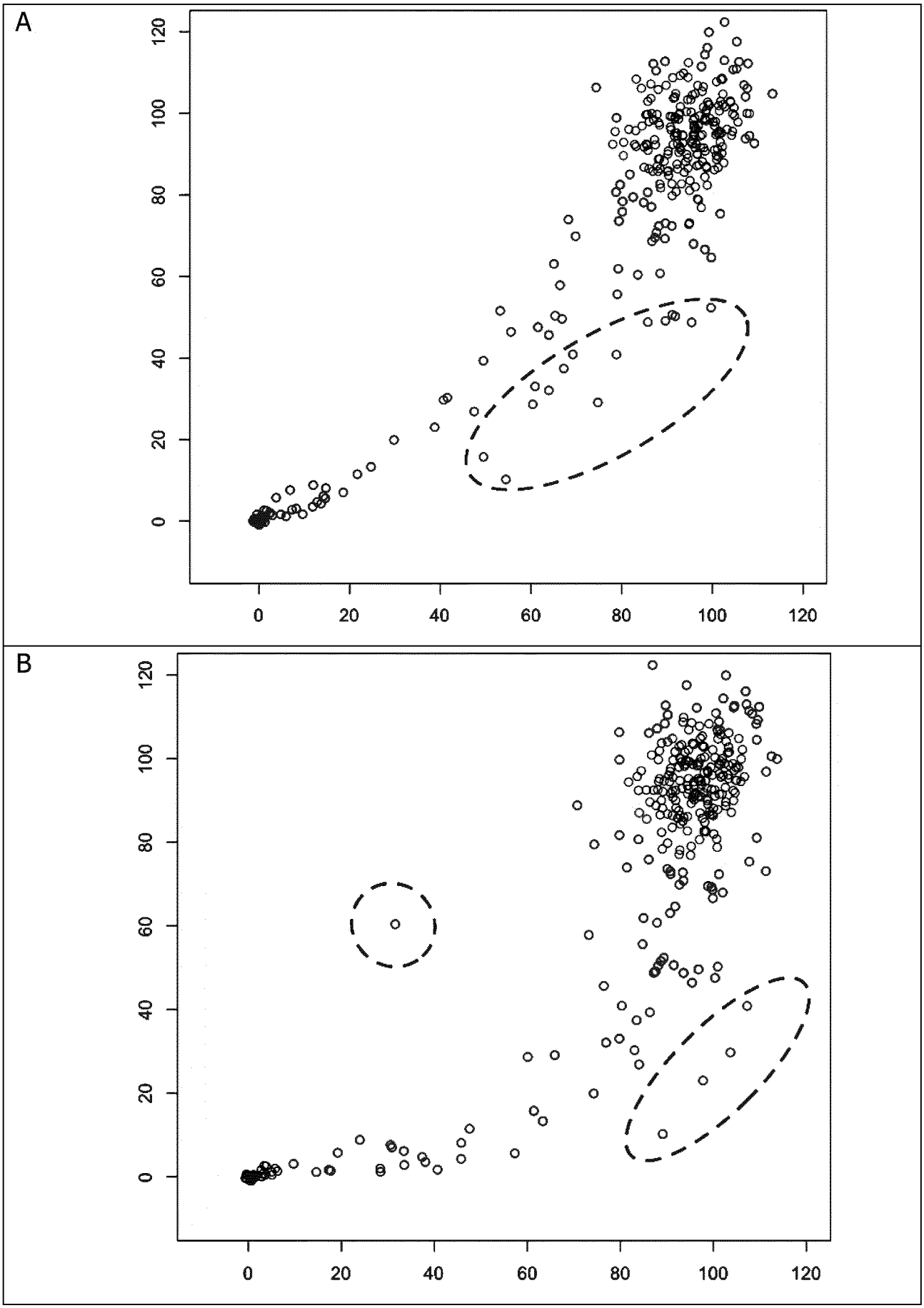


FIGURE 10

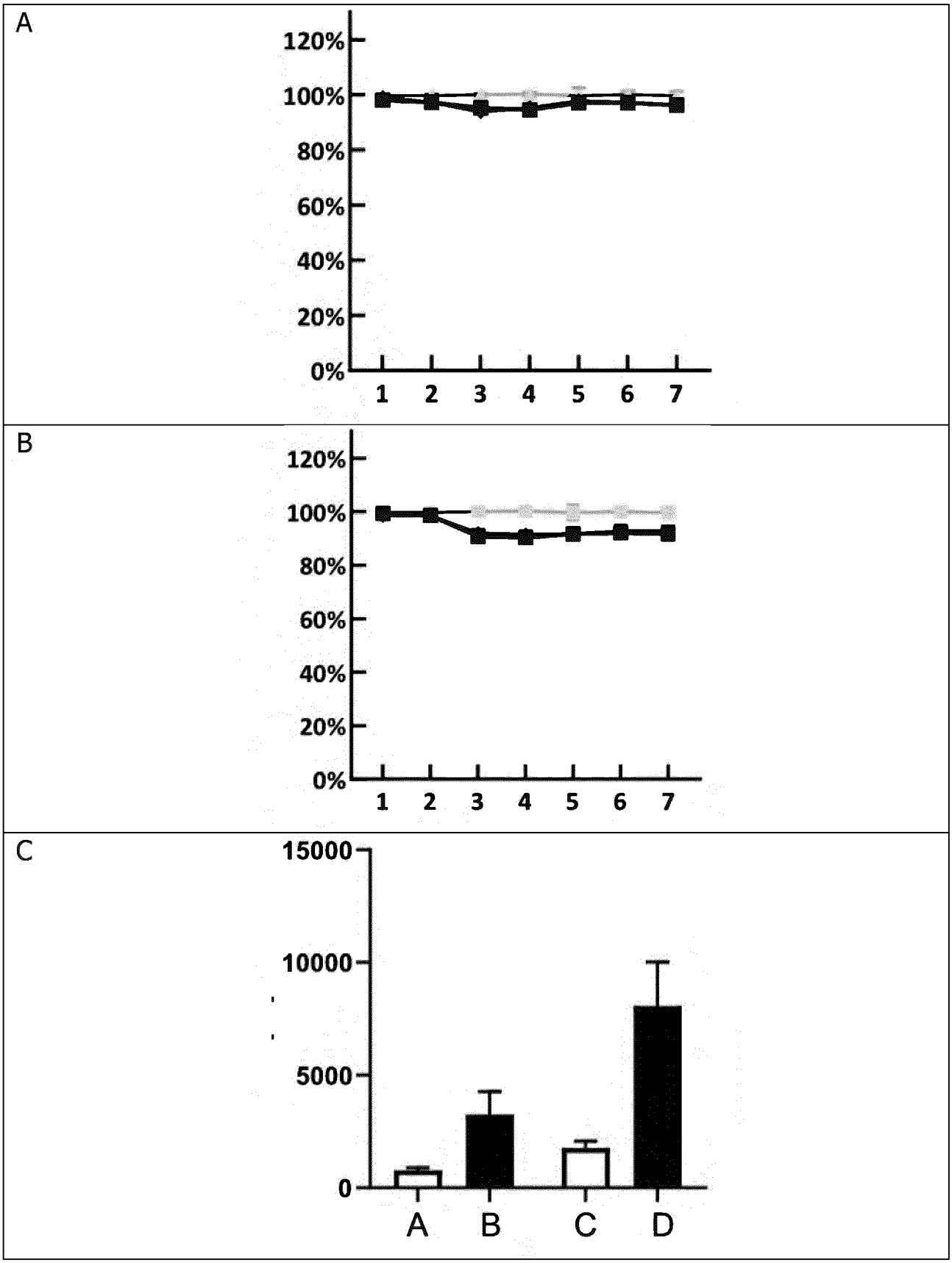

A
120%
100%
80%
60%
40%
20%
0%
1 2 3 4 5 6 7
B
120%
100%
80%
60%
40%
20%
0%
1 2 3 4 5 6 7
C
15000
10000
5000
0
A B C D

FIGURE 11

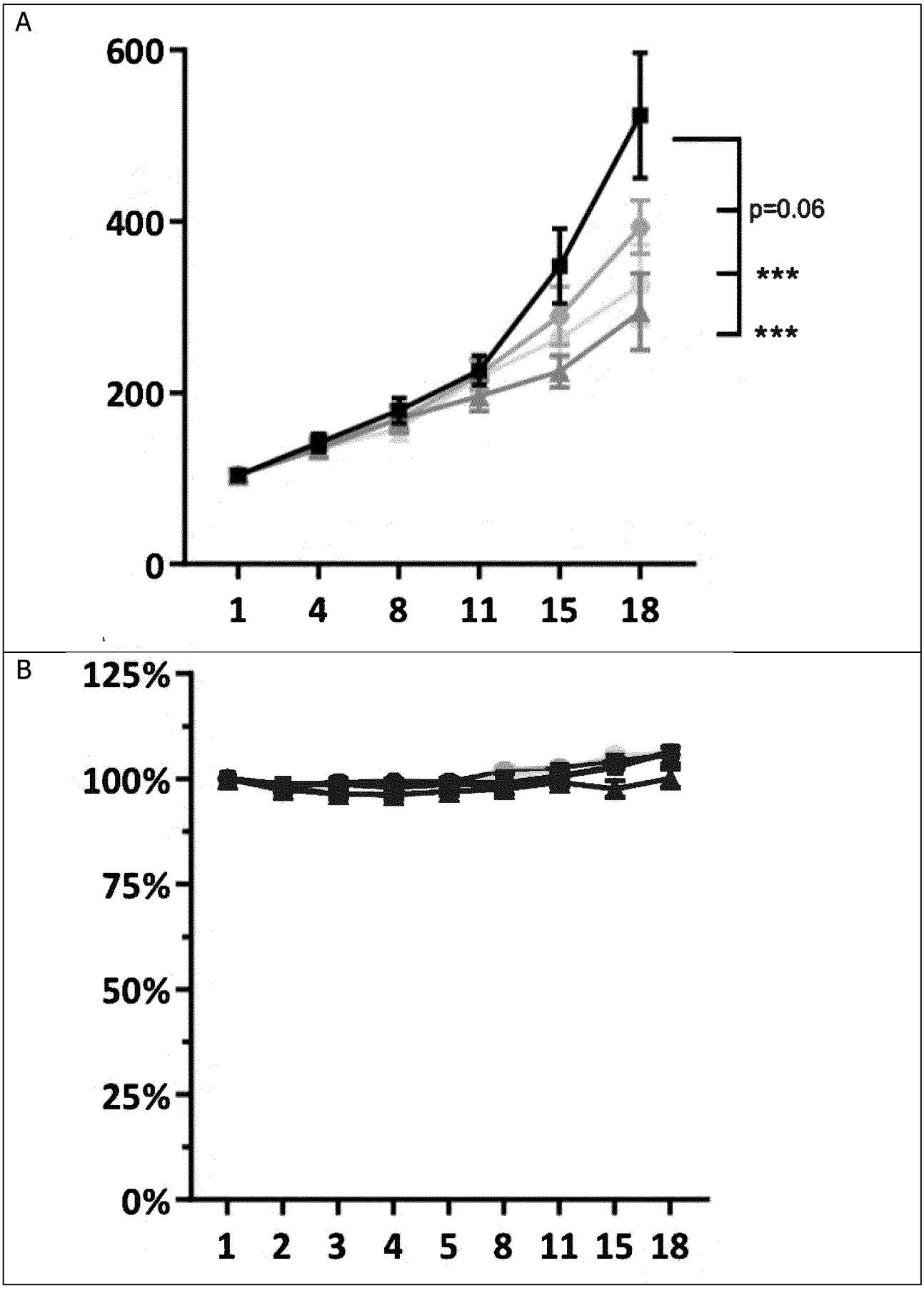

A
600
400
200
0
1
4
8
11
15
18
p=0.06
***
***
B
125%
100%
75%
50%
25%
0%
1
2
3
4
5
8
11
15
18

FIGURE 12

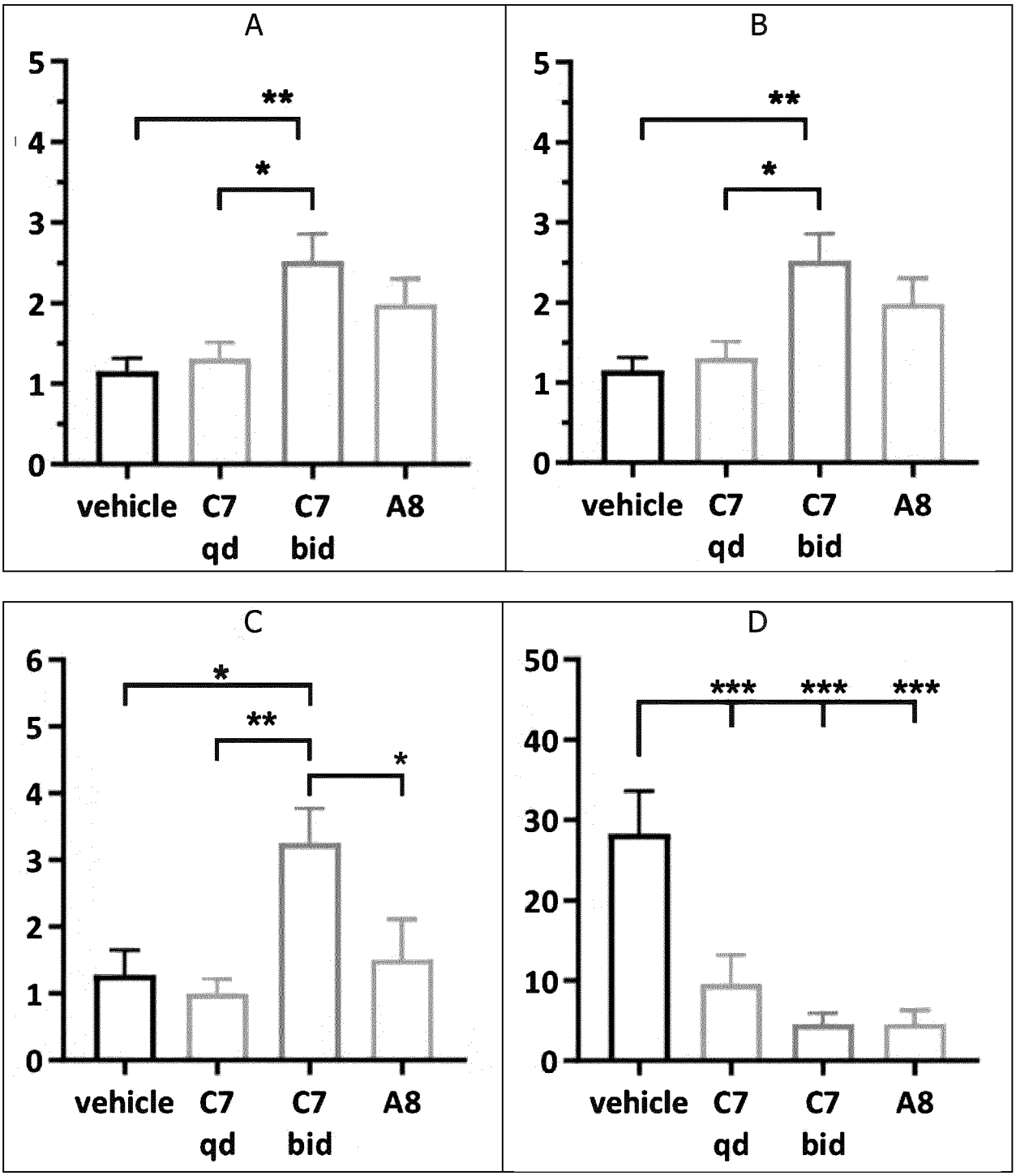


FIGURE 13

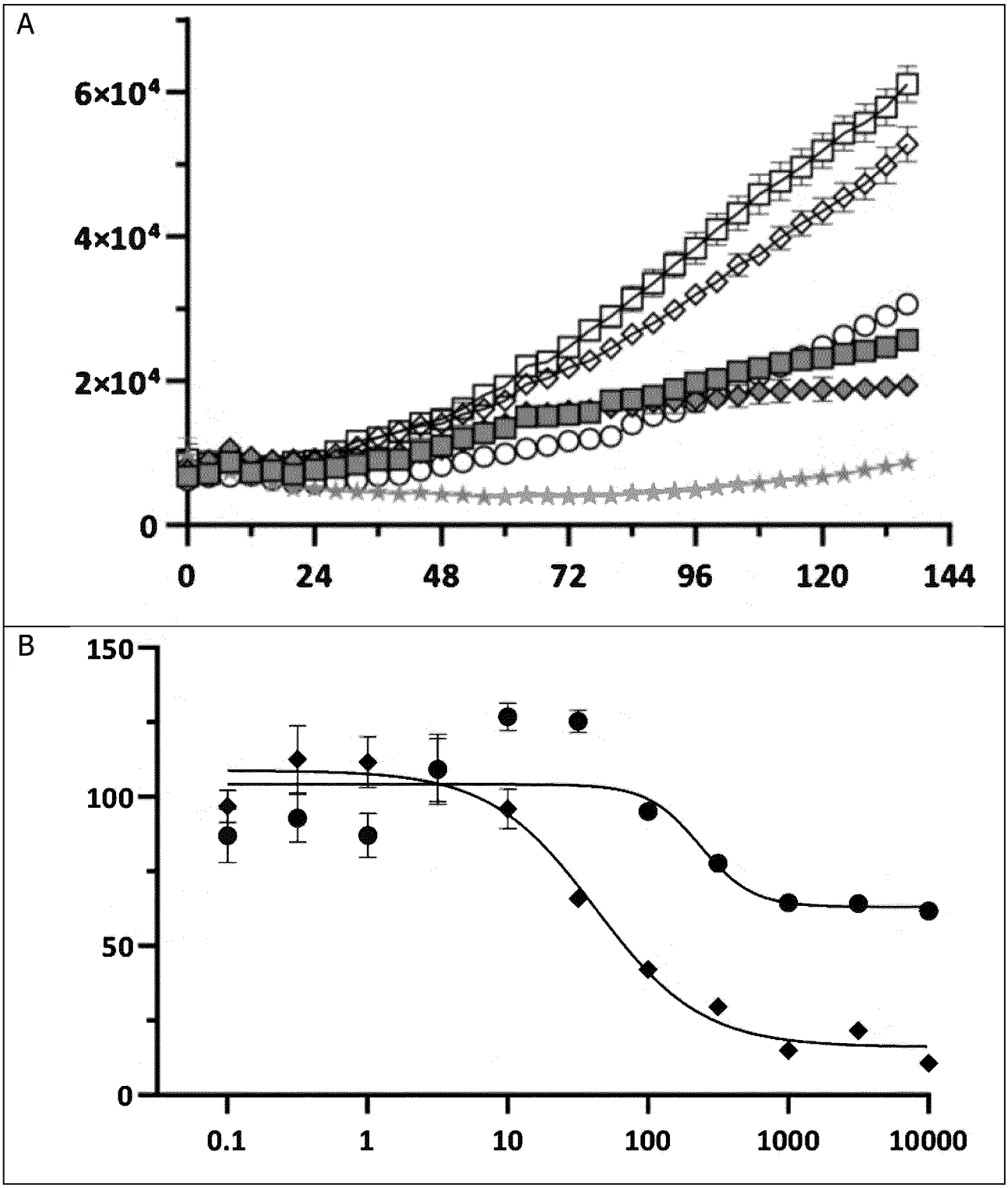

A
6×10⁴
4×10⁴
2×10⁴
0
0
24
48
72
96
120
144
B
150
100
50
0
0.1
1
10
100
1000
10000

FIGURE 14

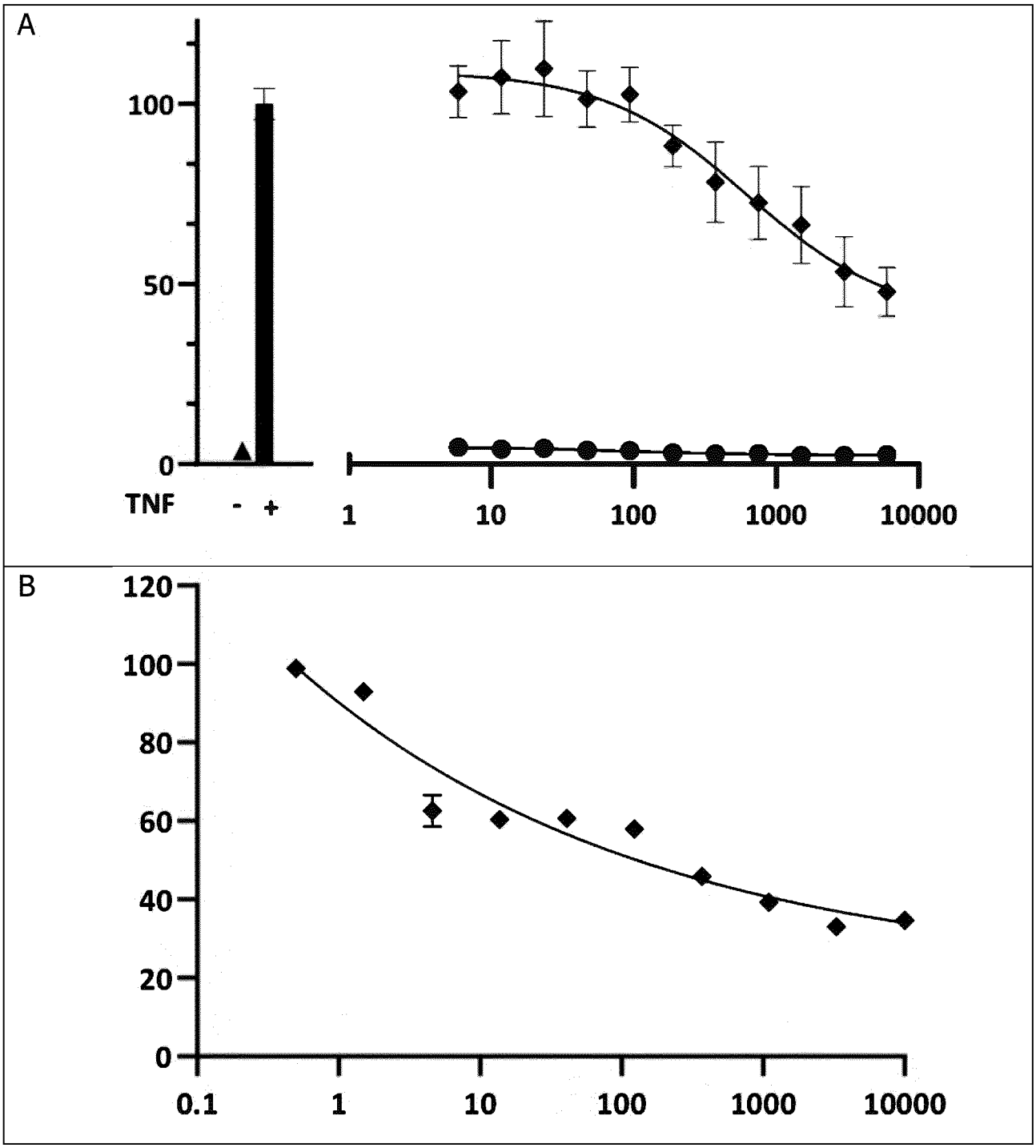
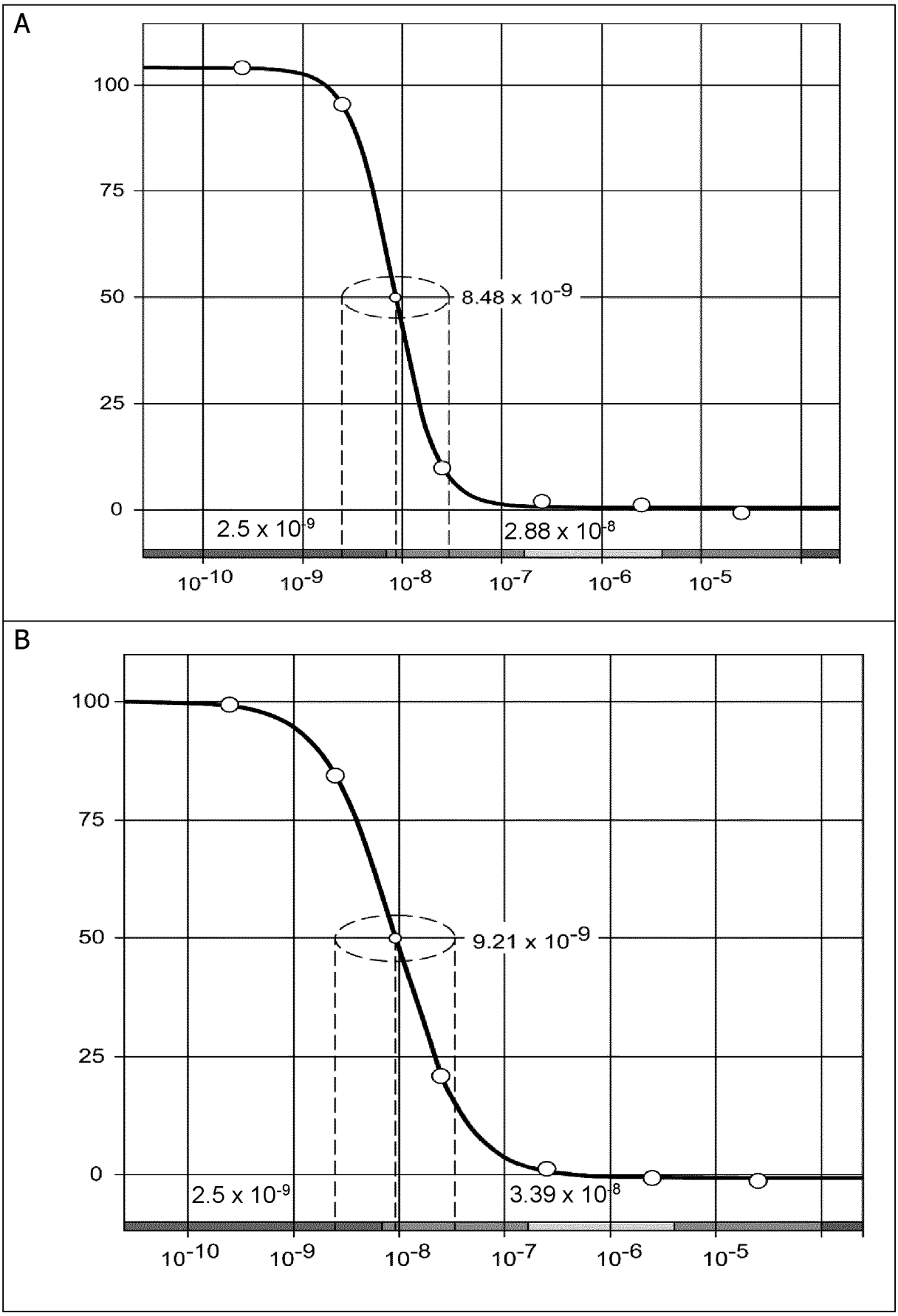

A
100
50
0
TNF
-
+
1
10
100
1000
10000
B
120
100
80
60
40
20
0
0.1
1
10
100
1000
10000

FIGURE 15



SUBSTITUTE SHEET (RULE 26)

FIGURE 16

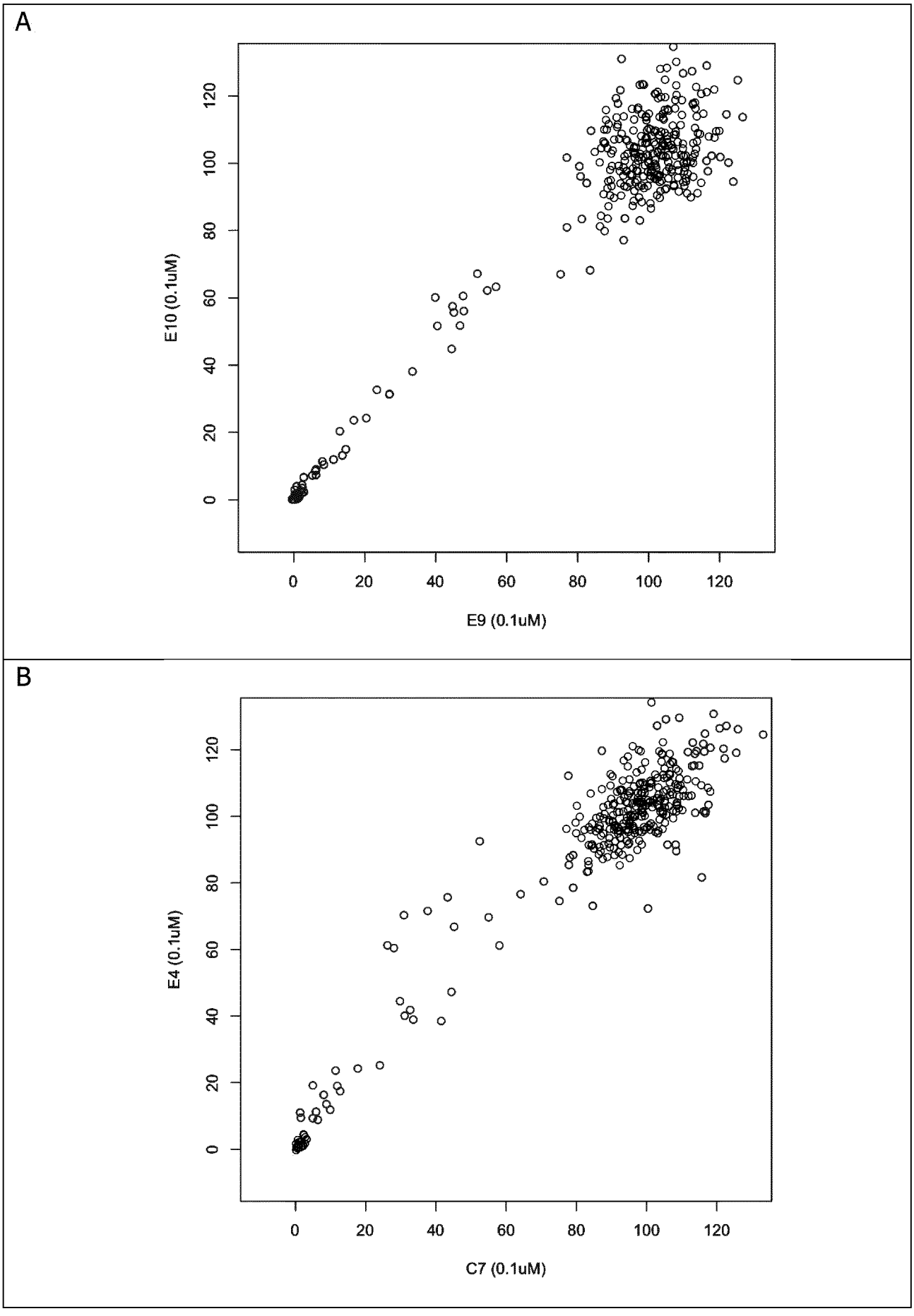

A
E10 (0.1uM)
E9 (0.1uM)
0
20
40
60
80
100
120
B
E4 (0.1uM)
C7 (0.1uM)
0
20
40
60
80
100
120

FIGURE 17

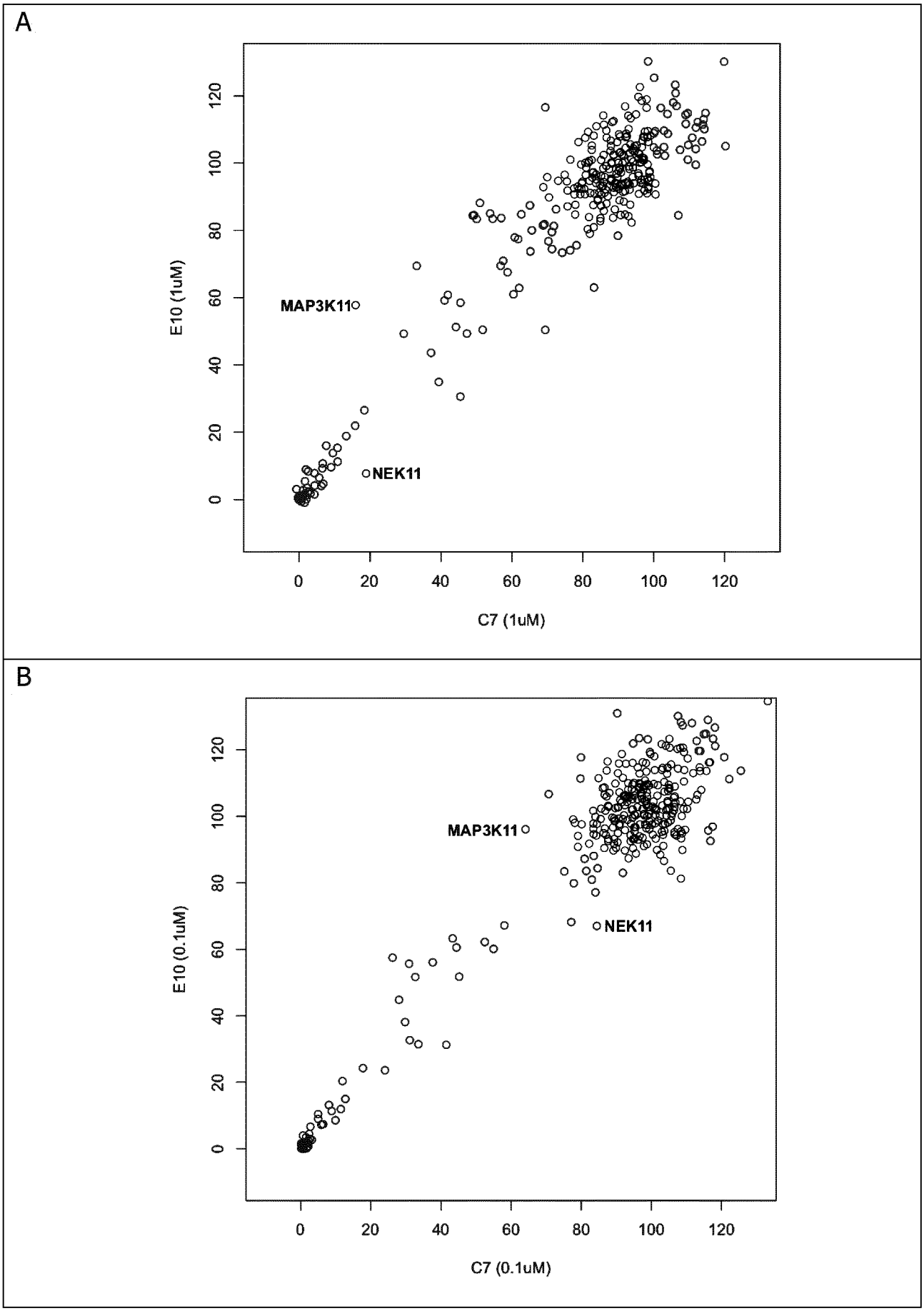

A
E10 (1uM)
C7 (1uM)
MAP3K11
NEK11
0
20
40
60
80
100
120
B
E10 (0.1uM)
C7 (0.1uM)
MAP3K11
NEK11
0
20
40
60
80
100
120

FIGURE 18

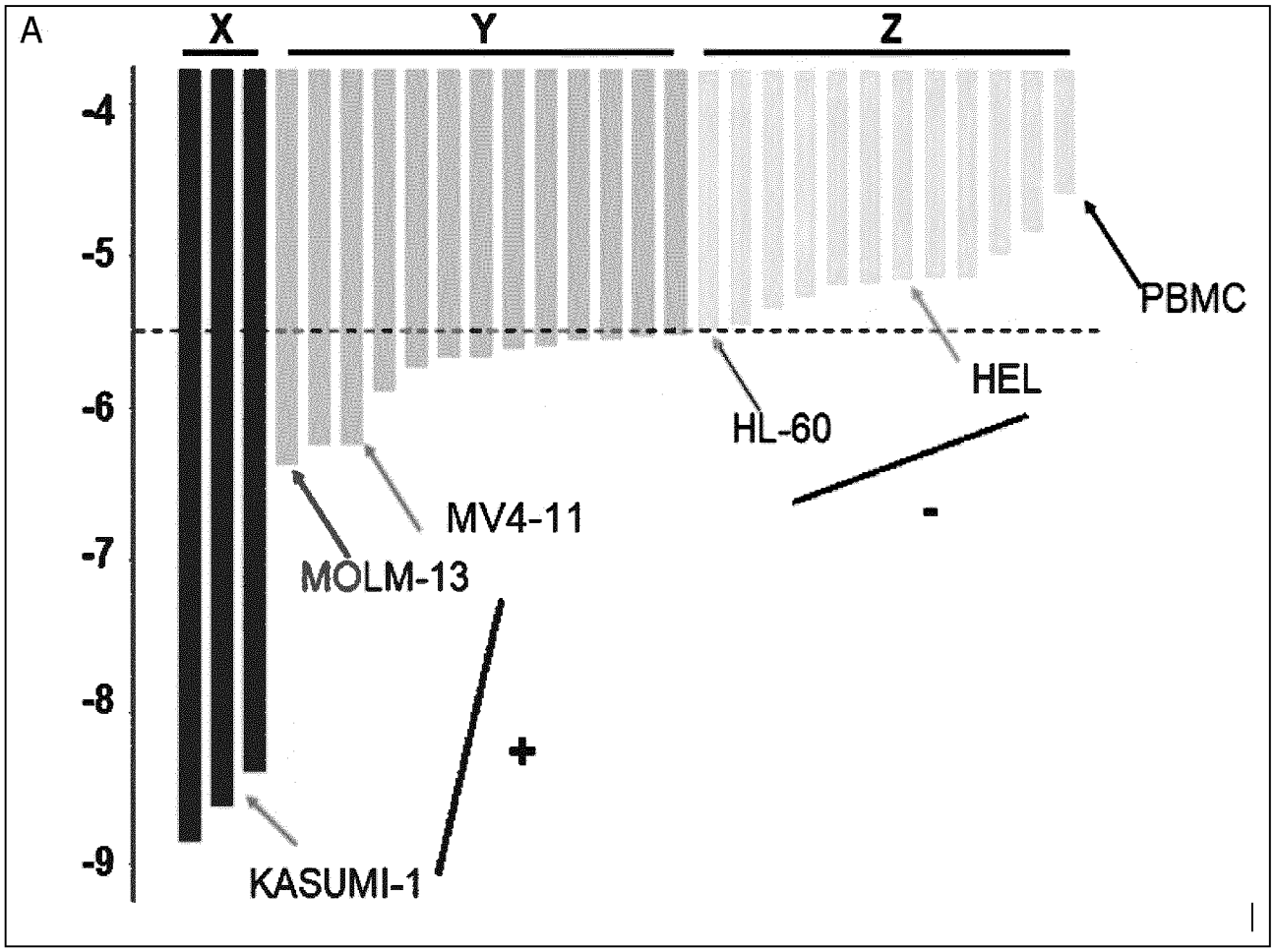


FIGURE 18 (CONT)

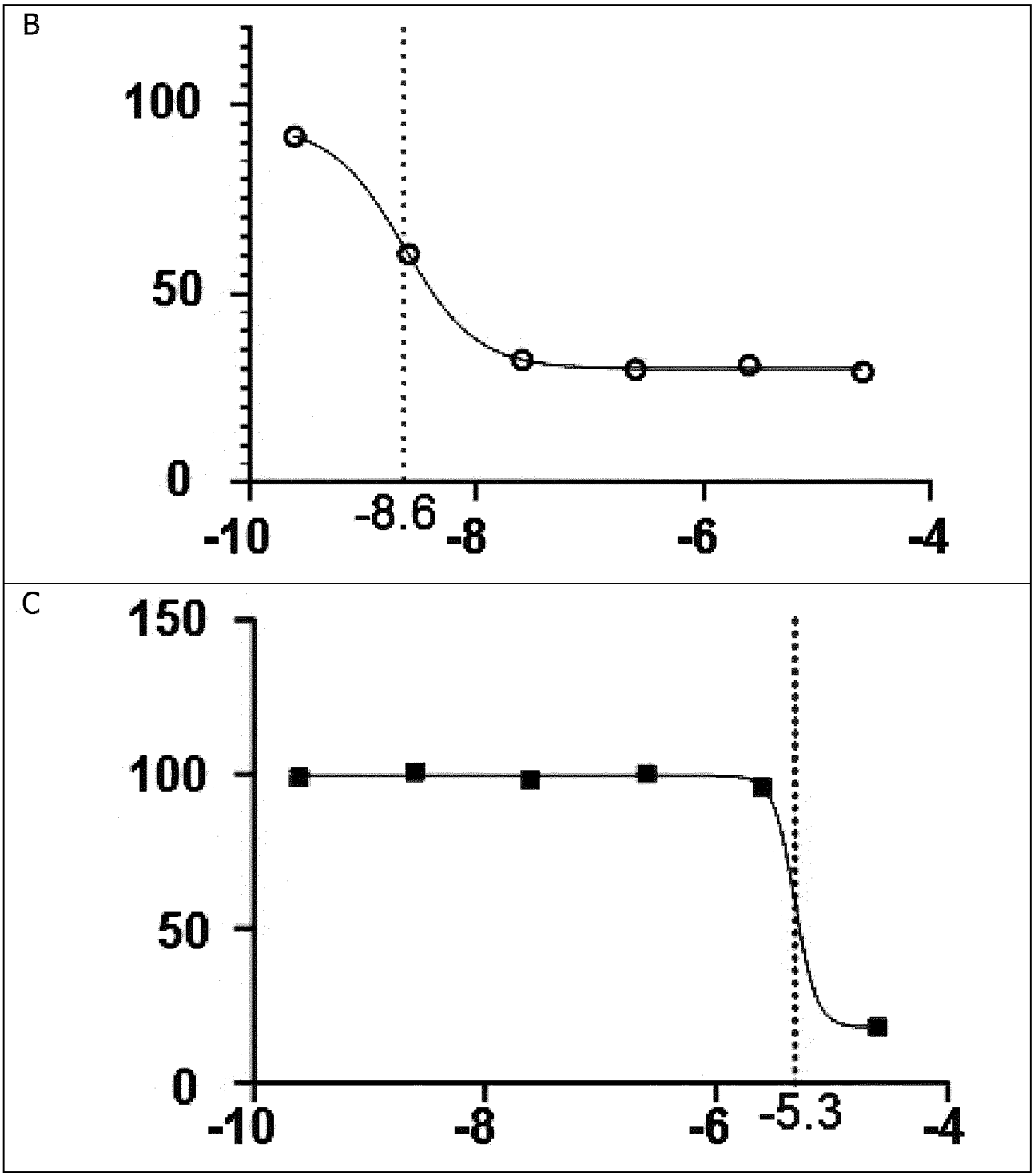
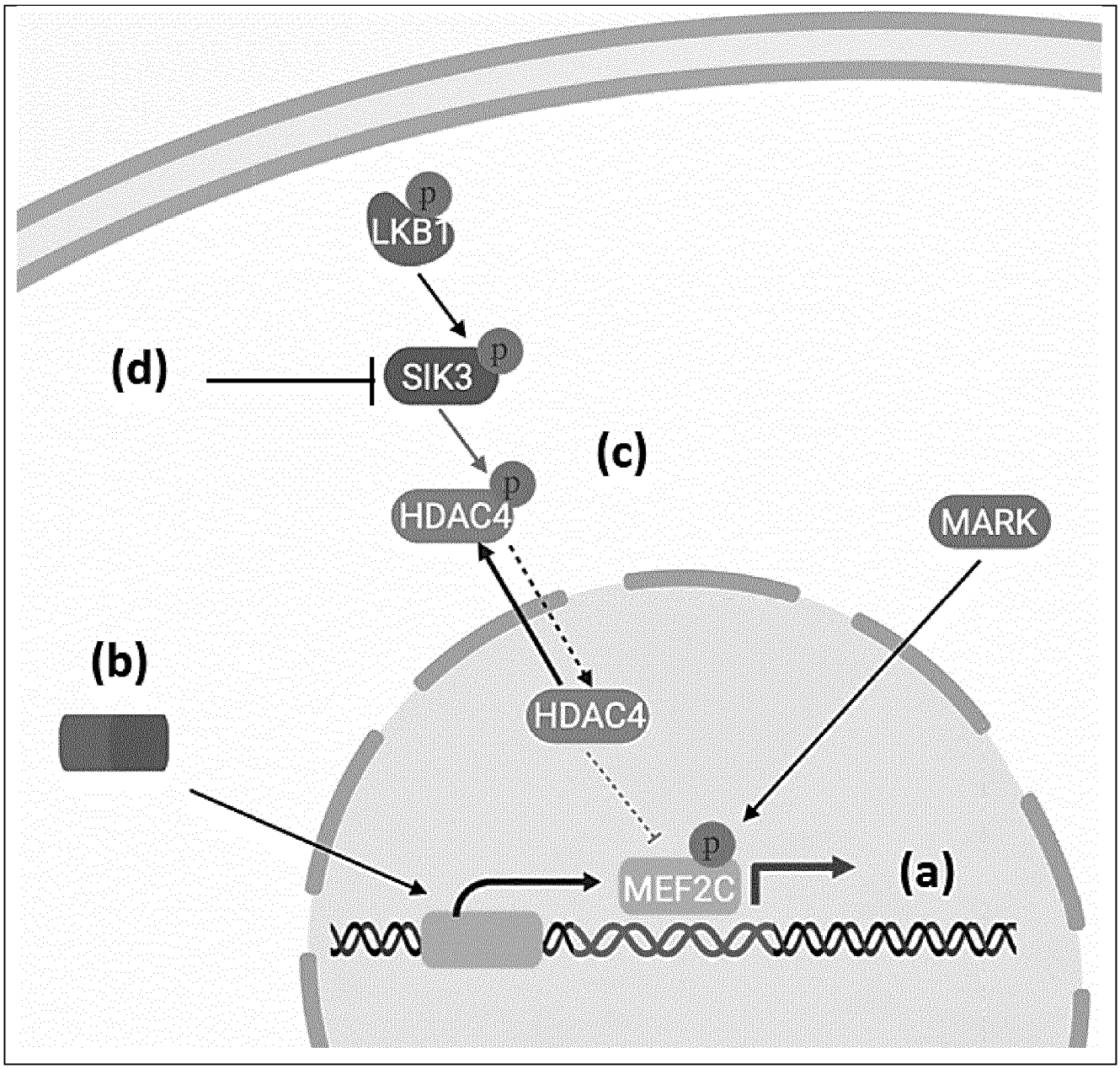


FIGURE 19



SUBSTITUTE SHEET (RULE 26)

FIGURE 20

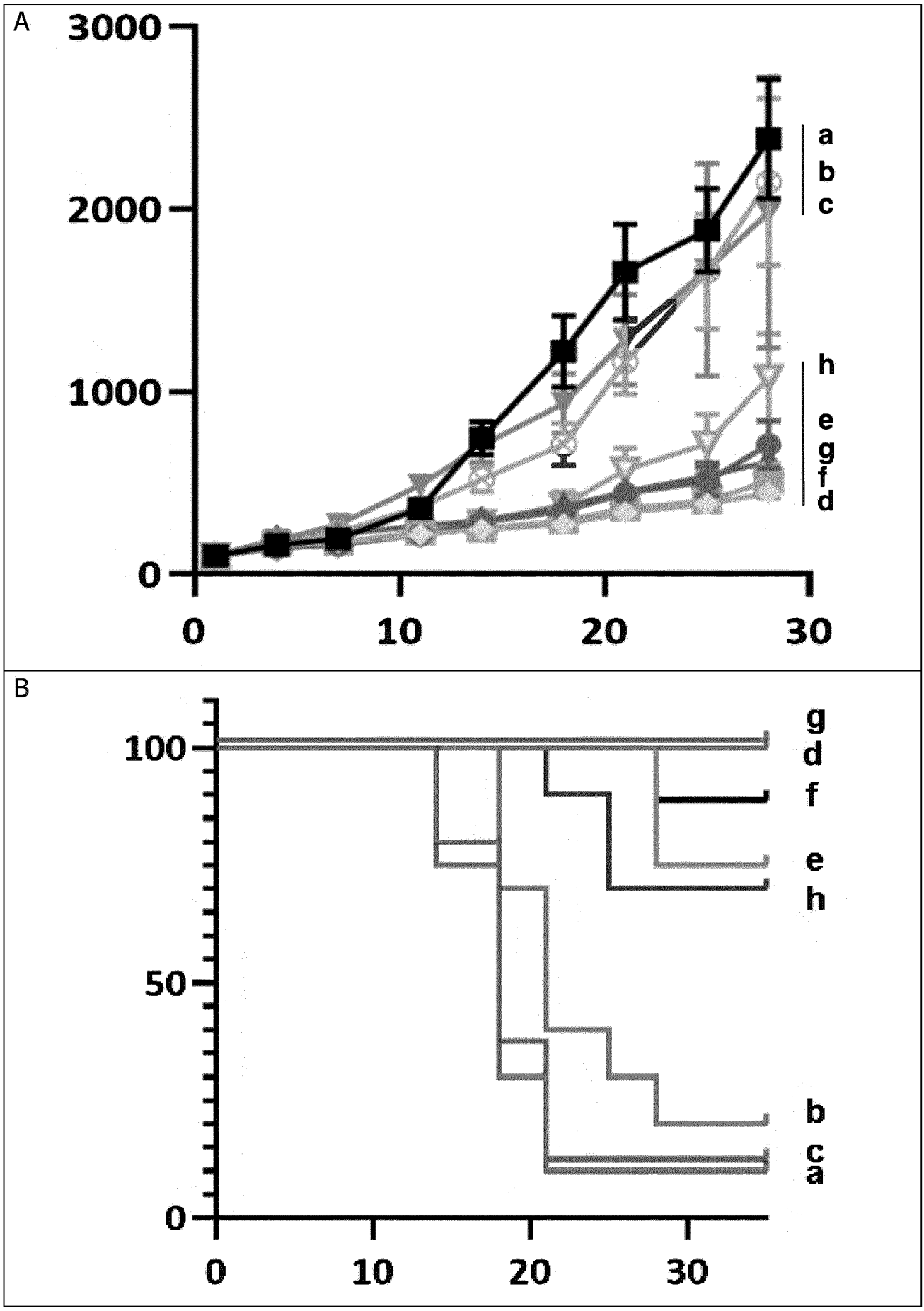

A
3000
2000
1000
0
0
10
20
30
a
b
c
h
e
g
f
d
B
100
50
0
0
10
20
30
g
d
f
e
h
b
c
a

FIGURE 20 (cont)

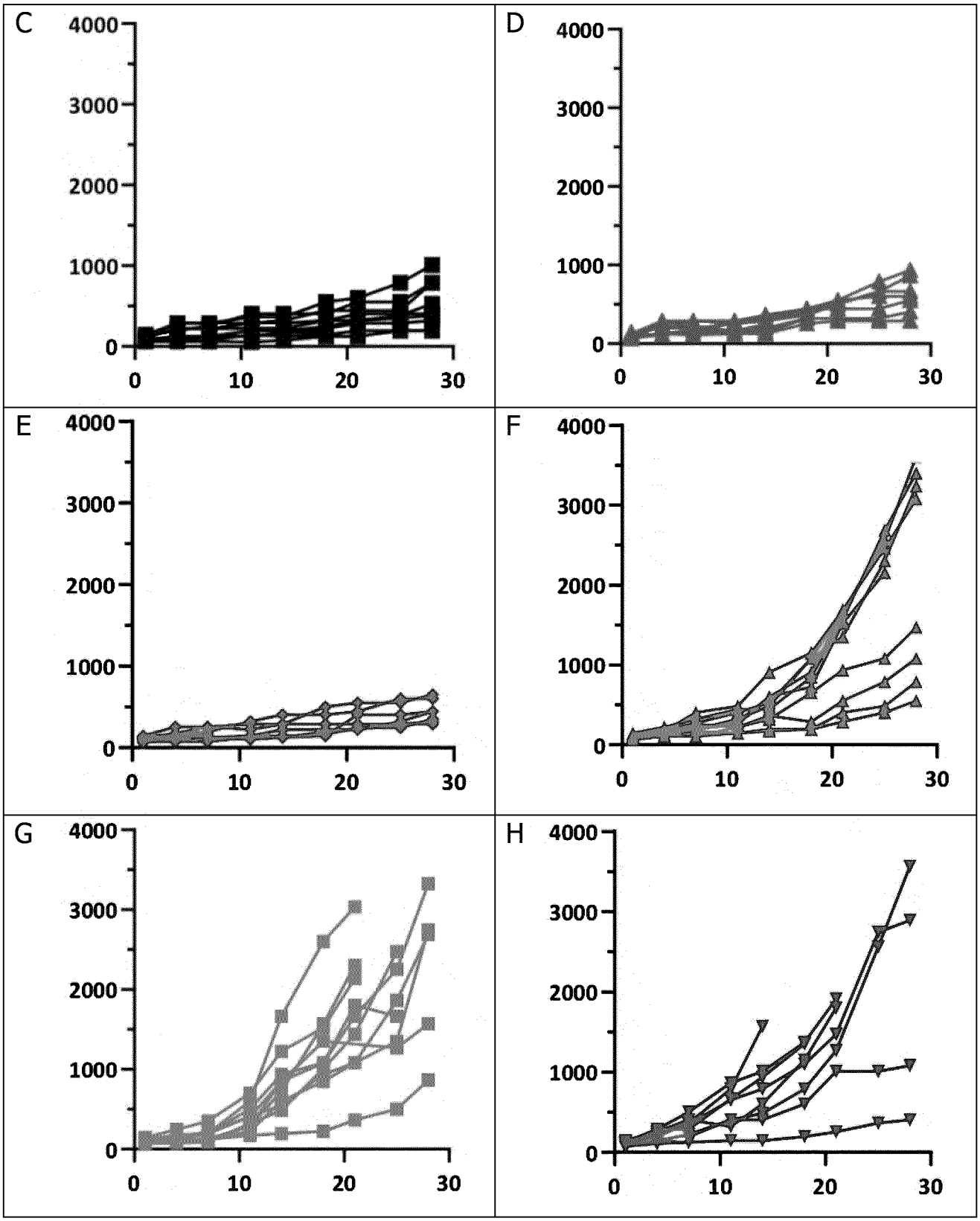


FIGURE 21

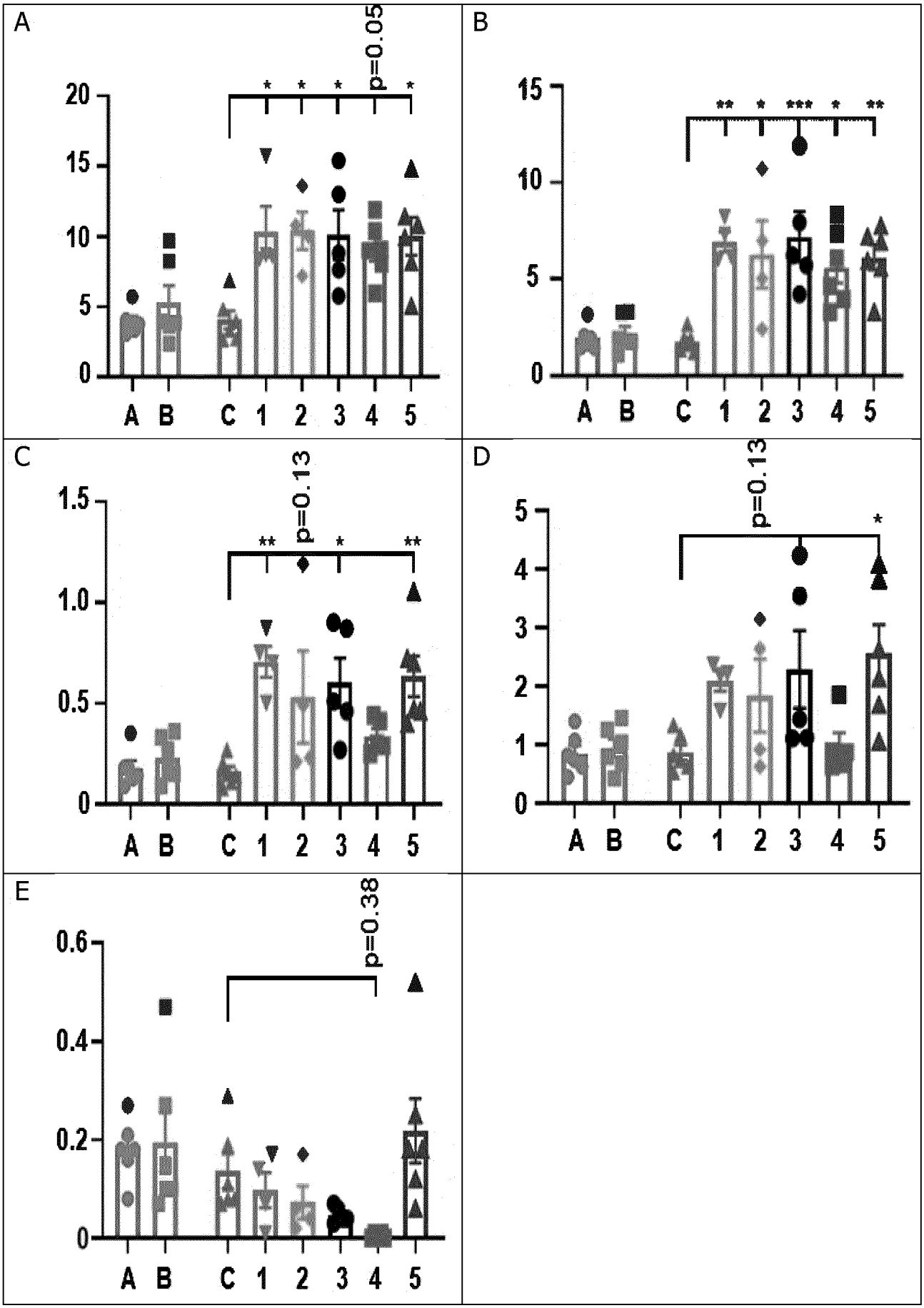

A
p=0.05
20
15
10
5
0
A B C 1 2 3 4 5
B
15
10
5
0
A B C 1 2 3 4 5
C
p=0.13
1.5
1.0
0.5
0
A B C 1 2 3 4 5
D
p=0.13
5
4
3
2
1
0
A B C 1 2 3 4 5
E
p=0.38
0.6
0.4
0.2
0
A B C 1 2 3 4 5

FIGURE 21 (cont)

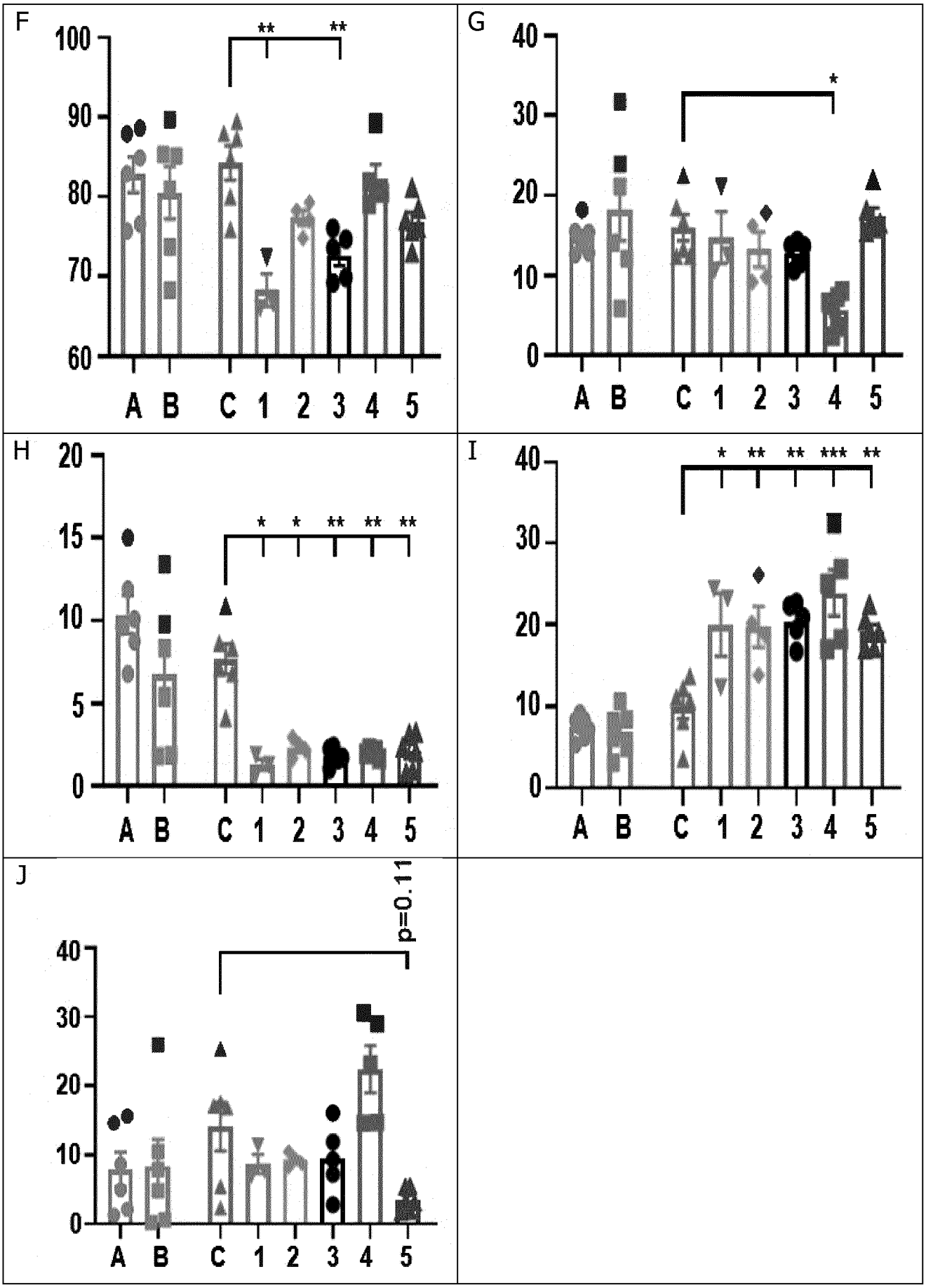


FIGURE 22

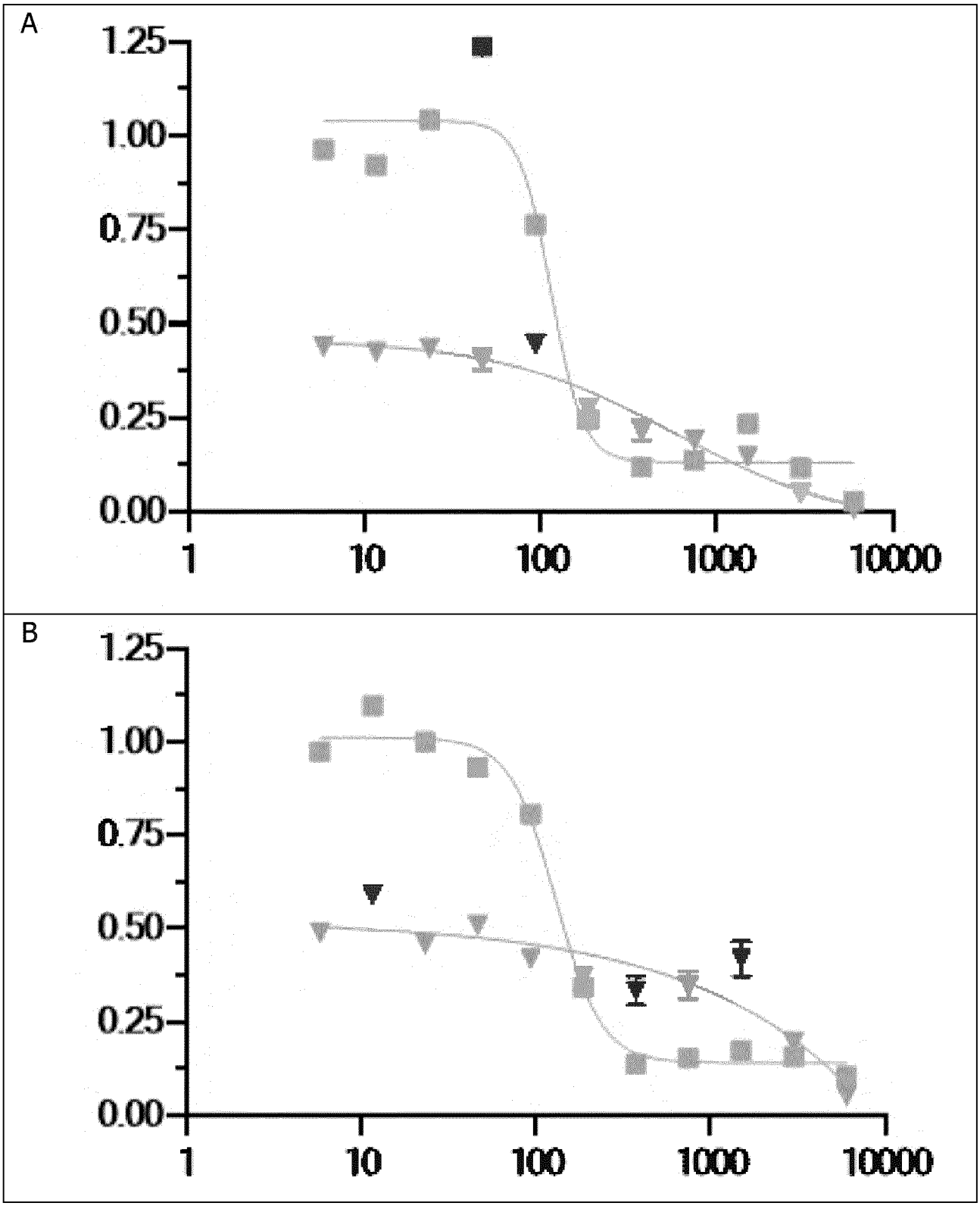

A
1.25
1.00
0.75
0.50
0.25
0.00
1
10
100
1000
10000
B
1.25
1.00
0.75
0.50
0.25
0.00
1
10
100
1000
10000

FIGURE 23

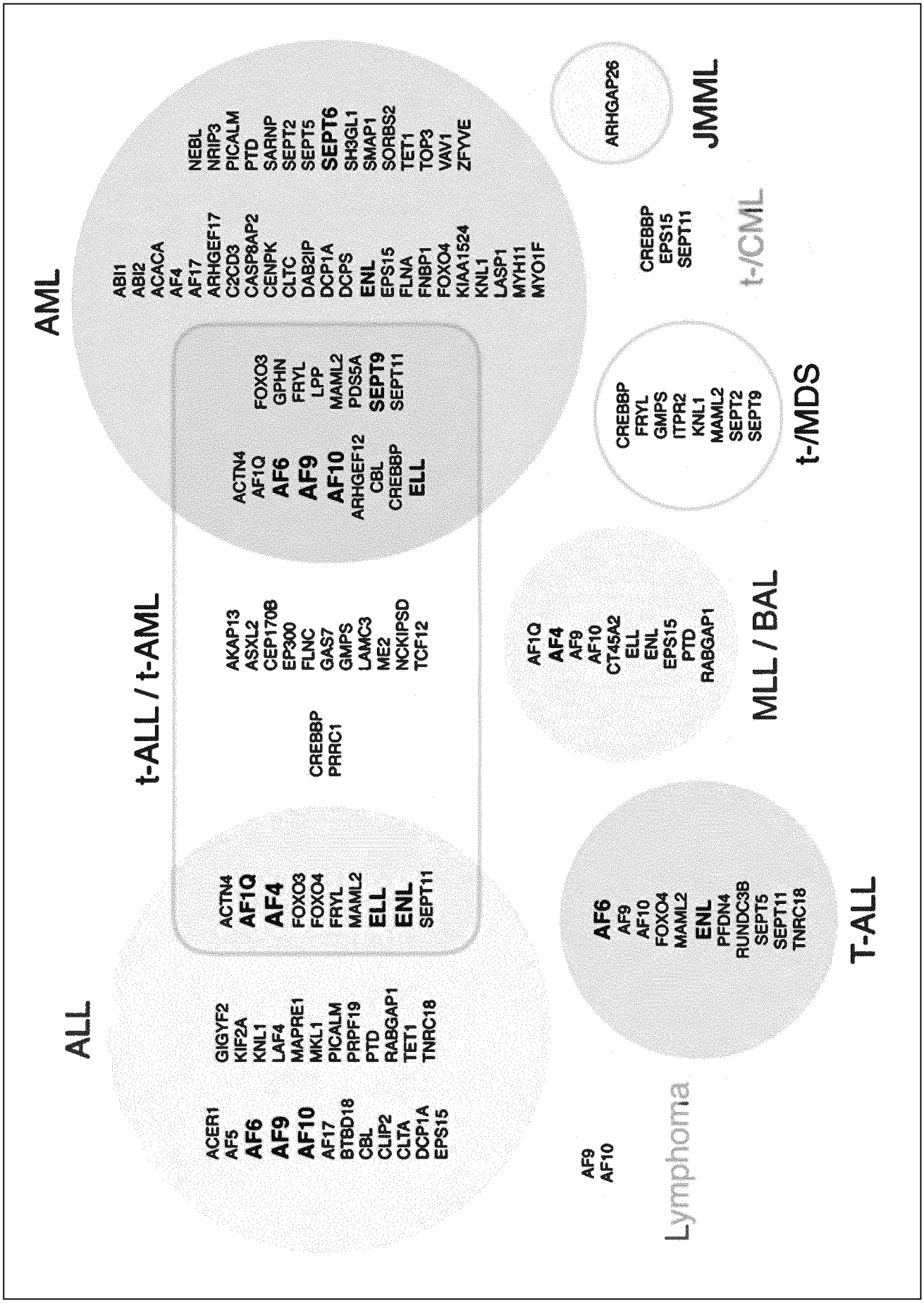

AML
ABI1
ABI2
ACACA
AF4
AF17
ARHGEF17
C2CD3
CASP8AP2
CENPK
CLTC
DAB2IP
DCP1A
DCPS
ENL
EPS15
FLNA
FNBP1
FOXO4
KIAA1524
KNL1
LASP1
MYH11
MYO1F
NEBL
NRIP3
PICALM
PTD
SARNP
SEPT2
SEPT5
SEPT6
SH3GL1
SMAP1
SORBS2
TET1
TOP3
VAV1
ZFYVE
ACTN4
AF1Q
AF6
AF9
AF10
ARHGEF12
CBL
CREBBP
ELL
FOXO3
GPHN
FRYL
LPP
MAML2
PDS5A
SEPT9
SEPT11
t-ALL / t-AML
AKAP13
ASXL2
CEP170B
EP300
FLNC
GAS7
GMPS
LAMC3
ME2
NCKIPSD
TCF12
CREBBP
PRRC1
ARHGAP26
CREBBP
EPS15
SEPT11
t-/CML
JMML
CREBBP
FRYL
GMPS
ITPR2
KNL1
MAML2
SEPT2
SEPT9
t-/MDS
AF1Q
AF4
AF9
AF10
CT45A2
ELL
ENL
EPS15
PTD
RABGAP1
MLL / BAL
ALL
ACTN4
AF1Q
AF4
FOXO3
FOXO4
FRYL
MAML2
ELL
ENL
SEPT11
GIGYF2
KIF2A
KNL1
LAF4
MAPRE1
MKL1
PICALM
PRPF19
PTD
RABGAP1
TET1
TNRC18
ACER1
AF5
AF6
AF9
AF10
AF17
BTBD18
CBL
CLIP2
CLTA
DCP1A
EPS15
AF6
AF9
AF10
FOXO4
MAML2
ENL
PFDN4
RUNDC3B
SEPT5
SEPT11
TNRC18
T-ALL
AF9
AF10
Lymphoma

FIGURE 24

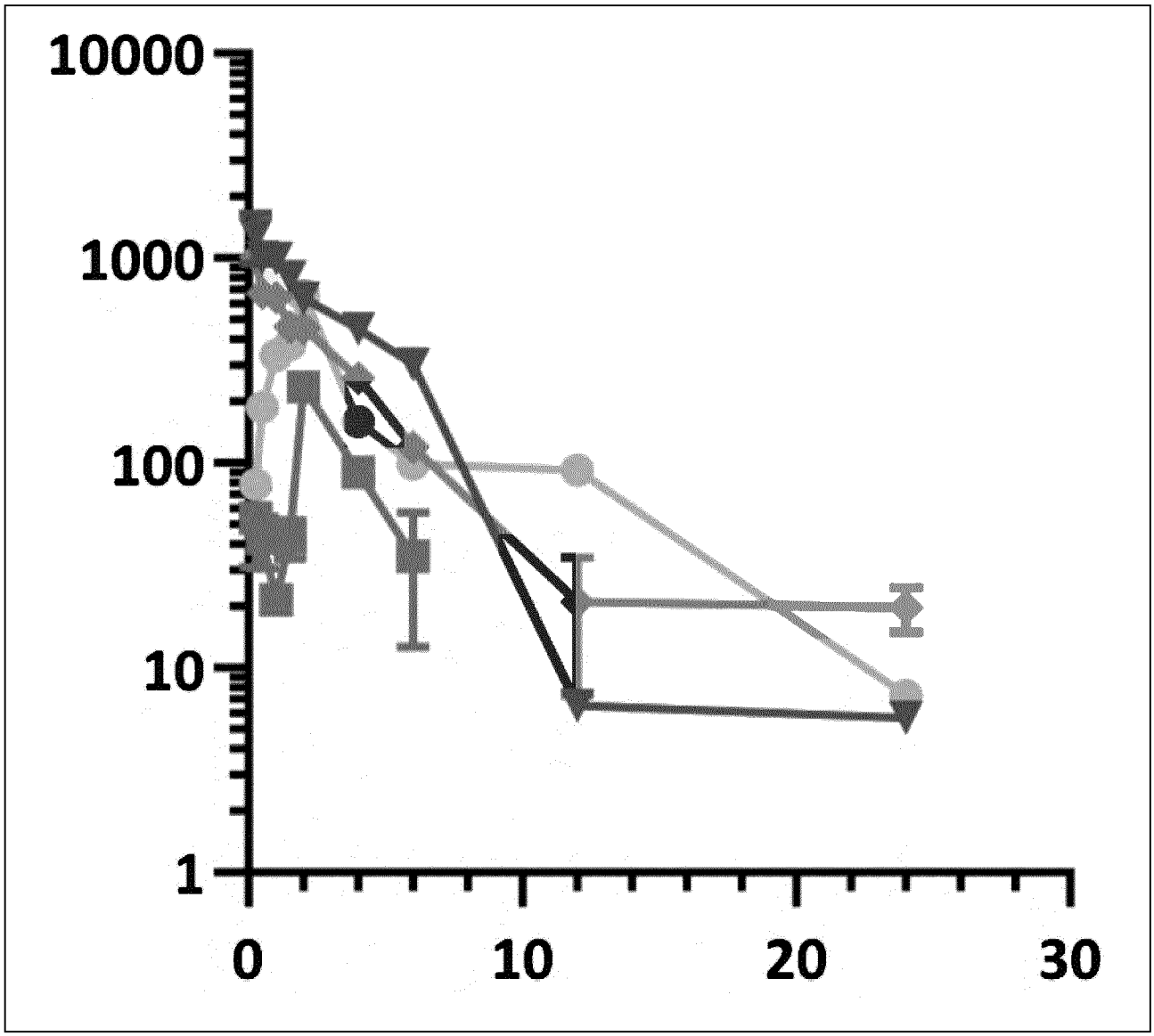


FIGURE 25

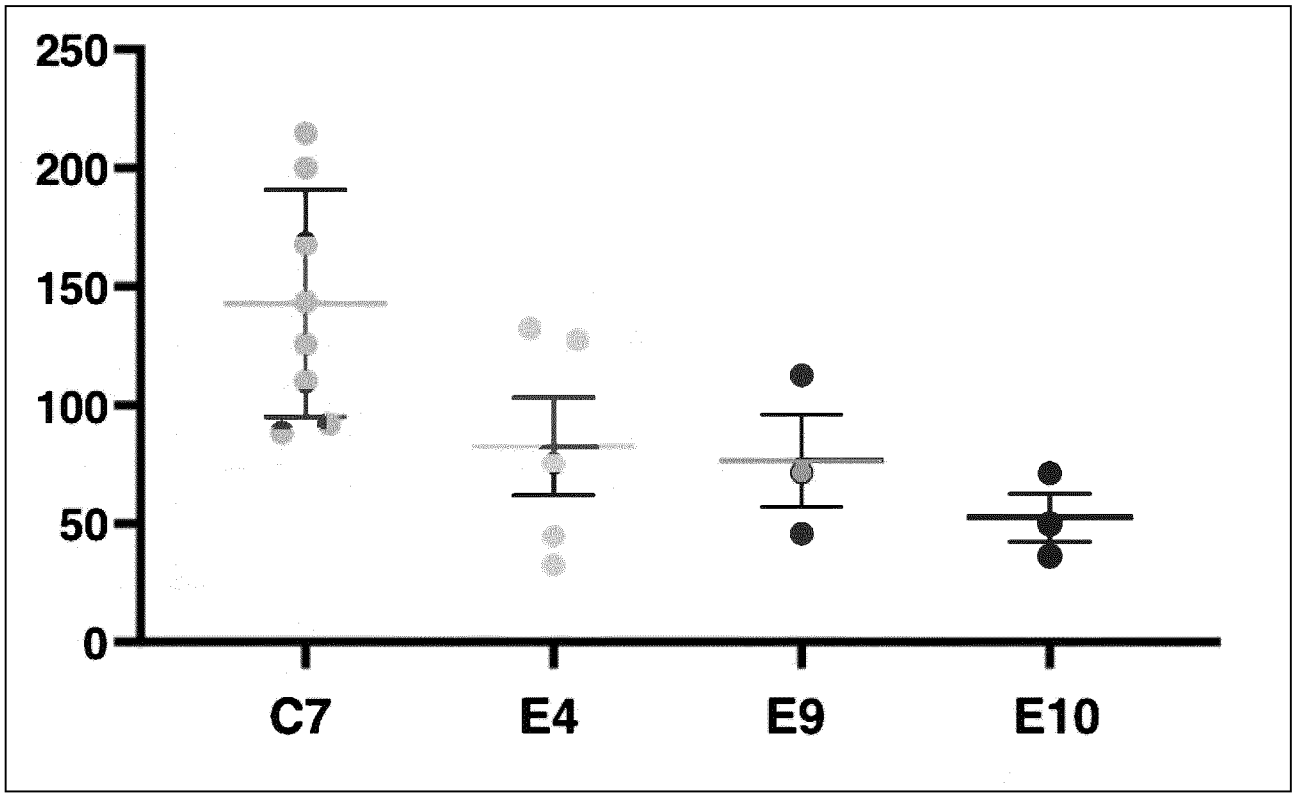


FIGURE 26

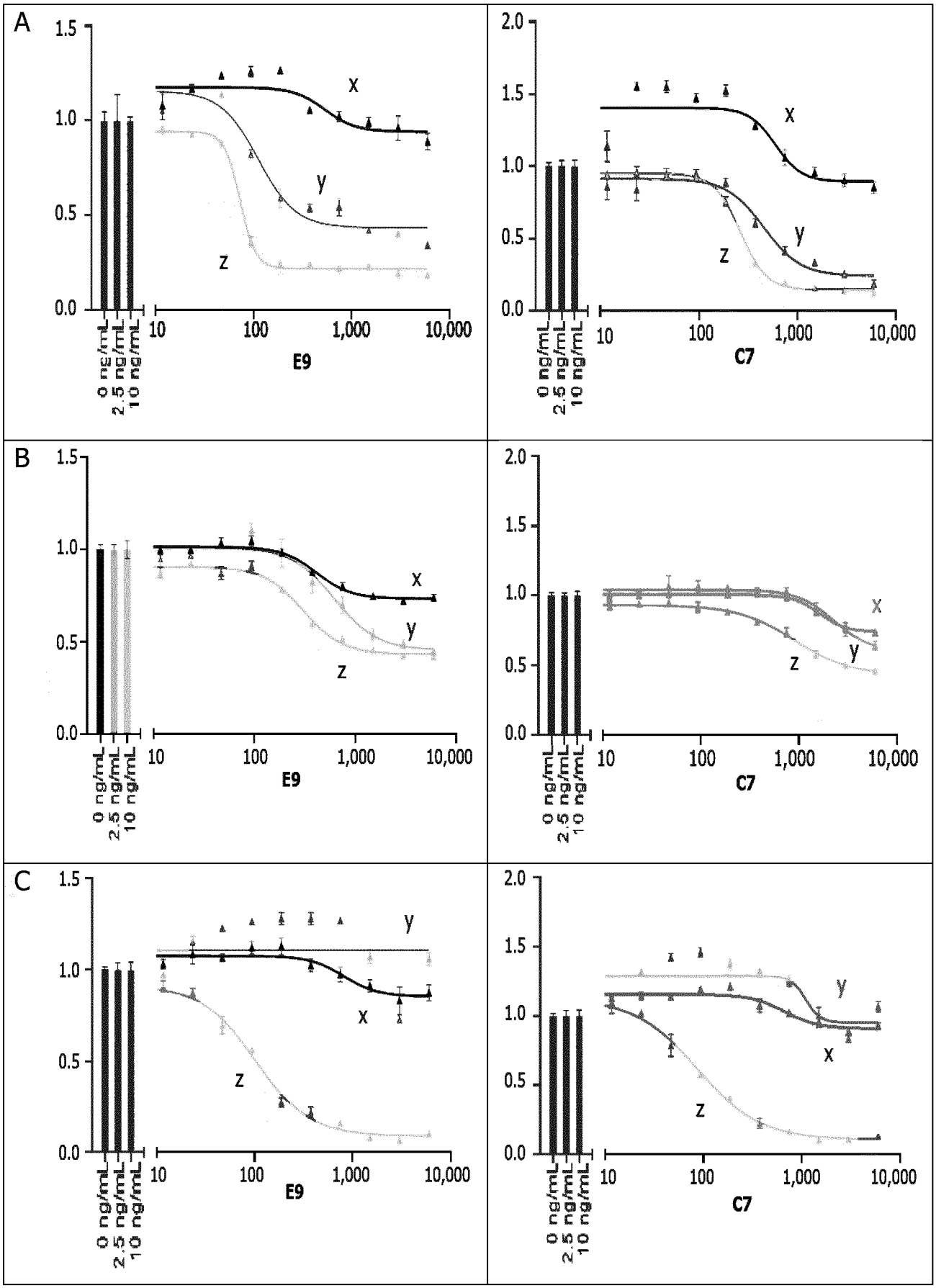

A
B
C
1.5
1.0
0.5
0.0
2.0
x
y
z
0 ng/mL
2.5 ng/mL
10 ng/mL
10
100
1,000
10,000
E9
C7

FIGURE 27

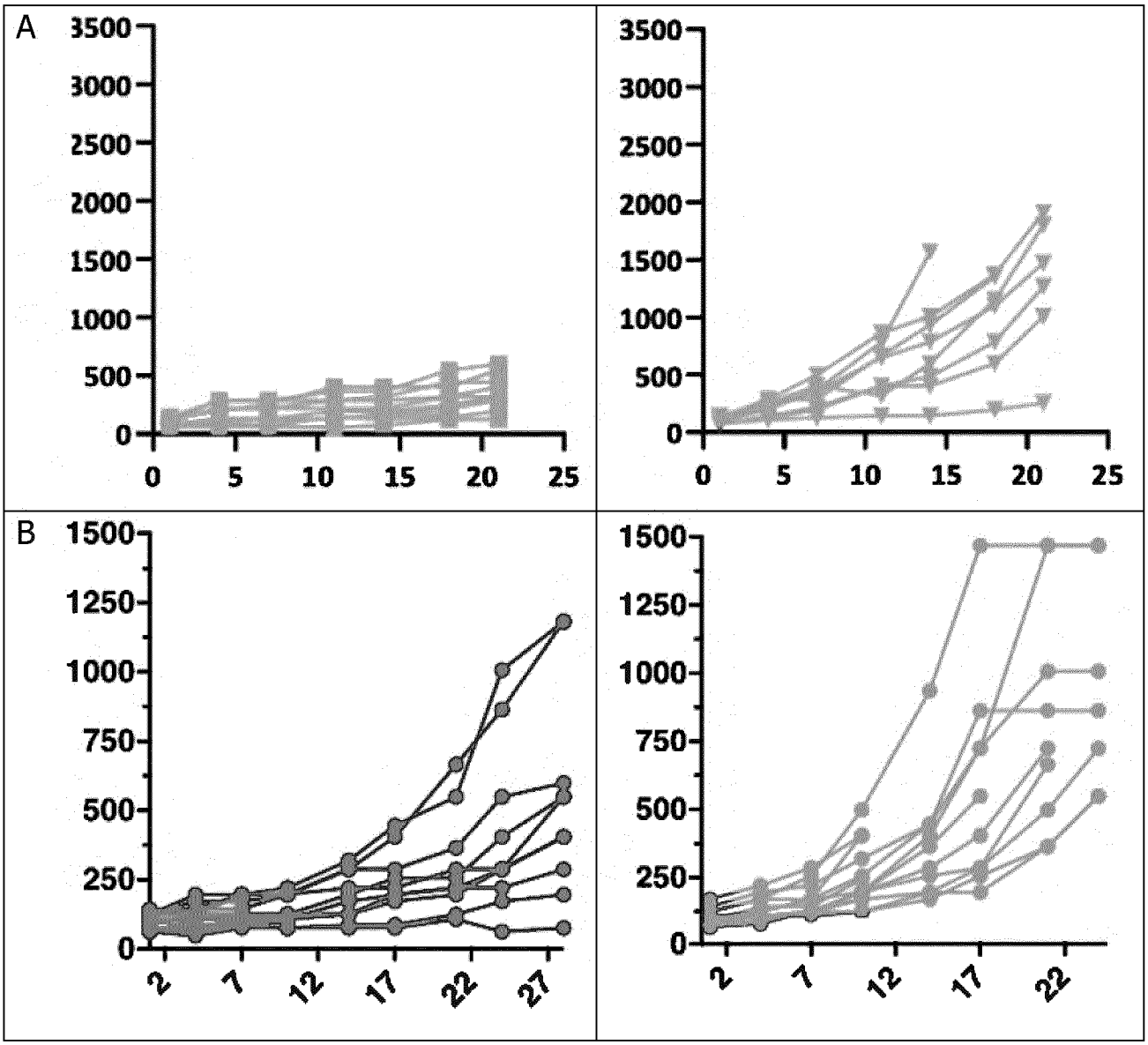

A
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
B
1500
1250
1000
750
500
250
0
2
7
12
17
22
27

FIGURE 28

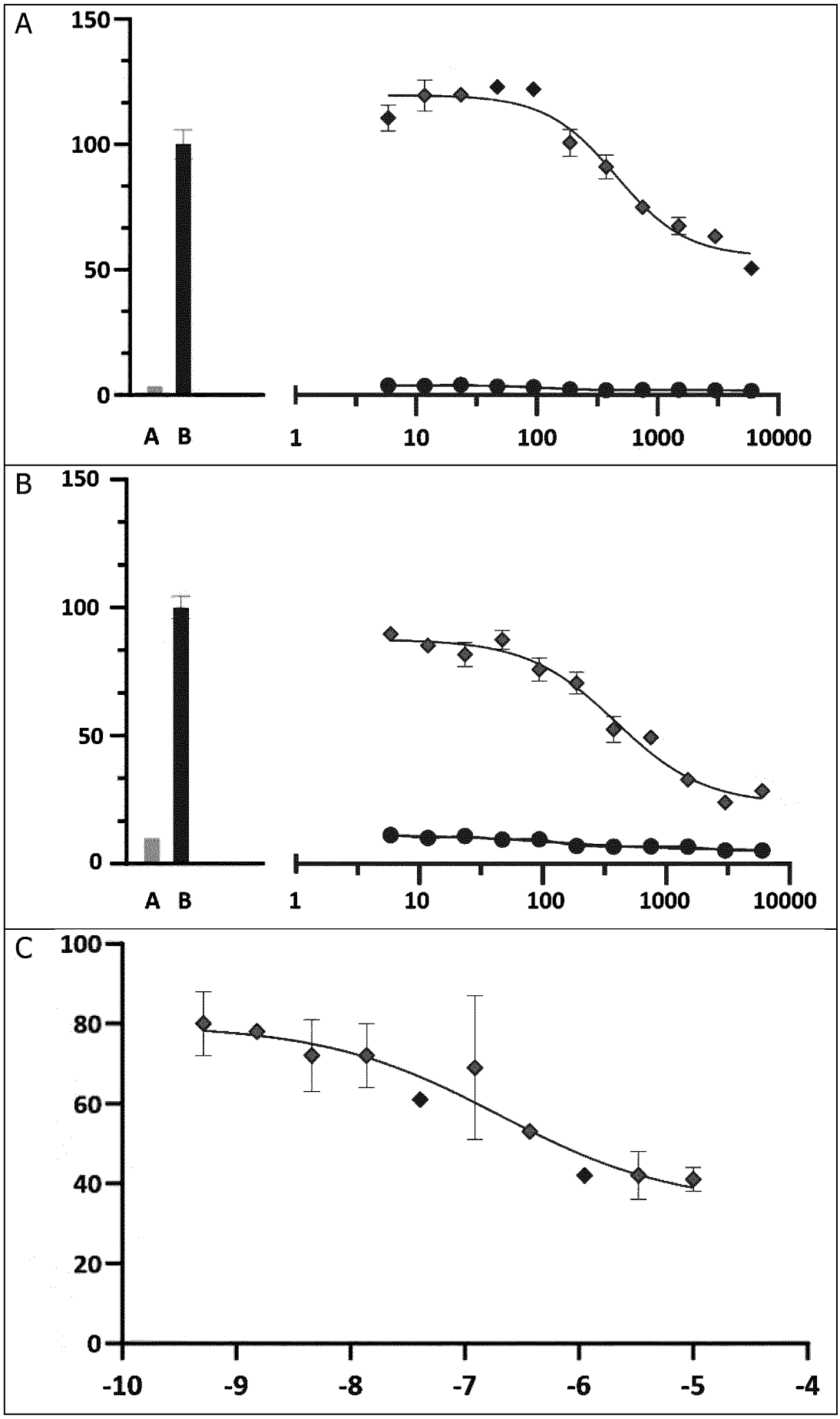

A
150
100
50
0
A B
1
10
100
1000
10000
B
150
100
50
0
A B
1
10
100
1000
10000
C
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
-4

FIGURE 29

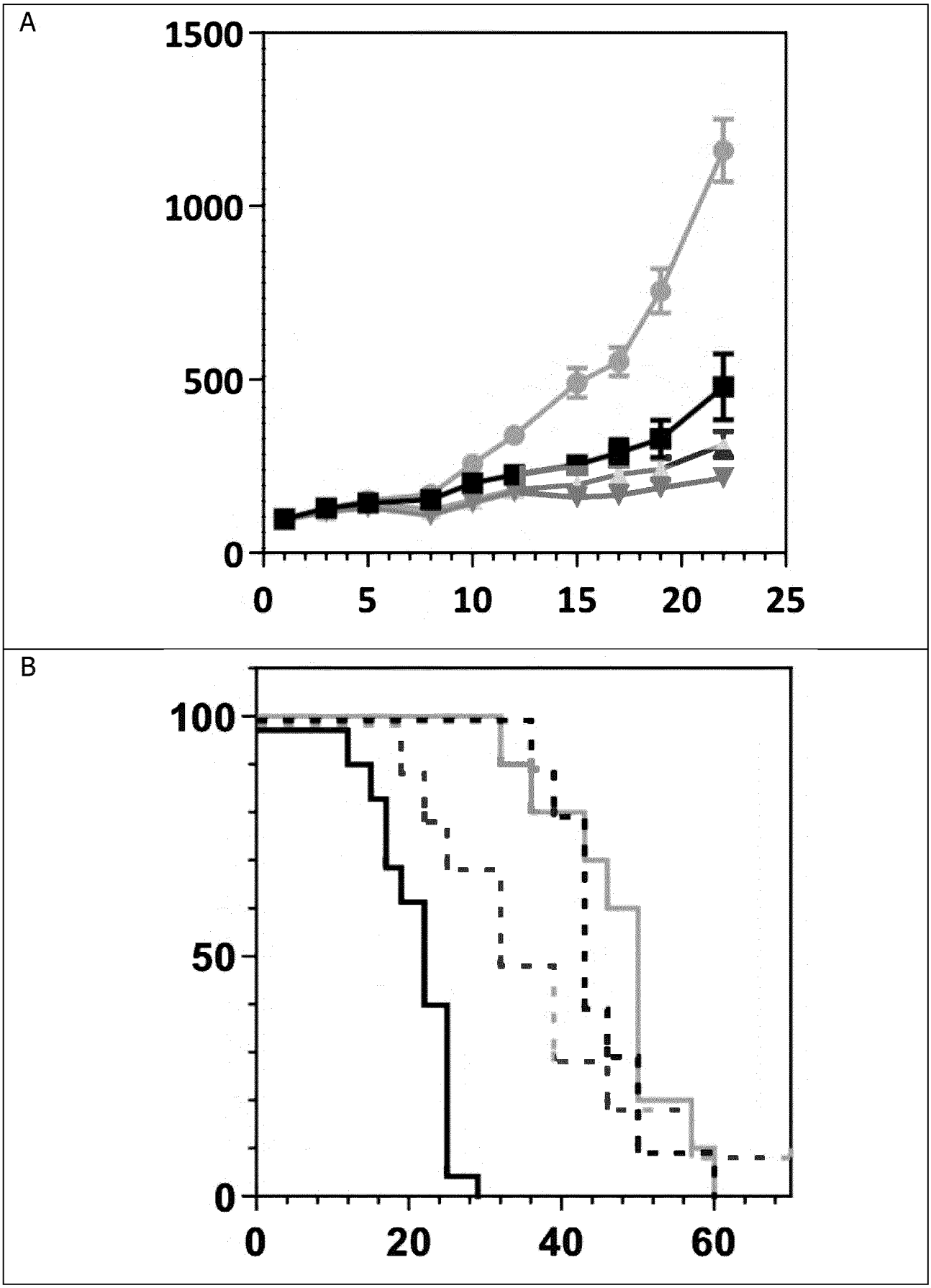


FIGURE 29 (cont)

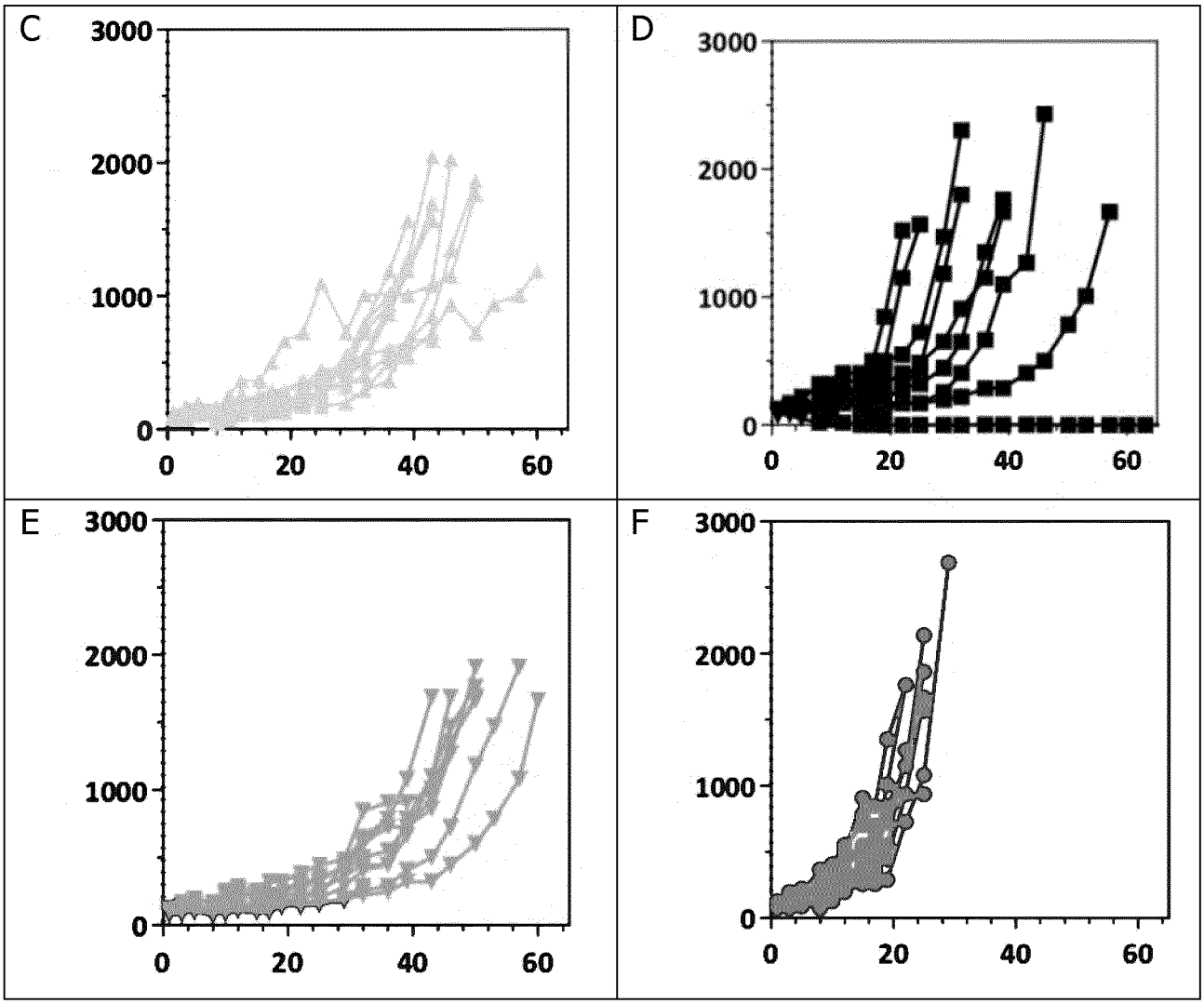


FIGURE 30