Triazolopyrazine derivatives

BACKGROUND OF THE INVENTION

The invention had the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

The present invention relates to compounds and to the use of compounds in which the inhibition, regulation and/or modulation of signal transduction by kinases, in particular tyrosine kinases, furthermore to pharmaceutical compositions which comprise these compounds, and to the use of the compounds for the treatment of kinase-induced diseases.

Because protein kinases regulate nearly every cellular process, including metabolism, cell proliferation, cell differentiation, and cell survival, they are attractive targets for therapeutic intervention for various disease states. For example, cell-cycle control and angiogenesis, in which protein kinases play a pivotal role are cellular processes associated with numerous disease conditions such as but not limited to cancer, inflammatory diseases, abnormal angiogenesis and diseases related thereto, atherosclerosis, macular degeneration, diabetes, obesity, and pain.

One of the key events in the signaling pathway following the activation of mast cells is activation of the tyrosine kinase Syk. Mast cells play a critical role in asthma and allergic disorders by releasing pro-inflammatory mediators and cytokines. Antigen-mediated aggregation of FcεRJ, the high-affinity receptor for IgE, results in activation of mast cells. This triggers a series of signaling events resulting in the release of mediators, including histamine, proteases, leukotrienes and cytokines. These mediators cause increased vascular permeability, mucus production, bronchoconstriction, tissue degradation and inflammation, thus playing key roles in the etiology and symptoms of asthma and allergic disorders. Syk kinase acts as a central initiator of all subsequent signaling leading to mediator

release. The critical role of Syk kinase in the signaling path was demonstrated by the complete inhibition of mediator release by a protein containing the SH2 domains of Syk kinase that functioned as an inhibitor of Syk kinase (J. A.Taylor et al, Molec. and Cell Biol, 15: 4149-4157 (1995).

Syk (Spleen-Tyrosine-Kinase) is a 72 kDa non-receptor tyrosine kinase belonging to the subfamily of intracellular tyrosine kinases that comprises ZAP70, Pyk2, Abl, Tie2, KDR and HER, among others. Syk is a major regulator of FcR (FcγRI, II, III, FcεRI, FcαR) and BCR signaling and is expressed throughout hematopoietic lineage, as well as in fibroblasts, osteoclasts, hepatocytes, epithelial and neuronal cells. In addition to the C terminal kinase domain, SYK exhibits two SH2 domains and over 10 autophosphorylation sites[1].

By means of both its SH2 domains SYK is specifically recruited to phosphorylated ITAMs (Immunoreceptor Tyrosine-based Activation Motifs present in immunoreceptors such as FcγRI, IIA, IIIA, FcαR, FcεRI and BCR, expressed by monocytes, macrophages, mast cells, neutrophils and B cells) and specifically mediates immunoreceptor signaling triggered by activation of those receptors in mast cells, B cells, macrophages, monocytes, neutrophils, eosinophils, NK cells, DC cells platelets and osteoclasts[1,2].

Upon BCR cross linking, tyrosine residues at the ITAM motifs of the cytosolic tail of the Igα/Igβ are phosphorylated by the Src-family kinase Lyn, generating docking sites for SYK that is thus recruited to the BCR immunocomplex. SYK is then phosphorylated and activated by the Src-family kinase Lyn. Upon activation, SYK will phosphorylate the adaptor protein BLNK allowing its interaction with both BTK and $PLC\gamma_2$ via their respective SH2 domains. SYK phosphorylated -and thus activated- BTK will in turn phosphorylate and activate $PLC\gamma_2$ leading to IP_3 formation, Ca^{2+} mobilization, PKC and MAPK activation and consequent NFAT, AP-1 and NFκB transcription factor activation, resulting in activation and surface marker expression, cytokine release, survival and proliferation of B cells[3]. In mast cells, allergen activated FcεRI is phosphorylated by LYN and FYN and recruits

SYK which is in turn phosphorylated by LYN and further autophosphorylated, becoming fully activated. Activated SYK phosphorylates the two adaptor molecules NTAL and LAT creating more docking sites for SH2 containing proteins such as PLCγ_1, vav, and the p85 regulatory subunit of PI3K, resulting in mast cell degranulation and cytokine production[4]. Syk's critical role in signal transduction of mast cells is confirmed by reproducible observation that the 10-15% of basophils (circulating mast cells) from human donors that cannot degranulate have reduced amounts of Syk protein[5,6]. In addition, SYK is required for the bone resorption activity of osteoclasts. Upon stimulation of osteoclasts by $\alpha v\beta 3$ integrin, SYK becomes phosphorylated, most likely by c-Src, in a DAP-12 / FcγRII dependent mechanism, leading to SPL-76 and Vav3 phosphorylation and subsequent cytoskeletal reorganisation. SYK deficient osteoclasts are inactive and show defective cytoskeletal reorganisation. In correlation with this, SYK deficient embryos show defective skeletal mass[7,8].

BCR-mediated activation of B-cells in the lymph nodes, as well as FcR-mediated activation of dendritic cells, monocytes, macrophages, neutrophils and mast cells in the joints, are essential components of the cellular patho-physiological mechanisms taking place during rheumaoid arthritis (RA). Moreover, activation of osteoclasts leads to the bone and cartilage destruction which are hallmarks of this pathology[9]. SYK signaling should therefore play a pivotal role during the development of arthritis, both at the periphery and on the site of inflammation[10]. Indeed, an orally available Syk inhibitor R406 -developed by Rigel- induced a significant improvement of clinical scores and significantly reduced serum cytokine concentrations, as well as bone erosion, in a murine model of RA[11,12]. Moreover, this inhibitor has shown efficacy (ACR scores improvement) and good tolerability in RA Phase II studies in humans[13,14,15].

In SLE B cells contriubute essentially towards pathogenesis via production of autoanibodies resulting in immune complex formation, stimulation of Fc receptors and finally in an excessive and chronic activation of inflammation. In a murine model of SLE treatment with a Syk inhibitor resulted in a reduction of numbers of

class-switched germinal center , marginal zone, newly formed and follicular B cells and therefore in disease mitigating effects[18].

Although TCR signals are transmited by the intracellular tyrosine kinase ZAP-70 in thymocytes and naïve T cells, several studies indicate that differentiated effector T cells, such as those involved in the pathophysiology of Multiple sclerosis (MS) or systemic lupus erythematosus (SLE), show a down regulation of the TCRzeta chain and a concomitant upregulation of the TCR/CD3 chain and its interaction with FcRγ. Those studies show that the TCR/CD3/FcRgamma complex in effector cells recruits and activates Syk, instead of ZAP-70, tyrosine kinase. This physiologic switch in TCR signaling occurs exclusively in effector, and not naive or memory T cells[16,17,18]. Not surprisingly then, SYK inhibitors have been shown to delay disease progression and to improve survival in murine models of SLE[17,18,19,20,21].

SYK inhibitors may also find a use in asthma, allergy, multiple sclerosis and other diseases such as thrombocytopenia purpura and T or B cell lymphomas[1,10, 14,22-35].

Treatment of prediseased NZB/W mice with a Syk inhibitor prevented the development of renal disease demonstrated by reduced glomerular sclerosis, tubular damage, proteinuria and BUN levels[18].

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In addition to mast cells, Syk is expressed in other hematopoietic cells including B cells, where it is thought to play an essential role in transducing signals required for the transition of immature B cells into mature recirculating B cells (M. Turner et al, Immunology Today, 21: 148 (2000). B cells are reported to play an important role in some inflammatory conditions such as lupus (O. T. Chan etal., Immunological Rev, 169: 107-121 (1999) and rheumatoid arthritis (A. Gause et al, Biodrugs, 15(2): 73-79 (2001).

Syk was also reported to be an element of the signaling cascade in beta-amyloid and prion fibrils leading to production of neurotoxic products (C. K. Combs et al., J. Neuroscl, 19: 928-939 (1999). Furthermore, an inhibitor of Syk blocked the production of these neurotoxic products. Thus furopyridine derivatives would potentially be useful in the treatment of Alzheimer's disease and related neuroinflammatory diseases. Another report (Y. Kuno et al. , Blood, 97, 1050-1055 (2001) demonstrates that Syk plays an important role in malignant progression. A TEL-Syk fusion protein was found to transform hematopoietic cells suggesting a role in the pathogenesis of hematopoietic malignancies. Therefore furopyridine derivatives may be useful in the treatment of certain types of cancers.

Other protein tyrosine kinases involved in hematologic malignancies include ABL (ABLI), ARG (ABL2), PDGFβR, PDGFaR, JAK2, TRKC, FGFRI, FGFR3, FLT3, and FRK.

The Janus kinases (JAK) are a family of tyrosine kinases consisting of JAKI, JAK2, JAK3 and TYK2. The JAKs play a critical role in cytokine signaling. The down-stream substrates of the JAK family of kinases include the signal transducer and activator of transcription (STAT) proteins. JAK/STAT signaling has been implicated in the mediation of many abnormal immune responses such as allergies, asthma, autoimmune diseases such as transplant (allograft) rejection,

rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis, as well as in solid and hematologic malignancies such as leukemia and lymphomas (for a review of the pharmaceutical intervention of the JAK/STAT pathway see Frank, Mol. Med. 5, 432:456 (1999), and Seidel et al, Oncogene 19, 2645-2656 (2000). JAK2 is a well validated target with strong potential in the treatment of myeloproliferative disorders (MPDs), which include polycythemia vera (PV), essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia, chronic myelomonocytic leukemia, chronic eosinophilic leukemia, hypereosinophilic syndrome and systematic mast cell disease.

Fms-like tyrosine kinase 3 (FLT3), which is also known as FLK-2 (fetal liver kinase 2) and STK-I (stem cell kinase 1), plays an important role in the proliferation and differentiation of hematopoietic stem cells. FLT3 receptor kinase is expressed in normal hematopoietic cells, placenta, gonads, and brain. However, this enzyme is expressed at very high levels on the cells of more than 80% of myelogenous patients and of a fraction of acute lymphoblastic leukemia cells. Furthermore, the enzyme can also be found on cells from patients with chronic myelogenous leukemia in lymphoid blast crisis. It has been reported that FLT3 kinase is mutated in 30% of acute myeloid leukemia (AML) and in a subset of acute lymphoblastic leukemia (ALL) as well (Gilliland et al, Blood 100, 1532-1542 (2002); Stirewalt etal, Nat. Rev. Cancer, 3, 650-665 (2003). The most common activating mutations in FLT3 are internal tandem duplications within the juxtamembrane region, while point mutations, insertions, or deletions in the kinase domain are less common. Some of these mutant FLT3 kinases are constitutively active. FLT3 mutations have been associated with a poor prognosis (Malempati et al., Blood, 104, 11 (2004). More than a dozen known FLT3 inhibitors are being developed and some have shown promising clinical effects against AML (Levis et al Int. J. Hematol, 52, 100- 107 (2005).

It has been reported that some of small-molecule FLT3 inhibitors are effective in inducing apoptosis in cell lines with FLT3-activating mutations and prolonging survival of mice that express mutant FLT3 in their bone marrow cells (Levis et al,

Blood, 99, 3885-3891 (2002); Kelly et al, Cancer Cell, 1, 421-432 (2002); Weisberg et al, Cancer Cell, 1, 433-443 (2002); Yee et al, Blood, 100, 2941-2949 (2002).

In particular, the present invention relates to compounds and to the use of compounds in which the inhibition, regulation and/or modulation of signal transduction by Syk plays a role.

The synthesis of small compounds which specifically inhibit, regulate and/or modulate signal transduction by tyrosine kinases in particular Syk, is therefore desirable and an aim of the present invention.
Moreover, aim of this invention is the synthesis of new compounds for the prevention and treatment of rheumatoid arthritis, systemic lupus, asthma, allergic rhinitis, ITP, multiple sclerosis, leukemia, breast cancer and maligna melanoma. Surprisingly we have identified furopyridines that inhibit selectively SYK, BTK, KDR, Src, Zap70, Fak, Pyk2, Flt3 or Jak or inhibit a selection of these kinases.

Moreover, compounds of formula I inhibit serin kinase GCN2.
Many strategies of cancer treatment of solid tumors focus on the surgically removal of the tumor mass as far as possible and the subsequent eradication of any residual tumor cells by radiotherapy and chemotherapy with cytotoxic agents or inhibitors that target cancer cell pathways more specifically. However, the success of such approach is limited and often does not persist. This is mainly due to the narrow therapeutic window for such cytotoxic agents (specificity and side effects) and to the capability of cancer calls to adapt to the selective pressure applied by cytotoxic or other inhibitory agents. The survival of a small number of tumor (stem) cells that acquired resistance to the initial treatment can be sufficient to seed the regrowth of a tumor. These relapses are in most cases more difficult to treat compared to that of the initial tumors. As a consequence the more successful targeting of tumor cells may require

targeting multiple survival and escape mechanism of tumor cells in parallel (Muller & Prendegast 2007).

Development of malignancies is accompanied by a major roll up of the cellular physiology. During this process several qualities are acquired by the cancer cells that are basis for immortalization or insensitivity to growth inhibitory signals. In addition the tumor cells also modify the interaction with the microenvironment and beyond. The latter area includes the strategies of tumor cells to escape from the immunological surveillance (Muller & Prendegast 2007). The immune surveillance limits malignant growth but also provides a selective pressure triggering the evolution of mechanisms for evading the immune response as reviewed by [Dunn et al. 2004]. Essentially it has been frequently observed that ablation of T cell immunity is sufficient to increase tumor incidence [Shankaran et al. 2001] and it is believed that immune escape is affecting tumor dormancy versus progression, promoting invasion and metastasis and negatively impacts on therapeutic response.

Several mechanistic studies discovered that immune escape has an important interface with metabolic alterations within the tumor microenvironment. Here important roles in mediating immune tolerance to antigens have been associated to the catabolism of the essential amino acids tryptophan and arginine, carried out by the enzymes indoleamine 2,3-dioxygenase (IDO) and arginase I (ARG), respectively (Bronte and Zanovello, 2005; Muller et al., 2005b; Muller and Prendergast, 2007; Munn and Mellor, 2007; Popovic et al., 2007).

IDO is a single-chain oxidoreductase that catalyzes the degradation of tryptophan to kynurenine. IDO is not responsible for catabolizing excess dietary tryptophan but to modulate tryptophan level in a local environment. Elevations in tryptophan catabolism in cancer patients manifest in significantly altered serum concentration of tryptophan or catabolites and this was correlated to IDO which is commonly elevated in tumors and draining lymph

nodes. According to several publications IDO over-expression is associated with poor prognosis in cancer [Okamoto et al 2005; Brandacher et al, 2006]. T cells appear to be preferentially sensitive to IDO activation, such that when starved for tryptophan they cannot divide and as a result cannot become activated by an antigen presented to them. Munn and Mellor and their colleagues, revealed that IDO modulates immunity by suppressing T-cell activation and by creating peripheral tolerance to tumor antigens (Mellor and Munn, 2004). These mechanism encompass the subversion of immune cells recruited by the tumor cell to its immediate microenvironment or to the tumor-draining lymph nodes Here the tumor antigens that were scavenged by antigen-presenting cells are cross-presented to the adaptive immune system. In addition to being directly toleragenic, mature DCs have the capacity to expand regulatory Tcells (Tregs) [Moser 2003].

Beside tryptophan catabolism the conversion of arginine is increased in a tumor-conditioned microenvironment, and numerous reports indicate a role for the activation of arginases during tumor growth and development. In tumor-infiltrating myeloid cells, arginine is converted by arginase I (ARG1), arginase II (ARG2) to urea and ornithine and oxidized by the inducible form of nitric oxide synthase (NOS2) to citrulline and nitric oxide (NO).

Increased ARG activity is frequently observed in patients with colon, breast, lung, and prostate cancer [Cederbaum 2004] correlating with the over-expression of ARG and NOS found in prostate cancers [Keskinege et al. 2001, Aaltoma et al. 2001, Wang et al. 2003]. It was shown that ARG activity in infiltrating macrophages impairs antigen-specific T cell responses and the expression of the CD3 receptor. Moreover the cumulative activity of ARG and NOS in tumor associated myeloid cells can generate inhibitory signals to antigen-specific T lymphocytes that eventually lead to apoptosis [Bronte 2003 a; 2003b].

Both, the IDO and the ARG related mechanism merge at the point of sensing the depleted concentration of the respective amino acid concentration. During amino acid deprivation, the eIF2 kinase EIF2AK4 called general control nonderepressible 2 (GCN2) is interacting with the intracellular accumulating

deacylated tRNA. As a consequence the GCN2 is assumed to change from an auto-inhibited to an active conformation and further activate by auto-phosphorylation. Then the only known substrate protein eIF2a becomes phosphorylated and as a consequence the complex for translation initiation is inhibited [Harding et al. 2000,]. This diminishes the general Cap-dependent translation initiation and by this the corresponding protein production. On the other hand this induces the specific expression of stress related target genes mainly by cap-independent initiation via the activating transcription factor 4 (ATF4). By expressing the respective stress response proteins, e.g. enzymes in the in amino acid metabolism, the cell tries to compensate the particular cell stress [Wek et al. 2006]. If the stress persists, the same pathway will switch to promoting cell death via transcription of the pro-apoptotic transcription factor, CCAAT/enhancer-binding protein homologous protein (CHOP) [Oyadomari 2004]. It was shown that, tryptophan starvation triggers a GCN2- dependent stress signaling pathway In T cells altering eIF2aphosphorylation and translational initiation leading to a cell growth arrest (Munn et al. 2005). Sharma, et al. [2007] published on the direct IDO-induced and GCN2-dependent activation of mature Tregs. Similarly Fallarino et al [2006] found a GCN2-dependent conversion of CD4+CD25- cells to CD25+FoxP3+ Tregs producing IL-10 and TGF□. Rodriguez et al. [2007] identified that activation of the GCN2 pathway via tryptophan or arginine depletion in combination with TCR signaling leads to CD3□ chain down regulation, cell cycle arrest and anergy.

Importantly the GCN2 pathway is not only important for the tumoral immune escape but also plays an active role in modulating tumor survival directly. Ye et al [2010] found that the aforementioned transcription factor ATF4 is over-expressed inhuman solid tumors, suggesting an important function in tumour progression. Amino acid and glucose deprivation are typical stresses found in solid tumours and activated the GCN2 pathway to up-regulate ATF4 target genes involved in amino acid synthesis and transport. GCN2 activation/overexpression and increased phospho-eIF2a were observed in

human and mouse tumors compared with normal tissues and abrogation of ATF4 or GCN2 expression significantly inhibited tumor growth in vivo. It was concluded that the GCN2-eIF2a-ATF4 pathway is critical for maintaining metabolic homeostasis in tumor cells.

Over all the present biology makes an interference with the ARG/IDO pathway attractive for braking up the tumoral immune escape by adaptive mechanism. The interference of GCN2 function is here of particular interest as it is a merging point of the two pathways, the IDO and ARG, as well as it provides additional opportunities to impede with the tumor metabolism directly.

Several pathway inhibitors are already considered as immune modulators. These inhibitors address mainly the enzymatic function of the IDO or ARG proteins (Muller and Scherle, 2006). The application of the arginase inhibitor, N-hydroxy-nor-L-Arg blocks growth of s.c. 3LL lung carcinoma in mice [Rodriguez 2004]. The NO-donating aspirins like NCX 4016 (2-(acetyloxy)benzoic acid 3-(nitrooxymethyl) phenyl ester) have been reported to interfer with the inhibitory enzymatic activities of myeloid cells. Orally administered NO aspirin normalized the immune status of tumor-bearing hosts, increased the number and function of tumor-antigen-specific T lymphocytes, and enhanced the preventive and therapeutic effectiveness of the antitumor immunity elicited by cancer vaccination (DeSanto 2005)
The substrate analogue 1 methyl-tryptophan (1MT) and related molecules have been used widely to target IDO in the cancer context and other settings. Studies by Friberg et al. (2002) and Uyttenhove et al. (2003) demonstrated that 1MT can limit the growth of tumors over-expressing IDO. However 1MT was unable to elicit tumor regression in several tumor models, suggesting only modest antitumor efficacy when IDO inhibition was applied as a monotherapy. In contrast, the combinatory treatment with 1MT and a variety of cytotoxic chemotherapeutic agents elicited regression of established MMTV-neu/HER2 tumors, which responded poorly to any single-agent therapy [Muller et al 2005a]. Immunodepletion of CD4+ or CD8+ T cells from the mice, before

treatment abolished the combinatorial efficacy observed in this model, confirming the expectation that 1MT acted indirectly through activation of T cell-mediated antitumor immunity. Important evidence that IDO targeting is essential to 1MT action was provided by the demonstration that 1MT lacks antitumor activity in mice that are genetically deficient for IDO [Hou et al., 2007]

The inhibition of GCN2 would enable to combine the two pathway branches of amino acrid starvation induced immunoediting and would reduce the options for the tumor to circumvent the inhibition of either branch. Moreover, as detailed above, the GCN2 inhibition provides the opportunity for interfering with the tumor metabolism at the same time what may enhance the efficacy of a monotherapy or a combination therapy with other anticancer approaches.

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It has been found that the compounds according to the invention and salts thereof have very valuable pharmacological properties while being well tolerated.

The present invention specifically relates to compounds of the formula I which inhibit, regulate and/or modulate signal transduction by Syk, to compositions which comprise these compounds, and to processes for the use thereof for the treatment of Syk-induced diseases and complaints.

The compounds of the formula I can furthermore be used for the isolation and investigation of the activity or expression of Syk. In addition, they are particularly suitable for use in diagnostic methods for diseases in connection with unregulated or disturbed Syk activity.

The host or patient can belong to any mammalian species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

The susceptibility of a particular cell to treatment with the compounds according to the invention can be determined by in vitro tests. Typically, a culture of the cell is combined with a compound according to the invention at various concentrations for a period of time which is sufficient to allow active agents such as anti IgM to induce a cellular response such as expression of a surface marker, usually between about one hour and one week. In vitro testing can be carried out using cultivated cells from blood or from a biopsy sample. The amount of surface marker expressed are assessed by flow cytometry using specific antibodies recognising the marker.

The dose varies depending on the specific compound used, the specific disease, the patient status, etc. A therapeutic dose is typically sufficient considerably to reduce the undesired cell population in the target tissue while the viability of the patient is maintained. The treatment is generally continued until a considerable reduction has occurred, for example an at least about 50% reduction in the cell burden, and may be continued until essentially no more undesired cells are detected in the body.

For identification of a signal transduction pathway and for detection of interactions between various signal transduction pathways, various scientists have developed suitable models or model systems, for example cell culture models (for example Khwaja et al., EMBO, 1997, 16, 2783-93) and models of transgenic animals (for example White et al., Oncogene, 2001, 20, 7064-7072). For the determination of certain stages in the signal transduction cascade, interacting compounds can be utilised in order to modulate the signal (for example Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention can also be used as reagents for testing kinase-dependent signal transduction pathways in animals and/or cell culture models or in the clinical diseases mentioned in this application.

Measurement of the kinase activity is a technique which is well known to the person skilled in the art. Generic test systems for the determination of the kinase activity using substrates, for example histone (for example Alessi et al., FEBS Lett. 1996, 399, 3, pages 333-338) or the basic myelin protein, are described in the literature (for example Campos-González, R. and Glenney, Jr., J.R. 1992, J. Biol. Chem. 267, page 14535).

For the identification of kinase inhibitors, various assay systems are available. In scintillation proximity assay (Sorg et al., J. of. Biomolecular Screening, 2002, 7, 11-19) and flashplate assay, the radioactive phosphorylation of a protein or peptide as substrate with γATP is measured. In the presence of an inhibitory

compound, a decreased radioactive signal, or none at all, is detectable. Furthermore, homogeneous time-resolved fluorescence resonance energy transfer (HTR-FRET) and fluorescence polarisation (FP) technologies are suitable as assay methods (Sills et al., J. of Biomolecular Screening, 2002, 191-214).

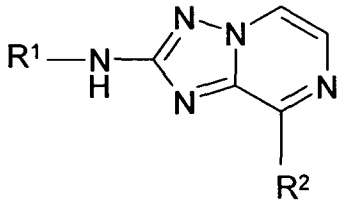
Other non-radioactive ELISA assay methods use specific phospho-antibodies (phospho-ABs). The phospho-AB binds only the phosphorylated substrate. This binding can be detected by chemiluminescence using a second peroxidase-conjugated anti-sheep antibody (Ross et al., 2002, Biochem. J.).

PRIOR ART

Other heterocyclic Syk inhibitors are described in WO2008/118823, WO2009/136995, WO 2010/027500.
Other heterocyclic compounds are described in WO2010/010188, WO2010/010184, WO2010/010189, WO2009/155551, WO2009/155565, WO2009/047514.

SUMMARY OF THE INVENTION

The invention relates to compounds of the formula I



I

in which

R^1 denotes Ar^1 or Het^1,

R^2 denotes Ar^2, Het^2, $NH(CH_2)_nAr^2$, $O(CH_2)_nAr^2$, $NR^3(CH_2)_nHet^2$, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, NHCyc or $NH(CH_2)_pNA_2$,

Ar^1 denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, Alk, $(CH_2)_nOH$, $(CH_2)_nOA$,

$(CH_2)_nCOOH$, $(CH_2)_nCOOA$, SO_2A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, SO_2NH_2, SO_2NHA, SO_2NA_2, $NHCONH_2$, NHCOA, NHCOAlk, $NHCOCH=CH(CH_2)_pNA_2$, CHO, COA, SO_3H, $O(CH_2)_pNH_2$, $O(CH_2)_pNHA$, $O(CH_2)_pNA_2$, $COHet^3$, $S(CH_2)_nHet^3$, $(CH_2)_nHet^3$ and/or $O(CH_2)_nHet^3$,

Ar^2 denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, OAr^3, benzyloxy, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, SO_2A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $CONH(CH_2)_pOA$, $CONH(CH_2)_pOH$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, SO_2NH_2, SO_2NHA, SO_2NA_2, OSO_2A, $NHCONH_2$, NHCOA, CHO, COA, SO_3H, $O(CH_2)_pNH_2$, $O(CH_2)_pNHA$, $O(CH_2)_pNA_2$, $CONHAr^3$, $NHCOAr^3$, $CONHHet^3$, $NHCOHet^3$, $NHSO_2A$, $COHet^3$, $(CH_2)_nHet^3$, $S(CH_2)_nHet^3$ and/or $O(CH_2)_nHet^3$,

Het^1 denotes a mono- or bicyclic unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,

Het^2 denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by Hal, A, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, $(CH_2)_nOH$, $(CH_2)_nOA$, $NHSO_2A$, $NASO_2A$, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, SO_2A, SO_2A and/or =O,

Het^3 denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, Hal, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $(CH_2)_nOH$, $(CH_2)_nOA$, COOA, Ar^3 and/or =O,

R^3	denotes H or alkyl having 1, 2, 3 or 4 C-atoms,	
A	denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O, NH, S, SO, SO_2 and/or by CH=CH groups,	
	or	
	cyclic alkyl having 3-7 C atoms,	
Cyc	denotes cyclic alkyl having 3-7 C atoms, which may be unsubstituted or monosubstituted by NH_2,	
Alk	denotes alkenyl or alkinyl having 2, 3, 4, 5 or 6 C-atoms,	
Ar^3	denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A,	
Hal	denotes F, Cl, Br or I,	
n	denotes 0, 1, 2, 3 or 4,	
p	denotes 1, 2, 3 or 4,	

and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds.

Moreover, the invention relates to pharmaceutically acceptable derivatives of compounds of formula I.

The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alkoxides.

The term pharmaceutically acceptable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound of formula I that can hydrolyze, oxidize, or otherwise

react under biological conditions (in vitro or in vivo) to provide an active compound, particularly a compound of formula I. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a compound of formula I that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. In certain embodiments, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well- known methods, such as those described by Burger 's Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and Design and Application of Prodrugs (H.Bundgaard ed., 1985, Harwood Academic Publishers Gmfh).

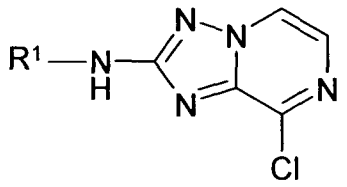
The expression "effective amount" denotes the amount of a medicament or of a pharmaceutical active ingredient which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.
In addition, the expression "therapeutically effective amount" denotes an amount which, compared with a corresponding subject who has not received this amount, has the following consequence:
improved treatment, healing, prevention or elimination of a disease, syndrome, condition, complaint, disorder or side-effects or also the reduction in the advance of a disease, complaint or disorder.
The expression "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

The invention also relates to the use of mixtures of the compounds of the formula I, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.
These are particularly preferably mixtures of stereoisomeric compounds.

"Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution.

The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I and pharmaceutically usable salts, solvates, tautomers and stereoisomers thereof, characterised in that

a) a compound of the formula II



II

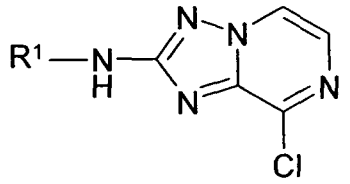
is reacted with a compound of the formula III

R^2-L III

in which R^2 has the meaning indicated in Claim 1,
and L denotes a boronic acid or a boronic acid ester group,
in a Suzuki-type coupling

or

b) a compound of the formula II



II

is reacted with a compound of the formula III

R^2-L III

in which R^2 has the meaning indicated in Claim 1,
and L denotes an NH_2 or OH

and/or

a base or acid of the formula I is converted into one of its salts.

Above and below, the radicals R^1 and R^2 have the meanings indicated for the formula I, unless expressly stated otherwise.

A denotes alkyl, this is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. A preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1- , 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1- , 2- , 3- or 4-methylpentyl, 1,1- , 1,2- , 1,3- , 2,2- , 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl.
A very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.
Moreover, A denotes e.g. CH_2OCH_3, CH_2CH_2OH, $OCH_2CH_2NH_2$, CH_2NHCH_2 or $NHCH_2CH_3$.
Cyclic alkyl (cycloalkyl) and cyc preferably denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Alk denotes unbranched or branched alkenyl or alkinyl having 2, 3, 4, 5 or 6 C-atoms, preferably denotes isopropenyl, prop-2-inyl, vinyl oder allyl.

Ar^1 denotes, for example, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-cyanophenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-formylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-aminosulfonylphenyl, o-, m- or p-[2-(morpholin-4-yl)ethoxy]phenyl, o-, m- or p-[3-(N,N-diethylamino)propoxy]phenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar^1 furthermore preferably denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$.

Ar^2 denotes, for example, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)-phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-cyanophenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-formylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-aminosulfonylphenyl, o-, m- or p-(morpholin-4-ylcarbonyl)phenyl, o-, m- or p-(morpholin-4-ylcarbonyl)phenyl, o-, m- or p-(3-oxomorpholin-4-yl)phenyl, o-, m- or p-(piperidinylcarbonyl)phenyl, o-, m- or p-[2-(morpholin-4-yl)ethoxy]phenyl, o-, m- or p-[3-(N,N-diethylamino)-propoxy]phenyl, o-, m- or p-[3-(3-diethylaminopropyl)ureido]phenyl, o-, m- or p-(3-diethylaminopropoxycarbonylamino)phenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylamino-phenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar^2 furthermore preferably denotes phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, OAr^3, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$,

$[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, $NHCOAr^3$, $NHSO_2A$, OSO_2A, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$.

Ar^3 preferably denotes phenyl.

Irrespective of further substitutions, Het^1 denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4-, -5-yl or 2,1,3-benzoxadiazol-5-yl, azabicyclo[3.2.1]octyl or dibenzofuranyl.

Het^1 preferably denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O.

Irrespective of further substitutions, Het^2 denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4-, -5-yl or 2,1,3-benzoxadiazol-5-yl, azabicyclo[3.2.1]octyl or dibenzofuranyl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Irrespective of further substitutions, Het^2 can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-,-2-,-3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxo-

methylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxofuranyl, 3,4-dihydro-2-oxo-1*H*-quinazolinyl, 2,3-dihydrobenzoxazolyl, 2-oxo-2,3-dihydro-benzoxazolyl, 2,3-dihydrobenzimidazolyl, 1,3-dihydroindole, 2-oxo-1,3-dihydroindole or 2-oxo-2,3-dihydrobenzimidazolyl.

Het^2 preferably denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, quinoxalinyl, benzimidazolyl, benzothiophenyl, benzotriazolyl, indolyl, indolinyl, naphthyridinyl, dihydronaphthyridinyl, terahydronaphtyridinyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, furopyridinyl, indazolyl, benzo[1,4]oxazinyl, pyrido[3,2-b][1,4]oxazinyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, CHO, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, SO_2A, SO_2A and/or =O.

Irrespective of further substitutions, Het^3 denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-

benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4-, -5-yl or 2,1,3-benzoxadiazol-5-yl, azabicyclo[3.2.1]octyl or dibenzofuranyl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Irrespective of further substitutions, Het^3 can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-,-2-,-3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxo-methylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxofuranyl, 3,4-dihydro-2-oxo-1*H*-quinazolinyl, 2,3-dihydrobenzoxazolyl, 2-oxo-2,3-dihydro-benzoxazolyl, 2,3-dihydrobenzimidazolyl, 1,3-dihydroindole, 2-oxo-1,3-dihydroindole or 2-oxo-2,3-dihydrobenzimidazolyl.

Het^3 preferably denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O.

Furthermore, Het^3 denotes 1,3-oxazinanyl, 1,4-dihydropyridinyl, 1,2,3,4-tetrahydro-6-pyridinyl, tetrahydropyranyl, 1,4-dioxanyl, 1,3-dioxanyl, hexahydropyridazinyl or hexahydropyrimidinyl.

Hal preferably denotes F, Cl or Br, but also I, particularly preferably F or Cl.

Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

The compounds of the formula I may have one or more chiral centres and can therefore occur in various stereoisomeric forms. The formula I encompasses all these forms.

Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae Ia to Ig, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which

in Ia	Het^1	denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O;
in Ib	Het^2	denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl,

			pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, quinoxalinyl, benzimidazolyl, benzothiophenyl, benzotriazolyl, indolyl, indolinyl, naphthyridinyl, dihydronaphthyridinyl, terahydronaphtyridinyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, furopyridinyl, indazolyl, benzo[1,4]oxazinyl, pyrido[3,2-b][1,4]oxazinyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, CHO, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, SO_2A, SO_2A and/or =O;
	in Ic	Het^3	denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O;
	in Id	A	denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O and/or NH, or cyclic alkyl having 3-7 C atoms;
	in Ie	Ar^1	denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$;

in If	Ar^2	denotes phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, OAr^3, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, $NHCOAr^3$, $NHSO_2A$, OSO_2A, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$;
in Ig	R^1	denotes Ar^1 or Het^1,
	R^2	denotes Ar^2, Het^2, $NH(CH_2)_nAr^2$, $O(CH_2)_nAr^2$, $NR^3(CH_2)_nHet^2$, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, NHCyc or $NH(CH_2)_pNA_2$,
	Ar^1	denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,
	Ar^2	denotes phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, OAr^3, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, $NHCOAr^3$, $NHSO_2A$, OSO_2A, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,
	Het^1	denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,
	Het^2	denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, furyl, thienyl, pyrrolyl, imidazolyl,

pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, quinoxalinyl, benzimidazolyl, benzothiophenyl, benzotriazolyl, indolyl, indolinyl, naphthyridinyl, dihydronaphthyridinyl, terahydronaphtyridinyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, furopyridinyl, indazolyl, benzo[1,4]oxazinyl, pyrido[3,2-b][1,4]oxazinyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, CHO, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, SO_2A, SO_2A and/or =O,

Het^3 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O,

R^3 denotes H or alkyl having 1, 2, 3 or 4 C-atoms,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O and/or NH,

or

cyclic alkyl having 3-7 C atoms,

Cyc denotes cyclic alkyl having 3-7 C atoms, which may be unsubstituted or monosubstituted by NH_2,

Ar^3 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A,

n denotes 0, 1, 2, 3 or 4,

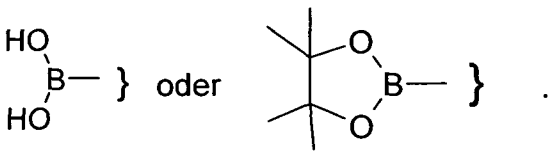
p denotes 1, 2, 3 or 4,;

and pharmaceutically usable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise Use can also be made here of variants known per se which are not mentioned here in greater detail.

The starting compounds of the formulae II and III are generally known. If they are novel, however, they can be prepared by methods known per se.
The pyridazinones of the formula II used are, if not commercially available, generally prepared by the method of W. J. Coates, A. McKillop, Synthesis, 1993, 334-342.

Compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a compound of the formula III.
In the compounds of the formula III, L preferably denotes



The reaction is generally carried out under conditions of a Suzuki-type coupling. Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -30° and 140°, normally between 0° and 100°, in particular between about 60° and about 90°. Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such

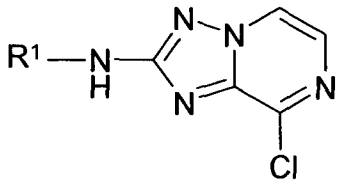
as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

Particular preference is given to ethanole, toluene, dimethoxyethane, 1,4-dioxane and/or water.

Moreover, compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a compound of the formula III wherein L preferably denotes NH_2 or OH. The reaction is generally carried out under conditions known to the skilled artisan and which are known and suitable for the said reaction.It is furthermore possible to convert a compound of the formula I into another compound of the formula I, for example by reducing nitro groups to amino groups (for example by hydrogenation on Raney nickel or Pd/carbon in an inert solvent, such as methanol or ethanol).

Free amino groups can furthermore be acylated in a conventional manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide, advantageously in an inert solvent, such as dichloro-methane or THF, and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

Moreover, the invention relates to the compounds of the formula II



II

in which

R^1 denotes Ar^1 or Het^1,

Ar^1 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,

Het^1 denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,

Het^3 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O,

R^3 denotes H or alkyl having 1, 2, 3 or 4 C-atoms,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O and/or NH,

or

cyclic alkyl having 3-7 C atoms,

Cyc denotes cyclic alkyl having 3-7 C atoms, which may be unsubstituted or monosubstituted by NH_2,

Ar^3 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A,

n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

Preferred meanings of the radicals are the same as described for compounds of the formula I.

Compounds of formula II are useful intermediates for the preparation of compounds of formula I.

Moreover, compounds of formula II show Syk inhibitory activity and hence, can be used as medicaments.

Pharmaceutical salts and other forms

The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also encompasses the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and

monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine,

ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C_1-C_4)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C_1-C_4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C_{10}-C_{18})alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C_1-C_4)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds according to the invention can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

Particular preference is given to hydrochloride, dihydrochloride, hydrobromide, maleate, mesylate, phosphate, sulfate and succinate.

The acid-addition salts of basic compounds of the formula I are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner. The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to

certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds according to the invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the expression "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic

properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the

pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate,

carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tabletting machine, giving lumps of non-uniform shape, which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compound. Syrups can be prepared by dissolving the compound

in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

The compounds of the formula I and salts, solvates and physiologically functional derivatives thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

The compounds of the formula I and the salts, solvates and physiologically functional derivatives thereof can also be delivered using monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyrans,

polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size,

for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the formula I depends on a number of factors, including, for example, the age and weight of the animal, the precise condition that requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as a single dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention *per se*. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.

The disclosed compounds of the formula I can be administered in combination with other known therapeutic agents including agents for the treatment of RA (rheumatoid arthritis). As used here, the term "agents for the treatment of RA" relates to any agent which is administered to a patient with RA for the purposes of treating the RA.

The medicaments below are preferably, but not exclusively, combined with the compounds of the formula I:

1. NSAIDs (non-steroidal anti-inflammatory drugs) and analgesics
2. Glucocorticoids (low oral doses)
3. Conventional disease-modifying antirheumatic drugs (DMARDs)
    - Methotrexate
    - Leflunomide
    - Sulfasalazine
    - Hydroxycloroquine

- Azathioprine
- Ciclosporin
- Minocycline
- Gold

4. Biologic response modifiers (BRMs) --> target molecules/ immune cells involved in the inflammatory process, and include the following agents:

- TNF inhibitors
    - etanercept (Enbrel)
    - infliximab (Remicade)
    - adalimumab (Humira)
- B-cell-directed therapy
    - rituximab (Rituxan)
- T-cell/B-cell coactivation signal inhibitor
    - abatacept (Orencia)

- IL-1 receptor antagonist
    - anakinra (Kineret)

	MECHANISM OF ACTION
Golimumab	Fully humanized monoclonal antibody to TNF
Certolizumab pegol	Anti -TNF agent with just the Fab portion attached to the polyethylene glycol
Tocilizumab	Humanized monoclonal anti-IL-6 antibody that binds to the soluble and membrane-expresses IL-6 receptor
Ocrelizumab	Humanized-second generation anti-CD20 antibody that depletes B cells
Ofatumumab	Human monoclonal anti-CD20 IgG1 antibody
Denosumab	Fully humanized monoclonal antibody that binds to and inhibits the receptor activator for nuclear factor-kB ligand
TRU-015	New class of CD20-directed protein therapeutics
Oral small molecules (JAK, Syk, MAP kinase inhibitors)	Cytoplasmic targets
Tolerogens (dnaJP1)	Immunotherapy based on T-cell tolerization

A combined treatment of this type can be achieved with the aid of simultaneous, consecutive or separate dispensing of the individual components of the treatment. Combination products of this type employ the compounds according to the invention.

The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of a compound of the formula I and/or pharmaceutically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and

(b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound of the formula I and/or pharmaceutically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

"Treating" as used herein, means an alleviation, in whole or in part, of symptoms associated with a disorder or disease, or slowing, or halting of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder in a subject at risk for developing the disease or disorder.

The term "effective amount" in connection with a compound of formula (I) can mean an amount capable of alleviating, in whole or in part, symptoms associated with a disorder or disease, or slowing or halting further progression or worsening of those symptoms, or preventing or providing prophylaxis for the disease or disorder in a subject having or at risk for developing a disease disclosed herein, such as inflammatory conditions, immunological conditions, cancer, metabolic conditions or conditions treatable or preventable by inhibition of a kinase or a kinase pathway, in one embodiment, the Syk, FLT-3, JAK1 and/or JAK2 and /or JAK3 and/or BTKpathway. In one embodiment an effective amount of a compound of formula (I) is an amount that inhibits a kinase in a cell, such as, for example, in vitro or in vivo. In some embodiments, the effective amount of the compound of formula (I) inhibits the kinase in a cell

by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 99%, compared to the activity of the kinase in an untreated cell. The effective amount of the compound of formula (I), for example in a pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight in unit dosage for both oral and parenteral administration.

USE

The present compounds are suitable as pharmaceutical active ingredients for mammals, especially for humans, in the treatment of tyrosine kinase-induced diseases.

The present invention encompasses the use of the compounds of the formula I and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment or prevention of rheumatoid arthritis, systemic lupus, asthma, allergic rhinitis, ITP, multiple sclerosis, leukemia, breast cancer and maligna melanoma.

Examples of inflammatory diseases include rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reaction and the like.

Also encompassed is the use of the compounds of the formula I and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment or prevention of a tyrosine kinase-induced disease or a tyrosine kinase-induced condition in a mammal, in which to this method a therapeutically effective amount of a compound according to the invention is administered to a sick mammal in need of such treatment. The therapeutic amount varies according to the specific disease and can be determined by the person skilled in the art without undue effort.

The present invention also encompasses the use compounds of the formula I and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment or prevention of retinal vascularisation.

The expression "tyrosine kinase-induced diseases or conditions" refers to pathological conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities, including proliferation, adhesion and migration and differentiation. Diseases associated with tyrosine kinase activity include proliferation of tumour cells, pathological neovascularisation that promotes the growth of solid tumours, ocular neovascularisation (diabetic retinopathy, age-induced macular degeneration and the like) and inflammation (psoriasis, rheumatoid arthritis and the like).

The present invention specifically relates to compounds of the formula I and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios,
for the use for the treatment of diseases in which the inhibition, regulation and/or modulation inhibition of Syk plays a role.

The present invention specifically relates to compounds of the formula I and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the use for the inhibition of Syk.

The present invention specifically relates to compounds of the formula I and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the use for the treatment of rheumatoid arthritis, systemic lupus, asthma, allergic rhinitis, ITP, multiple sclerosis, leukemia, breast cancer, maligna melanoma.

The present invention specifically relates to methods for treating or preventing an inflammatory condition, immunological condition, autoimmune condition, allergic condition, rheumatic condition, thrombotic condition, cancer, infection, neurodegenerative disease, neuroinflammatory disease, cardiovascular disease

or metabolic condition, comprising administering to a subject in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, tautomer, stereoisomer or solvate thereof.

In another aspect provided herein are methods of inhibiting a kinase in a cell expressing said kinase, comprising contacting said cell with an effective amount of a compound of formula I or a pharmaceutically acceptable salt, tautomer, stereoisomer or solvate thereof. In one embodiment the kinase is Syk, FLT3, JAK1 or JAK2 or JAK3 or BTK, or mutants or isoforms thereof, or combinations of two or more thereof.

Representative immunological conditions that compounds of formula I are useful for treating or preventing include, but are not limited to, Behcet's syndrome, non-allergy mast cell diseases (e.g., mastocytosis and treatment of anaphylaxis), ankylosing spondylitis, osteoarthritis, rheumatoid arthritis (RA), multiple sclerosis, lupus, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, Grave's disease, transplant rejection, humoral transplant rejection, non-humoral transplant rejection, cellular transplant rejection, immune thrombocytopenic purpura (ITP), idiopathic thrombocytopenic purpura, diabetes, immunological response to bacterial, parasitic, helminth infestation or viral infection, eczema, dermatitis, graft versus host disease, Goodpasture's disease, hemolytic disease of the newborn, autoimmune hemolytic anemia, anti-phospholipid syndrome, ANCA-associated vasculitis, Churg-Strauss syndrome, Wegeners granulomatosus, pemphigus vulgaris, serum sickness, mixed cryoglobulinemia, peripheral neuropathy associated with IgM antibody, microscopic polyangiitis, Hashimoto's thyroiditis, Sjogrens syndrome, fibrosing conditions (such as those dependent on the innate or adaptive immune systems or local mesenchyma cells) or primary biliary cirrhosis.

Representative autoimmune conditions that compounds of formula I are useful for treating or preventing include, but are not limited to, autoimmune hemolytic anemia (A1HA), Behcet's syndrome, Crohn's disease, type I diabetes,

Goodpasture's disease, Grave's disease, Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, lupus, multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, pemphigus vulgaris, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, ulcerative colitis, or Wegeners granulomatosus.

Representative allergic conditions that compounds of formula I are useful for treating or preventing include, but are not limited to, anaphylaxis, hay fever, allergic conjunctivitis, allergic rhinitis, allergic asthma, atopic dermatitis, eczema, urticaria, mucosal disorders, tissue disorders and certain gastrointestinal disorders.

Representative rheumatic conditions that compounds of formula I are useful for treating or preventing include, but are not limited to, rheumatoid arthritis, gout, ankylosing spondylitis, or osteoarthritis.

Representative inflammatory conditions that compounds of formula I are useful for treating or preventing include, but are not limited to, non-ANCA (anti-neutrophil cytoplasmic autoantibody) vasculitis (e.g., wherein Syk function is associated with neutrophil adhesion, diapedesis and/or activation), psoriasis, asthma, allergic rhinitis, allergic conjunctivitis, chronic urticaria, hives, anaphylaxis, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, gout, Crohn's disease, mucous colitis, ulcerative colitis, allergy to intestinal antigens (such as gluten enteropathy), diabetes (e.g., Type I diabetes and Type II diabetes) and obesity. In some embodiments, the inflammatory condition is a dermatologic condition, such as, for example, psoriasis, urticaria, hives, eczema, scleroderma, or dermatitis. In other embodiments, the inflammatory condition is an inflammatory pulmonary condition, such as, for example, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), or adult/acute respiratory distress syndrome (ARDS). In other embodiments, the inflammatory condition is a gastrointestinal condition, such as, for example, inflammatory bowel disease, ulcerative colitis, Crohn's disease, idiopathic inflammatory bowel disease, irritable bowel syndrome, or spastic colon.

Representative infections that compounds of formula I are useful for treating or preventing include, but are not limited to, bacterial, parasitic, prion, viral infections or helminth infestation.

Representative cancers that compounds of formula I are useful for treating or preventing include, but are not limited to, cancer of the head, neck, eye, mouth, throat, esophagus, bronchus, larynx, pharynx, chest, bone, lung, colon, rectum, stomach, prostate, urinary bladder, uterine, cervix, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, brain, central nervous system, solid tumors and blood-borne tumors.

Representative cardiovascular diseases that compounds of formula I are useful for treating or preventing include, but are not limited to, restenosis, atherosclerosis and its consequences such as stroke, myocardial infarction, ischemic damage to the heart, lung, gut, kidney, liver, pancreas, spleen or brain.

Representative metabolic conditions that compounds of formula I are useful for treating or preventing include, but are not limited to, obesity and diabetes (e.g. , Type I and II diabetes). In a particular embodiment, provided herein are methods for the treatment or prevention of insulin resistance. In certain embodiments, provided herein are methods for the treatment or prevention of insulin resistance that leads to diabetes (e.g., Type II diabetes). In another embodiment, provided herein are methods for the treatment or prevention of syndrome X or metabolic syndrome. In another embodiment, provided herein are methods for the treatment or prevention of Type II diabetes, Type I diabetes, slow-onset Type I diabetes, diabetes insipidus (e.g., neurogenic diabetes insipidus, nephrogenic diabetes insipidus, dipsogenic diabetes insipidus, or gestagenic diabetes insipidus), diabetes mellitus, gestational diabetes mellitus, polycystic ovarian syndrome, maturity-onset diabetes, juvenile diabetes, insulin-dependant diabetes, non-insulin dependant diabetes, malnutrition-related diabetes, ketosis-prone diabetes, pre-diabetes (e.g. , impaired glucose metabolism), cystic fibrosis related diabetes, hemochromatosis and ketosis-resistant diabetes.

Representative neurodegenerative and neuroinflammatory diseases that compounds of formula I are useful for treating or preventing include, but are not limited to, Huntington's disease, Alzheimer's disease, viral (e.g., HIV) or bacterial-associated encephalitis and damage.

In another embodiment, provided herein are methods for the treatment or prevention of fibrotic diseases and disorders. In a particular embodiment, provided herein are methods for the treatment or prevention of idiopathic pulmonary fibrosis, myelofibrosis, hepatic fibrosis, steatofibrosis and steatohepatitis.

In another embodiment, provided herein are methods for the treatment or prevention of diseases associated with thrombotic events such as but not limited to atherosclerosis, myocardial infarction and ischemic stroke.

The following abbreviations refer respectively to the definitions below:
aq (aqueous), h (hour), g (gram), L (liter), mg (milligram), MHz (Megahertz), min. (minute), mm (millimeter), mmol (millimole), mM (millimolar), m.p. (melting point), eq (equivalent), mL (milliliter), L (microliter), ACN (acetonitrile), AcOH (acetic acid), $CDCl_3$ (deuterated chloroform), CD_3OD (deuterated methanol), CH_3CN (acetonitrile), c-hex (cyclohexane), DCC (dicyclohexyl carbodiimide), DCM (dichloromethane), DIC (diisopropyl carbodiimide), DIEA (diisopropylethyl-amine), DMF (dimethylformamide), DMSO (dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsulfoxide), EDC (1-(3-dimethyl-amino-propyl)-3-ethylcarbodiimide), ESI (Electro-spray ionization), EtOAc (ethyl acetate), Et_2O (diethyl ether), EtOH (ethanol), HATU (dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl-ammonium hexafluorophosphate), HPLC (High Performance Liquid Chromatography), i-PrOH (2-propanol), K_2CO_3 (potassium carbonate), LC (Liquid Chromatography), MeOH (methanol), $MgSO_4$ (magnesium sulfate), MS (mass spectrometry), MTBE (Methyl tert-butyl ether), $NaHCO_3$ (sodium bicarbonate), $NaBH_4$ (sodium borohydride), NMM (N-methyl morpholine), NMR (Nuclear Magnetic Resonance), PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), RT (room temperature), Rt (retention time), SPE (solid phase extraction), TBTU (2-(1-H-benzotriazole-1-yl)-1,1,3,3-

tetramethyluromium tetrafluoro borate), TEA (triethylamine), TFA (trifluoroacetic acid), THF (tetrahydrofuran), TLC (Thin Layer Chromatography), UV (Ultraviolet).

Description of the in vitro assays

SYK flash plate assay

The kinase assay is performed either as 384-well Flashplate assay (for e.g. Topcount measurement) or as 384-well Image-Flashplate assay (for LEADseeker measurement).
2.5 nM SYK, 400 nM Biotin-Aha-Aha-KEDPDYEWPSAKK
and 10 µM ATP (spiked with 0.3 µCi 33P-ATP/well) are incubated in a total volume of 50 µl (60 mM Hepes, 10 mM $MgCl_2$, 1.2 mM Dithiothreitol, 0.02 % Brij35, 0.1 % BSA , pH 7.5) with or without test compound for 1 hours at 30°C. The reaction is stopped with 25µl 200 mM EDTA. After 30 Min at 30 °C the liquid is removed and each well washed thrice with 100 µl 0.9% sodium chloride solution. Non-specific reaction is determined in presence of 0.1 µM Staurosporine. Radioactivity is measured with Topcount (when using Flashplates) or with LEADseeker (when using Image-Flashplates) respectively. Results (e.g. IC50-values) are calculated with program tools provided by the IT-department (e.g. Symyx Assay Explorer, Genedata Screener).

Enzymatic assays using the Caliper LifeSciences Technology

The assays described here are performed on the Caliper Life Sciences LC3000 system This technology provides data on enzyme activity via measurement of the relative amounts of phosphorylated or unphosphorylated fluorescently labelled substrate peptide at the end of an enzymatic reaction. These different states of peptide are resolved by applying a potential difference across the sample. The presence of the charged phosphate group on the product (as opposed to the substrate) causes a different peptide mobility between the two peptides. This is visualized by excitation of the fluorescent label on the substrate and product peptides and represented as peaks within the analysis software.

In order to measure inhibitor activity of kinase inhibitors on this technology, a TTP Mosquito liquid handling instrument is used to place 0.25 ul of the appropriate concentration of inhibitor in 100% DMSO (for a dose response curve calculation) into each well of a 384-well plate. To this reaction components are added to a final volume of 25 ul. The table below indicates the sequences and concentrations for the assays described in this report. Standard components are 1 mM DTT (Sigma, D0632), 1 mM MgCl2 (Sigma, M1028), 100 mM HEPES pH 7.5 (Calbiochem, 391338), 0.015% Brij-35 (Sigma, B4184).

Enzyme	Enzyme Concentration (ng/ul)	ATP Concentration (uM)	Peptide Sequence (@ 1 uM)
Syk (BPS Bioscience, CA, USA)	0.06	5	FITC-AHA-KEDPDYEWPSAKKK-NH2
KDR (BPS Bioscience, CA, USA)	3.3	160	FITC-AHA-EEPLYWSFPAKKK-NH2
Src (Carna Bioscience, Kobe, Japan)	0.1	36	FITC-AHA-EEPLYWSFPAKKK-NH2
ZAP-70 (BPS Bioscience, CA, USA)	0.5	5	FITC-AHA-EDPIYEFLPAKKK-NH2
FAK (Carna Bioscience, Kobe, Japan)	3	100	FITC-AHA-KKSRGDYMTMQIG-NH2
PYK2 (Carna Bioscience, Kobe, Japan)	0.25	50	FITC-AHA-SIESDIYAEIPDETLRR-NH2
FLT3 (BPS Bioscience, CA, USA)	5.7	350	FITC-AHA-EAIYAAPFAKKK-NH2
JAK2 (Carna Bioscience, Kobe, Japan)	0.025	13	FITC-AHA-gpkgtgyiktelisvs
BTK (Carna Bioscience, Kobe, Japan)	0.2	75	FITC-AHA-EEPLYWSFPAKKK-NH2
Lyn	0.1	15	FITC-AHA-

(Carna Bioscience, Kobe, Japan)			EEPLYWSFPAKKK-NH2
Fyn (Carna Bioscience, Kobe, Japan)	0.0075	50	FITC-AHA-EEPLYWSFPAKKK-NH2

The reaction is incubated for 90 min at 25 C, and then stopped by the addition of 70 ul of Stop buffer (100 mM HEPES pH 7.5, 0.015% Brij-35, 10 mM EDTA (Sigma, E7889)).

The plate is read on a Caliper LC 3000 in an Off-Chip mobility shift assay format, on a 12-sipper chip. Unphosphorylated substrate and phosphorylated product peptide resolve as separate peaks allowing direct measurement of percentage of conversion of substrate to product. The percent conversion can be plotted against concentration of inhibitor to produce a sigmoidal dose response curve, from which an IC50 can be calculated using GeneData Condoseo or a similar product.Cellular activity assays

1. BCR crosslinking-induced BLNK phosphorylation

Ramos cells incubated overnight in IMDM medium containing 5% FCS were resuspended in IMDM medium without serum (3.3 x10^6 cells/ml). 90 µl of cell suspension (300'000 cells) were incubated with 10 µl of SYK inhibitors (in 3 % DMSO) for 20 minutes at 37°C, in 96 well plates. After preincubation with inhibitors, cells were activated with 10 µg / ml of goat antihuman anti-IgM for 10 minutes at 37°C. After stimulation, cells were fixed by addition of 80 µl of 4% paraformaldehyde followed by a 10 minutes incubation at RT and fixed in 0.1 % Triton X-100 in PBS. BLNK phosphorylation was detected by flow cytometry after staining of the cells with anti-BLNK-pY84-PE antibodies from BD pharmingen, for 45 minutes at RT.

BLNK phosphorylation in $CD19^+$ peripheral blood mononuclear cells (PBMC) isolated from buffy coats of healthy volunteers was performed using the same

protocol and staining the cells with a mixture of anti-BLNK-pY84-PE, anti CD-19 PerCp and Anti-IgM APC antibodies from BD Pharmingen.

2. BCR crosslinking-induced CD69 up-regulation

To quantify anti-IgM-induced CD69 up-regulation in peripheral blood mononuclear cells, 90 µl of PBMC cell suspension (containing 1 x 10^6 cells) were preincubated with 10 µl of SYK inhibitors (in 3% DMSO) for 1 h at 37°C/5%CO_2. After preincubation with inhibitors cells were stimulated with 10 µg / ml of goat antihuman anti-IgM during 18 hours at 37°C/5%CO_2. After stimulation cells were stained with a cocktail containing goat IgG (1:200 dilution), CD19-PerCpCy5.5 (5 µl) and CD69-APC (3 µl) antibodies in PBS containing 4 % FCS. CD69 expression in $CD19^+$ cells was quantified by flow cytometry.

In vivo Assays

CIA

For induction of collagen-induced arthritis (CIA) male DBA/1 mice are injected with 500 µl pristane i.p. on day -21. On day 0 mice are immunized with 100 µg chicken collagen type II (CII) in Complete Freund's Adjuvant (CFA) intradermally, distributed over pinnae and one site on the back on day 0. On day 21, mice will receive an i.p. booster immunization (100 µg) with soluble CII in PBS. Dosing of Syk inhibitor will be prophylactic: starting day 0 and continued until day 10 and before boost starting on day 20 and continued until day 30. Compounds will be administered orally twice a day at doses of 3, 10 and 30 mg/kg.
Body weight and clinical score will be recorded on a daily basis. Arthritis severity is graded using a clinical scoring system based on the assessment of inflammation in individual paws. The scale for this clinical score ranges from 0-4 for each individual paw.

GIA

For induction of Glucose-6-phosphate isomerase-induced arthritis (GIA) female DBA/1 mice are immunized with 100 µg G6PI in Complete Freund's Adjuvant

(CFA) intradermally, distributed over pinnae and one site on the back on day 0. Dosing of Syk inhibitor will be prophylactic starting day 0 and continued until day 14. Compounds will be administered orally twice a day at doses of 3, 10 and 30 mg/kg.

Body weight and clinical score will be recorded on a daily basis. Arthritis severity is graded using a clinical scoring system based on the assessment of inflammation in individual paws. The scale for this clinical score ranges from 0-4 for each individual paw.

Above and below, all temperatures are indicated in°C. In the following examples, "conventional work-up" means: water is added if necessary, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallisation. Rf values on silica gel; eluent: ethyl acetate/methanol 9:1.

Mass spectrometry (MS): EI (electron impact ionisation) M^+
FAB (fast atom bombardment) $(M+H)^+$
ESI (electrospray ionisation) $(M+H)^+$

APCI-MS (atmospheric pressure chemical ionisation - mass spectrometry) $(M+H)^+$.

Mass spectrometry (MS): EI (electron impact ionisation) M^+
FAB (fast atom bombardment) $(M+H)^+$
ESI (electrospray ionisation) $(M+H)^+$

APCI-MS (atmospheric pressure chemical ionisation - mass spectrometry) $(M+H)^+$.

m.p. = melting point

HPLC data provided in the examples described below (retention time given) were obtained as followed:

method A:

1 min 99 % A,
in 2.5 min from 99 % A to 100 % B,
followed by 1.5 min 100 % B and 1 min 99 % A.
Column: Chromolith SpeedRod RP-18e; 50-4.6mm;
detection 220 nM (solvent A: H_20 (0.1 % TFA),
solvent B: ACN (0.1% TFA);

method F: In 8 min from 98 % A to 100 % B,
within 0.1 min to 98% A,
during 1.9 min 98 % A (solvent A H_20 (0.1 % TFA), solvent B: ACN (0.1% TFA));
column: Xbridge C8 5 µM, 4.6 x 50 mm; flow rate: 2 mL/min.

LCMS data provided in the examples are given with retention time, purity and/or mass in m/z. The results were obtained as followed: mass spectrum: LC/MS Waters ZMD (ESI) or Hewlett Packard System of the HP 1100 series (ion source: electrospray (positive mode); scan: 100-1000 m/z; fragmentation-voltage: 60 V; gas-temperature: 300°C, DAD: 220 nm; flow rate: 2.4 ml/min. The used splitter reduced the flow rate after the DAD for the MS to 0,75ml/min; column: Chromolith Speed ROD RP-18e 50-4.6; solvent: LiChrosolv-quality from the company Merck KGaA or as mentionend in the method;
method B: A-0.1% HCOOH, B-MeOH: flow-1.0ml/min.; column: Atlantis C8 (50X4.6mm 5Um, +ve mode);
method C: A-10mM, B- MeOH: flow 1.0 ml/min, column: XBridge C8 (30X2.1mm 3.5Um, +ve mode);
method D: A-0.1% TFA in H_2O, B- 0.1% TFA in ACN: flow-2.0ml/min; column: XBridge C8 (50X4.6mm 3.5Um, +ve mode;
method E: within 2.8 min from 96% C to 100 % D, followed by 0.5 min 100 %D and within 0.1 min to 96 % C; column Chromolith SpeedRod RP-18e; 50-4.6mm; detection 220 nM; solvent C: H_2O (0.05 % HCOOH), solvent D: ACN (0.05 % HCOOH).
Preparative HPLC was performed on a Agilent 1200; column: Chromolith prep RP 18e Merck KGaA; mobile phase: 0.1% formic acid in water / 0.1% formic acid in acetonitrile.
^1H NMR was recorded on Bruker DPX-300, DRX-400 or AVII-400 spectrometer, using residual signal of deuterated solvent as internal reference. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 2.49 ppm for ^1H

NMR in DMSO-d_6). ^{1}H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, and number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

The microwave chemistry is performed on a single mode microwave reactor EmrysTM Optimiser from Personal Chemistry.

GCN2: Assay principle & conditions

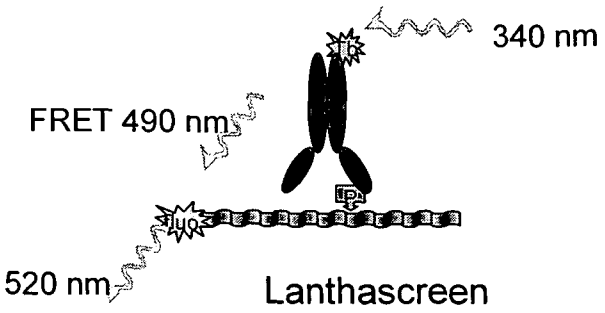
This assay can quantificate the activity of the serin kinase GCN2 (general control non-derepressible-2).

This kinase is involved in the stress metabolism of cells. It is activated upon starvation (amino acid depletion). Its natural substrate is eIF2a (eukaryotic initiation factor 2 alpha subunit), a translation factor, which gets activated (phosphorylated) by GCN2 in case of an amino acid bottleneck in the cells. This in turn leads to a halt of the protein synthesis. Inhibition of GCN2 results in stopping this mechanism: The cell can not stop protein production upon "starvation" stress.

The assay is run in two steps: the enzymatic reaction and the detection step. In the first step GCN2 is incubated with 10 µM ATP and 80 nM of the GFP-labelled substrate eIF2alpha at room temperature.

The enzymatic reaction is stopped by addition of EDTA. The amount of phosphorylated eIF2alpha is determined by TR-FRET (Lanthascreen): A complex is formed consisting of antibody and GFP labelled phospho-eIF2a, which allows a FRET upon exitation at 340 nm.

The GCN2-activity is directly proportional to the ratio of fluorescence units at the emission wavelenghth 520 nm (phosphopeptide-sensitive wavelength = emission of GFP) to the units at 495 nm (reference wavelength = emission of Terbium-chelate).



Final concentrations in the enzymatic reaction

Hepes, pH 7.0	50 mM
$MgCl_2$	10 mM
$MnCl_2$	5 mM
BSA	0.1%
DMSO	1%
ATP	10 uM
DTT	2 mM
GFP-eIF2a	80 nM (substrate)
GCN2	*30 nM (enzyme)*

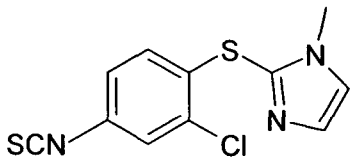
Assay procedure

4 uL	**enzyme** solution (in assay buffer)
1.5 uL	**compound** (in cmpd dilution buffer/6.3% DMSO)
Incubation	20 min at RT
4 uL	**substrate**/ATP mix (in assay buffer)
Incubation	90 min at RT
10 uL	stop/**detection** mix (in antibody dilution buffer)
Incubation	60 min at RT
Readout	Lanthascreen 340/495/520

EXAMPLES

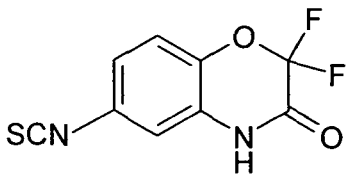
Preparation of reactants

2-(2-Chloro-4-isothiocyanato-phenylsulfanyl)-1-methyl-4,5-dihydro-1H-imidazole ("A1")



To a stirred solution of 3-chloro-4-(1-methyl-4,5-dihydro-1H-imidazol-2-ylsulfanyl)-phenylamine (5.0 g, 21 mmol) and diisopropylethylamine (5.37 g, 41.6 mmol) in dry tetrahydrofuran at 0 °C under N_2 inert atmosphere, thiophosgene (2.39 g, 21 mmol) in tetrahydrofuran was added dropwise and stirred for 20 minutes. When the reaction was completed, the reaction mixture was concentrated at room temperature and taken in dichloromethane (100 mL), washed with water (2 x 50 mL) and dried over anhydrous $MgSO_4$ to get the product as a brown solid (5.8 g, 99%). TLC: pet ether / ethyl acetate (8/2) R_f – 0.4. LCMS (method A): mass found ($M+H^+$, 282.0), Rt (min): 3.43, area % 71.5 (max); ^1H NMR (400 MHz, DMSO-d_6): δ 7.72 (d, J = 2.16 Hz, 1H), 7.57 (s, 1H), 7.31 (m, 1H), 7.28 (m, 1H), 6.43 (d, J = 8.56 Hz, 1H), 3.61(s, 3H).

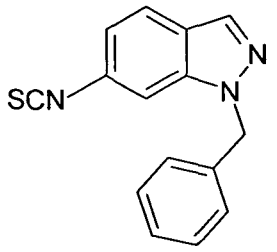
2,2-Difluoro-6-isothiocyanato-4H-benzo[1,4]oxazin-3-one ("A2")



Intermediate "A2" was prepared as a brown solid (2.2 g, 91%) following the protocol used for the intermediate "A1" starting from 6-amino-2,2-difluoro-4H-

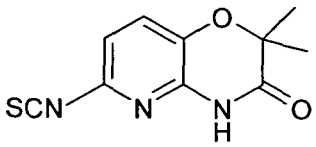
benzo[1,4]oxazin-3-on. TLC: pet ether / ethyl acetate (8/2) R_f – 0.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (br s, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.21 (m, 1H), 7.04 (s, 1H).

1-Benzyl-6-isothiocyanato-1H-indazole ("A3")



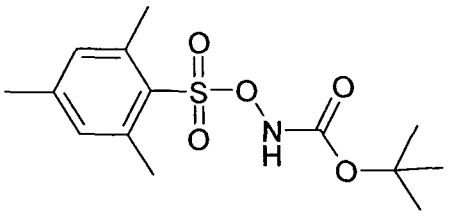
Intermediate "A3" was prepared as a brown solid (2.9 g, 98%) following the protocol used for the intermediate "A1" starting from 1-benzyl-1H-indazol-6-ylamine. TLC: pet ether / ethyl acetate (8/2) R_f – 0.4. LCMS (method B): mass found ($M+H^+$, 266.2), Rt (min): 4.58 area % 94.8 (max); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.97 (s, 1H), 7.82 (d, *J* = 8.52 Hz, 1H), 7.24 (m, 5H), 7.15 (m, 1H), 5.64 (s, 2H).

6-Isothiocyanato-2,2-dimethyl-4H-pyrido[3,2-b]oxazin-3-one ("A4")



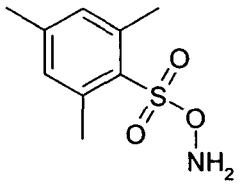
Intermediate "A4" was prepared as a brown solid (2.0 g, 83%) following the protocol used for the intermediate A1 starting from 6-amino-2,2-dimethyl-4H-pyrido[3,2-b]oxazin-3-one. TLC: pet ether / ethyl acetate (8/2) R_f – 0.4. LCMS (method A): mass found ($M+H^+$, 236.0), Rt (min): 4.12 area % 83.8 (max), 82.18 (220 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.44 (br s, 1H), 7.43 (d, *J* = 8.24 Hz, 1H), 6.99 (d, *J* = 8.24 Hz, 1H), 1.42 (s, 6H).

N-(tert.-Butoxycarbonyl)-*O*-(mesitylsulfonyl)-hydroxylamine



To a solution of 2-mesitylene sulphonyl chloride (2.0 g, 9.14 mmol) in dry THF (50 mL), was added N-Boc-hydroxylamine (1.21 g, 9.14 mmol) and cooled to 0 °C under N_2 atmosphere. The reaction mixture was stirred for 5 minutes. To this mixture triethylamine (1.1 g, 11 mmol) was added slowly over 10 minutes. The reaction mixture was stirred for 1 hour at 0 °C and upon completion, the solvent removed in vacuo. The residue was redissolved in dichloromethane (50 mL) and washed with water (2 x 50 mL), 10% aqueous $NaHCO_3$ (50 mL) and dried over $MgSO_4$. It was then concentrated under reduced pressure at room temperature to get the product as an off white solid; (2.1 g, 73%). TLC: pet ether / ethyl acetate (8/2) R_f – 0.4. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 11.16 (s, 1H), 7.12 (s, 2H), 2.49 (s, 6H), 2.28 (s, 3H), 1.23 (s, 9H).

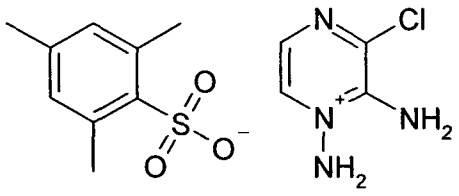
2-[(Aminoxy)-sulfonyl]-1,3,5-trimethylbenzene



To the solid product *N*-(tert.-butoxycarbonyl)-*O*-(mesitylsulfonyl)-hydroxylamine (2.1 g, 6.6 mmol) was added trifluoroacetic acid (20 mL) slowly at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes followed slowly by water (60 mL). The reaction was left at 0°C for 15 minutes. The solid precipitated was filtered and washed several times with water until the pH of the filtrate was neutral. The white solid (1.4 g, 98%) was dried in the Buchner funnel

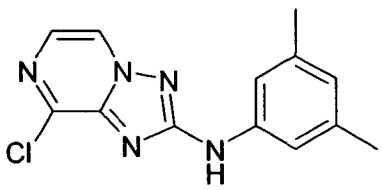
and used immediately for the next reaction; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.73 (s, 2H), 2.48 (s, 6H), 2.15 (s, 3H).

1,2-Diamino-3-chloro-pyrazinium mesitylenate



To a solution of 2-amino-3-chloro-pyrazine (1.4 g, 11 mmol) in dry dichloromethane (25 mL) at 0 °C under N_2 atmosphere was added 2-[(aminoxy)-sulfonyl]-1,3,5-trimethylbenzene (2.91 g, 13.5 mmol) over 10 minutes. The reaction mixture was stirred for 30 minutes at RT. To this reaction mixture, diethyl ether (100 mL) was added and stirred for 15 minutes. The solid precipitated was filtered and washed with diethyl ether to afford the product as a light brown solid (3 g, 80%); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.07 (br s, 2H), 8.11 (d, *J* = 4.28 Hz, 1H), 7.78 (d, *J* = 4.2 Hz, 1H), 7.28 (s, 1H), 6.72 (s, 1H), 2.48 (s, 6H), 2.15 (s, 3H).

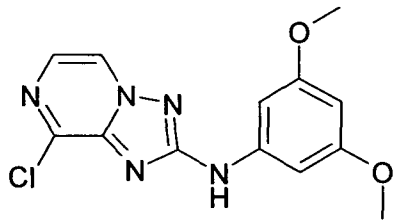
8-Chloro- [1, 2, 4] triazolo [1, 5-a] pyrazin-2-yl-(3, 5-dimethyl-phenyl)-amine ("B1")



To a solution of 3,5-dimethylisothiocyanate (200 mg, 1.2 mmol) in dichloro-methane and N,N-dimethylformamide (1:1) (5.0 mL) were added 1,2-diamino-3-chloro-pyrazinium mesitylenate (0.59 g, 0.0017 mol) and diisopropylethylamine (791 mg, 6.1 mmol). The reaction mixture was stirred for 1 hour. EDCI (93 mg, 5 mmol) was added and the solution stirred for 2 hours at room temperature before being concentrated to dryness. The residue was taken up in water and stirred for 5

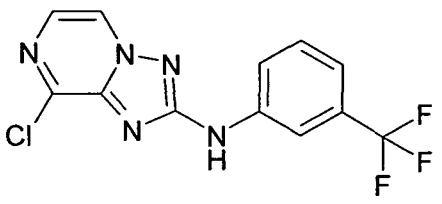
minutes and the solid precipitated was filtered, washed with water, dried to get the product as a light brown solid (0.25 g, 75%). TLC: pet ether / ethyl acetate (6/4) R_f – 0.4. LCMS (method A): mass found ($M+H^+$, 274.0), Rt (min): 4.47 area % 98.0 (max), 98.47 (254 nm); ^1H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H), 8.95 (d, J = 4.28 Hz, 1H), 7.91 (d, J = 4.32 Hz, 1H), 7.28 (s, 2H), 6.58 (s, 1H), 2.24(s, 6H).

8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-(3,5-dimethoxy-phenyl)-amine ("B2")



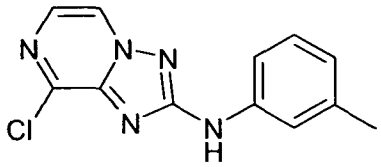
To a solution of 3,5-dimethoxyisothiocyanate (0.4 g, 2 mmol) in dichloromethane and N, N-dimethylformamide (1:1) (25.0 mL) were added 1,2-diamino-3-chloro-pyrazinium mesitylenate (0.98 g, 2.8 mmol) and diisopropylethylamine (1.32 g, 10 mmol). The reaction mixture was stirred for 1 hour, followed by addition of EDCI (0.79 g, 4 mmol). The reaction was stirred for 5 hours at room temperature and concentrated to dryness. The residue was taken up in water and stirred for 15 minutes. The solid precipitated was filtered, washed with water, dried to get the product as a light brown solid (0.5 g, 80%). TLC: chloroform/methanol (9/1) R_f – 0.5. LCMS (method A): mass found ($M+H^+$, 306.0), Rt (min): 3.81 area % 98.7 (max), 98.77 (254 nm); ^1H NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H), 8.95 (d, J = 4.32 Hz, 1H), 7.91 (d, J = 4.32 Hz, 1H), 6.91 (m, 2H), 6.13 (m, 1H), 3.73 (s, 6H).

8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-(3-trifluoromethyl-phenyl)-amine ("B3")



To a solution of 3-(trifluoromethyl)isothiocyanate (0.6 g, 3 mmol) in dichloromethane and N,N-dimethylformamide (1:1) (25.0 mL) were added 1,2-diamino-3-chloro-pyrazinium mesitylenate (1.42 g, 4.1 mmol) and diisopropylethylamine (1.9 g, 14.5 mmol). It was stirred for 1 hour, EDCI (1.12 g, 6 mmol) added and the reaction mixture stirred for 2 hours at room temperature. When the reaction was completed, it was concentrated to dryness and the residue that was taken up in water stirred for 5 minutes. The solid precipitated was filtered, washed with water, dried to get the product as a light brown solid (0.8 g, 87%). TLC: chloroform/methanol (9.5/0.5) R_f – 0.5. LCMS (method A): mass found ($M+H^+$, 314.0), Rt (min): 4.75 area % 95.9 (max), 96.13(254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.55 (s, 1H), 9.00 (d, J = 4 Hz, 1H), 8.07 (s, 1H), 7.97 (d, J = 4.32 Hz, 1H), 7.90 (d, J = 7.92 Hz, 1H), 7.56 (t, J = 8.04 Hz, 1H), 7.27(d, J = 7.64 Hz, 1H).

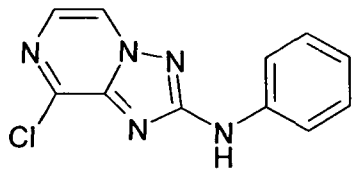
8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-m-tolyl-amine ("B4")



To a solution of m-tolylisothiocyanate (0.25 g, 1.6 mmol) in dichloromethane and N,N-dimethylformamide (1:1) (15.0 mL), 1,2-diamino-3-chloro-pyrazinium mesitylenate (0.8 g, 2.3 mmol), diisopropylethylamine (1.07 g, 8.3 mmol) were added and stirred for 1 hour. EDCI (0.64 g, 3.3 mol) was added and stirred for 6 hours at room temperature. The reaction mixture was concentrated to dryness and the residue taken up in water. It was stirred for 5 minutes and the solid precipitated was filtered, washed with water, dried to get the product as a light brown solid (0.35 g, 80.8%). TLC: chloroform/methanol (9.5/0.5) R_f – 0.5. LCMS (method A): mass found ($M+H^+$, 260.0), Rt (min): 4.13 area % 97.4 (max), 97.11(254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (s, 1H), 8.94 (d, J = 4.32

Hz, 1H), 7.92 (d, *J* = 4.28 Hz, 1H), 7.50 (d, *J* = 8.12 Hz, 1H), 7.43 (s, 1H), 7.19 (t, *J* = 7.76 Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 2.29 (s, 3H).

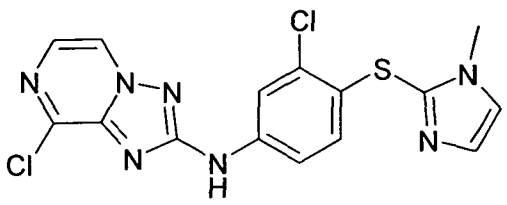
8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-phenyl-amine ("B5")



To a solution of phenylisothiocyanate (0.25 g, 1.8 mmol) in dichloromethane and N,N-dimethylformamide (1:1) (15.0 mL), 1,2-diamino-3-chloro-pyrazinium mesitylenate (0.89 g, 2.5 mmol), diisopropylethylamine (1.19 g, 9.2 mmol) were added and stirred for 1 hour. EDCI (0.7 g, 3.7 mmol) was added and stirred for 6 hours at room temperature. The reaction mixture was concentrated and the residue was taken in water and stirred for 5 minutes, the solid precipitated was filtered, washed with water, dried to get the product as a light brown solid (0.4 g, 88%). TLC: chloroform/methanol (9.5/0.5) R_f – 0.5. LCMS (method A): mass found ($M+H^+$, 246.0), Rt (min): 3.74 area % 98.2 (max), 98.39 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H), 8.95 (d, *J* = 4.28 Hz, 1H), 7.93 (d, *J* = 4.28 Hz, 1H), 7.67 (m, 2H), 7.32 (t, *J* =8.63 Hz, 2H), 6.94 (t, *J* = 7.32 Hz, 1H).

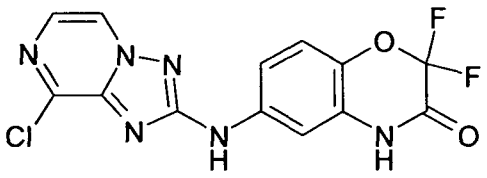
Examples "B6" – "B9" were prepared following the above procedures.

[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-(8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("B6")



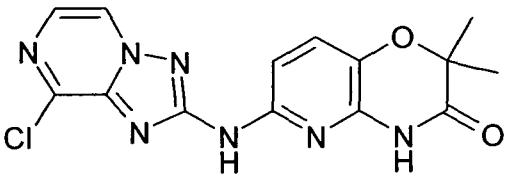
Light brown solid, 49.5 mg (yield: 73.2%), HPLC purity: 94.1%, Rt: 2.9 min, observed $[M+H]^+$ 392.0; ^1H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.97 (d, J = 4.28 Hz, 1H), 7.95 (d, J = 4.36 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.46 (m, 2H), 7.10 (s, 1H), 6.70 (d, J = 8.72 Hz, 1H), 3.62 (s, 3H).

6-(8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-2,2-difluoro-4H-benzo[1,4]oxazin-3-one ("B7")



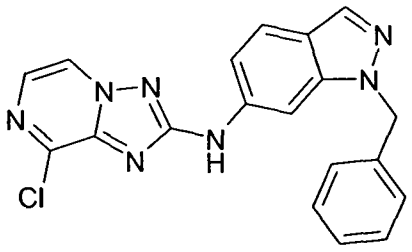
Off white solid, 16.9 mg (yield: 72.2%), HPLC purity: 97%, Rt: 3.85 min, observed $[M+H]^+$ 353.0; ^1H NMR (400 MHz, DMSO-d_6) δ 11.99 (br s, 1H), 10.31 (s, 1H), 8.88 (d, J = 4.12 Hz, 1H), 7.94 (d, J = 4.08 Hz, 1H), 7.49 (s, 1H), 7.41 (d, J = 8.84 Hz, 1H), 7.26 (m, 1H).

6-(8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-2,2-dimethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one ("B8")



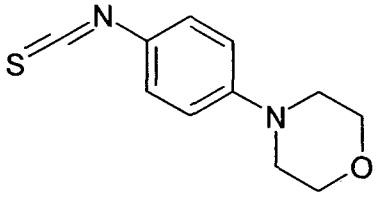
Light brown solid, 25.8 mg (yield: 71.4%), HPLC purity: 98.6%, Rt: 3.47 min, observed $[M+H]^+$ 346.0; ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (br s, 1H), 10.29 (s, 1H), 8.95 (d, J = 4.32 Hz, 1H), 7.95 (d, J = 4.36 Hz, 1H), 7.64 (d, J = 8.68 Hz, 1H), 7.41 (d, J = 8.64 Hz, 1H), 1.39 (s, 6H).

(1-Benzyl-1H-indazol-6-yl)-(8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("B9")



Light brown solid, 43.5 mg (yield: 75.3%), HPLC purity: 97.2%, Rt: 4.28 min, observed $[M+H]^+$ 376.0; ^1H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.96 (d, J = 4.28 Hz, 1H), 8.13 (s, 1H), 7.97 (m, 2H), 7.68 (d, J = 8.72 Hz, 1H), 7.26 (m, 6H), 5.56 (s, 2H).

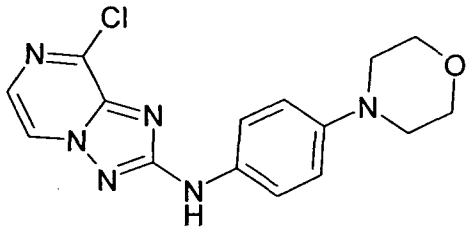
4-(4-Isothiocyanato-phenyl)-morpholine



To a stirring solution of 4-morpholino-4-yl-phenylamine (2 g, 11.22 mmol) and diisopropylethylamine (2.89 g, 22.42 mmol) in dry dichloromethane (100 ml) at 0 ^0C under N_2, thiophosgene (1.54 g, 13.46 mmol) in dichloromethane is added dropwise and stirred for 30 minutes. The reaction mixture is quenched with water (100 ml) and the layers are separated, the organic layer is washed with water (50 ml X2) and dried over anhydrous $MgSO_4$ to get the product as brown crystalline solid (2.4 g, 97.56%); TLC: pet ether/ethyl acetate (6/4) R_f – 0.5;

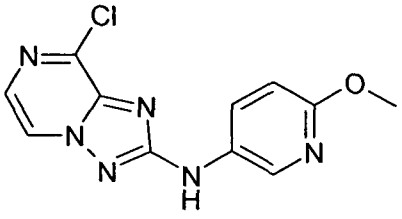
^1H-NMR (400 MHz, DMSO-d_6): δ [ppm] 7.29 (d, *J* = 6.92 Hz, 2H), 6.95 (d, *J* = 6.96 Hz, 2H), 3.71 (t, *J* = 4.96 Hz, 4H), 3.14 (t, *J* = 4.84 Hz, 4H).

(8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-(4-morpholin-4-yl-phenyl)-amine



To a solution of 4-morpholinophenylisothiocyanate (2 g, 8.99 mmol) in dry dichloromethane (200 ml), 1,2-diamino-pyrazinium mesitylenate (3.86 g, 11.24 mmol), diisopropylethylamine (5.81 g, 44.99 mmol) and EDCI (3.44 g, 17.98 mmol) are added and stirred for 6 hours. The reaction mixture is concentrated and the residue is taken in water (100 ml), triturated and filtered, washed with water (50 ml X2) and dried, the crude solid is purified by silica column using (60-120) mesh to get the titled product as light brown solid (2.5g, 84.17%); TLC: chloroform/methanol (9.5/0.5) R_f – 0.3; HPLC puritiy (method A) 98%; Rt (min): 2.21; LCMS: mass found (M+, 331.0), Rt (min): 2.08; ^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] 9.85 (s, 1H), 8.90 (d, J = 4.32 Hz, 1H), 7.90 (d, J = 4.32 Hz, 1H), 7.52 (dd, J = 7.04, 2.00 Hz, 2H), 6.93 (d, J = 9.04 Hz, 2H), 3.73 (t, J = 4.92 Hz, 4H), 3.02 (t, J = 4.80 Hz, 4H).

(8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-(6-methoxy-pyridin-3-yl)-amine

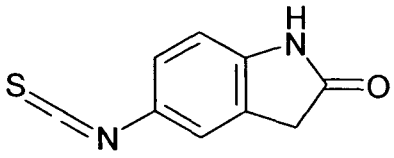


To a solution of 2-methoxypyridyl-5-isothiocyanate (3 g, 18.07 mmol) in dry dichloromethane (200 ml), 1,2-diamino-pyrazinium mesitylenate (7.77 g, 22.5 mmol), diisopropylethylamine (11.67 g, 90.35 mmol) and EDCI (3.44 g, 36.14 mmol) are added and stirred for 6 hours. The reaction mixture is concentrated and the residue is taken in water(100 ml), triturated and filtered, washed with water (50 ml X2) and 50% diethylether in hexane to get the titled product as light brown solid (4 g, 80.32 %); TLC: chloroform/methanol (9.5/0.5) R_f – 0.3;

HPLC purity (method A) 98%, Rt (min): 2.41; LCMS: mass found (M+, 277.0), Rt (min): 2.36);

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] 10.02 (s, 1H), 8.91 (d, *J* = 4.32 Hz, 1H), 8.46 (d, *J* = 2.72 Hz, 1H), 7.97 (dd, *J* = 8.88, 2.84 Hz, 1H), 7.93 (d, *J* = 4.32 Hz, 1H), 6.83 (d, *J* = 8.88 Hz, 1H), 3.81 (s, 3H).

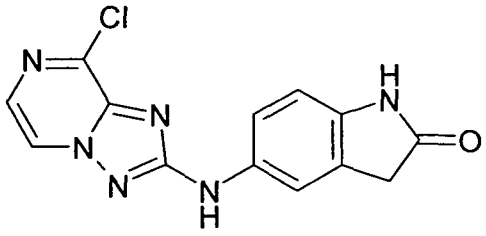
5-Isothiocyanato-1,3-dihydro-indol-2-one



To a stirring solution of 5-amino-1,3-dihydro-indol-2-one hydrochloride (2 g, 10.83 mmol) and diisopropylethylamine (4.19 g, 32.49 mmol) in dry dichloromethane (100 ml) at 0 ^{0}C under N_2, thiophosgene (1.49 g, 10.83 mmol) in dichloromethane is added dropwise and stirred for 30 minutes. The reaction mixture is quenched with water (100 ml) and the layers are separated, the organic layer is washed with water (50 ml X2) and dried over anhydrous $MgSO_4$ to get the product as brown crystalline solid (2.03 g, 99.02 %); TLC: chloroform/methanol (9.5/0.5) R_f – 0.5;

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] 10.60 (s, 1H), 7.31 (s, 1H), 7.25 (d, *J* = 7.88 Hz, 1H), 6.82 (d, *J* = 8.24 Hz, 1H), 3.50 (s, 2H).

5-(8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one



To a solution of 5-isothiocyanato-1,3-dihydro-indol-2-one (2.3 g, 12.09 mmol) in dry dichloromethane (200ml), 1,2-diamino-pyrazinium mesitylenate (5.21 g, 15.12 mmol), diisopropylethylamine (7.81 g, 60.45 mmol) and EDCI (4.63 g, 24.18 mmol) are added and stirred for 6 hours. The reaction mixture is concentrated and the residue is taken in water (100 ml), triturated and filtered,

the crude solid is purified by silica column using (60-120) mesh to get the titled product as yellow solid (2.0 g, 55%); TLC: chloroform/methanol (9.5/0.5) R_f – 0.3; HPLC purity (method A): 97%, Rt (min): 2.40; LCMS: mass found (M+, 301.0), Rt (min): 2.36;
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] 10.24 (s, 1H), 9.95 (s, 1H), 8.92 (d, *J* = 4.32 Hz, 1H), 7.91 (d, *J* = 4.28 Hz, 1H), 7.56 (s, 1H), 7.44 (dd, *J* = 8.38, 2.20 Hz, 1H), 6.77 (d, *J* = 8.36 Hz, 1H), 3.49 (s, 2H).

General procedures for compounds

Method 1

[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("C114")
To a solution of (8-chloro-[1,2,4]triazolo[1,5-a]pyrazine-2-yl]-(3,5-dimethoxy-phenyl)-amine (0.2 g, 0.65 mmol, 1 eq) in a mixture of dimethoxy ethane (3 ml) and water (1 ml), 3-aminomethylphenyl boronic acid (0.28 g, 1.31 mmol, 2 eq), sodium carbonate (0.14 g, 1.31 mmol, 2eq)) and dichlorobis(triphenyl-phospine)palladium (II) (0.023 g, 0.03 mmol, 5%) are taken in a microwave vial and heated at 120 ^{0}C for 2 hours. The reaction mixture is concentrated and the residue is taken in dichloromethane (10 ml X1), washed with brine solution (10 ml X1), the organic layer is dried over anhydrous $MgSO_4$ and concentrated. The crude product obtained is purified by silica gel column using (230-400) mesh to get the titled product as yellow solid.

Method 2

(4-Morpholin-4-yl-phenyl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C289")
To a solution of (8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-(4-morpholin-4-yl-phenyl)-amine (0.15 g, 0.45 mmol, 1 eq) in a mixture of ethanol : toluene (1:4)

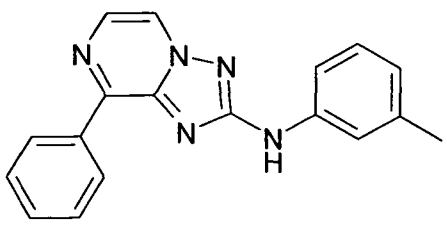
(10 ml) is taken in a dry pressure tube, palladium acetate (0.01 g, 0.045 mmol, 0.1 eq), anhydrous potassium carbonate (0.125 g, 0.90 mmol, 2 eq), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, S-Phos (0.027 g, 0.06 mmol, 0.13 eq) and 2-phenoxyphenylboronic acid (0.19 g, 0.90 mmol, 2 eq) are added and the reaction mixture is degasified with nitrogen. The reaction mixture is heated to 120 ^{0}C for 1 hour. The reaction mixture is concentrated and the residue is taken in 25% methanol in dichloromethane (50 ml) and filtered through celite to remove the inorganics and the filtrate is concentrated and purified by silica column using (230-400) mesh to get the product as pale yellow solid.

Method 3

N-{2-Methyl-3-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-3-trifluoromethyl-benzamide ("C299")

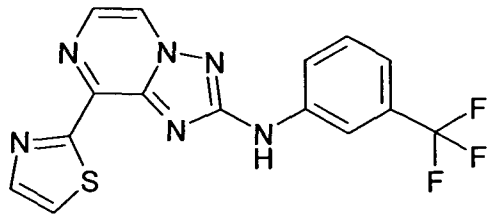
To a solution of [8-(3-amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine (0.125 g, 0.31 mmol, 1 eq) in dry dichloromethane (25 ml), triethylamine (0.062 g, 0.62 mmol, 2 eq) is added and stirred for 5 minutes, the reaction mixture is cooled and 3-(trifluoromethyl)benzoyl-chloride (0.072 g, 0.34 mmol, 1.1 eq) is added and stirred for 2 hours. The reaction mixture is quenched with water and the separated organic layer is washed with 10% aq. $NaHCO_3$ (20 ml X1), water (20 ml X1) brine solution (20 ml X1), dried over anhydrous $MgSO_4$ and concentrated. The crude product obtained is triturated with ethylacetate(10 ml) to get the product as pale yellow solid.

(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-m-tolyl-amine ("C1")



(8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-m-tolyl-amine (75 mg, 0.2 mmol), phenyl boronic acid (70 mg, 0.5 mmol), anhydrous potassium carbonate (79 mg, 0.5 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl(10 mg, 0.02 mmol) and palladium acetate (3.2 mg, 0.01 mmol) are taken in a mixture of toluene:ethanol (4:1, 3 mL) in a sealed tube and heated to 120^{0}C for 30 minutes. The reaction mixture is passed through celite and washed with methanol (10 mL). The filtrate is concentrated and purified by flash chromatography on a silica gel column using (230-400) mesh to get the product as an off white solid (44 mg, 51%). TLC: chloroform/methanol (9/1) R_f – 0.2; LCMS (method A): mass found (M+H$^+$, 302.0), Rt (min): 5.07 area % 99.7 (max), 99.6 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.99 (s, 1H), 8.91 (d, *J* = 4.24 Hz, 1H), 8.71 (m, 2H), 8.21(d, *J* = 4.24 Hz, 1H), 7.59 (m, 5H), 7.20 (m, 1H), 6.75 (d, *J* = 7.72 Hz, 1H), 2.31 (s, 3H).

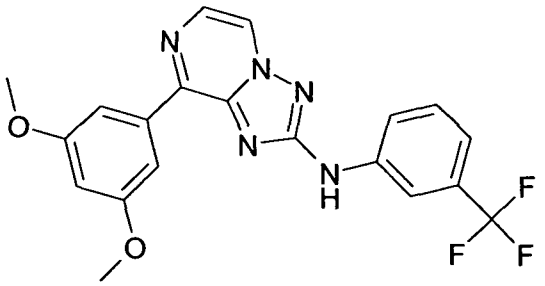
8-(1,3-thiazol-5-yl)-*N*-[3-(trifluoromethyl)-phenyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-2-amine ("C2")



8-Chloro-*N*-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*a*]pyrazin-2-amine (100 mg, 0.319 mmol), 2-thiazolyl zinc bromide (0.5 M in THF, 5 mL, 0.478 mmol), sodium carbonate (2M) (0.24 mL, 0.5 mmol) and tetrakis(triphenyl phosphine) palladium (11 mg, 0.05 mmol) are dissolved and degassed in a mixture of toluene:ethanol (1:1, 4 mL). The reaction mixture is heated 4 hours at 90^{0}C in a sealed tube. When the reaction is completed, the reaction mixture is cooled down to rt and filtrated through a celite pad and washed with ethyl acetate (10 mL). The filtrate is concentrated and purified by flash chromatography on a silica gel column using (60-120) mesh to get the product as a yellow solid (6.6 mg, 6%); LCMS

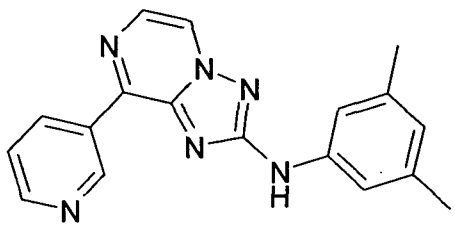
(method A): mass found ($M+H^+$, 363), Rt (min): 4.50 area % 95.5 (max), 93.5 (254 nm).

(8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine ("C3")



Following the protocol used for "C1", the title compound is obtained starting from (8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluromethyl-phenyl)-amine and dimethoxy phenyl boronic acid as an off white solid (41 mg, 41%). TLC: chloroform/methanol (9/1) R_f – 0.2; LCMS (method A): mass found ($M+H^+$, 416.0), Rt (min): 5.50 area % 99.7 (max), 99.18(254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.45 (s, 1H), 8.95 (d, J = 4.2 Hz, 1H), 8.25 (d, J = 4.24 Hz, 1H), 8.14 (s, 1H), 7.96 (m, 3H), 7.55 (t, J = 7.88 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 6.70 (m, 1H), 3.85 (s, 6H).

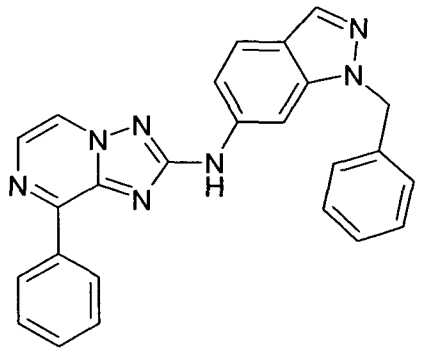
(3,5-Dimethyl-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C4")



Following the protocol used for "C1", the title compound is obtained starting from (8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3,5-dimethylphenyl)-amine and 3-pyridyl boronic acid as a a light brown solid (49 mg, 57%); TLC: chloroform:methanol (9/1) R_f – 0.2; LCMS (method A): mass found ($M+H^+$, 317.0), Rt (min): 3.52 area % 98.6 (max), 98.8 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ

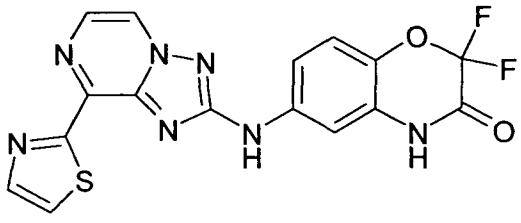
[ppm] 9.95 (s, 1H), 9.84 (d, J = 2 Hz, 1H), 8.96 (m, 2H), 8.73 (m, 1H), 8.25(d, J = 4.2 Hz, 1H), 7.62 (m, 1H), 7.36 (s, 2H), 6.59 (s, 1H), 2.26 (s, 6H).

(1-Benzyl-1H-indazol-6-yl)-(8-phenyl-[1,2,4]trizolo[1,5-a]pyrazin-2-yl)-amine ("C5")



Following the protocol used for "C1", the title compound is obtained starting from (1-benzyl-1H-indazol-6-yl)-(8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine and phenyl boronic acid as a a yellow solid (22 mg, 19.6%); TLC: chloroform/methanol (9/1) R_f – 0.2. LCMS (method A): mass found ($M+H^+$, 418.0), Rt (min): 4.99 area % 92.7 (max), 93.2 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.33 (s, 1H), 8.93 (d, J = 4.2 Hz, 1H), 8.74 (m, 2H), 8.30 (m, 2H), 7.98 (s, 1H), 7.68 (d, J = 8.64 Hz, 1H), 7.54 (m, 3H), 7.30 (m, 6H), 5.59 (s, 2H).

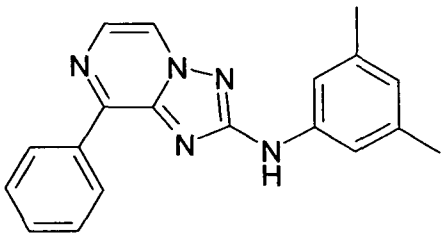
2,2-Difluoro-6-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-4H-benzo[1,4]oxazin-3-one ("C6")



Following the protocol used for "C2", the title compound is obtained starting from 6-(8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-2,2-difluoro-4H-benzo[1,4]oxazin-3-one and 2- thiazolyl zinc bromide as an orange solid (20.3 mg, 18.2%); LCMS (method A): mass found ($M+H^+$, 395), Rt (min): 3.52 area % 90.4 (max), 91.7 (254 nm).

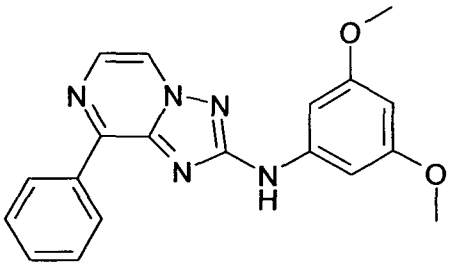
Examples "C7" – "C13", "C15" – "C23" and "C25" – "C27" are prepared following the protocol used for "C1". Examples "C14" and "C24" are prepared following the protocol used for "C2".

(3,5-Dimethyl-phenyl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C7")



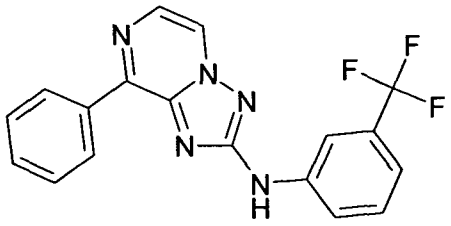
Off white solid, 57.1 mg (yield: 65.7%), HPLC purity: 98.8%, Rt: 5.35 min, observed $[M+H]^+$ 316.3; ^1H NMR (400 MHz, DMSO) δ [ppm] 9.87 (s, 1H), 8.90 (d, J = 4.2, 1H), 8.77 – 8.70 (m, 2H), 8.22 (d, J = 4.2, 1H), 7.75 – 7.50 (m, 3H), 7.38 (s, 2H), 6.60 (s, 1H), 2.28 (s, 6H).

(3,5-Dimethoxy-phenyl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C8")



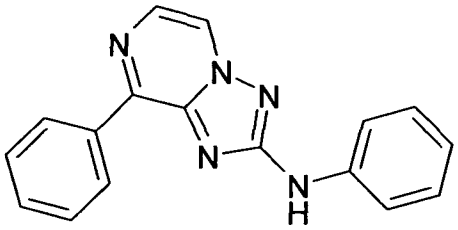
Off white solid, 43.7 mg (yield: 51.1%), HPLC purity: 92.4%, Rt: 4.76 min, observed $[M+H]^+$ 348.0; ^1H NMR (400 MHz, DMSO) δ [ppm] 10.00 (s, 1H), 8.90 (d, J = 4.2, 1H), 8.78 – 8.67 (m, 2H), 8.24 (d, J = 4.2, 1H), 7.68 – 7.41 (m, 3H), 7.05 (d, J = 2.2, 2H), 6.13 (t, J = 2.2, 1H), 3.77 (s, 6H).

(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine ("C9")



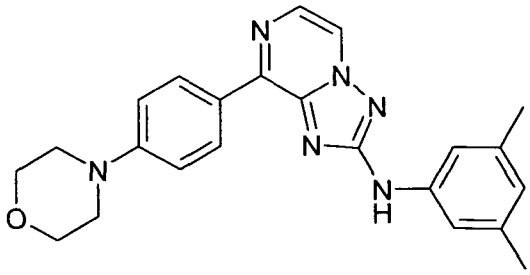
Yellow solid, 42.1 mg (yield: 49.4%), HPLC purity: 94.5%, Rt: 5.47 min, observed $[M+H]^+$ 356.0.

Phenyl-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C10")



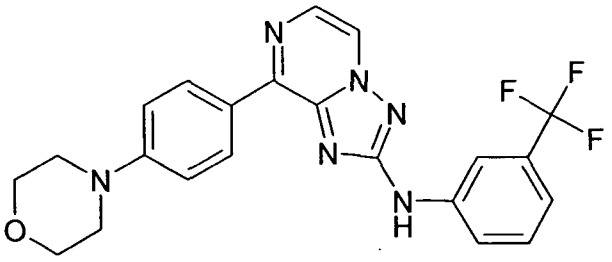
Off white solid, 27.3 mg (yield: 31%), HPLC purity: 97.3%, Rt: 4.75 min, observed $[M+H]^+$ 288.0.

(3,5-Dimethyl-phenyl)-[8-(4-morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C11")



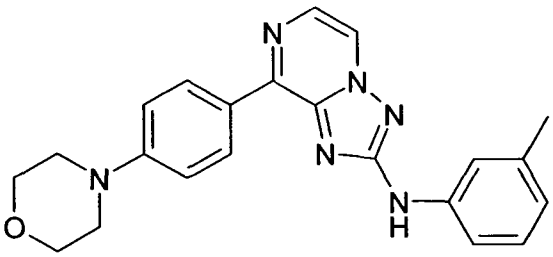
Yellow solid, 28.01 mg (yield: 25.4%), HPLC purity: 94%, Rt: 4.81 min, observed $[M+H]^+$ 401.0.

[8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3-trifluoromethyl-phenyl)-amine ("C12")



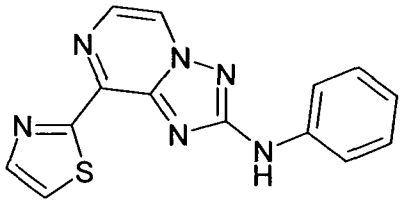
Off white solid, 9.57 mg (yield: 7.9%), HPLC purity: 97.9%, Rt: 5.01 min, observed $[M+H]^+$ 441.0.

[8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-m-tolyl-amine ("C13")



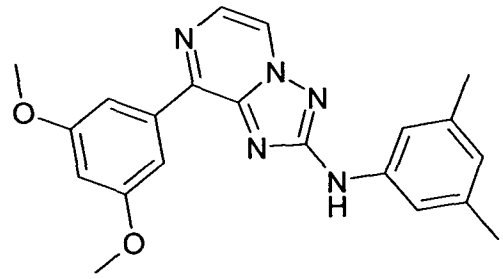
Light brown solid, 51.05 mg (yield: 48%), HPLC purity: 96.6%, Rt: 4.53 min, observed $[M+H]^+$ 387.0.

Phenyl-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C14")



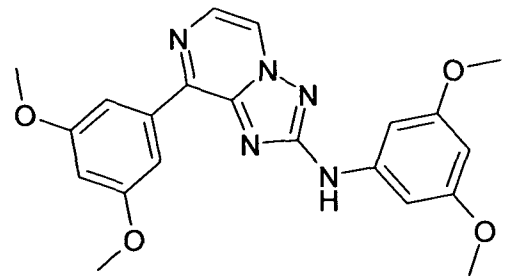
Orange solid, 2.7 mg (yield: 3%), HPLC purity: 95.6%, Rt: 3.68 min, observed $[M+H]^+$ 295.0.

[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethyl-phenyl)-amine ("C15")



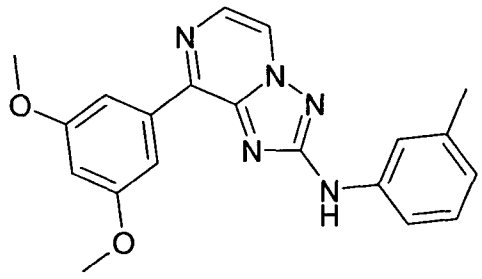
Light brown solid, 25.5 mg (yield: 24.7%), HPLC purity: 97.2%, Rt: 5.39 min, observed $[M+H]^+$ 376.0.

(3,5-Dimethoxy-phenyl)-[8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C16")



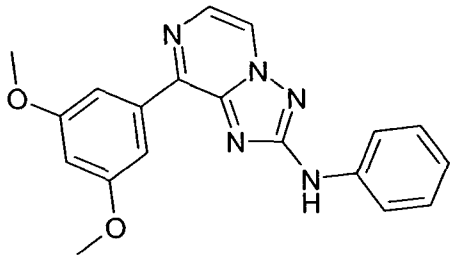
Off white solid, 40.9 mg (yield: 39.8%), HPLC purity: 93.7%, Rt: 4.92 min, observed $[M+H]^+$ 408.0.

[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-m-tolyl-amine ("C17")



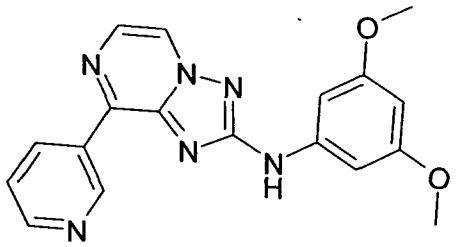
Off white solid, 47.4 mg (yield: 45.2%), HPLC purity: 98%, Rt: 5.16 min, observed $[M+H]^+$ 362.0.

[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-phenyl-amine ("C18")



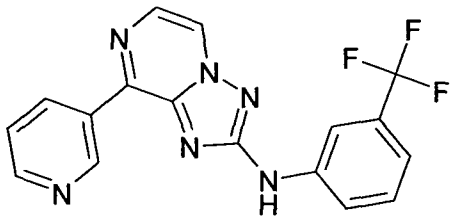
Off white solid, 19.5 mg (yield: 18.3%), HPLC purity: 96.6%, Rt: 4.88 min, observed $[M+H]^+$ 348.0.

(3,5-Dimethoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C19")



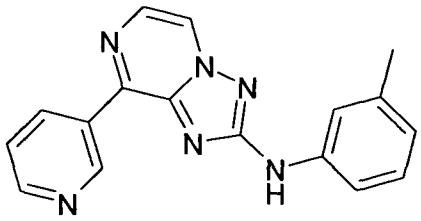
Light brown solid, 21.9 mg (yield: 25.5%), HPLC purity: 97.4%, Rt: 3.01 min, observed $[M+H]^+$ 349.0; ^1H NMR (400 MHz, DMSO) δ [ppm] 10.04 (s, 1H), 9.88 (dd, J = 2.2, 0.7, 1H), 9.07 – 8.91 (m, 2H), 8.73 (dd, J = 4.8, 1.7, 1H), 8.28 (d, J = 4.2, 1H), 7.62 (ddd, J = 8.1, 4.8, 0.8, 1H), 7.04 (d, J = 2.2, 2H), 6.14 (t, J = 2.2, 1H), 3.77 (s, 6H).

(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine ("C20")



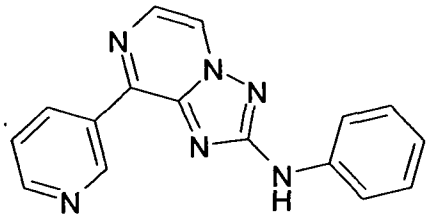
Off white solid, 30 mg (yield: 35.1%), HPLC purity: 98.7%, Rt: 3.69 min, observed $[M+H]^+$ 357.0.

(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-m-tolyl-amine ("C21")



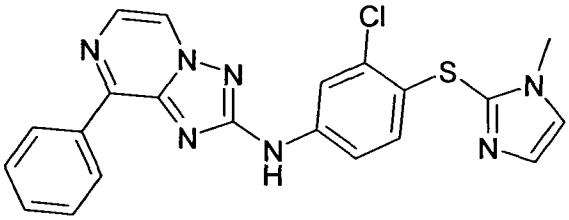
Yellow solid, 42.7 mg (yield: 48.7%), HPLC purity: 97.9%, Rt: 3.14 min, observed $[M+H]^+$ 303.0.

Phenyl-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C22")



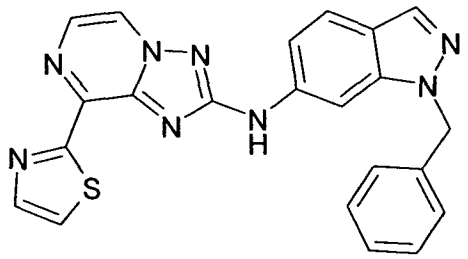
Yellow solid, 21.4 mg (yield: 24.2%), HPLC purity: 97.2%, Rt: 2.84 min, observed $[M+H]^+$ 289.0.

[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C23")



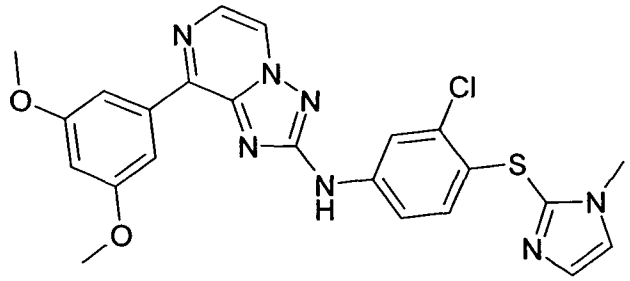
Off white solid, 18.77 mg (yield: 14.1%), HPLC purity: 97.3%, Rt: 3.76 min, observed $[M+H]^+$ 434.0.

(1-Benzyl-1H-indazol-6-yl)-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C24")



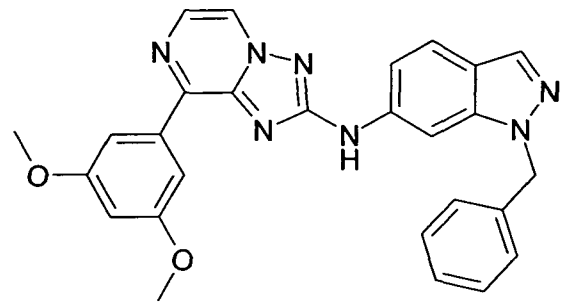
Yellow solid, 4 mg (yield: 2.9%), HPLC purity: 99.8%, Rt: 4.2 min, observed $[M+H]^+$ 425.0.

[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-[8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C25")



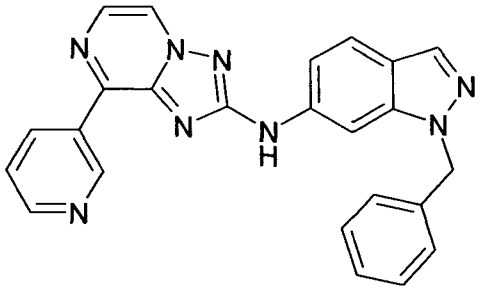
Light brown solid, 20.9 mg (yield: 13.8%), HPLC purity: 95.4%, Rt: 3.85 min, observed $[M+H]^+$ 494.0.

(1-Benzyl-1H-indazol-6-yl)-[8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C26")



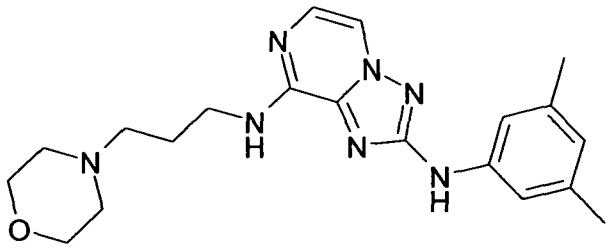
Off white solid, 76.28 mg (yield: 59.8%), HPLC purity: 93.6%, Rt: 5.14 min, observed $[M+H]^+$ 478.3.

(1-Benzyl-1H-indazol-6-yl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C27")



Yellow solid, 6.22 mg (yield: 5.5%), HPLC purity: 96.5%, Rt: 3.49 min, observed $[M+H]^+$ 419.0.

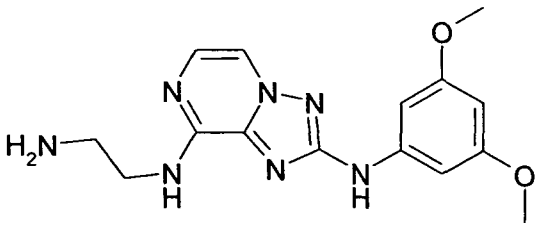
N^2-(3,5-Dimethyl-phenyl)-N^8-(3-morpholin-4-yl-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C28")



8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3,5-dimethyl-phenyl)-amine (0.05 g, 0.1 mmol) and 3-morpholinopropylamine (1 mL) are taken in a sealed tube and heated at 130 ^{0}C for 12 hours. The reaction mixture is concentrated and purified by flash column chromatography on silica gel (230-400) mesh to get the product as a brown gummy solid (0.045 g, 64.5%); TLC: chloroform / methanol (9/1) R_f – 0.2; LCMS (method A): mass found ($M+H^+$, 382.0), Rt (min): 3.16 area % 98.9 (max), 99.1 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.30 (s, 1H), 7.95 (d, J = 4.56 Hz, 1H), 7.41 (m, 2H), 7.28 (s, 2H), 6.51 (s, 1H), 3.57 (t, J = 4.52 Hz, 4H), 3.49 (m, 2H), 2.49 (m, 6H), 2.23 (s, 6H), 1.77 (m, 2H).

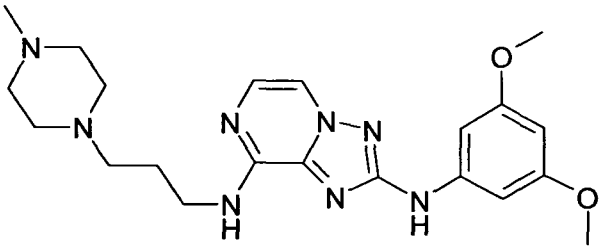
Examples "C29" – "C57" are prepared starting from the corresponding amines following the protocol for "C28".

N^8-(2-Amino-ethyl)-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C29")



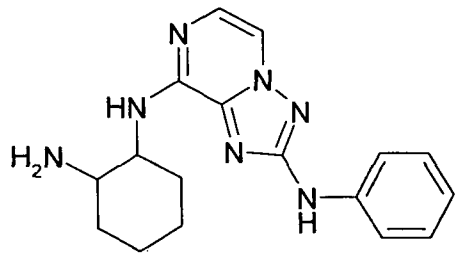
Off white solid, 23.2 mg (yield: 42.9%), HPLC purity: 98.1%, Rt: 2.75 min, observed $[M+H]^+$ 330.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.49 (s, 1H), 8.06 (d, J = 4.48 Hz, 1H), 7.64 (br s, 2H), 7.46 (d, J = 4.56 Hz, 2H), 6.93 (m, 2H), 6.08 (m, 1H), 3.72 (s, 6H), 3.69 (m, 2H), 3.07 (t, J = 6.08 Hz, 2H).

N^2-(3,5-Dimethoxy-phenyl)-N^8-[3-(4-methyl-piperazin-1-yl)-propyl]-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C30")



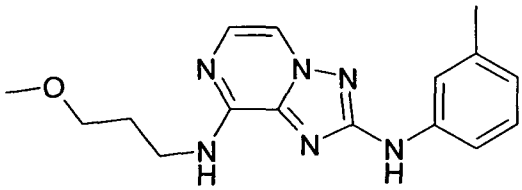
Light brown solid, 55.1 mg (yield: 78.7%), HPLC purity: 99%, Rt: 2.56 min, observed $[M+H]^+$ 427.2; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.44 (s, 1H), 7.95 (d, J = 4.48 Hz, 1H), 7.43 (d, J = 4.48 Hz, 1H), 7.34 (m, 1H), 6.91 (m, 2H), 6.06 (m, 1H), 3.72 (s, 6H), 3.47 (m, 2H), 2.35 (m, 10H), 2.13 (s, 3H), 1.76 (m, 2H).

N^8-(2-Amino-cyclohexyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C31")



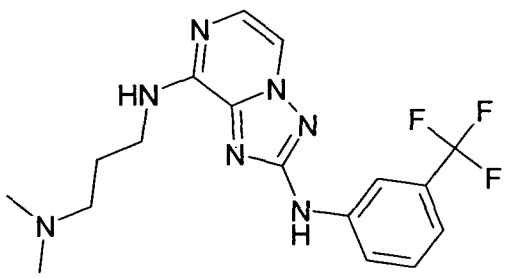
Light brown solid, 6.22 mg (yield: 9.4%), HPLC purity: 98.9%, Rt: 3.03 min, observed $[M+H]^+$ 324.3; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.50 (s, 1H), 7.99 (m, 1H), 7.71 (d, J = 8 Hz, 1H), 7.43 (m, 1H), 7.27 (m, 2H), 7.14 (d, J = 7.64 Hz, 1H), 6.87 (m, 1H), 3.91 (m,1H), 2.94 (m, 1H), 1.98 (m, 2H), 1.69 (m, 2H), 1.59 (m, 1H), 1.38 (m, 4H).

N^8-(3-Methoxy-propyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C32")



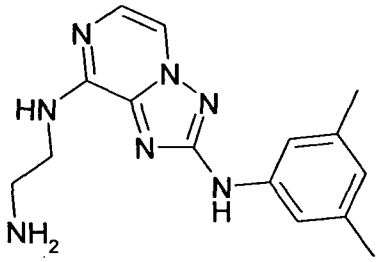
Off white solid, 17.8 mg (yield: 29.4%), HPLC purity: 99.3%, Rt: 3.3 min, observed $[M+H]^+$ 313.3; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.43 (s, 1H), 7.95 (d, J = 3.64 Hz, 1H), 7.53 (d, J = 8.22 Hz, 1H), 7.44 (s, 2H), 7.28 (m, 1H), 7.14 (m, 1H), 6.70 (d, J = 7.04 Hz, 1H), 3.52 (m, 2H), 3.41 (m, 2H), 3.24 (s, 3H), 2.28 (s, 3H), 1.86 (m, 2H).

N^8-(3-Dimethylamino-propyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C33")



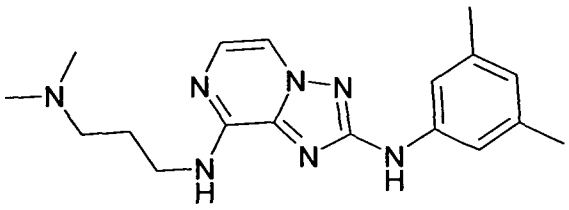
Off white solid, 44.7 mg (yield: 73.6%), HPLC purity: 99.2%, Rt: 3.42 min, observed $[M+H]^+$ 380.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.94 (s, 1H), 8.03 (m, 2H), 7.96 (s, 1H), 7.57 (t, J = 5.84, 1H), 7.48 (m, 2H), 7.19 (d, J = 7.68 Hz, 1H), 3.53 (m, 2H), 2.72 (m, 2H), 2.48 (s, 6H), 1.87 (m, 2H).

N^8-(2-Amino-ethyl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C34")



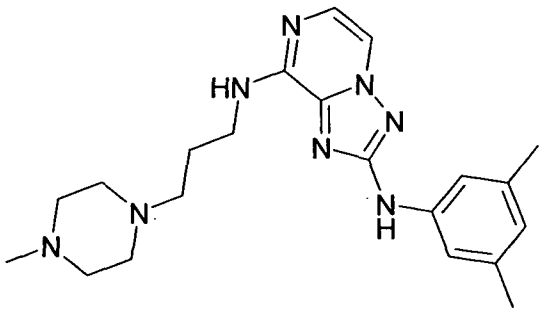
Light brown solid, 51.1 mg (yield: 93.5%), HPLC purity: 94.6%, Rt: 3.16 min, observed $[M+H]^+$ 298.3.

N^8-(3-Dimethylamino-propyl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C35")



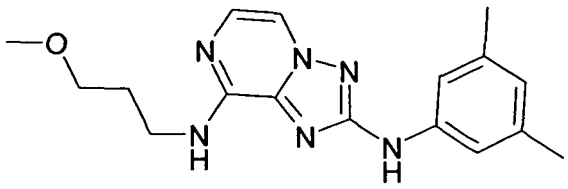
Brown gummy solid, 17.5 mg (yield: 28.1%), HPLC purity: 97.9%, Rt: 3.13 min, observed $[M+H]^+$ 340.3.

N^2-(3,5-Dimethyl-phenyl)-N^8-[3-(4-methyl-piperazin-1-yl)-propyl]-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C36")



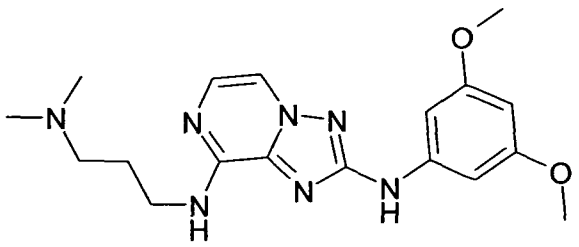
Brown gummy solid, 53.8 mg (yield: 74.3%), HPLC purity: 90.8%, Rt: 2.98 min, observed $[M+H]^+$ 395.3.

N^2-(3,5-Dimethyl-phenyl)-N^8-(3-methoxy-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C37")



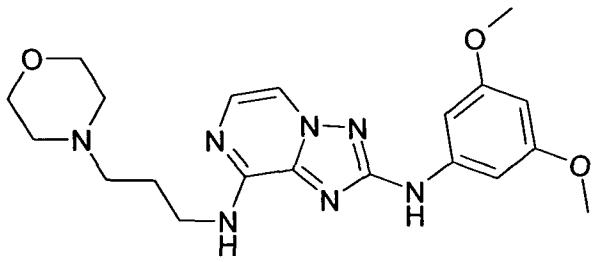
Brown gummy solid, 37.8 mg (yield: 63.1%), HPLC purity: 97.8%, Rt: 3.59 min, observed $[M+H]^+$ 327.3.

N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-dimethylamino-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C38")



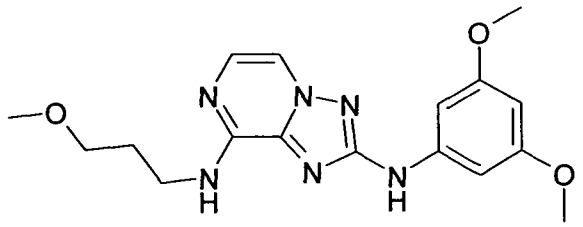
Brown gummy solid, 55.5 mg (yield: 90.9%), HPLC purity: 98.4%, Rt: 2.72 min, observed $[M+H]^+$ 372.3.

N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-morpholin-4-yl-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C39")



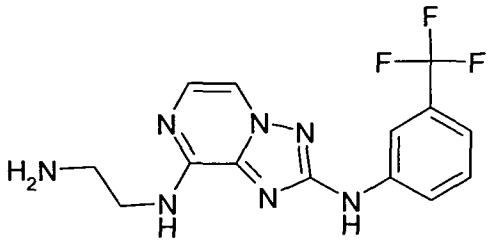
Light brown solid, 60.7 mg (yield: 89.4%), HPLC purity: 98.3%, Rt: 2.78 min, observed $[M+H]^+$ 414.3.

N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-methoxy-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C40")



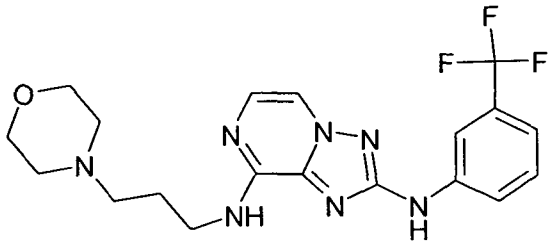
Brown gummy solid, 56 mg (yield: 95.1%), HPLC purity: 97.7%, Rt: 3.13 min, observed $[M+H]^+$ 359.3.

N^8-(2-Amino-ethyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C41")



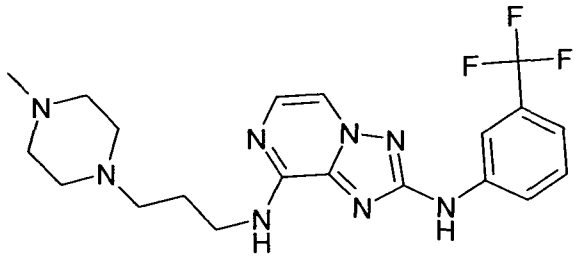
Light brown solid, 70.4 mg (yield: 86.9%), HPLC purity: 94.9%, Rt: 3.44 min, observed $[M+H]^+$ 338.0.

N^8-(3-Morpholin-4-yl-propyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C42")



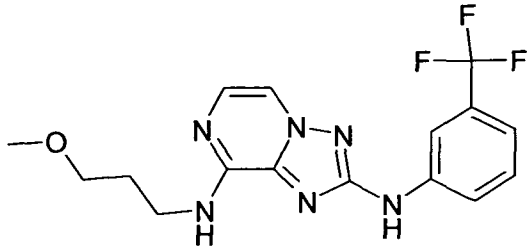
Off white solid, 48.8 mg (yield: 72.4%), HPLC purity: 97.1%, Rt: 3.42 min, observed $[M+H]^+$ 422.0.

N^8-[3-(4-Methyl-piperazin-1-yl)-propyl]-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C43")



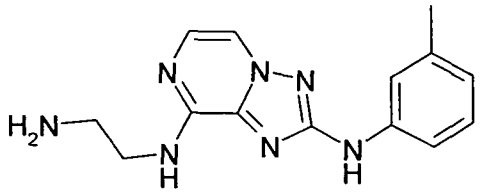
Brown gummy solid, 48.7 mg (yield: 70%), HPLC purity: 96.9%, Rt: 3.23 min, observed $[M+H]^+$ 435.3.

N^8-(3-Methoxy-propyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C44")



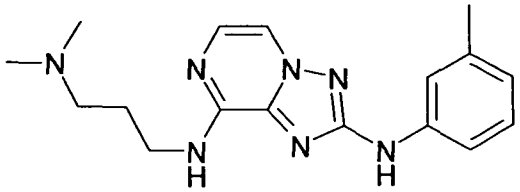
Light brown solid, 44.2 mg (yield: 75.4%), HPLC purity: 99.5%, Rt: 3.81 min, observed $[M+H]^+$ 367.0.

N^8-(2-Amino-ethyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C45")



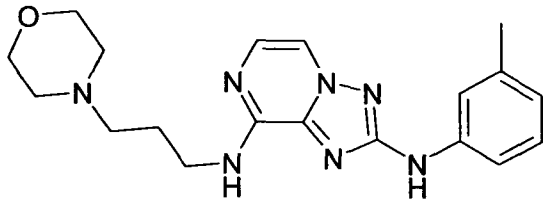
Off white solid, 16.54 mg (yield: 30.2%), HPLC purity: 93.7%, Rt: 2.8 min, observed $[M+H]^+$ 284.0.

N^8-(3-Dimethylamino-propyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C46")



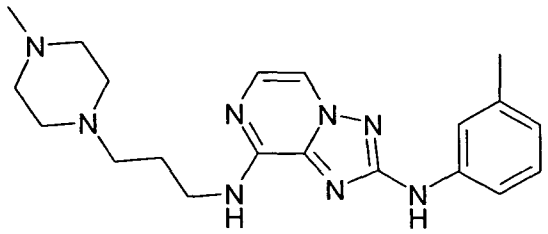
Off white solid, 49.2 mg (yield: 78.1%), HPLC purity: 99.2%, Rt: 2.77 min, observed $[M+H]^+$ 326.3.

N^8-(3-Morpholin-4-yl-propyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C47")



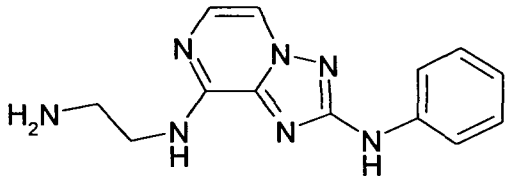
Brown gummy solid, 11.06 mg (yield: 15.6%), HPLC purity: 99.2%, Rt: 2.88 min, observed $[M+H]^+$ 368.3.

N^8-[3-(4-Methyl-piperazin-1-yl)-propyl]-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C48")



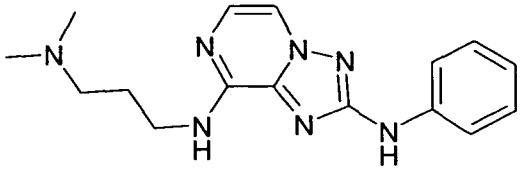
Brown gummy solid, 30.38 mg (yield: 41.3%), HPLC purity: 98.3%, Rt: 2.73 min, observed $[M+H]^+$ 381.3.

N^8-(2-Amino-ethyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C49")



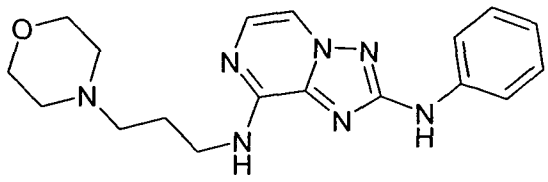
Off white solid, 7.18 mg (yield: 13%), HPLC purity: 92.9%, Rt: 2.49 min, observed $[M+H]^+$ 270.0.

N^8-(3-Dimethylamino-propyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C50")



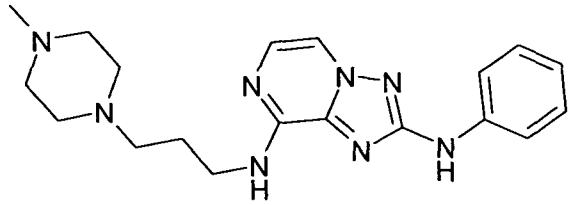
Off white solid, 27.69 mg (yield: 43.4%), HPLC purity: 96.8%, Rt: 2.52 min, observed $[M+H]^+$ 312.3.

N^8-(3-Morpholin-4-yl-propyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C51")



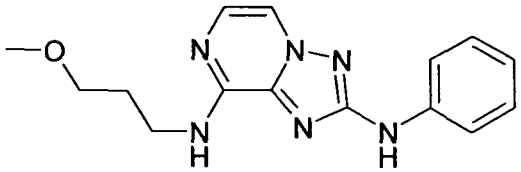
White solid, 18.28 mg (yield: 25.4%), HPLC purity: 98.8%, Rt: 2.58 min, observed $[M+H]^+$ 354.3.

N^8-[3-(4-Methyl-piperazin-1-yl)-propyl]-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C52")



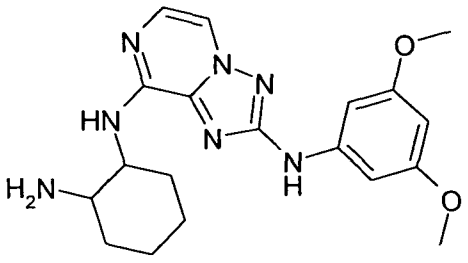
Light brown solid, 64.4 mg (yield: 85.8%), HPLC purity: 97.4%, Rt: 2.38 min, observed $[M+H]^+$ 367.3.

N^8-(3-Methoxy-propyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C53")



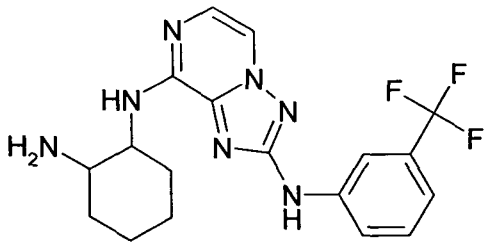
White solid, 29.65 mg (yield: 48.5%), HPLC purity: 98.6%, Rt: 2.96 min, observed $[M+H]^+$ 299.3.

N^8-(2-Amino-cyclohexyl)-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C54")



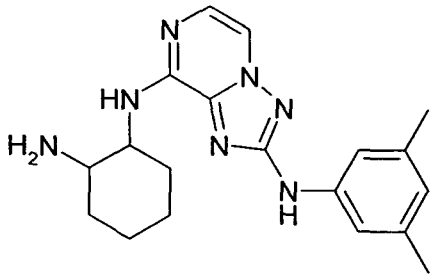
Light brown solid, 31.1 mg (yield: 49.4%), HPLC purity: 97.2%, Rt: 3.2 min, observed $[M+H]^+$ 384.3.

N^8-(2-Amino-cyclohexyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C55")



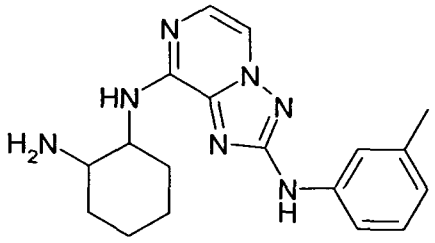
Orange solid, 29 mg (yield: 46.3%), HPLC purity: 96%, Rt: 3.76 min, observed $[M+H]^+$ 392.0.

N^8-(2-Amino-cyclohexyl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C56")



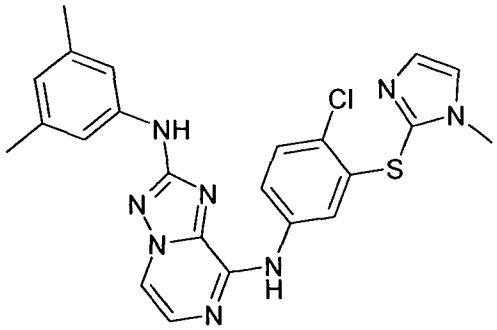
Light brown solid, 23.2 mg (yield: 36%), HPLC purity: 95.7%, Rt: 4.13 min, observed $[M+H]^+$ 352.3.

N^8-(2-Amino-cyclohexyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C57")



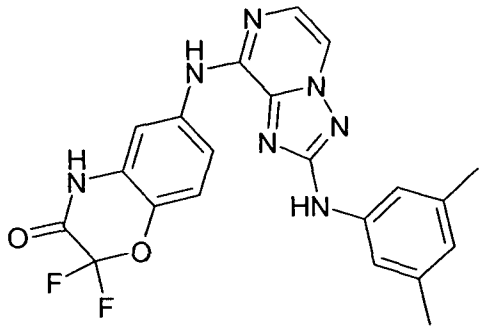
Light brown solid, 8.54 mg (yield: 13.1%), HPLC purity: 95.1%, Rt: 3.3 min, observed $[M+H]^+$ 338.3.

N^8-{3-Chloro-4-[(1-methyl-1*H*-imidazol-2-yl)thio]phenyl}-*N*^{2}-(3,5-dimethyl-phenylamino) [1,2,4]triazolo[1,5-*a*]pyrazine-2,8-diamine ("C58")



8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl-(3,5-dimethyl-phenyl)-amine (0.1 g, 0.3 mmol), tris(dibenzylideneacetone)dipalladium(0) (14.0 mg, 0.01 mmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (14.4 mg, 0.03 mmol) and 3-chloro-4-[(1-methyl-1*H*-imidazol-2-yl)thio]aniline (96.6 mg, 0.4 mmol) are taken in dry 1,4 dioxane (3 mL). Lithiumhexamethyldiisilylamide (1M in tetrahydrofuran) (0.15 mL, 0.1 mmol) is added and the reaction mixture irradiated in the microwave at 150^{0}C for 45 minutes. The reaction mixture is then quenched with dry methanol (1 mL) and passed through a celite pad. The filtrate is concentrated and purified by flash column chromatography column using silica gel (230-400) mesh to get the titled product as an off white solid (27 mg, 10.4%); TLC: pet ether/ethylacetate (6/4) R_f - 0.4. LCMS (method A): mass found (M+H$^+$, 477.0), Rt (min): 4.39 area % 90.1 (max), 91.0 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.69 (s, 1H), 9.38 (s, 1H), 8.30 (t, *J* = 4.76 Hz, 2H), 7.79 (m, 1H), 7.61 (d, *J* = 4.48 Hz, 1H), 7.50 (m, 1H), 7.33 (s, 2H), 7.12 (m, 1H), 6.61 (m, 1H), 6.54 (s, 1H), 3.63(s, 3H), 2.49(s, 6H) .

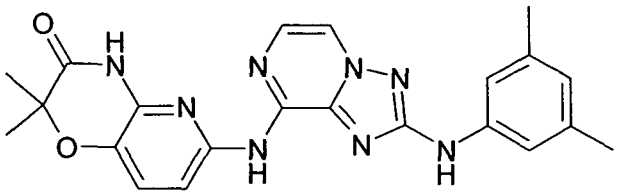
6-({2-[(3,5-Dimethylphenyl)amino][1,2,4]triazolo[1,5-*a*]pyrazin-8-yl}amino)-2,2-difluoro-2*H*-1,4-benzoxazin-3(4*H*)-one ("C59")



8-Chloro-[1,2,4] triazolo[1,5-a]pyrazin-2-yl-(3,5-dimethyl-phenyl)-amine (0.075 g, 0.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.01 g, 0.01 mmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.01 g, 0.02 mmol) and 6-amino-2,2-difluoro-2*H*-1,4-benzoxazin-3(4*H*)-one (0.049 g, 0.2 mmol) are taken in dry 1,4 dioxane (2 mL). Sodiumhexamethyldiisilylamide (1M in tetrahydrofuran) (0.27 mL, 0.2 mmol) is added and the reaction irradiated in the microwave at 150^{0}C for 30 minutes. The reaction mixture is quenched with dry methanol (1 mL) and passed through a celite pad. The filtrate is concentrated and purified by flash column chromatography using Silica gel (230-400) mesh to get the titled product as an off white solid (10 mg, 10.4%). TLC: pet ether/ethylacetate (6/4) R_f - 0.4. LCMS (method A): mass found ($M+H^+$, 438), Rt (min): 5.11 area % 93.7 (max), 94.4 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 11.99 (s, 1H), 9.63 (s, 1H), 9.39 (s, 1H), 8.27 (d, J = 4.48 Hz, 1H), 7.93 (d, J = 2.44 Hz, 1H), 7.63 (m, 1H), 7.57 (d, J = 4.48 Hz, 1H), 7.35 (s, 2H), 7.27 (d, J = 8.92 Hz, 1H), 6.55 (s, 1H), 2.25 (s, 6H).

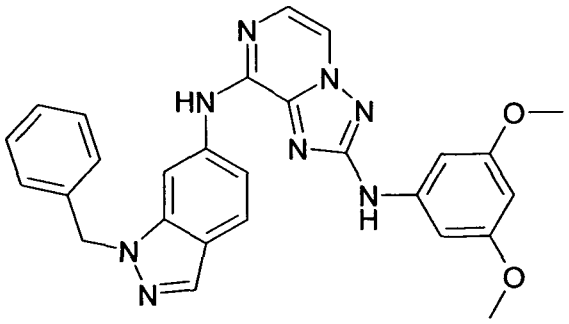
Examples "C60" – "C88" are synthesized following the general protocol used for the "C58". Preferentially, Examples "C66", "C69", "C71" and "C74" can be also synthesized using the protocol for "C59".

6-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino]-2,2-dimethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one ("C60")



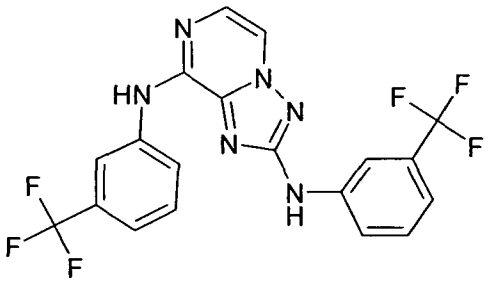
Yellow solid, 31.5 mg (yield: 13.3%), HPLC purity: 94.3%, Rt: 3.99 min, observed $[M+H]^+$ 431.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 11.15 (s, 1H), 9.62 (s, 1H), 8.34 (d, J = 4.52 Hz, 1H), 8.31 (s, 1H), 7.91 (d, J = 8.52 Hz, 1H), 7.63 (d, J = 4.52 Hz, 1H), 7.44 (d, J = 8.56 Hz, 1H), 7.29 (s, 2H), 6.55 (s, 1H), 2.25 (s, 6H), 1.42 (s, 6H).

N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C61")



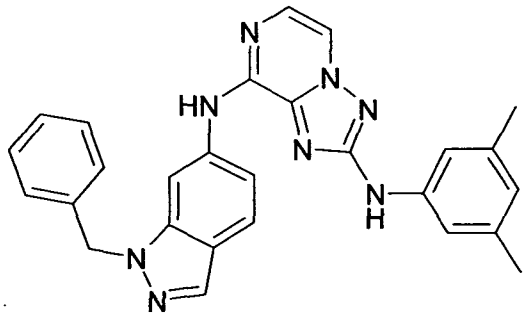
Light brown solid, 59.4 mg (yield: 24.5%), HPLC purity: 99.2%, Rt: 5.08 min, observed $[M+H]^+$ 493.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.55 (d, J = 5.36 Hz, 2H), 8.42 (s, 1H), 8.27 (d, J = 4.44 Hz, 1H), 8.01 (s, 1H), 7.67 (m, 1H), 7.62 (m, 1H), 7.57 (m, 1H), 7.30 (m, 2H), 7.25 (m, 3H), 6.97 (d, J = 2.12Hz, 2H), 6.08 (t , J = 2.04 Hz, 1H), 5.58 (s, 2H), 3.73 (s, 6H).

N^2,N^8-Bis-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C62")



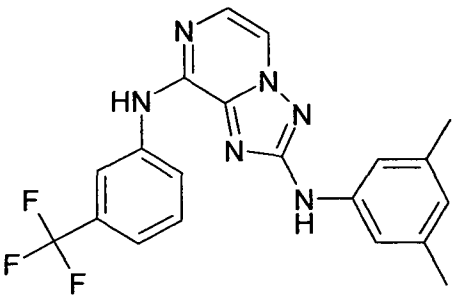
White solid, 21.1 mg (yield: 30.1%), HPLC purity: 99.5%, Rt: 6.07 min, observed $[M+H]^+$ 439.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 8.24 (br s, 1H), 7.97 (m, 2H), 7.90 (s, 1H), 7.77 (m, 1H), 7.69 (d, J = 4.52 Hz, 2H), 7.49 (m, 2H), 7.36 (d, J = 7.76 Hz, 1H), 7.30 (m, 1H), 7.03 (s, 1H).

N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C63")



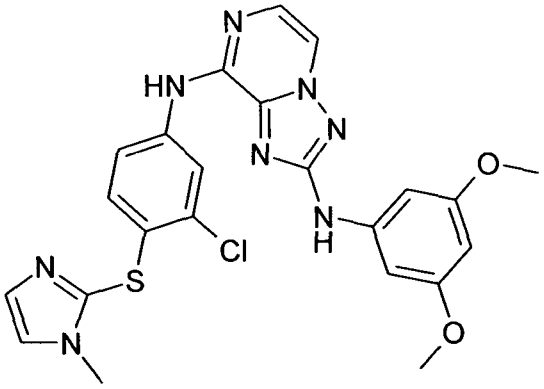
Off white solid, 13 mg (yield: 5.1%), HPLC purity: 97.6%, Rt: 5.56 min, observed $[M+H]^+$ 461.2.

N^2-(3,5-Dimethyl-phenyl)-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C64")



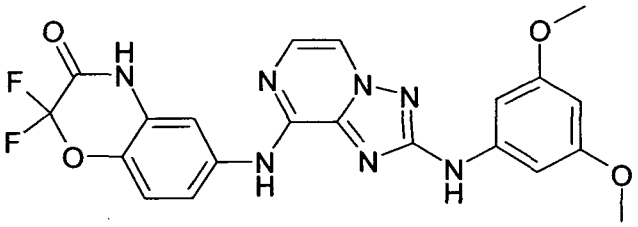
White solid, 30.94 mg (yield: 14.1%), HPLC purity: 98.3%, Rt: 5.94 min, observed $[M+H]^+$ 399.0.

N^8-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C65")



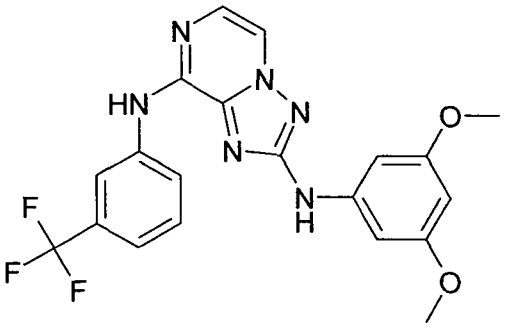
Light brown solid, 9.57 mg (yield: 3.8%), HPLC purity: 90.3%, Rt: 3.97 min, observed $[M+H]^+$ 509.0.

6-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino]-2,2-difluoro-4H-benzo[1,4]oxazin-3-one ("C66")



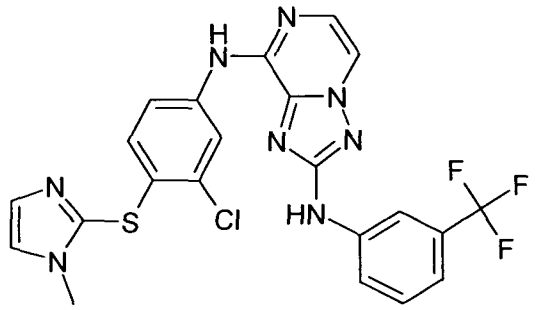
Light brown solid, 13.1 mg (yield: 5.7%), HPLC purity: 93.4%, Rt: 4.73 min, observed $[M+H]^+$ 470.0.

N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C67")



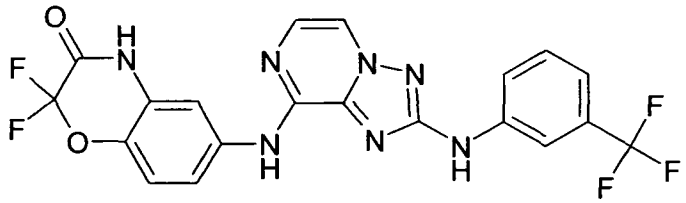
Off white solid, 13.1 mg (yield: 6.2%), HPLC purity: 99.5%, Rt: 5.52 min, observed $[M+H]^+$ 431.0.

N^8-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C68")



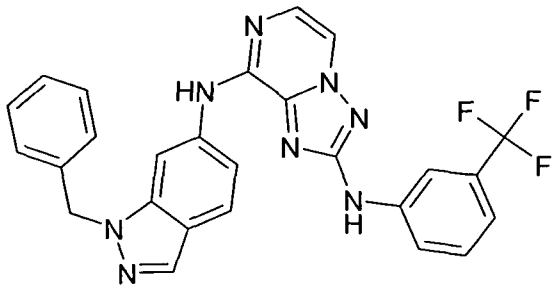
Light brown solid, 9 mg (yield: 3.6%), HPLC purity: 90.1%, Rt: 4.55 min, observed $[M+H]^+$ 517.0.

2,2-Difluoro-6-[2-(3-trifluoromethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino]-4H-benzo[1,4]oxazin-3-one ("C69")



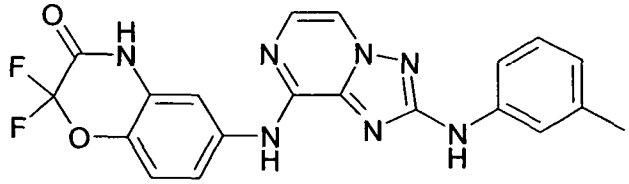
Off white solid, 38.7 mg (yield: 16.9%), HPLC purity: 97%, Rt: 5.32 min, observed $[M+H]^+$ 478.0.

N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C70")



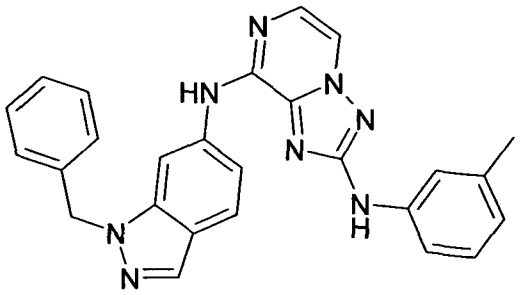
Off white solid, 31.9 mg (yield: 13.3%), HPLC purity: 98.8%, Rt: 5.68 min, observed $[M+H]^+$ 501.0.

2,2-Difluoro-6-(2-m-tolylamino-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino)-4H-benzo[1,4]oxazin-3-one ("C71")



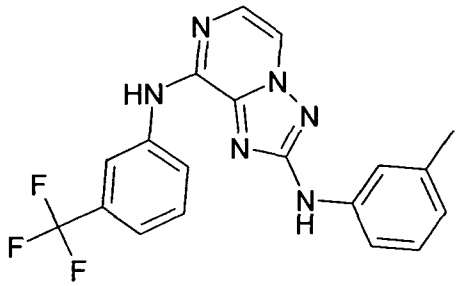
Light brown solid, 17.9 mg (yield: 7.2%), HPLC purity: 95.6%, Rt: 4.91 min, observed $[M+H]^+$ 424.0.

N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C72")



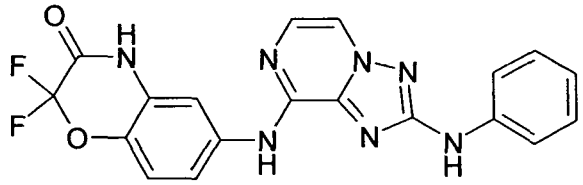
Light brown solid, 20.5 mg (yield: 7.9%), HPLC purity: 97.3%, Rt: 5.32 min, observed $[M+H]^+$ 447.0.

N^2-m-Tolyl-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C73")



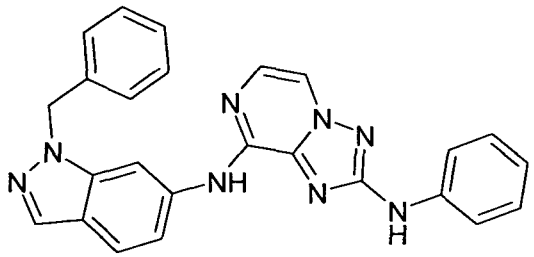
Off white solid, 39.52 mg (yield: 17.7%), HPLC purity: 95.7%, Rt: 5.74 min, observed $[M+H]^+$ 385.0.

2,2-Difluoro-6-(2-phenylamino-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino)-4H-benzo[1,4]oxazin-3-one ("C74")



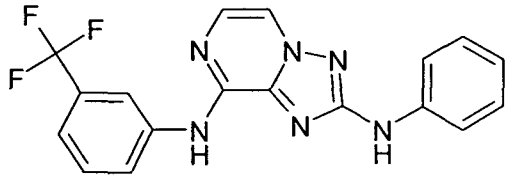
Off white solid, 20.1 mg (yield: 8.5%), HPLC purity: 94.8%, Rt: 4.68 min, observed $[M+H]^+$ 410.0.

N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C75")



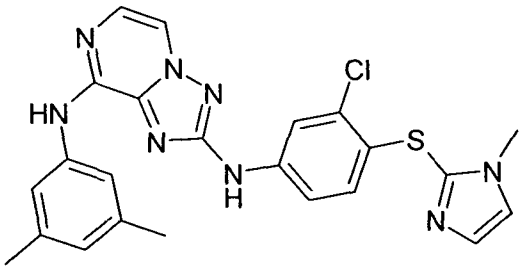
Light brown solid, 11 mg (yield: 4.1%), HPLC purity: 98.5%, Rt: 5.12 min, observed $[M+H]^+$ 433.0.

N^2-Phenyl-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C76")



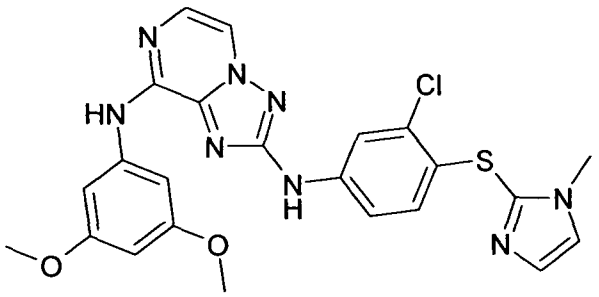
Off white solid, 40.94 mg (yield: 18%), HPLC purity: 99.3%, Rt: 5.54 min, observed $[M+H]^+$ 371.0.

N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C77")



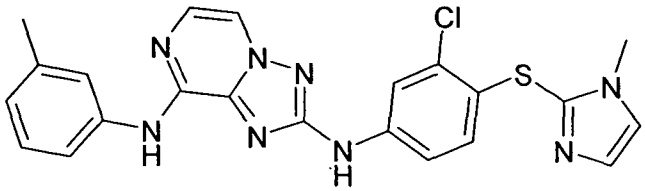
Off white solid, 41.3 mg (yield: 28.2%), HPLC purity: 92.3%, Rt: 6.64 min, observed $[M+H]^+$ 477.0.

N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C78")



Off white solid, 11.8 mg (yield: 7.6%), HPLC purity: 94%, Rt: 3.97 min, observed $[M+H]^+$ 509.0.

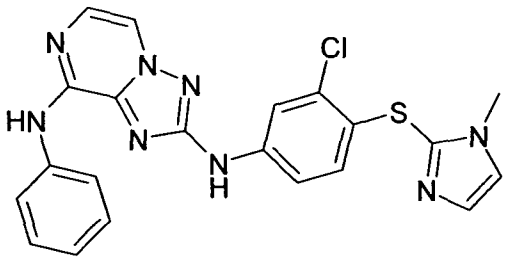
N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C79")



Light brown solid, 49.4 mg (yield: 27.8%), HPLC purity: 95.9%, Rt: 6.38 min, observed $[M+H]^+$ 463.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.96 (s, 1H), 9.28 (s, 1H), 8.23 (d, J = 4.44 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.73 (m, 3H),

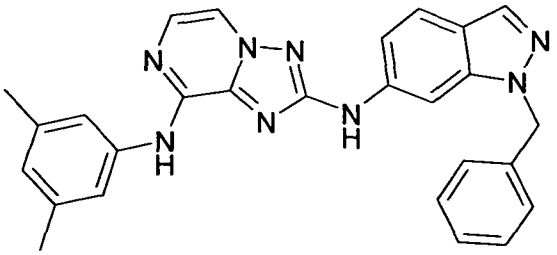
7.60 (d, J = 4.48 Hz, 1H), 7.47 (s, 1H), 7.21 (m, 1H), 7.10 (s, 1H), 6.86 (m, 1H), 6.68 (d, J = 8.76 Hz, 1H), 3.62 (s, 3H), 2.30 (s, 3H).

N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C80")



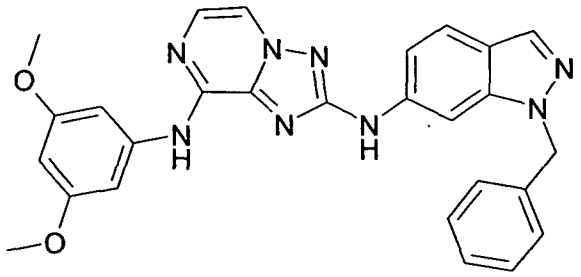
Off white solid, 43 mg (yield: 25%), HPLC purity: 96.4%, Rt: 3.78 min, observed $[M+H]^+$ 449.0.

N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C81")



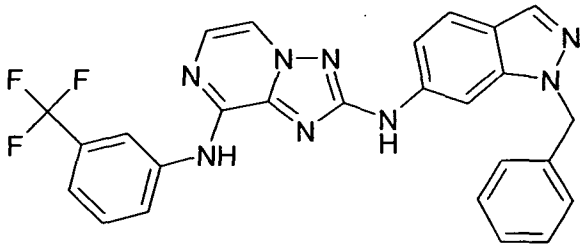
Off white solid, 47.09 mg (yield: 31.9%), HPLC purity: 98.4%, Rt: 5.28 min, observed $[M+H]^+$ 461.2, ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.90 (s, 1H), 9.15 (s, 1H), 8.28 (s, 1H), 8.22(d, J = 4.44 Hz, 1H), 7.95 (s, 1H), 7.62 (m, 4H), 7.28 (m, 6H), 6.70 (s, 1H), 5.66 (s, 2H), 2.27 (s, 6H).

N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C82")



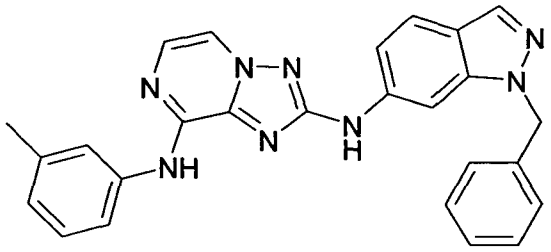
Off white solid, 54.16 mg (yield: 34.3%), HPLC purity: 96.3%, Rt: 5.04 min, observed $[M+H]^+$ 493.0.

N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C83")



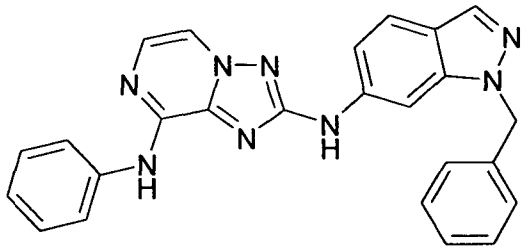
Off white solid, 31.6 mg (yield: 19.7%), HPLC purity: 99.5%, Rt: 5.7 min, observed $[M+H]^+$ 501.0.

N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C84")



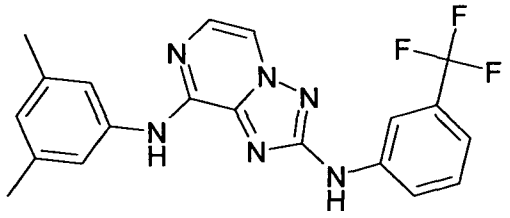
Off white solid, 50.32 mg (yield: 35.2%), HPLC purity: 98.5%, Rt: 5.06 min, observed $[M+H]^+$ 447.0.

N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C85")



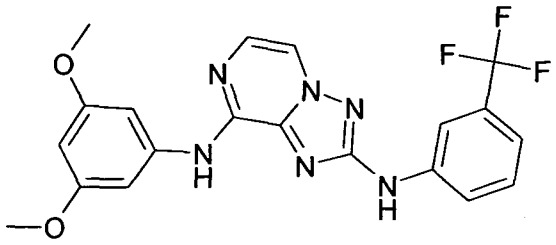
Off white solid, 20.51 mg (yield: 14.8%), HPLC purity: 96.9%, Rt: 4.91 min, observed $[M+H]^+$ 433.3.

N^8-(3,5-Dimethyl-phenyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C86")



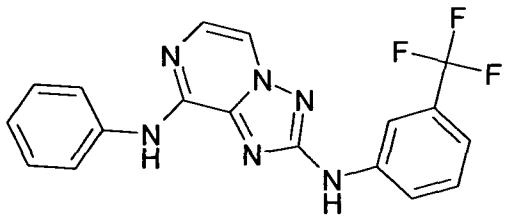
Off white solid, 46.2 mg (yield: 26.7%), HPLC purity: 97.5%, Rt: 5.63 min, observed $[M+H]^+$ 399.0; ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.02 (s, 1H), 9.16 (s, 1H), 8.25 (d, J = 4.48 Hz, 1H), 8.18 (m, 1H), 7.95 (s, 1H), 7.62 (d, J = 4.48 Hz, 1H), 7.54 (m, 3H), 7.22 (d, J = 8.12 Hz, 1H), 6.69 (s, 1H), 2.27(s, 6H).

N^8-(3,5-Dimethoxy-phenyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C87")



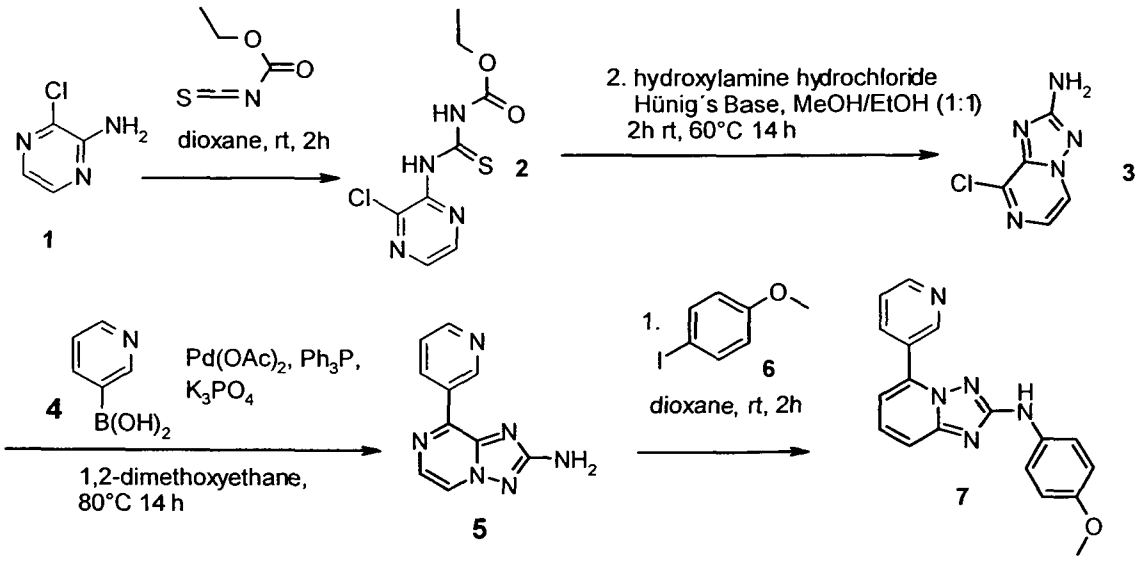
Off white solid, 19.7 mg (yield: 13.2%), HPLC purity: 99.1%, Rt: 5.43 min, observed $[M+H]^+$ 431.0.

N^8-Phenyl-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("C88")

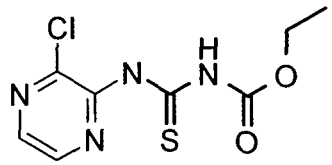


Off white solid, 69.1 mg (yield: 53.6%), HPLC purity: 99.3%, Rt: 5.28 min, observed $[M+H]^+$ 371.0.

Alternatively the following synthesis route can be applied:



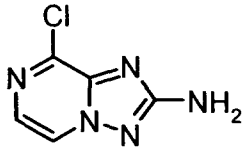
1-(3-Chloro-pyrazin-2-yl)-3-acetoxyethyl-urea



1 g (7.7 mmol) 3-Chloro-pyrazin-2-ylamine are dissolved in a mixture of 40 ml DCM and 20 ml THF. Then 1 ml (8.5 mmol) of ethoxycarbonylthioisocyanate are added. The resulting mixture is stirred 14 h at 46°C until by HPLC no further formation of product is detectable. For work-up, the reaction mixture is

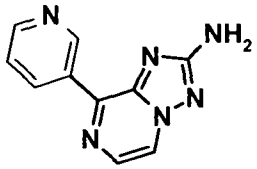
concentrated in vacuo. The crude product (1.95 g, 60%, of a yellow solid) is used in the next reaction step without further purification;
LCMS (method C): mass found ($M+H^+$, 261), HPLC (method D): Rt (min): 2.73 area % 62 (220 nm); ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] 11.99 (s, 1H), 9.63 (s, 1H), 9.39 (s, 1H), 8.27 (d, *J* = 4.48 Hz, 1H), 7.93 (d, *J* = 2.44 Hz, 1H), 7.63 (m, 1H), 7.57 (d, *J* = 4.48 Hz, 1H), 7.35 (s, 2H), 7.27 (d, *J* = 8.92 Hz, 1H), 6.55 (s, 1H), 2.25 (s, 6H).

8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine



1.6 g (23.2 mmol) hydroxylamine hydrochloride are suspended in 20 ml of a 1:1 mixture of ethanol and methanol. Then 2.4 ml (13.9 mmol) DIPEA are added and the mixture is stirred at ambient temperature for 1 h. At that time, the reaction suspension is added to 2 g (4.6 mmol, 62 % content) 1-(3-chloro-pyrazin-2-yl)-3-acetoxyethyl-urea and refluxed for 2 h. The reaction is cooled to room temperature filtered and washed with water. The product is isolated after drying in a vacuum oven (60 °C) (790 mg, 4.65 mmol, 100 %); LCMS (method C): mass found ($M+H^+$, 170), HPLC (method D) Rt (min): 2.14 area % 100 (220 nm); ^1H NMR (400 MHz, DMSO-d_6) δ [ppm] 8.83 (d, *J* = 4.3, 1H), 7.92 (d, *J* = 4.3, 1H), 6.77 (s, 2H).

8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine



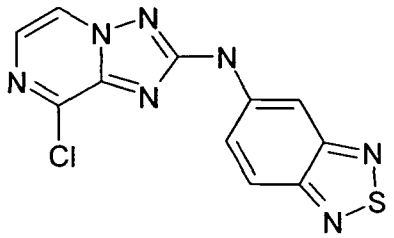
100 mg (0.6 mmol) of 8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine, 50 mg 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0,2 eq., 0.1 mmol), 149 mg (1.8 mmol) sodium hydrogencarbonate, 3 ml ethyleneglycole ether and 1 ml of de-ionized water are mixed in glass vial. 86 mg (0.72 mmol, 1,2 eq.) of

pyridine-3-boronic acid are added in portions to the suspension. By the help of a canula, nitrogen is bubbled through the suspension for a few minutes. After that time, 13 mg palladium(II)acetate (0,1 eq., 0.05 mmol) are added, the vial is closed with a septum and the reaction mixture is heated to 90°C, stirring 14 h.

Another 43 mg pyridine-3-boronic acid (0,6 eq.), 50 mg 2-dicyclohexyl-phosphino-2',6'-dimethoxybiphenyl (0,2 äq.) und 13 mg palladium acetate (0,1 eq.) are added and the reaction is heated again to 90 °C for 14 h. The reaction is filtered over celite which is consequently washed with ethanol. The filtrate is concentrated in vacuo. The resulting 180 mg crude product are absorbed to Isolute HM-N and purified on Silica 60. Fractions containing the desired product are combined and concentrated in vacuo. The desired product is thus isolated as a reddish-brown solid in 17% yield (21 mg, LCMS (method: polar-TFA.M): mass found ($M+H^+$, 213), HPLC (method D) Rt (min): 2.08 area % 100 (220 nm); ^1H NMR (400 MHz, DMSO-d_6) δ [ppm] 9.80 (dd, J = 2.2, 0.8, 1H), 8.96 – 8.92 (m, 1H), 8.74 (d, J = 4.2, 1H), 8.70 (dd, J = 4.8, 1.7, 1H), 8.15 (d, J = 4.2, 1H), 7.60 (ddd, J = 8.1, 4.8, 0.8, 1H), 6.65 (s, 2H).

Compounds of this type can be converted further yielding similar compounds to the ones prepared in the abovementioned examples "C1" – "C59" by standard Buchwald coupling conditions.

Benzo[1,2,5]thiadiazol-5-yl-(8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("B10")

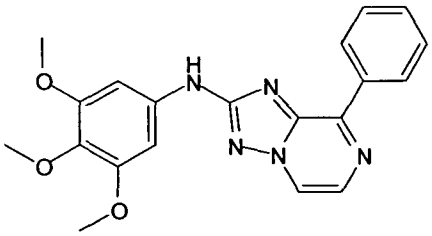


100 mg (0.6 mmol) of 8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine, 190 mg (0.9 mmol) 5-bromo-2,1,3-benzothiadiazole, 68 mg (0.1 mmol) 9,9-

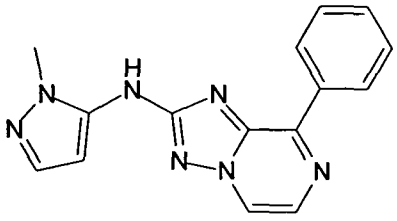
dimethyl-4,5-bis(diphenylphosphino)xanthene , 578 mg (1.8 mmol) cesium carbonate and 34 mg bis(dibenzylideneacetone)palladium are dissolved in 1 ml dioxane and stirred at 90 °C for 14 h. HPLC and LC-MS analysis show formation of the product (LCMS (method C): mass found ($M+H^+$, 303), HPLC (method D) Rt (min): 3.07.

Following compounds are synthesized analogously to "C2"

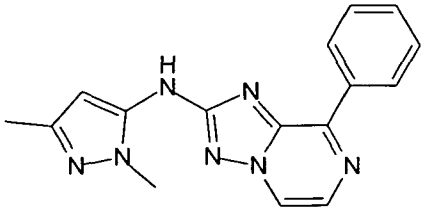
(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine ("C89")



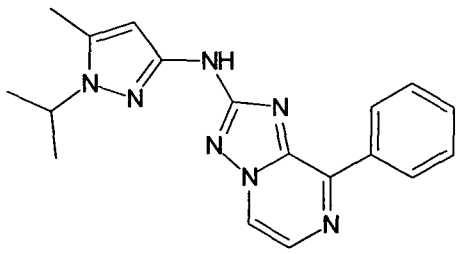
(2-Methyl-2H-pyrazol-3-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C90")



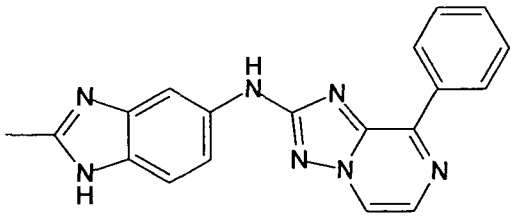
(2,5-Dimethyl-2H-pyrazol-3-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C91")



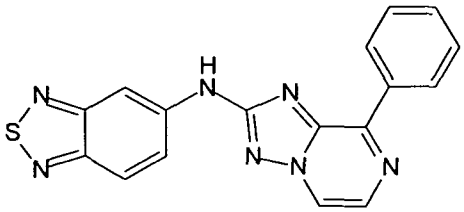
(1-Isopropyl-5-methyl-1H-pyrazol-3-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C92")



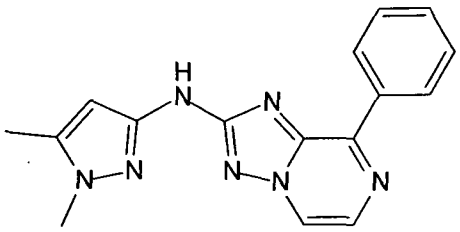
(2-Methyl-1H-benzimidazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C93")



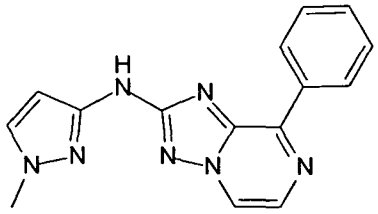
Benzo[1,2,5]thiadiazol-5-yl-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C94")



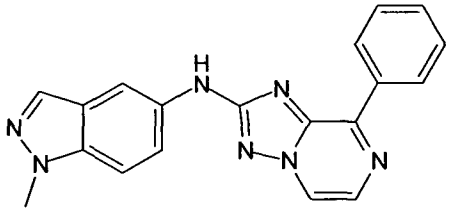
(1,5-Dimethyl-1H-pyrazol-3-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C95")



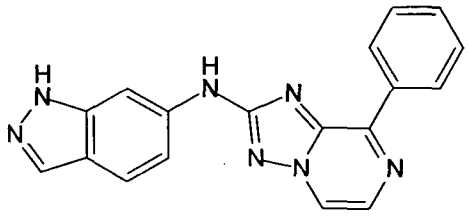
(1-Methyl-1H-pyrazol-3-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C96")



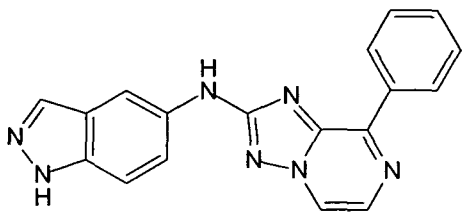
(1-Methyl-1H-indazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C97")



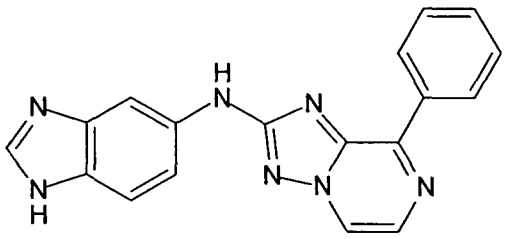
(1H-Indazol-6-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C98")



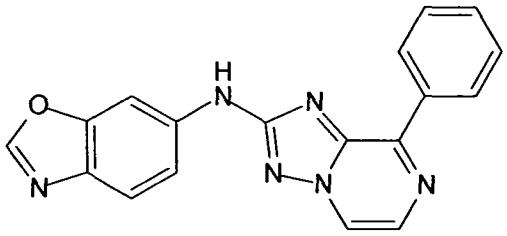
(1H-Indazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C99")



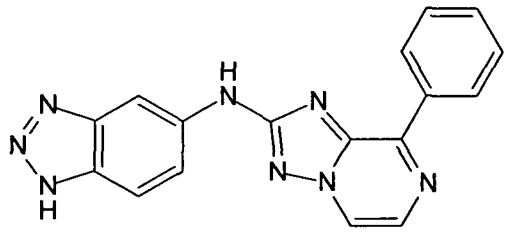
(1H-Benzimidazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C100")



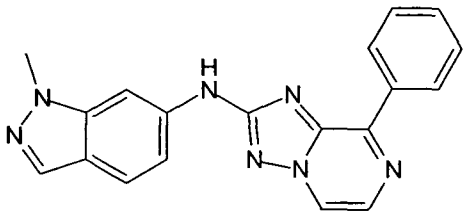
Benzoxazol-6-yl-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C101")



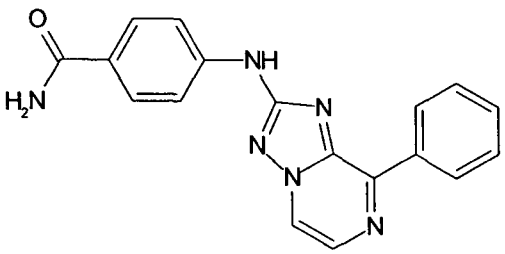
(1H-Benzotriazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C102")



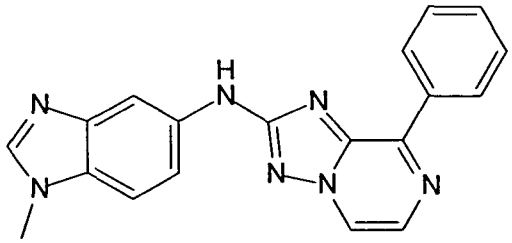
(1-Methyl-1H-indazol-6-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C103")



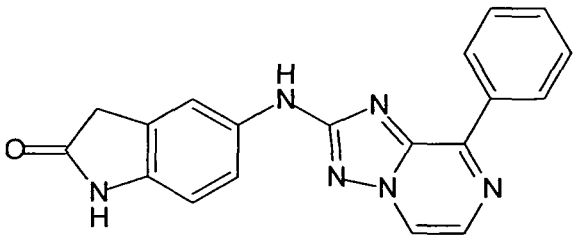
4-(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-benzamide ("C104")



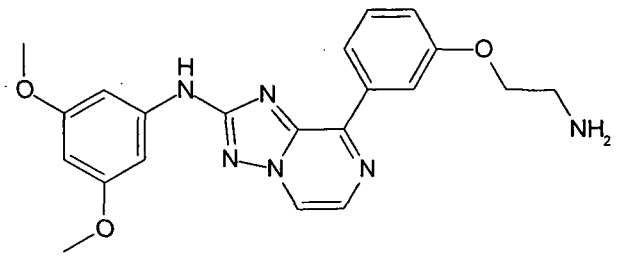
(1-Methyl-1H-benzoimidazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C105")



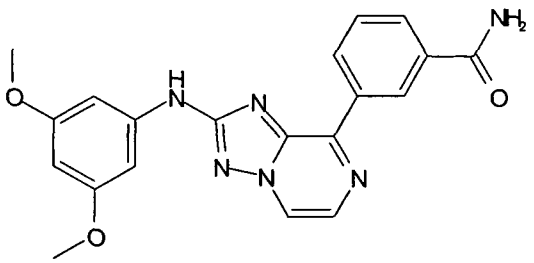
5-(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one ("C106")



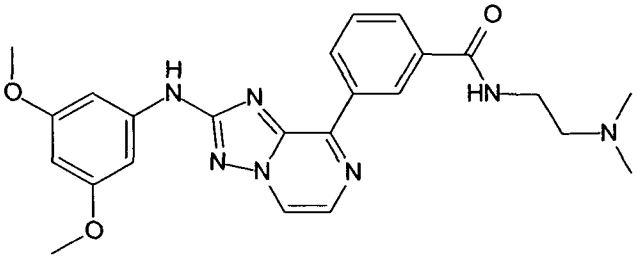
{8-[3-(2-Amino-ethoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(3,5-dimethoxy-phenyl)-amine ("C107")



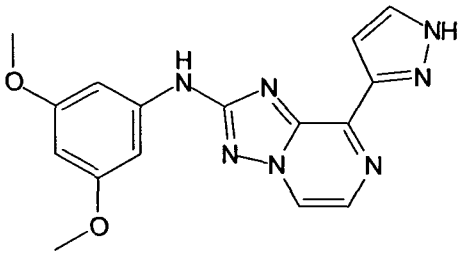
3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C108")



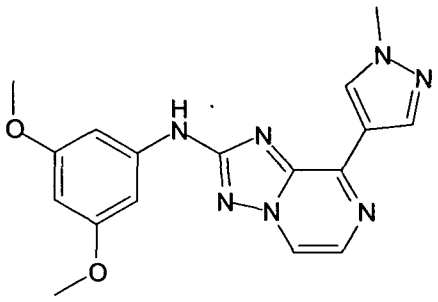
3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-N-(2-dimethylamino-ethyl)-benzamide ("C109")



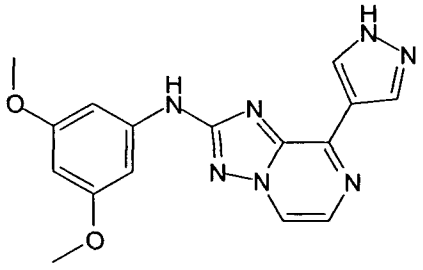
(3,5-Dimethoxy-phenyl)-[8-(1H-pyrazol-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C110")



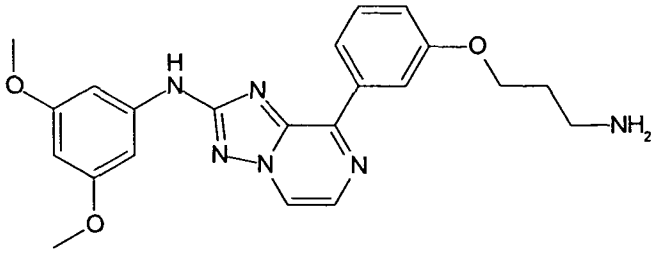
(3,5-Dimethoxy-phenyl)-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C111")



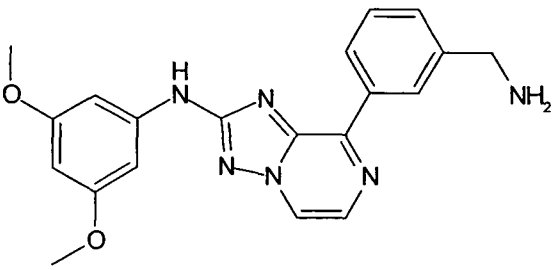
(3,5-Dimethoxy-phenyl)-[8-(1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C112")



{8-[3-(3-Amino-propoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(3,5-dimethoxy-phenyl)-amine ("C113")



[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("C114")

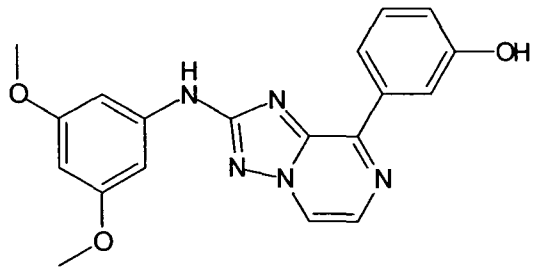


The compound is synthesized as described in method 1.

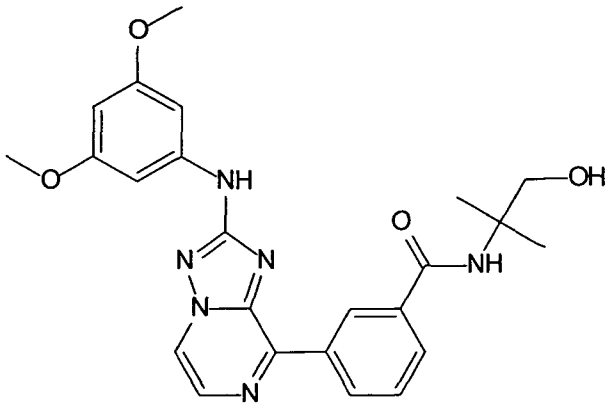
HPLC purity (method A): 95%, RT 3.23 min, LCMS: (method A) 377.0 (M+H), RT. 3.14 min, 95%;

^{1}HNMR (400 MHz, DMSO-d_6): δ [ppm] 10.03 (s, 1H), 8.93 (d, *J* = 4.20 Hz, 1H), 8.77 (td, *J* = 6.99, 1.92 Hz, 1H), 8.61 (s, 1H), 8.24 (s, 1H), 7.60-7.54 (m, 2H), 7.04 (d, *J* = 2.20 Hz, 2H), 6.13 (t, *J* = 2.20 Hz, 1H), 5.47 (br s, 2H), 3.98 (s, 2H), 3.76 (s, 6H).

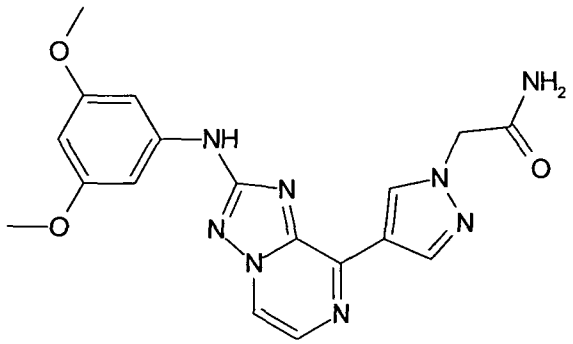
3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C115")



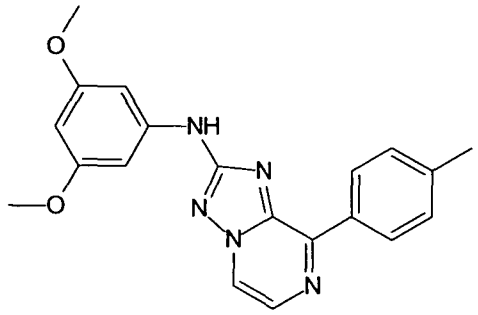
3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide ("C116")



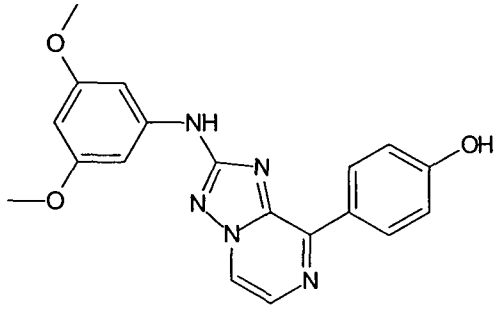
2-{4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyrazol-1-yl}-acetamide ("C117")



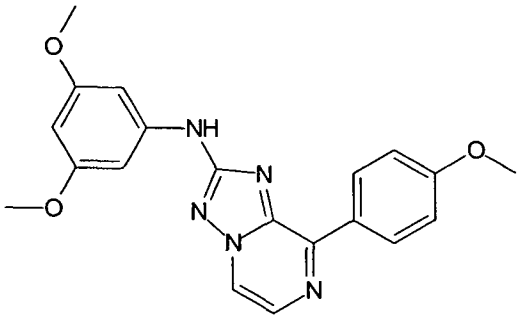
(3,5-Dimethoxy-phenyl)-(8-p-tolyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C118")



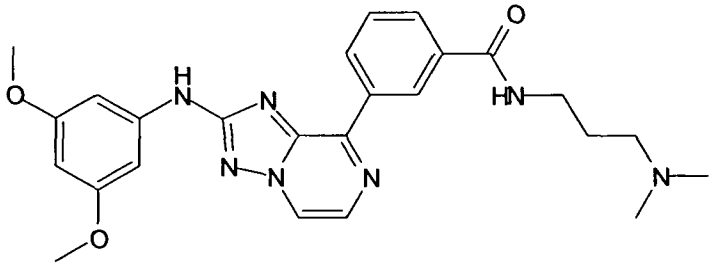
4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C119")



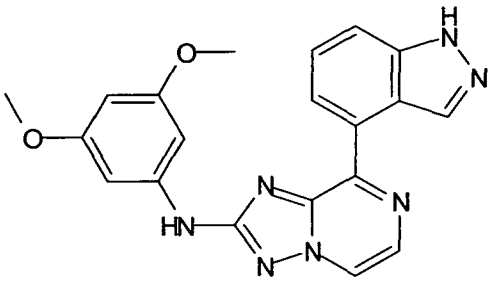
(3,5-Dimethoxy-phenyl)-[8-(4-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C120")



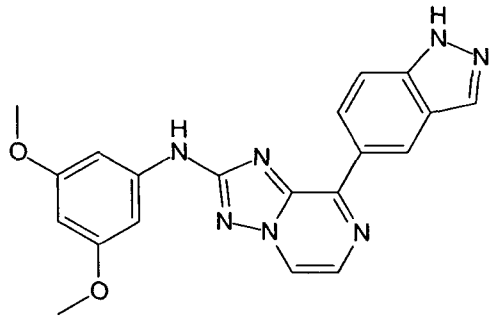
3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-N-(3-dimethylamino-propyl)-benzamide ("C121")



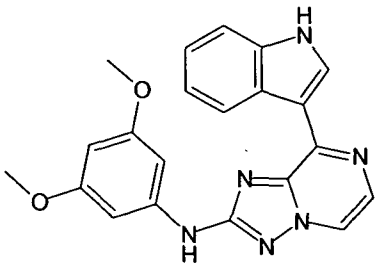
(3,5-Dimethoxy-phenyl)-[8-(1H-indazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C122")



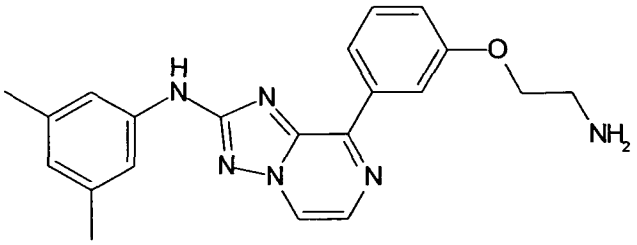
(3,5-Dimethoxy-phenyl)-[8-(1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C123")



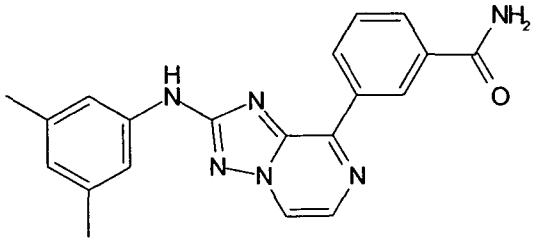
(3,5-Dimethoxy-phenyl)-[8-(1H-indol-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C124")



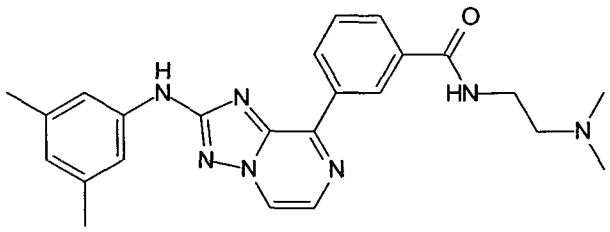
{8-[3-(2-Amino-ethoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(3,5-dimethyl-phenyl)-amine ("C125")



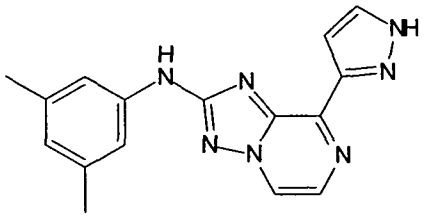
3-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C126")



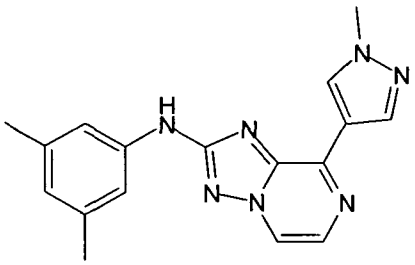
N-(2-Dimethylamino-ethyl)-3-[2-(3,5-dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C127")



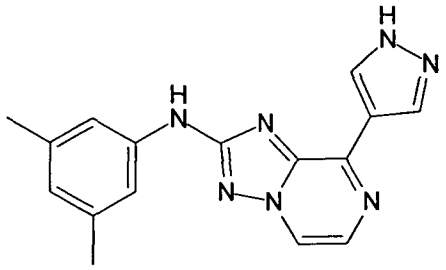
(3,5-Dimethyl-phenyl)-[8-(1H-pyrazol-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C128") .



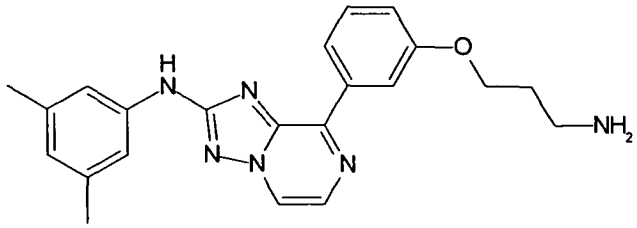
(3,5-Dimethyl-phenyl)-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C129")



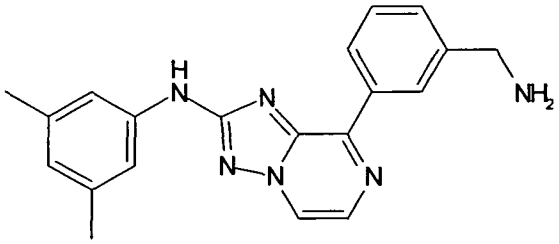
(3,5-Dimethyl-phenyl)-[8-(1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C130")



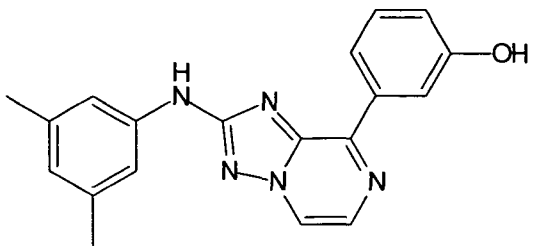
{8-[3-(3-Amino-propoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(3,5-dimethyl-phenyl)-amine ("C131")



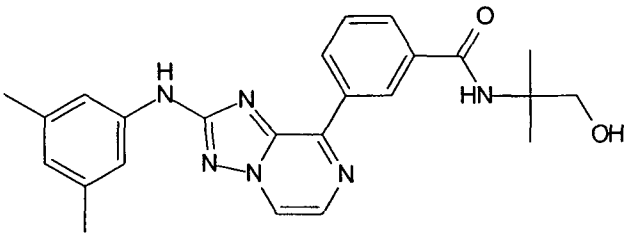
[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethyl-phenyl)-amine ("C132")



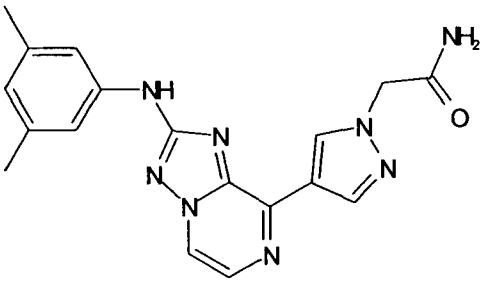
3-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C133")



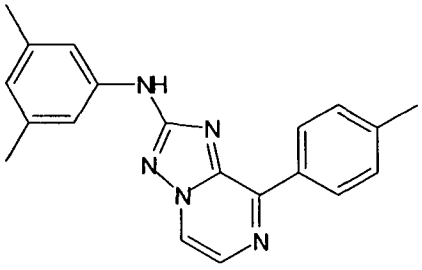
3-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide ("C134")



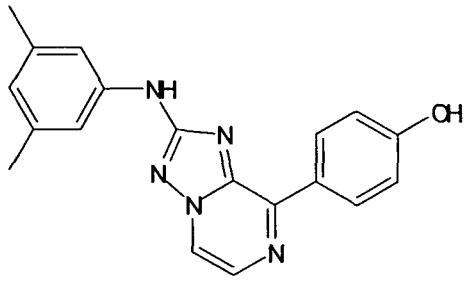
2-{4-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyrazol-1-yl}-acetamide ("C135")



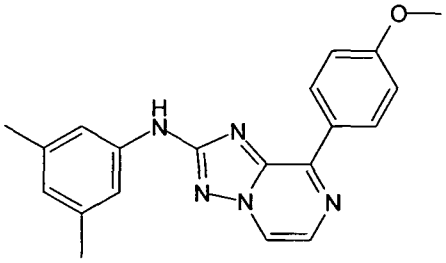
(3,5-Dimethyl-phenyl)-(8-p-tolyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C136")



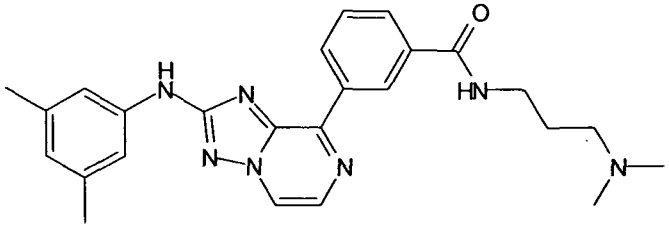
4-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C137")



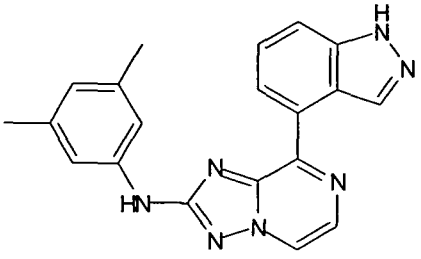
(3,5-Dimethyl-phenyl)-[8-(4-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C138")



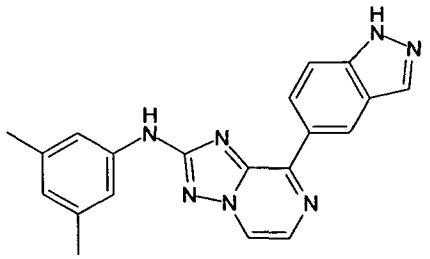
N-(3-Dimethylamino-propyl)-3-[2-(3,5-dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C139")



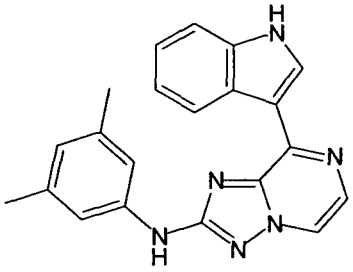
(3,5-Dimethyl-phenyl)-[8-(1H-indazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C140")



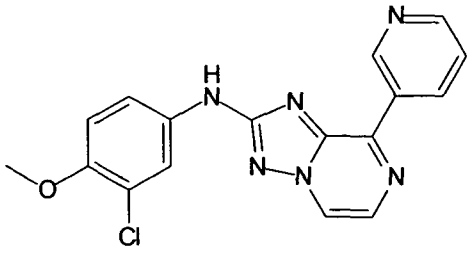
(3,5-Dimethyl-phenyl)-[8-(1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C141")



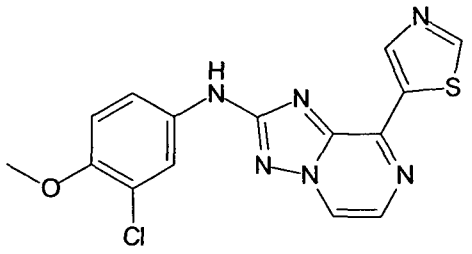
(3,5-Dimethyl-phenyl)-[8-(1H-indol-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C142")



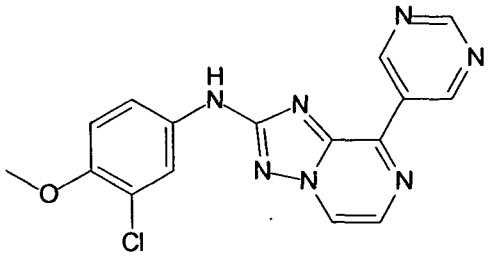
(3-Chloro-4-methoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C143")



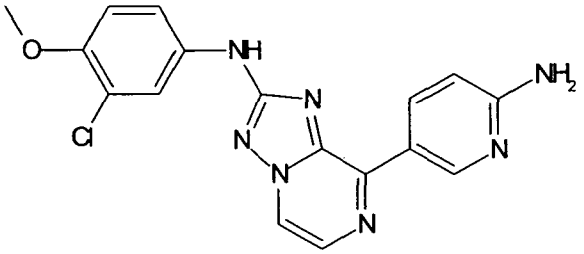
(3-Chloro-4-methoxy-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C144")



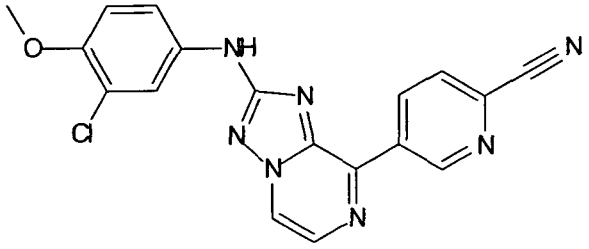
(3-Chloro-4-methoxy-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C145")



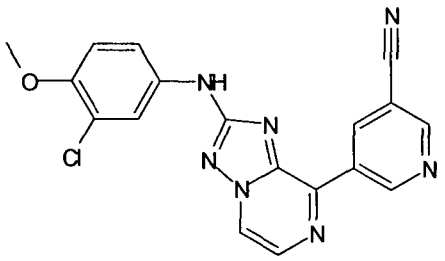
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3-chloro-4-methoxy-phenyl)-amine ("C146")



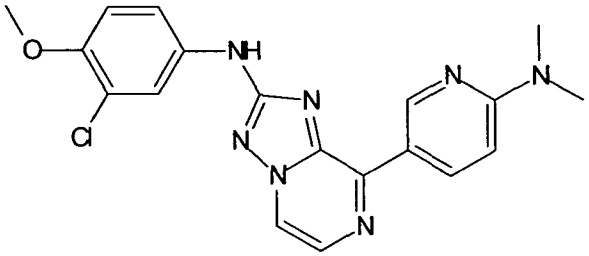
5-[2-(3-Chloro-4-methoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C147")



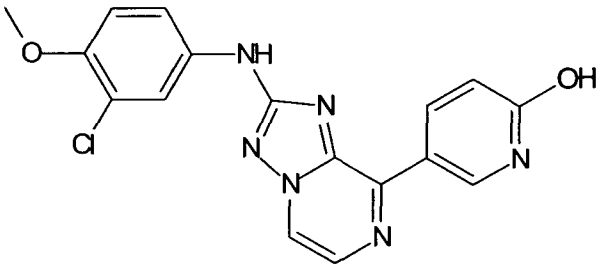
5-[2-(3-Chloro-4-methoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C148")



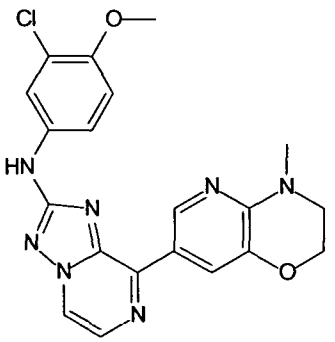
(3-Chloro-4-methoxy-phenyl)-[8-(6-dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C149")



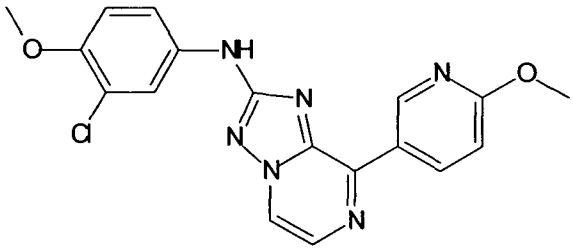
5-[2-(3-Chloro-4-methoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C150")



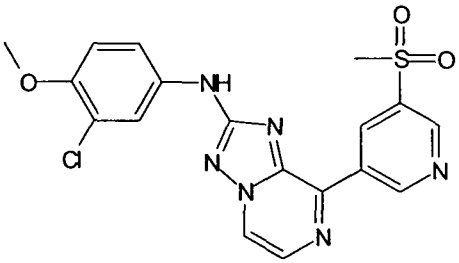
(3-Chloro-4-methoxy-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C151")



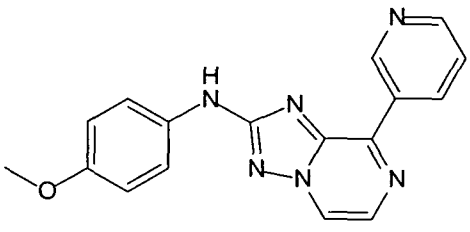
(3-Chloro-4-methoxy-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C152")



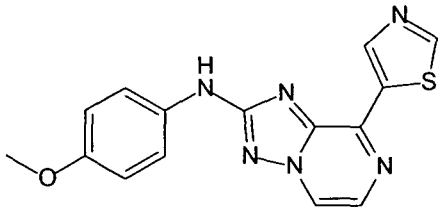
(3-Chloro-4-methoxy-phenyl)-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C153")



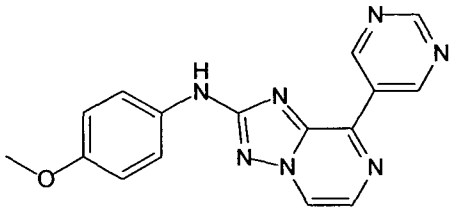
(4-Methoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C154")



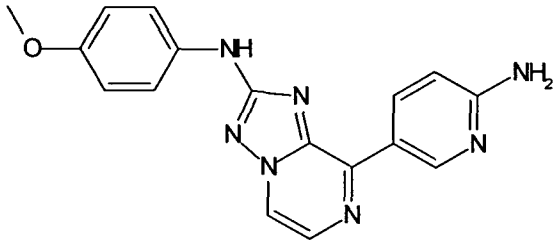
(4-Methoxy-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C155")



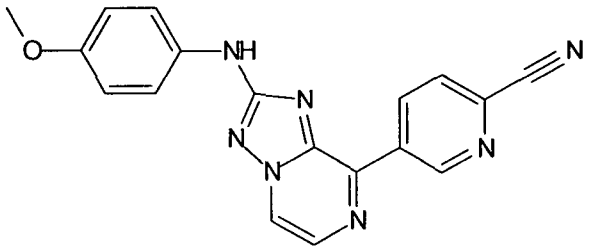
(4-Methoxy-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C156")



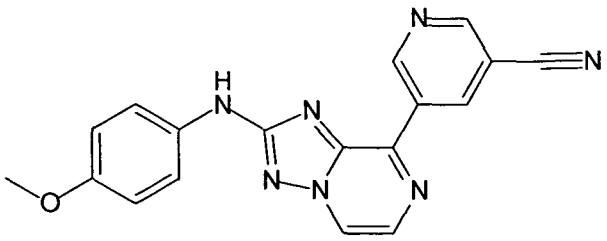
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-methoxy-phenyl)-amine ("C157")



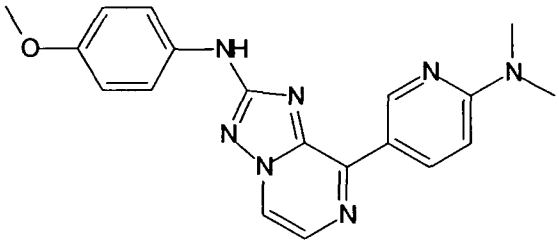
5-[2-(4-Methoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C158")



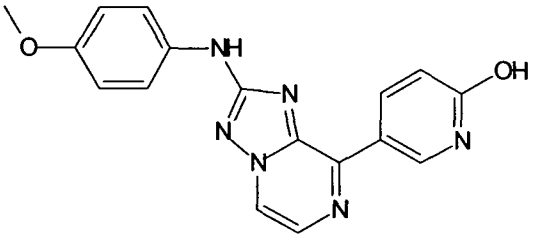
5-[2-(4-Methoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C159")



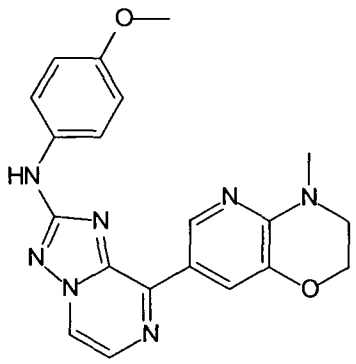
[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-methoxy-phenyl)-amine ("C160")



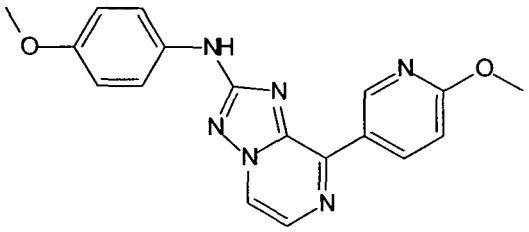
5-[2-(4-Methoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C161")



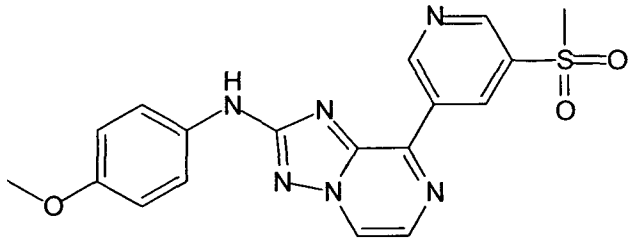
(4-Methoxy-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C162")



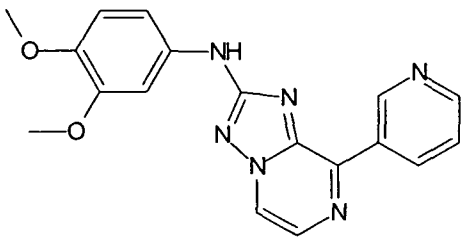
(4-Methoxy-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C163")



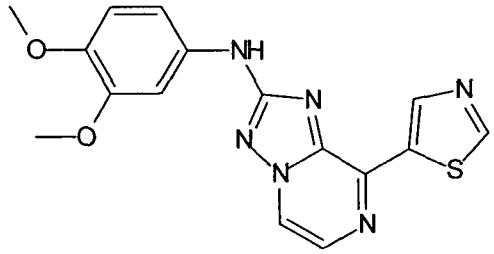
[8-(5-Methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-methoxy-phenyl)-amine ("C164")



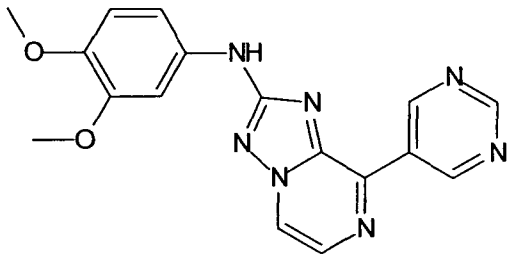
(3,4-Dimethoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C165")



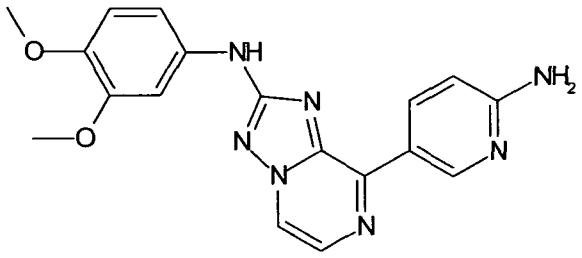
(3,4-Dimethoxy-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C166")



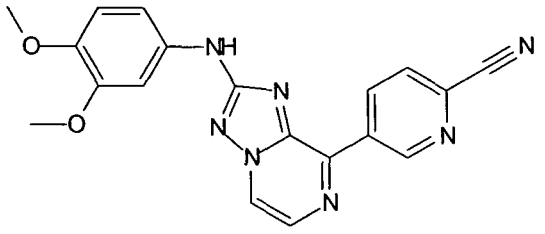
(3,4-Dimethoxy-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C167")



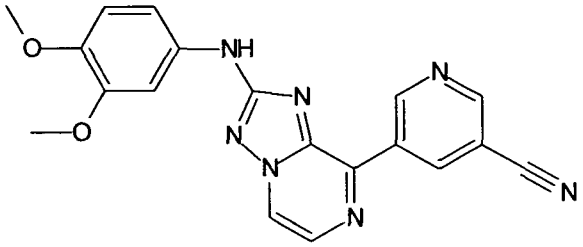
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,4-dimethoxy-phenyl)-amine ("C168")



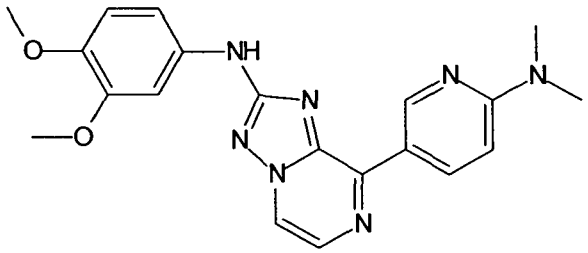
5-[2-(3,4-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C169")



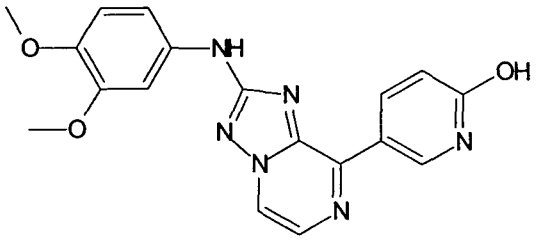
5-[2-(3,4-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C170")



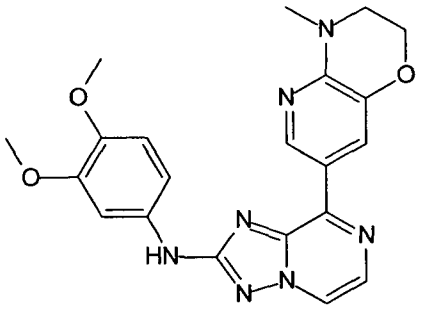
(3,4-Dimethoxy-phenyl)-[8-(6-dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C171")



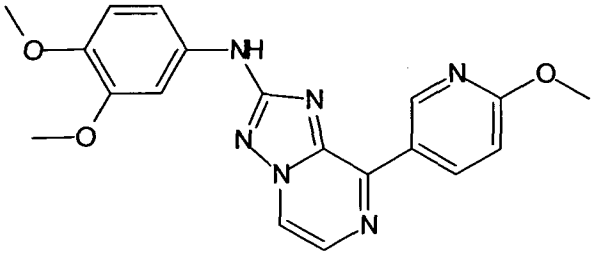
5-[2-(3,4-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C172")



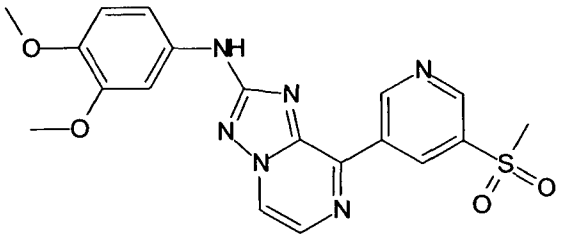
(3,4-Dimethoxy-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C173")



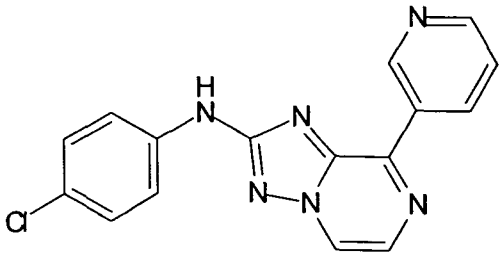
(3,4-Dimethoxy-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C174")



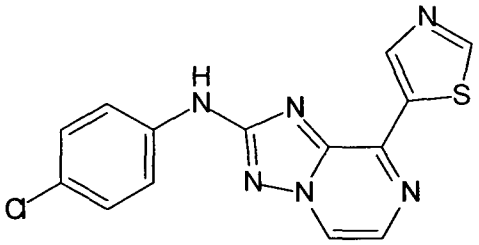
(3,4-Dimethoxy-phenyl)-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C175")



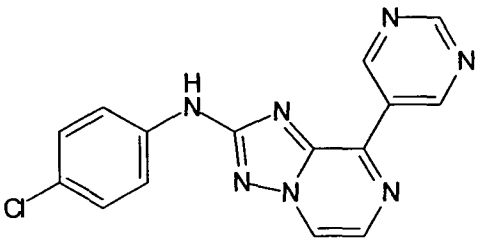
(4-Chloro-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C176")



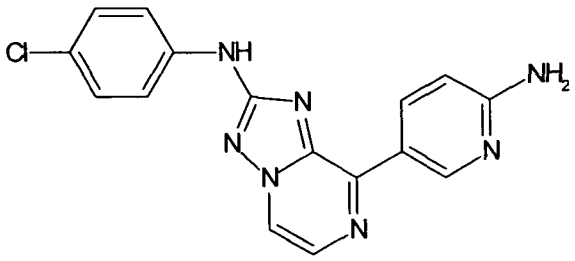
(4-Chloro-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C177")



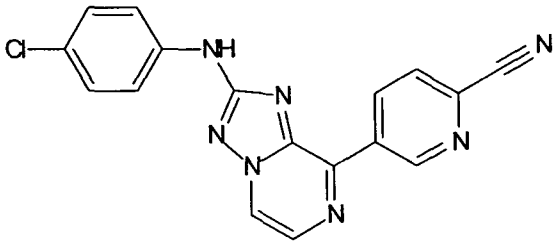
(4-Chloro-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C178")



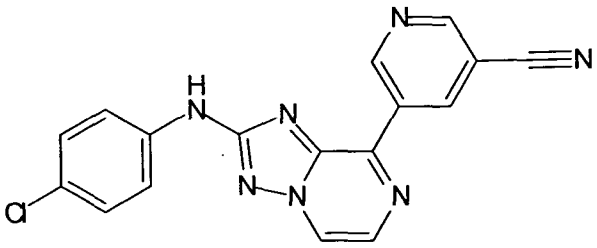
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-chloro-phenyl)-amine ("C179")



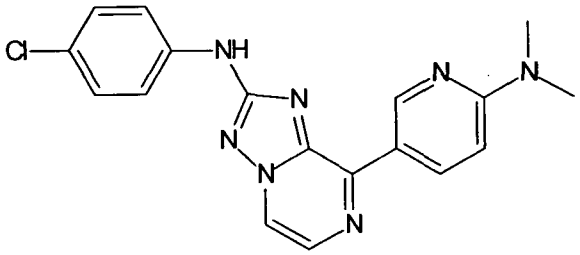
5-[2-(4-Chloro-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C180")



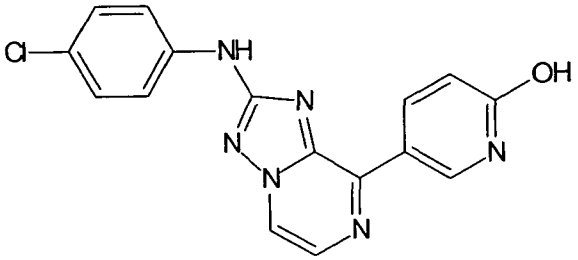
5-[2-(4-Chloro-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C181")



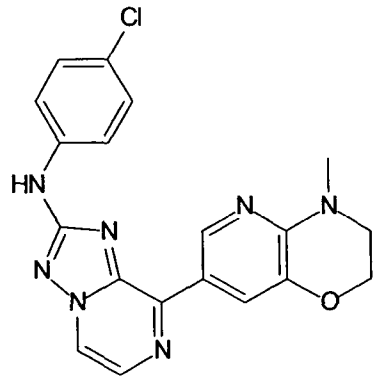
(4-Chloro-phenyl)-[8-(6-dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C182")



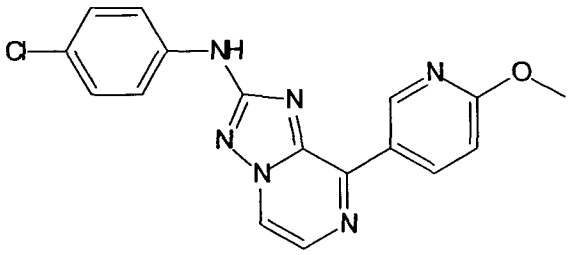
5-[2-(4-Chloro-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C183")



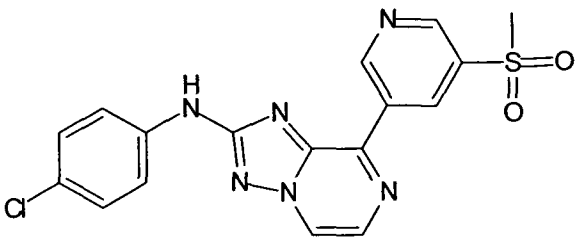
(4-Chloro-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C184")



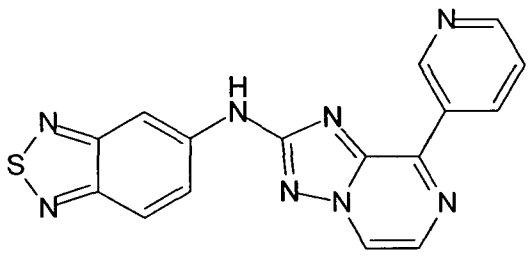
(4-Chloro-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C185")



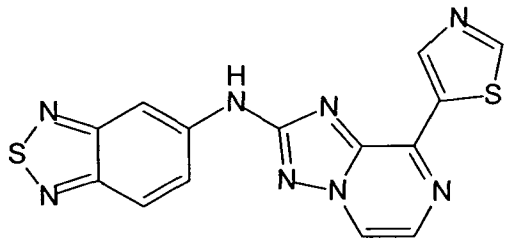
(4-Chloro-phenyl)-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C186")



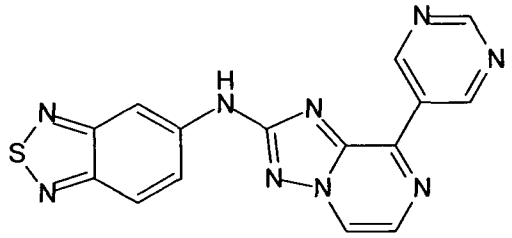
Benzo[1,2,5]thiadiazol-5-yl-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C187")



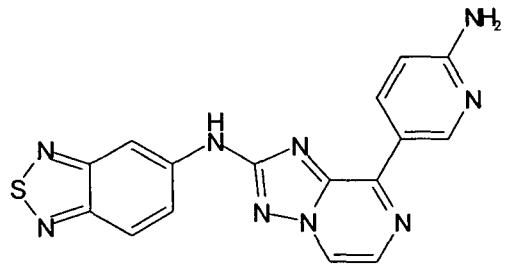
Benzo[1,2,5]thiadiazol-5-yl-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C188")



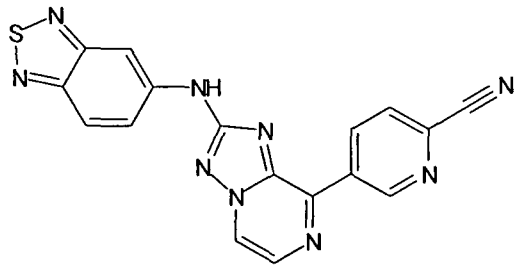
Benzo[1,2,5]thiadiazol-5-yl-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C189")



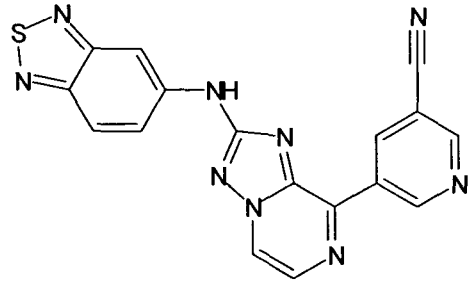
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-benzo[1,2,5]thiadiazol-5-yl-amine ("C190")



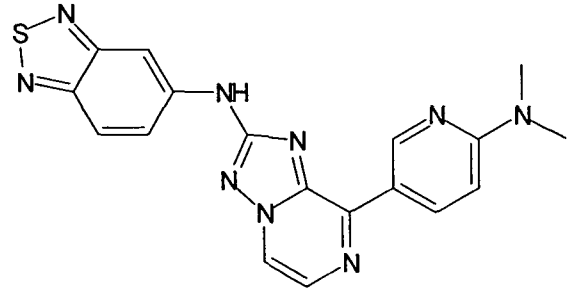
5-[2-(Benzo[1,2,5]thiadiazol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C191")



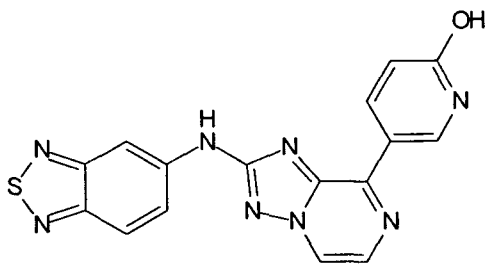
5-[2-(Benzo[1,2,5]thiadiazol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C192")



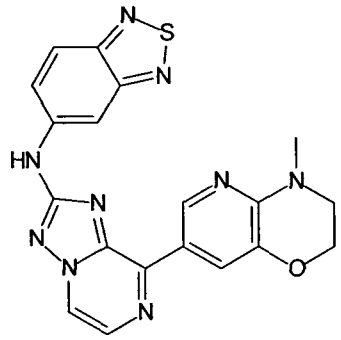
Benzo[1,2,5]thiadiazol-5-yl-[8-(6-dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C193")



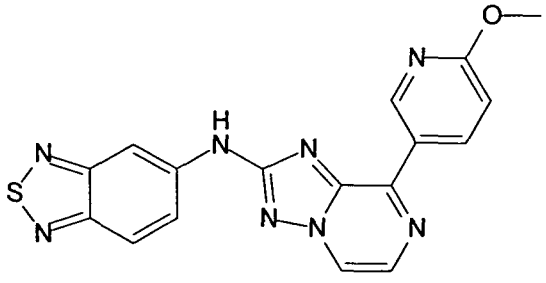
5-[2-(Benzo[1,2,5]thiadiazol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C194")



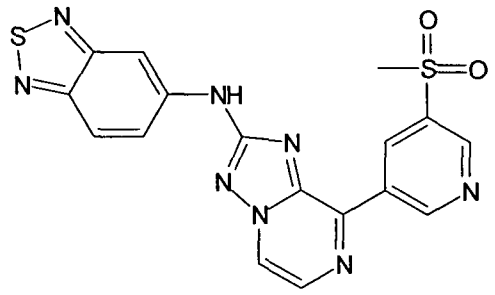
Benzo[1,2,5]thiadiazol-5-yl-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C195")



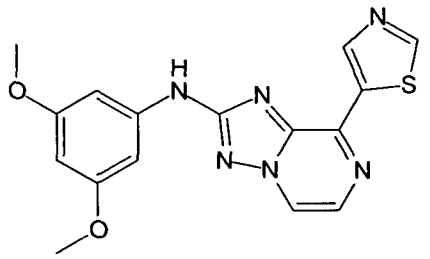
Benzo[1,2,5]thiadiazol-5-yl-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C196")



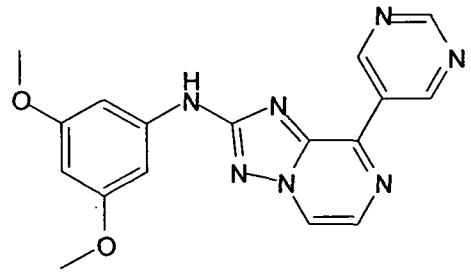
Benzo[1,2,5]thiadiazol-5-yl-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C197")



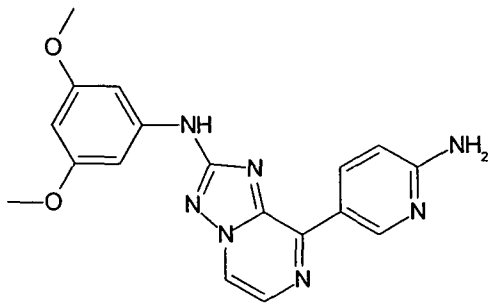
(3,5-Dimethoxy-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C198")



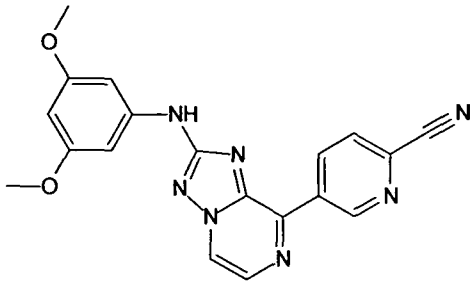
(3,5-Dimethoxy-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C199")



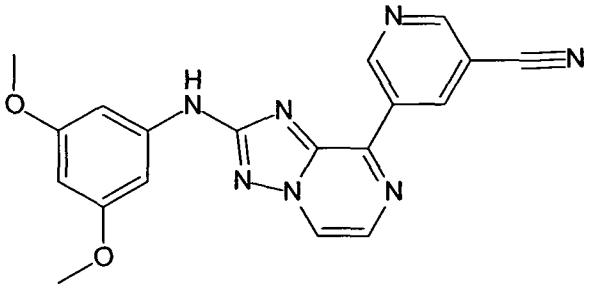
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("C200")



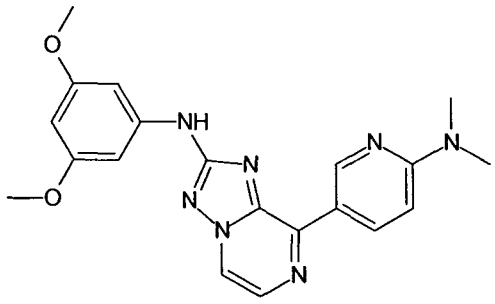
5-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C201")



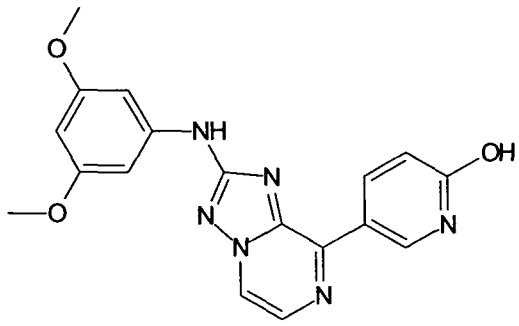
5-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C202")



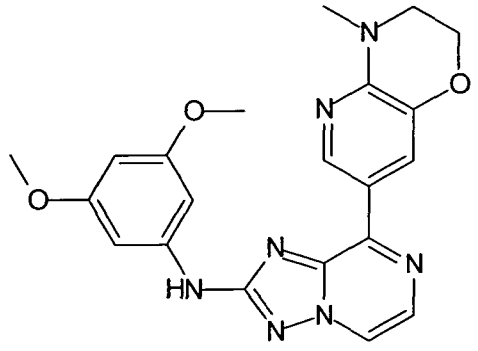
(3,5-Dimethoxy-phenyl)-[8-(6-dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C203")



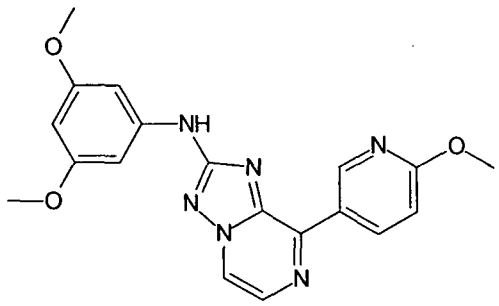
5-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C204")



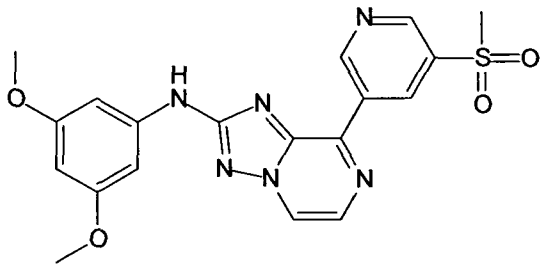
(3,5-Dimethoxy-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C205")



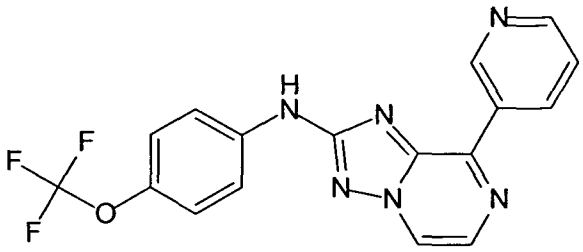
(3,5-Dimethoxy-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C206")



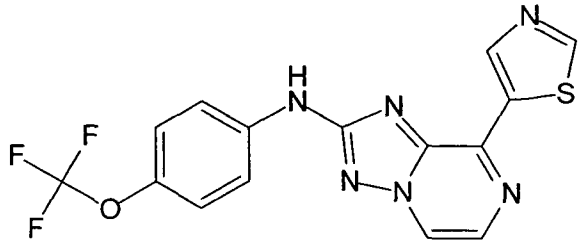
(3,5-Dimethoxy-phenyl)-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C207")



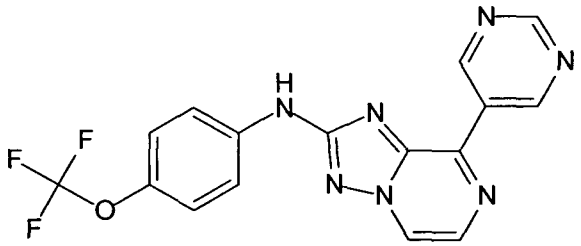
(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(4-trifluoromethoxy-phenyl)-amine ("C208")



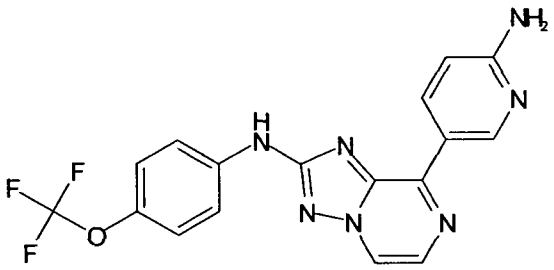
(8-Thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(4-trifluoromethoxy-phenyl)-amine ("C209")



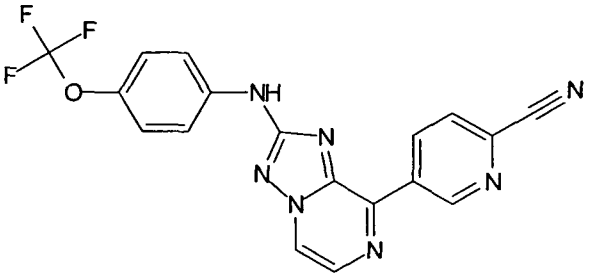
(8-Pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(4-trifluoromethoxy-phenyl)-amine ("C210")



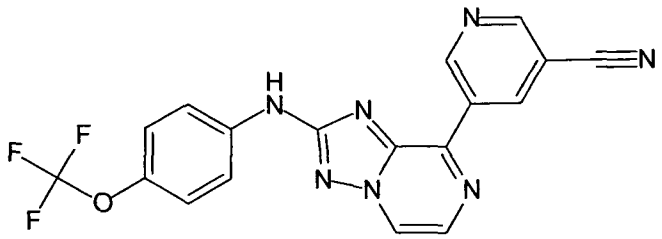
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-trifluoromethoxy-phenyl)-amine ("C211")



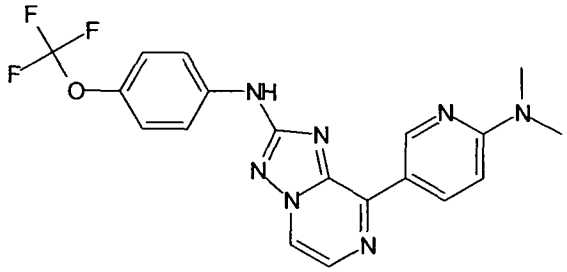
5-[2-(4-Trifluoromethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C212")



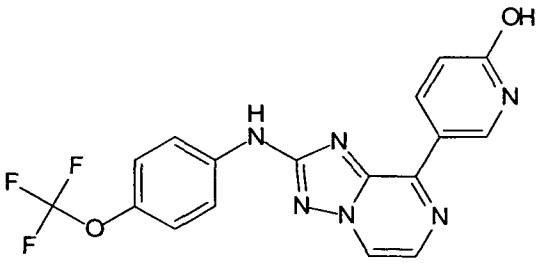
5-[2-(4-Trifluoromethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C213")



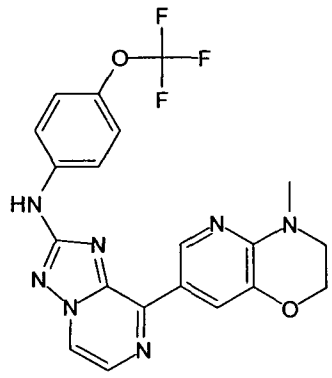
[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-trifluoromethoxy-phenyl)-amine ("C214")



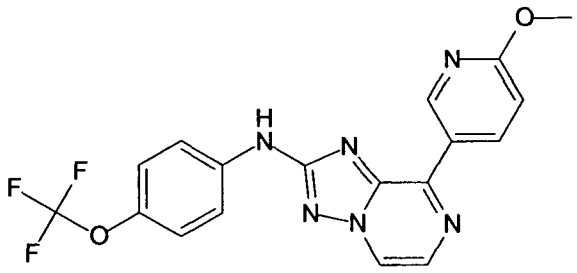
5-[2-(4-Trifluoromethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C215")



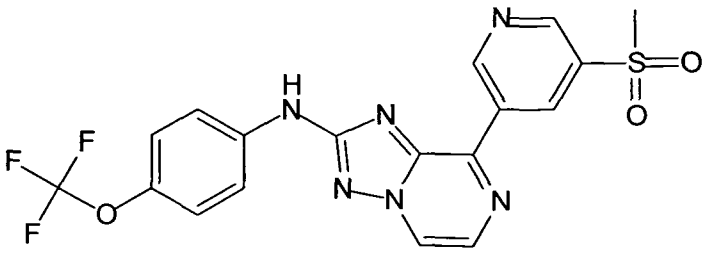
[8-(4-Methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-trifluoromethoxy-phenyl)-amine ("C216")



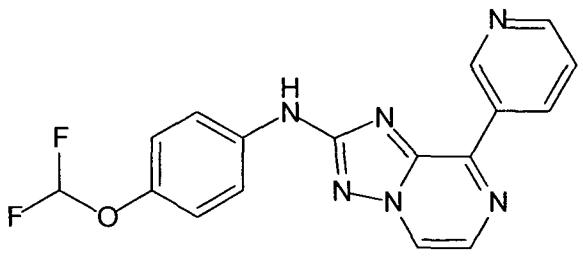
[8-(6-Methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-trifluoromethoxy-phenyl)-amine ("C217")



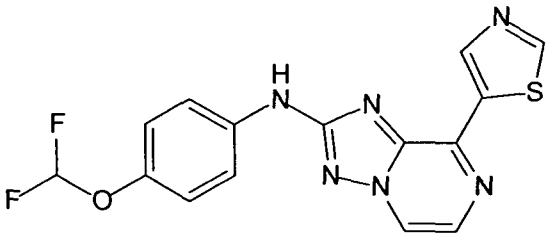
[8-(5-Methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-trifluoromethoxy-phenyl)-amine ("C218")



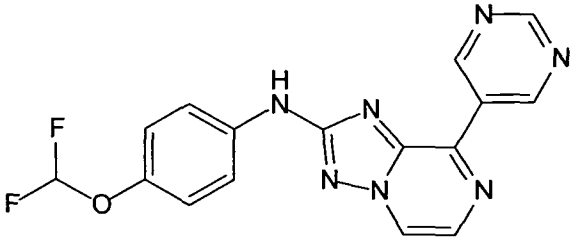
(4-Difluoromethoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C219")



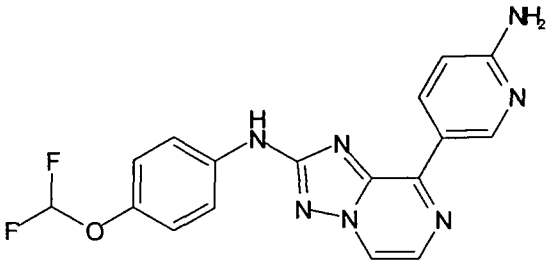
(4-Difluoromethoxy-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C220")



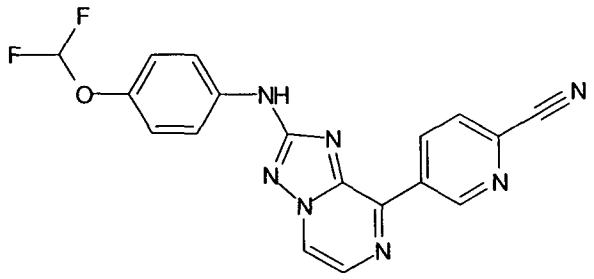
(4-Difluoromethoxy-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C221")



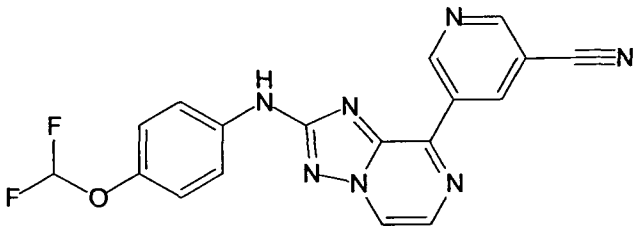
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-difluoromethoxy-phenyl)-amine ("C222")



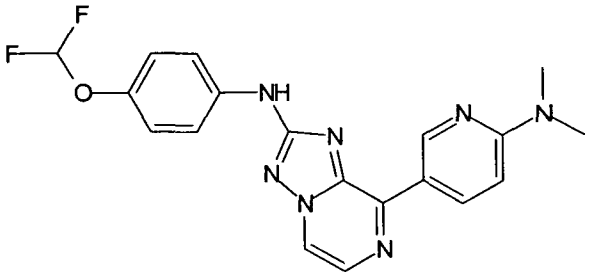
5-[2-(4-Difluoromethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C223")



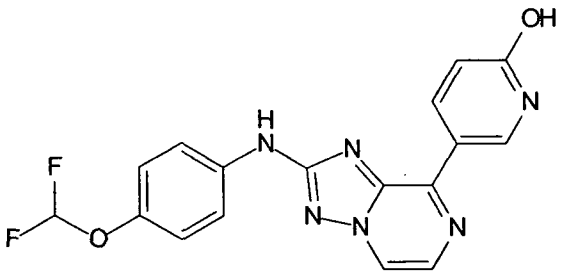
5-[2-(4-Difluoromethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C224")



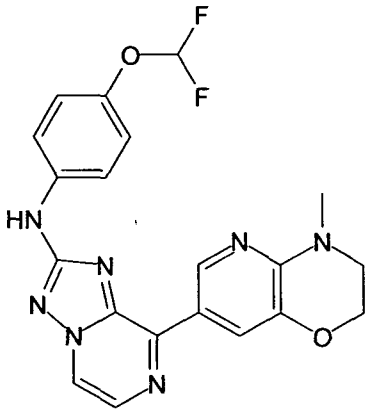
(4-Difluoromethoxy-phenyl)-[8-(6-dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C225")



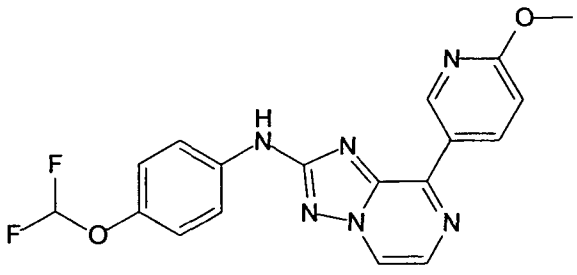
5-[2-(4-Difluoromethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C226")



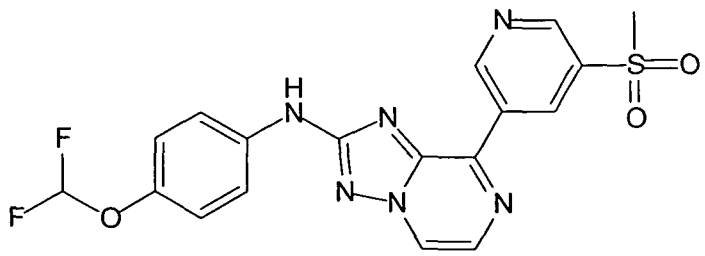
(4-Difluoromethoxy-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C227")



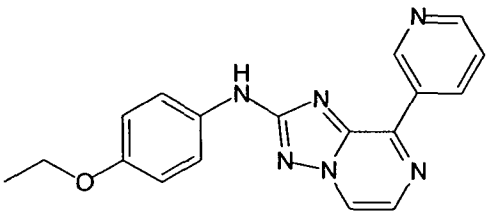
(4-Difluoromethoxy-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C228")



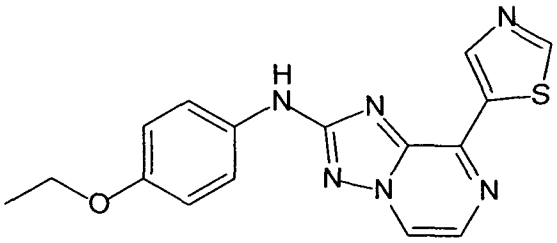
(4-Difluoromethoxy-phenyl)-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C229")



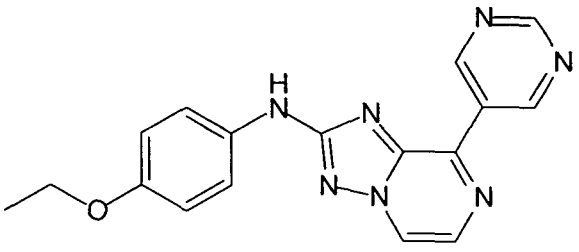
(4-Ethoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C230")



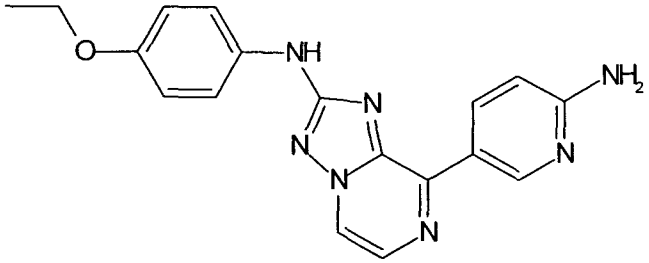
(4-Ethoxy-phenyl)-(8-thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C231")



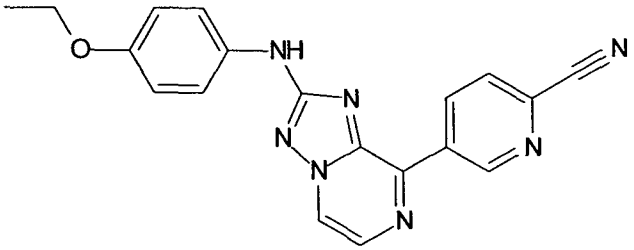
(4-Ethoxy-phenyl)-(8-pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C232")



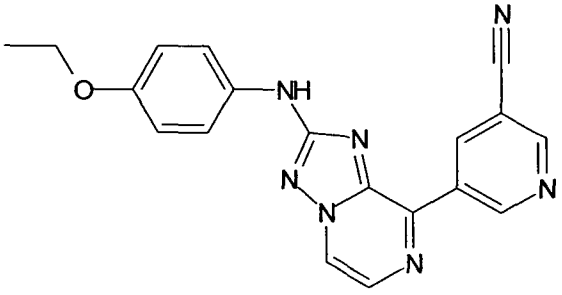
[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-ethoxy-phenyl)-amine ("C233")



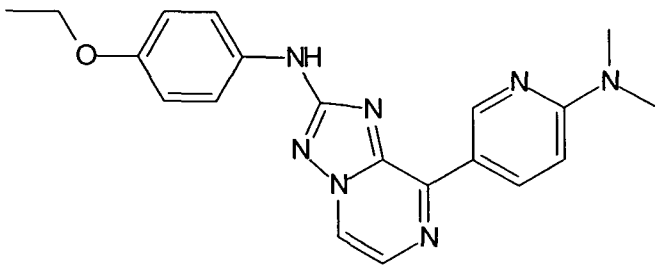
5-[2-(4-Ethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C234")



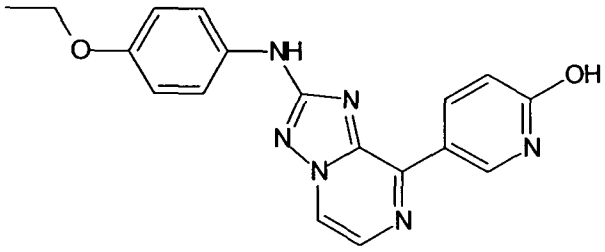
5-[2-(4-Ethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C235")



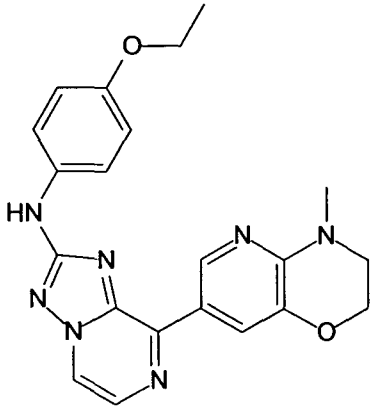
[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-ethoxy-phenyl)-amine ("C236")



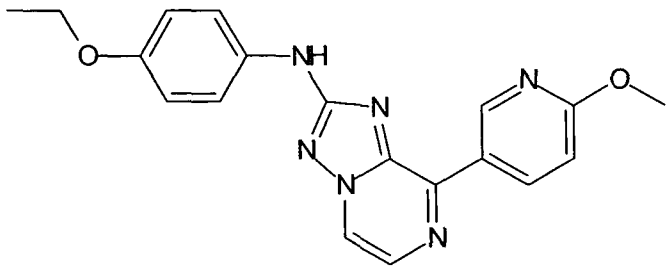
5-[2-(4-Ethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C237")



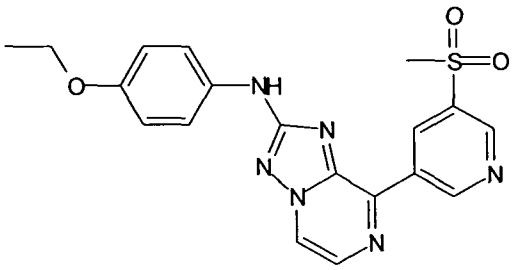
(4-Ethoxy-phenyl)-[8-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C238")



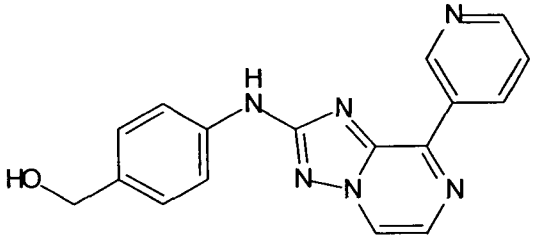
(4-Ethoxy-phenyl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C239")



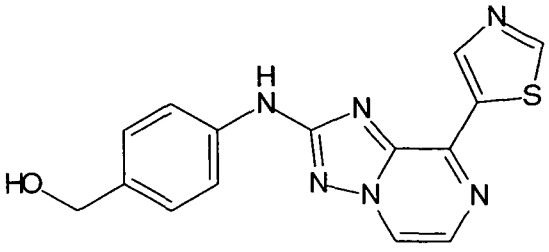
(4-Ethoxy-phenyl)-[8-(5-methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C240")



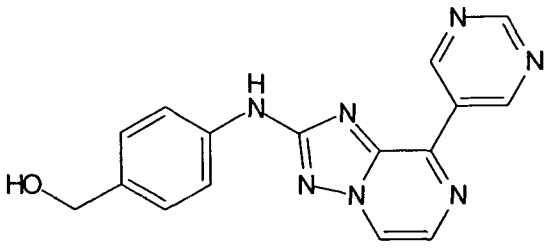
[4-(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-phenyl]-methanol ("C241")



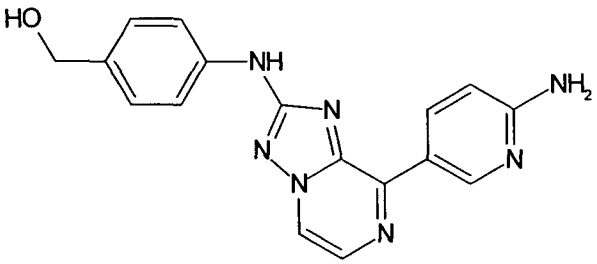
[4-(8-Thiazol-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-phenyl]-methanol ("C242")



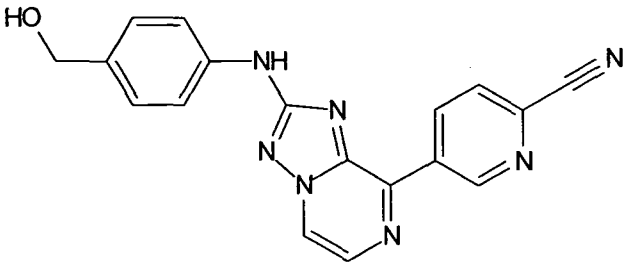
[4-(8-Pyrimidin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-phenyl]-methanol ("C243")



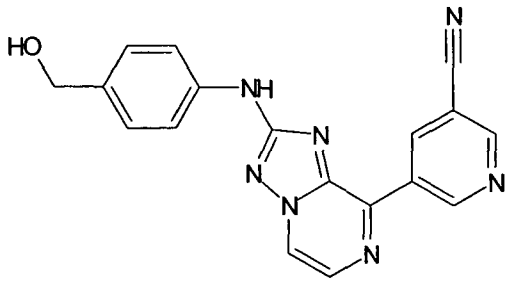
{4-[8-(6-Amino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-phenyl}-methanol ("C244")



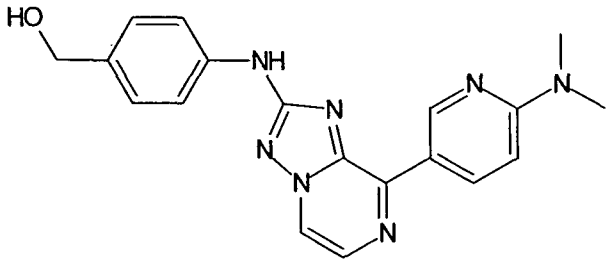
5-[2-(4-Hydroxymethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridine-2-carbonitrile ("C245")



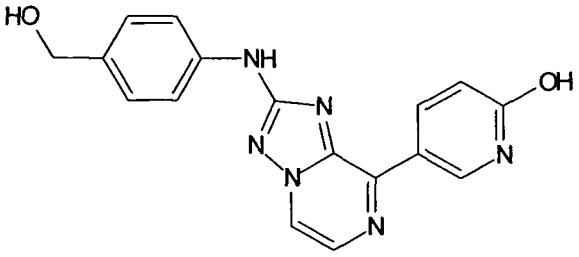
5-[2-(4-Hydroxymethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-nicotinonitrile ("C246")



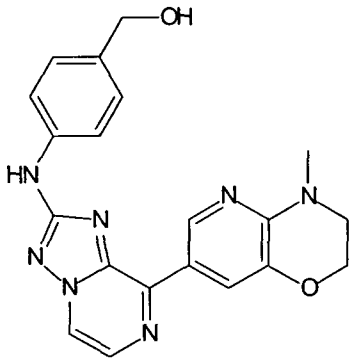
{4-[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-phenyl}-methanol ("C247")



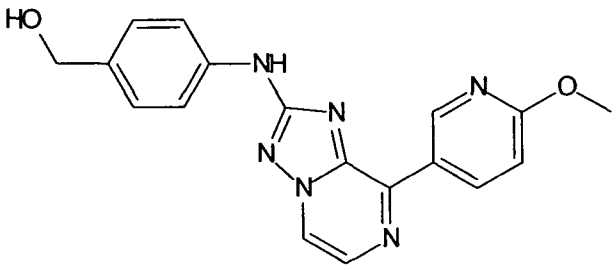
5-[2-(4-Hydroxymethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyridin-2-ol ("C248")



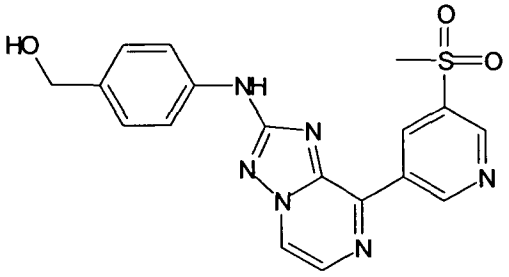
{4-[8-(4-Methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-phenyl}-methanol ("C249")



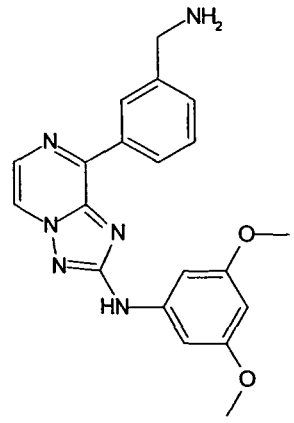
{4-[8-(6-Methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-phenyl}-methanol ("C250")



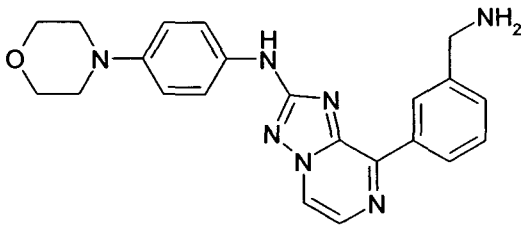
{4-[8-(5-Methanesulfonyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-phenyl}-methanol ("C251")



[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("C252")

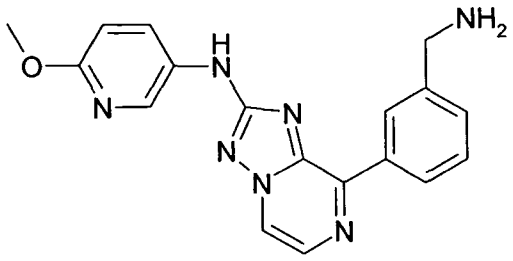


[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("C253")



The compound is synthesized as described in method 2.
HPLC purity (Method A): 96%, RT 2.13 min, (Max), 93.80% (254nm);
LCMS: (method A) 402.0 (M+H), RT. 2.02 min; ^{1}HNMR (400 MHz, DMSO-d_6): δ [ppm] 9.77 (s, 1H), 8.87 (d, *J* = 4.00 Hz, 1H), 8.67-8.63 (m, 2H), 7.69 (d, *J* = 4.2 Hz, 1H), 7.62-7.60 (m, 2H), 7.69 (d, *J* = 4.72 Hz, 2H), 6.94 (d, *J* = 8.00 Hz, 2H), 3.90 (s, 2H), 3.73 (t, *J* = 4.00 Hz, 4H), 3.02 (t, *J* = 4.00 Hz, 4H).

[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(6-methoxy-pyridin-3-yl)-amine ("C254")

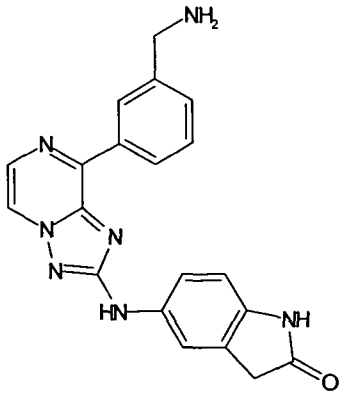


The compound is synthesized as described in method 2.

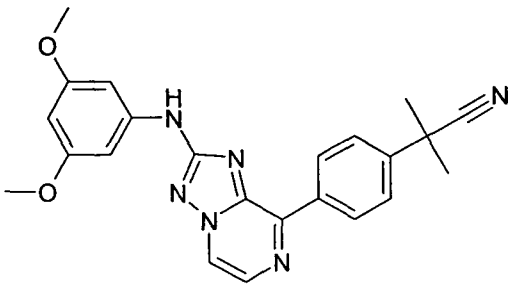
HPLC purity (method A): 98% RT 2.34 min; LCMS: (method A) 348.0 (M+H), RT. 2.26 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.99 (s, 1H), 8.93 (d, *J* = 4.00 Hz, 1H), 8.85-8.80 (m, 1H), 8.64 (s, 1H), 8.53 (d, *J* = 4.00 Hz, 1H), 8.25-8.22 (m, 3H), 8.06 (dd, *J* = 8.00, 4.00 Hz, 1H), 7.66-7.65 (m, 2H), 6.85 (d, *J* = 8.00 Hz, 1H), 4.14 (s, 2H), 3.82 (s, 3H).

5-[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one ("C255")



2-{4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-2-methyl-propionitrile ("C256")

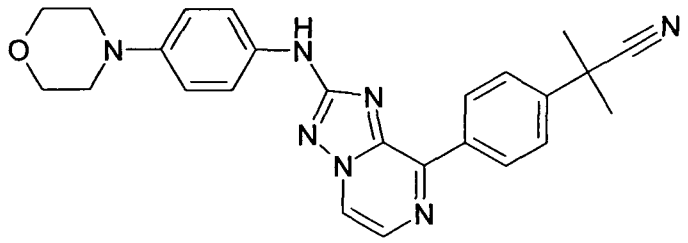


The compound is synthesized as described in method 2.

HPLC purity (method A): 96% RT 5.10 min; LCMS: (method A) 415.3 (M+H), RT. 4.87 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.04 (s, 1H), 8.92 (d, *J* = 4.40 Hz, 1H), 8.73 (d, *J* = 8.00 Hz, 2H), 8.24 (d, *J* = 4.00 Hz, 1H), 7.71 (d, *J* = 8.00 Hz, 2H), 7.03 (d, *J* = 2.00 Hz, 2H), 6.13 (t, *J* = 2.00 Hz, 1H), 3.75 (s, 6H), 1.75 (s, 6H).

2-Methyl-2-{4-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-propionitrile ("C257")

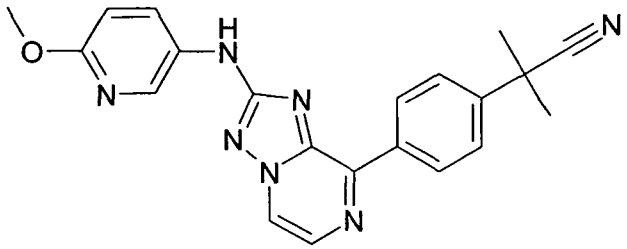


The compound is synthesized as described in method 2.

HPLC purity (method A): 99%, RT 3.69 min, LCMS: (method A) 440.0 (M+H), RT. 3.67 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.78 (s, 1H), 8.88 (d, *J* = 4.00 Hz, 1H), 8.74 (d, *J* = 8.00 Hz, 2H), 8.20 (d, *J* = 4.00 Hz, 1H), 7.73 (d, *J* = 8.00 Hz, 2H), 7.60 (d, *J* = 8.00 Hz, 2H), 6.95 (d, *J* = 8.00 Hz, 2H), 3.73 (t, *J* = 4.00 Hz, 4H), 3.03 (t, *J* = 4.00 Hz, 4H), 1.75 (s, 6H).

2-{4-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-2-methyl-propionitrile ("C258")

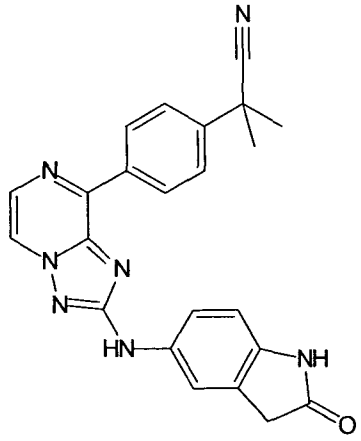


The compound is synthesized as described in method 2.

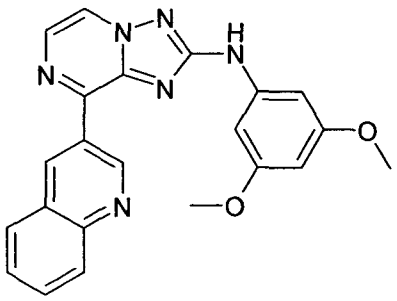
HPLC purity (method A): 98%, RT 4.06 min; LCMS: (method A) 386.0 (M+H), RT. 4.06 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.97 (s, 1H), 8.89 (d, *J* = 8.00 Hz, 1H), 8.73 (d, *J* = 8.00 Hz, 2H), 8.54 (d, *J* = 2.80 Hz, 1H), 8.24 (d, *J* = 4.00 Hz, 1H), 8.03 (dd, *J* = 10.00, 4.00 Hz, 1H), 7.73 (d, *J* = 8.00 Hz, 2H), 6.85 (d, *J* = 8.00 Hz, 1H), 3.82 (s, 3H), 1.75 (s, 6H).

2-Methyl-2-{4-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-propionitrile ("C259")



(3,5-Dimethoxy-phenyl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C260")



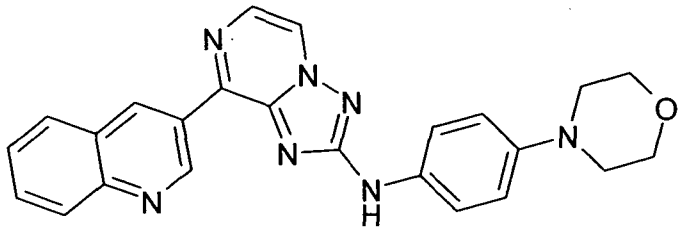
The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 3.74 min; LCMS: (method A) 399.2 (M+H), RT. 3.71 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.10 (s, 1H), 10.04 (d, J = 3.20 Hz, 1H), 9.63 (d, J = 3.20 Hz, 1H), 9.00 (d, J = 4.00 Hz, 1H), 8.33 (d, J = 4.00 Hz,

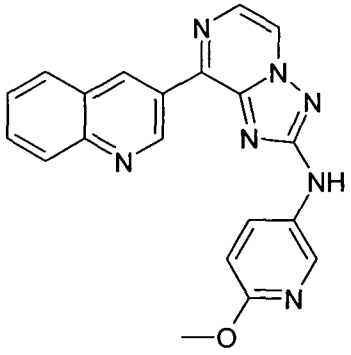
1H), 8.14-8.12 (m, 2H), 7.89-7.85 (m, 1H), 7.74-7.70 (m, 1H), 7.06 (d, J = 4.00 Hz, 2H), 6.15 (t, J = 2.00 Hz, 1H), 3.76 (s, 6H).

(3,5-Dimethoxy-phenyl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C261")



The compound is synthesized as described in method 2.
HPLC purity (method A): 100%, RT 2.54 min, LCMS: (method A) 424.3 (M+H), RT. 2.43 min;
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.04 (d, J = 2.00 Hz, 1H), 9.86 (s, 1H), 9.64 (d, *J* = 4.00 Hz, 1H), 8.95 (d, *J* = 4.00 Hz, 1H), 8.29 (d, *J* = 4.00 Hz, 1H), 8.12 (t, *J* = 8.00 Hz, 2H), 7.89-7.85 (m, 1H), 7.74-7.70 (m, 1H), 7.64-7.61 (m, 2H), 6.97 (d, *J* = 8.00 Hz, 2H), 3.74 (t, *J* = 4.00 Hz, 4H), 3.04 (t, *J* = 4.00 Hz, 4H).

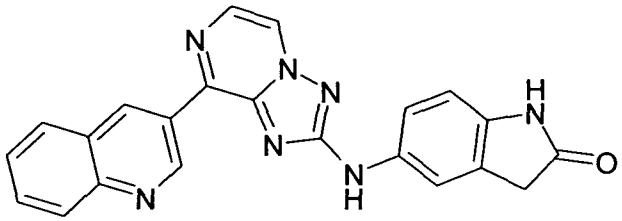
(6-Methoxy-pyridin-3-yl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C262")



The compound is synthesized as described in method 2.
HPLC purity (method A): 100%, RT 2.78 min, LCMS: (method A) 370.0 (M+H), RT. 2.68 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.04 (d, *J* = 2.00 Hz, 2H), 9.61 (d, *J* = 4.00 Hz, 1H), 8.97 (d, *J* = 4.00 Hz, 1H), 8.56 (d, *J* = 3.60 Hz, 1H), 8.32-8.30 (m, 1H), 8.14-8.05 (m, 3H), 7.89-7.85 (m, 1H), 7.74-7.70 (m, 1H), 6.88 (d, *J* = 12.00 Hz, 1H), 3.83 (s, 3H).

5-(8-Quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one ("C263")

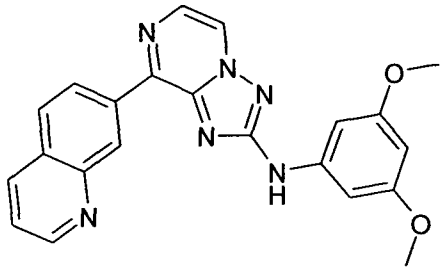


The compound is synthesized as described in method 2.

HPLC purity (method A): 95%, RT 2.61 min; LCMS: (method A) 394.0 (M+H), RT. 2.55 min, 93.71% (Max), 95.02% (254 nm);

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.25 (s, 1H), 10.02 (d, *J* = 4.00 Hz, 1H), 9.95 (s, 1H), 9.66 (s, 1H), 8.97 (d, *J* = 4.00 Hz, 1H), 8.30 (d, *J* = 4.00 Hz, 1H), 8.12 (t, *J* = 4.00 Hz, 2H), 7.87 (t, *J* = 8.00 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, *J* = 8.00 Hz, 1H), 6.80 (d, *J* = 8.00 Hz, 1H), 3.52 (s, 2H).

(3,5-Dimethoxy-phenyl)-(8-quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C264")



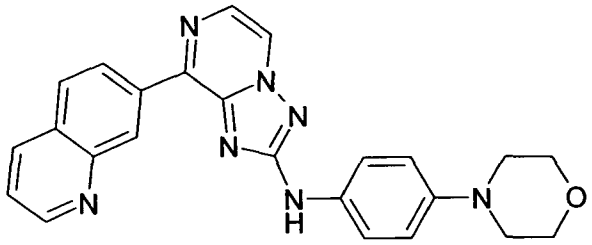
The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 3.44 min, LCMS: (method A) 399.2 (M+H), RT. 3.45 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.15 (s, 1H), 9.69 (t, *J* = 2.00 Hz, 1H),

9.00-8.97 (m, 2H), 8.77 (d, *J* = 8.00 Hz, 1H), 8.45-8.43 (m, 1H), 8.32-8.30 (m, 1H), 8.14 (d, *J* = 8.00 Hz, 1H), 7.61 (dd, *J* = 8.00, 4.00 Hz, 1H), 7.08 (d, *J* = 2.00 Hz, 2H), 6.13 (t, *J* = 4.00 Hz, 1H), 3.79 (s, 6H).

(4-Morpholin-4-yl-phenyl)-(8-quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C265")

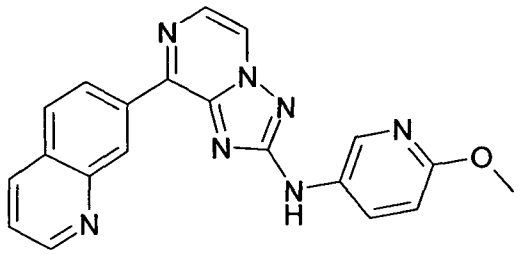


The compound is synthesized as described in method 2.

HPLC purity (method A): 99%, RT 2.34 min; LCMS: (method A) 424.0 (M+H), RT. 2.34 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.92 (s, 1H), 9.66 (s, 1H), 9.00 (dd, J = 4.20, 3.60 Hz, 1H), 8.94 (d, *J* = 4.00 Hz, 1H), 8.78 (dd, *J* = 8.00, 4.00 Hz, 1H), 8.43 (d, *J* = 8.00 Hz, 1H), 8.28 (d, *J* = 4.00 Hz, 1H), 8.15 (d, *J* = 8.00 Hz, 1H), 7.64-7.59 (m, 3H), 6.95 (d, *J* = 8.00 Hz, 2H), 3.74 (t, *J* = 4.00 Hz, 4H), 3.03 (t, *J* = 4.00 Hz, 4H).

(6-Methoxy-pyridin-3-yl)-(8-quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C266")



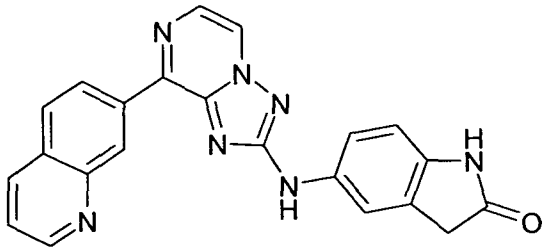
The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 2.63 min, LCMS: (method A) 370.0 (M+H), RT. 2.61 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.10 (s, 1H), 9.64 (s, 1H), 9.00 (dd, *J*

= 4.00, 4.00 Hz, 1H), 8.96 (d, *J* = 4.00 Hz, 1H), 8.77 (d, *J* = 8.00 Hz, 1H), 8.58 (d, *J* = 4.00 Hz, 1H), 8.44 (d, *J* = 8.00 Hz, 1H), 8.31 (d, *J* = 4.00 Hz, 1H), 8.16 (d, *J* = 8.00 Hz, 1H), 8.05 (dd, *J* = 11.60, 4.00 Hz, 1H), 7.62 (dd, *J* = 8.00, 4.00 Hz, 1H), 6.86 (d, *J* = 8.00 Hz, 1H), 3.83 (s, 3H).

5-(8-Quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one ("C267")

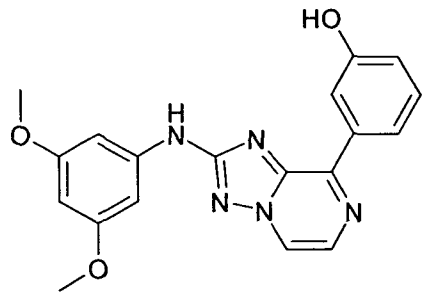


The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 2.47 min, LCMS: (method A) 394.0 (M+H), RT. 2.33 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.25 (s, 1H), 10.02 (s, 1H), 9.68 (s, 1H), 9.01 (dd, *J* = 4.18, 1.72 Hz, 1H), 8.96 (d, *J* = 4.24 Hz, 1H), 8.78 (dd, *J* = 8.68, 1.72 Hz, 1H), 8.44 (d, *J* = -7.68 Hz, 1H), 8.28 (d, *J* = 4.20 Hz, 1H), 8.16 (d, *J* = 8.68 Hz, 1H), 7.68 (s, 1H), 7.63-7.60 (m, 1H), 7.55 (dd, *J* = 8.38, 2.16 Hz, 1H), 6.80 (d, *J* = 8.40 Hz, 1H), 3.52 (s, 2H).

3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C268")

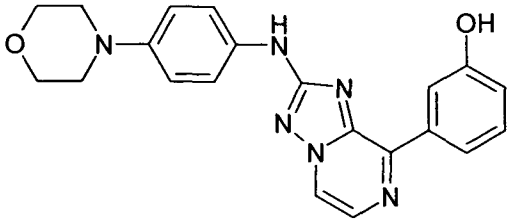


The compound is synthesized as described in method 2.

HPLC purity (method A): 99%, RT 4.13 min; LCMS: (method A) 364.0 (M+H), RT. 4.03 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.01 (s, 1H), 9.64 (s, 1H), 8.88 (d, *J* = 8.00 Hz, 1H), 8.24-8.20 (m, 2H), 8.10-8.09 (m, 1H), 7.34 (t, *J* = 8.00 Hz, 1H), 7.04 (d, *J* = 4.00 Hz, 2H), 6.95-6.92 (m, 1H), 6.11 (t, *J* = 4.00 Hz, 1H), 3.75 (s, 6H).

3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C269")

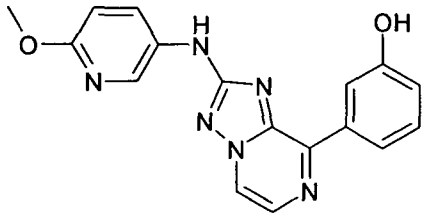


The compound is synthesized as described in method 2.

HPLC purity (method A): 94%, RT 2.68 min, LCMS: (method A) 389.0 (M+H), RT. 2.66 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.75 (s, 1H), 9.63 (s, 1H), 8.84 (d, J = 4.00 Hz, 1H), 8.21 (d, J = 8.00 Hz, 1H), 8.16 (d, J = 4.00 Hz, 1H), 8.08 (t, J = 2.80 Hz, 1H), 7.59 (d, J = 8.00 Hz, 2H), 7.35 (t, J = 8.00 Hz, 1H), 6.95-6.92 (m, 3H), 3.73 (t, J = 4.00 Hz, 4H), 3.02 (t, J = 4.00 Hz, 4H).

3-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("C270")

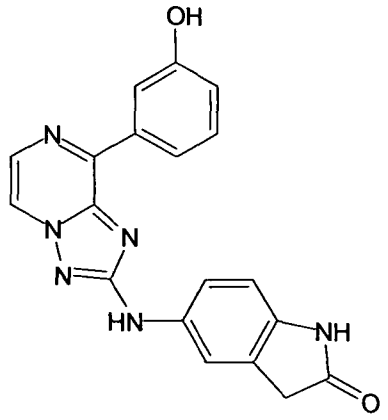


The compound is synthesized as described in method 2.

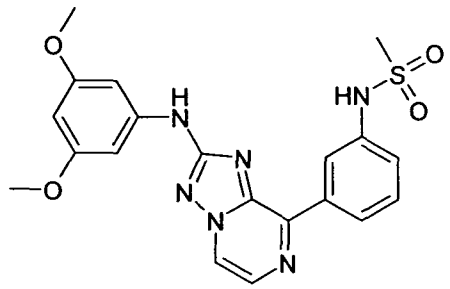
HPLC purity (method A): 98%, RT 2.95 min, LCMS: (method A) 335.0 (M+H), RT. 2.91 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.95 (s, 1H), 9.65 (s, 1H), 8.85 (d, *J* = 4.00 Hz, 1H), 8.53 (d, *J* = 3.20 Hz, 1H), 8.20-8.18 (m, 2H), 8.07-8.06 (m, 1H), 8.03 (dd, *J* = 8.00, 4.00 Hz, 1H), 7.36 (t, *J* = 7.96 Hz, 1H), 6.95 (d, *J* = 4.00 Hz, 1H), 6.93 (d, *J* = 4.00 Hz, 1H), 3.81 (s, 3H).

5-[8-(3-Hydroxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one ("C271")



N-{3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide ("C272")

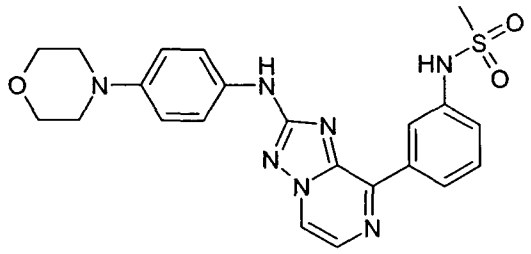


The compound is synthesized as described in method 2.

HPLC purity (method A): 95%, RT 4.14 min, LCMS: (method A) 441.0 (M+H), RT. 4.11 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.01 (s, 1H), 9.92 (s, 1H), 8.93 (d, *J* = 4.00 Hz, 1H), 8.65-8.63 (m, 1H), 8.39 (t, *J* = 3.60 Hz, 1H), 8.25 (d, *J* = 4.00 Hz, 1H), 7.52 (t, *J* = 8.00 Hz, 1H), 7.40-7.37 (m, 1H), 7.03 (d, *J* = 4.00 Hz, 2H), 6.12 (t, *J* = 3.60 Hz, 1H), 3.75 (s, 6H), 3.03 (s, 3H).

N-{3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide ("C273")

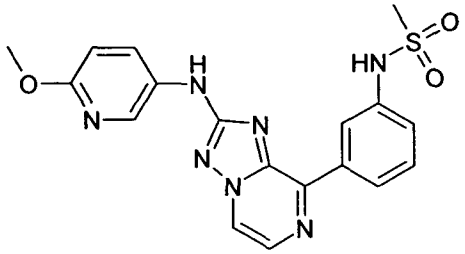


The compound is synthesized as described in method 2.

HPLC purity (method A): 97%, RT 2.83 min, LCMS: (method A) 466.3 (M+H), RT. 2.68 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.92 (s, 1H), 9.75 (s, 1H), 8.88 (d, *J* = 4.00 Hz, 1H), 8.59 (d, *J* = 8.00 Hz, 1H), 8.44-8.43 (m, 1H), 8.20 (d, *J* = 4.00 Hz, 1H), 7.60 (d, *J* = 8.00 Hz, 2H), 7.54 (t, *J* = 8.00 Hz, 1H), 7.38-7.35 (m, 1H), 6.94 (d, *J* = 12.00 Hz, 2H), 3.73 (t, *J* = 4.00 Hz, 4H), 3.03-3.01 (m, 7H).

N-{3-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide ("C274")

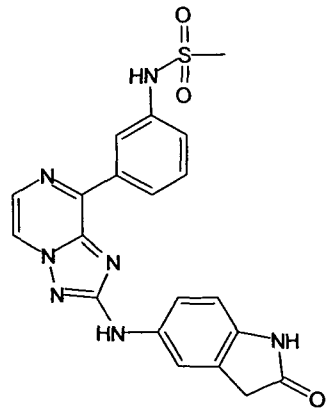


The compound is synthesized as described in method 2.

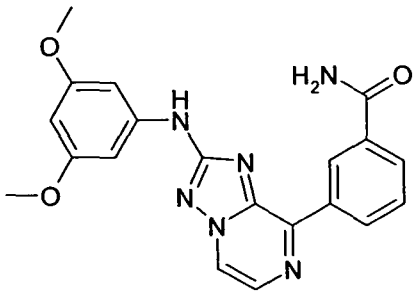
HPLC purity (method A): 98%, RT 3.06 min; LCMS: (method A) 412.0 (M+H), RT. 3.03 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.94 (s, 2H), 8.89 (d, *J* = 4.00 Hz, 1H), 8.55-8.53 (m, 2H), 8.47-8.46 (m, 1H), 8.24 (d, *J* = 4.00 Hz, 1H), 8.07 (dd, *J* = 8.00, 4.00 Hz, 1H), 7.55 (t, *J* = 8.00 Hz, 1H), 7.37 (d, *J* = 8.00 Hz, 1H), 6.83 (d, *J* = 8.92 Hz, 1H), 3.82 (s, 3H), 3.04 (s, 3H).

N-{3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide ("C275")



3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C276")

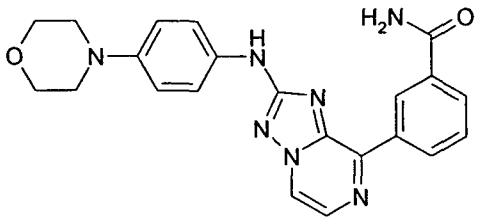


The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 3.68 min; LCMS: (method A) 391.3 (M+H), RT. 3.53 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.05 (s, 1H), 9.04 (t, *J* = 4.00 Hz, 1H), 8.95 (d, *J* = 4.00 Hz, 1H), 8.90-8.87 (m, 1H), 8.30-8.25 (m, 1H), 8.11 (s, 1H), 8.01-7.99 (m, 1H), 7.64 (t, *J* = 8.00 Hz, 1H), 7.48 (s, 1H), 7.03 (d, *J* = 4.00 Hz, 2H), 6.12 (t, *J* = 2.40 Hz, 1H), 3.74 (s, 6H).

3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C277")

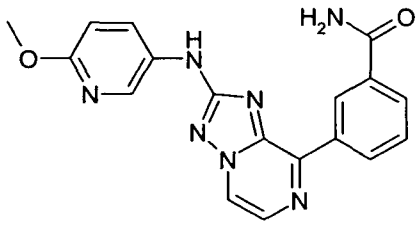


The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 2.45 min; LCMS: (method A) 416.0 (M+H), RT. 2.43 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.81 (s, 1H), 9.14 (t, *J* = 3.60 Hz, 1H), 8.90 (d, *J* = 4.00 Hz, 1H), 8.87-8.84 (m, 1H), 8.22 (d, *J* = 4.00 Hz, 1H), 8.10 (s, 1H), 7.99 (dd, *J* = 6.00, 4.00 Hz, 1H), 7.67-7.61 (m, 3H), 7.49 (s, 1H), 6.94 (d, *J* = 8.00 Hz, 2H), 3.74 (t, *J* = 8.00 Hz, 4H), 3.02 (t, *J* = 4.00 Hz, 4H).

3-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C278")

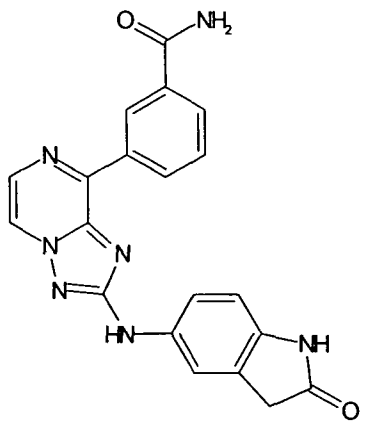


The compound is synthesized as described in method 2.

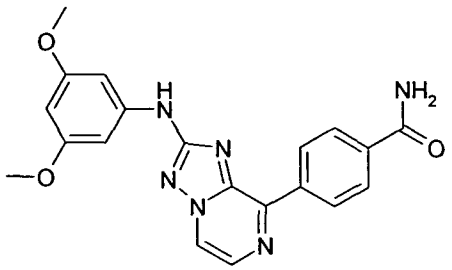
HPLC purity (method A): 98%, RT 2.57 min; LCMS: (method A) 362.0 (M+H), RT. 2.45 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.00 (s, 1H), 9.13 (t, *J* = 3.60 Hz, 1H), 8.91 (d, *J* = 4.00 Hz, 1H), 8.85-8.82 (m, 1H), 8.51 (d, *J* = 4.00 Hz, 1H), 8.25 (d, *J* = 4.00 Hz, 1H), 8.11 (dd, *J* = 8.00, 4.00 Hz, 2H), 8.01-7.99 (m, 1H), 7.66 (t, *J* = 8.00 Hz, 1H), 7.49 (s, 1H), 6.84 (d, *J* = 8.00 Hz, 1H), 3.82 (s, 3H).

3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C279")



4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C280")

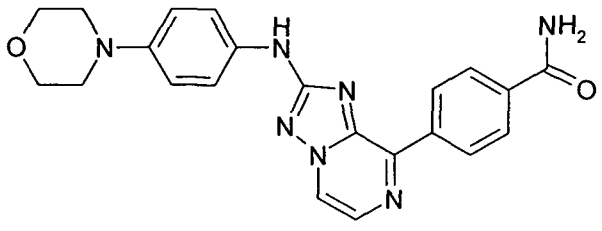


The compound is synthesized as described in method 2.

HPLC purity (method A): 96%, RT 3.60 min, LCMS: (method A) 391.3 (M+H), RT. 3.47 min;

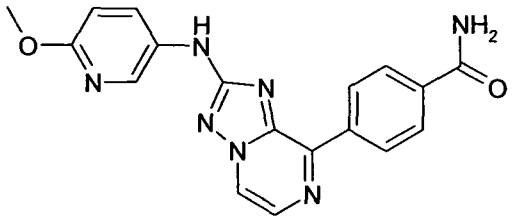
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.07 (s, 1H), 8.96 (d, *J* = 4.00 Hz, 1H), 8.80 (d, *J* = 8.00 Hz, 2H), 8.27 (d, *J* = 4.00 Hz, 1H), 8.12 (s, 1H), 8.05-8.03 (m, 2H), 7.52 (br s, 1H), 7.03 (d, *J* = 2.40 Hz, 2H), 6.13 (t, *J* = 4.00 Hz, 1H), 3.76 (s, 6H).

4-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C281")



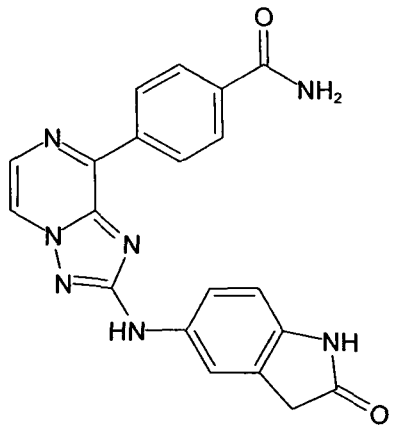
The compound is synthesized as described in method 2.
HPLC purity (method A): 97%, RT 2.33 min, LCMS: (method A) 416.0 (M+H), RT. 2.32 min;
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.83 (s, 1H), 8.91 (d, *J* = 4.00 Hz, 1H), 8.79 (dd, *J* = 8.00, 4.00 Hz, 2H), 8.22 (d, *J* = 4.00 Hz, 1H), 8.10 (s, 1H), 8.05 (dd, *J* = 6.00, 4.00 Hz, 2H), 7.61-7.58 (m, 2H), 7.50 (s, 1H), 6.95 (d, *J* = 8.00 Hz, 2H), 3.73 (t, *J* = 4.00 Hz, 4H), 3.03 (t, *J* = 4.00 Hz, 4H).

4-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C282")

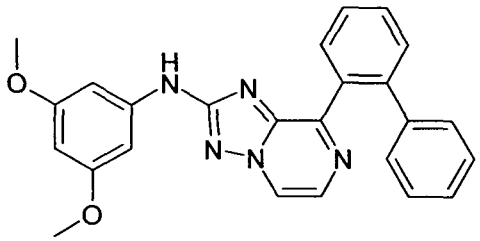


The compound is synthesized as described in method 2.
HPLC purity (method A): 98%, RT 2.52 min, LCMS: (method A) 362.0 (M+H), RT. 2.39 min;
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.02 (s, 1H), 8.92 (d, *J* = 4.20 Hz, 1H), 8.77 (d, *J* = 8.48 Hz, 2H), 8.55 (d, *J* = 2.80 Hz, 1H), 8.26 (d, *J* = 4.20 Hz, 1H), 8.11-8.02 (m, 4H), 7.51 (s, 1H), 6.85 (d, *J* = 8.88 Hz, 1H), 3.82 (s, 3H).

4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide ("C283")

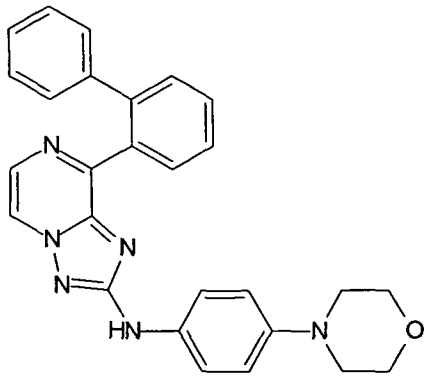


(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3,5-dimethoxy-phenyl)-amine ("C284")

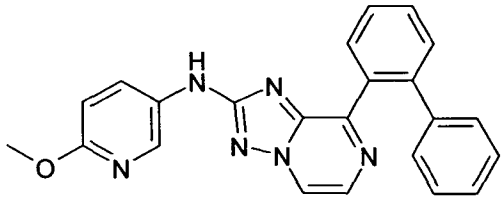


The compound is synthesized as described in method 2.
HPLC purity (method A): 97%, RT 5.06 min; LCMS: (method A) 424.2 (M+H), RT. 5.10 min;
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.81 (s, 1H), 8.80 (d, *J* = 4.00 Hz, 1H), 8.00 (d, *J* = 4.00 Hz, 1H), 7.72 (d, *J* = 2.00 Hz, 1H), 7.63-7.59 (m, 1H), 7.54-7.50 (m, 2H), 7.18-7.12 (m, 3H), 7.08-7.06 (m, 2H), 6.84 (d, *J* = 3.60 Hz, 2H), 6.08 (t, *J* = 4.00 Hz, 1H), 3.70 (s, 6H).

(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(4-morpholin-4-yl-phenyl)-amine ("C285")

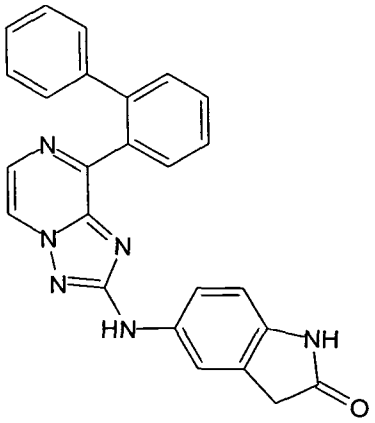


(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(6-methoxy-pyridin-3-yl)-amine ("C286")

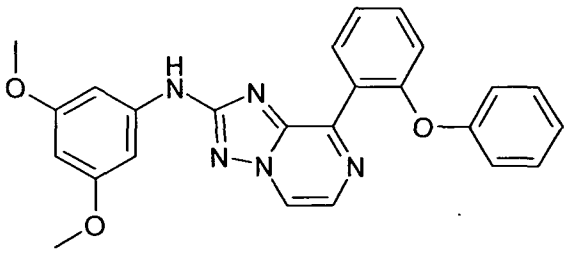


The compound is synthesized as described in method 2.
HPLC purity (method A): 99%, RT 3.98 min; LCMS: (method A) 395.0 (M+H), RT. 3.89 min;
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.72 (s, 1H), 8.77 (d, *J* = 4.00 Hz, 1H), 8.34 (d, *J* = 4.00 Hz, 1H), 8.02 (d, *J* = 4.00 Hz, 1H), 7.85-7.83 (m, 1H), 7.70 (d, *J* = 8.00 Hz, 1H), 7.64-7.60 (m, 1H), 7.55-7.51 (m, 2H), 7.18-7.12 (m, 3H), 7.09-7.07 (m, 2H), 6.80 (d, *J* = 12.00 Hz, 1H), 3.79 (s, 3H).

5-(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one ("C287")

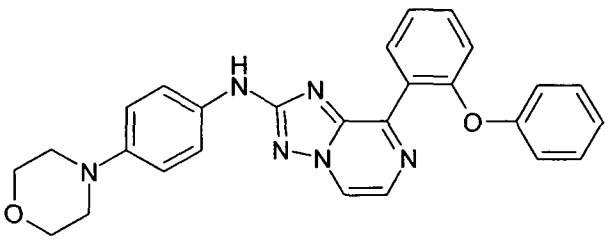


(3,5-Dimethoxy-phenyl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C288")



The compound is synthesized as described in method 2.
HPLC purity (method A): 95%, RT 5.09 min; LCMS: (method A) 440.3 (M+H), RT. 5.01 min;
^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 8.31 (d, *J* = 4.00 Hz, 1H), 8.10 (d, *J* = 4.00 Hz, 1H), 7.77 (dd, *J* = 7.00, 2.00 Hz, 1H), 7.49-7.44 (m, 1H), 7.31-7.27 (m, 1H), 7.22-7.18 (m, 2H), 7.10-7.06 (m, 2H), 6.99-6.94 (m, 3H), 6.82 (d, *J* = 2.80 Hz, 2H), 6.17 (t, *J* = 4.00 Hz, 1H), 3.82 (s, 6H).

(4-Morpholin-4-yl-phenyl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C289")

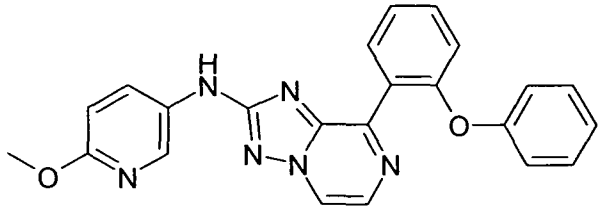


The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 3.68 min; LCMS: (method A) 465.3 (M+H), RT. 3.62 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.70 (s, 1H), 8.81 (d, *J* = 4.00 Hz, 1H), 8.08 (d, *J* = 4.00 Hz, 1H), 7.71 (dd, *J* = 8.00, 4.00 Hz, 1H), 7.54-7.49 (m, 3H), 7.32-7.28 (m, 1H), 7.26-7.22 (m, 2H), 7.03-6.98 (m, 2H), 6.93-6.89 (m, 4H), 3.72 (t, *J* = 4.00 Hz, 4H), 3.01 (t, *J* = 8.00 Hz, 4H).

(6-Methoxy-pyridin-3-yl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C290")

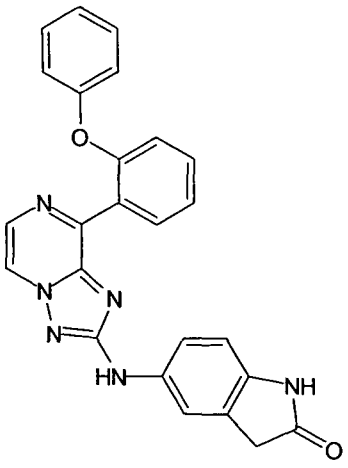


The compound is synthesized as described in method 2.

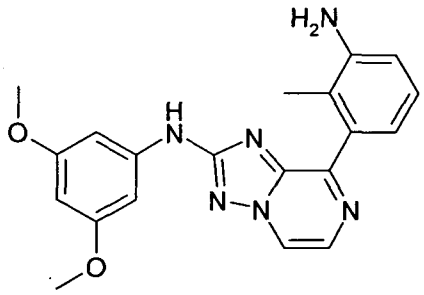
HPLC purity (method A): 98%, RT 4.14 min, LCMS: (method A) 411.0 (M+H), RT. 4.15 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.84 (s, 1H), 8.82 (d, *J* = 8.00 Hz, 1H), 8.45 (d, *J* = 4.00 Hz, 1H), 8.12 (d, *J* = 4.00 Hz, 1H), 7.92-7.91 (m, 1H), 7.72-7.70 (m, 1H), 7.54-7.50 (m, 1H), 7.31 (t, *J* = 8.00 Hz, 1H), 7.23 (t, *J* = 8.00 Hz, 2H), 7.03-7.01 (m, 2H), 6.90-6.89 (m, 2H), 6.81 (d, *J* = 12.00 Hz, 1H), 3.80 (s, 3H).

5-[8-(2-Phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one ("C291")



[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("C292")

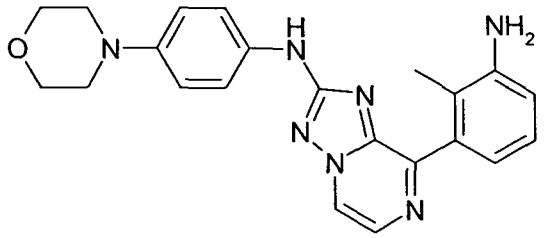


The compound is synthesized as described in method 1.

HPLC purity (method A): 99%, RT 3.07 min, LCMS: (method A) 377.3 (M+H), RT. 3.97 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.90 (s, 1H), 8.88 (d, *J* = 4.00 Hz, 1H), 8.17 (d, *J* = 4.00 Hz, 1H), 6.99 (t, *J* = 8.00 Hz, 1H), 6.91 (d, *J* = 4.00 Hz, 2H), 6.75 (d, *J* = 8.00 Hz, 2H), 6.08 (t, *J* = 3.20 Hz, 1H), 5.00 (s, 2H), 3.70 (s, 6H), 1.93 (s, 3H).

[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("C293")

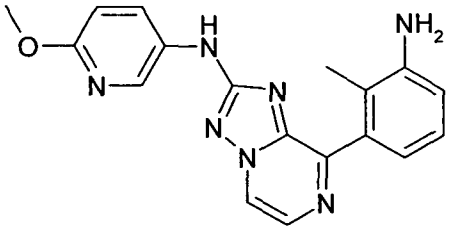


The compound is synthesized as described in method 1.

HPLC purity (method A): 98%, RT 1.93 min; LCMS: (method A) 402.0 (M+H), RT. 1.81 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.64 (s, 1H), 8.84-8.82 (m, 1H), 8.12 (d, *J* = 4.00 Hz, 1H), 7.51-7.47 (m, 2H), 6.99 (t, *J* = 4.00 Hz, 1H), 6.91-6.88 (m, 2H), 6.76-6.73 (m, 2H), 4.99 (s, 2H), 3.72 (t, *J* = 8.00 Hz, 4H), 3.00 (t, *J* = 4.00 Hz, 4H), 1.91 (s, 3H).

[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(6-methoxy-pyridin-3-yl)-amine ("C294")

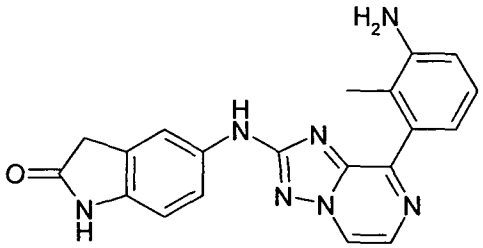


The compound is synthesized as described in method 1.

HPLC purity (method A): 99%, RT 2.16 min;LCMS: (method A) 348.0 (M+H), RT. 2.06 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.84 (s, 1H), 8.85 (d, *J* = 4.36 Hz, 1H), 8.46-8.45 (m, 1H), 8.16 (d, *J* = 4.32 Hz, 1H), 7.92 (dd, *J* = 8.92, 2.84 Hz, 1H), 7.01 (t, *J* = 7.68 Hz, 1H), 6.81-6.74 (m, 3H), 5.01 (s, 2H), 3.32 (s, 3H), 1.93 (s, 3H).

5-[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one ("C295")

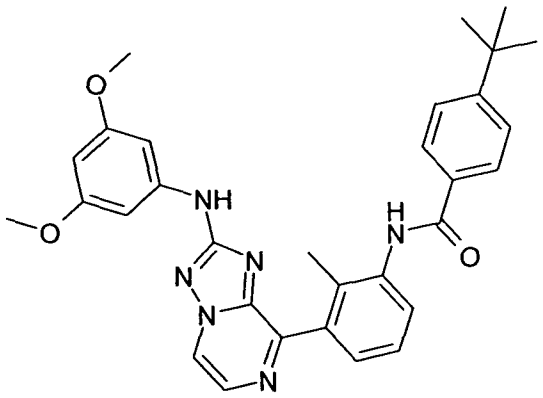


The compound is synthesized as described in method 1.

HPLC purity (method A): 95%, RT 3.52 min; LCMS: (method A) 372.0 (M+H), RT. 1.90 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.22 (s, 1H), 9.76 (s, 1H), 8.85 (d, *J* = 4.36 Hz, 1H), 8.13 (d, *J* = 4.00 Hz, 1H), 7.53 (s, 1H), 7.44-7.42 (m, 1H), 7.00 (t, *J* = 7.72 Hz, 1H), 6.76-6.72 (m, 3H), 5.01 (br s, 2H), 3.47 (s, 2H), 1.92 (s, 3H).

4-tert-Butyl-N-{3-[2-(3,5-dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-2-methyl-phenyl}-benzamide ("C296")

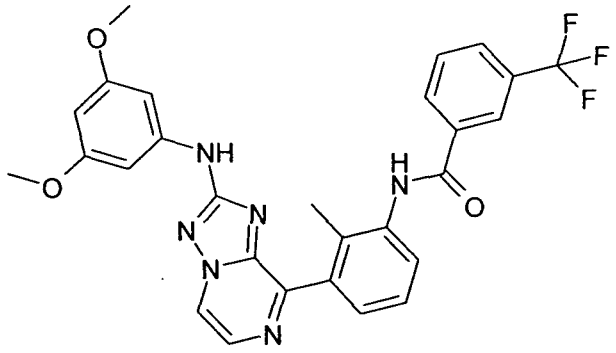


The compound is synthesized as described in method 3.

HPLC purity (method A): 100%, RT 5.44 min; LCMS: (method A) 537.3 (M+H), RT. 5.35 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.95 (d, J = 8.00 Hz, 2H), 8.94 (d, J = 4.00 Hz, 1H), 8.22 (d, J = 4.00 Hz, 1H), 7.94 (dd, *J* = 8.00, 4.00 Hz, 2H), 7.55-7.53 (m, 3H), 7.48-7.46 (m, 1H), 7.36 (t, *J* = 8.00 Hz, 1H), 6.91 (d, *J* = 4.00 Hz, 2H), 6.09 (t, *J* = 2.00 Hz, 1H), 3.70 (s, 6H), 2.15 (s, 3H), 1.31 (s, 9H).

N-{3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-2-methyl-phenyl}-3-trifluoromethyl-benzamide ("C297")

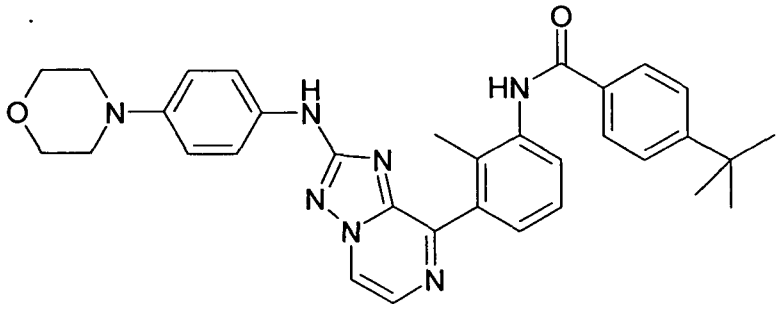


The compound is synthesized as described in method 3.

HPLC purity (method A): 97%, RT 5.12 min; LCMS: (method A) 549.0 (M+H), RT. 4.95 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.31 (s, 1H), 9.96 (s, 1H), 8.95 (d, *J* = 4.00 Hz, 1H), 8.33-8.29 (m, 2H), 8.23 (d, *J* = 4.00 Hz, 1H), 7.98 (d, *J* = 8.00 Hz, 1H), 7.80 (t, *J* = 8.00 Hz, 1H), 7.58-7.56 (m, 1H), 7.49 (d, *J* = 8.00 Hz, 1H), 7.38 (t, *J* = 8.00 Hz, 1H), 6.91 (d, *J* = 2.40 Hz, 2H), 6.09 (t, *J* = 3.20 Hz, 1H), 3.70 (s, 6H), 2.16 (s, 3H).

4-tert-Butyl-N-{2-methyl-3-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-benzamide ("C298")



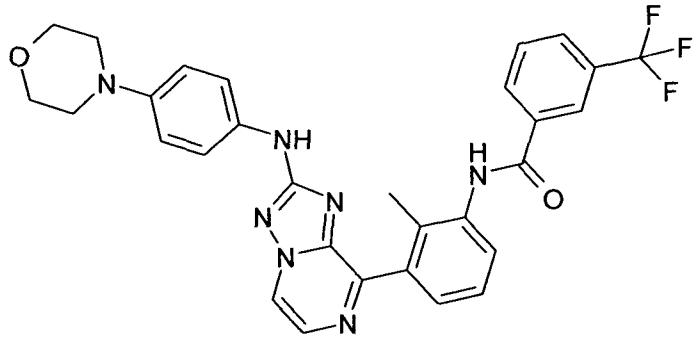
The compound is synthesized as described in method 3.

HPLC purity (method A): 98%, RT 4.28 min, LCMS: (method A) 562.3 (M+H), RT. 4.20 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.95 (s, 1H), 9.71 (s, 1H), 8.89 (d, *J* = 4.00 Hz, 1H), 8.18 (d, *J* = 4.00 Hz, 1H), 7.94 (dd, *J* = 6.40, 2.80 Hz, 2H),

7.55-7.46 (m, 6H), 7.36 (t, *J* = 8.00 Hz, 1H), 6.91 (d, *J* = 8.00 Hz, 2H), 3.72 (t, *J* = 4.00 Hz, 4H), 3.00 (t, *J* = 4.00 Hz, 4H), 2.14 (s, 3H), 1.31 (s, 9H).

N-{2-Methyl-3-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-3-trifluoromethyl-benzamide ("C299")

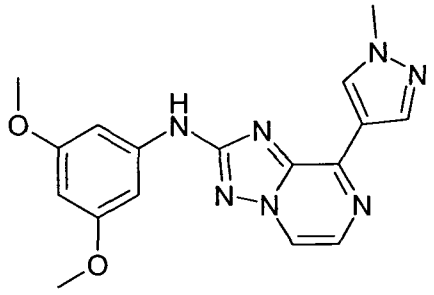


The compound is synthesized as described in method 3.

HPLC purity (method A): 97%, RT 3.91 min, LCMS: (method A) 574.0 (M+H), RT. 3.81 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.32 (s, 1H), 9.71 (s, 1H), 8.90 (d, *J* = 4.00 Hz, 1H), 8.33-8.30 (m, 2H), 8.18 (d, *J* = 8.00 Hz, 1H), 7.98 (d, *J* = 8.00 Hz, 1H), 7.80 (t, *J* = 8.00 Hz, 1H), 7.55.7.47 (m, 4H), 7.38 (t, *J* = 8.00 Hz, 1H), 6.92-6.90 (m, 2H), 3.72 (t, *J* = 4.00 Hz, 4H), 3.01 (t, *J* = 8.00 Hz, 4H), 2.15 (s, 3H).

(3,5-Dimethoxy-phenyl)-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C300")

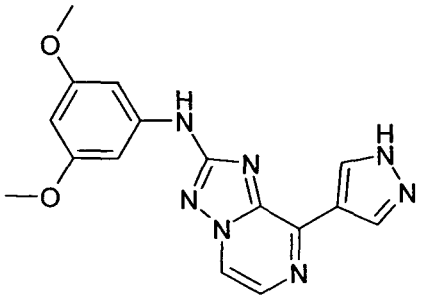


The compound is synthesized as described in method 1.

HPLC purity (method A): 97%, RT 3.64 min, LCMS: (method A) 352.0 (M+H), RT. 3.5 min;

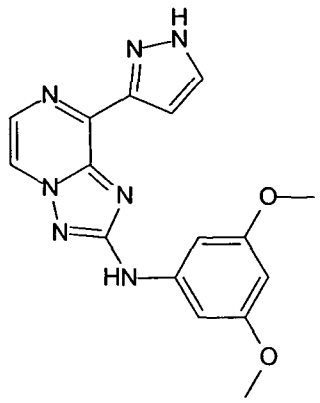
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.92 (s, 1H), 8.72 (d, *J* = 4.32 Hz, 1H), 8.65 (s, 1H), 8.40 (s, 1H), 8.06 (d, *J* = 4.36 Hz, 1H), 7.02 (d, *J* = 2.24 Hz, 2H), 6.12 (t, *J* = 2.16 Hz, 1H), 3.96 (s, 3H), 3.76 (s, 6H).

(3,5-Dimethoxy-phenyl)-[8-(1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C301")

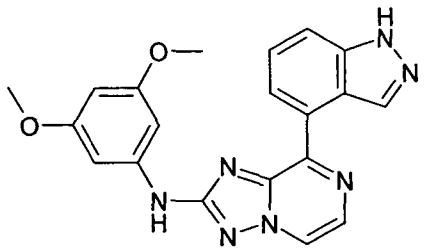


The compound is synthesized as described in method 1.
HPLC purity (method A): 95%, RT 3.34 min, LCMS: (method A) 338.0 (M+H), RT. 3.23 min;
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 13.40 (s, 1H), 9.90 (s, 1H), 8.73-8.71 (m, 2H), 8.44 (d, *J* = 1.76 Hz, 1H), 8.06 (d, *J* = 4.28 Hz, 1H), 7.02 (d, *J* = 2.20 Hz, 2H), 6.12 (t, *J* = 2.20 Hz, 1H), 3.76 (s, 6H).

(3,5-Dimethoxy-phenyl)-[8-(1H-pyrazol-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C302")



(3,5-Dimethoxy-phenyl)-[8-(1H-indazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("C303")

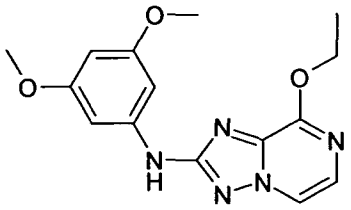


The compound is synthesized as described in method 1.

HPLC purity (method A): 95%, RT 4.03 min; LCMS: (method A) 388.3 (M+H), RT. 3.91 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 13.31 (s, 1H), 10.06 (s, 1H), 8.92-8.93 (m, 2H), 8.82 (t, *J* = 1.40 Hz, 1H), 8.36 (d, *J* = 4.20 Hz, 1H), 7.75 (d, *J* = 8.32 Hz, 1H), 7.53 (dd, *J* = 8.24, 7.40 Hz, 1H), 7.05 (d, *J* = 2.20 Hz, 2H), 6.12 (t, *J* = 2.20 Hz, 1H), 3.76 (s, 6H).

(3,5-Dimethoxy-phenyl)-(8-ethoxy-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("C304")

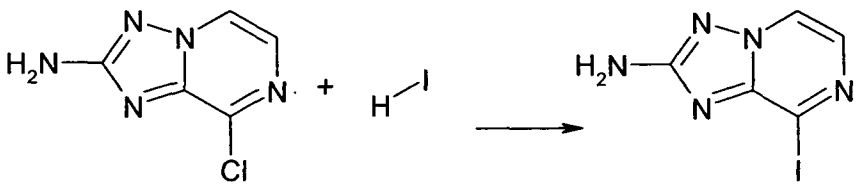


The compound is synthesized as described in method 2.

HPLC purity (method A): 98%, RT 4.12 min; LCMS: (method A) 316.0 (M+H), RT. 3.98 min;

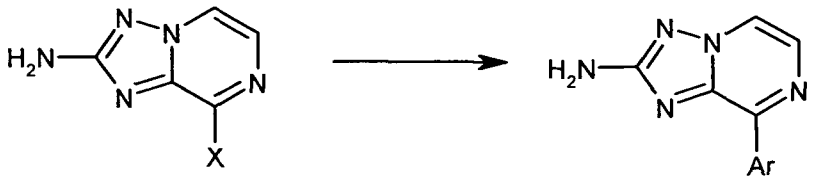
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.75 (s, 1H), 8.47 (d, *J* = 4.52 Hz, 1H), 7.59 (d, *J* = 4.52 Hz, 1H), 6.89 (d, *J* = 2.20 Hz, 2H), 6.09 (t, *J* = 2.20 Hz, 1H), 4.51 (q, *J* = 7.04 Hz, 2H), 3.72 (s, 6H), 1.41 (t, *J* = 7.04 Hz, 3H).

Synthesis of 8-Iodo-[1,2,4]triazolopyrazin-2-ylamine



8-Chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine (5.500 g; 32.43 mmol) is suspended in water (40.0 ml) before HI (67%, 21.855 ml; 194 mmol) is added. The mixture is stirred at 50°C for 14 h and monitored by HPLC. The mixture is cooled to Rt, diluted with water. After adding NaOH till pH 14 is reached, the resulting suspension is cooled to 0°C and all solids are filtered off giving 8-Iodo-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine (7.850 g; 30.074 mmol) as a yellow solid.

General procedure for Suzuki-Miyaura Coupling 1



1 Equivalent 8-halo-[1,2,4]triazolopyrazin-2-ylamine, 1.1 eq. boronic acid (or corresponding boronic ester), 0.03 eq. palladium(II)acetate, 0.06 eq X-Phos and 2 eq. potassiumcarbonate are given into a microwavetube charged with a stir bar. The tube is sealed, evacuated and backfilled with argon. A mixture of acetonitrile and water (2:1 v/v, 4mL / mmol) (briefly degassed by bubbling argon under ultra-sonic irradtion through the mixture for 10 min or evacuating and backfilling with argon) is added under nitrogene via syringe. The tube is heated at 150°C under microwave irradiation for an appropriate time and monitored by HPLC-MS. Upon completion, the mixture is diluted with ethylacetate, filtered over a plug of Celite and evaporated under reduced pressure.

The crude product is loaded on silica and purified via column chromatography.

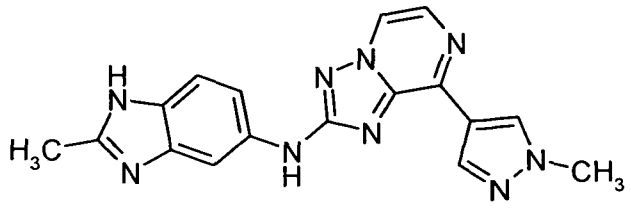
General Procedure for Buchwald-Hartwig amination 2

1 Eq. of triazolopyrazine, 1.1 eq. halogene coupling partner and 0.03 eq. chloro[2-dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-tri-isopropyl-1′,1-biphenyl[2-(2-aminoethyl)phenyl)Pd(II) (Brettphose-Precat) in a screw capped or microwave vial are dissolved in tert.-Butanol (5 mL / mmol). The mixture is degassed by evacuating and backfilling with nitrogene for 3 times before LHMDS (2 eq. 1.1 M in THF) is added and the reaction mixture is heated to 110°C and monitored by HPLC. Upon completion, the mixture is quenched with water, diluted with ethylacetate and filtered over Celite. The solvent is removed in Vaccuum and the residue purified via chromatography or preparative HPLC.

General Procedure for nucleophilic aromatic Substitution 3

To a microwave vial stir bar is added 1 eq. of triazolopyrazine, 1.1 eq. of the corresponding amine and potassium carbonate (2 eq). N,N-dimethylformamide (3 mL / mmol) is added and the suspension heated in the microwave at 180°C. The reaction is monitored by HPLC. Upon completion, the mixtured is diluted with ethylacetate, filtered over Celite and concentrated. The residue is purified via column chromatography or preparative HPLC.

(2-Methyl-1H-benzoimidazol-5-yl)-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D1")



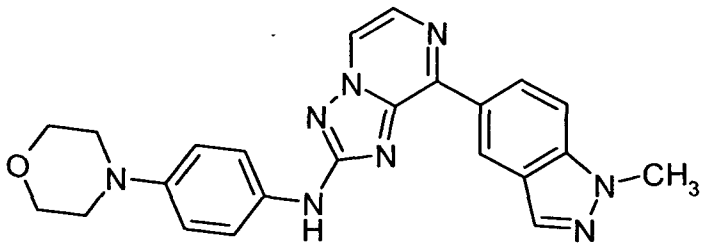
Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 1-methyl-1H-pyrazole-4-boronic-acid pinacol ester are converted following general procedure 1. Flash colulmn chromatography on silica with DCM and methanol as solvent system give the desired coupling product pure.

Step 2:

8-(1-Methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine and 5-bromo-2-methyl-1H-1,3-benzodiazole are coupled following general procedure 2. Purification via preparative HPLC gives "D1" as beige solid; HPLC purity (method E): 100%, Rt: 2.19 min, observed [MH+] = 346.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.77 (s, 1H), 8.71 (t, J=4.2, 1H), 8.69 (d, J=4.3, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 8.04 (dd, J=4.3, 1.6, 1H), 8.00 (s, 1H), 7.37 (ddd, J=13.9, 6.9, 3.6, 2H), 4.00 (s, 4H), 2.46 (s, 3H).

[8-(1-Methyl-1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("D2")



Step 1:

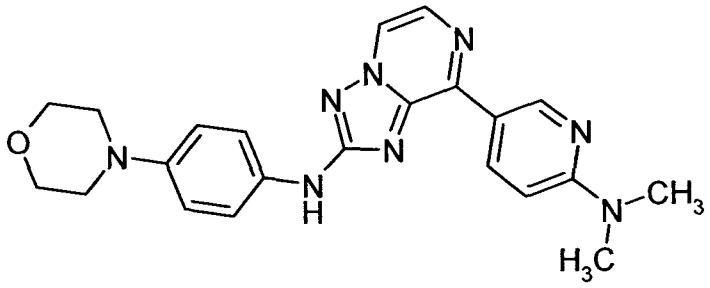
8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 1-methylindazole-5-boronic acid are reacted under Suzuki-conditions described in general procedure 1. Purification via column chromatographie (dichlormethane and ethanol as solvents) gives the desired intermediate.

Step 2:

Amination reaction is performed using general procedure 2 with 4-(4-chloro-phenyl)-morpholine as aryl-halide. Puricifation is performed via preparative HPLC and gives "D2";

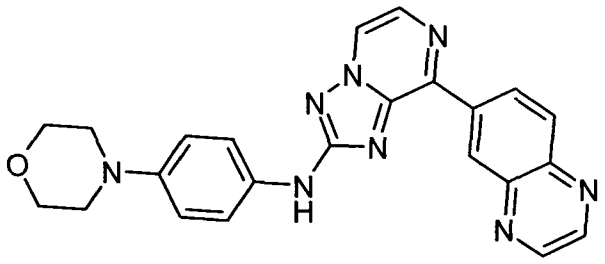
HPLC purity (method E): 95%, Rt.: 1.95 min, observed [MH+] 427.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.78 (s, 1H), 9.37 (d, J=0.6, 1H), 8.82 (d, J=4.2, 1H), 8.70 (dd, J=9.0, 1.5, 1H), 8.27 (d, J=0.7, 1H), 8.19 (d, J=4.2, 1H), 7.82 (d, J=9.0, 1H), 7.64 (d, J=9.0, 2H), 6.98 (d, J=9.1, 3H), 4.12 (s, 3H), 3.76 (d, J=4.9, 4H), 3.07 – 3.03 (m, 4H).

[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("D3")



Step 1:
Reaction of 8-chloro-[1,2,4]triazolopyrazin-2-ylamine and 2-(dimethylamino)-pyridine-5-boronic acid hydrochloride using general procedure 1 in this case with 6 mol-% chloro[2-dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-tri-isopropyl-1′,1-biphenxyl[2-(2-aminoethyl)phenyl)Pd(II) (Brettphose-Precat) instead of X-Phos gives after purification via flash chromatography (Silica, Cyclohexane, Ethylacetate as solvent) the desired product.
Step 2:
The Buchwald-Hartwig amination is done analogously to "D2" and gives "D3";
HPLC purity (method E): 100%, Rt.: 1.43 min, observed [MH+] = 417.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.65 (s, 1H), 9.53 (d, J=2.2, 1H), 8.76 – 8.67 (m, 2H), 8.08 (d, J=4.2, 1H), 7.62 – 7.56 (m, 2H), 6.95 (d, J=9.1, 2H), 6.82 (d, J=9.1, 1H), 5.75 (s, 0H), 3.78 – 3.71 (m, 4H), 3.15 (s, 6H), 3.08 – 3.00 (m, 4H).

(4-Morpholin-4-yl-phenyl)-(8-quinoxalin-6-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D4")



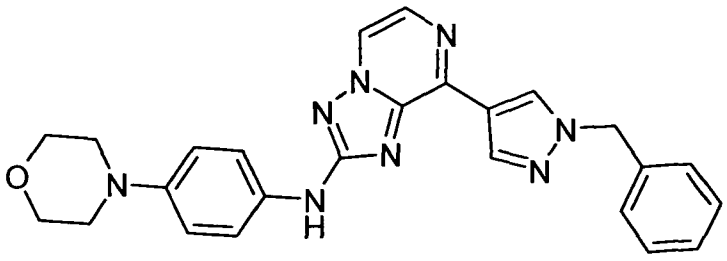
Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoxaline are coupled using general procedure 1. The crude material is purified via column chromatographie on SiO_2 (DCM and methanol as solvent).

Step 2:

Reaction is run under the conditions described for "D2" and gives "D4";
HPLC purity (method E): 98%, Rt: 1.89 min, observed [MH+] = 425.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.92 (s, 1H), 9.71 (d, J=1.9, 1H), 9.08 – 9.00 (m, 3H), 8.97 (d, J=4.2, 1H), 8.29 (dd, J=14.2, 6.5, 2H), 7.64 (d, J=9.0, 2H), 6.97 (d, J=9.0, 2H), 3.79 – 3.71 (m, 4H), 3.09 – 3.01 (m, 4H).

[8-(1-Benzyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("D5")



Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 1-benzyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole are reacted according to general

procedure 1. Compound is purified via chromatographie (SiO_2, dichloromethane / methanol as solvent).

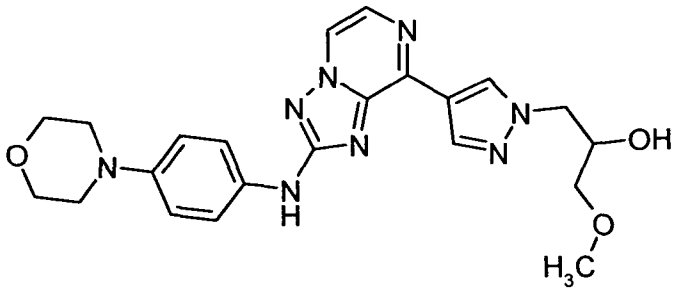
Step 2:

Reaction is done analogue to "D2" and gives "D5";

HPLC purity (method E): 98%, Rt.: 2.03 min, observed [MH+] = 453.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.63 (s, 1H), 8.75 (s, 1H), 8.68 (d, J=4.3, 1H), 8.46 – 8.41 (m, 1H), 8.03 (d, J=4.3, 1H), 7.59 (d, J=9.1, 2H), 7.38 (d, J=1.3, 1H), 7.37 (s, 1H), 7.33 (dd, J=7.3, 1.8, 3H), 6.94 (d, J=9.1, 2H), 5.50 (s, 2H), 3.79 – 3.70 (m, 4H), 3.08 – 2.99 (m, 4H).

1-Methoxy-3-{4-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyrazol-1-yl}-propan-2-ol ("D6")



Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 1-methoxy-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-propan-2-ol are reacted according to general procedure 1. Crude material is purified via flash chromatographie using dichloromethane and ethanol as eluent.

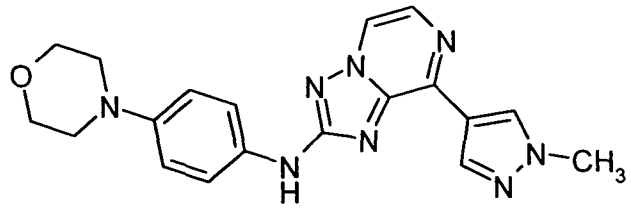
Step 2:

Reaction is performed analogous to "D2" and gives "D6";

HPLC purity (method E): 100%, Rt: 1.56 min, observed [MH+] 451.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.64 (s, 1H), 8.70 – 8.63 (m, 2H), 8.38 (s, 1H), 8.02 (d, J=4.3, 1H), 7.61 (d, J=8.9, 2H), 6.95 (d, J=9.0, 2H), 5.25 (d, J=5.3, 1H), 4.31 (dd, J=13.9, 3.8, 1H), 4.16 (dd, J=13.8, 7.5, 1H), 4.03 (dd, J=5.3, 3.6, 2H), 3.79 – 3.69 (m, 4H), 3.09 – 2.99 (m, 4H).

[8-(1-Methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("D7")



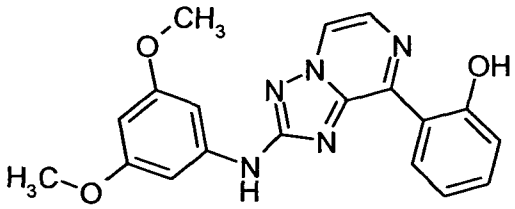
Step 1 is done analogously to "D1".

Step 2 is done analogously to "D2" and gives "D7";

HPLC purity (method E): 100%, Rt.: 1.56 min, observed [MH+]= 377.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 8.81 – 8.75 (m, 2H), 8.56 (s, 1H), 8.16 (d, J=4.5, 1H), 8.00 (d, J=9.1, 2H), 7.76 (d, J=9.1, 2H), 5.64 (s, 0H), 4.10 – 4.06 (m, 4H), 4.05 (s, 7H), 3.77 – 3.66 (m, 4H).

2-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol ("D8")



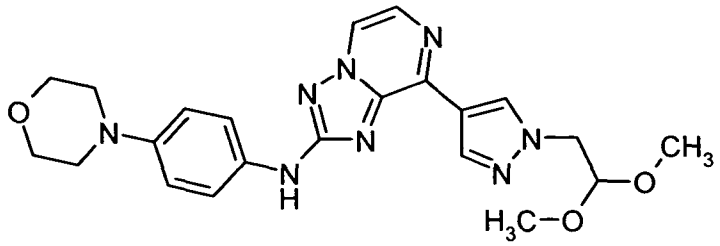
Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine (500 mg, 2.95 mmol), (2-hydroxy-phenyl)boronic acid (428 mg, 3.00 mmol), tripotassiumphosphate (1.29 g, 5.90 mmol), potassium hydroxide (148 mg, 2.65 mmol) and trans-Dichlorobis-(tricyclohexylphosphine)palladium(II) (153 mg, 0.21 mmol) are suspended in 9 mL 1,2-dimethoxyethane and 3 mL N,N-dimethylformamide. The mixture is briefly degassed prior to heating in the microwave (150°C, 2h). Upon completion, the mixture is filtered over a pad of Celite, concentrated and purified via column chromatography (DCM / EtOH as solvent).

Step 2:

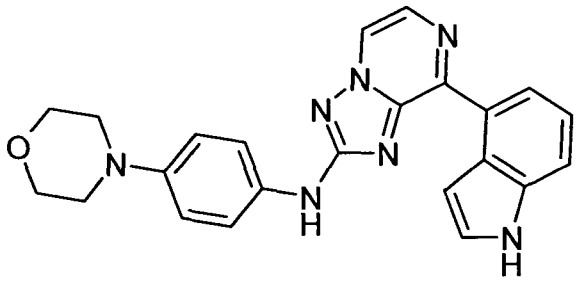
Reaction is run according to general procedure 2 using 1-chloro-3,5-dimethoxy-benzene as aryl halide to give compound "D8";
HPLC purity (method E): 98%, Rt.: 2.61 min, observed [MH+] = 364.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 13.87 (s, 1H), 10.12 (s, 1H), 9.38 (dd, J=8.1, 1.5, 1H), 8.98 (d, J=4.4, 1H), 8.21 (d, J=4.4, 1H), 7.49 – 7.42 (m, 1H), 7.07 – 6.98 (m, 4H), 6.16 (t, J=2.2, 1H), 3.79 (s, 6H).

{8-[1-(2,2-Dimethoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine ("D9")



Step 1:
8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 1-(2,2-dimethoxy-ethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole are reacted under the conditions described in general procedure 1.
Step 2:
Reaction is performed analogous to "D2" to give "D9";
HPLC purity (method E): 100%, Rt.: 1.73 min, observed [MH+] = 451.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.64 (s, 1H), 8.68 (d, J=5.1, 2H), 8.42 (s, 1H), 8.04 (d, J=4.3, 1H), 7.62 (d, J=9.0, 2H), 6.96 (d, J=9.1, 2H), 4.77 (s, 1H), 4.38 (d, J=5.4, 2H), 3.79 – 3.72 (m, 4H), 3.33 (s, 6H), 3.08 – 3.01 (m, 4H).

[8-(1H-Indol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine ("D10")



Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and indol-4-boronic acid are coupled in the manner described in general procedure 1.

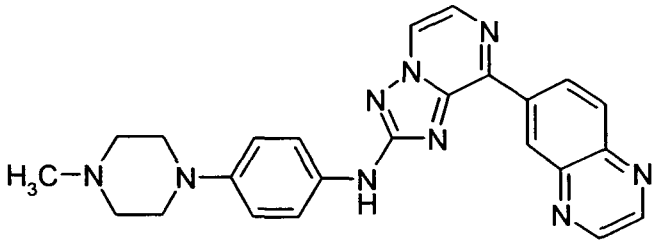
Step 2:

Reaction is performed analogous to "D2" to give "D10";

HPLC purity (method E): 100%, Rt.:1.82 min, observed [MH+] = 412.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 11.31 (s, 1H), 9.70 (s, 1H), 8.80 (d, J=4.2, 1H), 8.67 – 8.62 (m, 1H), 8.24 (d, J=4.2, 1H), 7.64 – 7.56 (m, 3H), 7.48 (t, J=2.7, 1H), 7.28 (dd, J=8.9, 6.6, 2H), 6.94 (d, J=9.1, 2H), 3.78 – 3.71 (m, 4H), 3.07 – 2.99 (m, 4H).

[4-(4-Methyl-piperazin-1-yl)-phenyl]-(8-quinoxalin-6-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D11")



Step 1:

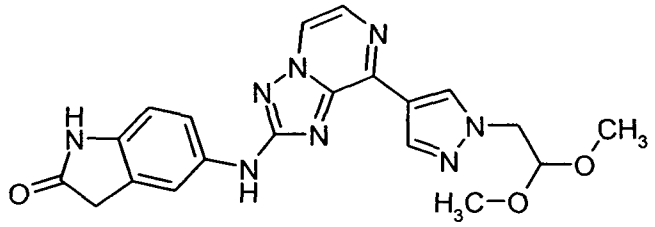
Suzuki Miyaura coupling of 8-iodo-[1,2,4]triazolopyrazin-2-ylamine and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoxaline under conditions described in standard procedure 1.

Step 2:

The reaction with 1-(4-bromo-phenyl)-4-methyl-piperazine as aryl halide is run according to general procedure 2 to give "D11";

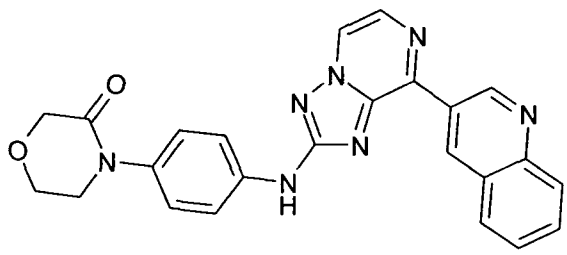
HPLC purity (method E): 100%, Rt.: 1.46 min, observed [MH+] = 438.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.89 (s, 1H), 9.71 (d, J=1.9, 1H), 9.07 – 9.00 (m, 3H), 8.96 (d, J=4.2, 1H), 8.29 (dd, J=12.3, 6.5, 2H), 7.62 (d, J=9.0, 2H), 6.96 (d, J=9.1, 2H), 3.14 – 3.03 (m, 4H), 2.48 (d, J=5.0, 4H), 2.24 (s, 3H).

5-{8-[1-(2,2-Dimethoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino}-1,3-dihydro-indol-2-one ("D12")



Step 1:
The intermediate is prepared analogously to "D9".
Step 2:
5-Bromo-1,3-dihydro-indol-2-one is reacted under Buchwald-Hartwig conditions described in procedure 2 to give "D12";
HPLC purity (method E): 100%, Rt.: 1.62 min, observed [MH+] = 421.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 10.21 (s, 1H), 9.72 (s, 1H), 8.72 – 8.66 (m, 2H), 8.40 (s, 1H), 8.04 (d, J=4.3, 1H), 7.65 (s, 1H), 7.53 (dd, J=8.4, 2.0, 1H), 6.79 (d, J=8.4, 1H), 4.76 (s, 1H), 4.37 (d, J=5.4, 2H), 3.51 (s, 2H), 3.32 (s, 6H).

4-[4-(8-Quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-phenyl]-morpholin-3-one ("D13")



Step 1:

Reaction of 3-quinolineboronic acid and 8-chloro-[1,2,4]triazolopyrazin-2-ylamine under conditions described in procedure 1 gives after column chromatography with cyclohexane / ethylacetate as solvent the desired intermediate.

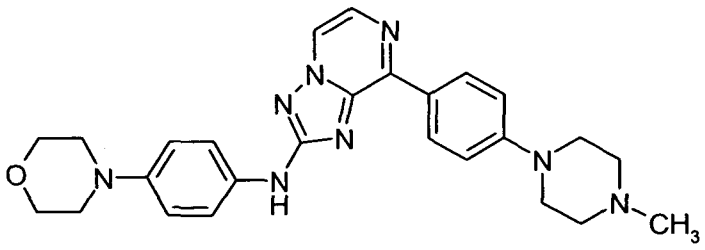
Step 2:

The reaction is run under standard conditions described in general procedure 2 using 4-(4-bromophenyl)morpholin-3-one as aryl halide to give "D13";

HPLC purity (method E): 100%, Rt.: 1.85 min, observed [MH+] = 438.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 10.22 (s, 1H), 10.05 (d, J=2.2, 1H), 9.67 (d, J=2.0, 1H), 9.00 (d, J=4.2, 1H), 8.34 (d, J=4.2, 1H), 8.19 – 8.11 (m, 2H), 7.89 (ddd, J=8.4, 6.9, 1.4, 1H), 7.83 – 7.71 (m, 3H), 7.40 – 7.34 (m, 2H), 4.20 (s, 2H), 3.99 (dd, J=5.8, 4.4, 2H), 3.76 – 3.69 (m, 2H).

{8-[4-(4-Methyl-piperazin-1-yl)-phenyl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine ("D14")



Step 1:

1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine and 8-chloro-[1,2,4]triazolopyrazin-2-ylamine are reacted to give the desired intermediate using general procedure 1.

Step 2:

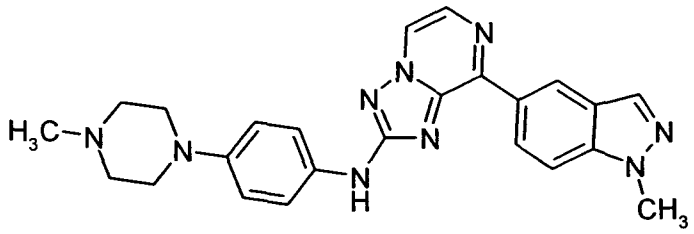
Reaction performed analogous to "D2" to give "D14";

HPLC purity (method E): 98%, Rt.: 1.43 min, observed [MH+] = 471.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.68 (s, 1H), 8.68 (dd, J=19.5, 6.6, 3H), 8.08 (d, J=4.2, 1H), 7.61 (d, J=9.0, 2H), 7.09 (d, J=9.1, 2H), 6.95 (d,

J=9.0, 2H), 3.80 – 3.69 (m, 4H), 3.34 – 3.31 (m, 4H), 3.09 – 2.99 (m, 4H), 2.49 – 2.45 (m, 4H), 2.24 (s, 3H).

[8-(1-Methyl-1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-[4-(4-methyl-piperazin-1-yl)-phenyl]-amine ("D15")



Step 1:

1-Methylindazole-5-boronic acid and 8-chloro-[1,2,4]triazolopyrazin-2-ylamine are reacted to give the desired intermediate using general procedure 1.

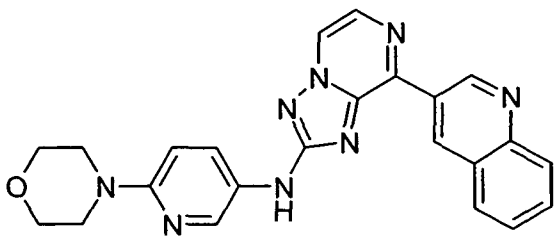
Step 2:

The reaction with 1-(4-bromo-phenyl)-4-methyl-piperazine as aryl halide is run according to general procedure 2 to give "D15";

HPLC purity (method E): 100%, Rt.: 1.50 min, observed [MH+] = 440.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.75 (s, 1H), 9.36 (d, J=0.6, 1H), 8.81 (d, J=4.2, 1H), 8.69 (dd, J=9.0, 1.5, 1H), 8.26 (s, 1H), 8.18 (d, J=4.2, 1H), 7.81 (d, J=9.0, 1H), 7.62 (d, J=9.0, 2H), 6.96 (d, J=9.1, 2H), 4.12 (s, 3H), 3.10 (s, 4H), 2.56 (s, 4H), 2.30 (s, 3H).

(6-Morpholin-4-yl-pyridin-3-yl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D16")



Step 1:

The intermediate is prepared analogously to "D13".

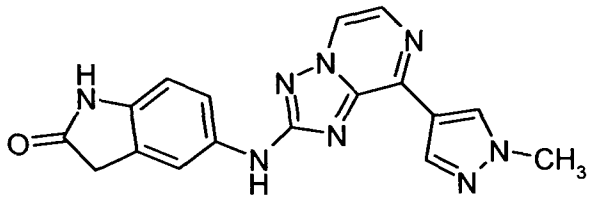
Step 2:

4-(5-Bromo-pyridin-2-yl)-morpholine is used as coupling partner for the amination following general procedure 2 to give "D16";

HPLC purity (method E): 100%; Rt.: 1.40 min, observed [MH+] = 425.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 10.06 (d, J=2.2, 1H), 9.86 (s, 1H), 9.62 (d, J=2.0, 1H), 8.94 (d, J=4.2, 1H), 8.56 (d, J=2.7, 1H), 8.31 (d, J=4.2, 1H), 8.17 – 8.10 (m, 2H), 8.01 (dd, J=9.1, 2.8, 1H), 7.89 (ddd, J=8.4, 7.0, 1.3, 1H), 7.77 – 7.70 (m, 1H), 6.93 (d, J=9.1, 1H), 3.78 – 3.70 (m, 4H), 3.41 – 3.37 (m, 4H).

5-[8-(1-Methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one ("D17")



Step 1:

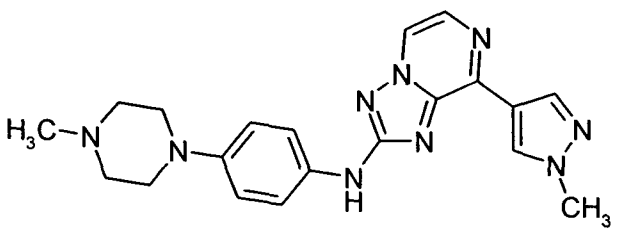
The intermediate is prepared analogously to "D1".

Step 2 is performed analogously to "D12" to give "D17";

HPLC purity (method E): 92%, Rt.: 1.49 min, observed [MH+] 347.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 10.20 (s, 1H), 9.70 (s, 1H), 8.71 – 8.62 (m, 2H), 8.36 (s, 1H), 8.02 (d, J=4.3, 1H), 7.64 (s, 1H), 7.52 (dd, J=8.4, 2.2, 1H), 6.79 (d, J=8.4, 1H), 3.98 (s, 3H), 3.50 (s, 2H).

[4-(4-Methyl-piperazin-1-yl)-phenyl]-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D18")



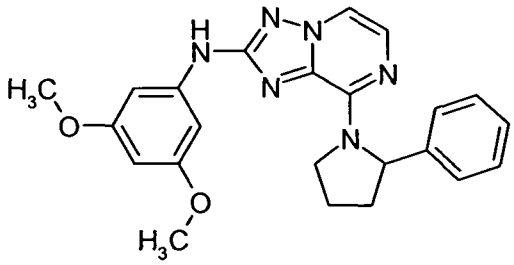
Step 1 is performed analogously to "D1".

Step 2 is done analogously to "D15" to give "D18";

HPLC purity (method E): 100%, Rt.: 1.38 min, observed [MH+] = 390.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]= 9.61 (s, 1H), 8.66 (d, J=4.3, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 8.02 (d, J=4.3, 1H), 7.60 (d, J=9.0, 2H), 6.96 (d, J=9.1, 2H), 3.98 (s, 3H), 3.11 (s, 3H), 2.64 (s, 4H), 2.35 (s, 3H).

(3,5-Dimethoxy-phenyl)-[8-(2-phenyl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D19")



Step 1:

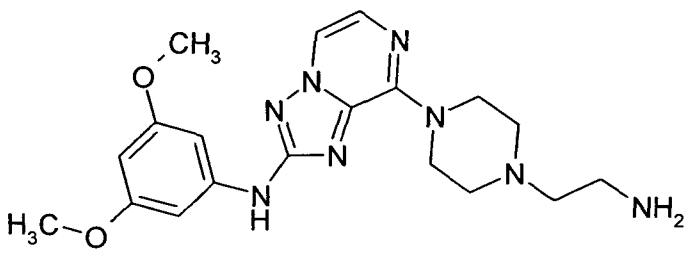
The reaction is performed using general procedure 3 and rac-2-phenyl-pyrrolidine as coupling partner.

Step 2 is done analogously to "D8" to give "D19";

HPLC purity (method E): 100%, Rt.: 2.52 min, observed [MH+] = 417.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.50 (s, 1H), 7.97 (d, J=4.4, 1H), 7.40 (d, J=4.1, 1H), 7.30 – 7.14 (m, 5H), 6.93 (d, J=2.0, 2H), 6.07 (t, J=2.2, 1H), 3.73 (s, 6H), 3.17 (d, J=3.6, 1H), 2.39 (dd, J=13.5, 6.5, 2H), 2.03 – 1.84 (m, 3H).

{8-[4-(2-Amino-ethyl)-piperazin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(3,5-dimethoxy-phenyl)-amine ("D20")



Step 1:

2-(2-Piperazin-1-ylethyl)isoindoline-1,3-dione is reacted with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine using the method described in general procedure 3.

Step 2 is done analogously to "D19".

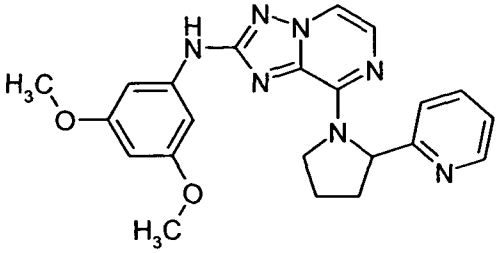
Step 3:

To a suspension of 2-[2-[4-[2-(3,5-dimethoxyanilino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]piperazin-1-yl]ethyl]isoindoline-1,3-dione in ethanol is added hydrazine (20eq) and the clear colorless solution is refluxed for 2 h and monitored by HPLC. The solvent is removed under reduced pressure and the residue purified via preparative HPLC yielding the title compound "D20";

HPLC purity (method E): 100%, Rt.:1.32 min, observed [MH+] = 399.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.76 (s, 1H), 8.44 (s, 2H), 8.32 (d, J=4.4, 1H), 7.64 (d, J=4.4, 1H), 6.91 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 5.24 (d, J=8.7, 1H), 4.14 (s, 8H), 3.73 (s, 6H), 3.70 – 3.59 (m, 2H), 3.35 – 3.18 (m, 2H).

(3,5-Dimethoxy-phenyl)-[8-(2-pyridin-2-yl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D21")



Step 1:

The reaction is performed using general procedure 3 and rac-2-pyrrolidin-2-ylpyridine as coupling partner.

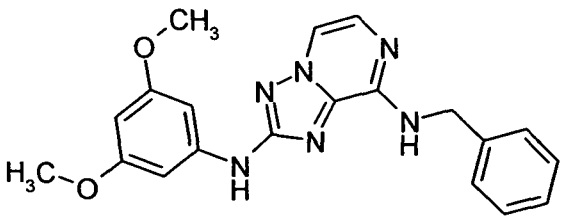
Step 2 is done analogously to "D8" to give "D21";

HPLC purity (method E): 100%, Rt.: 1.75 min, observed [MH+] = 418.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.52 (s, 1H), 8.51 – 8.46 (m, 1H), 8.16 (s, 1H), 7.99 (d, J=4.4, 1H), 7.65 (td, J=7.7, 1.8, 1H), 7.40 (s, 1H), 7.26 –

7.15 (m, 2H), 6.93 (s, 2H), 6.07 (t, J=2.2, 1H), 3.74 (s, 6H), 2.41 (tt, J=11.9, 7.8, 1H), 2.24 – 1.96 (m, 2H), 1.93 (s, 1H).

N8-Benzyl-N2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("D22")



Step 1:

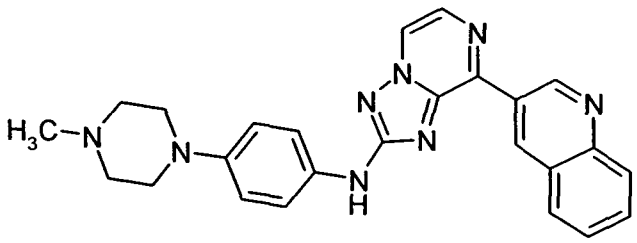
The reaction is performed using general procedure 3 and benzylamine as coupling partner.

Step 2 is done analogously to "D8" to give "D22";

HPLC purity (method E): 95%, Rt.: 2.33 min, observed [MH+] 377.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.47 (s, 1H), 7.99 (d, J=4.5, 1H), 7.89 (s, 1H), 7.42 (d, J=4.5, 1H), 7.32 (dt, J=13.2, 7.5, 4H), 7.22 (d, J=7.2, 1H), 6.94 (d, J=2.2, 2H), 6.08 (t, J=2.2, 1H), 4.71 (d, J=6.3, 2H), 3.73 (s, 6H).

[4-(4-Methyl-piperazin-1-yl)-phenyl]-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D23")



Step 1 is performed analogously to "D13".

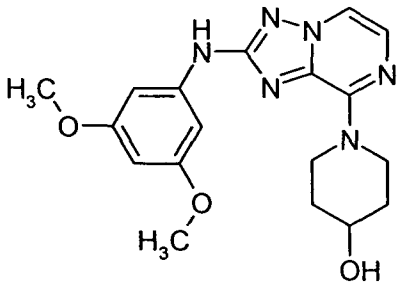
Step 2 is done analogously to "D15" to give "D23";

HPLC purity (method E): 100%, Rt.: 1.47 min, observed [MH+] = 437.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 10.05 (d, J=2.2, 1H), 9.80 (s, 1H), 9.64 (d, J=2.1, 1H), 8.94 (d, J=4.2, 1H), 8.29 (d, J=4.2, 1H), 8.18 – 8.09 (m, 2H), 7.88 (ddd, J=8.5, 6.9, 1.4, 1H), 7.73 (ddd, J=8.0, 7.0, 1.1, 1H), 7.69 –

7.57 (m, 2H), 7.04 – 6.93 (m, 2H), 3.14 – 3.03 (m, 4H), 2.49 – 2.45 (m, 13H), 2.23 (s, 3H).

1-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-piperidin-4-ol ("D24")



Step 1:

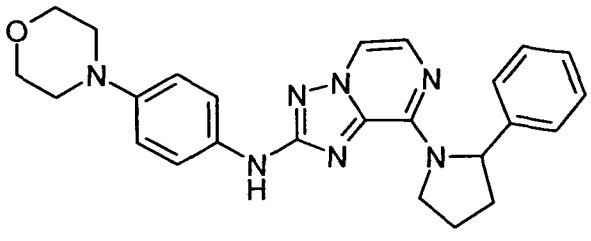
4-Hydroxypiperidin is reacted with with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine using 4 eq. of triethylamine.

Step 2 is done analogously to "D8" to give "D24";

HPLC purity (method E): 84%, Rt.: 1.83 min, observed [MH+] = 371.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.65 (s, 1H), 8.11 (d, J=4.3, 1H), 7.54 (d, J=4.3, 1H), 6.93 (d, J=2.2, 2H), 6.07 (t, J=2.1, 1H), 4.67 (dt, J=8.5, 3.9, 3H), 3.78 (ddd, J=12.3, 8.2, 3.8, 1H), 3.73 (s, 6H), 3.57 (ddd, J=12.9, 9.8, 2.9, 2H), 1.94 – 1.76 (m, 2H), 1.52 – 1.38 (m, 2H).

(4-Morpholin-4-yl-phenyl)-[8-(2-phenyl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D25")



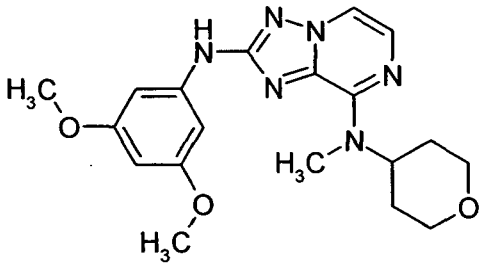
Step 1 is performed analogously to "D19".

Step 2 is done analogously to "D2" to give "D25";

HPLC purity (method E): 100%, Rt.: 2.02 min, observed [MH+] 442.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.32 – 9.11 (m, 1H), 7.97 – 7.90 (m, 1H), 7.45 – 7.39 (m, 3H), 7.31 – 7.25 (m, 2H), 7.24 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 6.95 – 6.80 (m, 2H), 6.10 – 5.66 (m, 1H), 4.40 – 3.94 (m, 2H), 3.78 – 3.69 (m, 4H), 3.07 – 2.95 (m, 4H), 2.45 – 2.31 (m, 2H), 2.04 – 1.95 (m, 1H), 1.93 – 1.47 (m, 2H).

N2-(3,5-Dimethoxy-phenyl)-N8-methyl-N8-(tetrahydro-pyran-4-yl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("D26")



Step 1:

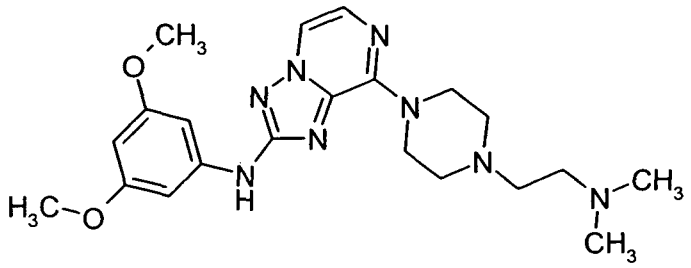
N-Methyl-N-tetrahydro-2H-pyran-4-ylamine is coupled with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine following general procedure 3.

Step 2 is done analogously to "D8" to give "D26";

HPLC purity (method E): 98%, Rt.: 2.06 min, observed [MH+] = 385.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.54 (s, 1H), 8.06 (d, J=4.3, 1H), 7.53 (d, J=4.3, 1H), 6.93 (d, J=2.2, 2H), 6.08 (t, J=2.2, 1H), 5.46 (t, J=11.7, 1H), 3.98 (dd, J=11.2, 4.3, 2H), 3.73 (s, 6H), 3.50 (dd, J=11.7, 10.4, 2H), 3.26 (s, 3H), 1.91 (qd, J=12.2, 4.6, 2H), 1.67 (dd, J=12.1, 2.3, 2H).

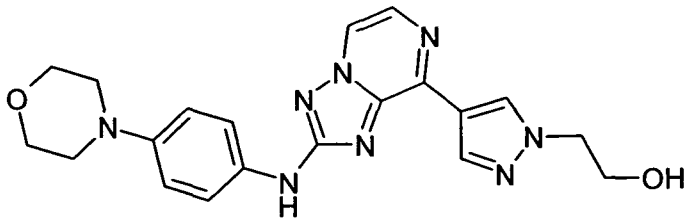
(3,5-Dimethoxy-phenyl)-{8-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-amine ("D27")



Step 1:

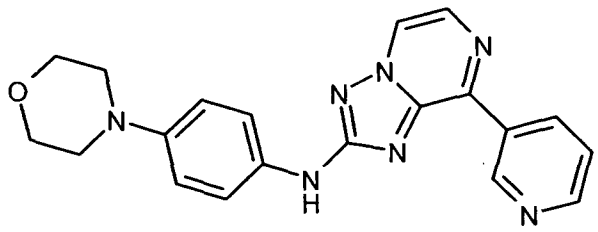
N,N-dimethyl-2-piperazin-1-yl-ethanamine is reacted with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine following general procedure 3.
Step 2 is done analogously to "D8" to give "D27";
HPLC purity (method E): 100%, Rt: 1.45 min, observed [MH+] = 427.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.66 (s, 1H), 8.19 (s, 1H), 8.15 (d, J=4.3, 1H), 7.55 (d, J=4.3, 1H), 6.92 (d, J=2.2, 2H), 6.07 (s, 1H), 4.08 (s, 4H), 3.72 (s, 6H), 2.58 – 2.52 (m, 4H), 2.46 (s, 4H), 2.22 (s, 6H).

2-{4-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyrazol-1-yl}-ethanol (D28")



Step 1:
Following general procedure 1 using 8-iodo-[1,2,4]triazolopyrazin-2-ylamine and 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-ethanol as coupling partners.
Step 2 is done analogously to "D2" to give "D28";
HPLC purity (method E): 100%, Rt.: 1.44 min, observed [MH+] = 407.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.64 (s, 1H), 8.72 – 8.63 (m, 2H), 8.39 (s, 1H), 8.02 (d, J=4.2, 1H), 7.61 (d, J=8.8, 2H), 6.95 (d, J=8.8, 2H), 4.99 (t, J=5.1, 1H), 4.28 (t, J=5.4, 2H), 3.81 (d, J=5.2, 2H), 3.78 – 3.68 (m, 4H), 3.04 (s, 4H).

(4-Morpholin-4-yl-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D29")



Step 1:

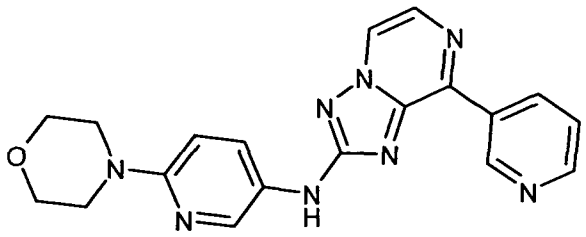
Pyridin-3-boronic acid and 8-chloro-[1,2,4]triazolopyrazin-2-ylamine are reacted using general procedure 1.

Step 2 is done analogously to "D2" to give "D29";

HPLC purity (method E): 100%, Rt:1.51 min, observed [MH+]= 374.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.85 (d, J=1.7, 1H), 9.79 (s, 1H), 8.96 (dt, J=8.1, 1.9, 1H), 8.92 (d, J=4.2, 1H), 8.73 (dd, J=4.7, 1.6, 1H), 8.24 (d, J=4.2, 1H), 7.65 – 7.62 (m, 1H), 7.61 (dd, J=7.3, 5.3, 2H), 6.96 (d, J=9.1, 2H), 3.78 – 3.71 (m, 4H), 3.08 – 3.01 (m, 4H).

(6-Morpholin-4-yl-pyridin-3-yl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D30")



Step 1:

Pyridin-3-boronic acid and 8-chloro-[1,2,4]triazolopyrazin-2-ylamine are reacted using general procedure 1.

Step 2:

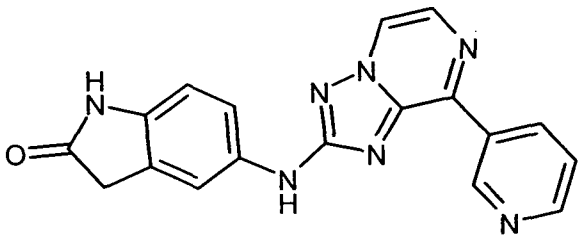
The intermediate from step 1 is reacted with 4-(5-bromopyridin-2-yl)morpholine using general procedure 2 to give "D30";

HPLC purity (method E): 100%, Rt:1.27 min, observed [MH+]= 375.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.86 – 9.79 (m, 2H), 8.94 (dt, J=8.1, 1.9, 1H), 8.93 – 8.89 (m, 1H), 8.73 (dd, J=4.8, 1.6, 1H), 8.54 (d, J=2.6, 1H),

8.25 (d, J=4.2, 1H), 8.20 (s, 0H), 7.94 (dd, J=9.1, 2.8, 1H), 7.63 (ddd, J=8.1, 4.8, 0.6, 1H), 6.90 (d, J=9.1, 1H), 3.76 – 3.69 (m, 4H), 3.38 – 3.35 (m, 4H).

5-(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one ("D31")



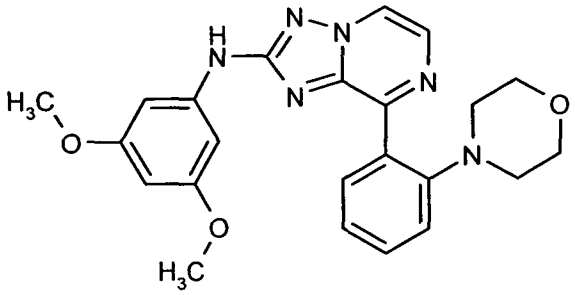
Step 1 is performed analogously to "D29".

Step 2 is done analogously to "D12" to give "D31";

HPLC purity (method E): 90%, Rt:1.66 min, observed [MH+]= 344.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 10.23 (s, 1H), 9.88 (s, 1H), 9.83 (d, J=1.7, 1H), 8.97 (dt, J=8.1, 1.9, 1H), 8.93 (d, J=4.2, 1H), 8.73 (dd, J=4.7, 1.6, 1H), 8.25 (d, J=4.2, 1H), 7.64 (dd, J=8.1, 4.7, 2H), 7.53 (dd, J=8.4, 2.1, 1H), 6.80 (dd, J=8.3, 2.5, 1H), 3.51 (s, 2H).

(3,5-Dimethoxy-phenyl)-[8-(2-morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D32")



Step1:

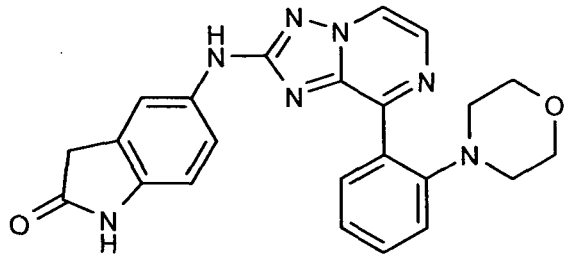
(2-Morpholinophenyl)boronic acid is used as boronic acid following procedure 1.

Step 2 is done analogously to "D8" to give "D32";

HPLC purity (method E): 95%, Rt:2.00 min, observed [MH+]= 433.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.83 (s, 1H), 8.92 – 8.86 (m, 1H), 8.20 – 8.13 (m, 1H), 7.56 – 7.44 (m, 2H), 7.28 – 7.15 (m, 2H), 6.94 – 6.89 (m, 2H), 6.08 (t, J=2.1, 1H), 3.70 (s, 6H), 3.27 – 3.23 (m, 4H), 2.83 – 2.72 (m, 4H).

5-[8-(2-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one ("D33")



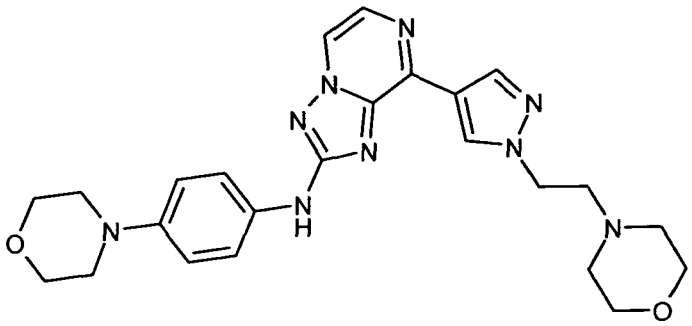
Step 1 is performed analogously to "D32".

Step 2 is done analogously to "D12" to give "D33";

HPLC purity (method E): 88%, Rt:1.55 min, observed [MH+]= 428.28;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 10.18 (s, 1H), 9.68 (s, 1H), 8.86 (d, J=4.3, 1H), 8.13 (d, J=4.3, 1H), 7.56 (s, 1H), 7.48 (dd, J=12.1, 4.5, 2H), 7.42 (dd, J=8.4, 2.1, 1H), 7.24 (d, J=7.8, 1H), 7.22 – 7.14 (m, 1H), 6.73 (d, J=8.4, 1H), 3.46 (s, 2H), 3.27 – 3.21 (m, 4H), 2.81 – 2.74 (m, 4H).

{8-[1-(2-Morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine ("D34")



Step 1:

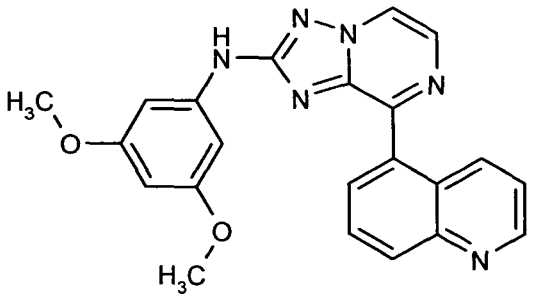
4-{2-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-ethyl}-morpholine is used as boronic acid and reacted with 8-chloro-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine following general procedure 1

Step 2 is done analogously to "D2" to give "D34";

HPLC purity (method E): 100%, Rt:1.29 min, observed [MH+]= 476.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.61 (s, 1H), 8.70 – 8.64 (m, 2H), 8.41 (s, 1H), 8.02 (d, J=4.3, 1H), 7.62 (d, J=9.0, 2H), 6.95 (d, J=9.1, 2H), 4.37 (t, J=6.4, 2H), 3.79 – 3.71 (m, 4H), 3.58 – 3.49 (m, 4H), 3.08 – 3.00 (m, 4H), 2.79 (t, J=6.5, 2H), 2.48 – 2.41 (m, 4H).

(3,5-Dimethoxy-phenyl)-(8-quinolin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D35")



Step 1:

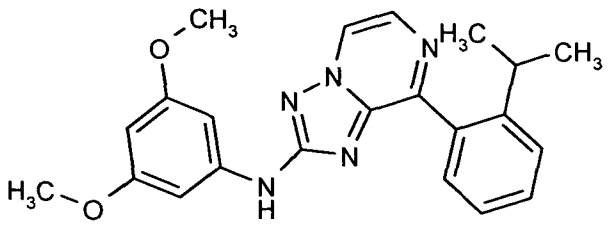
5-quinolylboronic acid is coupled with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine using general procedure 1.

Step 2 is done analogously to "D8" to give "D35";

HPLC purity (method E): 100%, Rt:1.83 min, observed [MH+]= 399.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.94 (s, 1H), 9.02 (d, J=4.3, 1H), 8.97 (dd, J=4.1, 1.6, 1H), 8.58 (d, J=8.1, 1H), 8.32 (d, J=4.3, 1H), 8.21 (d, J=8.4, 1H), 8.17 (dd, J=7.2, 1.0, 1H), 7.93 (dd, J=8.4, 7.3, 1H), 7.54 (dd, J=8.6, 4.1, 1H), 6.92 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 3.68 (s, 6H).

(3,5-Dimethoxy-phenyl)-[8-(2-isopropyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D36")



Step 1:

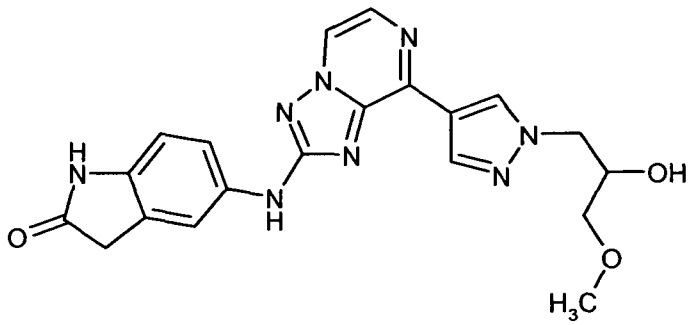
Suzuki coupling is performed using general procedure 1 with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine and (2-isopropylphenyl)boronic acid as reactants.

Step 2 is done analogously to "D8" to give "D36";

HPLC purity (method E): 95%, Rt:2.55 min, observed [MH+]= 390.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.87 (s, 1H), 8.91 (d, J=4.3, 1H), 8.20 (d, J=4.3, 1H), 7.61 – 7.44 (m, 3H), 7.31 (td, J=7.2, 1.8, 1H), 6.90 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 3.71 (s, 6H), 3.02 (dt, J=13.6, 6.9, 1H), 1.13 (d, J=6.8, 6H).

5-{8-[1-(2-Hydroxy-3-methoxy-propyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino}-1,3-dihydro-indol-2-one ("D37")



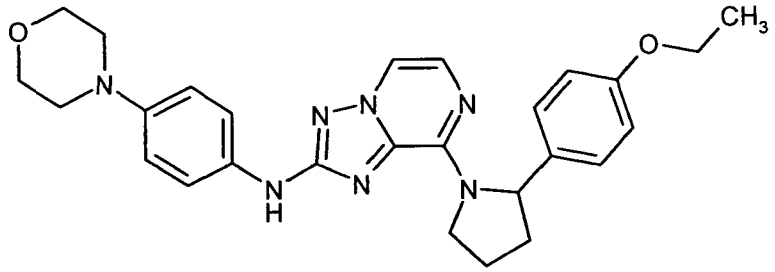
Step 1 is performed analogously to "D6".

Step 2 is done analogously to "D12" to give "D37";

HPLC purity (method E): 100%, Rt:1.53 min, observed [MH+]= 421.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 10.21 (s, 1H), 9.73 (s, 1H), 8.68 (dd, J=6.6, 4.8, 2H), 8.37 (s, 1H), 8.03 (d, J=4.3, 1H), 7.66 (s, 1H), 7.52 (dd, J=8.4, 2.2, 1H), 6.79 (d, J=8.4, 1H), 5.26 (d, J=5.4, 1H), 4.32 (dd, J=13.8, 3.8, 1H), 4.16 (dd, J=13.8, 7.5, 1H), 4.06 – 3.98 (m, 1H), 3.51 (s, 2H), 1.24 (s, 3H).

{8-[2-(4-Ethoxy-phenyl)-pyrrolidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine ("D38")



Step 1:

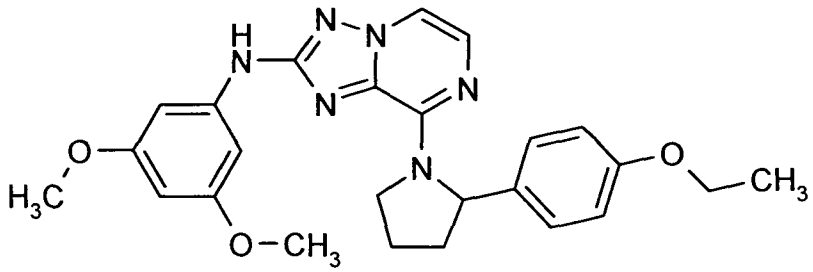
Following general procedure 3 rac 2-(4-Ethoxy-phenyl)-pyrrolidine was used as nulceophile.

Step 2 is done analogously to "D2" to give "D38";

HPLC purity (method E): 100%, Rt:2.15 min, observed [MH+]= 486.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.22 (s, 1H), 8.15 (s, 0H), 7.95 (d, J=4.4, 1H), 7.43 (s, 3H), 7.12 (d, J=8.6, 2H), 6.86 (dd, J=25.4, 8.8, 4H), 3.96 (q, J=7.0, 3H), 3.79 – 3.73 (m, 5H), 3.07 – 2.98 (m, 4H), 2.40 – 2.16 (m, 1H), 1.99 (ddd, J=15.6, 8.3, 5.0, 1H), 1.90 (d, J=7.1, 2H), 1.28 (dd, J=16.5, 9.5, 3H), 1.25 (s, 1H).

(3,5-Dimethoxy-phenyl)-{8-[2-(4-ethoxy-phenyl)-pyrrolidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-amine ("D39")



Step 1 is performed analogously to "D38".

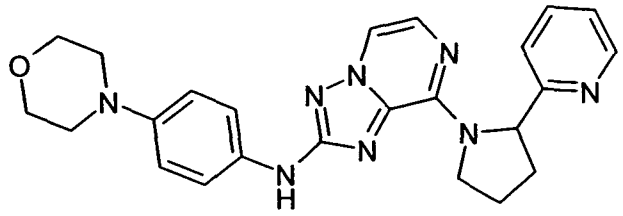
Step 2 is done analogously to "D8" to give "D39";

HPLC purity (method E): 100%, Rt:2.56 min, observed [MH+]= 461.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.52 (s, 1H), 7.98 (d, J=4.4, 1H), 7.42 (s, 1H), 7.12 (d, J=8.6, 2H), 6.93 (s, 2H), 6.80 (d, J=8.7, 2H), 6.08 (t, J=2.2,

1H), 3.95 (q, J=7.0, 2H), 3.74 (s, 6H), 2.36 (dd, J=12.6, 5.5, 1H), 2.11 – 1.92 (m, 2H), 1.89 (d, J=7.5, 2H), 1.28 (t, J=7.0, 3H).

(4-Morpholin-4-yl-phenyl)-[8-(2-pyridin-2-yl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine ("D40")



Step 1:

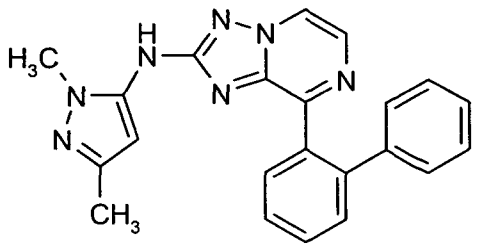
Rac-2-pyrrolidin-2-yl-pyridine is reacted as described in general procedure 3 with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine.

Step 2 is done analogously to "D2" to give "D40";

HPLC purity (method E): 93%, Rt:1.43 min, observed [MH+]= 443.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.22 (s, 1H), 8.53 (d, J=4.3, 1H), 8.16 (s, 0H), 7.95 (d, J=4.4, 1H), 7.67 (td, J=7.7, 1.8, 1H), 7.41 (s, 3H), 7.26 – 7.16 (m, 2H), 6.87 (d, J=8.9, 2H), 4.37 – 3.99 (m, 7H), 3.79 – 3.70 (m, 4H), 3.18 (s, 1H), 3.06 – 2.98 (m, 4H), 2.41 (tt, J=11.9, 7.7, 1H), 2.10 (d, J=6.0, 1H), 2.01 (ddd, J=10.2, 7.1, 3.9, 1H), 1.90 (d, J=17.7, 1H).

(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(2,5-dimethyl-2H-pyrazol-3-yl)-amine ("D41")



Step 1:

8-Chloro-[1,2,4]triazolopyrazin-2-ylamine and 2-biphenylboronic acid are reacted as described in general procedure 1.

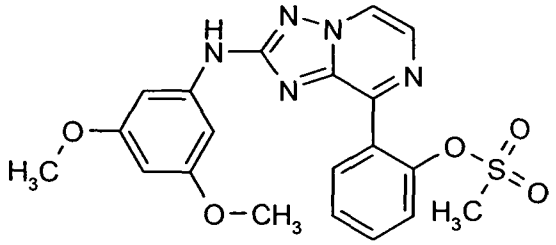
Step 2:

5-Chloro-1,3-dimethyl-pyrazole and intermediate from step 1 are coupled using general procedure 2 to give "D41";

HPLC purity (method E): 90%, Rt:1.96 min, observed [MH+]= 382.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.64 (s, 1H), 8.75 (d, J=4.3, 1H), 8.00 (d, J=4.3, 1H), 7.73 – 7.66 (m, 1H), 7.61 (dd, J=7.8, 1.7, 1H), 7.54 (d, J=7.5, 2H), 7.19 – 7.14 (m, 2H), 7.07 (dd, J=7.6, 1.7, 2H), 6.03 (s, 1H), 3.57 (s, 3H), 2.09 (s, 3H).

Methanesulfonic acid 2-[2-(3,5-dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl ester ("D42")



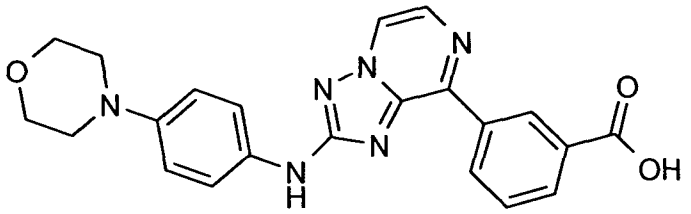
2-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol (1 eq.) is dissolved in dry dichloromethane and dry triethylamine (1.1 eq.) under an inert atmosphere.

Methanesulfonylchloride (2 eq.) is added and the reaction stirred at room temperature for 1h and monitored by HPLC. After complete conversion, the mixture is diluted with dichloromethane, filtered over a pad of celite and concentrated in vacuum. Column chromatographie on silica with ethylacetate and cyclohexane gives the title compound "D42";

HPLC purity (method E): 90%, Rt:2.12 min, observed [MH+]= 442.0;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.97 (s, 1H), 8.97 (d, J=4.3, 1H), 8.25 (d, J=4.3, 1H), 7.95 (dd, J=7.6, 1.6, 1H), 7.73 – 7.62 (m, 1H), 7.62 – 7.49 (m, 2H), 6.96 (d, J=2.1, 2H), 6.11 (t, J=2.1, 1H), 3.73 (s, 6H), 3.16 (s, 3H).

3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzoic acid ("D43")



Step 1:

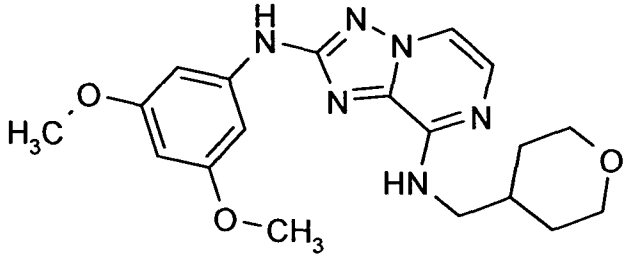
Following general procedure 1 using (3-methoxycarbonylphenyl)boronic acid and 8-iodo-[1,2,4]triazolopyrazin-2-ylamine as reactants.

Step 2 is done analogously to "D2" to give "D43";

HPLC purity (method E): 100%, Rt:1.80 min, observed [MH+]= 417.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.78 (s, 1H), 9.46 (s, 1H), 8.96 – 8.91 (m, 1H), 8.89 (d, J=4.2, 1H), 8.23 (d, J=4.2, 1H), 8.14 – 8.08 (m, 1H), 7.72 (t, J=7.8, 1H), 7.70 – 7.65 (m, 2H), 6.96 (d, J=9.1, 2H), 3.79 – 3.72 (m, 4H), 3.09 – 3.01 (m, 4H).

N2-(3,5-Dimethoxy-phenyl)-N8-(tetrahydro-pyran-4-ylmethyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("D44")



Step 1:

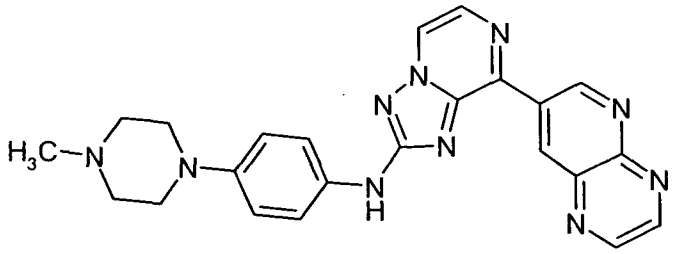
The intermediate is synthesized using general procedure 3 and 4-(aminomethyl)tetrahydropyran as nucleophile.

Step 2 is done analogously to "D8" to give "D44";

HPLC purity (method E): 100%, Rt:1.92 min, observed [MH+]= 385.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.44 (s, 1H), 7.97 (d, J=4.5, 1H), 7.46 (d, J=4.5, 1H), 7.35 (t, J=6.0, 1H), 6.94 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 3.85 (dd, J=11.4, 2.5, 2H), 3.74 (d, J=5.4, 7H), 3.45 (s, 1H), 3.40 (t, J=6.5, 2H), 3.29 – 3.23 (m, 3H), 1.99 (ddt, J=15.0, 11.2, 3.9, 1H), 1.62 (dd, J=12.8, 1.8, 2H), 1.32 – 1.16 (m, 2H), 1.12 (s, 1H).

[4-(4-Methyl-piperazin-1-yl)-phenyl]-(8-pyrido[2,3-b]pyrazin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D45")



Step 1:

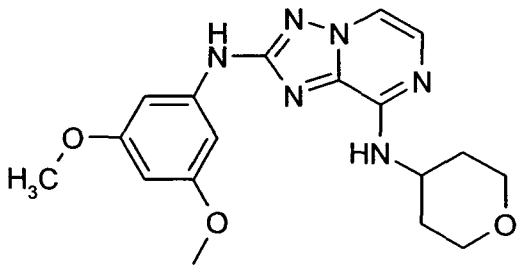
Suzuki Miyaura coupling is performed using 7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrido[2,3-b]pyrazine as boronic acid following procedure 1.

Step 2 is done analogously to "D11" to give "D45";

HPLC purity (method E): 100%, Rt:1.33 min, observed [MH+]= 439.2;

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 10.26 (d, J=2.4, 1H), 9.95 – 9.88 (m, 2H), 9.19 (dd, J=15.8, 1.8, 2H), 9.02 (d, J=4.2, 1H), 8.34 (d, J=4.2, 1H), 7.64 – 7.57 (m, 2H), 6.96 (d, J=9.1, 2H), 3.11 – 3.00 (m, 8H), 2.24 (s, 3H).

N2-(3,5-Dimethoxy-phenyl)-N8-(tetrahydro-pyran-4-yl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("D46")



Step 1:

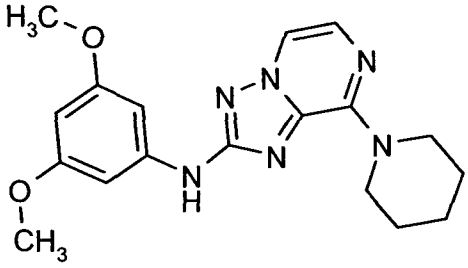
The reaction follows general procedure 3 with 4-aminotetrahydropyran as nucleophile.

Step 2 is done analogously to "D8" to give "D46";

HPLC purity (method E): 100%, Rt:1.90 min, observed [MH+]= 371.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.40 (s, 1H), 7.99 (d, J=4.5, 1H), 7.46 (d, J=4.5, 1H), 7.11 (d, J=8.0, 1H), 6.93 (d, J=2.2, 2H), 6.08 (t, J=2.2, 1H), 4.24 (ddd, J=11.1, 9.3, 5.9, 1H), 3.95 – 3.82 (m, 2H), 3.73 (d, J=6.8, 6H), 3.49 – 3.37 (m, 4H), 1.87 (dd, J=12.5, 2.3, 2H), 1.72 (qd, J=12.2, 4.4, 2H).

(3,5-Dimethoxy-phenyl)-(8-piperidin-1-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D47")



Step 1:

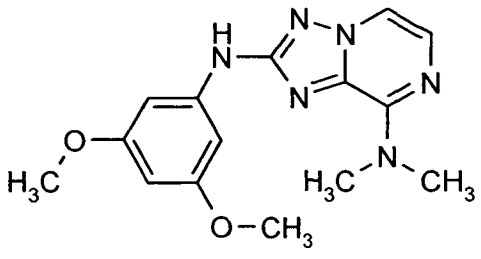
Piperidine is reacted using general procedure 3 with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine.

Step 2 is done analogously to "D8" to give "D47";

HPLC purity (method E): 100%, Rt:2.43 min, observed [MH+]= 355.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.65 (s, 1H), 8.10 (d, J=4.3, 1H), 7.54 (d, J=4.3, 1H), 6.94 (d, J=2.2, 2H), 6.07 (t, J=2.2, 1H), 5.75 (s, 1H), 4.15 – 4.04 (m, 4H), 3.73 (s, 6H), 1.82 – 1.65 (m, 2H), 1.63 (m, 4H).

N2-(3,5-Dimethoxy-phenyl)-N8,N8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("D48")

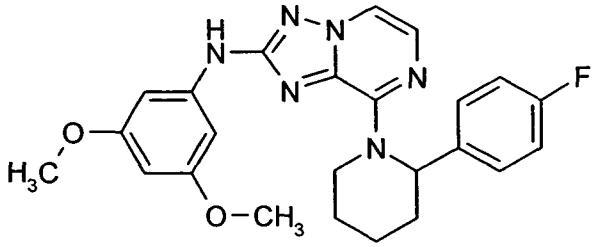


The reaction, analogously to "D47", gives the compound "D48";

HPLC purity (method E): 100%, Rt:1.91 min, observed [MH+]= 315.25;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.60 (s, 1H), 8.06 (d, J=4.3, 1H), 7.52 (d, J=4.3, 1H), 6.94 (d, J=2.2, 2H), 6.07 (t, J=2.2, 1H), 3.73 (s, 6H), 3.45 (s, 6H).

(3,5-Dimethoxy-phenyl)-{8-[2-(4-fluoro-phenyl)-piperidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-amine ("D49")



Step 1

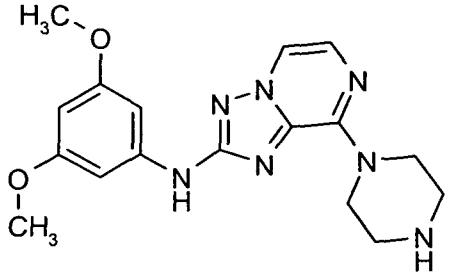
Rac-2-(4-fluorophenyl)piperidine is used as nucleophile according to general procedure 3.

Step 2 is done analogously to "D8" to give "D49";

HPLC purity (method E): 100%, Rt:2.85 min, observed [MH+]= 449.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.63 (s, 1H), 8.15 (d, J=4.3, 1H), 7.56 (d, J=4.3, 1H), 7.36 (dd, J=8.1, 5.6, 2H), 7.18 (t, J=8.9, 2H), 6.89 (d, J=2.2, 2H), 6.05 (t, J=2.2, 1H), 3.68 (s, 6H), 3.13 – 2.86 (m, 1H), 2.47 – 2.40 (m, 1H), 2.06 – 1.88 (m, 1H), 1.73 – 1.60 (m, 4H), 1.54 (ddd, J=12.8, 7.0, 3.3, 1H).

(3,5-Dimethoxy-phenyl)-(8-piperazin-1-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine ("D50")



Step 1:

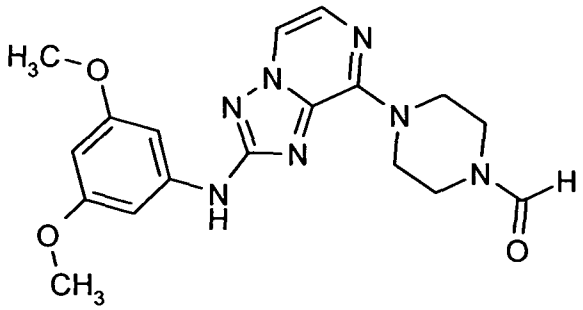
Piperazine is coupled with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine using general procedure 3.

Step 2 is done analogously to "D8" to give "D50";

HPLC purity (method E): 95%, Rt:1.45 min, observed [MH+]= 356.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.67 (s, 1H), 8.22 (s, 1H), 8.16 (d, J=4.3, 1H), 7.56 (d, J=4.3, 1H), 6.93 (d, J=2.2, 2H), 6.08 (t, J=2.2, 1H), 4.15 – 4.03 (m, 4H), 3.73 (s, 6H), 2.98 – 2.87 (m, 4H).

4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-piperazine-1-carbaldehyde ("D51")

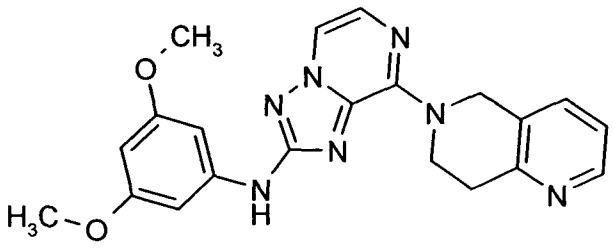


The reaction, analogously to "D50", gives the compound "D51";

HPLC purity (method E): 100%, Rt:1.89 min, observed [MH+]= 384.2;

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.71 (s, 1H), 8.22 (d, J=4.3, 1H), 8.13 (s, 1H), 7.60 (d, J=4.3, 1H), 6.93 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 4.20 – 4.05 (m, 4H), 3.74 (s, 6H), 3.56 (dd, J=10.4, 5.6, 4H).

[8-(7,8-Dihydro-5H-[1,6]naphthyridin-6-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("D52")



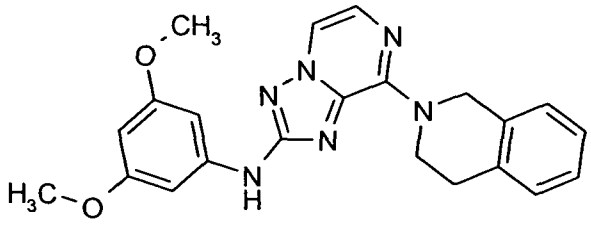
Step 1

5,6,7,8-Tetrahydro-1,6-naphthyridine is reacted with 8-chloro-[1,2,4]triazolopyrazin-2-ylamine using general procedure 3.

Step 2 is done analogously to "D8" to give "D52";

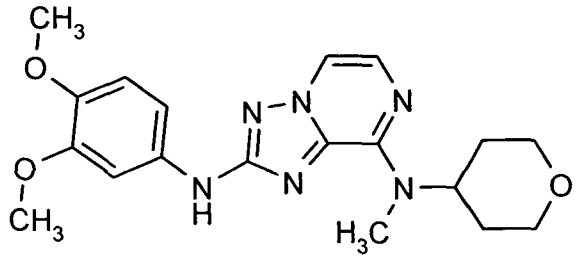
HPLC purity (method E): 100%, Rt:1.66 min, observed [MH+]= 404.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.71 (s, 1H), 8.42 – 8.36 (m, 1H), 8.19 (d, J=4.3, 1H), 7.66 (d, J=7.5, 1H), 7.59 (d, J=4.3, 1H), 7.25 (dd, J=7.7, 4.8, 1H), 6.96 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 5.18 (s, 2H), 4.59 (t, J=5.9, 2H), 3.75 (s, 6H), 3.07 (t, J=5.9, 2H).

[8-(3,4-Dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine ("D53")



Step 1:
1,2,3,4-Tetrahydroisochinolin is reacted according to general procedure 3.
Step 2 is done analogously to "D8" to give "D53";
HPLC purity (method E): 100%, Rt:2.66 min, observed [MH+]= 403.2;
^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.67 (s, 1H), 8.15 (d, J=4.4, 1H), 7.58 (d, J=4.4, 1H), 7.20 (dt, J=5.1, 4.3, 4H), 6.96 (d, J=2.2, 2H), 6.09 (t, J=2.2, 1H), 5.18 (s, 2H), 4.47 (t, J=5.9, 2H), 3.75 (s, 6H), 2.97 (t, J=5.8, 2H).

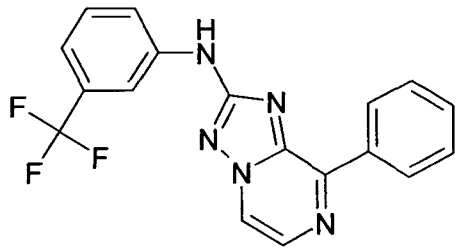
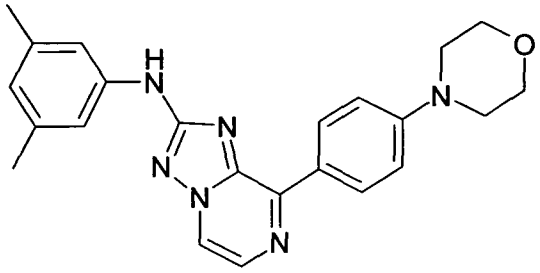
N2-(3,4-Dimethoxy-phenyl)-N8-methyl-N8-(tetrahydro-pyran-4-yl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine ("D54")

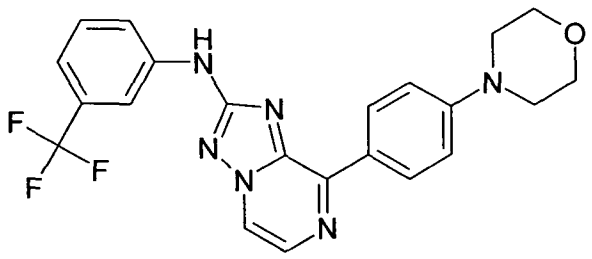
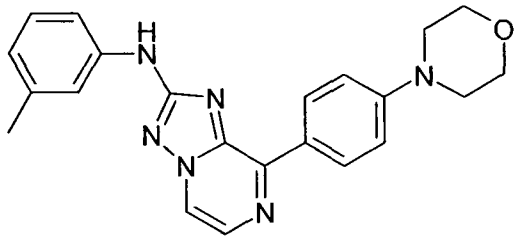
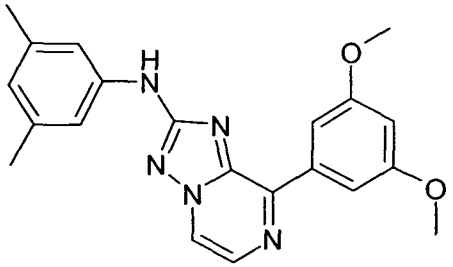


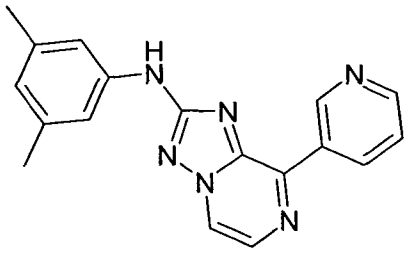
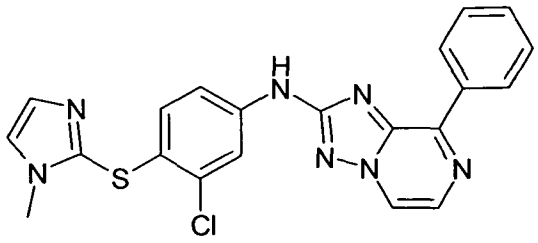
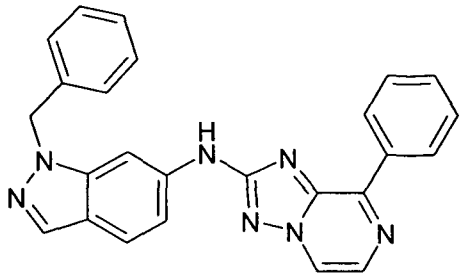
Step 1:
N-Methyl-N-tetrahydro-2H-pyran-4-ylamine is used as nucleophile according to general procedure 3.
Step 2:

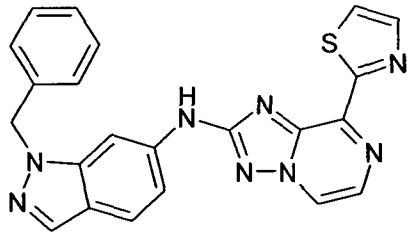
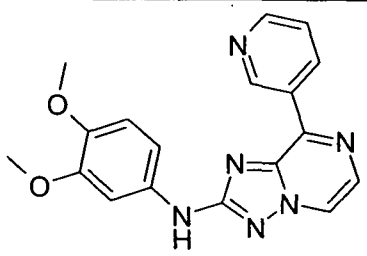
4-Bromo-1,2-dimethoxybenzene is used in the Buchwald-Hartwig amination using general procedure 2 to give "D54";
HPLC purity (method E): 100%, Rt:1.82 min, observed [MH+]= 385.2;
^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm] = 9.32 (s, 1H), 8.04 (d, J=4.3, 1H), 7.52 (d, J=4.3, 1H), 7.32 – 7.23 (m, 2H), 6.89 (d, J=8.7, 1H), 5.52 – 5.33 (m, 1H), 4.00 (dd, J=11.1, 4.3, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.47 (dd, J=11.7, 10.3, 3H), 3.28 (s, 3H), 1.92 (qd, J=12.3, 4.6, 2H), 1.68 (dd, J=12.1, 2.2, 2H).

The following compounds have been prepared analogously

compound no.	structure and / or name analytical data	IC_{50} GCN2 [μM]
"E1"	 (8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine Mass found (M+, 356.0), Rt (min): 5.47	
"E2"	 (3,5-Dimethyl-phenyl)-[8-(4-morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine Mass found (M+, 401.0), Rt (min): 4.81	<10

"E3"	 [8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3-trifluoromethyl-phenyl)-amine Mass found (M+, 441.0), Rt (min): 5.01	<10
"E4"	 [8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-m-tolyl-amine Mass found (M+, 387.0), Rt (min): 4.53	<10
"E5"	 [8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethyl-phenyl)-amine Mass found (M+, 376.0), Rt (min): 5.39	<10

"E6"	 (3,5-Dimethyl-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine LCMS (method A): mass found (M+, 317.0), Rt (min): 3.52 Area % -98.64 (Max), 98.80 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 9.95 (s, 1H), 9.84 (d, *J* = 2 Hz, 1H), 8.96 (m, 2H), 8.73 (m, 1H), 8.25(d, *J* = 4.2 Hz, 1H), 7.62 (m, 1H), 7.36 (s, 2H), 6.59 (s, 1H), 2.26 (s, 6H)	<10
"E7"	 [3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine Mass found (M+, 434.0), Rt (min): 3.76	<10
"E8"		<10

	(1-Benzyl-1H-indazol-6-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine LCMS (method A): mass found (M+, 418.0), Rt (min): 4.99 Area % -92.70 (Max), 93.19 (254 nm); ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 10.33 (s, 1H), 8.93 (d, *J* = 4.2 Hz, 1H), 8.74 (m, 2H), 8.30 (m, 2H), 7.98 (s, 1H), 7.68 (d, *J* = 8.64 Hz, 1H), 7.54 (m, 3H), 7.30 (m, 6H), 5.59 (s, 2H)	
"E9"	 (1-Benzyl-1H-indazol-6-yl)-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine Mass found (M+, 424.0), Rt (min): 4.20	<10
"E10"	 (3,4-Dimethoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine	<10

Pharmacological data

Table 1 Syk, Zap70, BTK, KDR, cSrc inhibition of some representative compounds of the formula I

Compound No.	IC_{50} (BLNK cell assay)	IC_{50} Syk (enzyme assay)	IC_{50} Zap70	IC_{50} BTK	IC_{50} KDR	IC_{50} cSRC
"B1"		C	B		C	
"B2"		C				C
"B3"						
"B5"		C	C			
"B6"		C	C			
"B7"		B				
"B8"						
"B9"		C				
"C1"		B	C		A	
"C2"		B				
"C3"						
"C4"		B			B	B
"C5"						
"C6"		C		C	C	C
"C7"		B				
"C8"		A		C	A	
"C9"		B			C	
"C10"		B			B	
"C11"		C			C	C
"C12"		C				
"C13"		B	C		B	C
"C14"		C	C	C	C	C
"C15"		B			C	
"C16"		A				

"C17"		B			C	
"C18"		A	C			
"C19"	C	A	C	C	B	B
"C20"		B			C	C
"C21"		B	C		B	
"C22"		C			B	C
"C23"		B	C		B	C
"C24"		B	C	C		
"C25"		C	C		C	
"C26"		B	B			
"C27"		B	C			
"C28"		C			B	C
"C29"		C			C	C
"C30"		C			C	C
"C32"		C	C		C	C
"C33"		C			C	C
"C34"		C	C		C	C
"C35"		C	C		C	C
"C36"		C	C		C	C
"C37"		C			C	
"C38"		C			C	C
"C39"		C			C	C
"C40"		C			C	C
"C41"		C	C		C	
"C42"		C	B		C	C
"C43"			C		C	
"C44"		C	C			
"C45"		C			C	
"C46"		C			C	C
"C47"		C	C		C	C

"C48"		C	B		C	C
"C49"		C			C	
"C50"		C	C		C	
"C51"			B		C	
"C52"			C		C	
"C53"		C			C	
"C54"		C				
"C56"		C			C	
"C57"		C			C	
"C60"			C			
"C68"		C				
"C71"		C				
"C73"		C				
"C75"			C			
"C76"		C	C			
"C77"		C	C			
"C78"		C	C			
"C79"		C	B			
"C80"		C	B			
"C81"		C	C			
"C82"			C			
"C84"			C			
"C85"			B			
"C86"			C			
"C87"			C			
"C88"			C			
"C114"		A			B	B
"C254"		B				
"C256"		A	C		B	B
"C260"		A				

"C261"	C	A	C		A	B
"C262"		B				
"C264"		A	C			B
"C265"	C	A	B		A	B
"C268"	C	A	B		A	B
"C269"		A	B		A	B
"C272"	C	A	B		A	B
"C274"		B				
"C277"		A			A	B
"C284"	C	A				
"C253"	C	A			A	B
"C263"		C	C			
"C276"		A			A	B
"C293"		B				
"C300"		A	C		B	B
"C301"		A	C		B	B
"C303"		A	A		B	A
"D1"	C	A			B	B
"D2"		A	C		A	B
"D3"		A	C		A	B
"D6"		B	C		B	B
"D10"	C	A	C		A	A
"D15"	C	A	C		B	B
"D18"	C	A	C		B	B
"D21"		B	C		C	C
"D23"	C	A	C		B	A

IC_{50}: < 0.3 μM = A 0.3 - 3 μM = B 3-50 μM = C

The compounds shown in Table 1 are particularly preferred compounds according to the invention.

The following examples relate to medicaments:

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 g of an active ingredient of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example F: Dragees

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

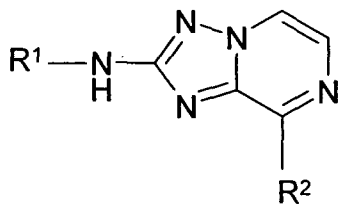
2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Patent Claims

1. Compounds of the formula I



I

in which

R^1 denotes Ar^1 or Het^1,

R^2 denotes Ar^2, Het^2, $NH(CH_2)_nAr^2$, $O(CH_2)_nAr^2$, $NR^3(CH_2)_nHet^2$, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, NHCyc or $NH(CH_2)_pNA_2$,

Ar^1 denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, Alk, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, SO_2A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, SO_2NH_2, SO_2NHA, SO_2NA_2, $NHCONH_2$, NHCOA, NHCOAlk, $NHCOCH=CH(CH_2)_pNA_2$, CHO, COA, SO_3H, $O(CH_2)_pNH_2$, $O(CH_2)_pNHA$, $O(CH_2)_pNA_2$, $COHet^3$, $S(CH_2)_nHet^3$, $(CH_2)_nHet^3$ and/or $O(CH_2)_nHet^3$,

Ar^2 denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, OAr^3, benzyloxy, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, SO_2A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $CONH(CH_2)_pOA$, $CONH(CH_2)_pOH$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, SO_2NH_2, SO_2NHA, SO_2NA_2, OSO_2A, $NHCONH_2$, NHCOA, CHO, COA, SO_3H, $O(CH_2)_pNH_2$, $O(CH_2)_pNHA$, $O(CH_2)_pNA_2$,

	$CONHAr^3$, $NHCOAr^3$, $CONHHet^3$, $NHCOHet^3$, $NHSO_2A$, $COHet^3$, $(CH_2)_nHet^3$, $S(CH_2)_nHet^3$ and/or $O(CH_2)_nHet^3$,
Het^1	denotes a mono- or bicyclic unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,
Het^2	denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetra-substituted by Hal, A, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, $NHSO_2A$, $NASO_2A$, SO_2A, SO_2A and/or =O,
Het^3	denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, Hal, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $(CH_2)_nOH$, $(CH_2)_nOA$, COOA, Ar^3 and/or =O,
R^3	denotes H or alkyl having 1, 2, 3 or 4 C-atoms,
A	denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O, NH, S, SO, SO_2 and/or by CH=CH groups, or cyclic alkyl having 3-7 C atoms,
Cyc	denotes cyclic alkyl having 3-7 C atoms, which may be unsubstituted or monosubstituted by NH_2,
Alk	denotes alkenyl or alkinyl having 2, 3, 4, 5 or 6 C-atoms,
Ar^3	denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A,
Hal	denotes F, Cl, Br or I,
n	denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which

Het^1 denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2 in which

Het^2 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, quinoxalinyl, benzimidazolyl, benzothiophenyl, benzotriazolyl, indolyl, indolinyl, naphthyridinyl, dihydronaphthyridinyl, terahydronaphtyridinyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, furopyridinyl, indazolyl, benzo[1,4]oxazinyl, pyrido[3,2-b][1,4]oxazinyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, $(CH_2)_nOH$, $(CH_2)_nOA$, CHO, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, SO_2A, SO_2A and/or =O,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

4. Compounds according to one or more of Claims 1-3 in which

Het^3 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

5. Compounds according to one or more of Claims 1-4 in which

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O and/or NH,

or

cyclic alkyl having 3-7 C atoms,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

6. Compounds according to one or more of Claims 1-5 in which

Ar^1 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds according to one or more of Claims 1-6 in which

Ar^2 denotes phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, OAr^3, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, $NHCOAr^3$, $NHSO_2A$, OSO_2A, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compounds according to one or more of Claims 1-7 in which

R^1 denotes Ar^1 or Het^1,

R^2 denotes Ar^2, Het^2, $NH(CH_2)_nAr^2$, $O(CH_2)_nAr^2$, $NR^3(CH_2)_nHet^2$, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, NHCyc or $NH(CH_2)_pNA_2$,

Ar^1 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,

Ar^2 denotes phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, OAr^3, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, $[C(R^3)_2]_nCN$, NO_2, $CONH(CH_2)_pNH_2$, $CONH(CH_2)_pNHA$, $CONH(CH_2)_pNA_2$, $(CH_2)_nCONH_2$, $(CH_2)_nCONHA$, $(CH_2)_nCONA_2$, $NHCOAr^3$, $NHSO_2A$, OSO_2A, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,

Het^1 denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or

benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,

Het^2 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, quinoxalinyl, benzimidazolyl, benzothiophenyl, benzotriazolyl, indolyl, indolinyl, naphthyridinyl, dihydronaphthyridinyl, terahydronaphtyridinyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, furopyridinyl, indazolyl, benzo[1,4]oxazinyl, pyrido[3,2-b][1,4]oxazinyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nNH_2$, $(CH_2)_nNHA$, $(CH_2)_nNA_2$, CN, CHO, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nAr^3$, $(CH_2)_nHet^3$, SO_2A, SO_2A and/or =O,

Het^3 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O,

R^3 denotes H or alkyl having 1, 2, 3 or 4 C-atoms,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in which one or two non-adjacent CH_2 groups may be replaced by O and/or NH,

or

cyclic alkyl having 3-7 C atoms,

Cyc denotes cyclic alkyl having 3-7 C atoms, which may be unsubstituted or monosubstituted by NH_2,

Ar^3 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A,

n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4,

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compounds according to Claim 1, selected from the group

No.	Name and/or structure
"C1"	(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-m-tolyl-amine
"C2"	8-(1,3-thiazol-5-yl)-*N*-[3-(trifluoromethyl)-phenyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-2-amine
"C3"	(8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine
"C4"	(3,5-Dimethyl-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C5"	(1-Benzyl-1H-indazol-6-yl)-(8-phenyl-[1,2,4]trizolo[1,5-a]pyrazin-2-yl)-amine
"C6"	2,2-Difluoro-6-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-4H-benzo[1,4]oxazin-3-one
"C7"	(3,5-Dimethyl-phenyl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C8"	(3,5-Dimethoxy-phenyl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C9"	(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine
"C10"	Phenyl-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine

"C11"	(3,5-Dimethyl-phenyl)-[8-(4-morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C12"	[8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3-trifluoromethyl-phenyl)-amine
"C13"	[8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-m-tolyl-amine
"C14"	Phenyl-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C15"	[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethyl-phenyl)-amine
"C16"	(3,5-Dimethoxy-phenyl)-[8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C17"	[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-m-tolyl-amine
"C18"	[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-phenyl-amine
"C19"	(3,5-Dimethoxy-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C20"	(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine
"C21"	(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-m-tolyl-amine
"C22"	Phenyl-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C23"	[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C24"	(1-Benzyl-1H-indazol-6-yl)-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C25"	[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-[8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine

"C26"	(1-Benzyl-1H-indazol-6-yl)-[8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C27"	(1-Benzyl-1H-indazol-6-yl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C28"	N^2-(3,5-Dimethyl-phenyl)-N^8-(3-morpholin-4-yl-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C29"	N^8-(2-Amino-ethyl)-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C30"	N^2-(3,5-Dimethoxy-phenyl)-N^8-[3-(4-methyl-piperazin-1-yl)-propyl]-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C31"	N^8-(2-Amino-cyclohexyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C32"	N^8-(3-Methoxy-propyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C33"	N^8-(3-Dimethylamino-propyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C34"	N^8-(2-Amino-ethyl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C35"	N^8-(3-Dimethylamino-propyl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C36"	N^2-(3,5-Dimethyl-phenyl)-N^8-[3-(4-methyl-piperazin-1-yl)-propyl]-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C37"	N^2-(3,5-Dimethyl-phenyl)-N^8-(3-methoxy-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C38"	N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-dimethylamino-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C39"	N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-morpholin-4-yl-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C40"	N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-methoxy-propyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine

"C41"	N^8-(2-Amino-ethyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C42"	N^8-(3-Morpholin-4-yl-propyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C43"	N^8-[3-(4-Methyl-piperazin-1-yl)-propyl]-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C44"	N^8-(3-Methoxy-propyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C45"	N^8-(2-Amino-ethyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C46"	N^8-(3-Dimethylamino-propyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C47"	N^8-(3-Morpholin-4-yl-propyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C48"	N^8-[3-(4-Methyl-piperazin-1-yl)-propyl]-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C49"	N^8-(2-Amino-ethyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C50"	N^8-(3-Dimethylamino-propyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C51"	N^8-(3-Morpholin-4-yl-propyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C52"	N^8-[3-(4-Methyl-piperazin-1-yl)-propyl]-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C53"	N^8-(3-Methoxy-propyl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C54"	N^8-(2-Amino-cyclohexyl)-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C55"	N^8-(2-Amino-cyclohexyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine

"C56"	N^8-(2-Amino-cyclohexyl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C57"	N^8-(2-Amino-cyclohexyl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C58"	*N*^{8}-{3-Chloro-4-[(1-methyl-1*H*-imidazol-2-yl)thio]phenyl}-*N*^{2}-(3,5-dimethyl-phenylamino) [1,2,4]triazolo[1,5-*a*]pyrazine-2,8-diamine
"C59"	6-({2-[(3,5-Dimethylphenyl)amino][1,2,4]triazolo[1,5-*a*]pyrazin-8-yl}amino)-2,2-difluoro-2*H*-1,4-benzoxazin-3(4*H*)-one
"C60"	6-[2-(3,5-Dimethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino]-2,2-dimethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one
"C61"	N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C62"	N^2,N^8-Bis-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C63"	N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C64"	N^2-(3,5-Dimethyl-phenyl)-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C65"	N^8-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C66"	6-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino]-2,2-difluoro-4H-benzo[1,4]oxazin-3-one
"C67"	N^2-(3,5-Dimethoxy-phenyl)-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C68"	N^8-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine

"C69"	2,2-Difluoro-6-[2-(3-trifluoromethyl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino]-4H-benzo[1,4]oxazin-3-one
"C70"	N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C71"	2,2-Difluoro-6-(2-m-tolylamino-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino)-4H-benzo[1,4]oxazin-3-one
"C72"	N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C73"	N^2-m-Tolyl-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C74"	2,2-Difluoro-6-(2-phenylamino-[1,2,4]triazolo[1,5-a]pyrazin-8-ylamino)-4H-benzo[1,4]oxazin-3-one
"C75"	N^8-(1-Benzyl-1H-indazol-6-yl)-N^2-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C76"	N^2-Phenyl-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C77"	N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C78"	N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C79"	N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C80"	N^2-[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-N^8-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C81"	N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-(3,5-dimethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C82"	N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine

"C83"	N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C84"	N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-m-tolyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C85"	N^2-(1-Benzyl-1H-indazol-6-yl)-N^8-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C86"	N^8-(3,5-Dimethyl-phenyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C87"	N^8-(3,5-Dimethoxy-phenyl)-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C88"	N^8-Phenyl-N^2-(3-trifluoromethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"C114"	[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine
"C253"	[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"C254"	[8-(3-Aminomethyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(6-methoxy-pyridin-3-yl)-amine
"C256"	2-{4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-2-methyl-propionitrile
"C257"	2-Methyl-2-{4-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-propionitrile
"C258"	2-{4-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-2-methyl-propionitrile
"C260"	(3,5-Dimethoxy-phenyl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C261"	(3,5-Dimethoxy-phenyl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C262"	(6-Methoxy-pyridin-3-yl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine

"C263"	5-(8-Quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one
"C264"	(3,5-Dimethoxy-phenyl)-(8-quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C265"	(4-Morpholin-4-yl-phenyl)-(8-quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C266"	(6-Methoxy-pyridin-3-yl)-(8-quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"C267"	5-(8-Quinolin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one
"C268"	3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol
"C269"	3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol
"C270"	3-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol
"C272"	N-{3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide
"C273"	N-{3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide
"C274"	N-{3-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-methanesulfonamide
"C276"	3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide
"C277"	3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide
"C278"	3-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide
"C280"	4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide

"C281"	4-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide
"C282"	4-[2-(6-Methoxy-pyridin-3-ylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzamide
"C284"	(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3,5-dimethoxy-phenyl)-amine
"C286"	(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(6-methoxy-pyridin-3-yl)-amine
"C288"	(3,5-Dimethoxy-phenyl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C289"	(4-Morpholin-4-yl-phenyl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C290"	(6-Methoxy-pyridin-3-yl)-[8-(2-phenoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C292"	[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine
"C293"	[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"C294"	[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(6-methoxy-pyridin-3-yl)-amine
"C295"	5-[8-(3-Amino-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one
"C296"	4-tert-Butyl-N-{3-[2-(3,5-dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-2-methyl-phenyl}-benzamide
"C297"	N-{3-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-2-methyl-phenyl}-3-trifluoromethyl-benzamide
"C298"	4-tert-Butyl-N-{2-methyl-3-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-benzamide

"C299"	N-{2-Methyl-3-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl}-3-trifluoromethyl-benzamide
"C300"	(3,5-Dimethoxy-phenyl)-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C301"	(3,5-Dimethoxy-phenyl)-[8-(1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C303"	(3,5-Dimethoxy-phenyl)-[8-(1H-indazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"C304"	(3,5-Dimethoxy-phenyl)-(8-ethoxy-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D1"	(2-Methyl-1H-benzoimidazol-5-yl)-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D2"	[8-(1-Methyl-1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"D3"	[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"D4"	(4-Morpholin-4-yl-phenyl)-(8-quinoxalin-6-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D5"	[8-(1-Benzyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"D6"	1-Methoxy-3-{4-[2-(4-morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyrazol-1-yl}-propan-2-ol
"D7"	[8-(1-Methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"D8"	2-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenol
"D9"	{8-[1-(2,2-Dimethoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine

"D10"	[8-(1H-Indol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(4-morpholin-4-yl-phenyl)-amine
"D11"	[4-(4-Methyl-piperazin-1-yl)-phenyl]-(8-quinoxalin-6-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D12"	5-{8-[1-(2,2-Dimethoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino}-1,3-dihydro-indol-2-one
"D13"	4-[4-(8-Quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-phenyl]-morpholin-3-one
"D14"	{8-[4-(4-Methyl-piperazin-1-yl)-phenyl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine
"D15"	[8-(1-Methyl-1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-[4-(4-methyl-piperazin-1-yl)-phenyl]-amine
"D16"	(6-Morpholin-4-yl-pyridin-3-yl)-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D17"	5-[8-(1-Methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one
"D18"	[4-(4-Methyl-piperazin-1-yl)-phenyl]-[8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D19"	(3,5-Dimethoxy-phenyl)-[8-(2-phenyl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D20"	{8-[4-(2-Amino-ethyl)-piperazin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(3,5-dimethoxy-phenyl)-amine
"D21"	(3,5-Dimethoxy-phenyl)-[8-(2-pyridin-2-yl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D22"	N8-Benzyl-N2-(3,5-dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"D23"	[4-(4-Methyl-piperazin-1-yl)-phenyl]-(8-quinolin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D24"	1-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-piperidin-4-ol

"D25"	(4-Morpholin-4-yl-phenyl)-[8-(2-phenyl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D26"	N2-(3,5-Dimethoxy-phenyl)-N8-methyl-N8-(tetrahydro-pyran-4-yl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"D27"	(3,5-Dimethoxy-phenyl)-{8-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-amine
"D28"	2-{4-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-pyrazol-1-yl}-ethanol
"D29"	(4-Morpholin-4-yl-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D30"	(6-Morpholin-4-yl-pyridin-3-yl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D31"	5-(8-Pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino)-1,3-dihydro-indol-2-one
"D32"	(3,5-Dimethoxy-phenyl)-[8-(2-morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D33"	5-[8-(2-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino]-1,3-dihydro-indol-2-one
"D34"	{8-[1-(2-Morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine
"D35"	(3,5-Dimethoxy-phenyl)-(8-quinolin-5-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D36"	(3,5-Dimethoxy-phenyl)-[8-(2-isopropyl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D37"	5-{8-[1-(2-Hydroxy-3-methoxy-propyl)-1H-pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamino}-1,3-dihydro-indol-2-one
"D38"	{8-[2-(4-Ethoxy-phenyl)-pyrrolidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-(4-morpholin-4-yl-phenyl)-amine

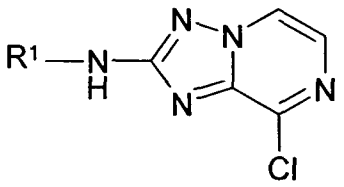
"D39"	(3,5-Dimethoxy-phenyl)-{8-[2-(4-ethoxy-phenyl)-pyrrolidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-amine
"D40"	(4-Morpholin-4-yl-phenyl)-[8-(2-pyridin-2-yl-pyrrolidin-1-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"D41"	(8-Biphenyl-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(2,5-dimethyl-2H-pyrazol-3-yl)-amine
"D42"	Methanesulfonic acid 2-[2-(3,5-dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-phenyl ester
"D43"	3-[2-(4-Morpholin-4-yl-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-benzoic acid
"D44"	N2-(3,5-Dimethoxy-phenyl)-N8-(tetrahydro-pyran-4-ylmethyl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"D45"	[4-(4-Methyl-piperazin-1-yl)-phenyl]-(8-pyrido[2,3-b]pyrazin-7-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D46"	N2-(3,5-Dimethoxy-phenyl)-N8-(tetrahydro-pyran-4-yl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"D47"	(3,5-Dimethoxy-phenyl)-(8-piperidin-1-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D48"	N2-(3,5-Dimethoxy-phenyl)-N8,N8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"D49"	(3,5-Dimethoxy-phenyl)-{8-[2-(4-fluoro-phenyl)-piperidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-amine
"D50"	(3,5-Dimethoxy-phenyl)-(8-piperazin-1-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"D51"	4-[2-(3,5-Dimethoxy-phenylamino)-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-piperazine-1-carbaldehyde
"D52"	[8-(7,8-Dihydro-5H-[1,6]naphthyridin-6-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine
"D53"	[8-(3,4-Dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethoxy-phenyl)-amine

"D54"	N2-(3,4-Dimethoxy-phenyl)-N8-methyl-N8-(tetrahydro-pyran-4-yl)-[1,2,4]triazolo[1,5-a]pyrazine-2,8-diamine
"E1"	(8-Phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-(3-trifluoromethyl-phenyl)-amine
"E2"	(3,5-Dimethyl-phenyl)-[8-(4-morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-amine
"E3"	[8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3-trifluoromethyl-phenyl)-amine
"E4"	[8-(4-Morpholin-4-yl-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-m-tolyl-amine
"E5"	[8-(3,5-Dimethoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]-(3,5-dimethyl-phenyl)-amine
"E6"	(3,5-Dimethyl-phenyl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"E7"	[3-Chloro-4-(1-methyl-1H-imidazol-2-ylsulfanyl)-phenyl]-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"E8"	(1-Benzyl-1H-indazol-6-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine
"E9"	(1-Benzyl-1H-indazol-6-yl)-(8-thiazol-2-yl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-amine

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

10. Process for the preparation of compounds of the formula I according to Claims 1-9 and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, characterised in that

a) a compound of the formula II



II

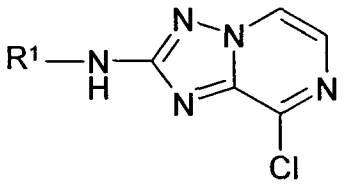
is reacted with a compound of the formula III

R^2-L III

in which R^2 has the meaning indicated in Claim 1,
and L denotes a boronic acid or a boronic acid ester group,
in a Suzuki-type coupling

or

b) a compound of the formula II



II

is reacted with a compound of the formula III

R^2-L III

in which R^2 has the meaning indicated in Claim 1,
and L denotes an NH_2 or OH

and/or

a base or acid of the formula I is converted into one of its salts.

11. Medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, solvates, tautomers and

stereoisomers thereof, including mixtures thereof in all ratios, and optionally an pharmaceutically acceptable carrier, excipient or vehicle.

12. Compounds of the formula I and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the use for the inhibition of Syk.

13. Compounds of the formula I and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the use for the treatment and/or prevention of inflammatory conditions, immunological conditions, autoimmune conditions, allergic conditions, rheumatic conditions, thrombotic conditions, cancer, infections, neurodegenerative diseases, neuroinflammatory diseases, cardiovascular diseases, and metabolic conditions, the methods comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

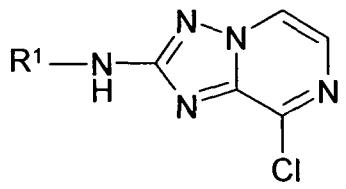
14. Compounds according to claim 13 for the use for the treatment and/or prevention of diseases selected from the group rheumatoid arthritis, systemic lupus, asthma, allergic rhinitis, ITP, multiple sclerosis, leukemia, breast cancer, maligna melanoma.

15. Medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

16. Set (kit) consisting of separate packs of
(a) an effective amount of a compound of the formula I and/or pharmaceutically acceptable salts, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios,
and

(b) an effective amount of a further medicament active ingredient.

17. Compounds of the formula II



II

in which

R^1 denotes Ar^1 or Het^1,

Ar^1 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal, A, $(CH_2)_nOH$, $(CH_2)_nOA$, $(CH_2)_nHet^3$ and/or $S(CH_2)_nHet^3$,

Het^1 denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, indazolyl, benzo[1,4]oxazinyl, 1,3- or 2,3-dihydro-indolyl or benzothiadiazolyl, each of which is unsubstituted or mono-, di- or trisubstituted A, OH, OA, Hal, $(CH_2)_nAr^3$ and/or =O,

Het^3 denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 2,3-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, tetrahydro-benzothiophenyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A and/or =O,

R^3 denotes H or alkyl having 1, 2, 3 or 4 C-atoms,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or in

which one or two non-adjacent CH_2 groups may be replaced by O and/or NH,
or
cyclic alkyl having 3-7 C atoms,

Cyc denotes cyclic alkyl having 3-7 C atoms, which may be unsubstituted or monosubstituted by NH_2,

Ar^3 denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A,

n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3 or 4

and pharmaceutically acceptable solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.