TITLE OF THE INVENTION

FUSED BICYCLIC mTOR INHIBITORS

BACKGROUND OF THE INVENTION

[1] The present invention is directed to bicyclic compounds that are inhibitors of mammalian Target Of Rapamycin (mTOR) kinase (also known as FRAP, RAFT, RAPT, SEP). In particular, the present invention is directed to fused bicyclic compounds that are mTOR inhibitors useful in the treatment of cancer.

[2] International Patent Publication WO 2001 019828 describes the preparation of heteroaromatic amines as protein kinase inhibitors. International Patent Publication WO 2005/047289 describes pyrrolopyrimidine compounds useful in treatment of cancer. Bergstrom et al., *J.Org. Chem.*, 56:5598-5602(1991) describes Palladium-Mediated Synthesis of C-5 Pyrimidine Nucleoside Thioethers from Disulfides and Mercurinucleosides.

[3] It has been shown that high levels of dysregulated mTOR activity are associated with variety of human cancers and several hamartoma syndromes, including tuberous sclerosis complex, the PTEN-related hamartoma syndromes and Peutz-Jeghers syndrome. Although rapamycin analogues are in clinical development for cancer as mTOR kinase inhibitor, the clinical out come with CCI-779 is just modest in breast and renal cancer patients. This is probably because rapamycin partially inhibits mTOR function through raptor-mTOR complex (mTORC1). It has been also found that 2/3 of the breast cancer and ½ of renal cancer patients are resistant to rapamycin therapy. With a recent discovery of rictor-mTOR complex (mTORC2) which is involved in phosphorylation of AKT (S473) that is important in regulation of cell survival and modulation of PKCα that plays a major role in regulation of actin cytoskeletal organization in a rapamycin-independent manner, and inhibition of these activities of mTOR is probably important for broader antitumor activity and better efficacy. Therefore, it is desirable to develop novel compounds that are direct inhibitors of mTOR kinase, which would inhibit mTORC1 and mTORC2.

[4] Rapamycin, a macrolide antibiotic has been shown to specifically inhibit mTOR kinase activity *in vitro* and *in vivo* in several studies. Although precise mechanism by which rapamycin inhibits mTOR function is not well understood, it is known that rapamycin first binds to FKBP12 (FK506 binding protein) and then binds to FRB domain of mTOR and thus inhibit mTOR activity by inducing conformational changes, which inhibits substrate binding. Rapamycin has been widely used as a specific mTOR inhibitor in preclinical studies to demonstrate role of mTOR in signal transduction and cancer. But rapamycin was not developed as a cancer therapy because of stability and solubility problems even though significant antitumor activity was observed in the NCI screening programme. However, synthesis of rapamycin analogues with superior solubility and stability properties has led to run the clinical trails with CCI-779, RAD001 and AP23573. The most advanced

rapamycin analogue, CCI-779 has shown modest anti-tumor activity in Phase II breast, renal carcinoma and mantle cell lymphoma clinical trials.

[5] The *Tor* genes were originally identified in yeast as the targets of the drug rapamycin. The structurally and functionally conserved mammalian counter part of yeast TOR, mTOR was later discovered. mTOR is a member of the phosphoinositide kinase-related kinase (PIKK) family, but rather than phosphorylating phosphoinositides, phosphorylates proteins on serine or threonine residues. Genetic studies have shown that mTOR is essential for cell growth and development in fruit flies, nematodes and mammals, and the disruption of the genes encoding mTOR results in lethality in all species. Several studies have demonstrated that mTOR has a central role in controlling cell growth, proliferation and metabolism. mTOR regulates a wide range of cellular functions, including translation, transcription, mRNA turnover, protein stability, actin cytoskeletal organization and autophagy. There are two mTOR complexes in mammalian cells. mTOR complex I (mTORC1) is a raptor-mTOR complex, which mainly regulates cell growth in a rapamycin-sensitive manner whereas mTOR complex II (mTORC2) is a rictor-mTOR complex, which regulates cytoskeletal organization in a rapamycin-insensitive manner.

[6] The best-characterized function of mTOR in mammalian cells is regulation of translation. Ribosomal S6 kinase (S6K) and eukaryotic initiation factor 4E binding protein 1 (4E-BP1), the most extensively studied substrates of mTOR, are key regulators of protein translation. S6K is the major ribosomal protein kinase in mammalian cells. Phosphorylation of S6 protein by S6K selectively increases the translation of mRNAs containing a tract of pyrimidines motif; these mRNAs often encode ribosomal proteins and other translational regulators. Thus, S6K enhances overall translation capacity of cells. 4E-BP1, another well-characterized mTOR target, acts as a translational repressor by binding and inhibiting the eukaryotic translation initiation factor 4E (eIF4E), which recognizes the 5' end cap of eukaryotic mRNAs. Phosphorylation of 4E-BP1 by mTOR results in a dissociation of 4E-BP1 from eIF4E, thereby relieving the inhibition of 4E-BP1 on eIF4E-dependent translation initiation. eIF4E overexpression enhances cell growth and transforms cells by increasing the translation of a subset of key growth-promoting proteins, including cyclin D1, c-Myc and VEGF. Therefore, mTOR-dependent regulation of both 4E-BP1 and S6K might be one mechanism by which mTOR positively regulates cell growth. mTOR integrates two of the most important extracellular and intracellular signals involved in the regulation of cell growth: growth factors and nutrients. Growth factor, such as insulin or IGF1 and nutrients, such as amino acids or glucose, enhance mTOR function, as evidenced by an increased phosphorylation of S6K and 4E-BP1. Rapamycin or dominant negative mTOR inhibits these effects, indicating that mTOR integrates the regulation of signals from growth factors and nutrients.

[7] Signalling pathways that are upstream and downstream of mTOR are often deregulated in variety of cancers, including breast, lung, kidney, prostate, blood, liver, ovarian, thyroid, GI tract and lymphoma. Oncogenes including overexpressed receptor tyrosine kinases and

constitutively activated mutant receptors activate PI3K-mediated signaling pathways. Additional alterations of the PI3K–mTOR pathway in human cancers include amplification of the p110 catalytic subunit of PI3K, loss of PTEN phosphatase function, amplification of AKT2, mutations in TSC1 or TSC2, and overexpression or amplification of eIF4E or S6K1. Mutation or loss of heterozygosity in TSC1 and TSC2 most often give rise to Tuberous Sclerosis (TSC) syndrome. TSC is rarely associated with malignant tumors, although patients with TSC are at risk for malignant renal cancer of clear-cell histology. Although inactivation of TSC might not lead to malignancy per se, deregulation of this pathway seems crucial for angiogenesis in developing malignancies. TSC2 regulates VEGF production through mTOR-dependent and –independent manner.

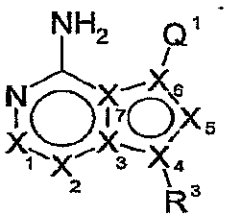
[8] With the recent discovery of rapamycin independent function of mTOR (by mTOR2) in phosphorylation AKT (at S473) that is important in regulation of cell survival and modulation of PKCα, which plays a major role in regulation of actin cytoskeletal organization, it is believed that inhibition of mTOR function by rapamycin is partial. Therefore, discovery of a direct mTOR kinase inhibitor, which would completely inhibit the function of both mTORC1 and mTORC2, is required for broader anti-tumor activity and better efficacy. Here we describe the discovery of direct mTOR kinase inhibitors, which can be used in the treatment of variety of cancers – including breast, lung, kidney, prostate, blood, liver, ovarian, thyroid, GI tract and lymphoma – and other indications such as rheumatoid arthritis, hamartoma syndromes, transplant rejection, IBD, multiple sclerosis and immunosuppression.

[9] Recent success of Tarceva™, an EGFR kinase inhibitor for the treatment of NSCLC and prior success with Gleevec™ for the treatment of CML indicate that it is possible to develop selective kinase inhibitors for the effective treatment of cancers. Although there are several anti-cancer agents including kinase inhibitors, there is still continuing need for improved anti-cancer drugs, and it would be desirable to develop new compounds with better selectivity, potency or with reduced toxicity or side effects.

[10] Thus, it is desirable to develop compounds that exhibit mTOR inhibition in order to treat cancer patients. Further, such compounds may be active in other kinases such as, for example, PI3K, Src, KDR, to add efficacy in breast, non-small cell lung cancer (NSCLC), renal cell carcinoma, mantle cell lymphoma, endometrial cancers, or other hamartoma syndromes.

SUMMARY OF THE INVENTION

[11] Compounds represented by Formula (I)

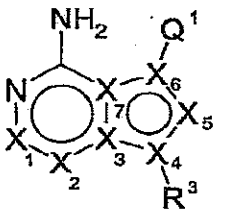


(I)

or a pharmaceutically acceptable salt thereof, are inhibitors of mTOR and useful in the treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

[12] The compounds of the present invention are represented by Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X_1, and X_2 are each independently N or C–$(E^1)_{aa}$;

X_5 is N, C–$(E^1)_{aa}$, or N–$(E^1)_{aa}$;

X_3, X_4, X_6, and X_7 are each independently N or C;

wherein at least one of X_3, X_4, X_5, X_6, and X_7 is independently N or N–$(E^1)_{aa}$;

R^3 is C_{0-10}alkyl, cycloC_{3-10}alkyl, aminomethylcycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl or heterobicycloC_{5-10}alkyl any of which is optionally substituted by one or more independent G^{11} substituents;

Q^1 is –$A(R^1)_mB(W)_n$ or –$B(G^{11})_nA(Y)_m$;

A and B are respectively, 5 and 6 membered aromatic or heteroaromatic rings, fused together to form a 9-membered heteroaromatic system excluding 5-benzo[*b*]furyl and 3-indolyl; and excluding 2-indolyl, 2-benzoxazole, 2-benzothiazole, 2-benzimidazolyl, 4-aminopyrrolopyrimidin-5-yl, 4 -aminopyrrolopyrimidin-6-yl, and 7-deaza-7-adenosinyl derivatives when X_1 and X_5 are CH, X_3, X_6 and X_7 are C, and X_2 and X_4 are N;

or Q^1 is –$A(R^1)_mA(Y)_m$, wherein each A is the same or different 5-membered aromatic or heteroaromatic ring, and the two are fused together to form an 8-membered heteroaromatic system;

R^1 is independently, hydrogen, –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{1-6}alkyl, –C_{0-8}alkylcycloC_{3-8}alkyl, –C_{0-8}alkyl-$NR^{311}S(O)_{0-2}R^{321}$, –$C_{0-8}$alkyl-$NR^{311}S(O)_{0-2}NR^{321}R^{331}$, –$C_{0-8}$alkyl-$S(O)_{0-2}NR^{311}R^{321}$, –$C_{0-8}$alkyl-$NR^{311}COR^{321}$, –$C_{0-8}$alkyl-$NR^{311}CO_2R^{321}$, –$C_{0-8}$alkyl-$NR^{311}CONR^{321}R^{331}$, –$C_{0-8}$alkyl-$CONR^{311}R^{321}$, –$C_{0-8}$alkyl-$CON(R^{311})S(O)_{0-2}R^{321}$, –$C_{0-8}$alkyl-$CO_2R^{311}$, -$C_{0-8}$alkyl-$S(O)_{0-2}R^{311}$, –$C_{0-8}$alkyl-O-$C_{1-8}$alkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylcyclo$C_{3-8}$alkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylheterocyclyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylaryl, –$C_{0-8}$alkylaryl, –$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkylheterocyclyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylcyclo$C_{3-}$

$_{8}$cycloalkyl, –C_{0-8}alkyl-S-C_{0-8}alkylheterocyclyl, -C_{0-8}alkyl-S-C_{0-8}alkylaryl, –C_{0-8}alkyl-S-C_{0-8}alkylhetaryl, –C_{0-8}alkyl-N(R^{311})-C_{0-8}alkyl, –C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylC_{3-8}cycloalkyl, –C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylaryl, –C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylhetaryl, –C_{0-8}alkyl-$NR^{311}R^{321}$, –C_{2-8}alkenyl, –C_{2-8}alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not N-methyl-2-indolyl, N-(phenylsulfonyl)-2-indolyl, or N-tert-butoxycarbonyl

W is independently, hydrogen, –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl (optionally substituted with 1 or more R^{31} groups), hetaryl (optionally substituted with 1 or more R^{31} groups), C_{1-6}alkyl, –C_{0-8}alkylC_{3-8}cycloalkyl, –C_{0-8}alkyl-$NR^{312}S(O)_{0-2}R^{322}$, –$C_{0-8}$alkyl-$NR^{311}S(O)_{0-2}NR^{321}R^{331}$, –$C_{0-8}$alkyl-$NR^{311}CO_2R^{321}$, –$C_{0-8}$alkyl-CON($R^{311}$)$S(O)_{0-2}R^{321}$, –$C_{0-8}$alkyl-$S(O)_{0-2}NR^{312}R^{322}$, –$C_{0-8}$alkyl-$NR^{312}COR^{322}$, –$C_{0-8}$alkyl-$NR^{312}CONR^{322}R^{332}$, –$C_{0-8}$alkyl-$CONR^{312}R^{322}$, –$C_{0-8}$alkyl-$CO_2R^{312}$, –$C_{0-8}$alkyl$S(O)_{0-2}R^{312}$, –$C_{0-8}$alkyl-O-$C_{1-8}$alkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylcyclyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylheterocycloalkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylaryl, –Oaryl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkylaryl, –$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkylheterocyclyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkyl$C_{3-8}$cycloalkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylheterocycloalkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylaryl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkyl-N($R^{312}$)-$C_{0-8}$alkyl, –$C_{0-8}$alkyl-N($R^{312}$)-$C_{0-8}$alkyl$C_{3-8}$cycloalkyl, –$C_{0-8}$alkyl-N($R^{312}$)-$C_{0-8}$alkylheterocycloalkyl, –$C_{0-8}$alkyl-N($R^{312}$)-$C_{0-8}$alkylaryl, –$C_{0-8}$alkyl-N($R^{312}$)-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkyl-$NR^{312}R^{322}$, –$C_{2-8}$alkenyl, –$C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not 4-benzyloxy-2-indolyl;

Y is independently, hydrogen, –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{0-6}alkyl, –C_{0-8}alkylC_{3-8}cycloalkyl, –C_{0-8}alkyl-$NR^{311}S(O)_{0-2}R^{321}$, –$C_{0-8}$alkyl-$NR^{311}S(O)_{0-2}NR^{321}R^{331}$, –$C_{0-8}$alkyl-$NR^{311}CO_2R^{321}$, –$C_{0-8}$alkyl-CON($R^{311}$)$S(O)_{0-2}R^{321}$, –$C_{0-8}$alkyl-$S(O)_{0-2}NR^{311}R^{321}$, –$C_{0-8}$alkyl-$NR^{311}COR^{321}$, –$C_{0-8}$alkyl-$NR^{311}CONR^{321}R^{331}$, –$C_{0-8}$alkyl-$CONR^{311}R^{321}$, –$C_{0-8}$alkyl-$CO_2R^{311}$, –$C_{0-8}$alkyl$S(O)_{0-2}R^{311}$, –$C_{0-8}$alkyl-O-$C_{1-8}$alkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkyl$C_{3-8}$cycloalkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylheterocycloalkyl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylaryl, –$C_{0-8}$alkyl-O-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkylaryl, –$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkylheterocyclyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkyl$C_{3-8}$cycloalkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylheterocycloalkyl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylaryl, –$C_{0-8}$alkyl-S-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkyl-N($R^{311}$)-$C_{0-8}$alkyl, –$C_{0-8}$alkyl-N($R^{311}$)-$C_{0-8}$alkyl$C_{3-8}$cycloalkyl, –$C_{0-8}$alkyl-N($R^{311}$)-$C_{0-8}$alkylheterocycloalkyl, –$C_{0-8}$alkyl-N($R^{311}$)-$C_{0-8}$alkylaryl, –$C_{0-8}$alkyl-N($R^{311}$)-$C_{0-8}$alkylhetaryl, –$C_{0-8}$alkyl-$NR^{311}R^{321}$, –$C_{2-8}$alkenyl, –$C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not 2-carboxy-5-benzo[*b*]thiophenyl;

G^{11} is halo, oxo, –CF_3, –OCF_3, –OR^{312}, –$NR^{312}R^{322}$, –$C(O)R^{312}$, –$C(O)C_{3-8}$cycloalkyl, –CO_2C_{3-8}cycloalkyl, –CO_2R^{312}, –$C(=O)NR^{312}R^{322}$, –NO_2, –CN, –$S(O)_{0-2}R^{312}$, –$SO_2NR^{312}R^{322}$, $NR^{312}(C=O)R^{322}$, $NR^{312}C(=O)OR^{322}$, $NR^{312}C(=O)NR^{322}R^{332}$, $NR^{312}S(O)_{0-2}R^{322}$, –$C(=S)OR^{312}$, –$C(=O)SR^{312}$, –$NR^{312}C(=NR^{322})NR^{332}R^{341}$, –$NR^{312}C(=NR^{322})OR^{332}$, –$NR^{312}C(=NR^{322})SR^{332}$, –$OC(=O)OR^{312}$, –$OC(=O)NR^{312}R^{322}$, –$OC(=O)SR^{312}$, –$SC(=O)OR^{312}$, –$SC(=O)NR^{312}R^{322}$,

–P(O)OR^{312}OR^{322}, C_{1-10}alkylidene, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, –C_{1-10}alkoxyC_{1-10}alkyl, –C_{1-10}alkoxyC_{2-10}alkenyl, –C_{1-10}alkoxyC_{2-10}alkynyl, –C_{1-10}alkylthioC_{1-10}alkyl, –C_{1-10}alkylthioC_{2-10}alkenyl, –C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, –cycloC_{3-8}alkylC_{1-10}alkyl, –cycloC_{3-8}alkenylC_{1-10}alkyl, –cycloC_{3-8}alkylC_{2-10}alkenyl, –cycloC_{3-8}alkenylC_{2-10}alkenyl, –cycloC_{3-8}alkylC_{2-10}alkynyl, –cycloC_{3-8}alkenylC_{2-10}alkynyl, –heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or –heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, –OR^{313}, –NR^{313}R^{323}, –C(O)R^{313}, $–CO_2$R^{313}, –C(=O)NR^{313}R^{323}, $–NO_2$, –CN, –S(O)$_{0-2}$R^{313}, $–SO_2$NR^{313}R^{323}, –NR^{313}C(=O)R^{323}, –NR^{313}C(=O)OR^{323}, –NR^{313}C(=O)NR^{323}R^{333}, –NR^{313}S(O)$_{0-2}$R^{323}, –C(=S)OR^{313}, –C(=O)SR^{313}, –NR^{313}C(=NR^{323})NR^{333}R^{342}, –NR^{313}C(=NR^{323})OR^{333}, –NR^{313}C(=NR^{323})SR^{333}, –OC(=O)OR^{333}, –OC(=O)NR^{313}R^{323}, –OC(=O)SR^{313}, –SC(=O)OR^{313}, –P(O)OR^{313}OR^{323}, or –SC(=O)NR^{313}R^{323} substituents;

or G^{11} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, where the attachment point is from either the left or right as written, where any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, –OR^{313}, –NR^{313}R^{323}, –C(O)R^{313}, $–CO_2$R^{313}, –C(=O)NR^{313}R^{323}, $–NO_2$, –CN, –S(O)$_{0-2}$R^{313}, $–SO_2$NR^{313}R^{323}, –NR^{313}C(=O)R^{323}, –NR^{313}C(=O)OR^{323}, –NR^{313}C(=O)NR^{323}R^{333}, –NR^{313}S(O)$_{0-2}$R^{323}, –C(=S)OR^{313}, –C(=O)SR^{313}, –NR^{323}C(=NR^{313})NR^{333}R^{342}, –NR^{313}C(=NR^{323})OR^{333}, –NR^{313}C(=NR^{323})SR^{333}, –OC(=O)OR^{313}, –OC(=O)NR^{313}R^{323}, –OC(=O)SR^{313}, –SC(=O)OR^{313}, –P(O)OR^{313}OR^{323}, or –SC(=O)NR^{313}R^{323} substituents; provided that G^{11} is not *N*-CH_2CO_2H when R^3 is 4-piperidinyl;

R^{31}, R^{32}, R^{33}, R^{311}, R^{321}, R^{331}, R^{312}, R^{322}, R^{332}, R^{341}, R^{313}, R^{323}, R^{333}, and R^{342}, in each instance, is independently

C_{0-8}alkyl optionally substituted with an aryl, heterocyclyl or hetaryl substituent, or C_{0-8}alkyl optionally substituted with 1-6 independent halo, -CON(C_{0-8}alkyl)(C_{0-8}alkyl), -CO(C_{0-8}alkyl), -OC_{0-8}alkyl, -Oaryl, -Ohetaryl, -Oheterocyclyl, -S(O)$_{0-2}$aryl, -S(O)$_{0-2}$hetaryl, -S(O)$_{0-2}$heterocyclyl, -S(O)$_{0-2}C_{0-8}$alkyl, -N(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CO(C_{1-8}alkyl), -N(C_{0-8}alkyl)CO(C_{3-8}cycloalkyl), -N(C_{0-8}alkyl)CO_2(C_{1-8}alkyl), -S(O)$_{1-2}$N(C_{0-8}alkyl)(C_{0-8}alkyl), -NR^{11}S(O)$_{1-2}$(C_{0-8}alkyl), -CON(C_{3-8}cycloalkyl)(C_{3-8}cycloalkyl), -CON(C_{0-8}alkyl)(C_{3-8}cycloalkyl), -N(C_{3-8}cycloalkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{3-8}cycloalkyl)CON(C_{3-8}cycloalkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CON(C_{3-8}cycloalkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CO_2(C_{3-8}cycloalkyl), -N(C_{3-8}cycloalkyl)CO_2(C_{3-8}cycloalkyl), S(O)$_{1-2}$N(C_{0-8}alkyl)(C_{3-8}cycloalkyl), -NR^{11}S(O)$_{1-2}$(C_{3-8}cycloalkyl), C_{2-8}alkenyl, C_{2-8}alkynyl, CN, CF_3, OH, or optionally substituted aryl substituents; such that each of the above aryl, heterocyclyl, hetaryl, alkyl or cycloalkyl groups may be optionally, independently substituted with –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl, hetaryl, C_{0-6}alkyl, C_{0-8}alkylcyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)–S(O)$_{0-2}$–(C_{0-8}alkyl), –C_{0-8}alkyl-S(O)$_{0-2}$–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{0-8}alkyl–N(C_{0-}

$_{8}$alkyl)CO(C_{0-8}alkyl), –C_{0-8}alkyl–N(C_{0-8}alkyl)CO–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{0-8}alkyl-CO–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{1-8}alkyl-CO_2–(C_{0-8}alkyl), –C_{0-8}alkylS(O)$_{0-2}$–(C_{0-8}alkyl), –C_{0-8}alkyl-O-C_{1-8}alkyl, –C_{0-8}alkyl-O-C_{0-8}alkylcyclyl, –C_{0-8}alkyl-O-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl-O-C_{0-8}alkylaryl, –C_{0-8}alkyl-O-C_{0-8}alkylhetaryl, –C_{0-8}alkyl-S-C_{0-8}alkyl, –C_{0-8}alkyl-S-C_{0-8}alkylcyclyl, –C_{0-8}alkyl-S-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl-S-C_{0-8}alkylaryl, –C_{0-8}alkyl-S-C_{0-8}alkylhetaryl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylcyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylaryl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylhetaryl, C_{2-8}alkenyl, C_{2-8}alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$,

–C_{0-8}alkyl–C_{3-8}cycloalkyl,

-C_{0-8}alkyl-O-C_{0-8}alkyl,

–C_{0-8}alkyl-N(C_{0-8}alkyl)(C_{0-8}alkyl),

–C_{0-8}alkyl-S(O)$_{0-2}$-C_{0-8}alkyl, or

heterocyclyl optionally substituted with 1-4 independent C_{0-8}alkyl, cyclyl, or substituted cyclyl substituents;

E^1 in each instance is independently halo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^{31}R^{32}$, $-C(=O)R^{31}$, $-CO_2R^{31}$, $-CONR^{31}R^{32}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-S(O)_{0-2}NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{31})SR^{31}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-SC(=O)NR^{31}R^{32}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, –C_{1-10}alkoxyC_{1-10}alkyl, –C_{1-10}alkoxyC_{2-10}alkenyl, –C_{1-10}alkoxyC_{2-10}alkynyl, –C_{1-10}alkylthioC_{1-10}alkyl, –C_{1-10}alkylthioC_{2-10}alkenyl, –C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, –cycloC_{3-8}alkylC_{1-10}alkyl, –cycloC_{3-8}alkenylC_{1-10}alkyl, –cycloC_{3-8}alkylC_{2-10}alkenyl, –cycloC_{3-8}alkenylC_{2-10}alkenyl, –cycloC_{3-8}alkylC_{2-10}alkynyl, –cycloC_{3-8}alkenylC_{2-10}alkynyl, –heterocyclyl–C_{0-10}alkyl, –heterocyclyl–C_{2-10}alkenyl, or –heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(=O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $-S(=O)_{0-2}R^{31}$, $-SO_2NR^{31}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{31}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{31}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, or $-SC(=O)NR^{31}R^{32}$ substituents;

or E^1 in each instance is independently aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, where the attachment point is from either the left or right as written, where any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-S(O)_{0-2}NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$,

$-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, or $-SC(=O)NR^{31}R^{32}$ substituents;

in the cases of $-NR^{31}R^{32}$, $-NR^{311}R^{321}$, $-NR^{312}R^{322}$, $-NR^{332}R^{341}$, $-NR^{313}R^{323}$, and $-NR^{323}R^{333}$, the respective R^{31} and R^{32}, R^{311} and R^{321}, R^{312} and R^{322}, R^{331} and R^{341}, R^{313} and R^{323}, and R^{323} and R^{333} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring in each instance independently is optionally substituted by one or more independent $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl, hetaryl, $C_{0-6}alkyl$, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)S(O)_{0-2}C_{0-8}alkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)S(O)_{0-2}N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CO_2(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CON((C_{0-8}alkyl))S(O)_{0-2}(C_{0-8}alkyl)$, $-C_{0-8}alkyl-S(O)_{0-2}N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CO(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CON(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CO_2(C_{0-8}alkyl)$, $-C_{0-8}alkylS(O)_{0-2}(C_{0-8}alkyl)$, $-C_{0-8}alkyl-O-C_{0-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylcyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, -Oaryl, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $C_{2-8}alkenyl$, $C_{2-8}alkynyl$, NO_2, CN, CF_3, OCF_3, or $OCHF_2$ substituents; wherein said ring in each instance independently optionally includes one or more heteroatoms other than the nitrogen;

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3, or 4;

aa is 0 or 1; and

provided that Formula I is not

trans-4-[8-amino-1-(7-chloro-4-hydroxy-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexanecarboxylic acid,

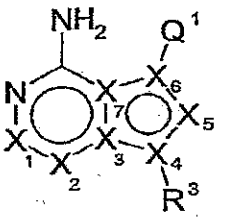
cis-3-[8-amino-1-(7-chloro-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclobutanecarboxylic acid,

trans-4-{8-amino-1-[7-(3-isopropyl)phenyl-1*H*-indol-2-yl]imidazo[1,5-*a*]pyrazin-3-yl}cyclohexanecarboxylic acid or

trans-4-{8-amino-1-[7-(2,5-dichloro)phenyl-1*H*-indol-2-yl]imidazo[1,5-*a*]pyrazin-3-yl}cyclohexanecarboxylic acid.

SUMMARY

[12a] In a first aspect, there is provided a compound represented by Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X_1, and X_2 are each independently N or C–$(E^1)_{aa}$;

X_5 is N, C–$(E^1)_{aa}$, or N–$(E^1)_{aa}$;

X_3, X_4, X_6, and X_7 are each independently N or C;

wherein at least one of X_3, X_4, X_5, X_6, and X_7 is independently N or N–$(E^1)_{aa}$;

R^3 is C_{0-10}alkyl, cycloC_{3-10}alkyl, aminomethylcycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl or heterobicycloC_{5-10}alkyl any of which is optionally substituted by one or more independent G^{11} substituents;

Q^1 is $-A(R^1)_mB(W)_n$ or $-B(G^{11})_nA(Y)_m$;

A and B are respectively, 5 and 6 membered aromatic or heteroaromatic rings, fused together to form a 9-membered heteroaromatic system excluding 5-benzo[*b*]furyl and 3-indolyl; and excluding 2-indolyl, 2-benzoxazole, 2-benzothiazole, 2-benzimidazolyl, 4-aminopyrrolopyrimidin-5-yl, 4 -aminopyrrolopyrimidin-6-yl, and 7-deaza-7-adenosinyl derivatives when X_1 and X_5 are CH, X_3, X_6 and X_7 are C, and X_2 and X_4 are N;

or Q^1 is $-A(R^1)_mA(Y)_m$, wherein each A is the same or different 5-membered aromatic or heteroaromatic ring, and the two are fused together to form an 8-membered heteroaromatic system;

R^1 is independently, hydrogen, –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{1-6}alkyl, $-C_{0-8}$alkylC$_{3-8}$cycloalkyl, $-C_{0-8}$alkyl-$NR^{311}S(O)_{0-2}R^{321}$, $-C_{0-8}$alkyl-$NR^{311}S(O)_{0-2}NR^{321}R^{331}$, $-C_{0-8}$alkyl-$S(O)_{0-2}NR^{311}R^{321}$, $-C_{0-8}$alkyl-$NR^{311}COR^{321}$, $-C_{0-8}$alkyl-$NR^{311}CO_2R^{321}$, $-C_{0-8}$alkyl-$NR^{311}CONR^{321}R^{331}$, $-C_{0-8}$alkyl-$CONR^{311}R^{321}$, $-C_{0-8}$alkyl-$CON(R^{311})S(O)_{0-2}R^{321}$, $-C_{0-8}$alkyl-CO_2R^{311}, -C_{0-8}alkyl-$S(O)_{0-2}R^{311}$, $-C_{0-8}$alkyl-O-C_{1-8}alkyl, $-C_{0-8}$alkyl-O-C_{0-8}alkylC$_{3-8}$cycloalkyl, $-C_{0-8}$alkyl-O-C_{0-8}alkylheterocyclyl, $-C_{0-8}$alkyl-O-C_{0-8}alkylaryl, $-C_{0-8}$alkylaryl, $-C_{0-8}$alkylhetaryl, $-C_{0-8}$alkylheterocyclyl, $-C_{0-8}$alkyl-O-C_{0-8}alkylhetaryl, $-C_{0-8}$alkyl-S-C_{0-8}alkyl, $-C_{0-8}$alkyl-S-C_{0-8}alkylC$_{3-8}$cycloalkyl, $-C_{0-8}$alkyl-S-C_{0-8}alkylheterocyclyl, -C_{0-8}alkyl-S-C_{0-8}alkylaryl, $-C_{0-8}$alkyl-S-C_{0-8}alkylhetaryl, $-C_{0-8}$alkyl-N(R^{311})-C_{0-8}alkyl, $-C_{0-8}$alkyl-N(R^{311})-C_{0-8}alkylC$_{3-8}$cycloalkyl, $-C_{0-8}$alkyl-N(R^{311})-C_{0-8}alkylheterocyclyl, $-C_{0-8}$alkyl-N(R^{311})-C_{0-8}alkylaryl, $-C_{0-8}$alkyl-N(R^{311})-C_{0-8}alkylhetaryl, –

C_{0-8}alkyl-$NR^{311}R^{321}$, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not N-methyl-2-indolyl, N-(phenylsulfonyl)-2-indolyl, or N-tert-butoxycarbonyl;

W is independently, hydrogen, $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{1-6}alkyl, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-NR^{312}S(O)_{0-2}R^{322}$, $-C_{0-8}alkyl-NR^{311}S(O)_{0-2}NR^{321}R^{331}$, $-C_{0-8}alkyl-NR^{311}CO_2R^{321}$, $-C_{0-8}alkyl-CON(R^{311})S(O)_{0-2}R^{321}$, $-C_{0-8}alkyl-S(O)_{0-2}NR^{312}R^{322}$, $-C_{0-8}alkyl-NR^{312}COR^{322}$, $-C_{0-8}alkyl-NR^{312}CONR^{322}R^{332}$, $-C_{0-8}alkyl-CONR^{312}R^{322}$, $-C_{0-8}alkyl-CO_2R^{312}$, $-C_{0-8}alkylS(O)_{0-2}R^{312}$, $-C_{0-8}alkyl-O-C_{1-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylcyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, $-C_{0-8}alkylaryl$, $-C_{0-8}alkylhetaryl$, $-C_{0-8}alkylheterocyclyl$, -Oaryl, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylhetaryl$, $C_{0-8}alkyl-NR^{312}R^{322}$, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not 4-benzyloxy-2-indolyl;

Y is independently, hydrogen, $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{0-6}alkyl, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-NR^{311}S(O)_{0-2}R^{321}$, $-C_{0-8}alkyl-NR^{311}S(O)_{0-2}NR^{321}R^{331}$, $-C_{0-8}alkyl-NR^{311}CO_2R^{321}$, $-C_{0-8}alkyl-CON(R^{311})S(O)_{0-2}R^{321}$, $-C_{0-8}alkyl-S(O)_{0-2}NR^{311}R^{321}$, $-C_{0-8}alkyl-NR^{311}COR^{321}$, $-C_{0-8}alkyl-NR^{311}CONR^{321}R^{331}$, $-C_{0-8}alkyl-CONR^{311}R^{321}$, $-C_{0-8}alkyl-CO_2R^{311}$, $-C_{0-8}alkylS(O)_{0-2}R^{311}$, $-C_{0-8}alkyl-O-C_{1-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, $-C_{0-8}alkylaryl$, $-C_{0-8}alkylhetaryl$, $-C_{0-8}alkylheterocyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-NR^{311}R^{321}$, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not 2-carboxy-5-benzo[*b*]thiophenyl;

G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{312}$, $-NR^{312}R^{322}$, $-C(O)R^{312}$, $-C(O)C_{3-8}$cycloalkyl, $-CO_2C_{3-8}$cycloalkyl, $-CO_2R^{312}$, $-C(=O)NR^{312}R^{322}$, $-NO_2$, $-CN$, $-S(O)_{0-2}R^{312}$, $-SO_2NR^{312}R^{322}$, $NR^{312}(C=O)R^{322}$, $NR^{312}C(=O)OR^{322}$, $NR^{312}C(=O)NR^{322}R^{332}$, $NR^{312}S(O)_{0-2}R^{322}$, $-C(=S)OR^{312}$, $-C(=O)SR^{312}$, $-NR^{312}C(=NR^{322})NR^{332}R^{341}$, $-NR^{312}C(=NR^{322})OR^{332}$, $-NR^{312}C(=NR^{322})SR^{332}$, $-OC(=O)OR^{312}$, $-OC(=O)NR^{312}R^{322}$, $-OC(=O)SR^{312}$, $-SC(=O)OR^{312}$, $-SC(=O)NR^{312}R^{322}$, $-P(O)OR^{312}OR^{322}$, C_{1-10}alkylidene, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $-C_{1-10}alkoxyC_{1-10}alkyl$, $-C_{1-10}alkoxyC_{2-10}alkenyl$, $-C_{1-10}alkoxyC_{2-10}alkynyl$, $-C_{1-10}alkylthioC_{1-10}alkyl$, $-C_{1-10}alkylthioC_{2-10}alkenyl$, $-C_{1-10}alkylthioC_{2-10}alkynyl$, $cycloC_{3-8}$alkyl, $cycloC_{3-8}$alkenyl, $-cycloC_{3-8}alkylC_{1-10}alkyl$, $-cycloC_{3-}$

$_8$alkenylC_{1-10}alkyl, –cycloC_{3-8}alkylC_{2-10}alkenyl, –cycloC_{3-8}alkenylC_{2-10}alkenyl, –cycloC_{3-8}alkylC_{2-10}alkynyl, –cycloC_{3-8}alkenylC_{2-10}alkynyl, –heterocyclyl–C_{0-10}alkyl, –heterocyclyl–C_{2-10}alkenyl, or –heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{313}$, $–NR^{313}R^{323}$, $–C(O)R^{313}$, $–CO_2R^{313}$, $–C(=O)NR^{313}R^{323}$, $–NO_2$, –CN, $–S(O)_{0-2}R^{313}$, $–SO_2NR^{313}R^{323}$, $–NR^{313}C(=O)R^{323}$, $–NR^{313}C(=O)OR^{323}$, $–NR^{313}C(=O)NR^{323}R^{333}$, $–NR^{313}S(O)_{0-2}R^{323}$, $–C(=S)OR^{313}$, $–C(=O)SR^{313}$, $–NR^{313}C(=NR^{323})NR^{333}R^{342}$, $–NR^{313}C(=NR^{323})OR^{333}$, $–NR^{313}C(=NR^{323})SR^{333}$, $–OC(=O)OR^{333}$, $–OC(=O)NR^{313}R^{323}$, $–OC(=O)SR^{313}$, $–SC(=O)OR^{313}$, $–P(O)OR^{313}OR^{323}$, or $–SC(=O)NR^{313}R^{323}$ substituents;

or G^{11} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, where the attachment point is from either the left or right as written, where any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, $–OR^{313}$, $–NR^{313}R^{323}$, $–C(O)R^{313}$, $–CO_2R^{313}$, $–C(=O)NR^{313}R^{323}$, $–NO_2$, –CN, $–S(O)_{0-2}R^{313}$, $–SO_2NR^{313}R^{323}$, $–NR^{313}C(=O)R^{323}$, $–NR^{313}C(=O)OR^{323}$, $–NR^{313}C(=O)NR^{323}R^{333}$, $–NR^{313}S(O)_{0-2}R^{323}$, $–C(=S)OR^{313}$, $–C(=O)SR^{313}$, $–NR^{323}C(=NR^{313})NR^{333}R^{342}$, $–NR^{313}C(=NR^{323})OR^{333}$, $–NR^{313}C(=NR^{323})SR^{333}$, $–OC(=O)OR^{313}$, $–OC(=O)NR^{313}R^{323}$, $–OC(=O)SR^{313}$, $–SC(=O)OR^{313}$, $–P(O)OR^{313}OR^{323}$, or $–SC(=O)NR^{313}R^{323}$ substituents; provided that G^{11} is not *N*-CH_2CO_2H when R^3 is 4-piperidinyl;

R^{31}, R^{32}, R^{33}, R^{311}, R^{321}, R^{331}, R^{312}, R^{322}, R^{332}, R^{341}, R^{313}, R^{323}, R^{333}, and R^{342}, in each instance, is independently

C_{0-8}alkyl optionally substituted with an aryl, heterocyclyl or hetaryl substituent, or C_{0-8}alkyl optionally substituted with 1-6 independent halo, -CON(C_{0-8}alkyl)(C_{0-8}alkyl), -CO(C_{0-8}alkyl), -OC_{0-8}alkyl, -Oaryl, -Ohetaryl, -Oheterocyclyl, -S(O)$_{0-2}$aryl, -S(O)$_{0-2}$hetaryl, -S(O)$_{0-2}$heterocyclyl, -S(O)$_{0-2}C_{0-8}$alkyl, -N(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CO(C_{1-8}alkyl), -N(C_{0-8}alkyl)CO(C_{3-8}cycloalkyl), -N(C_{0-8}alkyl)CO_2(C_{1-8}alkyl), S(O)$_{1-2}$N(C_{0-8}alkyl)(C_{0-8}alkyl), $-NR^{11}$S(O)$_{1-2}$(C_{0-8}alkyl), -CON(C_{3-8}cycloalkyl)(C_{3-8}cycloalkyl), -CON(C_{0-8}alkyl)(C_{3-8}cycloalkyl), -N(C_{3-8}cycloalkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{3-8}cycloalkyl)CON(C_{3-8}cycloalkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CON(C_{3-8}cycloalkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CO_2(C_{3-8}cycloalkyl), -N(C_{3-8}cycloalkyl)CO_2(C_{3-8}cycloalkyl), S(O)$_{1-2}$N(C_{0-8}alkyl)(C_{3-8}cycloalkyl), $-NR^{11}$S(O)$_{1-2}$(C_{3-8}cycloalkyl), C_{2-8}alkenyl, C_{2-8}alkynyl, CN, CF_3, OH, or optionally substituted aryl substituents; such that each of the above aryl, heterocyclyl, hetaryl, alkyl or cycloalkyl groups may be optionally, independently substituted with –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl, hetaryl, C_{0-6}alkyl, –C_{0-8}alkylcyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)–S(O)$_{0-2}$–(C_{0-8}alkyl), –C_{0-8}alkyl-S(O)$_{0-2}$–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{0-8}alkyl–N(C_{0-8}alkyl)CO(C_{0-8}alkyl), –C_{0-8}alkyl–N(C_{0-8}alkyl)CO–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{0-8}alkyl-CO–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{1-8}alkyl-CO_2–(C_{0-8}alkyl), –C_{0-8}alkylS(O)$_{0-2}$–(C_{0-8}alkyl), –C_{0-8}alkyl-O-C_{1-8}alkyl, –C_{0-8}alkyl-O-C_{0-8}alkylcyclyl, –C_{0-8}alkyl-O-C_{0-8}alkylheterocyclyl, –C_{0-}

$_{8}$alkyl-O-C_{0-8}alkylaryl, –C_{0-8}alkyl-O-C_{0-8}alkylhetaryl, –C_{0-8}alkyl-S-C_{0-8}alkyl, –C_{0-8}alkyl-S-C_{0-8}alkylcyclyl, –C_{0-8}alkyl-S-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl-S-C_{0-8}alkylaryl, –C_{0-8}alkyl-S-C_{0-8}alkylhetaryl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylcyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylaryl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylhetaryl, –C_{2-8}alkenyl, –C_{2-8}alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$,

–C_{0-8}alkyl–C_{3-8}cycloalkyl,

-C_{0-8}alkyl-O-C_{0-8}alkyl,

–C_{0-8}alkyl-N(C_{0-8}alkyl)(C_{0-8}alkyl),

–C_{0-8}alkyl-S(O)$_{0-2}$-C_{0-8}alkyl, or

heterocyclyl optionally substituted with 1-4 independent C_{0-8}alkyl, cyclyl, or substituted cyclyl substituents;

E^1 in each instance is independently halo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^{31}R^{32}$, $-C(=O)R^{31}$, $-CO_2R^{31}$, $-CONR^{31}R^{32}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-S(O)_{0-2}NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{31})SR^{31}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-SC(=O)NR^{31}R^{32}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, –C_{1-10}alkoxyC_{1-10}alkyl, –C_{1-10}alkoxyC_{2-10}alkenyl, –C_{1-10}alkoxyC_{2-10}alkynyl, –C_{1-10}alkylthioC_{1-10}alkyl, –C_{1-10}alkylthioC_{2-10}alkenyl, –C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, –cycloC_{3-8}alkylC_{1-10}alkyl, –cycloC_{3-8}alkenylC_{1-10}alkyl, –cycloC_{3-8}alkylC_{2-10}alkenyl, –cycloC_{3-8}alkenylC_{2-10}alkenyl, –cycloC_{3-8}alkylC_{2-10}alkynyl, –cycloC_{3-8}alkenylC_{2-10}alkynyl, –heterocyclyl–C_{0-10}alkyl, –heterocyclyl–C_{2-10}alkenyl, or –heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(=O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $-S(=O)_{0-2}R^{31}$, $-SO_2NR^{31}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{31}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{31}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, or $-SC(=O)NR^{31}R^{32}$ substituents;

or E^1 in each instance is independently aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, where the attachment point is from either the left or right as written, where any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-S(O)_{0-2}NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, or $-SC(=O)NR^{31}R^{32}$ substituents;

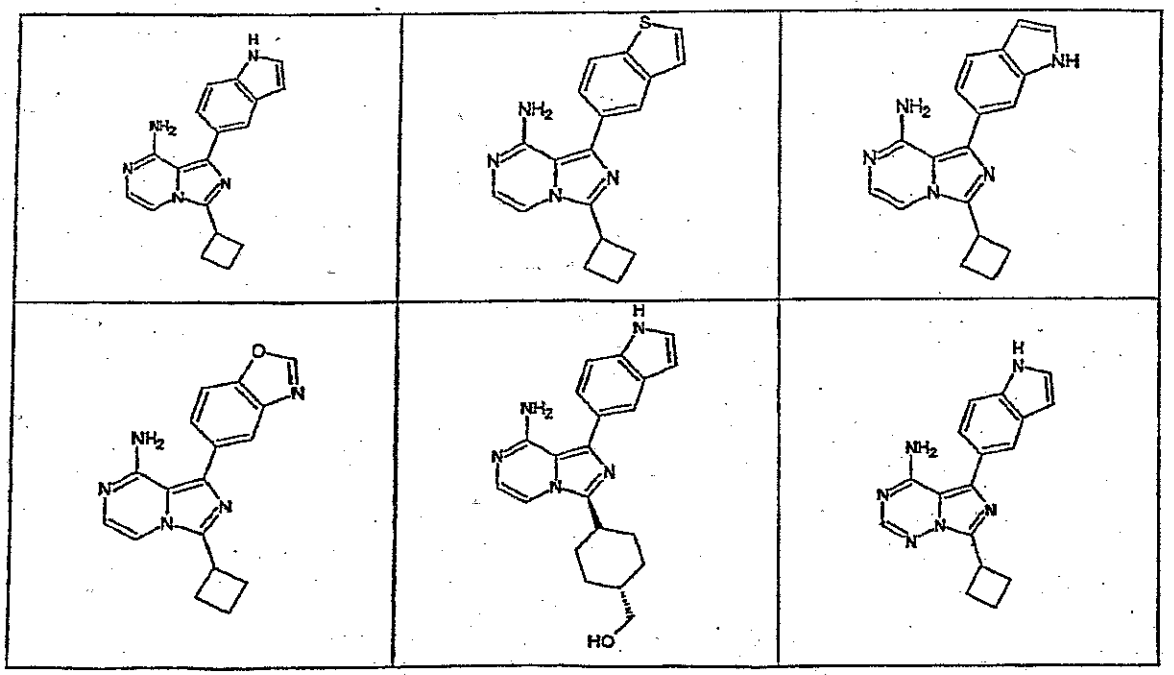
in the cases of $-NR^{31}R^{32}$, $-NR^{311}R^{321}$, $-NR^{312}R^{322}$, $-NR^{332}R^{341}$, $-NR^{313}R^{323}$, and $-NR^{323}R^{333}$, the respective R^{31} and R^{32}, R^{311} and R^{321}, R^{312} and R^{322}, R^{331} and R^{341}, R^{313} and R^{323}, and R^{323} and R^{333} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring in each instance independently is optionally substituted by one or more independent $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl, hetaryl, $C_{0-6}alkyl$, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)S(O)_{0-2}C_{0-8}alkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)S(O)_{0-2}N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CO_2(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CON((C_{0-8}alkyl))S(O)_{0-2}(C_{0-8}alkyl)$, $-C_{0-8}alkyl-S(O)_{0-2}N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CO(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CON(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CO_2(C_{0-8}alkyl)$, $-C_{0-8}alkylS(O)_{0-2}(C_{0-8}alkyl)$, $-C_{0-8}alkyl-O-C_{0-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylcyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, $-Oaryl$, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $C_{2-8}alkenyl$, $C_{2-8}alkynyl$, NO_2, CN, CF_3, OCF_3, or $OCHF_2$ substituents; wherein said ring in each instance independently optionally includes one or more heteroatoms other than the nitrogen;

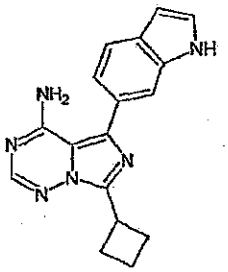
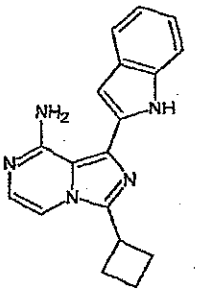
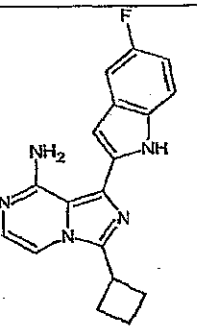
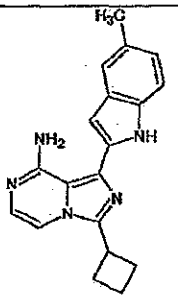
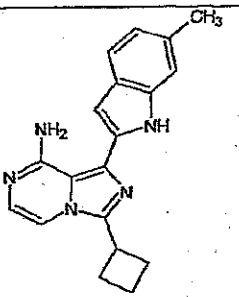
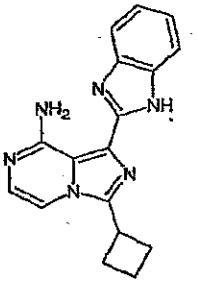
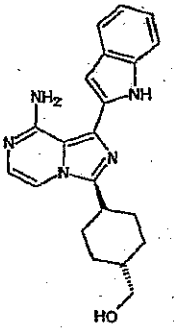
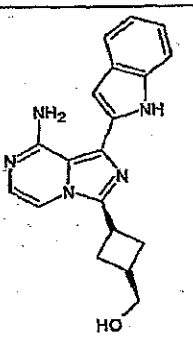
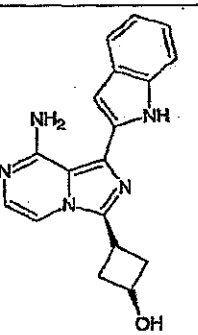
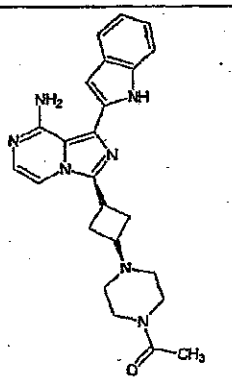
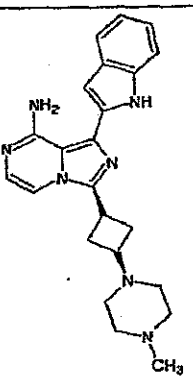
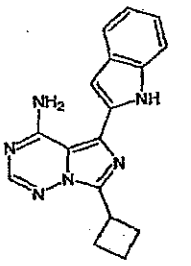
m is 0, 1, 2, or 3;

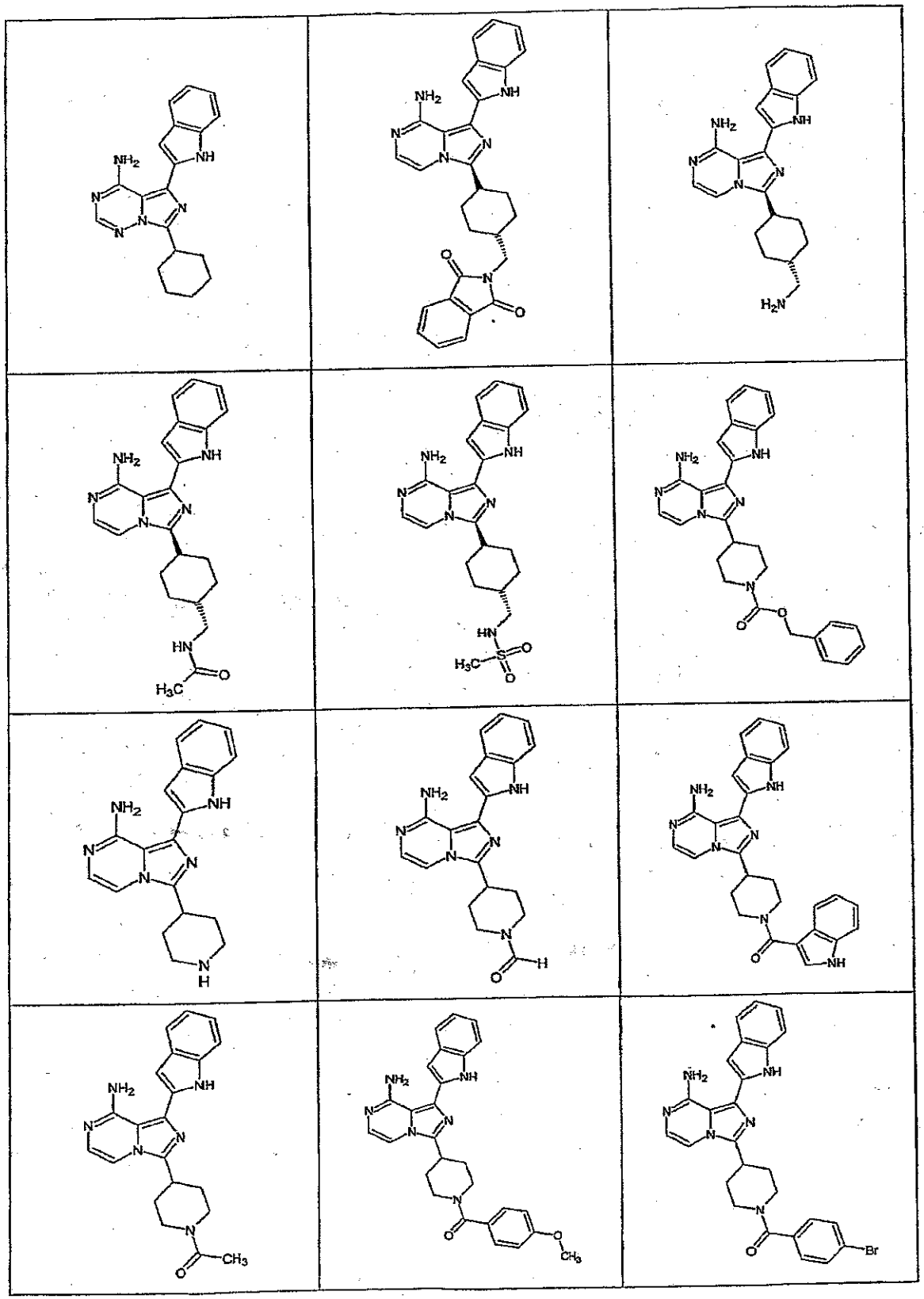
n is 0, 1, 2, 3, or 4; and

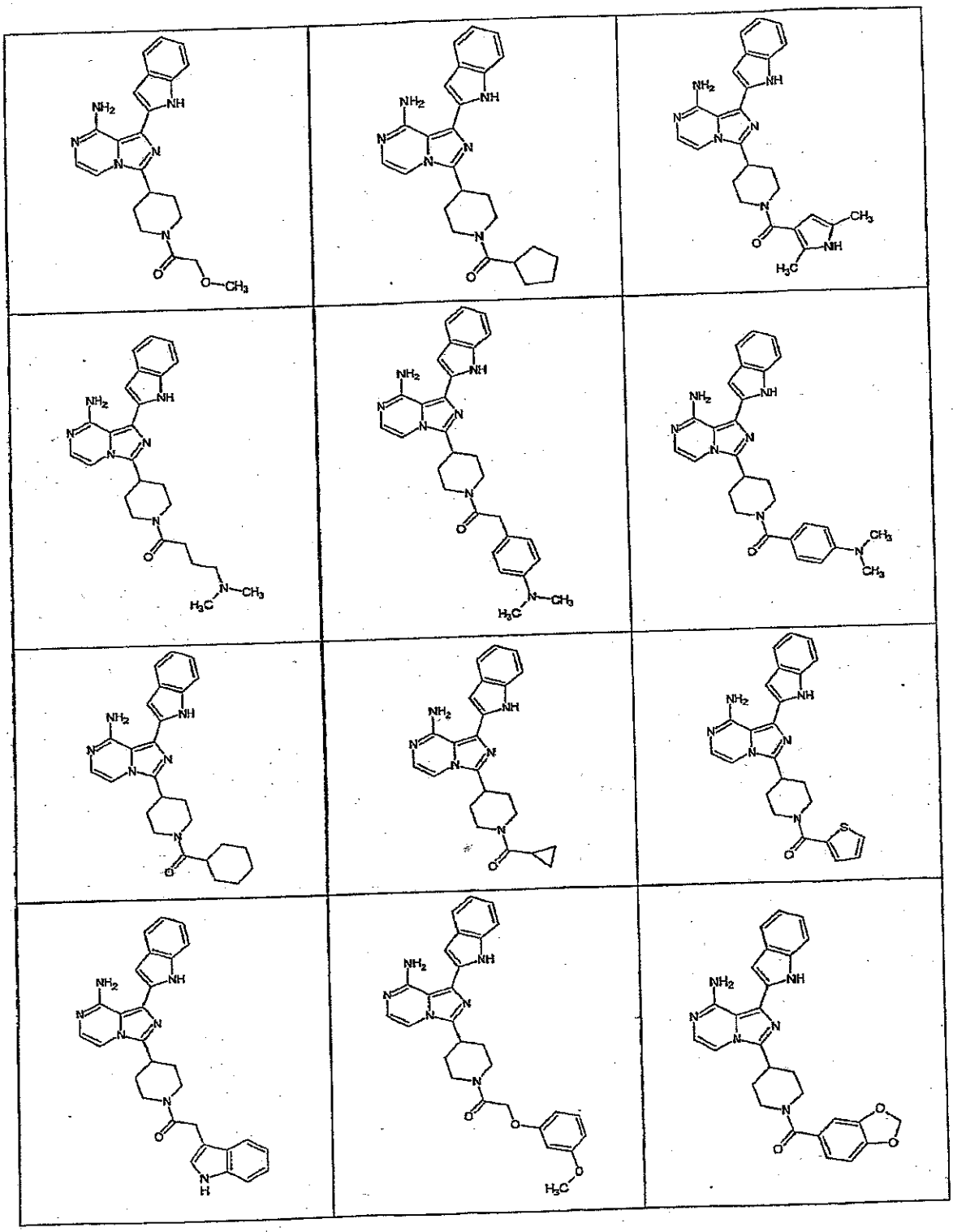
aa is 0 or 1; and provided that the compound is not *trans*-4-[8-amino-1-(7-chloro-4-hydroxy-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexanecarboxylic acid, *cis*-3-[8-amino-1-(7-chloro-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclobutanecarboxylic acid, *trans*-4-{8-amino-1-[7-(3-isopropyl)phenyl-1*H*-indol-2-yl]imidazo[1,5-*a*]pyrazin-3-yl}cyclohexanecarboxylic acid, or *trans*-4-{8-amino-1-[7-(2,5-dichloro)phenyl-1*H*-indol-2-yl]imidazo[1,5-*a*]pyrazin-3-yl}cyclohexane carboxylic acid,

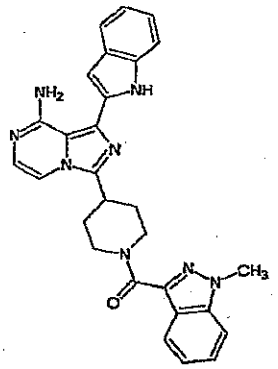
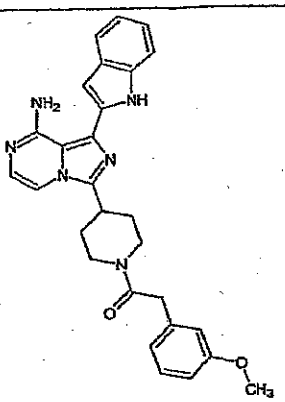
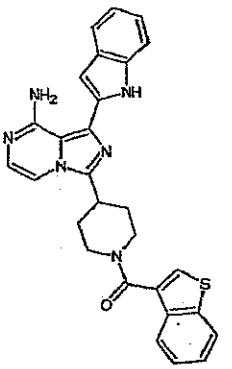
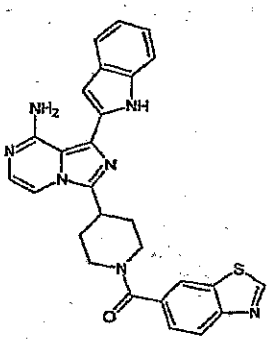
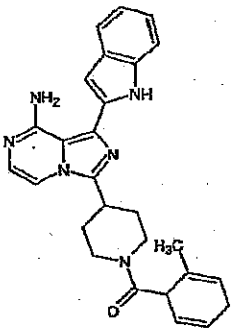
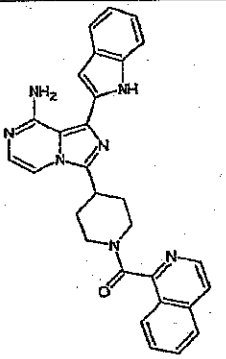
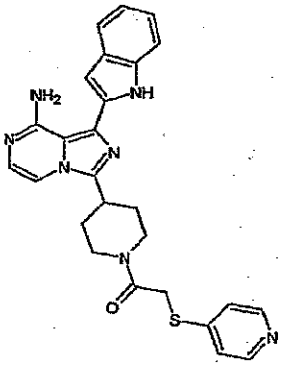
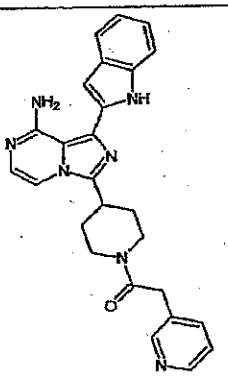
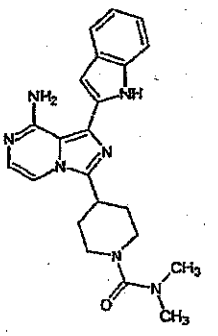
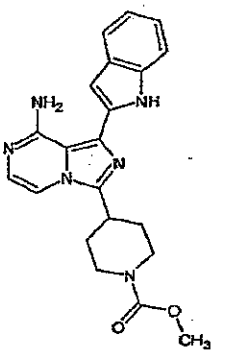
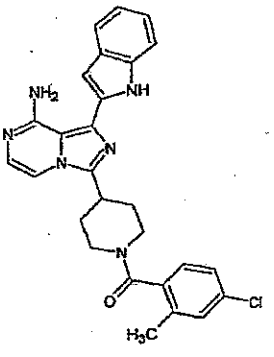
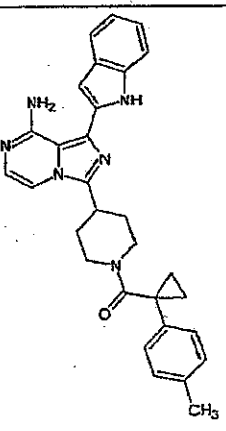
wherein the compound is selected from any one of the following structures

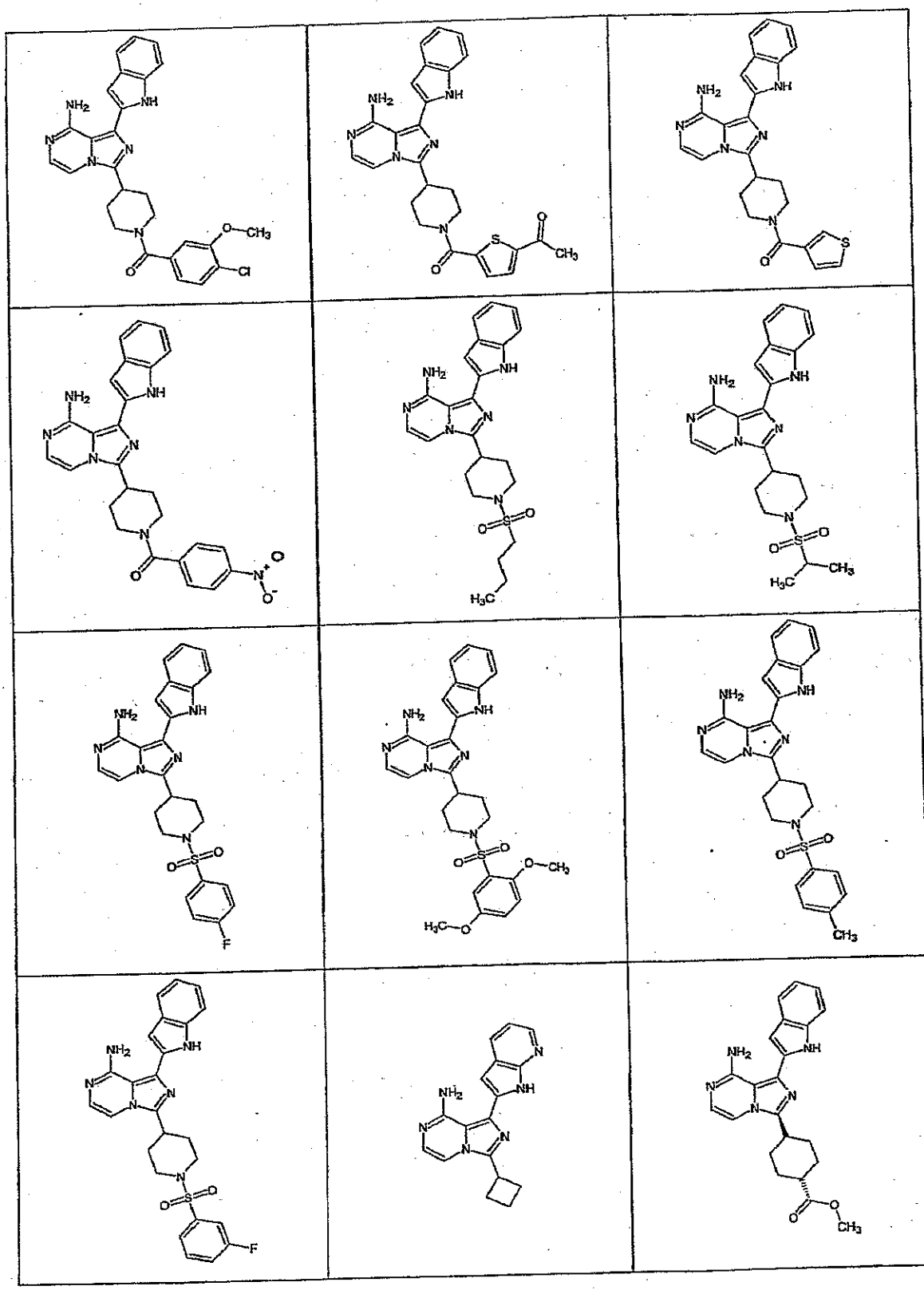


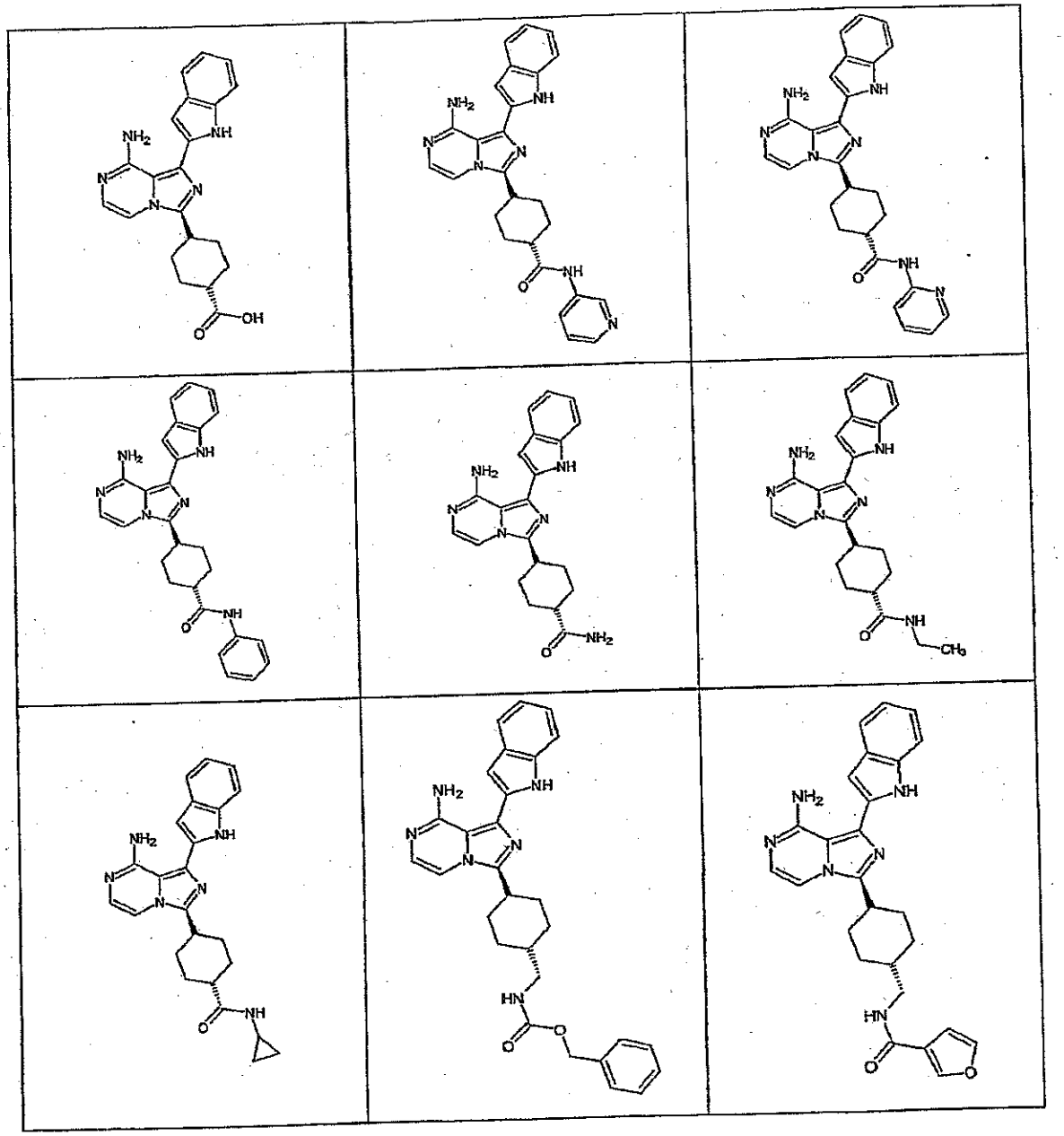
		
		
		
		

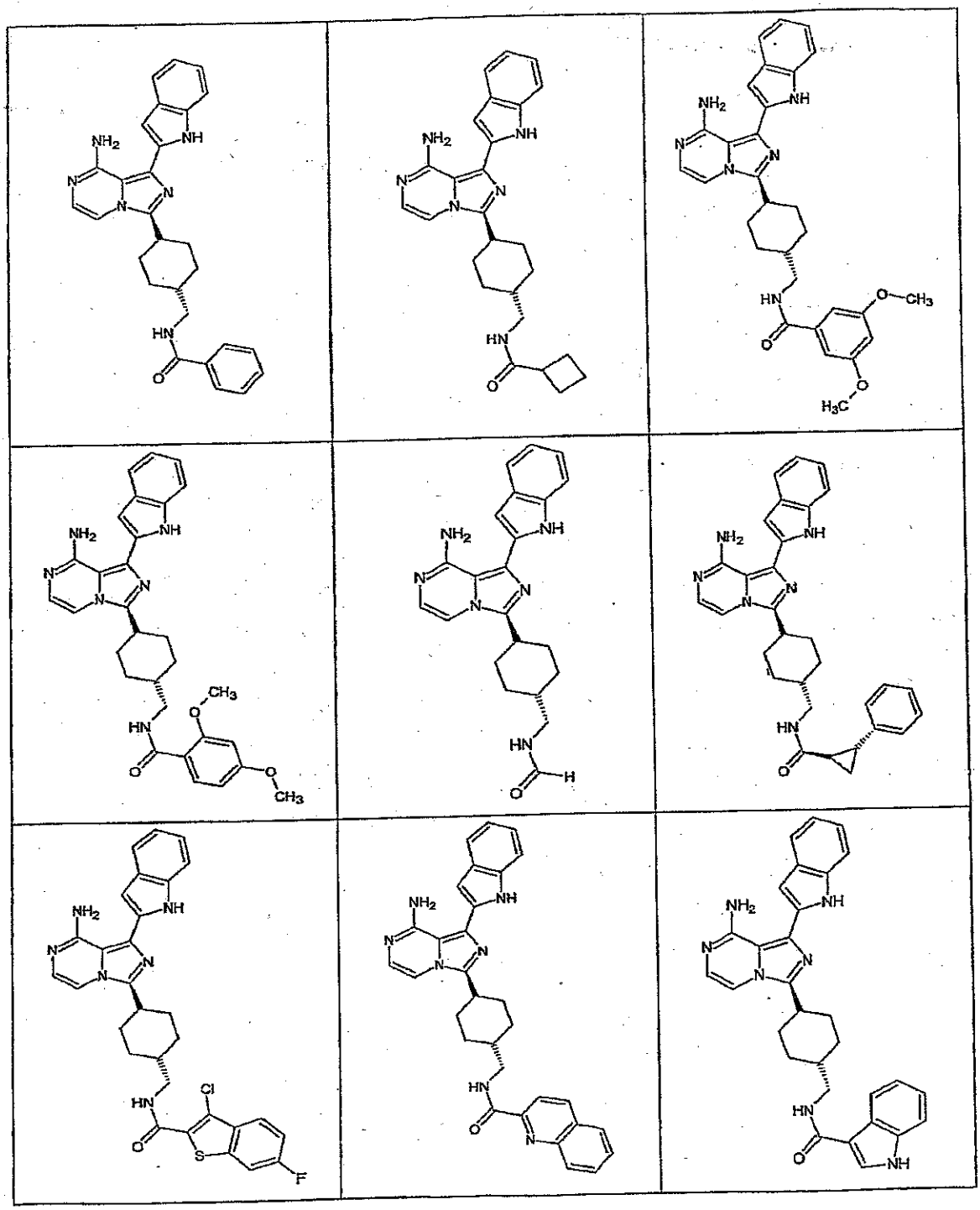


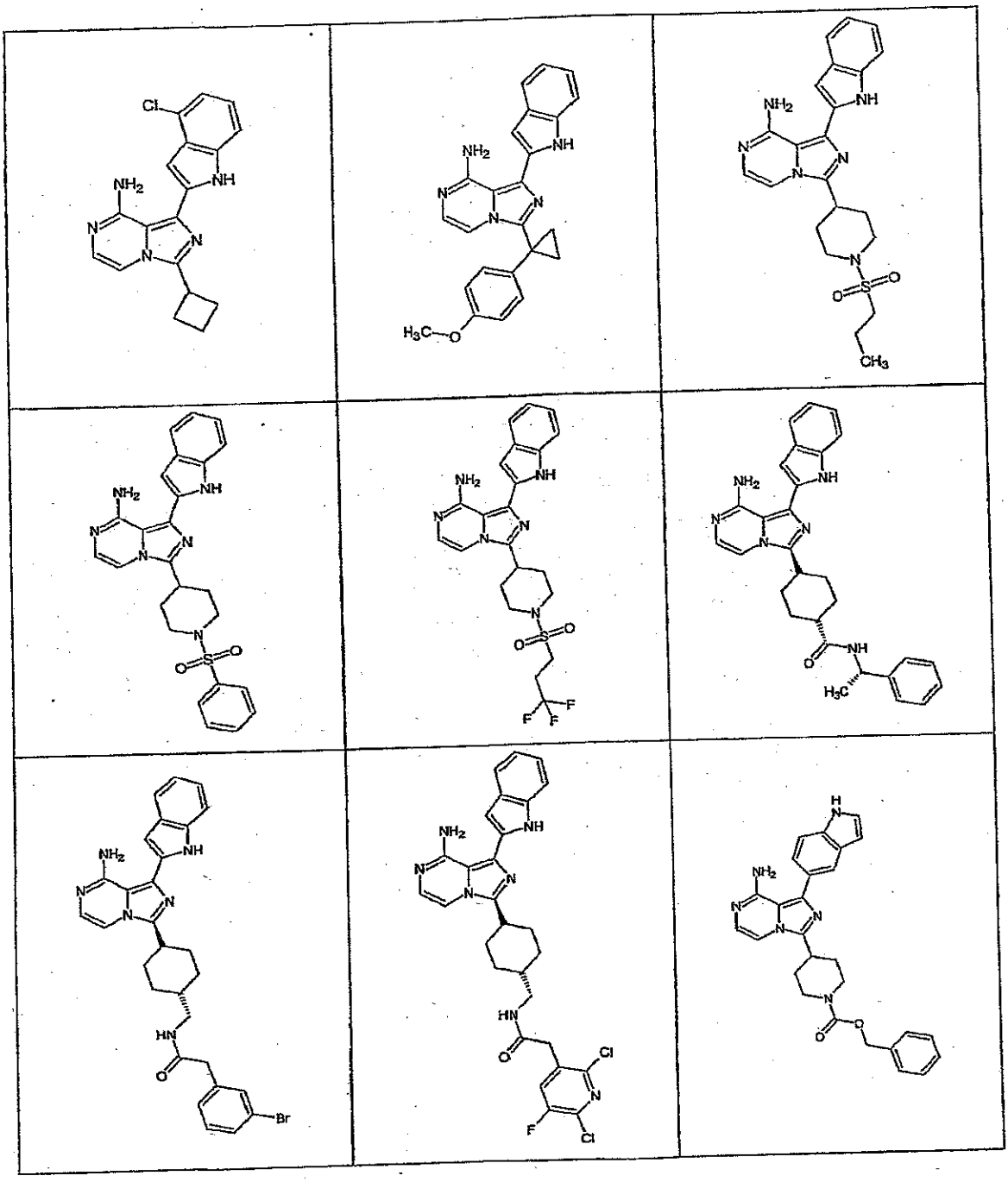


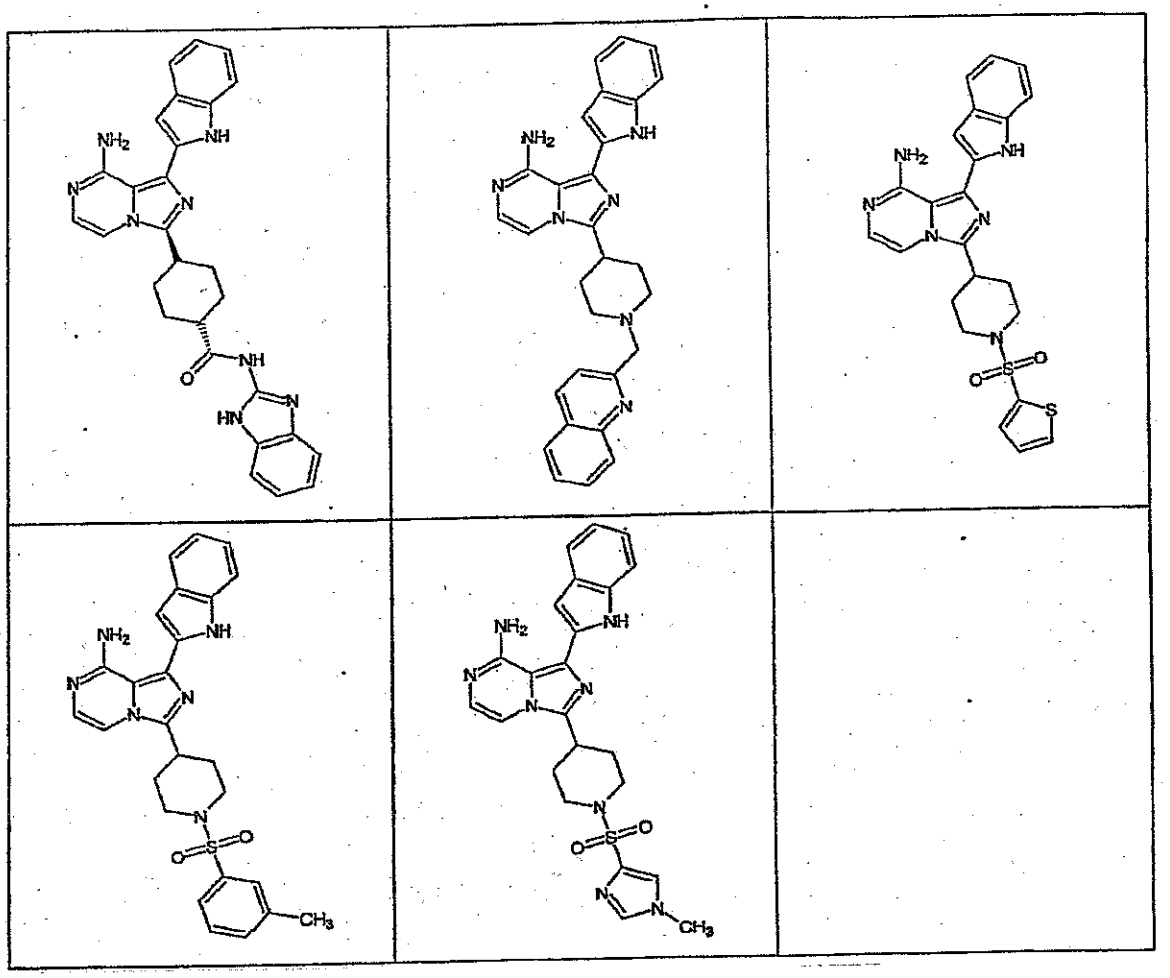
		
		
		
		

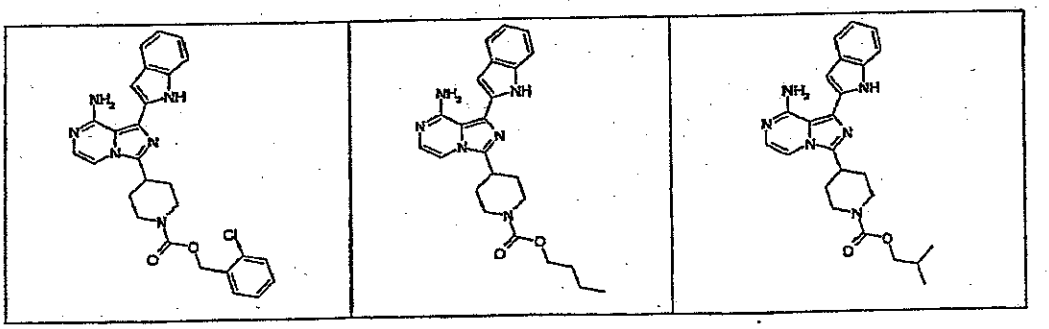


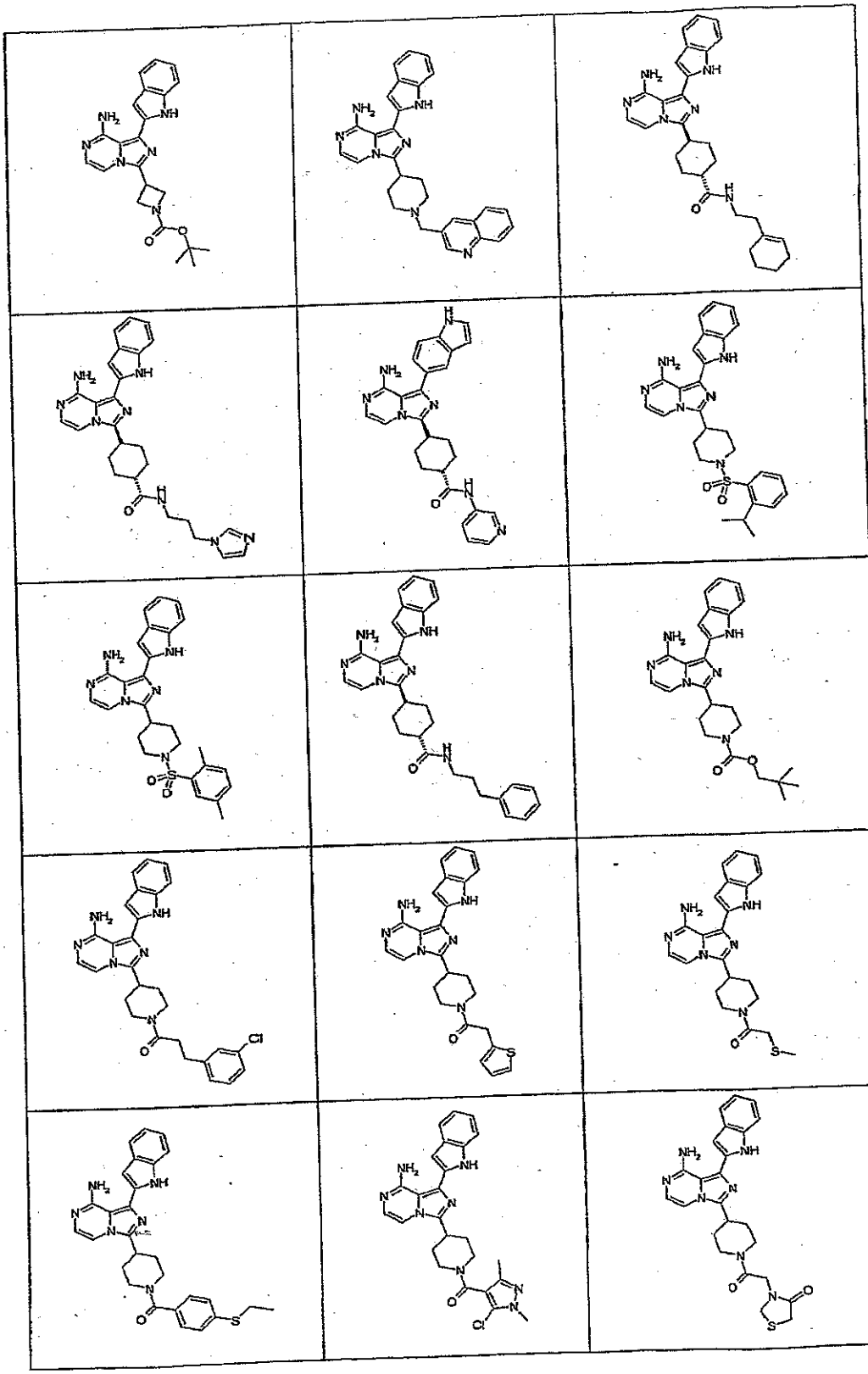


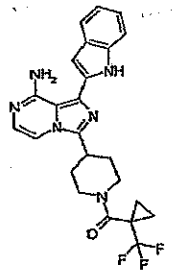
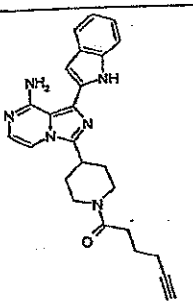
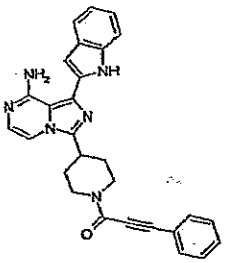
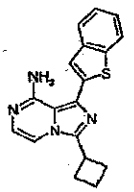
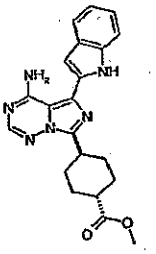
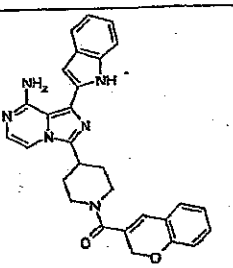
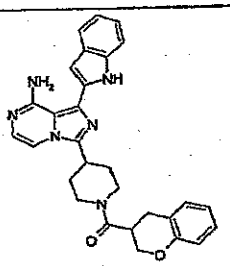
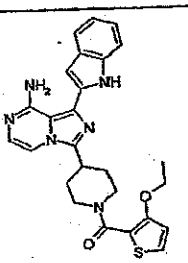
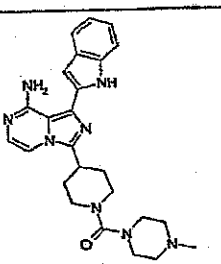
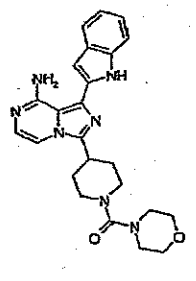
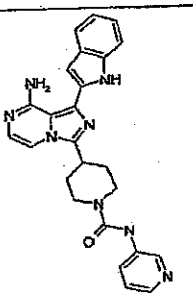
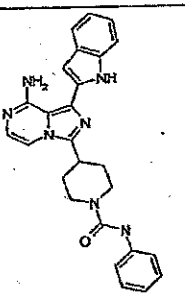
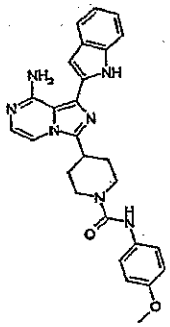
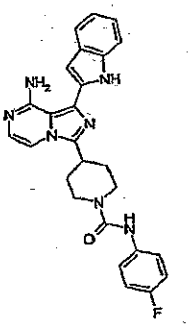
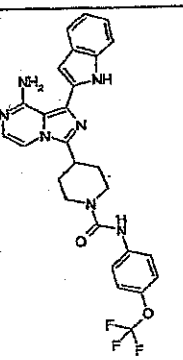


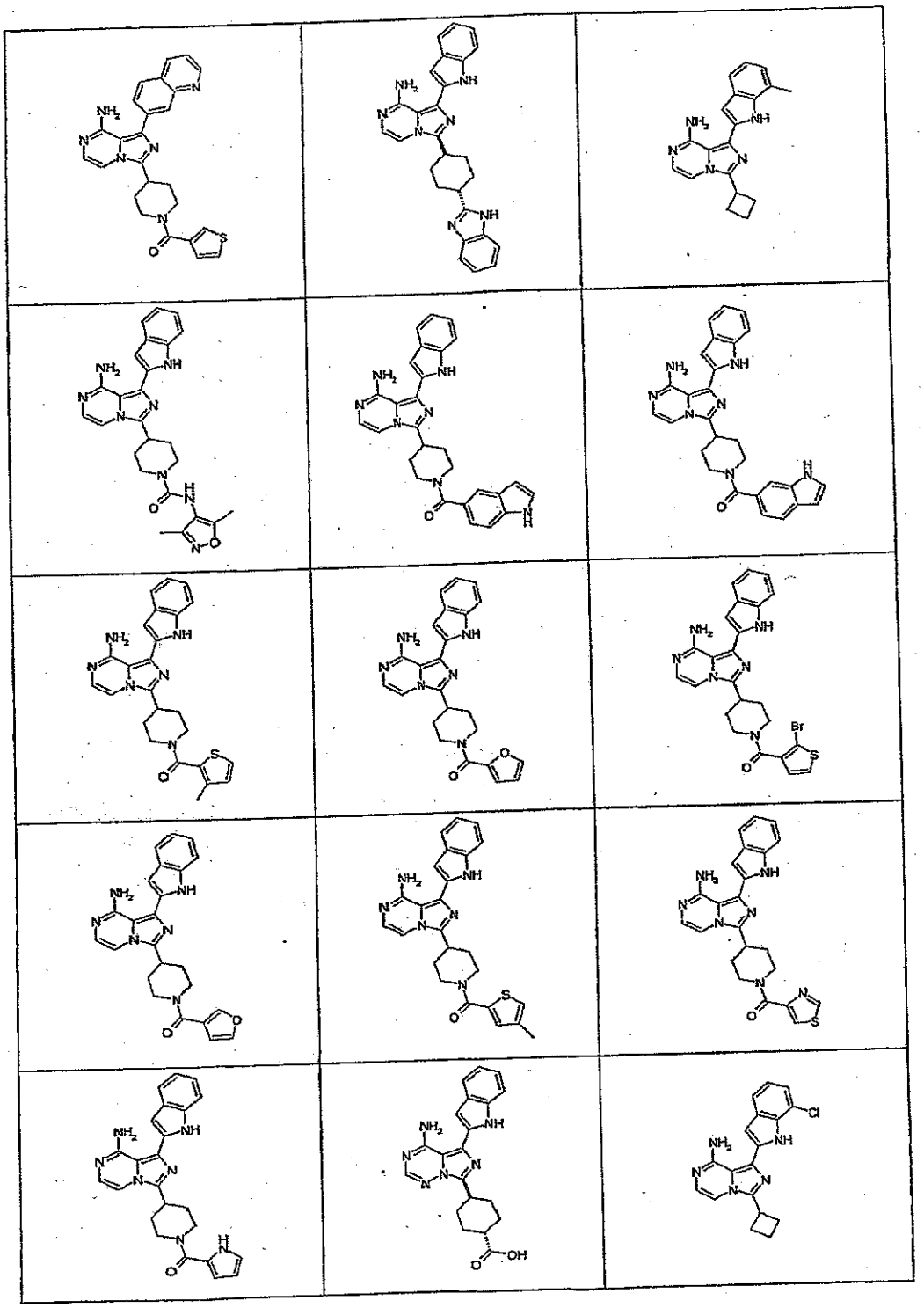


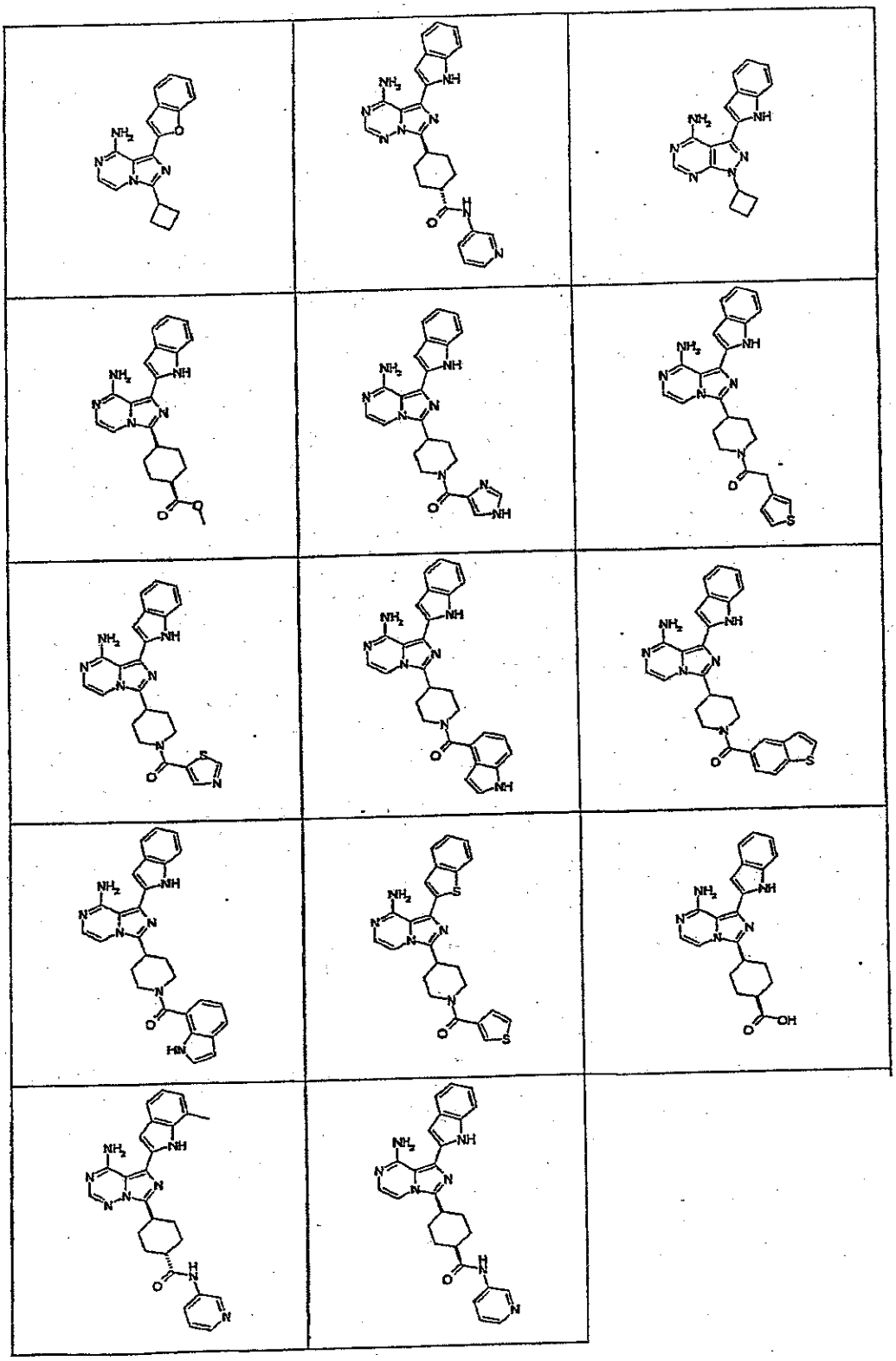


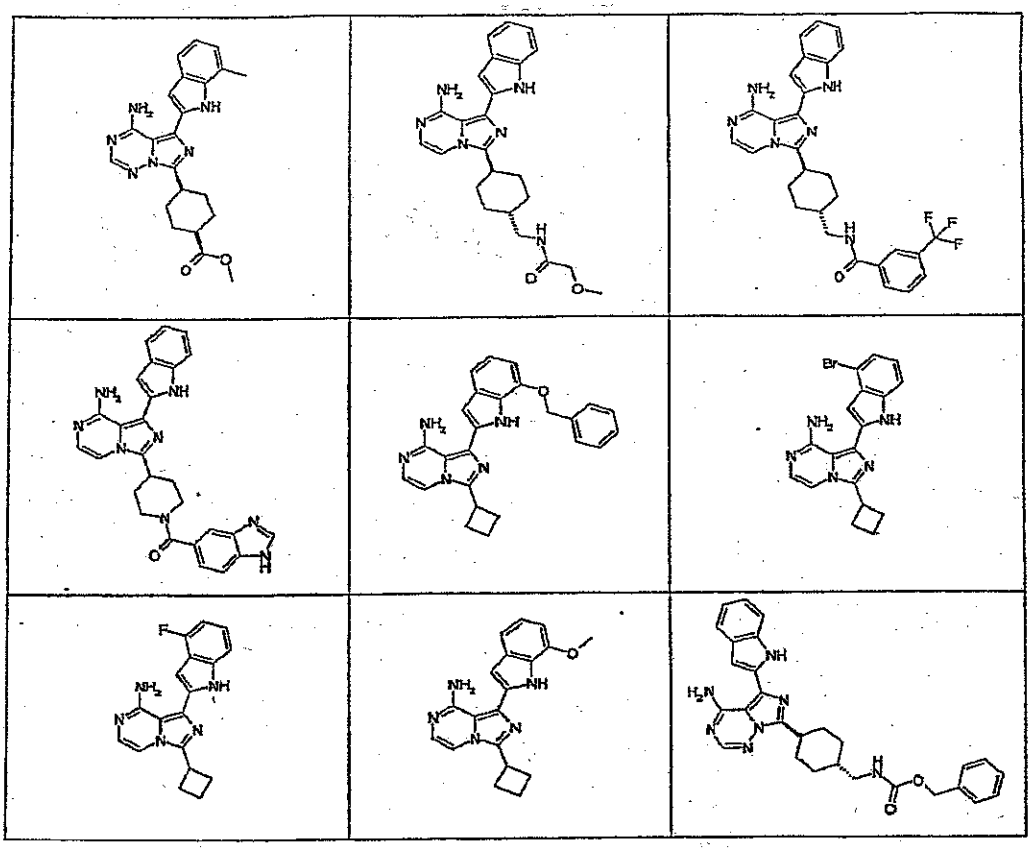


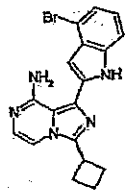
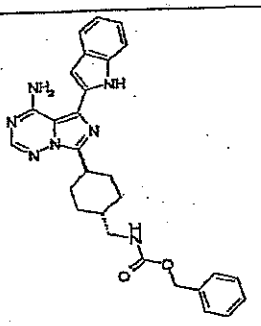
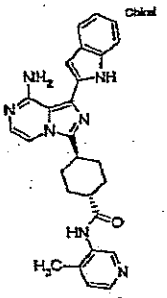
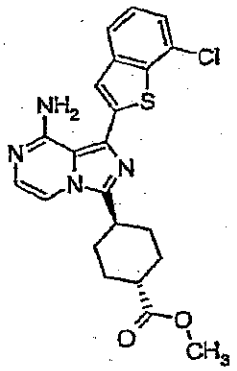
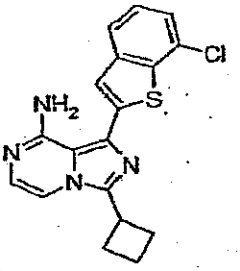
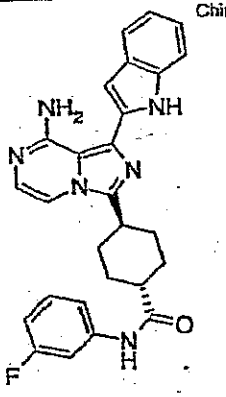
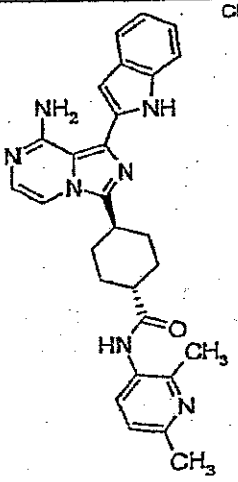
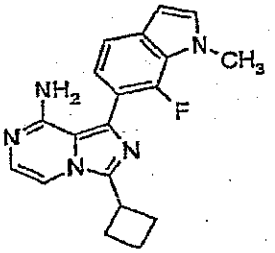
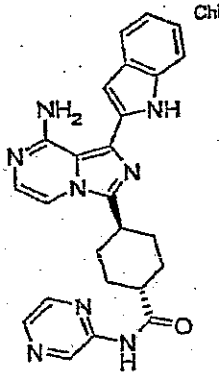


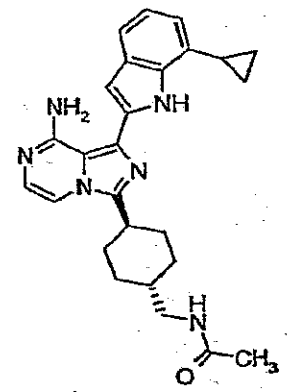
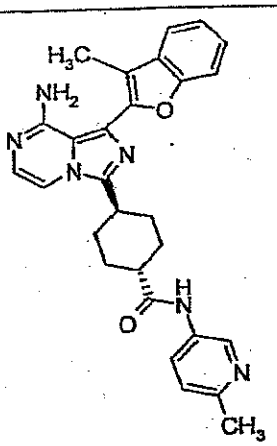
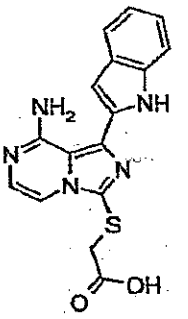
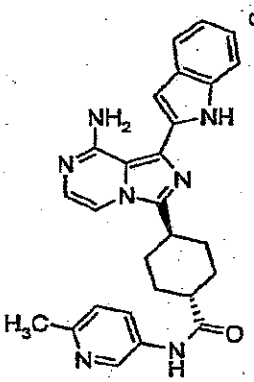
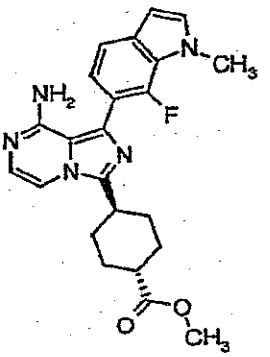
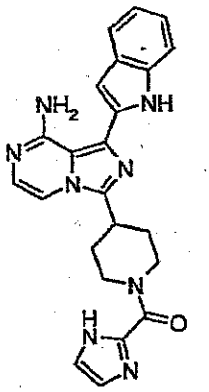
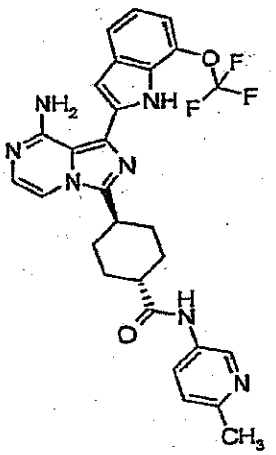
		
		
		
		
		

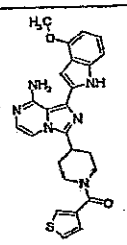
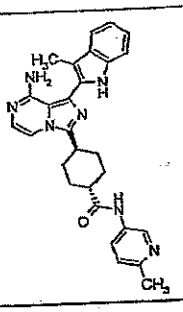
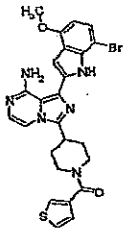
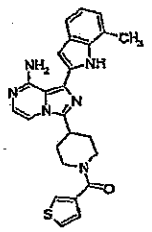
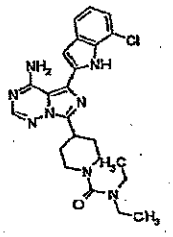
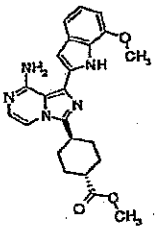
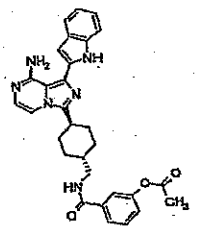
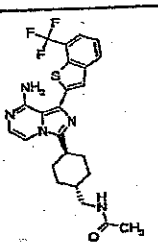
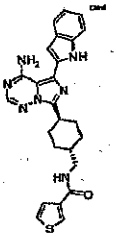
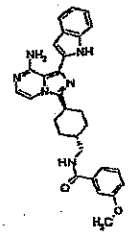
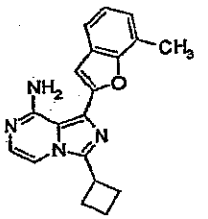
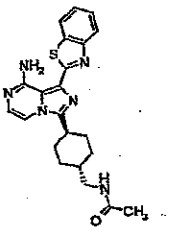
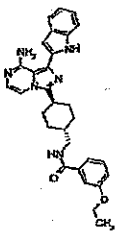
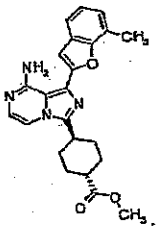
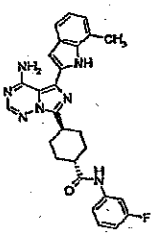
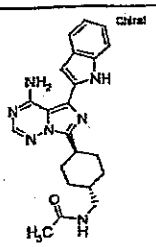
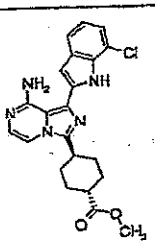
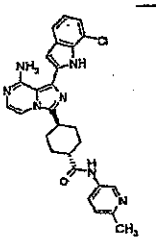


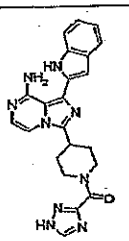
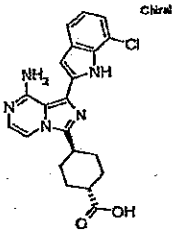
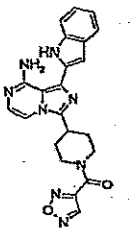
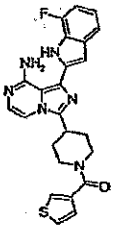
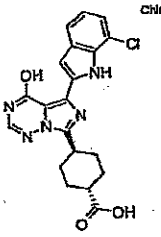
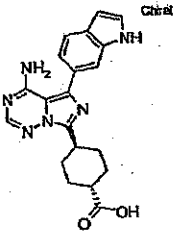
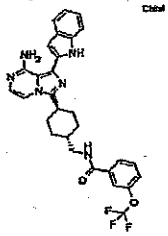
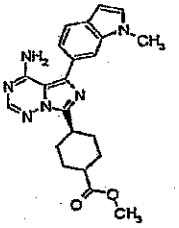
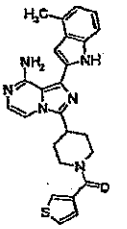
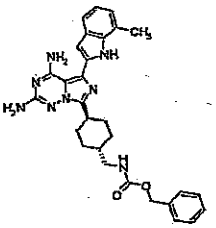
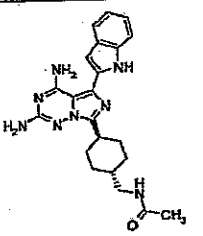
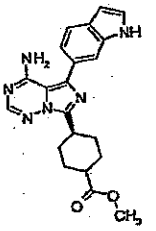
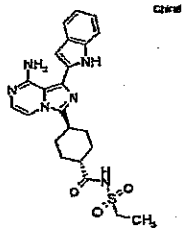
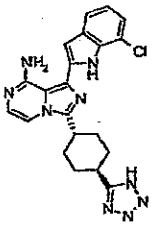
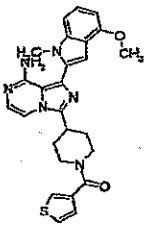
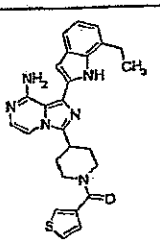
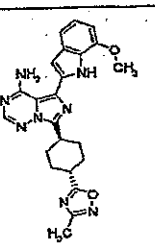
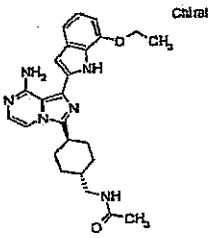


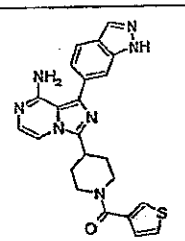
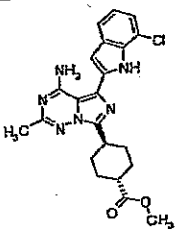
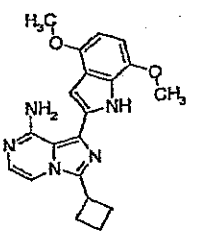
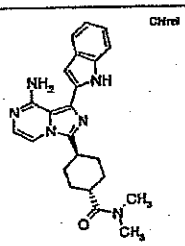
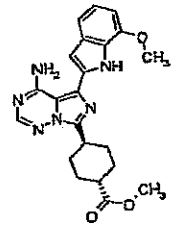
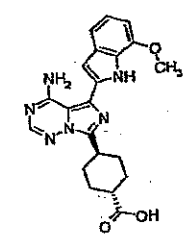
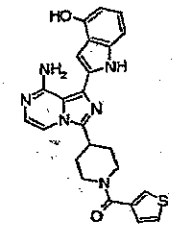
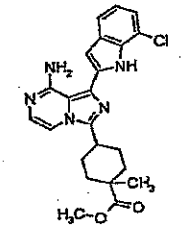
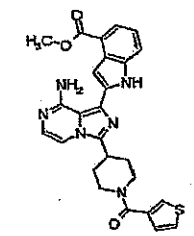
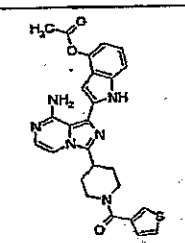
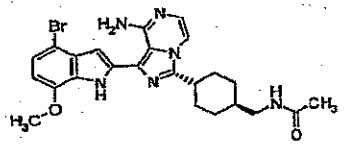
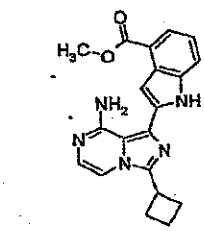
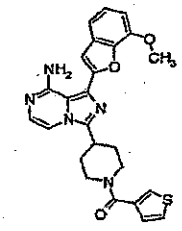
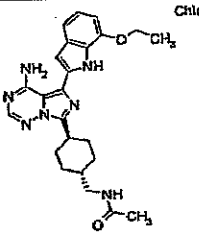
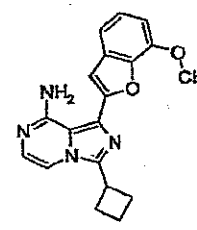
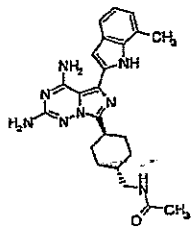
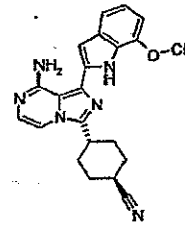
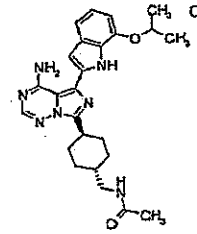


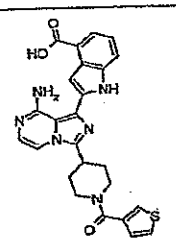
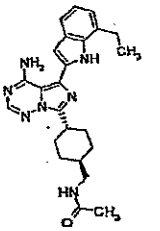
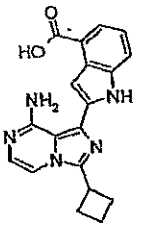
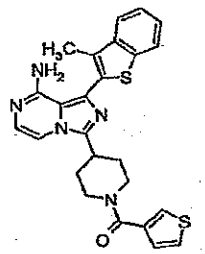
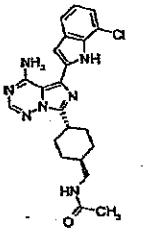
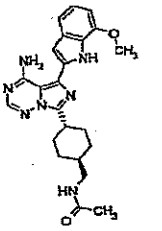
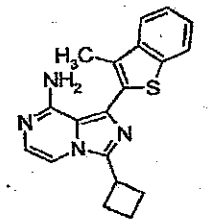
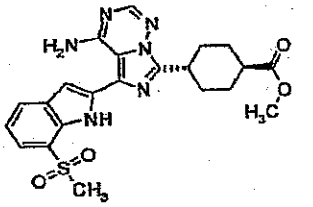
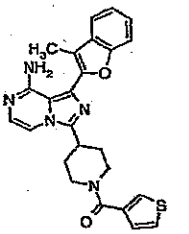
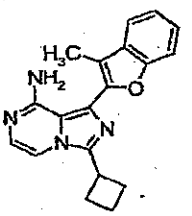
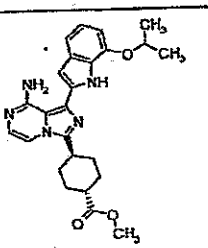
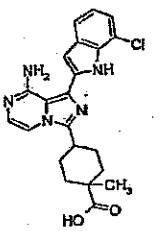
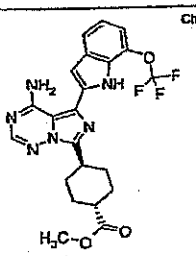
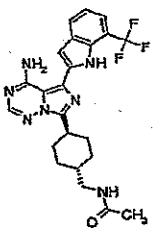
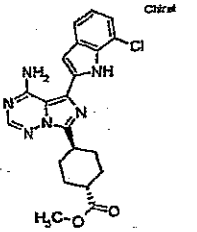
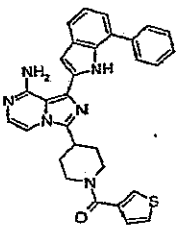
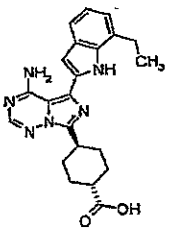
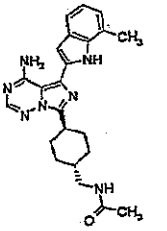
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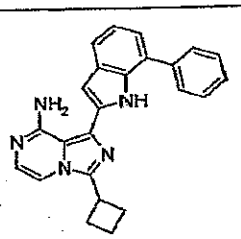
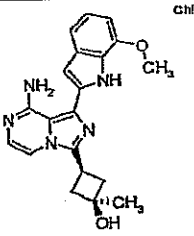
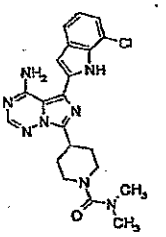
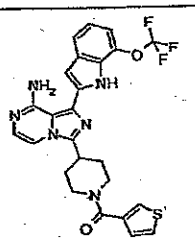
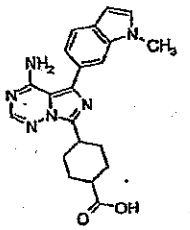
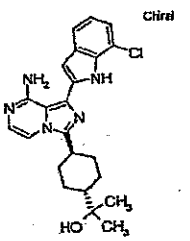
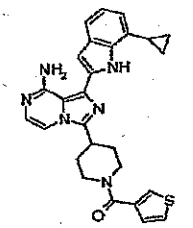
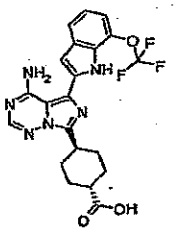
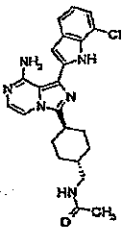
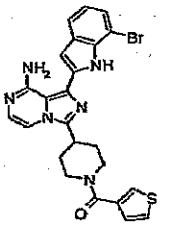
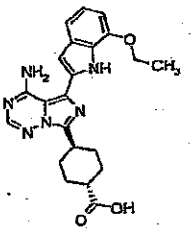
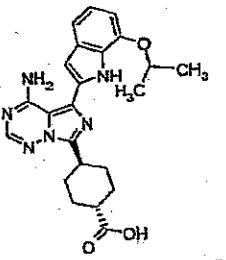
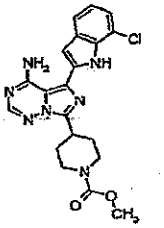
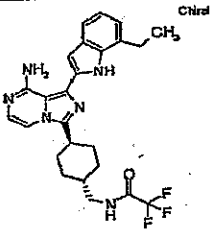
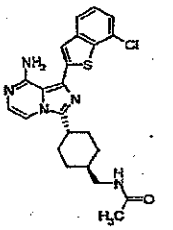
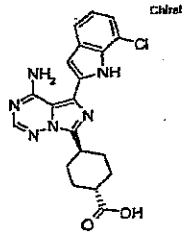
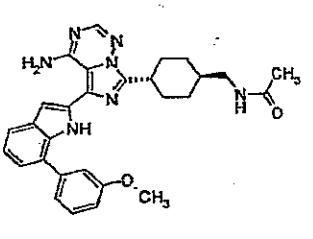
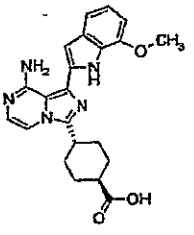
		
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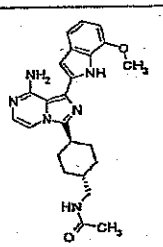
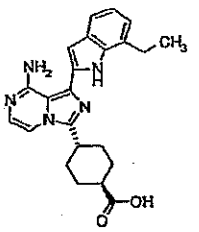
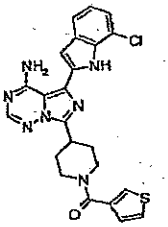
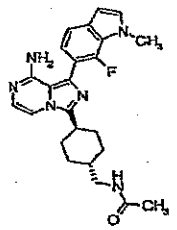
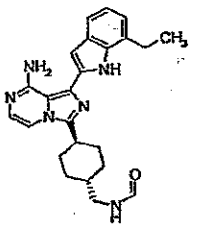
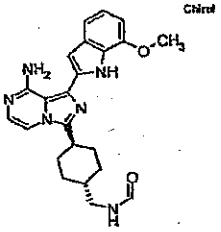
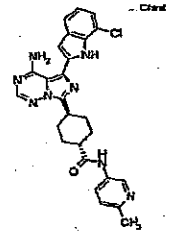
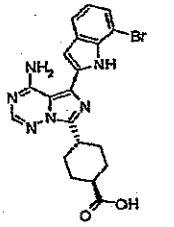
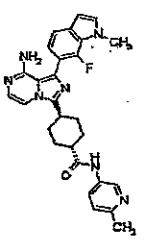
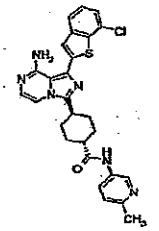
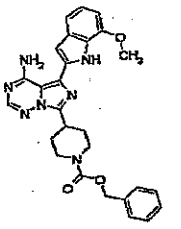
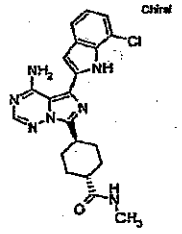
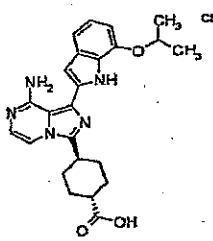
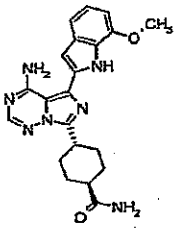
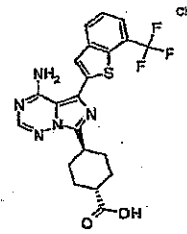
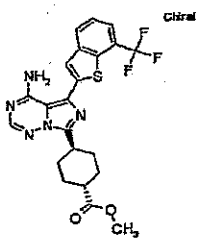
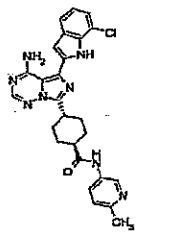
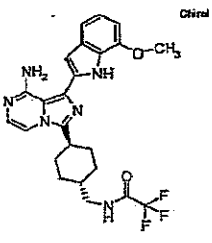
		
		
		
		
		
		

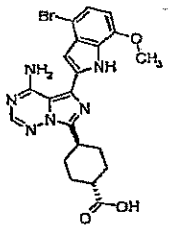
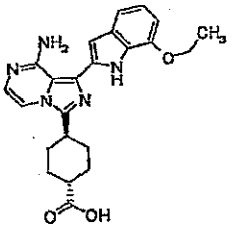
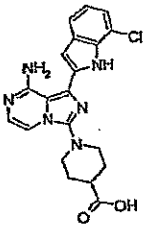
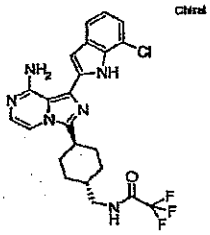
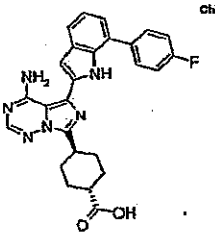
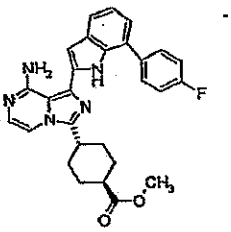
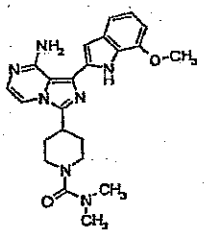
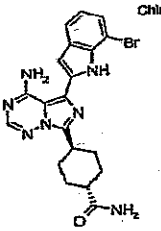
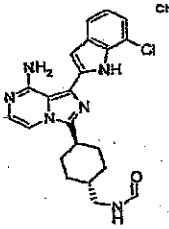
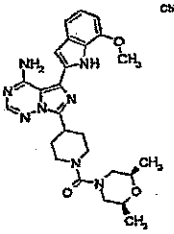
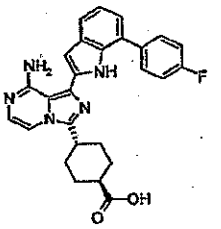
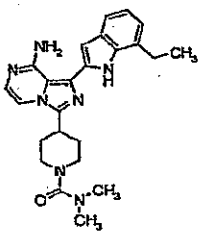
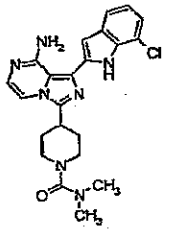
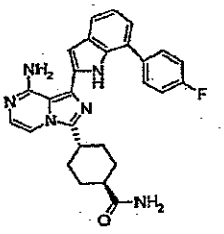
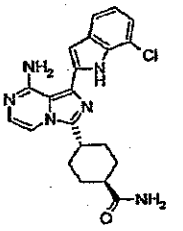
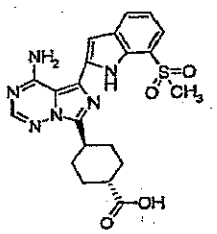
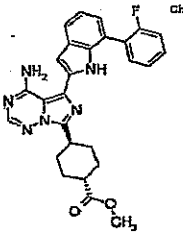
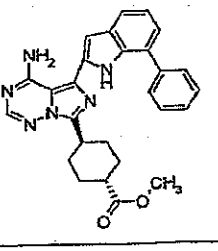
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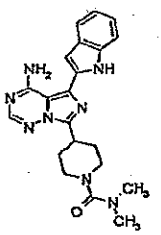
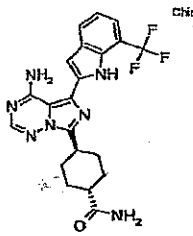
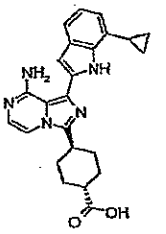
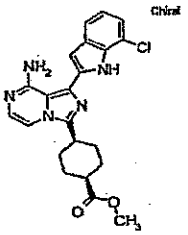
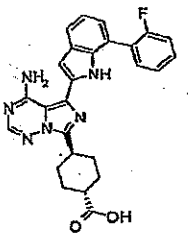
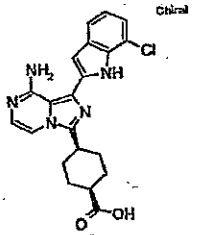
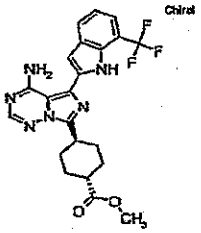
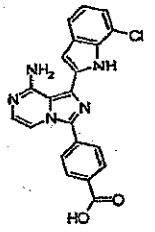
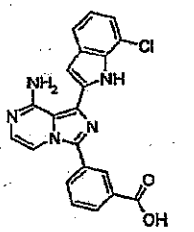
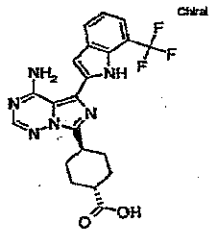
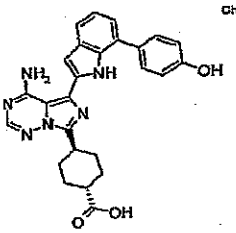
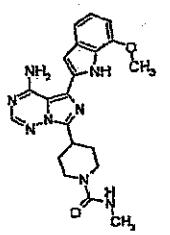
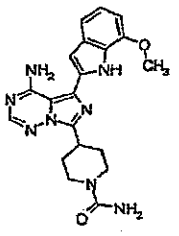
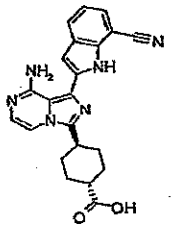
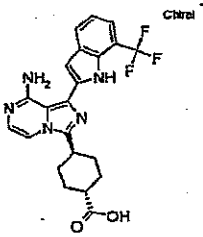
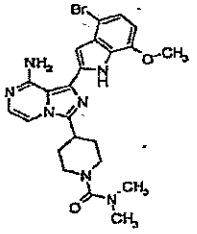
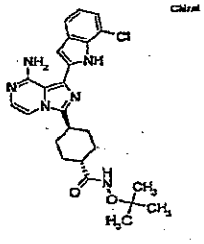
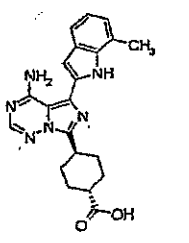
		
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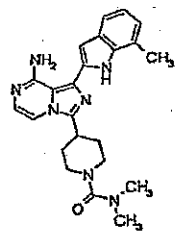
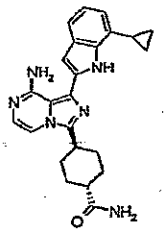
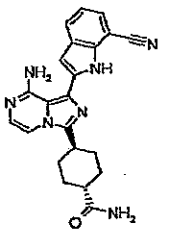
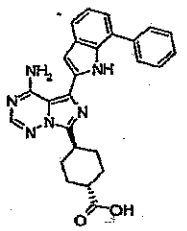
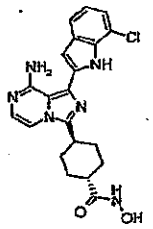
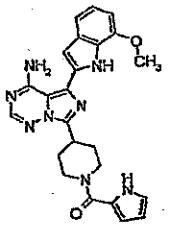
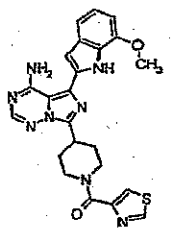
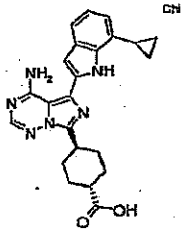
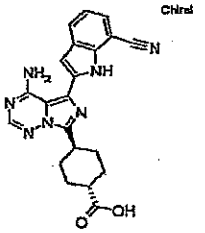
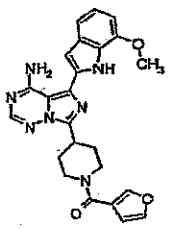
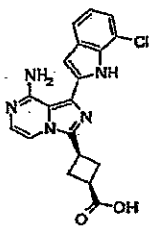
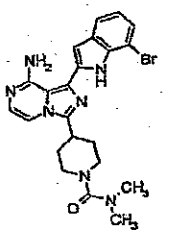
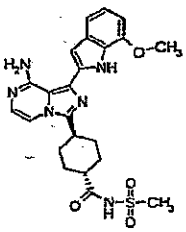
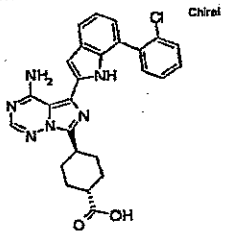
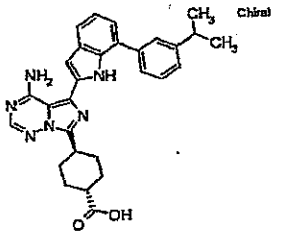
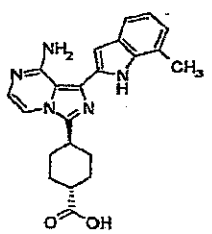
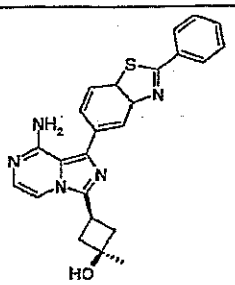
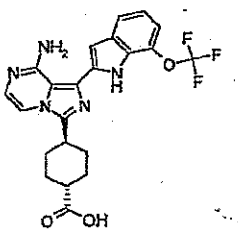
		
		
		
		
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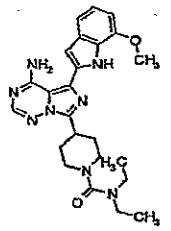
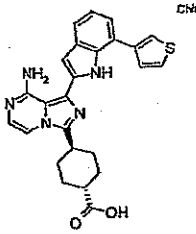
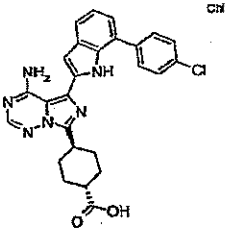
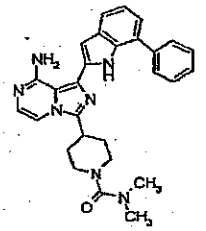
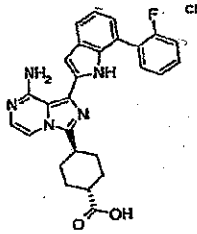
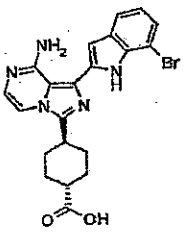
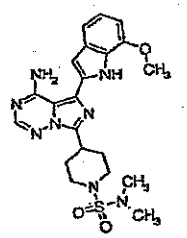
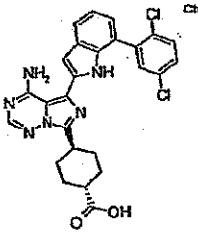
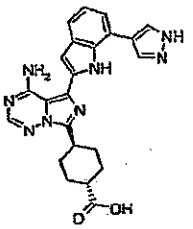
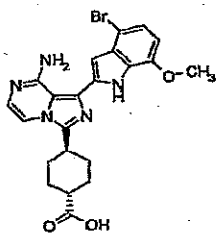
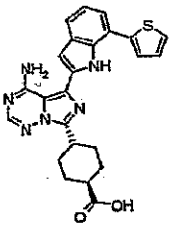
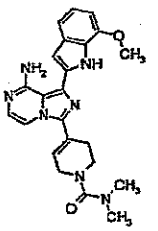
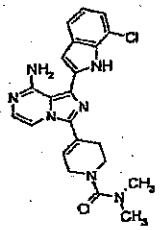
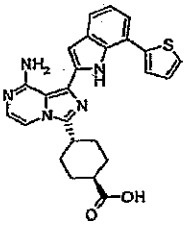
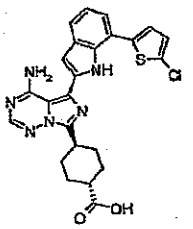
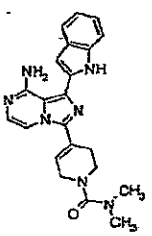
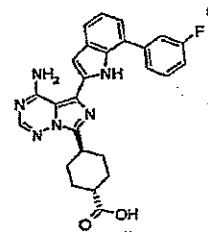
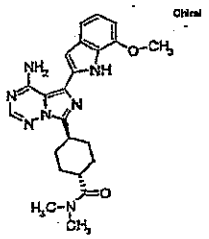
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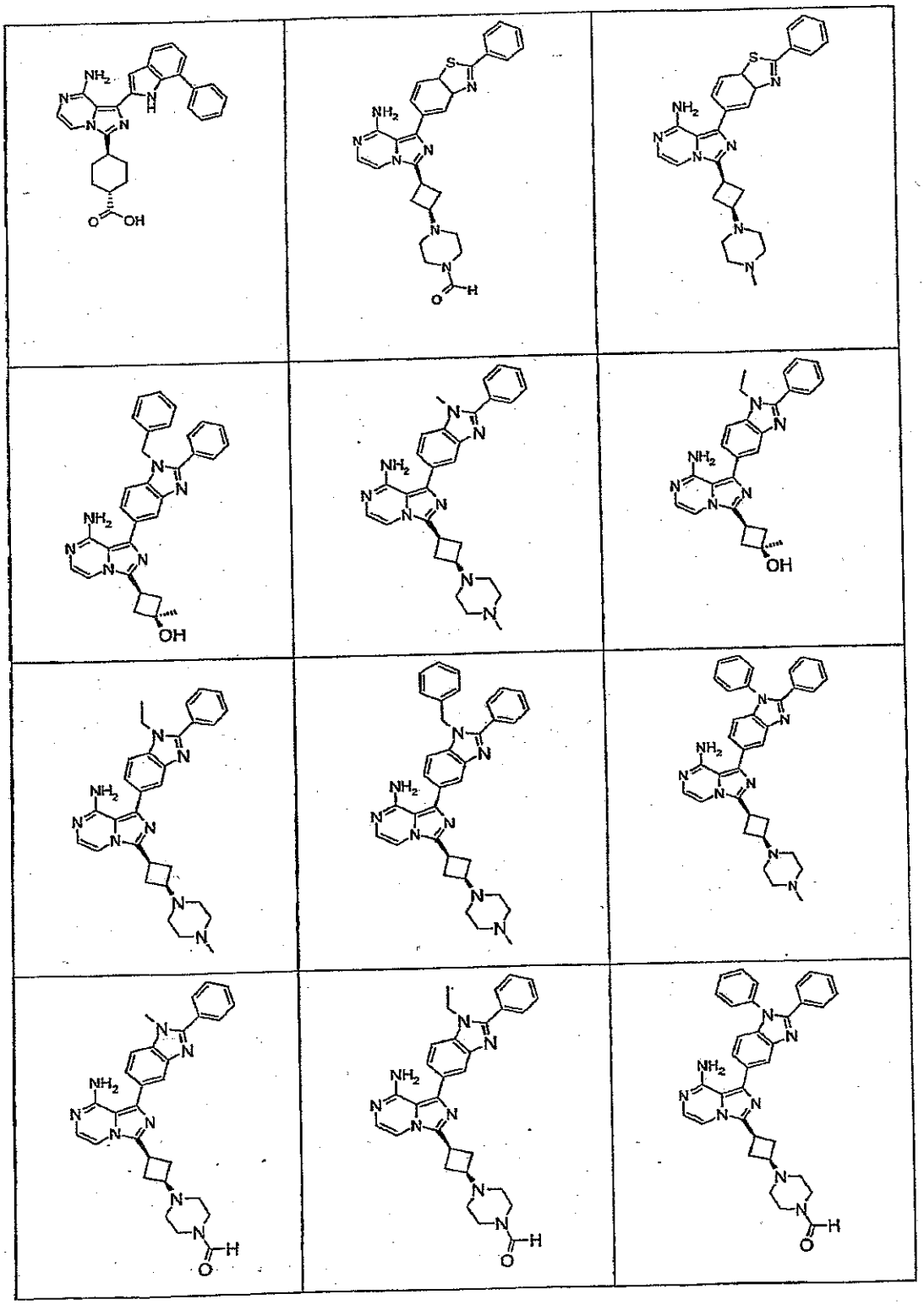
		
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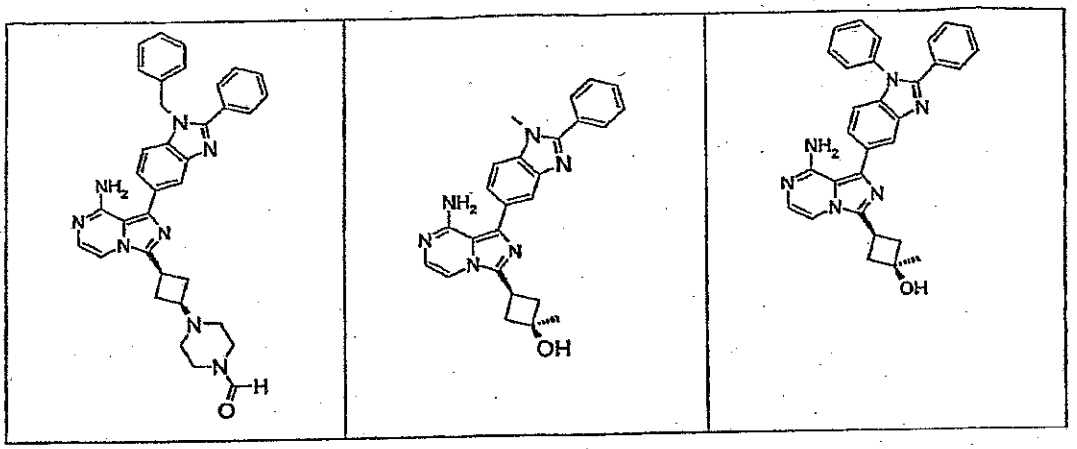
		
		
		
		
		
		

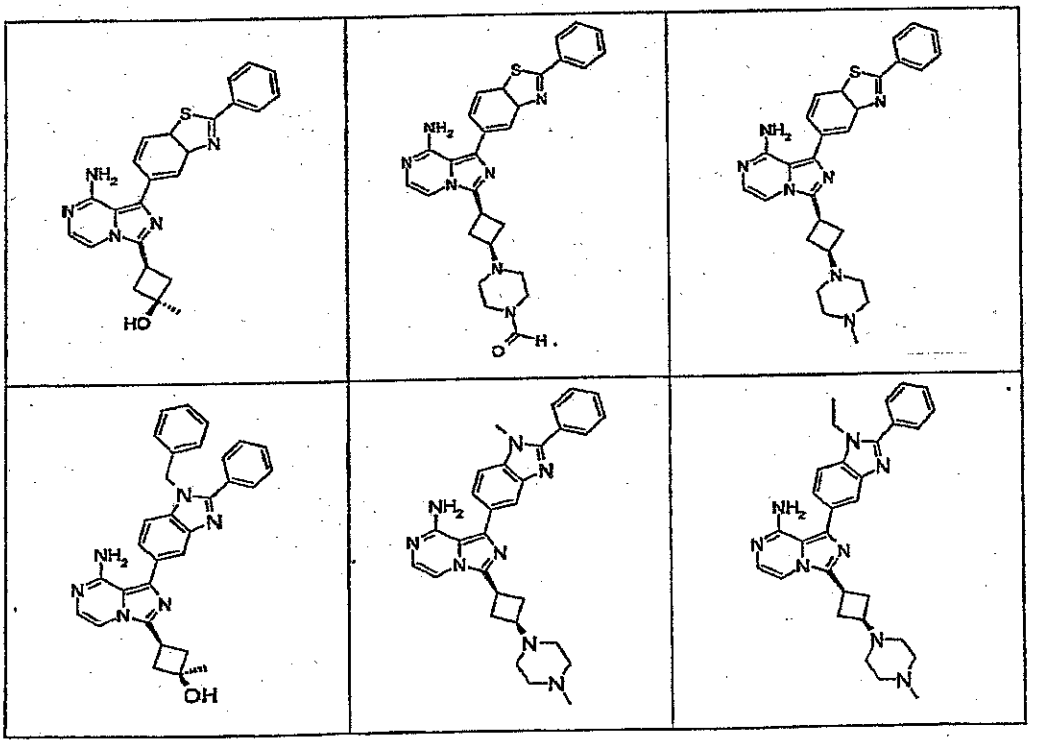
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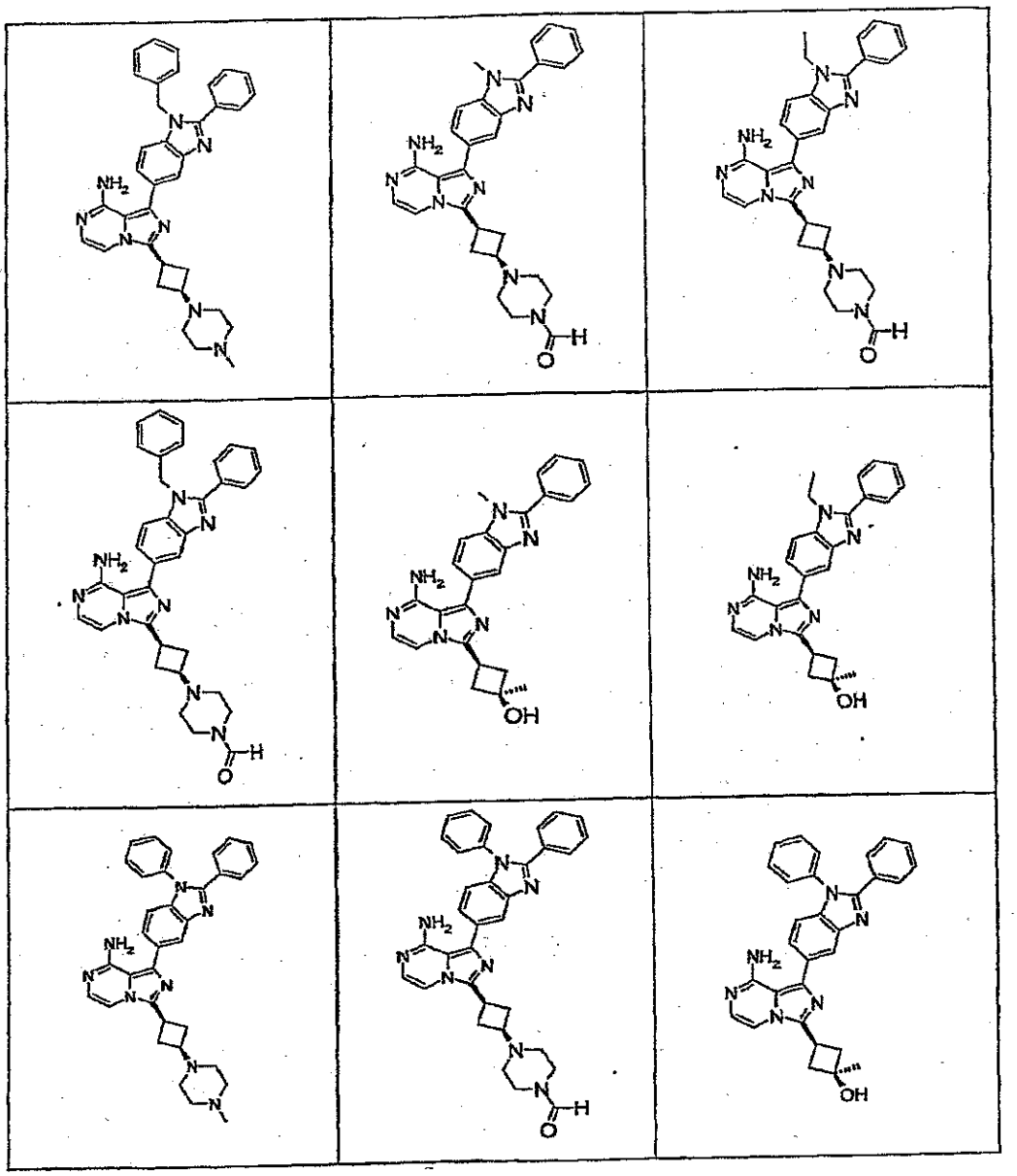
		
		
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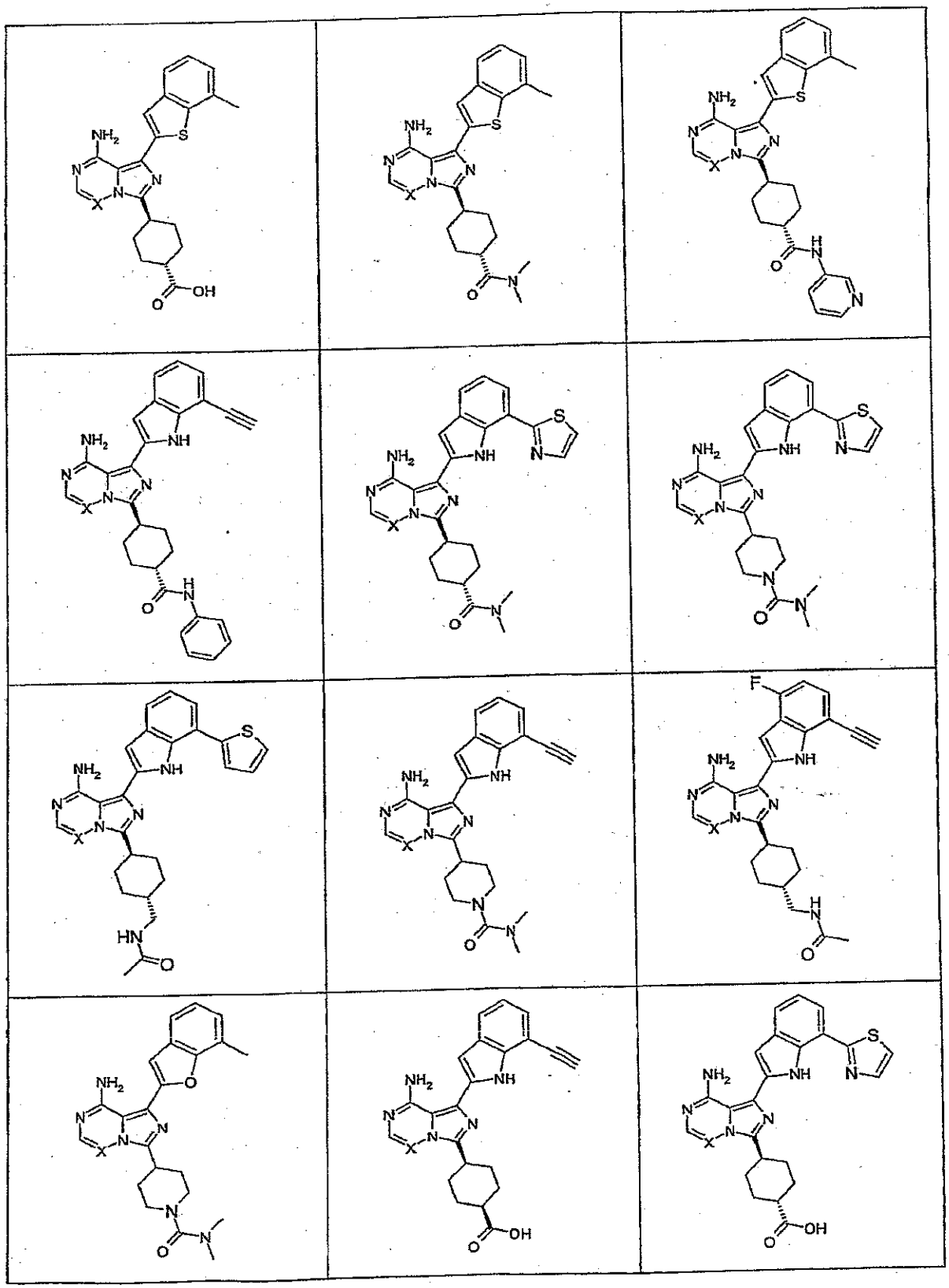
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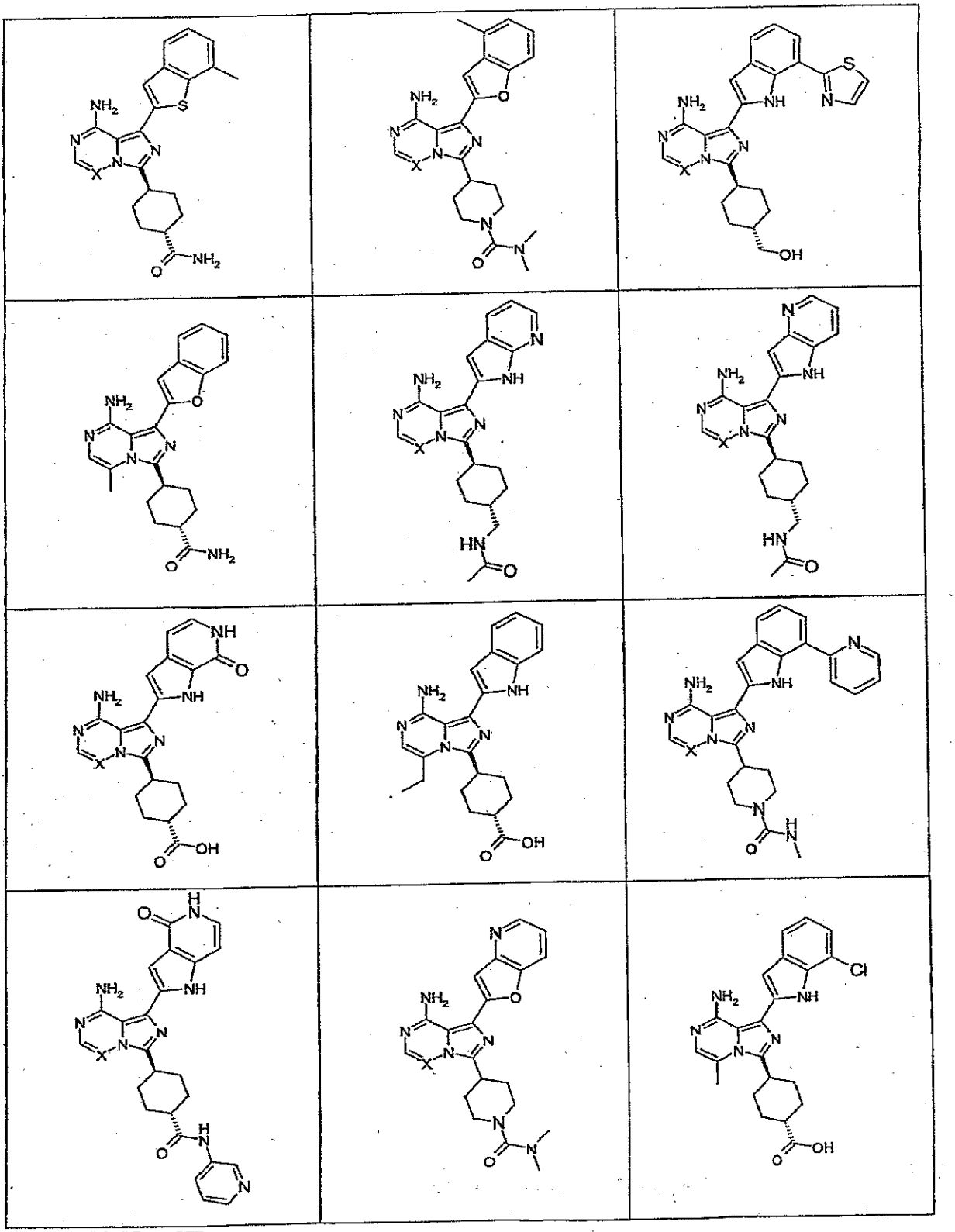












wherein X is N or CH;

or a pharmaceutically acceptable salt thereof.

[12b] In a second aspect, there is provided a composition comprising a compound as disclosed above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[12c] In a third aspect, there is provided the use of the compound as disclosed above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of hyperproliferative disorder.

[13] According to an embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; and the other variables are as described above for Formula I.

[14] In an embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is $-A(R^1)_mB(W)_n$; and the other variables are as described above for Formula I.

[15] In another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is $-B(G^{11})_nA(Y)_m$; and the other variables are as described above for Formula I.

[16] In yet another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted indolyl; and the other variables are as described above for Formula I.

[17] In still another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted benzothienyl; and the other variables are as described above for Formula I.

[18] In an embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted benzimidazolyl; and the other variables are as described above for Formula I.

[19] In another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are CH; X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted benzoxazolyl; and the other variables are as described above for Formula I.

[20] According to another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; and the other variables are as described above for Formula I.

[21] In an embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is $-A(R^1)_mB(W)_n$; and the other variables are as described above for Formula I.

[22] In another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is $-B(G^{11})_nA(Y)_m$; and the other variables are as described above for Formula I.

[23] In yet another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is

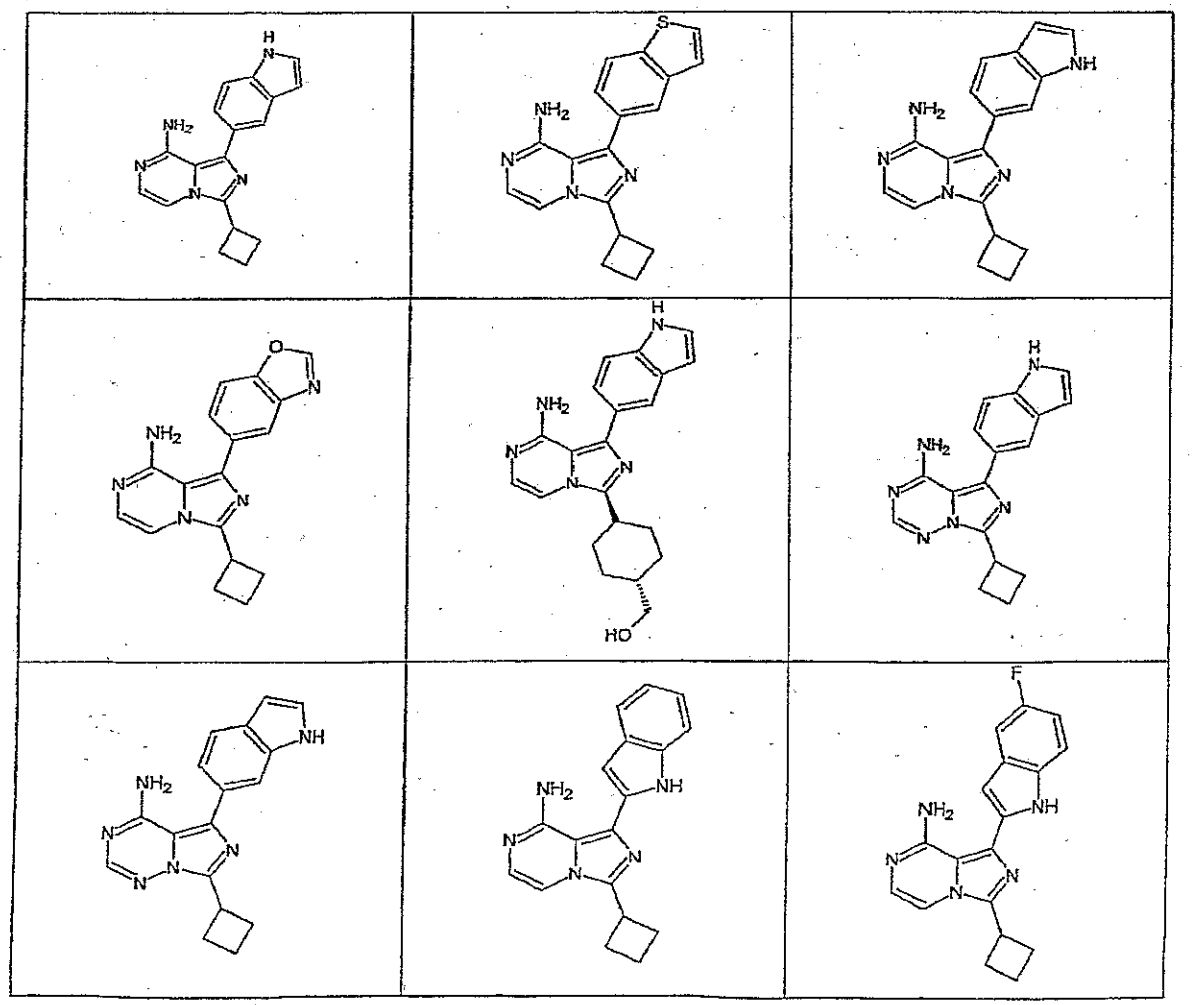
CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted indolyl; and the other variables are as described above for Formula I.

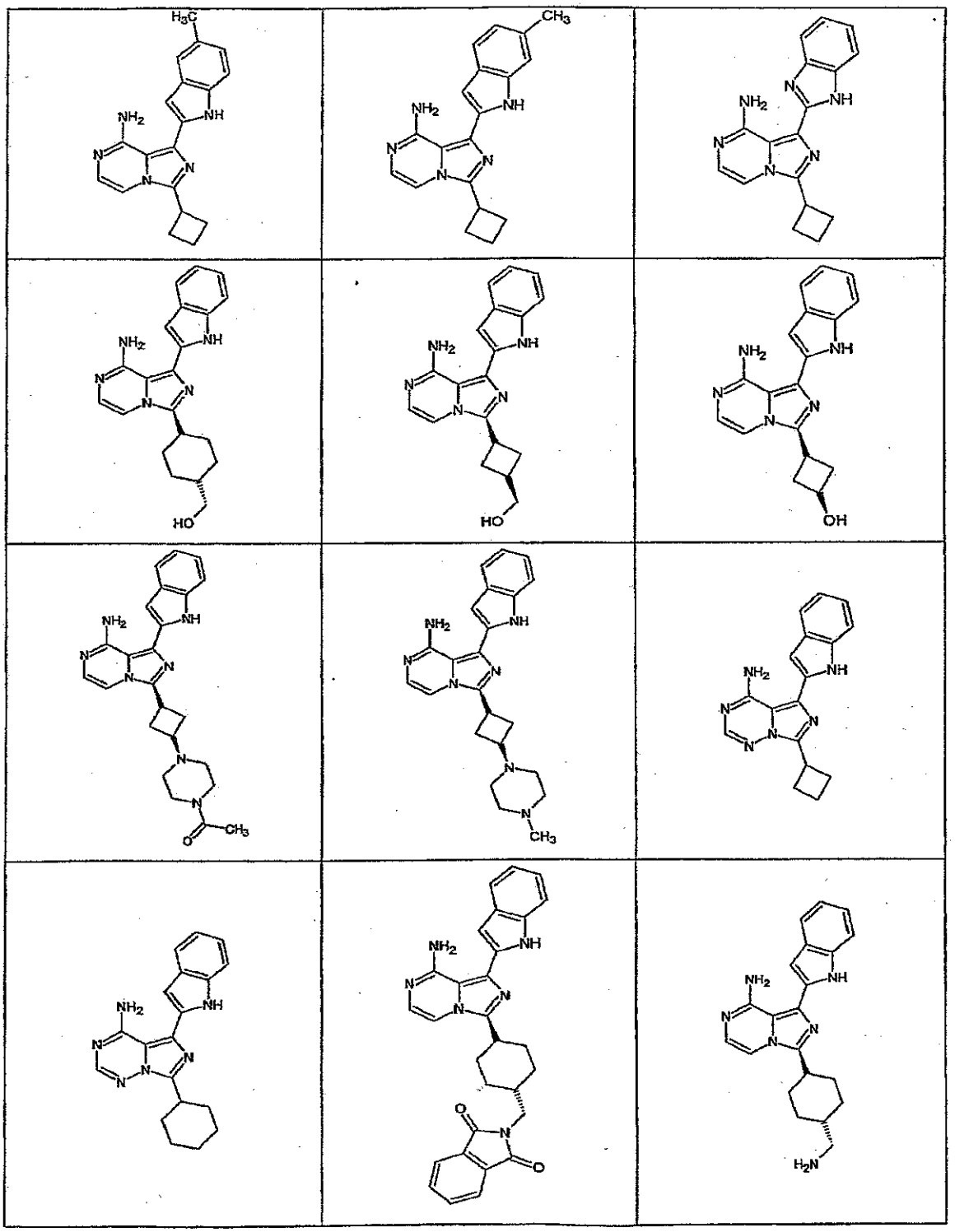
[24] In still another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted benzimidazolyl; and the other variables are as described above for Formula I.

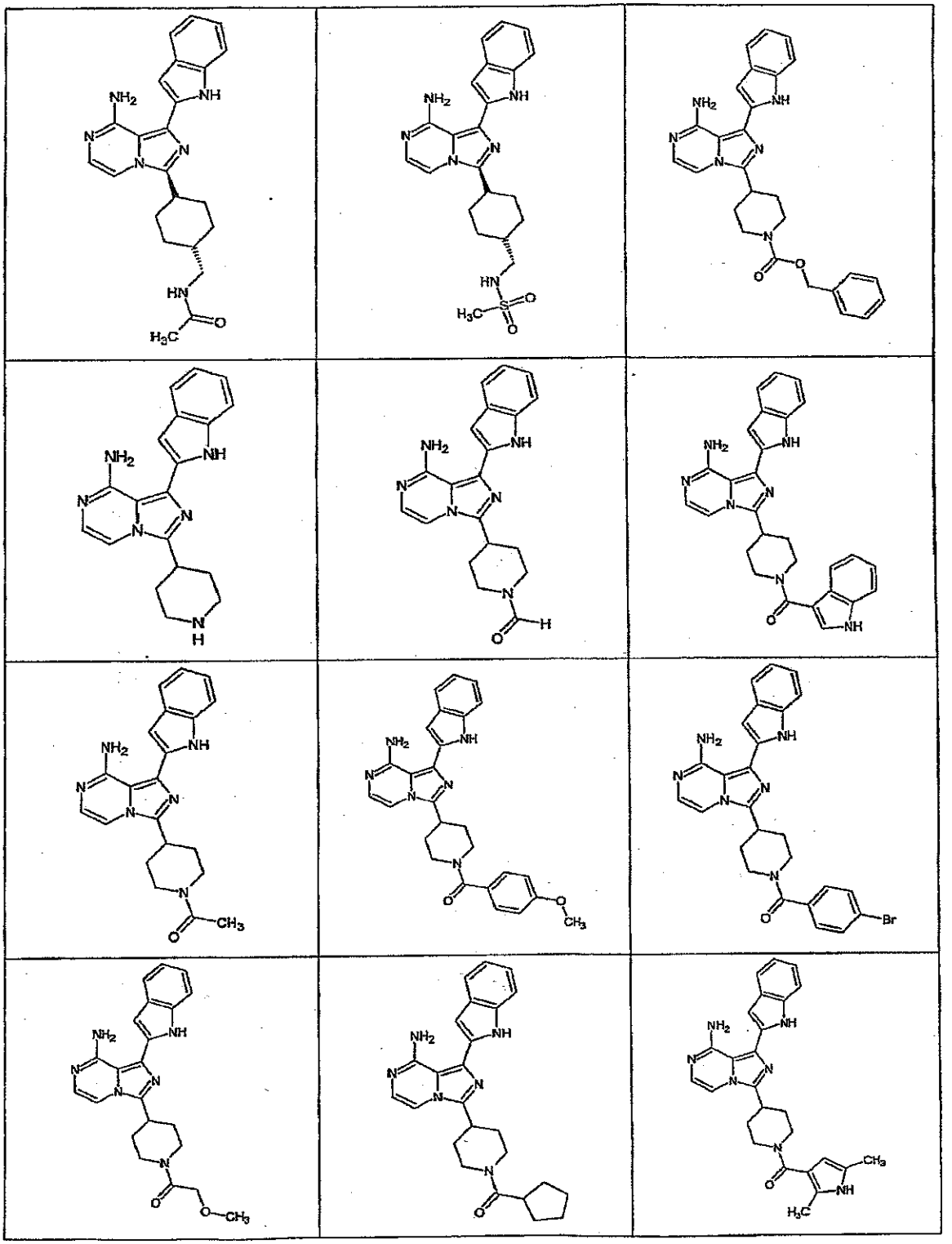
[25] In another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted benzoxazolyl; and the other variables are as described above for Formula I.

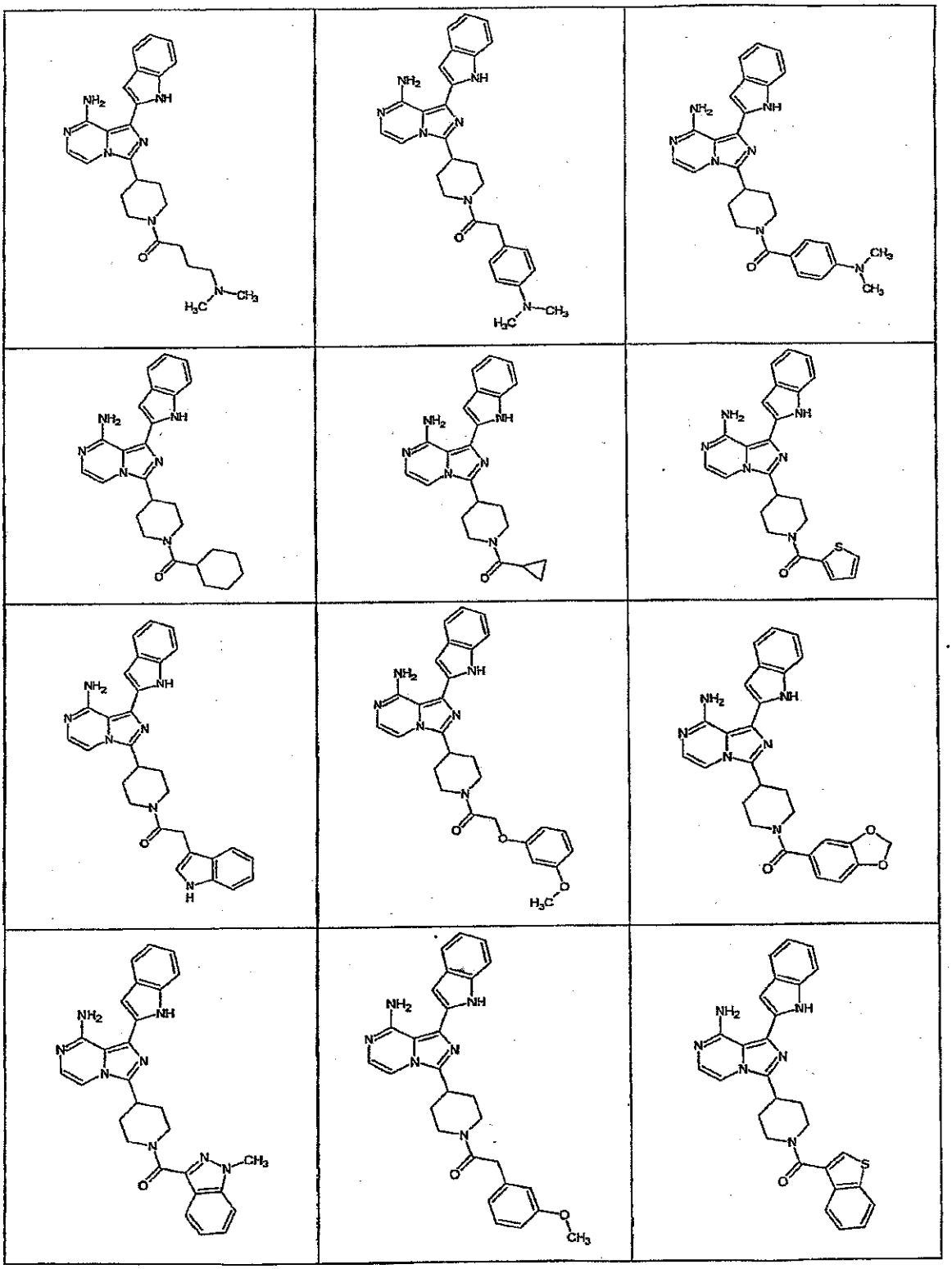
[26] In yet still another embodiment of the present disclosure, the compounds are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1 is CH; X_2, X_3 and X_5 are N; and X_4, X_6 and X_7 are C; Q^1 is optionally substituted benzothienyl; and the other variables are as described above for Formula I.

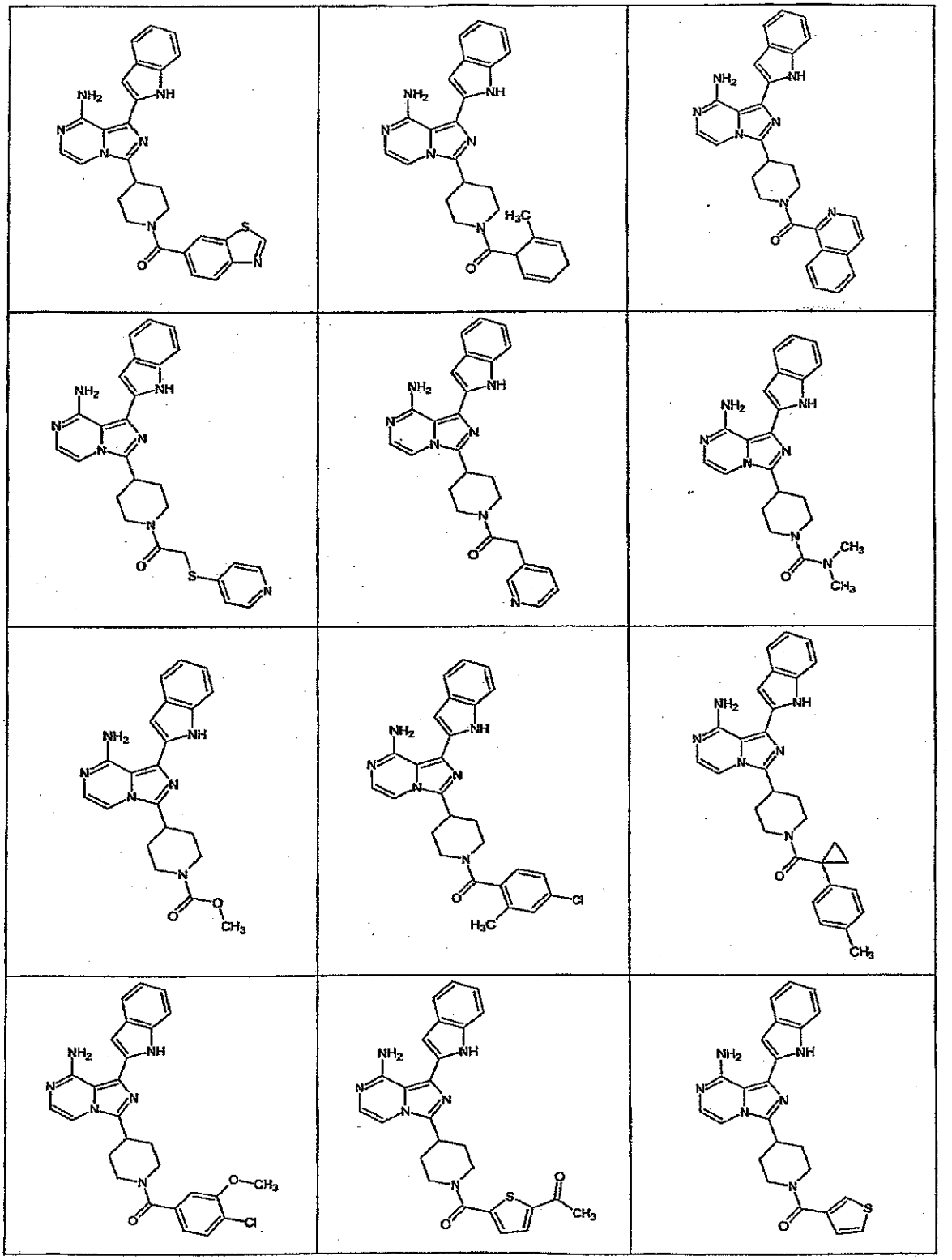
[27] The compounds of the present disclosure include:

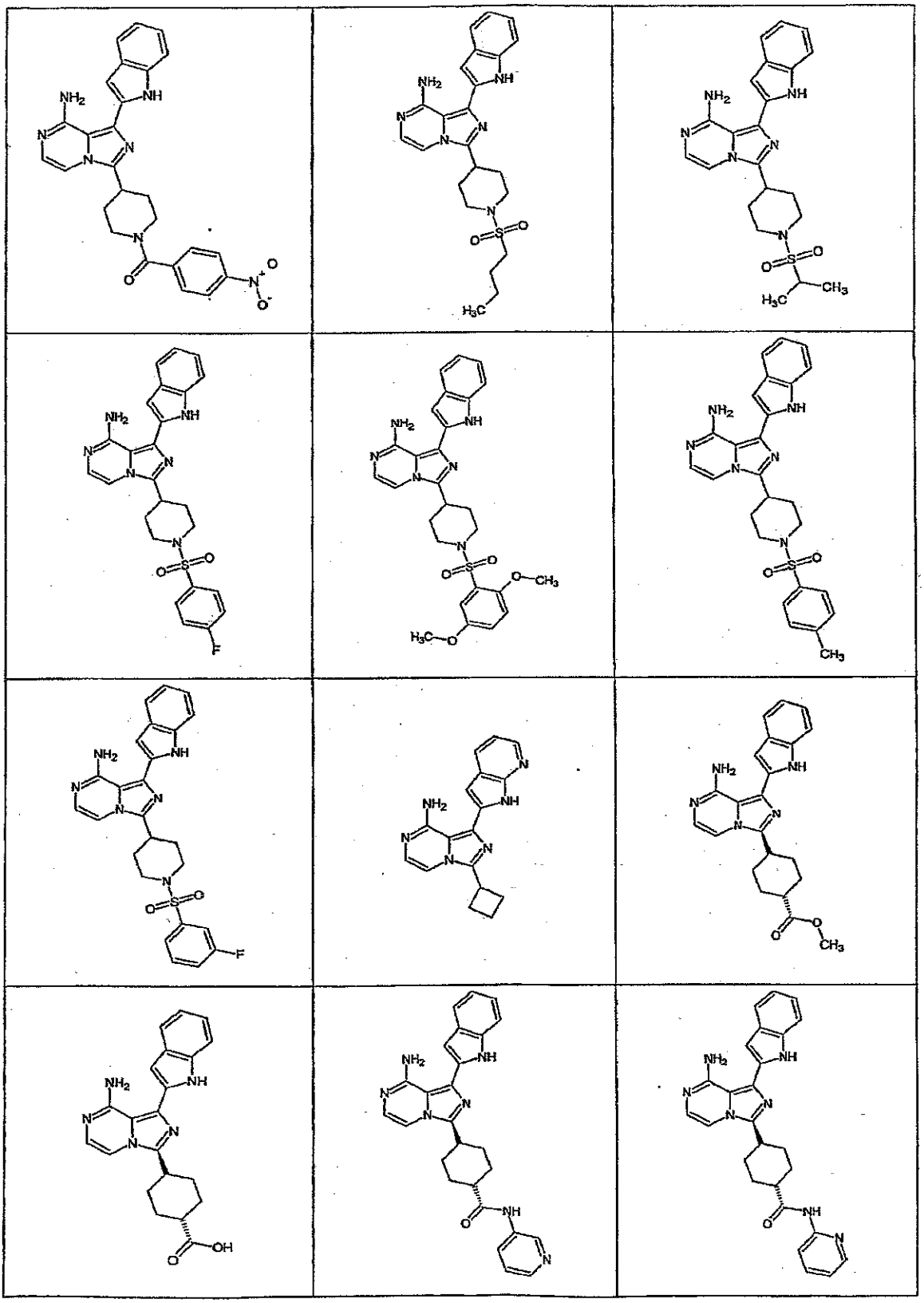


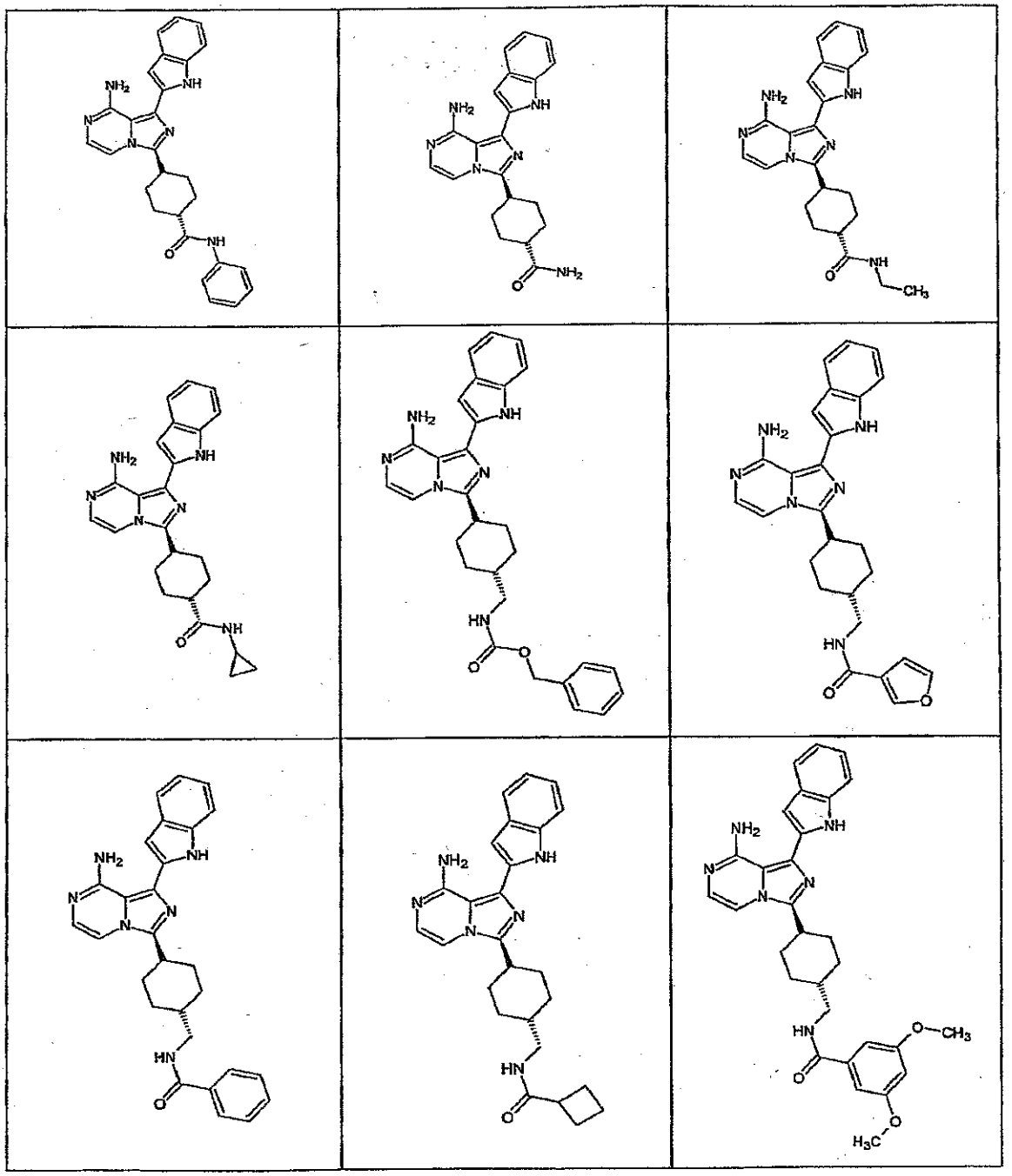


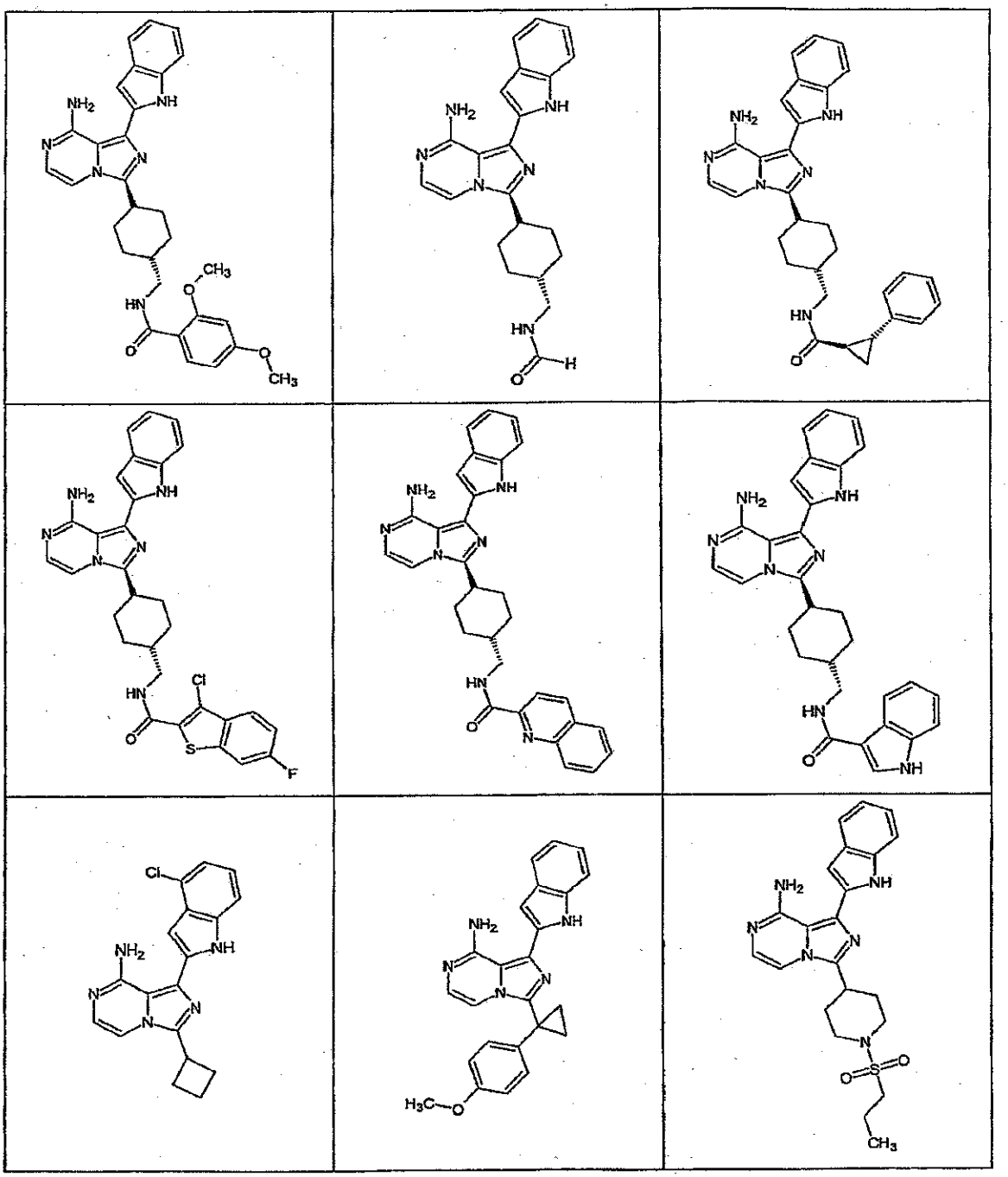


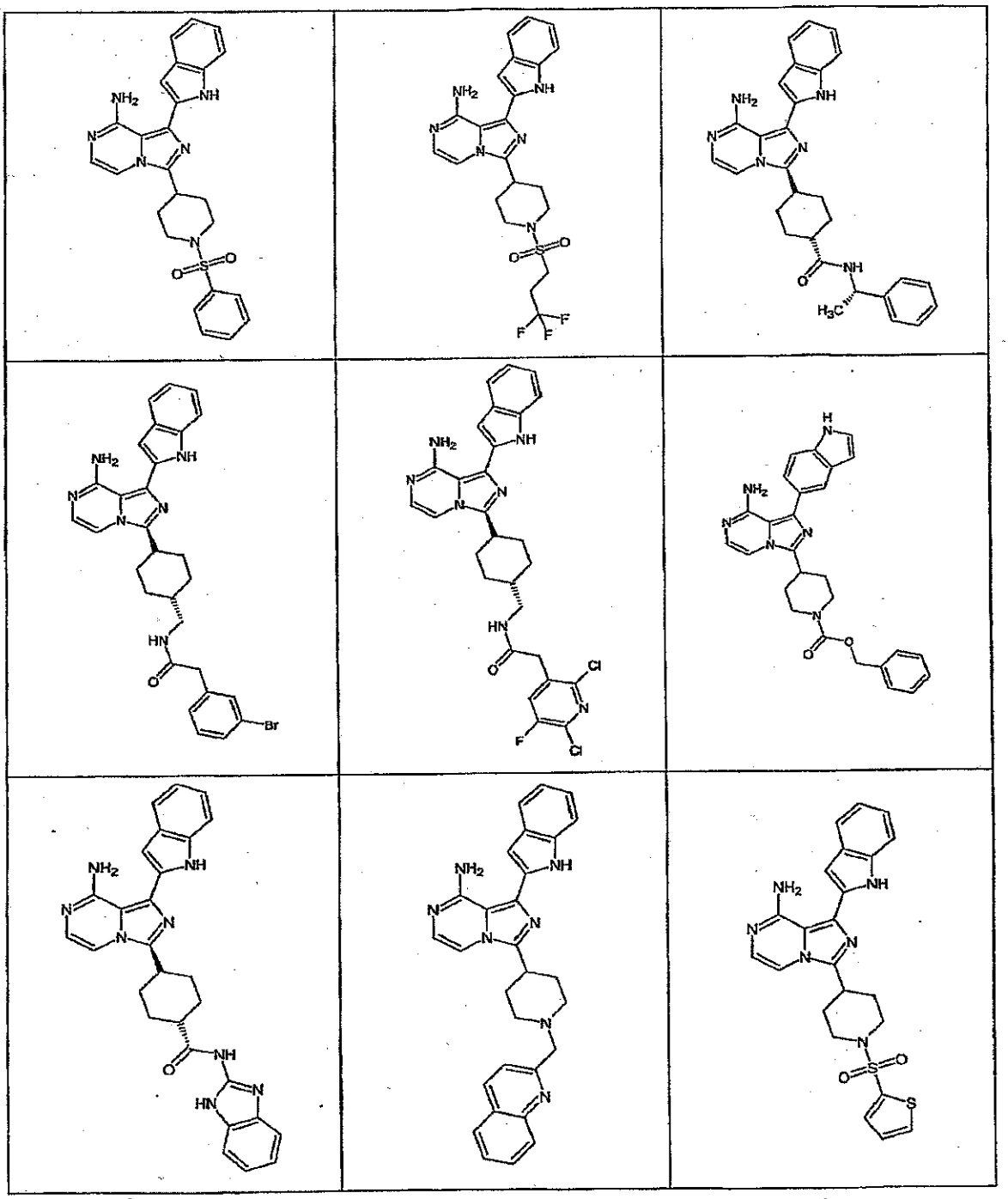


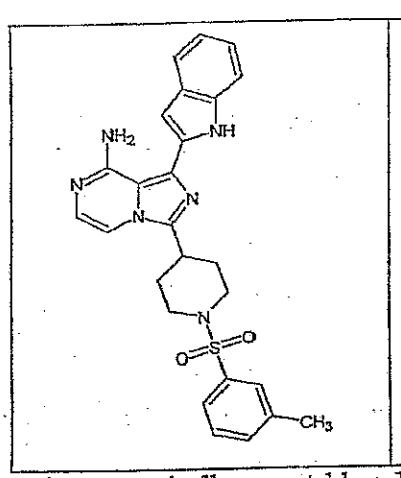
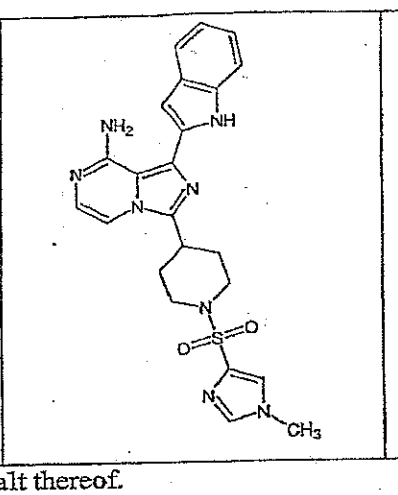










or a pharmaceutically acceptable salt thereof.

[28] The present disclosure includes a composition comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

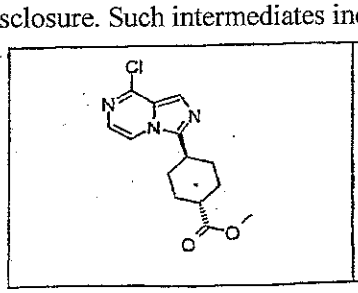
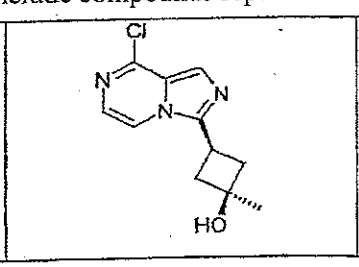
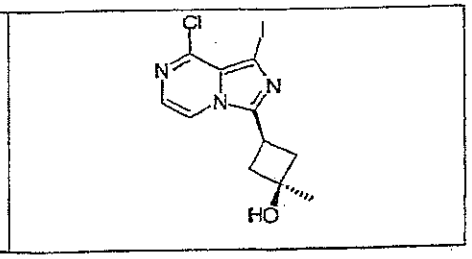
[29] The present disclosure includes a composition comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof; and an anti-neoplastic, anti-tumor, anti-angiogenic, or chemotherapeutic agent.

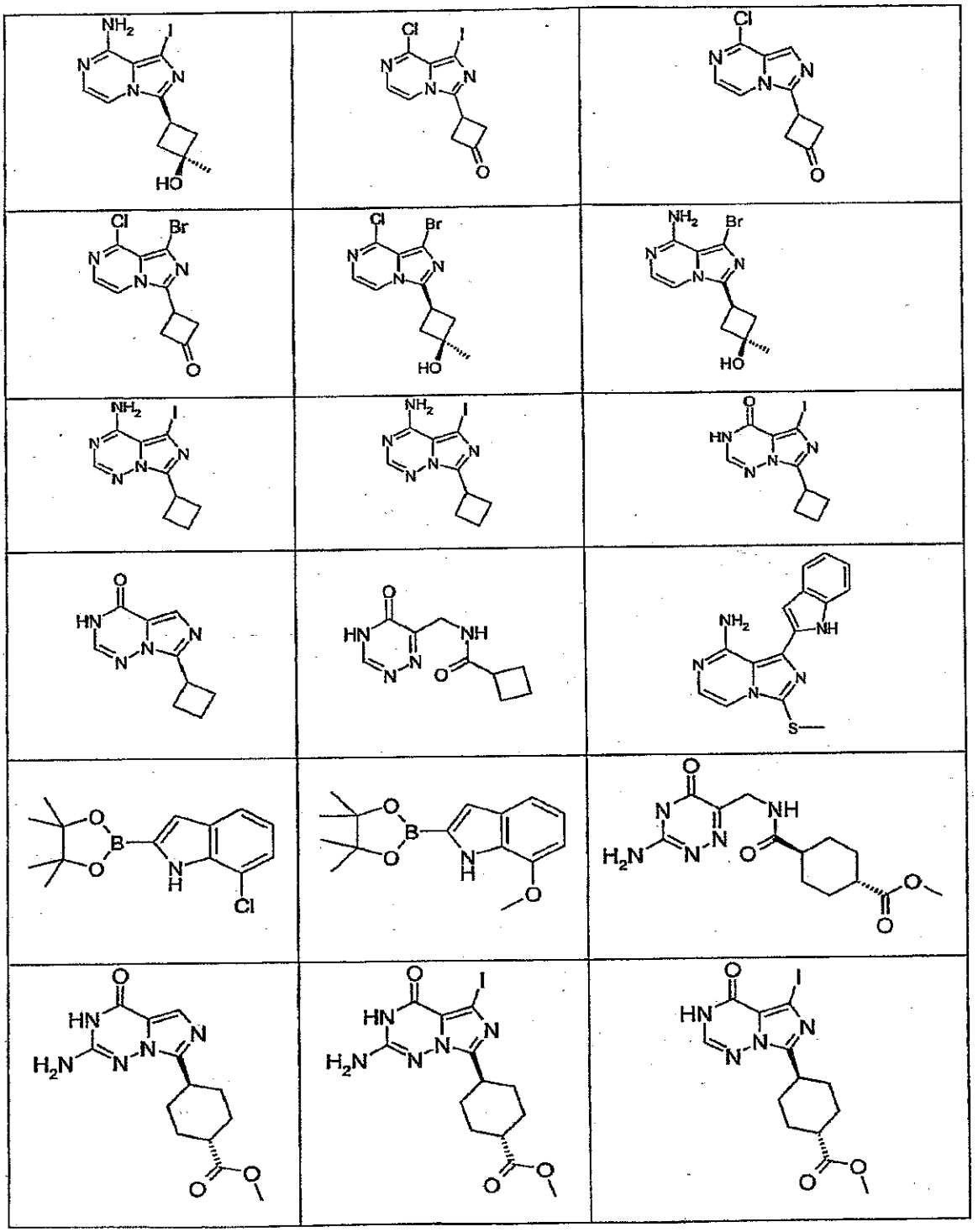
[30] The present disclosure includes a method of treatment of hyperproliferative disorder comprising a step of administering an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof.

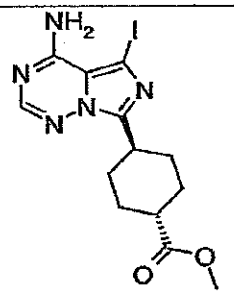
[31] The present disclosure includes a method of treatment of hyperproliferative disorder comprising a step of administering an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, wherein the hyperproliferative disorder is breast cancer, lung cancer, non-small cell lung cancer, kidney cancer, renal cell carcinoma, prostate cancer, cancer of the blood, liver cancer, ovarian cancer, thyroid cancer, endometrial cancer, cancer of the GI tract, lymphoma, renal cell carcinoma, mantle cell lymphoma, or endometrial cancer.

[32] The present disclosure includes a method of treatment of rheumatoid arthritis, hamartoma syndromes, transplant rejection, IBD, multiple sclerosis or immunosuppression diseases comprising a step of administering an effective amount of the compound according to Formula I, or a pharmaceutically acceptable salt thereof.

[33] The present disclosure includes intermediates useful in making the compounds of the disclosure. Such intermediates include compounds represented by



or a pharmaceutically acceptable salt thereof.

[34] In all of the above circumstances forbidden or unstable valences, N-S, N-halogen bonds are excluded.

[35] As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanyl, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

[36] As used herein, "C_{0-4}alkyl" for example is used to mean an alkyl having 0-4 carbons – that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group.

[37] The terms "cycloalkyl", "carbocyclic ring", cyclic", or "cyclyl" mean 3-10 membered mono or polycyclic aromatic, partially aromatic or non-aromatic ring carbocycles containing no heteroatoms, and include mono-, bi-, and tricyclic saturated carbocycles, as well as fused and bridged systems. Such fused ring systems can include one ring that is partially or fully unsaturated, such as a benzene ring, to form fused ring systems, such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl and carbocyclic rings include C_{3-8}cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene, adamantane, indanyl, 1,2,3,4-tetrahydronaphthalene and the like.

[38] The term "halogen" includes fluorine, chlorine, bromine, and iodine atoms.

[39] The term "carbamoyl" unless specifically described otherwise means -C(O)-NH- or -NH-C(O)-.

[40] The term "aryl" is well known to chemists. The preferred aryl groups are phenyl and naphthyl.

[41] The term "hetaryl" is well known to chemists. The term includes 5- or 6-membered heteroaryl rings containing 1–4 heteroatoms chosen from oxygen, sulfur, and nitrogen in which oxygen and sulfur are not next to each other. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl,

thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. The term "hetaryl" includes hetaryl rings with fused carbocyclic ring systems that are partially or fully unsaturated, such as a benzene ring, to form a benzofused hetaryl. For example, benzimidazole, benzoxazole, benzothiazole, benzofuran, quinoline, isoquinoline, quinoxaline, and the like.

[42] Unless otherwise stated, the terms "heterocyclic ring", "heterocycle", "heterocyclic", and "heterocyclyl" are equivalent, and is defined as for cyclic but also contains one or more atoms chosen independently from N, O, and S (and the N and S oxides), provided such derivatives exhibit appropriate and stable valencies. The terms include 4–8-membered saturated rings containing one or two heteroatoms chosen from oxygen, sulfur, and nitrogen. Examples of heterocyclic rings include azetidine, oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, thiazolidine, oxazolidine, oxazetidine, pyrazolidine, isoxazolidine, isothiazolidine, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, homopiperazine, morpholine, thiomorpholine, and the like. Other examples of heterocyclic rings include the oxidized forms of the sulfur-containing rings. Thus, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, thiomorpholine-1-oxide, thiomorpholine-1,1-dioxide, tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, thiazolidine-1-oxide, and thiazolidine-1,1-dioxide are also considered to be heterocyclic rings. The term "heterocyclic" also includes fused ring systems, including het-het fused systems, and can include a carbocyclic ring that is partially or fully unsaturated, such as a benzene ring, to form benzofused heterocycles. For example, 3,4,-dihydro-1,4-benzodioxine, tetrahydroquinoline, tetrahydroisoquinoline, isoindoline and the like.

[43] Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present disclosure includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present disclosure includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[44] The disclosure also encompasses a pharmaceutical composition that is comprised of a compound of Formula I in combination with a pharmaceutically acceptable carrier.

[45] Preferably the composition is comprised of a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I as described above (or a pharmaceutically acceptable salt thereof).

[46] Moreover, within this preferred embodiment, the disclosure encompasses a pharmaceutical composition for the treatment of disease by inhibition of mTor, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above (or a pharmaceutically acceptable salt thereof).

[47] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present disclosure is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium slats. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N',N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylameine, trimethylamine, tripropylamine, tromethamine and the like.

[48] When the compound of the present disclosure is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

[49] The pharmaceutical compositions of the present disclosure comprise a compound represented by formula I (or a pharmaceutically acceptable salt thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[50] In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this disclosure can be combined as the active ingredient in intimate admixture with a

pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present disclosure can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[51] Thus, the pharmaceutical compositions of this disclosure may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[52] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[53] In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

[54] A tablet containing the composition of this disclosure may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a

mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

[55] For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material, which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

[56] Pharmaceutical compositions of the present disclosure suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[57] Pharmaceutical compositions of the present disclosure suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[58] Pharmaceutical compositions of the present disclosure can be in a form suitable for topical sue such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this disclosure, or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

[59] Pharmaceutical compositions of this disclosure can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. He suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[60] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as

diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

[61] The compounds and compositions of the present disclosure are useful in the treatment of cancers of the breast, lung, kidney, prostate, blood, liver, ovarian, thyroid, GI tract and lymphoma. The compounds and compositions are useful against cancers including non-small cell lung cancer (NSCLC), renal cell carcinoma, mantle cell lymphoma, and endometrial cancers. Further, the compounds and compositions are useful in treating other indications such as rheumatoid arthritis, hamartoma syndromes, transplant rejection, irritable bowel disease (IBD), multiple sclerosis and immunosuppression.

[62] Generally, dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, cancers of the breast, lung, kidney, prostate, blood, liver, ovarian, thyroid, GI tract and lymphoma may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

[63] Dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of non-small cell lung cancer (NSCLC), renal cell carcinoma, mantle cell lymphoma, and endometrial cancers, or alternatively about 0.5mg to about 7g per patient per day. They may be treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

[64] Dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of rheumatoid arthritis, hamartoma syndromes, transplant rejection, irritable bowel disease (IBD), multiple sclerosis and immunosuppression, or alternatively about 0.5mg to about 7g per patient per day. They may be treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

[65] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Biochemical Assay for Inhibition of mTOR Activity:

[66] The ability of compounds to inhibit the mTOR kinase activity was determined in an *in vitro* immunoprecipitation (IP) kinase assay using recombinant 4E-BP1 as a substrate. The assay

determines the ability of compounds to inhibit phosphorylation of 4E-BP1 a well-known physiological substrate of mTOR. The immunocapture mTOR complex from HeLa cells is incubated with various concentrations of compounds and His-tag 4E-BP1 in kinase assay buffer prior to addition of ATP to start the reaction at RT. The reaction is stopped after 30 mins and the phosphorylated His-tag 4E-BP1 is captured on a Nickel-chelate plate overnight at 4°C. The phosphothreonine content of 4E-BP1 is then measured using phospho-4E-BP1 (T37/46) primary antibody and corresponding anti rabbit IgG HRP conjugated, secondary antibody. The secondary antibody has a reporter enzyme (eg. horseradish peroxidase, HRP) covalently attached, such that binding of primary antibody to phosphorylated 4E-BP1 can be determined quantitatively which is equal to the amount secondary antibody bound to it. The amount of secondary antibody can be determined by incubation with an appropriate HRP substrate.

The stock reagents used are as follows:

Cell lysis buffer:

[67] 40 mM HEPES, pH 7.5 containing 120 mM NaCl, 1mM EDTA, 10 mM sodium pyrophosphate, 10 mM β-glycerophosphate, 50 mM sodium fluoride, 1.5 mM sodium vanadate and 0.3% CHAPS.

Complete mini EDTA-free protease inhibitors (Roche, catalog #11 836 170 001)

HeLa cell pellets (Paragon Bioservices)

Protein G coated plates for immunoprecipitation (Pierce, catalog #15131)

mTOR (aka FRAP) N-19 antibody (Santa Cruz Biotechnology, catalog #sc-1549)

IP Wash Buffer:

[68] 50 mM HEPES, pH 7.5 containing 150 mM NaCl

Kinase Buffer:

[69] 20 mM HEPES, pH 7.5 containing 10 mM MgCl2, 4 mM MnCl2, 10 mM b-mercaptoethanol and 200 uM sodium vanadate. Make fresh for assay.

Recombinant 4E-BP1 (aka PHAS I) (Calbiochem, catalog #516675)

[70] Dilute 4E-BP1 stock (1 mg/mL) 120 times in kinase assay buffer to obtain a concentration of 0.25 ug/well in 30 uL

ATP Solution

[71] Prepare 330 uM ATP stock in kinase buffer

Ni-chelate Plate (Pierce, catalog #15242)

Antibody Dilution Buffer:

[72] TBST containing 5% skim milk

Phospho-4E-BP1 (T37/46) Antibody:

[73] 1:1000 dilution of phospho-4E-BP1 (T37/46) antibody (Cell Signaling Technology, catalog # 9459) in antibody dilution buffer

Donkey anti rabbit IgG, HRP conjugated

[74] 1:10,000 dilution of anti rabbit IgG HRP conjugated (GE Healthcare, Catalog# NA934) in antibody dilution buffer

HRP substrate:

[75] Chemiluminescent reagents (Pierce, catalog# 37074)

Assay Protocol:

[76] HeLa cell lysate was prepared in bulk by homogenizing 25g of cell pellet in 60mL of cell lysis buffer and then, centrifuged at 12,000rpm for 30min. The clear supernatant was transferred to fresh tube, aliquoted, quickly frozen and stored at –80°C until use.

[77] Protein G coated 96-well plate is washed once with lysis buffer and 50μL of diluted mTOR antibody is added to each well, and incubated at RT for 30-60min. Then, 50μg of HeLa cell lysate was added to each well in 50μL of lysis buffer and incubated at 4°C in a cold room on a shaker for 2-3h. Lysate was removed and the plate was washed with 100μL of complete lysis buffer for 3 times. The plate was further washed 2 times with 100μL of high salt wash buffer. Diluted 4E-BP1 (substrate) is added to each well in 30μL. The compounds were added in various concentrations in 5μL to each well. The drug concentrations varied from 30μM to 0.1μM. The final DMSO concentration was 1%. Only DMSO was added to positive control wells. For negative control wells, no ATP solution was added but instead 15μL of kinase buffer was added, the reaction was started by addition of ATP in 15μL to a final concentration of 100μM to rest of the wells except negative control wells. The reaction was carried out for 30min at RT. Then, 45μL of the reaction mixture was transferred to Ni-chelate plate and incubated overnight at 4°C. The plate was washed once with antibody dilution buffer and 50μL of diluted phospho-4E-BP1 antibody was added to each well, and incubated at RT for 1h. Then, the plate was washed 4 times with TBST and 50uL of diluted anti-rabbit secondary antibody was added to each plate, and incubated at RT for 1h. The plate was washed 4 times with 100μL of TBST. To each well, 50μL of Pierce Femto chemiluminescent reagent was added and the chemiluminescence was measured using victor machine.

[78] Comparison of the assay signals obtained in the presence of compound with those of positive and negative controls, allows the degree of inhibiton of phospho-4E-BP1 phosphorylation to be determined over a range of compound concentrations. These inhibiton values were fitted to a sigmoidal dose-response inhibition curve to determine the IC_{50} values (i.e. the concentration of the compound that inhibits phosphorylation of 4E-BP1 by 50%).

mTOR Cell-based Mechanistic Assay to Measure the Inhibition of Phosphorylation of 4E-BP1 (T37/46)

[79] MDA-MB-231 cells were plated in 96 well plates at $2x10^4$ cells/well in 90 ul of complete growth medium and incubated at 37°C O/N in a CO_2 incubator. Cells were treated with various compounds in a dose response manner for 3h at 37°C in a CO_2 incubator before making cell lysates to measure inhibition of phosphorylation of 4E-BP1 at T37/46. Cell lysates were transferred to a 96-well plate coated with 4E-BP1 antibodies to capture phospho-4E-BP1 (T37/46) and incubated

O/N at 4°C. The amount of phospho-4E-BP1 in each well is further measured by incubating the wells with anti-rabbit phospho-4E-BP1 (T37/46) antibodies and a corresponding goat anti-rabbit IgG conjugated to HRP. Amount of HRP present in each well is measured by a chemiluminescence method, which corresponds to amount of phospho-4E-BP1 in each well. IC_{50} values were determined using a 6-point dose response curve.

Biochemical Assay for Inhibition of IGF-1R Activity:

[80] IGF-1R inhibition was shown in a tyrosine kinase assay using purified GST fusion protein containing the cytoplasmic kinase domain of human IGF-1R expressed in Sf9 cells. This assay is carried out in a final volume of 90 µL containing 1-100nM (depending on the specific activity) in an Immulon-4 96-well plate (Thermo Labsystems) pre-coated with 1µg/well of substrate poly-glu-tyr (4:1 ratio) in kinase buffer (50mM Hepes, pH 7.4, 125mM NaCl, 24mM $MgCl_2$, 1mM $MnCl_2$, 1% glycerol, 200µM Na_3VO_4, and 2mM DTT). The enzymatic reaction was initiated by addition of ATP at a final concentration of 100µM. After incubation at room temperature for 30 minutes, the plates were washed with 2mM Imidazole buffered saline with 0.02% Tween-20. Then the plate was incubated with anti-phosphotyrosine mouse monoclonal antibody pY-20 conjugated with horse radish peroxidase (HRP) (Calbiochem) at 167ng/mL diluted in phosphate buffered saline (PBS) containing 3% bovine serum albumin (BSA), 0.5% Tween-20 and 200µM Na_3VO_4 for 2 hours at room temperature. Following 3X 250µL washes, the bound anti-phosphotyrosine antibody was detected by incubation with 100µl/well ABTS (Kirkegaard & Perry Labs, Inc.) for 30 minutes at room temperature. The reaction was stopped by the addition of 100µl /well 1% SDS, and the phosphotyrosine dependent signal was measured by a plate reader at 405/490 nm.

[81] The **EXAMPLES** of this invention demonstrated at least one of the following:

[82] I) Inhibited phosphorylation of 4E-BP1 by immunocaptured human mTOR as determined in the **Biochemical Assay for Inhibition of mTOR Activity** with IC_{50} values between 0.001µM and 11.00µM. It is advantageous that the IC_{50} values be less than 1.00µM and more advantageous that the IC_{50} values be below 0.1µM. Even more advantageous, the IC_{50} values be less than 0.01µM.

[83] II) Inhibited the phosphorylation of 4E-BP1 (T37/46) in the **mTOR Cell-based Mechanistic Assay** with IC_{50} values below 40µM.

[84] III) Inhibition of IGF-1R in the **Biochemical Assay for Inhibition of IGF-1R Activity** with IC_{50} values less than 15µM.

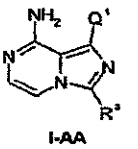
EXPERIMENTAL

[85] The following schemes, intermediates and examples serve to demonstrate how to synthesize compounds of this invention, but in no way limit the invention. Additionally, the

following abbreviations are used: Me for methyl, Et for ethyl, iPr or iPr for isopropyl, n-Bu for n-butyl, t-Bu for tert-butyl, Ac for acetyl, Ph for phenyl, 4Cl-Ph or (4Cl)Ph for 4-chlorophenyl, 4Me-Ph or (4Me)Ph for 4-methylphenyl, (p-CH3O)Ph for p-methoxyphenyl, (p-NO2)Ph for p-nitrophenyl, 4Br-Ph or (4Br)Ph for 4-bromophenyl, 2-CF3-Ph or (2CF3)Ph for 2-trifluoromethylphenyl, DMAP for 4-(dimethylamino)pyridine, DCC for 1,3-dicyclohexylcarbodiimide, EDC for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt for 1-hydroxybenzotriazole, HOAt for 1-hydroxy-7-azabenzotriazole, TMP for tetramethylpiperidine, n-BuLi for n-butyllithium, CDI for 1,1'-carbonyldiimidazole, DEAD for diethyl azodicarboxylate, PS-PPh3 for polystyrene triphenylphosphine, DIEA for diisopropylethylamine, DIAD for diisopropyl azodicarboxylate, DBAD for di-tert-butyl azodicarboxylate, HPFC for high performance flash chromatography, rt or RT for room temperature, min for minute, h for hour, Bn for benzyl, and LAH for lithium aluminum hydride.

[86] Accordingly, the following are compounds that are useful as intermediates in the formation of mTOR inhibiting **EXAMPLES.**

[87] The compounds of Formula I of this invention and the intermediates used in the synthesis of the compounds of this invention were prepared according to the following methods. Method A was used when preparing compounds of Formula I-AA

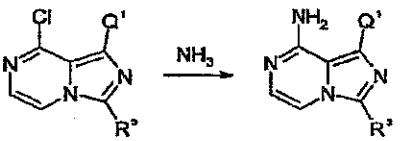


I-AA

as shown below in **Scheme 1:**

Method A:

Scheme 1



II I-AA

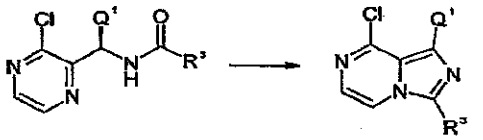
[88] where Q^1 and R^3 are as defined previously for compound of Formula I.

[89] In a typical preparation of compounds of Formula I-AA, compound of Formula II was reacted with ammonia in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvents were isopropanol and a mixture of THF and isopropanol. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 120°C. The above process to produce compounds of the present

invention was preferably carried in a sealed reaction vessel such as but not limited to a thick walled glass reaction vessel or a stainless steel Parr bomb. An excess amount of the reactant, ammonia, was preferably used.

[90] The compounds of Formula II of **Scheme 1** were prepared as shown below in **Scheme 2.**

Scheme 2



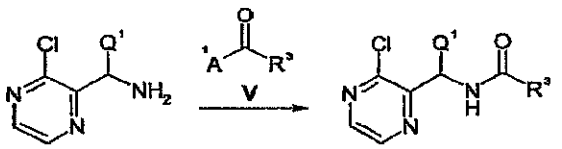
III II

where Q^1 and R^3 are as defined previously for compound of Formula I.

[91] In a typical preparation of a compound of Formula II, an intermediate of Formula III was treated with $POCl_3$ or the isolated "Vilsmeier salt" [CAS# 33842-02-3] in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; acetonitrile; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used or no solvent was used. The preferred solvents included methylene chloride and acetonitrile. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 20°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[92] The compounds of Formula III of **Scheme 2** were prepared as shown below in **Scheme 3**:

Scheme 3



IV III

where Q^1 and R^3 are as defined previously for compound of Formula I and A^1 = OH, alkoxy, or a leaving group such as a halogen or imidazole.

[93] In a typical preparation, of a compound of Formula III, a compound of Formula IV and compound of Formula V were reacted under suitable amide coupling conditions. Suitable conditions include but are not limited to treating compounds of Formula IV and V (when A^1 = OH) with coupling reagents such as DCC or EDC in conjunction with DMAP, HOBt, HOAt and the like. Suitable solvents for use in the above process included, but were not limited to, ethers such as

tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvents were methylene chloride and DMF. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about rt. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Alternatively, compounds of Formula IV and V (where A^1 = F, Cl, Br, I) were reacted with bases such as triethylamine or ethyldiisopropylamine and the like in conjunction with DMAP and the like. Suitable solvents for use in this process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was methylene chloride. The above process was carried out at temperatures between about –20°C and about 40°C. Preferably, the reaction was carried out between 0°C and 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of compounds of Formula IV and V (where A^1 = F, Cl, Br, I) and base and substochiometric amounts of DMAP were preferably used although higher or lower amounts were used if desired. Additionally, other suitable reaction conditions for the conversion of a compound of Formula IV to a compound of Formula III can be found in Larock, R. C. Comprehensive Organic Transformations, 2nd ed.; Wiley and Sons: New York, 1999, pp 1941-1949.

[94] The compounds of Formula IV of **Scheme 3** were prepared as shown below in **Scheme 4:**

Scheme 4



VI IV

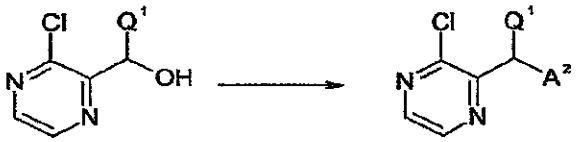
where Q^1 is as defined previously for compound of Formula I and A^2 = phthalimido or N_3.

[95] In a typical preparation, of a compound of Formula IV, a compound of Formula VI is reacted under suitable reaction conditions in a suitable solvent. When A^2 = phthalimido, suitable conditions include treatment of compound of Formula VI with hydrazine in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride; alcoholic solvents such

as methanol and ethanol. If desired, mixtures of these solvents may be used, however the preferred solvent was ethanol. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. In the transformation of compound of Formula VI to IV, if $A^2 = N_3$, then one skilled in the art would recognize that typical azide reduction conditions could be employed, including but not limited to PPh_3 and water or hydrogenation in the presence of a metal catalyst such as palladium.

[96] The compounds of Formula VI of **Scheme 4** were prepared as shown below in **Scheme 5**:

Scheme 5



VII **VI**

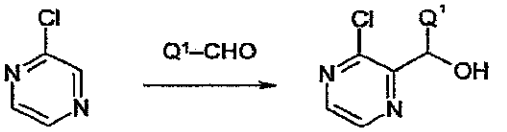
where Q^1 is as defined previously for compound of Formula I and A^2 = phthalimido or N_3.

[97] In a typical preparation of a compound of Formula VI (when A^2 = phthalimido), a compound of Formula VII was reacted with a phthalimide under typical Mitsunobu conditions in a suitable solvent in the presence of suitable reactants. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was THF. Suitable reactants for use in the above process included, but were not limited to, triphenylphosphine and the like, and an azodicarboxylate (DIAD, DEAD, DBAD). The preferred reactants were triphenylphosphine or resin-bound triphenylphosphine (PS-PPh_3), and DIAD. The above process may be carried out at temperatures between about -78°C and about 100°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Generally, one equivalent or a slight excess, 1.1 equivalents, of triphenylphosphine, DIAD and phthalimide was used per equivalent of compound of Formula VII. Additionally, compound of Formula VII can be reacted with Ts_2O, Ms_2O, Tf_2O, TsCl, MsCl, or $SOCl_2$ in which the hydroxy group is converted to a leaving group such as its respective tosylate, mesylate, triflate, or halogen such as chloro and subsequently reacted with an amine equivalent such as $NH(Boc)_2$, phthalimide, potassium phthalimide, or sodium

azide. Conversion of the amine equivalents by known methods such as by treating under acidic conditions ($NH(Boc)_2$), with hydrazine (phthalimide) as shown in **Scheme 4**, or with triphenylphosphine/water (azide) will afford the desired amine as shown in **Scheme 4**.

[98] The compounds of Formula VII of **Scheme 5** were prepared from aldehydes Q^1–CHO and a 2-chloropyrazine VIII as shown below in **Scheme 6**:

Scheme 6



VIII VII

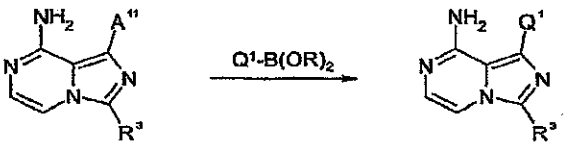
where Q^1 is as defined previously for compound of Formula I.

[99] In a typical preparation, of a compound of Formula VII, a compound of Formula VIII was reacted under suitable reaction conditions in a suitable solvent with a compound of Formula Q^1–CHO. Suitable conditions included but were not limited to treating compounds of Formula VIII with a base such as lithium tetramethylpiperidide (Li-TMP) followed by treating with compounds of Formula Q^1–CHO. Lithium tetramethylpiperidide may be prepared by reacting tetramethylpiperidine with n-butyllithium at –78°C and warming up to 0°C. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like. Polar solvents such as hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), and the like may be added if necessary. If desired, mixtures of these solvents were used, however, the preferred solvent was THF. The above process may be carried out at temperatures between about –80°C and about 20°C. Preferably, the reaction was carried out at –78°C to 0°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[100] The compounds of Formula I of this invention and the intermediates used in the synthesis of the compounds of this invention were also prepared according to the following methods. Method AA was used when preparing compounds of Formula I-AA from compound of Formula I-AAA as shown below in **Scheme 7**:

Method AA:

Scheme 7



I-AAA I-AA

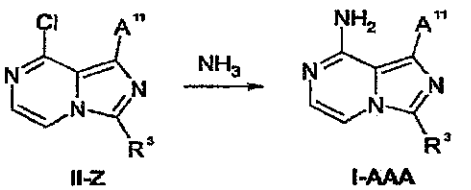
where Q^1 and R^3 are as defined previously for compound of Formula I, A^{11} = halogen such as Cl, Br, or I and $B(OR)_2$ = suitable boronic acid/ester.

[101] In a typical preparation of compounds of Formula I-AA, compound of Formula I-AAA was reacted with a suitable boronic acid/ester (Q^1-$B(OR)_2$) in a suitable solvent via typical Suzuki coupling procedures. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, dioxane, dimethoxyethane, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was dimethoxyethane/water. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 60°C and about 100°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[102] One skilled in the art will appreciate that alternative methods may be applicable for preparing compounds of Formula I-AA from I-AAA. For example, compound of Formula I-AAA could be reacted with a suitable organotin reagent Q^1–$SnBu_3$ or the like in a suitable solvent via typical Stille coupling procedures.

[103] The compounds of Formula I-AAA of **Scheme 7** were prepared as shown below in **Scheme 8**.

Scheme 8



II-Z I-AAA

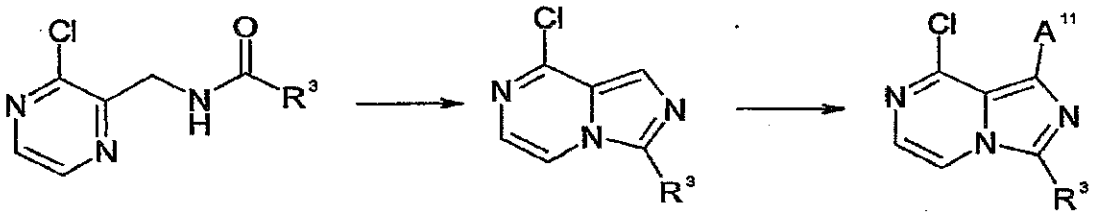
where R^3 is as defined previously for compound of Formula I and A^{11} = halogen such as Cl, Br, or I.

[104] In a typical preparation of compounds of Formula I-AAA, compound of Formula II-Z was reacted with ammonia in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvents were isopropanol and a mixture of THF and isopropanol. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 120°C. The above process to produce compounds of the present

invention was preferably carried in a sealed reaction vessel such as but not limited to a thick walled glass reaction vessel or a stainless steel Parr bomb. An excess amount of the reactant, ammonia, was preferably used.

[105] The compounds of Formula II-Z of **Scheme 8** were prepared as shown below in **Scheme 9.**

Scheme 9

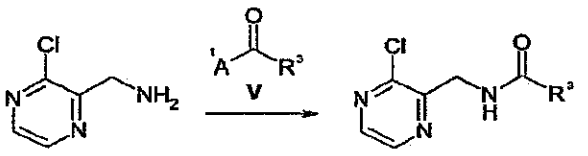


where R^3 is as defined previously for compound of Formula I and A^{11} = halogen such as Cl, Br, or I.

[106] In a typical preparation of a compound of Formula II-Z, intermediate III-Z was converted to compound of Formula II-Z'. Intermediate of Formula III-Z was treated with $POCl_3$ in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; acetonitrile; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used. The preferred solvents included methylene chloride and acetonitrile. The above process was carried out at temperatures between about –78°C and about 120°C. Preferably, the reaction was carried out between 20°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. In the conversion of compound of Formula III-Z to II-Z', suitable halogenating agent were used, but were not limited to, Br_2, I_2, Cl_2, *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-iodosuccinimide. The preferred halogenating agent was *N*-iodosuccinimide. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was DMF. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 75°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[107] The compounds of Formula III-Z of **Scheme 9** were prepared as shown below in **Scheme 10:**

Scheme 10



IV-Z III-Z

where R^3 is as defined previously for compound of Formula I and A^1 = OH, alkoxy, or a leaving group such as chloro or imidazole.

[108] In a typical preparation, of a compound of Formula III-Z, a compound of Formula IV-Z and compound of Formula V were reacted under suitable amide coupling conditions. Suitable conditions include but are not limited to treating compounds of Formula IV-Z and V (when A^1 = OH) with coupling reagents such as DCC or EDC in conjunction with DMAP, HOBt, HOAt and the like. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was methylene chloride. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Additionally, if compound of Formula IV-Z was a salt or bis-salt, a suitable base was required and included, but was not limited to, diisopropylethylamine or triethylamine. Alternatively, compounds of Formula IV-Z and V (where A^1 = F, Cl, Br, I) were reacted with bases such as triethylamine or ethyldiisopropylamine and the like in conjunction with DMAP and the like. Suitable solvents for use in this process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was methylene chloride. The above process was carried out at temperatures between about –20°C and about 40°C. Preferably, the reaction was carried out between 0°C and 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of compounds of Formula IV-Z and V (where A^1 = F, Cl, Br, I) and base and substochiometric amounts of DMAP were preferably used although higher or lower amounts were used if desired. Additionally, other suitable reaction conditions for the conversion of an amine (compound of Formula IV-Z) to an amide (compound of

Formula III-Z) can be found in Larock, R. C. Comprehensive Organic Transformations, 2nd ed.; Wiley and Sons: New York, 1999, pp 1941-1949.

[109] The compounds of Formula IV-Z of **Scheme 10** were prepared as shown below in **Scheme 11:**

Scheme 11



VI-Z IV-Z

where A^2 is phthalimido or N_3.

[110] In a typical preparation, of a compound of Formula IV-Z, a compound of Formula VI-Z is reacted under suitable reaction conditions in a suitable solvent. When A^2 = phthalimido, suitable conditions include treatment of compound of Formula VI-Z with hydrazine in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride; alcoholic solvents such as methanol and ethanol. If desired, mixtures of these solvents may be used, however the preferred solvent was ethanol. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[111] The compounds of Formula VI-Z of **Scheme 11** were prepared as shown below in **Scheme 12:**

Scheme 12



VII-Z VI-Z

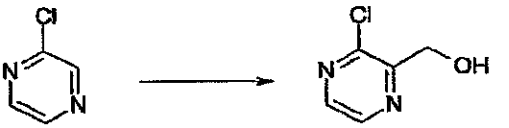
where A^2 = phthalimido or N_3.

[112] In a typical preparation of a compound of Formula VI-Z (when A^2 = phthalimido), a compound of Formula VII-Z was reacted with a phthalimide under typical Mitsunobu conditions in a suitable solvent in the presence of suitable reactants. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents

were used, however, the preferred solvent was THF. Suitable reactants for use in the above process included, but were not limited to, triphenylphosphine and the like, and an azodicarboxylate (DIAD, DEAD, DBAD). The preferred reactants were triphenylphosphine or resin-bound triphenylphosphine (PS-PPh_3) and DIAD. The above process may be carried out at temperatures between about –78°C and about 100°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Generally, 1.0 or 1.1 equivalents of triphenylphosphine, DIAD and phthalimide was used per equivalent of compound of Formula VII-Z. Additionally, compound of Formula VII-Z can be reacted with Ts_2O, Ms_2O, Tf_2O, TsCl, MsCl, or $SOCl_2$ in which the hydroxy group is converted to a leaving group such as its respective tosylate, mesylate, triflate, or halogen such as chloro and subsequently reacted with an amine equivalent such as $NH(Boc)_2$, phthalimide, potassium phthalimide or sodium azide. Conversion of the amine equivalents by known methods such as by treating under acidic conditions ($NH(Boc)_2$), with hydrazine (phthalimide) as shown in **Scheme 4**, or with triphenylphosphine/water (azide) will afford the desired amine as shown in **Scheme 4**.

[113] The compounds of Formula VII-Z of **Scheme 12** were prepared from 2-chloropyrazine VIII as shown below in **Scheme 13**:

Scheme 13



VIII VII-Z

[114] In a typical preparation, of a compound of Formula VII-Z, a compound of Formula VIII was reacted under suitable reaction conditions in a suitable solvent. Suitable reaction conditions included, but were not limited to, treating compounds of Formula VIII with a base such as lithium tetramethylpiperidide (Li-TMP) followed by treatment with a reagent containing a carbonyl equivalent followed by treatment with a suitable reducing agent. Lithium tetramethylpiperidide may be prepared by reacting tetramethylpiperidine with n-butyllithium at –78°C and warming up to 0°C. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like. Polar solvents such as hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), and the like may be added if necessary. If desired, mixtures of these solvents were used, however, the preferred solvent was THF. Suitable carbonyl equivalent reagents include, but are not limited to, formamides such as DMF or suitable chloroformate such as methyl or ethyl chloroformate. After addition of the suitable carbonyl equivalent reagent, the reaction if charged with a polar protic solvent such as, but not limited to,

methanol or ethanol followed by treatment with a suitable reducing agent such as sodium borohydride. The above process may be carried out at temperatures between about –80°C and about 20°C. Preferably, the reaction was carried out at –78°C to 0°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[115] The compounds of Formula X-Z (Q^1–CHO) of **Scheme 6** were prepared as shown below in **Scheme 14:**

Scheme 14



where Q1 is as defined previously for compound of Formula I.

[116] In a typical preparation, of a compound of Formula X-Z (Q^1–CHO), a compound of Formula IX-Z (Q^1–CH_3) was reacted with a suitable oxidizing agent under suitable reaction conditions. Suitable oxidizing agents included, but were not limited to, selenium dioxide. Suitable reaction conditions for use in the above process included, but were not limited to, heating a mixture of selenium dioxide and compounds of Formula IX-Z (Q^1–CH_3) neat or in a suitable solvent such as, but not limited to, chlorobenzene or sulpholane. The above process may be carried out at temperatures between about 120°C and about 180°C. Preferably, the reaction was carried out at 150°C to 165°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Preferably, 1–1.5eq. selenium dioxide were used although higher or lower amounts were used if desired. Alternatively, a compound of Formula IX-Z (Q^1–CH_3) was reacted first with a halogenating agent and a radical initiator under suitable reaction conditions in a suitable solvent to give a compound of Formula Q^1–CH_2–Hal (wherein Hal = Cl or Br) that was then further reacted with DMSO and a base under suitable reaction conditions to give a compound of Formula X-Z (Q^1–CHO). Suitable halogenating agents included, but were not limited to, bromine, N-bromosuccinimide, and chlorine. Preferably, N-bromosuccinimide was used. Suitable radical initiators included, but were not limited to, 2,2'-azobisisobutyronitrile (AIBN) and UV light. Preferably, AIBN was used. Preferably, carbon tetrachloride was used as solvent for the halogenation step, although other halogenated solvents may be added. The halogenation may be carried out at temperatures between about 60°C and about 100°C. Preferably, the reaction was carried out at about 80°C. Suitable bases included, but were not limited to, sodium hydrogencarbonate, sodium dihydrogenphosphate, disodium hydrogenphosphate, and collidine. Preferably, sodium hydrogencarbonate was used. DMSO was preferably used as solvent although other solvents may be added. The second step may be carried out at temperatures between about 40°C and about 140°C. Preferably, the reaction was carried out at about 90°C. Additionally,

other suitable reaction conditions for the conversion of Q^1–CH_3 to Q^1–CHO can be found in Larock, R. C. Comprehensive Organic Transformations, 2nd ed.; Wiley and Sons: New York, 1999, pp 1205–1207 and 1222–1224.

[117] The compounds of Formula XIV-Z (Q^1-$B(OR)_2$) of **Scheme 7** were prepared as shown below in **Scheme 15**:

Scheme 15

$$Q^1\text{-}A^{111} \longrightarrow Q^1\text{-}B(OR)_2$$

XIII-Z **XIV-Z**

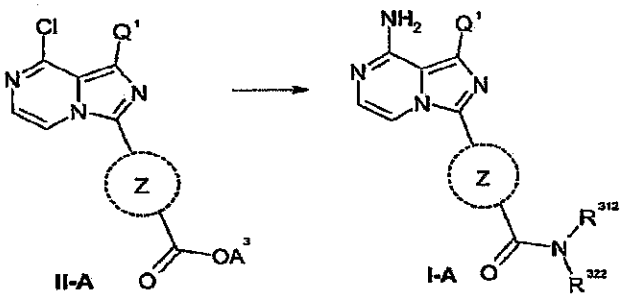
where Q^1 is as defined previously for compound of Formula I, A^{111} = OTf or halogen such as Cl, Br, or I and $B(OR)_2$ = suitable boronic acid/ester.

[118] In a typical preparation, of a compound of Formula XIV-Z (Q^1– $B(OR)_2$), a compound of Formula XIII-Z (Q^1– A^{111}) was reacted with a suitable metal catalyst and a suitable boronating agent under suitable reaction conditions. Suitable metal catalyst agents included, but were not limited to, $Pd(OAc)_2$ in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. Suitable boronating agents included, but were not limited to, bis(pinacolato)diboron. Suitable reaction conditions for use in the above process included, but were not limited to, heating a mixture of $Pd(OAc)_2$, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, KOAc, and bis(pinacol)borane in a suitable solvent such as, but not limited to, THF. The above process may be carried out at temperatures between about 20°C and about 100°C. Preferably, the reaction was carried out at 60°C to 80°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Preferably, 2–3eq. KOAc, 1–1.5eq. bis(pinacol)borane, 0.03–1eq. $Pd(OAc)_2$, and 0.09–3eq. 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride were used although higher or lower amounts were used if desired. Additionally, other suitable reaction conditions for the conversion of Q^1–A^{111} to Q^1– $B(OR)_2$ can be found in the literature which involve a variety of Q^1–A^{111} or aryl/heteroarylhalides and a variety of conditions (Biooganic & Medicinal Chemistry Letters, 2003, 12(22), 4001; Biooganic & Medicinal Chemistry Letters, 2003, 13(18), 3059; Chemical Communications (Cambridge, UK), 2003, 23, 2924; Synthesis, 2002, 17, 2503; Angewandte Chemie, International Ed., 2002, 41(16), 3056; Journal of the American Chemical Society, 2002, 124(3), 390; Organic Letters, 2002, 4(4), 541; Tetrahedron, 2001, 57(49), 9813; Journal of Organic Chemistry, 2000, 65(1), 164; Journal of Organic Chemistry, 1997, 62(19), 6458; Journal of Organometallic Chemistry, 1983, 259(3), 269). In some cases, compounds of Formula XIII-Z (Q^1–A^{111}) and XIV-Z (Q^1–$B(OR)_2$) are commercially available or synthesized according to literature procedures. In cases where neither are available, compounds of Formula XIII-Z (Q^1–A^{111}) and XIV-Z (Q^1– $B(OR)_2$) were synthesized via procedures described in the experimental section herein.

[119] Both R^3 and Q^1 in the compounds described herein in some instances contain functional groups that can be further manipulated. It would be appreciated by those skilled in the art that such manipulation of functional groups can be accomplished with key intermediates or with late stage compounds. Such functional group transformations are exemplified in the following **Schemes 16-26** as well as in the experimental section but are in no way meant to limit the scope of such transformations. Additionally, the chemistry shown in **Schemes 16-26** can also be applied to compounds of I-AAA, II-Z, and II-Z'.

[120] The compounds of Formula I-A (compounds of Formula I-AA where $R^3 = Z—CONR^{312}R^{322}$) were prepared as shown below in **Scheme 17:**

Scheme 16



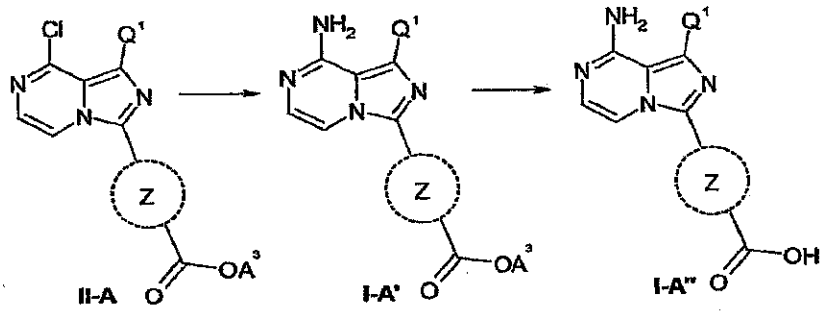
where Q^1, R^{312} and R^{322} are as defined previously for compound of Formula I and A^3 = hydrogen or alkyl such as methyl or ethyl.

[121] In a typical preparation of compound of Formula I-A, when A^3 = alkyl and R^{312} and R^{322} were both equal to H, reaction of compound of Formula II-A (compounds of Formula II where $R^3 = Z—CO_2A^3$) with ammonia in a suitable solvent, afforded compound of Formula I-A. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvents were isopropanol and a mixture of isopropanol/THF. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 120°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Additionally, in a typical preparation of compound of Formula I-A, compound of Formula II-A (when A^3 = H) was reacted with $HNR^{312}R^{322}$ followed by ammonia in a suitable solvent. When A^3 = H, typical coupling procedures as described in **Scheme 3** (conversion of CO_2H to COCl via treatment with $SOCl_2$ or oxalyl chloride followed by reaction with $HR^{312}R^{322}$ or treatment of CO_2H and $HR^{312}R^{322}$ with EDC or DCC in conjunction with DMAP, HOBT, or HOAt and the like) were employed to afford the

transformation of a carboxylic acid to an amide. When A^3 = alkyl such as methyl or ethyl, treatment of the ester with $Al(NR^{312}R^{322})$ afforded conversion of CO_2A^3 to $CO(NR^{312}R^{322})$. Subsequent treatment with ammonia afforded compounds of Formula I-A.

[122] The compounds of Formula I-A' (compounds of Formula I-AA where $R^3 = Z—CO_2A^3$) and I-A'' (compounds of Formula I-AA where $R^3 = Z—CO_2H$) were prepared as shown below in **Scheme 17**:

Scheme 17



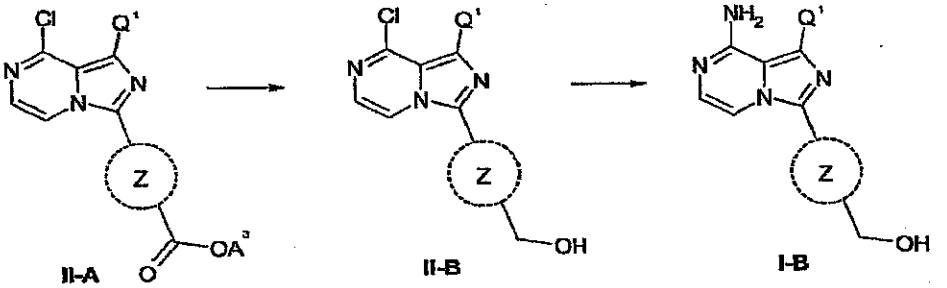
where Q^1 is as defined previously for compounds of Formula I and A^3 = alkyl such as methyl or ethyl.

[123] In a typical preparation of compound of Formula I-A', compound of Formula II-A was reacted with ammonia in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was isopropanol. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 100°C and about 120°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. In most cases, the reactions were run in a sealed tube. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Typically, an excess of ammonia was used and the reaction was monitored in order to ensure that additional of ammonia to the ester moiety did not occur to an appreciable extent. Additionally, in a typical preparation of compound of Formula I-A'', compound of Formula I-A' was reacted under typical saponification conditions such as NaOH in $THF/H_2O/MeOH$. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was a mixture of $THF/H_2O/MeOH$. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between rt and about 60°C. The above process to

produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[124] The compounds of Formula II-B (compounds of Formula II where $R^3 = Z—CH_2OH$) and I-B (compounds of Formula I-AA where $R^3 = Z—CH_2OH$) were prepared as shown below in **Scheme 18:**

Scheme 18

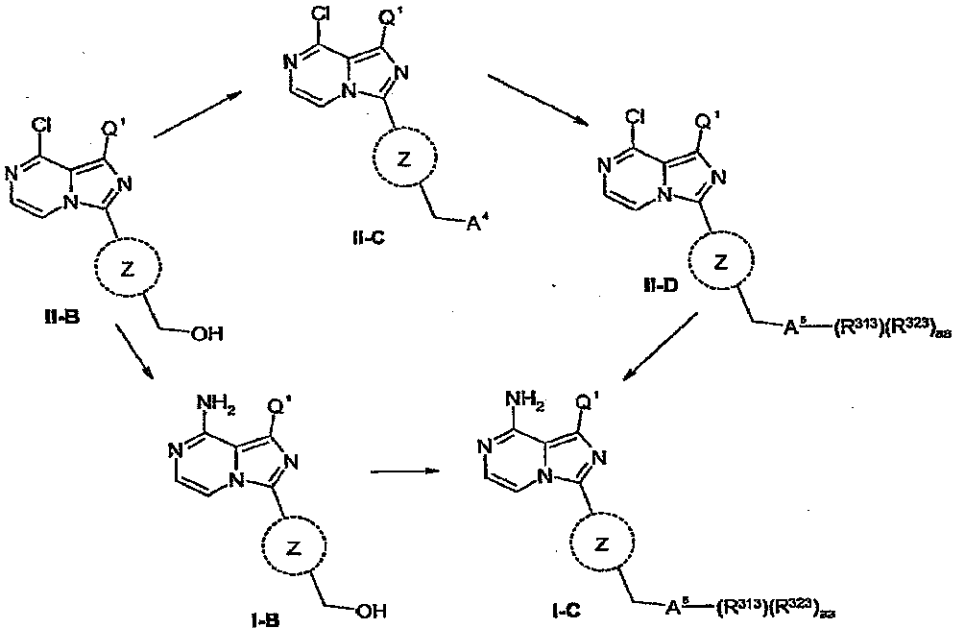


where Q^1 is as defined previously for compound of Formula I and A^3 = hydrogen or alkyl such as methyl or ethyl.

[125] In a typical preparation of compound of Formula I-B, compound of Formula II-A is treated with a suitable reducing agent such as lithium aluminum hydride in a suitable solvent, such as THF to afford compound of Formula II-B. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used. The preferred solvent was THF. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 0°C and about 50°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Subsequent treatment of compound of Formula II-B under previously described ammonolysis conditions (ammonia in isopropanol in a sealed tube at 120°C), afforded compound of Formula I-B.

[126] The compounds of Formula II-C (compounds of Formula II where $R^3 = Z—CH_2A^4$), II-D (compounds of Formula II where $R^3 = Z—CH_2A^5(R^{313})(R^{323})_{aa}$), I-B (compounds of Formula I-AA where $R^3 = Z—CH_2OH$) and I-C (compounds of Formula I-AA where $R^3 = Z—CH_2A^5(R^{313})(R^{323})_{aa}$) were prepared as shown below in **Scheme 19:**

Scheme 19

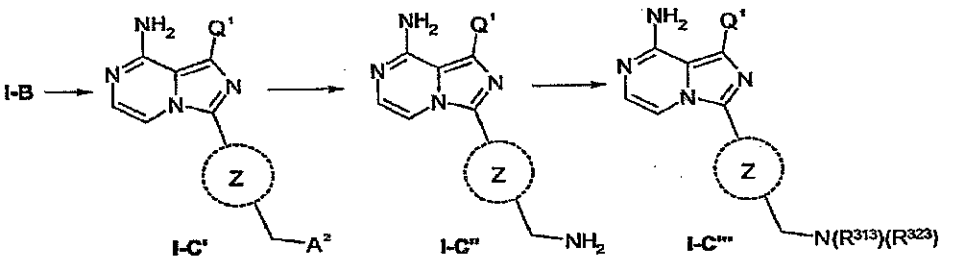


where Q^1, R^{313}, and R^{323} are as defined previously for compound of Formula I; A^4 = suitable leaving group such as OTs, OMs, OTf, or halo such as chloro, bromo, or iodo; d = 0 or 1; and A^5 = N, O or S.

[127] In a typical preparation of compound of Formula I-C, the hydroxy group of compound of Formula II-B was converted to a suitable leaving group, A^4, such as Cl or OTs, OMs, or OTf, by reaction with $SOCl_2$ or Ts_2O, Ms_2O, or Tf_2O to afford compound of Formula II-C. Reaction of compound of Formula II-C with $HA^5(R^{313})(R^{323})_{aa}$ afforded compound of Formula II-D. Subsequent reaction of compound of Formula II-D under previously described ammonolysis conditions afforded compound of Formula I-C. Additionally, compound of Formula II-B was converted to compound of Formula I-B as described previously in **Scheme 18**. Further conversion of compound of Formula I-B to compound of Formula I-C was accomplished by following the previously described conditions for the conversion of compound of Formula II-B to compound of Formula II-C and the further conversion of compound of Formula II-C to compound of Formula II-D (in the net conversion of OH to $A^5(R^{313})(R^{323})_{aa}$). Furthermore, compound of Formula II-B can be directly converted to compound of Formula II-D by treating compound of Formula II-B with various alkylating agent or with phenols via the Mitsunobu reaction to afford compounds Formula II-D (compounds of Formula II where $R^3 = CH_2\text{-}Z\text{-}A^5(R^{313})(R^{323})_{aa}$) in which A^5 = O, aa = 0, and R^{313} = alkyl or aryl).

[128] The compounds of Formula I-C' (compounds of Formula I-AA where R^3 = Z—CH_2—A^2), I-C'' (compounds of Formula I-AA where R^3 = Z—CH_2—NH_2), and I-C''' (compounds of Formula I-AA where R^3 = Z—CH_2—$N(R^{313})(R^{323})$) were prepared as shown below in **Scheme 20:**

Scheme 20

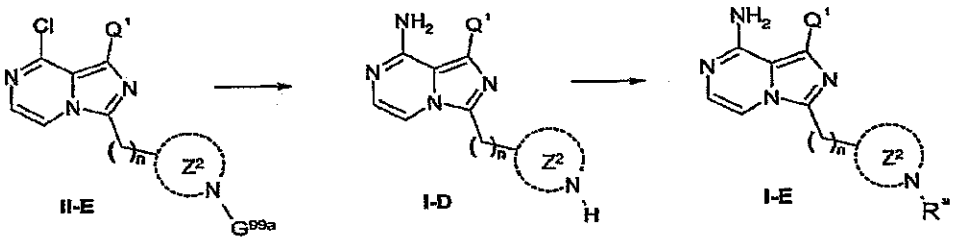


where Q^1, R^{313}, and R^{323} are as defined previously for compound of Formula I and A^2 = phthalimido or N_3.

[129] In a typical preparation of compounds of Formula I-C', I-C'', and I-C''', the hydroxy group of compound of Formula I-B was converted to A^2, following the procedures as described in **Scheme 5** for the conversion of compound of Formula VII to compound of Formula VI. Reaction of compound of Formula I-C' under conditions described in **Scheme 4** afforded compound of Formula I-C''. Reaction of compound of Formula I-C'' with, but not limited to various alkylating agents, various aldehydes/ketones under reductive amination conditions, various acylating agents such as acetic anhydride, benzoyl chlorides, or with carboxylic acids in the presence of EDC or DCC with HOBT or HOAT, or with sulphonylating agents such as Ts_2O or $MeSO_2Cl$ afforded compounds of Formula I-C'''. For example, in a typical preparation of compounds of Formula I-C''', a compound of Formula I-C'' is treated with a suitable acylating agent in the presence of a suitable base in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was chloroform. Suitable bases for use in the above process included, but were not limited to, trialkylamines such as diisopropylethylamine, triethylamine, or resin bound trialkylamines such as PS-DIEA. The preferred base was PS-DIEA. In the case where the suitable acylating agent was acetic anhydride, the conversion of compound of Formula I-C'' to compound of Formula I-C''' where R^{313} = H and R^{323} = $COCH_3$ was accomplished. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 0°C and about 20°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[130] The compounds of Formula I-D (compounds of Formula I-AA where R^3 = $(CH_2)_n$—Z^2—H and Z^2 is a heterocyclyl ring containing a nitrogen atom connected to H) and I-E (compounds of Formula I-AA where R^3 = $(CH_2)_n$—Z^2—R^{31} and Z^2 is a heterocyclyl ring containing a nitrogen atom connected to R^{31}) were prepared as shown below in **Scheme 21:**

Scheme 21

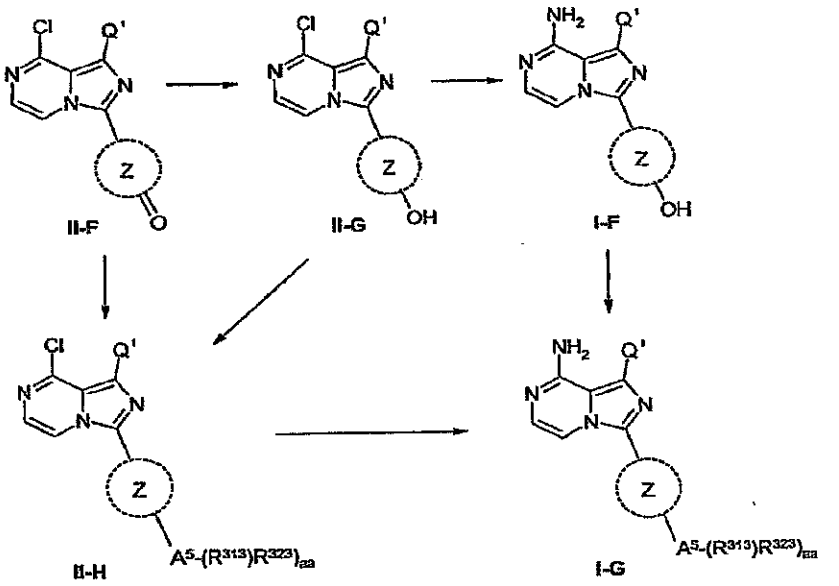


where Q^1 and R^{31} are as defined previously for compound of Formula I, G^{99a} is $C(=O)A^6$ or CO_2A^6, n = 0-5, and A^6 = alkyl, aryl, or aralkyl.

[131] In a typical preparation of compound of Formula I-E, compound of Formula II-E is treated with suitable reagents capable of converting N—G^{99a} to N—H and therefore afford compound of Formula I-D. For example, treatment of compound of Formula II-E (when G^{99a} is equal to CO_2Bn) under previously described ammonolysis conditions followed by treatment with concentrated HCl and a suitable basic workup, affords compound of Formula I-D. Compound of Formula I-D can be subjected to various conditions including but not limited to reductive aminations, alkylations and ar(hetar)ylations, and acylations to afford amides, ureas, guanidines, carbamates, thiocarbamates, sulphonamides, and variously substituted nitrogen adducts to afford the net conversion of NH to NR^2.

[132] The compounds of Formula II-G (compounds of Formula II where $R^3 = Z^3$—OH), II-H (compounds of Formula II where $R^3 = Z$—$A^5(R^{313})(R^{323})_{aa}$), I-F (compounds of Formula I-AA where $R^3 = Z$—OH), and I-G (compounds of Formula I-AA where $R^3 = Z$—$A^5(R^{313})(R^{323})_{aa}$) were prepared as shown below in **Scheme 22:**

Scheme 22

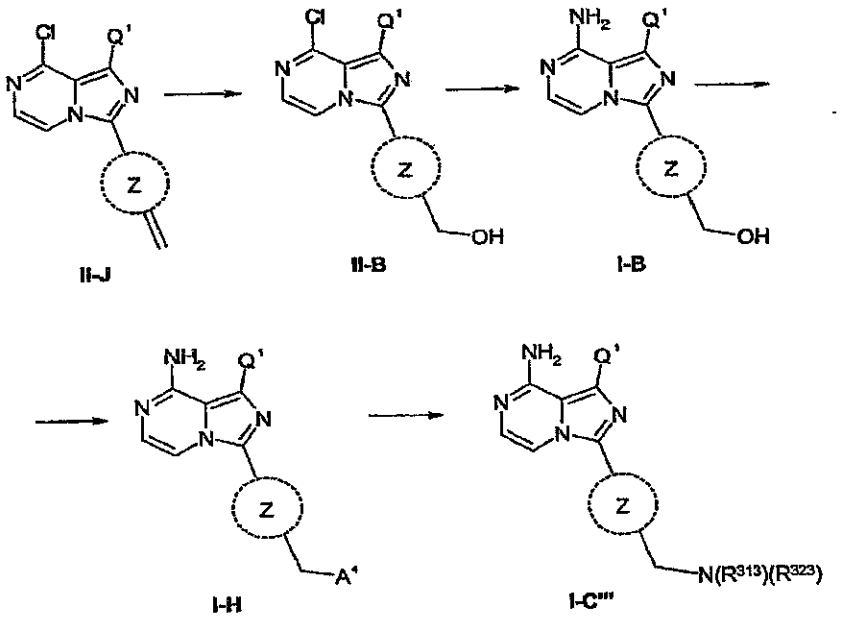


where Q^1, R^{313}, and R^{323} are as defined previously for compound of Formula I; aa = 0 or 1; and A^5 = N, O or S.

[133] In a typical preparation of compound of Formula I-F and I-G, the following transformations occurred: Compound of Formula II-F was reduced with a suitable reducing agent in a suitable solvent, such as sodium borohydride in methanol to afford compound of Formula II-G. Compound of Formula II-G was subjected to previously described ammonolysis conditions to afford compound of Formula I-F. Additionally, compounds of Formula II-F can be reacted with various amines under reductive amination conditions ($NaBH_3CN$ or $NaBH(OAc)_3$ with $HA^5(R^{313})(R^{323})_{aa}$ where d = 0, A^5 = N, and R^{313} and R^{323} are as previously described for compound of Formula I) to afford compounds of Formula II-H where d = 0, A^5 = N, and R^{313} and R^{323} are as previously described for compound of Formula I. Subsequent reaction of compounds of Formula II-H (compounds of Formula II where $R^3 = Z—A^5(R^{313})(R^{323})_{aa}$ where d = 0, A^5 = N, and R^{313} and R^{323} are as previously described for compound of Formula I) with previously described ammonolysis conditions afforded compounds of Formula I-G. Furthermore, compounds of Formula II-H from II-G and I-G from I-F can be synthesized according to the conditions described in **Scheme 19** for the transformations of II-B to II-D and I-B to I-C, respectively.

[134] The compounds of Formula I-C''' (compounds of Formula I-AA where $R^3 = Z—CH_2—N(R^{313})(R^{323})$) were prepared as shown below in **Scheme 23**:

Scheme 23



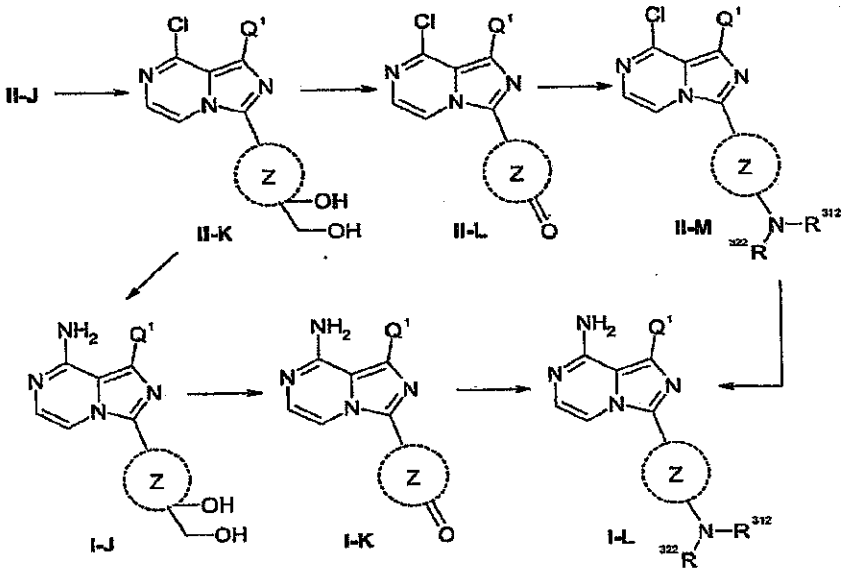
where Q', R^{313}, and R^{323} are as defined previously for compound of Formula I and A^4 = suitable leaving group such as Cl, OTs, OMs or OTf.

[135] In a typical preparation of compound of Formula I-C''' (compounds of Formula I-AA where $R^3 = Z—CH_2—N(R^{313})(R^{323})$), the following transformations occurred: Compounds of Formula II-J (compounds of Formula II where $R^3 = Z{=}CH_2$) were reacted with a suitable hydroborating agent such as diborane, 9-borabicyclo[3.3.1]nonane (9-BBN), catecholborane and the

like, in a suitable solvent such as THF followed by treatment with an suitable oxidizing agent such as hydrogen peroxide in basic aqueous solution or $NaBO_3 \cdot H_2O$ to afford compounds of Formula II-B. Further reaction of compounds of Formula II-B with previously described ammonolysis conditions afforded compounds of Formula I-B. The hydroxy group of compounds of Formula I-B was then converted to a suitable leaving group, A^4, such OTs, OMs, or OTf, by reaction with Ts_2O, Ms_2O, or Tf_2O, respectively, to afford compounds of Formula I-H. Further reaction of compounds of Formula I-H with $HN(R^{313})(R^{323})$ where R^{313} and R^{323} are as previously described for compounds of Formula I afforded compound of Formula I-C''' (compounds of Formula I-AA where $R^3 = Z—CH_2—N(R^{313})(R^{323})$).

[136] The compounds of Formula I-J (compounds of Formula I-AA where $R^3 = Z—OH(CH_2OH)$), I-K (compounds of Formula I-AA where $R^3 = Z{=}O$), and I-L (compounds of Formula I-AA where $R^3 = Z—NR^{313}R^{323}$) were prepared as shown below in **Scheme 24**:

Scheme 24



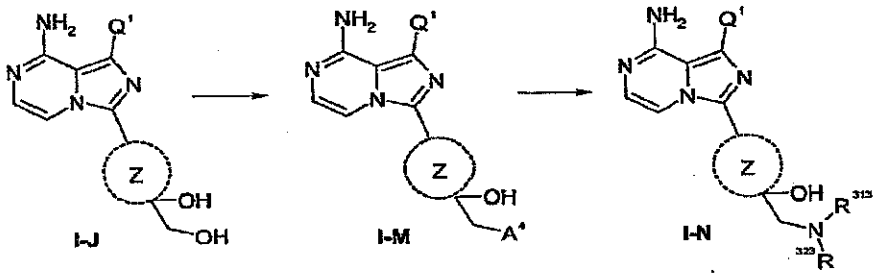
[137] where Q^1, R^{312} and R^{322} are as defined previously for compound of Formula I.

[138] In a typical preparation of compound of Formula I-J (compounds of Formula I-AA where $R^3 = Z—OH(CH_2OH)$), I-K (compounds of Formula I-AA where $R^3 = Z{=}O$), and I-L (compounds of Formula I-AA where $R^3 = Z—NR^{312}R^{322}$) compound of Formula II-J was treated under (compounds of Formula II where $R^3 = Z{=}CH_2$) was reacted with a suitable dihydroxylating agent such as osmium tetraoxide in the presence of NMO in a suitable solvent such as THF to afford compound of Formula II-K (compounds of Formula II where $R^3 = Z—OH(CH_2OH)$) as a mixture of cis and trans isomers. Compounds of Formula II-K (compounds of Formula II where $R^3 = Z—OH(CH_2OH)$) were treated with a suitable oxidizing agent, such as but not limited to, $NaIO_4$, converting the diol into a ketone moiety, affording compound of Formula II-L (compounds of Formula II where $R^3 = Z{=}O$). Compound of Formula II-L (compounds of Formula II where $R^3 =$

Z=O) was then treated under typical reductive amination conditions, involving a suitable amine, $HNR^{312}R^{322}$ and a suitable reducing agent, such as but not limited to, $NaBH(OAc)_3$ or $NaBH(CN)_3$, affording compound of Formula II-M (compounds of Formula II where $R^3 = Z—NR^{312}R^{322}$). Compound of Formula II-M (compounds of Formula II where $R^3 = Z—NR^{312}R^{322}$) was treated under ammonolysis conditions, ammonia in isopropanol in a stainless steel bomb at 110 °C, to afford compound of Formula I-L (compounds of Formula I-AA where $R^3 = Z—NR^{312}R^{322}$). Moreover, compound of Formula II-K (compounds of Formula II where $R^3 = Z—OH(CH_2OH)$) was treated under the ammonolysis conditions described above to afford compound of Formula I-J (compounds of Formula I-AA where $R^3 = Z—OH(CH_2OH)$) as a mixture of isomers. Compound of Formula I-J (compounds of Formula I-AA where $R^3 = Z—OH(CH_2OH)$) was treated with a suitable oxidizing agent, such as but not limited to, $NaIO_4$, converting the diol into a ketone moiety, affording compound of Formula I-K (compounds of Formula I-AA where $R^3 = Z=O$), which was treated under the typical reductive amination conditions described above to afford compound of Formula I-L (compounds of Formula I-AA where $R^3 = Z—NR^{312}R^{322}$).

[139] The compounds of Formula I-N (compounds of Formula I-AA where $R^3 = Z—OH(CH_2NR^{313}R^{323})$) were prepared as shown below in **Scheme 25**:

Scheme 25

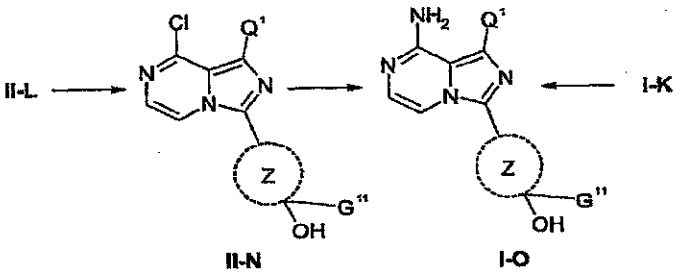


[140] where Q^1, R^{313}, and R^{323} are as defined previously for compound of Formula I; A^4 = suitable leaving group such as OTs, OMs, or OTf.

[141] In a typical preparation of compounds of Formula I-N (compounds of Formula I-AA where $R^3 = Z—OH(CH_2NR^{313}R^{323})$), the primary hydroxyl group of compound of Formula I-J (compounds of Formula I-AA where $R^3 = Z—OH(CH_2OH)$) was converted to a suitable leaving group, A^4, such as OTs, OMs, or OTf, by reaction with Ts_2O, Ms_2O, or Tf_2O in the presence of a suitable base such as diisopropylamine or pyridine and solvent such as THF or methylene chloride to afford compound of Formula I-M (compounds of Formula I-AA where $R^3 = Z—OH(CH_2A^4)$). Reaction of compound of Formula I-M (compounds of Formula I-AA where $R^3 = Z—OH(CH_2A^4)$) with $HN(R^{313})(R^{323})$ in a suitable solvent such as THF or methylene chloride afforded compound of Formula I-N (compounds of Formula I where $R^3 = Z—OH(CH_2NR^{313}R^{323})$).

[142] The compounds of Formula I-O (compounds of Formula I where $R^3 = Z^3—OH(G^{11})$) were prepared as shown below in **Scheme 26**:

Scheme 26

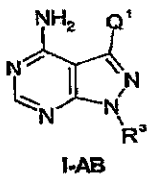


where Q^1 and G^{11} are as defined previously for compound of Formula I.

[143] In a typical preparation of compounds of Formula I-O (compounds of Formula I where $R^3 = Z—OH(G^{11})$), the ketone moiety of compound of Formula II-L (compounds of Formula II where $R^3 = Z=O$) was reacted with a suitable nucleophilic reagent such as MeMgBr or MeLi in a suitable solvent such as THF to afford compound of Formula II-N (compounds of Formula II where $R^3 = Z—OH(G^{11})$). Compound of Formula II-N (compounds of Formula II where $R^3 = Z—OH(G^{11})$) was reacted under ammonolysis conditions, ammonia in isopropanol in a stainless steel bomb at 110°C, to afford compound of Formula I-O (compounds of Formula I where $R^3 = Z—OH(G^{11})$). Additionally, compound of Formula I-O (compounds of Formula I where $R^3 = Z—OH(G^{11})$) was prepared by reacting compound of Formula I-K (compounds of Formula I-AA where $R^3 = Z=O$) with a suitable nucleophilic reagent such as MeMgBr or MeLi in a suitable solvent such as THF.

[144] The conversion of compounds of Formula I-PP' and I-P' to compounds of Formula I-RR an I-R, respectively may be accomplished by reaction with a boronic acid ester using so-called "Liebeskind-Srogl" conditions such as those described in *Organic Letters*, (2002), 4(6), 979 or *Synlett*, (2002), (3), 447.

[145] A compound of Formula I-AB is equal to compound of Formula I wherein $X_1 = CH$, X_2, X_4 and $X_5 = N$, and X_3, X_6 and $X_7 = C$; Q^1 is as defined for a compound of Formula I; R^3 is C_{0-10}alkyl, cycloC_{3-10}alkyl, aminomethylcycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterobicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents; and G^{11} is as defined for a compound of Formula I:

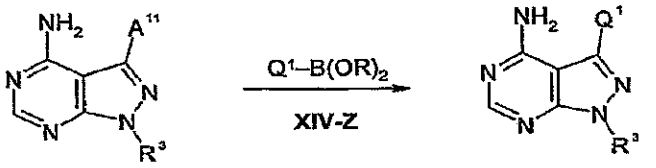


I-AB

[146] Method AB was used when preparing compounds of Formula I-AB as shown below in **Scheme 28:**

Method AB:

Scheme 28



I-ABA I-AB

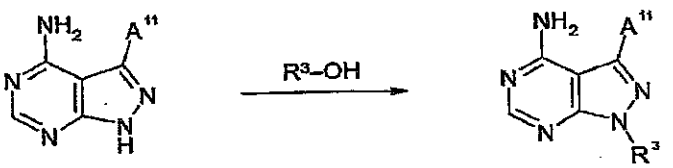
where Q^1 and R^3 are as defined previously for compound of Formula I-AB, A^{11} = halogen such as Cl, Br, or I, and Q^1–$B(OR)_2$ = suitable boronic acid/ester.

[147] In a typical preparation of compounds of Formula I-AB, compound of Formula I-ABA was reacted with a suitable boronic acid/ester of Formula XIV-Z (Q^1-$B(OR)_2$) in a suitable solvent via typical Suzuki coupling procedures. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent systems were THF/water and DMF/water. The above process was carried out at temperatures between about 20°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 100°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[148] One skilled in the art will appreciate that alternative methods may be applicable for preparing compounds of Formula I-AB from I-ABA. For example, compound of Formula I-ABA could be reacted with a suitable organotin reagent Q^1–$SnBu_3$ or the like in a suitable solvent via typical Stille coupling procedures.

[149] The compounds of Formula I-ABA wherein R^3 is $C_{1\text{-}10}$alkyl, cyclo$C_{3\text{-}10}$alkyl, bicyclo$C_{5\text{-}10}$alkyl, aralkyl, heteroaralkyl, heterocyclyl, heterobicyclo$C_{5\text{-}10}$alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents, of **Scheme 28** were prepared as shown below in **Scheme 29**:

Scheme 29



I-ABB I-ABA

where R^3 is $C_{1\text{-}10}$alkyl, cyclo$C_{3\text{-}10}$alkyl, bicyclo$C_{5\text{-}10}$alkyl, aralkyl, heteroaralkyl, heterocyclyl, heterobicyclo$C_{5\text{-}10}$alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one

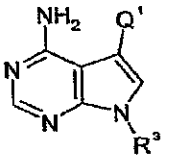
or more independent G^{11} substituents; G^{11} is as defined previously for compound of Formula I, and A^{11} = halogen such as Cl, Br, or I.

[150] In a typical preparation of a compound of Formula I-ABA, a compound of Formula I-ABB was reacted with an alcohol R^3–OH under typical Mitsunobu conditions in a suitable solvent in the presence of suitable reactants. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was THF. Suitable reactants for use in the above process included, but were not limited to, triphenylphosphine and the like, and an azodicarboxylate (DIAD, DEAD, DBAD). The preferred reactants were triphenylphosphine or resin-bound triphenylphosphine and DIAD. The above process may be carried out at temperatures between about –78°C and about 100°C. Preferably, the reaction was carried out between about 0°C and 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Generally, one equivalent of triphenylphosphine, DIAD, and R^3–OH was used per equivalent of compound of Formula I-ABB.

[151] Alternatively, the compounds of Formula I-ABA may be prepared by alkylating compounds of Formula I-ABB with an alkylating agent R^3–LG, wherein LG is a leaving group including, but not limited to, chloride, bromide, iodide, tosylate, mesylate, trifluoromethanesulfonate, under typical alkylation conditions known to someone skilled in the art.

[152] Preferably, in compounds of Formula I-ABB, A^{11} = Br and I. These compounds are known (A^{11} = I: H. B. Cottam *et al.*, *J. Med. Chem.* **1993**, *36*(22), 3424–3430; A^{11} = Br: T. S. Leonova et al., *Khim. Geterotsikl. Soedin.* **1982**, (7), 982–984).

[153] Compound of Formula I-AC is equal to compound of Formula I wherein X_1 and X_5 = CH, X_2 and X_4 = N, and X_3, X_6 and X_7 = C; Q^1 is as defined for a compound of Formula I; R^3 is C_{0-10}alkyl, cycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterobicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents; and G^{11} is as defined for a compound of Formula I:

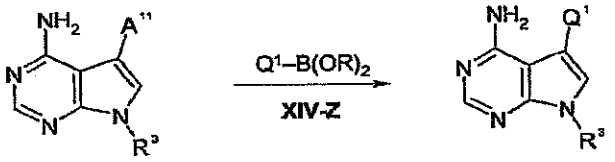


I-AC

[154] Method AC was used when preparing compounds of Formula I-AB as shown below in **Scheme 30:**

Method AC:

Scheme 30



I-ACA I-AC

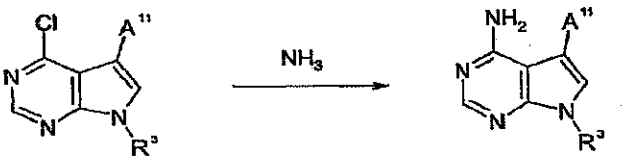
where Q^1 and R^3 are as defined previously for compound of Formula I-AC, A^{11} = halogen such as Cl, Br, or I and Q^1–$B(OR)_2$ = suitable boronic acid/ester.

[155] In a typical preparation of compounds of Formula I-AC, compound of Formula I-ACA was reacted with a suitable boronic acid/ester XIV-Z (Q^1-$B(OR)_2$) in a suitable solvent via typical Suzuki coupling procedures. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent systems were THF/water and DMF/water. The above process was carried out at temperatures between about 20°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 100°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[156] One skilled in the art will appreciate that alternative methods may be applicable for preparing compounds of formula I-AC from I-ACA. For example, compound of Formula I-ACA could be reacted with a suitable organotin reagent Q^1–$SnBu_3$ or the like in a suitable solvent via typical Stille coupling procedures.

[157] The compounds of Formula I-ACA of **Scheme 30** were prepared as shown below in **Scheme 31:**

Scheme 31



XV I-ACA

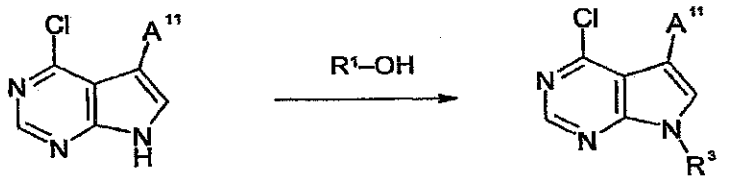
where R^3 is as defined previously for compound of Formula I-AC, and A^{11} = halogen such as Cl, Br, or I.

[158] In a typical preparation of compounds of Formula I-ACA, compound of Formula XV was reacted with ammonia in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like;

dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was isopropanol. The above process was carried out at temperatures between about –78°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 100°C. The above process to produce compounds of the present invention was preferably carried out in a glass pressure tube or a stainless steel reactor. Preferably, an excess of ammonia was used.

[159] The compounds of Formula XVA (= compounds of Formula XV of **Scheme 31** wherein R^3 is $C_{1\text{-}10}$alkyl, cyclo$C_{3\text{-}10}$alkyl, bicyclo$C_{5\text{-}10}$alkyl, aralkyl, heteroaralkyl, heterocyclyl, heterobicyclo$C_{5\text{-}10}$alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents) were prepared as shown below in **Scheme 32**:

Scheme 32



XVI **XVA**

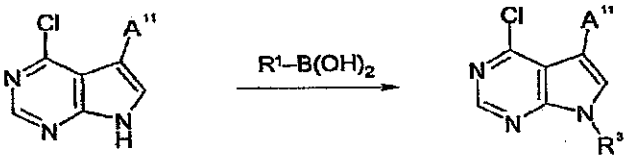
where R^3 is $C_{1\text{-}10}$alkyl, cyclo$C_{3\text{-}10}$alkyl, bicyclo$C_{5\text{-}10}$alkyl, aralkyl, heteroaralkyl, heterocyclyl, heterobicyclo$C_{5\text{-}10}$alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents; G^{11} is as defined previously for compound of Formula I; and A^{11} = halogen such as Cl, Br, or I.

[160] In a typical preparation of a compound of Formula XVA, a compound of Formula XVI was reacted with an alcohol R^3–OH under typical Mitsunobu conditions in a suitable solvent in the presence of suitable reactants. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was THF. Suitable reactants for use in the above process included, but were not limited to, triphenylphosphine and the like, and an azodicarboxylate (DIAD, DEAD, DBAD). The preferred reactants were triphenylphosphine or resin-bound triphenylphosphine and DIAD. The above process may be carried out at temperatures between about –78°C and about 100°C. Preferably, the reaction was carried out between about 0°C and 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Generally, one equivalent of triphenylphosphine, DIAD, and R^3–OH was used per equivalent of compound of Formula XVI.

[161] Alternatively, the compounds of Formula XVA may be prepared by alkylating compounds of Formula XVI with an alkylating agent R^3–LG, wherein LG is a leaving group including, but not limited to, chloride, bromide, iodide, tosylate, mesylate, trifluoromethanesulfonate, under typical alkylation conditions known to someone skilled in the art.

[162] The compounds of Formula XVB (= compounds of Formula XV of **Scheme 31** wherein R^3 is aryl or heteroaryl, optionally substituted by one or more independent G^{11} substituents) were prepared as shown below in **Scheme 33**:

Scheme 33



XVI **XVB**

where R^3 is aryl or heteroaryl, optionally substituted by one or more independent G^{11} substituents, G^{11} is as defined previously for compound of Formula I; and A^{11} = halogen such as Cl, Br, or I.

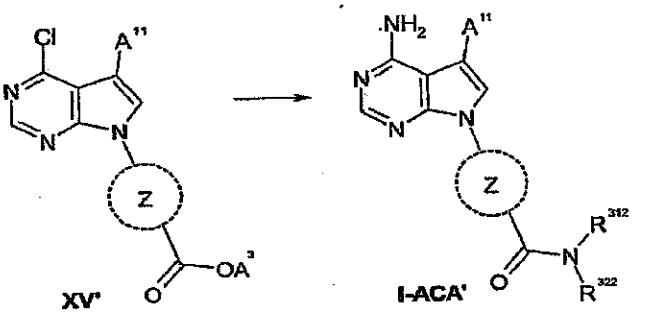
[163] In a typical preparation of compounds of Formula XVB, compound of Formula XVI was reacted with a suitable boronic acid of Formula R^3–$B(OH)_2$ in a suitable solvent via typical copper(II)-mediated coupling procedures. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, 1,4-dioxane, and the like; dimethylformamide (DMF); *N*-methylpyrrolidinone (NMP); chlorinated solvents such as methylene chloride (CH_2Cl_2). If desired, mixtures of these solvents were used, however, the preferred solvent was methylene chloride (CH_2Cl_2). Suitable reactants for use in the above process included, but were not limited to, copper(II) acetate ($Cu(OAc)_2$), copper(II) triflate ($Cu(OTf)_2$), and the like, and a base (pyridine, and the like). The preferred reactants were $Cu(OAc)_2$ and pyridine. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure under air, although higher or lower pressures could be used if desired. Preferably, the reaction was carried out at about 22°C. Generally, 1.5eq. of copper(II) acetate, 2eq. of pyridine, and 2eq. of boronic acid of Formula R^3–$B(OH)_2$ were used per equivalent of compound of Formula XVI.

[164] All compounds of Formula XVI are known in the literature (A^{11} = I: L. B. Townsend et al., *J. Med. Chem.* **1990**, *33*, 1984–92; A^{11} = Br, Cl: L. B. Townsend et al., *J. Med. Chem.* **1988**, *31*, 2086–2092). Preferably, A^{11} = Br and I.

[165] Both R^3 and Q^1 in the compounds described herein in some instances contain functional groups that can be further manipulated. It would be appreciated by those skilled in the art that such manipulation of functional groups could be accomplished with key intermediates or with late stage compounds. Such functional group transformations are exemplified in the following **Schemes 34–35** as well as in the experimental section but are in no way meant to limit the scope of such transformations.

[166] The compounds of Formula I-ACA' (= compounds of Formula I-ACA where R^3 = Z—$CONR^{312}R^{322}$) were prepared from compounds of Formula XV' (= compounds of Formula XV where R^3 = Z—CO_2A^3) as shown below in **Scheme 34**:

Scheme 34



where R^{312} and R^{322} are as defined previously for compound of Formula I; A^{11} = halogen such as Cl, Br, or I; and A^3 = hydrogen or alkyl such as methyl or ethyl.

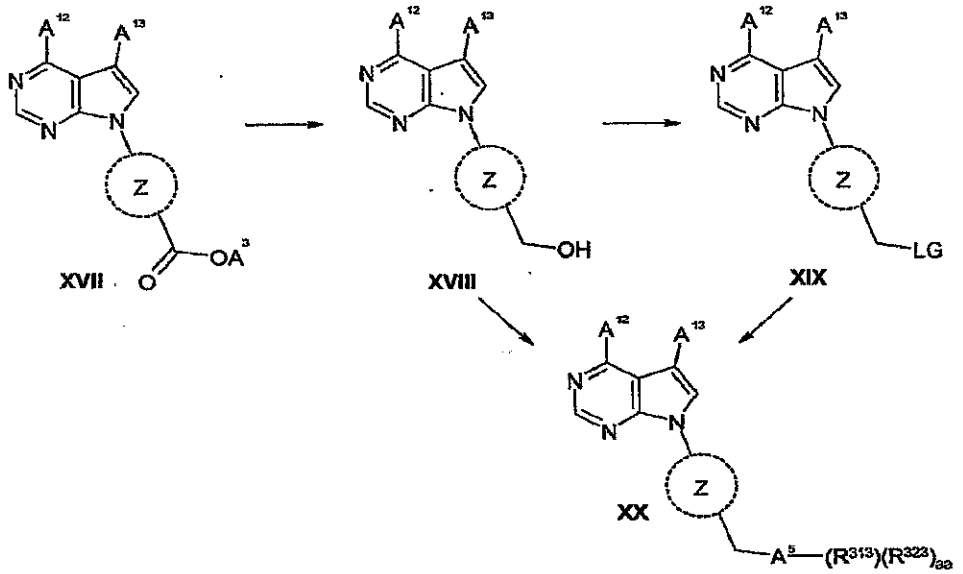
[167] In a typical preparation of compound of Formula I-ACA', when A^3 = alkyl and R^{312} and R^{322} were both equal to H, reaction of compound of Formula XV' with ammonia in a suitable solvent, afforded compound of Formula I-ACA'. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was isopropanol. The above process was carried out at temperatures between about –78°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 100°C. The above process to produce compounds of the present invention was preferably carried out in a glass pressure tube or a stainless steel reactor. Preferably, an excess of ammonia was used. Additionally, in a typical preparation of compound of Formula I-ACA' (compounds of Formula I-ACA where R^3 = Z—$CONR^{312}R^{322}$), compound of Formula XV' (compounds of Formula XV' where R^3= Z—CO_2A^3) was reacted with $HNR^{312}R^{322}$ followed by ammonia in a suitable solvent. When A^3 = H, typical coupling procedures (such as conversion of –CO_2H to –COCl via treatment with $SOCl_2$ or oxalyl chloride followed by reaction with $HNR^{312}R^{322}$ or treatment of –CO_2H and $HNR^{312}R^{322}$ with EDC or DCC in conjunction with DMAP, HOBT, or HOAt and the like) were employed to afford the transformation of a carboxylic acid to an amide. When A^3 = alkyl such as methyl or ethyl, treatment of the ester with $Al(NR^{312}R^{322})$ afforded conversion of –CO_2A^3 to –$CO(NR^{312}R^{322})$. Subsequent treatment with ammonia afforded compounds of Formula I-ACA'.

[168] The chemistry shown in **Scheme 34** can also be applied to compounds with Q^1 in place of A^{11}.

[169] The compounds of Formula XVIII (compounds of Formula XV, I-ACA, or I-AC where R^3 = Z—CH_2OH), XIX (compounds of Formula XV, I-ACA, or I-AC where R^3 = Z—CH_2LG),

and XX (compounds of Formula XV, I-ACA, or I-AC where $R^3 = Z—CH_2A^5(R^{313})(R^{323})_{aa}$) were prepared as shown below in **Scheme 35**:

Scheme 35



where Q^1, R^{313}, and R^{323} are as defined previously for compound of Formula I; LG = suitable leaving group such as tosylate, mesylate, trifluoromethanesulfonate, or halo such as chloro, bromo, or iodo; aa = 0 or 1; A^3 = hydrogen or alkyl such as methyl or ethyl; A^{11} = halogen such as Cl, Br, or I; A^{12} = Cl or NH_2; $A^{13} = A^{11}$ or Q^1; and A^5 = N, O or S.

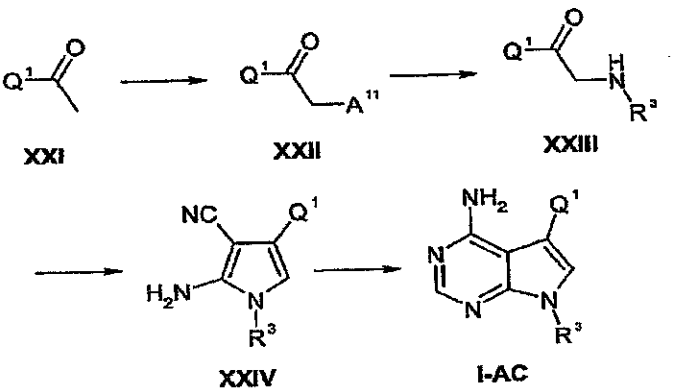
[170] The following table indicates the relations between the compounds of Formulas XVII–XX, A^{12}, A^{13}, compounds of Formulas I-AC, I-ACA, and XV, and R^3.

Compound of Formula...	**wherein A^{12} =**	**and A^{13} =**	**...is equal to Formula...**	**wherein R^3 =**
XVII	Cl	A^{11}	XV	$Z–CO_2A^3$
XVII	NH_2	A^{11}	I-ACA	$Z–CO_2A^3$
XVII	NH_2	Q^1	I-AC	$Z–CO_2A^3$
XVIII	Cl	A^{11}	XV	$Z–CH_2OH$
XVIII	NH_2	A^{11}	I-ACA	$Z–CH_2OH$
XVIII	NH_2	Q^1	I-AC	$Z–CH_2OH$
XIX	Cl	A^{11}	XV	$Z–CH_2LG$
XIX	NH_2	A^{11}	I-ACA	$Z–CH_2LG$
XIX	NH_2	Q^1	I-AC	$Z–CH_2LG$
XX	Cl	A^{11}	XV	$Z–CH_2A^5R^2(R^4)_d$
XX	NH_2	A^{11}	I-ACA	$Z–CH_2A^5R^2(R^4)_d$
XX	NH_2	Q^1	I-AC	$Z–CH_2A^5R^2(R^4)_d$

[171] In a typical preparation of compound of Formula XVIII (compounds of Formula XV, I-ACA, or I-AC, where $R^3 = Z—CH_2OH$), compound of Formula XVII (compounds of Formula XV, I-ACA, or I-AC, where $R^3 = Z—CO_2A^3$) is treated with a suitable reducing agent, such as lithium aluminum hydride or diisobutylaluminum hydride, in a suitable solvent, such as THF or methylene chloride, to afford compound of Formula XVIII. In a typical preparation of compound of Formula XX (compounds of Formula XV, I-ACA, or I-AC, where $R^3 = Z—CH_2A^5(R^{313})(R^{323})_{aa}$), the hydroxy group of compound of Formula XVIII was converted to a suitable leaving group, LG, such as Cl or tosylate, mesylate, or triflate, by reaction with $SOCl_2$ or Ts_2O, Ms_2O, or Tf_2O to afford compound of Formula XIX (compounds of Formula XV, I-ACA, or I-AC, where $R^3 = Z—CH_2LG$). Reaction of compound of Formula XIX with $HA^5(R^{313})(R^{323})_{aa}$ afforded compound of Formula XX. Furthermore, compound of Formula XVIII can be directly converted to compound of Formula XX by treating compound of Formula XVIII with various alkylating agents or under typical Mitsunobu reaction conditions to afford compounds of Formula XX (compounds of Formula XV, I-ACA, or I-AC, where $R^3 = Z—CH_2A^5(R^{313})(R^{323})_{aa}$) in which $A^5 = O$, aa = 0, and R^{313} = alkyl or aryl). Someone skilled in the art will choose the most appropriate stage during the sequence shown in **Scheme 35** to convert A^{12} = Cl to $A^{12} = NH_2$ as described in **Scheme 31**, and to convert $A^{13} = A^{11}$ to $A^{13} = Q^1$ as described in **Scheme 30**, if applicable.

[172] An alternative preparation of compounds of Formula I-AC is shown in **Scheme 36**.

Scheme 36



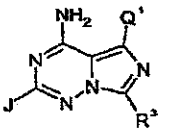
where Q^1 and R^3 are as defined previously for compound of Formula I; and A^{11} = halogen such as Cl, Br, or I.

[173] The compounds of Formula XXI may be prepared from aldehydes Q^1–CHO (see **Scheme 14** for their preparation) by addition of methyllithium or a methyl Grignard reagent, followed by oxidation of the resulting alcohol to the ketone of Formula XXI. Other compounds are commercially available or can be prepared by methods well known to someone skilled in the art, see: Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley and Sons: New York, 1999, 1197ff. Reaction of compounds of Formula XXI under typical halogenation conditions with typical halogenating agents including, but not limited to, Br_2, NBS, pyridinium perbromide, or $CuBr_2$ (for A^{11}

= Br), or NCS or SO_2Cl_2 (for A^{11} = Cl) gives the compounds of Formula XXII. Their reaction with amines of Formula H_2N–R^3 gives the aminoketones of Formula XXIII that are converted to aminocyanopyrroles of Formula XXIV by reaction with malononitrile under basic conditions. Finally, reaction of compounds of Formula XXIV under typical cyclization conditions gives the compounds of Formula I-AC. Conditions for this cyclization include, but are not limited to, heating with formamide; heating with formamide and ammonia; sequential treatment with a trialkyl orthoformate, ammonia, and a base; sequential treatment with formamidine and ammonia.

[174] It would be appreciated by those skilled in the art that in some situations, a substituent that is identical or has the same reactivity to a functional group which has been modified in one of the above processes, will have to undergo protection followed by deprotection to afford the desired product and avoid undesired side reactions. Alternatively, another of the processes described within this invention may be employed in order to avoid competing functional groups. Examples of suitable protecting groups and methods for their addition and removal may be found in the following reference: "Protective Groups in Organic Syntheses", T. W. Greene and P. G. M. Wuts, John Wiley and Sons, 1989.

[175] Compound of Formula I-AQ is equal to compound of Formula I wherein X_1 = CH; X_2, X_3 and X_5 = N; X_4, X_6, and X_7 = C and J=H or NH_2

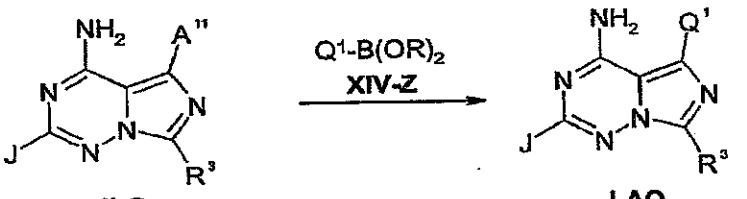


I-AQ

[176] Method AQ was used when preparing compounds of Formula I-AQ as shown below in **Scheme 37**:

Method AQ:

Scheme 37



II-Q I-AQ

where Q^1 and R^3 are as defined previously for compound of Formula I, A^{11} = halogen such as Cl, Br, or I; $B(OR)_2$ = suitable boronic acid/ester and J=H or NH_2.

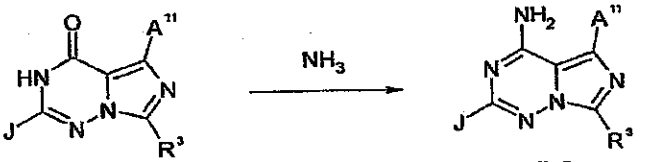
[177] In a typical preparation of compounds of Formula I-AQ, compound of Formula II-Q was reacted with a suitable boronic acid/ester (Q^1-$B(OR)_2$) in a suitable solvent via typical Suzuki coupling procedures. Suitable solvents for use in the above process included, but were not limited to, water, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol,

trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was glyme/water. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 80°C and about 100°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[178] One skilled in the art will appreciate that alternative methods may be applicable for preparing compounds of Formula I-AQ from II-Q. For example, compound of Formula II-Q could be reacted with a suitable organotin reagent Q^1–$SnBu_3$ or the like in a suitable solvent via typical Stille coupling procedures.

[179] The compounds of Formula II-Q of **Scheme 37** were prepared as shown below in **Scheme 38.**

Scheme 38



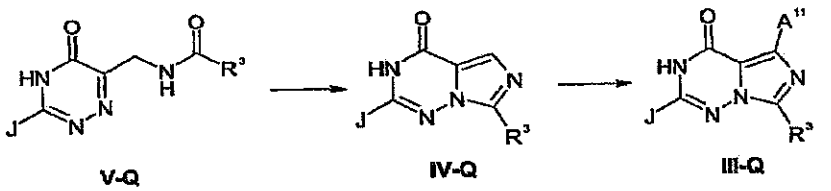
III-Q II-Q

where R^3 is as defined previously for compound of Formula I and A^{11} = halogen such as Cl, Br, or I; and J=H or NH_2.

[180] In a typical preparation of compounds of Formula II-Q, compound of Formula III-Q was reacted with phosphorus oxychloride ($POCl_3$) and triazole, and pyridine followed by ammonia (NH_3) in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was isopropanol. The above process was carried out at temperatures between about -20°C and about 50°C. Preferably, the reaction was carried out between 0°C and about 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[181] The compounds of Formula III-Q of **Scheme 38** were prepared as shown below in **Scheme 39.**

Scheme 39



V-Q IV-Q III-Q

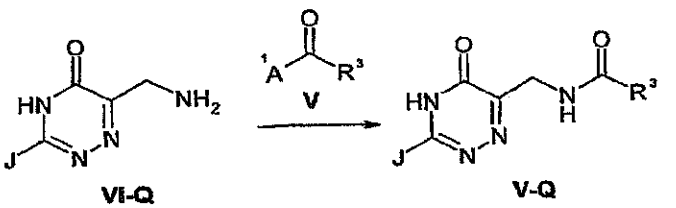
where R^3 is as defined previously for compound of Formula I; A^{11} = halogen such as Cl, Br, or I; and J=H or NH_2.

[182] In a typical preparation of a compound of Formula III-Q, intermediate V-Q was converted to compound of Formula IV-Q. Intermediate of Formula V-Q was treated with phosphorus oxychloride ($POCl_3$) in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like, chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$), and acetonitrile. If desired, mixtures of these solvents were used. The preferred solvent was acetonitrile. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Intermediate for Formula III-Q was prepared by reacting intermediate of Formula IV-Q with a suitable halogenating agent. Suitable halogenating agents included, but were not limited to, Br_2, I_2, Cl_2, *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-iodosuccinimide. The preferred halogenating agent was *N*-iodosuccinimide. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was DMF. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 75°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[183] Compounds of Formulae IV-Q and III-Q where J=NH_2 can be respectively converted into the compounds of Formulae IV-Q and III-Q where J=H, by diazotisation procedures known to those skilled in the art. A typical procedure includes the treatment of a compound of Formula IV-Q or III-Q where J=NH_2 with *tert*-butylnitrite in a suitable solvent such a THF or DMF.

[184] The compounds of Formula V-Q of **Scheme 39** were prepared as shown below in **Scheme 40**:

Scheme 40

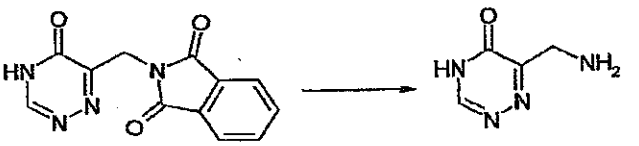


where R^1 is as defined previously for compound of Formula I; A^1 = OH, alkoxy, or a leaving group such as chloro or imidazole; and J = H or NH_2.

[185] In a typical preparation, of a compound of Formula V-Q, a compound of Formula VI-Q and compound of Formula V were reacted under suitable amide -coupling conditions. Suitable conditions include but are not limited to treating compounds of Formula VI-Q and V (when A^1 = OH) with coupling reagents such as DCC or EDC in conjunction with DMAP, HOBt, HOAt and the like, or reagents like EEDQ. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was methylene chloride. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Alternatively, compounds of Formula VI-Q and V (where A^1 = F, Cl, Br, I) were reacted with bases such as triethylamine or ethyldiisopropylamine and the like in conjunction with DMAP and the like. Suitable solvents for use in this process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; pyridine; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was DMF. The above process was carried out at temperatures between about –20°C and about 40°C. Preferably, the reaction was carried out between 0°C and 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of compounds of Formula VI-Q and V (where A^1 = F, Cl, Br, I) and base and substochiometric amounts of DMAP were preferably used although higher or lower amounts were used if desired. Additionally, other suitable reaction conditions for the conversion of an amine (compound of Formula VI-Q) to an amide (compound of Formula V-Q) can be found in Larock, R. C. *Comprehensive Organic Transformations,* 2nd ed.; Wiley and Sons: New York, **1999**, pp 1941-1949.

[186] The compounds of Formula VI-Q of **Scheme 40** where J=H were prepared as shown below in **Scheme 41**:

Scheme 41



VII-Q VI-Q

[187] In a typical preparation, of a compound of Formula VI-Q, a compound of Formula VII-Q is reacted under suitable reaction conditions in a suitable solvent. Suitable conditions include treatment of compound of Formula VII-Q with hydrazine or methyl hydrazine in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride; alcoholic solvents such as methanol and ethanol. If desired, mixtures of these solvents may be used, however the preferred solvents were ethanol and methylene chloride. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[188] Compounds of Formula VI-Q where J=NH_2 may be prepared according to the procedures described in *J.Het. Chem.*, (1984), **21**, 697.

[189] The compounds of Formula VII-Q of **Scheme 41** were prepared as shown below in **Scheme 42:**

Scheme 42



VIII-Q VII-Q

[190] In a typical preparation of a compound of Formula VII-Q, a compound of Formula VIII-Q was reacted with Raney Nickel in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was ethanol. The above process may be carried out at temperatures between about rt and about 100°C. Preferably, the reaction was carried out at about 80°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric

pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Additionally a compound of Formula VII-Q can be prepared by reacting a compound of Formula VIII-Q with a suitable oxidizing agent in a suitable solvent. A suitable oxidizing agent includes, but is not limited to hydrogen peroxide (H_2O_2), 3-chloro peroxybenzoic acid (mCPBA) and the like. Suitable solvents for use in the above process included, but were not limited to, ethers such as THF, glyme, and the like; DMF; DMSO; CH_3CN; and dimethylacetamide (DMA); chlorinated solvents such as CH_2Cl_2 or $CHCl_3$ If desired, mixtures of these solvents were used, however, the preferred solvent was DMA. The above process may be carried out at temperatures between about 0°C and 100°C. Preferably, the reaction was carried out at about rt to 70°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[191] The compounds of Formula VIII-Q of **Scheme 42** were prepared as shown below in **Scheme 43**:

Scheme 43



IX-Q VIII-Q

[192] In a typical preparation of a compound of Formula VIII-Q, a compound of Formula IX-Q was reacted with thiosemicarbazide and a suitable base in a suitable solvent. Suitable bases include, but were not limited to triethylamine, ethyldiisopropylamine and the like. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethylacetamide (DMA); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was ethanol. The above process may be carried out at temperatures between about rt and about 100°C. Preferably, the reaction was carried out between about 40°C and 80°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Compound of Formula IX-Q can be prepared according to literature procedures Knutsen, Lars J. S. et. al., *J. Chem. Soc. Perkin Trans 1: Organic and Bio-Organic Chemistry (1972-1999)*, **1984**, 229-238.

[193] It would be appreciated by those skilled in the art that in some situations, a substituent that is identical or has the same reactivity to a functional group which has been modified in one of the above processes, will have to undergo protection followed by deprotection to afford the desired product and avoid undesired side reactions. Alternatively, another of the processes described within this invention may be employed in order to avoid competing functional groups. Examples of suitable protecting groups and methods for their addition and removal may be found in the following reference: "Protective Groups in Organic Syntheses", T. W. Greene and P. G. M. Wuts, John Wiley and Sons, 1989.

[194] Method AW was also used when preparing compounds of Formula II-Q as shown below in **Scheme 44**:

Method AW:

Scheme 44



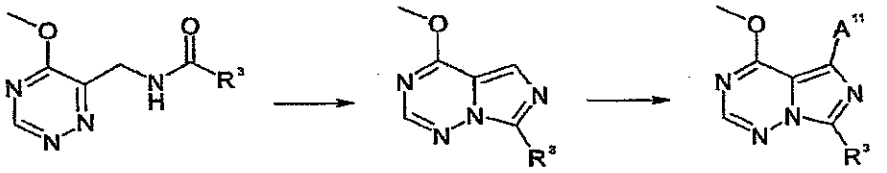
III-W II-Q

where Q^1 and R^3 are as defined previously for compound of Formula I, and A^{11} = halogen such as Cl, Br, or I.

[195] In a typical preparation of compounds of Formula II-Q, compound of Formula III-W was reacted with ammonia in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was isopropanol. The above process was carried out at temperatures between about 0°C and about 50°C. Preferably, the reaction was carried out at between 0°C and about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[196] The compounds of Formula III-W of **Scheme 44** were prepared as shown below in **Scheme 45**.

Scheme 45



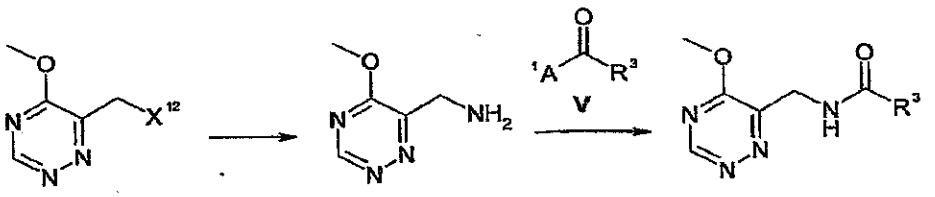
V-W IV-W III-W

where R^3 is as defined previously for compound of Formula I and A^{11} = halogen such as Cl, Br, or I.

[197] In a typical preparation of a compound of Formula III-W, compound V-W was converted to compound of Formula IV-W. Compound of Formula V-W was treated with phosphorus oxychloride ($POCl_3$) or the isolated "Vilsmeir salt" [CAS# 33842-02-3] in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like, chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$), and acetonitrile (CH_3CN). If desired, mixtures of these solvents were used. The preferred solvent was acetonitrile. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Compounds of Formula III-W were prepared by reacting compound of Formula IV-W with a suitable halogenating agent. Suitable halogenating agents included, but were not limited to, Br_2, I_2, Cl_2, *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-iodosuccinimide. The preferred halogenating agent was *N*-iodosuccinimide. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was DMF. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 75°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[198] The compounds of Formula V-W of **Scheme 45** were prepared as shown below in **Scheme 46.**

Scheme 46



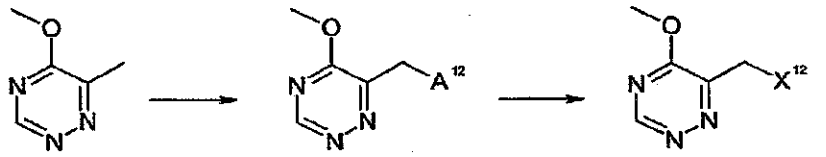
where R^3 is as defined previously for compound of Formula I, X^{12} = azido, or mono- or di-protected amino and A^1 = OH, alkoxy or a leaving group such as chloro or imidazole.

[199] In a typical preparation of a compound of Formula V-W, compound VI-W was reacted with compound V under suitable amide coupling conditions. Suitable conditions include but are not limited to those described for the conversion of compound XIII to compound XII as shown in **Scheme 10**. Compounds of Formula VI-W were prepared from compounds of Formula VII-W. A typical procedure for the conversion of compounds of Formula VII-W to compounds of Formula VI-W involves subjecting a compound of Formula VII-W, where X^{12} = azido, to reducing conditions such as, but not limited to, catalytic hydrogenation in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like, alcoholic solvents such as methanol, ethanol and the like, esters such as ethyl acetate, methyl acetate and the like. If desired, mixtures of these solvents were used. The preferred solvents were ethyl acetate and methanol. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Alternatively, when X^{12} = azido, the reduction to compounds of Formula VI-W could be achieved by treatment of a compound of Formula VII-W with triaryl- or trialkylphosphines in the presence of water in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), dioxane and the like, alcoholic solvents such as methanol, ethanol and the like, esters such as ethyl acetate, methyl acetate and the like, DMF, acetonitrile, and pyridine. If desired, mixtures of these solvents were used. The preferred solvents were THF and acetonitrile. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired.

[200] Where X^{12} = mono- or di-protected amino, the deprotection could be effected by the procedures known to those skilled in the art and as disclosed in: "Protective Groups in Organic Syntheses", T. W. Greene and P. G. M. Wuts, John Wiley and Sons, 1989.

[201] The compounds of Formula VII-W of **Scheme 46** were prepared as shown below in **Scheme 47**:

Scheme 47



IX-W VIII-W VII-W

where R_3 is as defined previously for compound of Formula I, X^{12} is as defined for a compound of Formula VII-W and A^{12} = iodo, bromo, chloro, tosylate, mesylate or other leaving group.

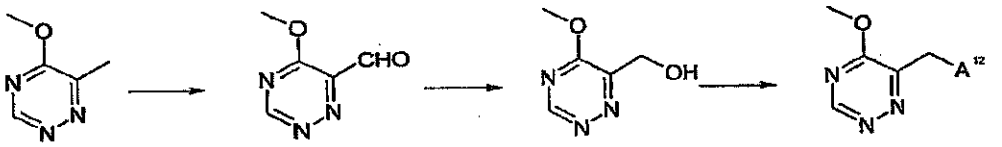
[202] In a typical preparation of a compound of Formula VII-W where X^{12} = azide, compound VIII-W was reacted with an azide salt, such as lithium or sodium azide in suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, alcoholic solvents such as ethanol, butanol and the like, esters such as ethyl acetate, methyl acetate and the like, DMF, acetonitrile, acetone DMSO. If desired, mixtures of these solvents were used. The preferred solvents were acetone and DMF. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Alternatively, where X^{12} = mono- or di-protected amino, compounds of Formula VIII-W were reacted with suitably protected amines where the protecting group is chosen such that the nucleophilic nature of the nitrogen is either retained or where it can be enhanced by the action of a reagent such as a base. Those skilled in the art will recognize that such protecting groups include, but are not limited to, benzyl, trityl, allyl, and alkyloxycarbonyl derivatives such as BOC, CBZ and FMOC.

[203] Compounds of Formula VIII-W where A^{12} = halogen, are prepared from compounds of Formula XI-W. In a typical procedure, compounds of Formula XI-W are treated with halogenating reagents such as but not limited to *N*-iodosuccinimide, *N*-bromosuccinimide, *N*-chlorosuccinimide, trichloroisocyanuric acid, *N,N'*-1,3-dibromo-5,5-dimethylhydantoin, bromine and iodine, preferably in the presence of one or more radical sources such as dibenzoyl peroxide, azobisisobutyronitrile or light in suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, chlorinated solvents such as carbon tetrachloride, dichloromethane, α,α,α-trifluorotoluene and the like, esters such as methyl formate, methyl acetate and the like, DMF, acetonitrile. If desired, mixtures of these solvents were used. The preferred solvents were carbon tetrachloride and α,α,α-trifluorotoluene. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was

preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired.

[204] Alternatively, compounds of Formula VIII-W where A^{12} = tosylate or mesylate were prepared from compounds of Formula X-W as shown in **Scheme 48**. In a typical preparation of a compound of Formula VIII-W, a compound of Formula X-W was reacted with a sulfonylating reagent such as methanesulfonyl chloride or *p*-toluenesulfonyl chloride in the presence of a base such as, but not limited to DIPEA or triethylamine in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above reaction included, but were not limited to, chlorinated solvents such as dichloromethane, 1,2-dichloroethane and the like, ethers such THF, diethylether and the like, DMF and acetonitrile. If desired, mixtures of these solvents were used. The preferred solvents were THF and dichloromethane. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired.

Scheme 48



IX-W XI-W X-W VIII-W

[205] Compounds of Formula X-W were prepared from compounds of Formula XI-W. In a typical preparation of a compound of Formula X-W, a compound of Formula XI-W was reacted with a reducing reagent such as, but not limited to, sodium borohydride, lithium borohydride or lithium aluminum hydride in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above reaction included, but were not limited to, ethers such THF, diethylether and the like, and alcohols such as ethanol, methanol, isopropanol and the like. If desired, mixtures of these solvents were used. The preferred solvents were THF and methanol. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired.

[206] Compounds of Formula XI-W were prepared from compounds of Formula XI-W. In a typical preparation of a compound of Formula XI-W, a compound of Formula IX-W was reacted with an oxidizing reagent such as, but not limited to, selenium dioxide, manganese dioxide, potassium permanganate and the like, in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above reaction included, but were not limited to, chlorinated solvents such as dichloromethane, 1,2-dichloroethane and the like, water, acetic acid and sulfolane. If desired, mixtures

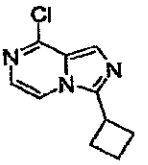
of these solvents were used. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired.

[207] Those skilled in the art will appreciate that compounds of Formula IX-W can be made by routes disclosed in the literature, for example as in *Bulletin de la Societe Chimique de France*, (1973), (6)(Pt. 2), 2126.

[208] Compounds of Formula I-AQ and/or their precursors may be subjected to various functional group interconversions as a means to access some functionalities that may not be introduced directly as a result of incompatible chemistries. Examples of such functional group manipulations applicable to compounds of Formula I-AQ and their precursors are similar, but not limited to, those described in **Schemes 16-27, 34** and **35** that related to compounds of Formula I-AA, I-P, I-P', I-Q, I-R, I-AB and I-AC.

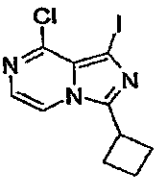
Experimental Procedures

8-Chloro-3-cyclobutyl-imidazo[1,5-*a*]pyrazine



[209] This compound was prepared using procedures analogous to that described for *trans*-methyl 4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate and its precursor *trans*-methyl 4-({[(3-chloropyrazin-2-yl)methyl]amino}carbonyl)cyclohexanecarboxylate, using cyclobutanecarboxylic acid in place of 4-(methoxycarbonyl)cyclohexanecarboxylic acid.

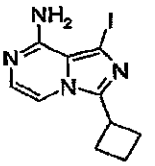
8-Chloro-3-cyclobutyl-1-iodoimidazo[1,5-*a*]pyrazine



[210] 8-Chloro-3-cyclobutylimidazo[1,5-*a*]pyrazine (1058mg, 5.1mmol) and NIS (1146mg, 5.1mmol) in anh DMF (10mL) were stirred at 60°C under Ar for 6h. The reaction was diluted with DCM (~400mL), washed (H_2O, brine), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude material by flash chromatography on silica gel (50g cartridge, 10:1 – 8:1- 7:1 – 6:1 hexanes:EtOAc) afforded the title compound as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 4.8 Hz, 1H), 3.75 (quintetd, J = 1.2 Hz, 8.4 Hz,

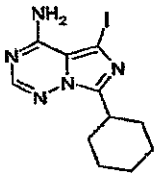
1H), 2.62-2.42 (m, 4H), 2.32-1.98 (m, 2H); MS (ES+): *m/z* 334.0 (100) [MH^+]; HPLC: t_R = 3.38 min (OpenLynx, polar_5min).

3-Cyclobutyl-1-iodoimidazo[1,5-*a*]pyrazin-8-amine



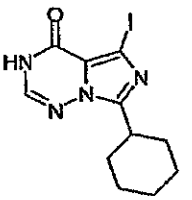
[211] A Parr bomb containing 8-chloro-3-cyclobutyl-1-iodoimidazo[1,5-*a*]pyrazine (759mg, 2.3mmol) in IPA (100mL) was saturated with NH_3(g) for 5min at 0°C then sealed and heated at 115°C for 38h. The reaction mixture was then concentrated under reduced pressure, partitioned between DCM (200mL) and H_2O (50mL) and extracted with DCM (50mL). Combined organic fractions were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide the title compound as a white solid; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.13 (d, J = 4.8 Hz, 1H), 7.01 (d, J = 5.2 Hz, 1H), 5.63 (br, 2H), 3.73 (quintetd, J = 0.8 Hz, 8.4 Hz, 1H), 2.60-2.38 (m, 4H), 2.20-1.90 (m, 2H); MS (ES+): *m/z* 315.9 (100) [MH^+]; HPLC: t_R = 1.75 min (OpenLynx, polar_5min).

7-Cyclohexyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-amine



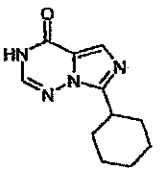
To a suspension of 1*H*-1,2,4-triazole (1g, 0.02mol) in acetonitrile (23mL) was added dropwise phosphoryl chloride (0.6mL, 0.007mol) and triethylamine (3mL, 0.02mol) at 0°C. To this mixture was added 7-cyclohexyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (77mg, 0.224mmol) and the resulting mixture refluxed overnight. The cooled mixture was then quenched with excess NH_3 in ^{i}PrOH (pH 8) stirred at rt for 30min. then filtered and the isolated solid washed with DCM. The filtrate was concentrated *in vacuo* and purified by chromatography over silica gel eluting with 2% MeOH in DCM to afford the 7-cyclohexyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-amine. ^{1}H NMR (400 MHz – DMSO-d6) δ 1.14 – 1.91 (m, 10H), 3.11 – 3.18 (m, 1H), 6.75 (br.s, 1H), 7.84 (s, 1H) 8.42 (bs, 1H); MS (ES+): m/z: 344.01 (100) [MH+]. HPLC: t_R = 3.10 min (OpenLynx: polar_5 min).

7-Cyclohexyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one



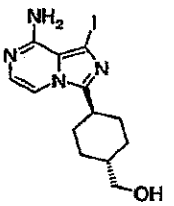
[212] To a solution of 7-cyclohexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (130mg, 0.6mmol) in DMF (0.6mL) was added *N*-iodosuccinimide (700mg, 0.003mol) and the reaction mixture stirred at 55°C for 20h. After this time the mixture was diluted with water (50mL) and extracted with EtOAc (4 x 40mL). The organic extracts were washed with water (4 x 40mL), treated with sodium thiosulfate and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford 7-cyclohexyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one. ^{1}H NMR (400 MHz – DMSO-d6) δ 1.34 – 1.37 (m, 3H), 1.52 – 1.56 (m, 2H), 1.76 – 1.88 (m, 5H), 3.06 – 3.08 (m, 1H) 7.87 (s, 1H) 11.78 (s, 1H); MS (ES+): m/z: 344.95 (100) [MH+]. HPLC: tr = 2.95 min (OpenLynx: polar_5 min).

7-Cyclohexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one



To a suspension of 6-aminomethyl-4*H*-[1,2,4]triazin-5-one (250mg, 1.98mmol) in DMF (7.5mL) was added 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (760mg, 2.38mmol), cyclohexanecarboxylic acid (305mg, 2.38mmol) and *N*,*N*-diisopropylethylamine (1.5mL, 8.6mmol). After 1h acetonitrile (40 mL) was added to the mixture followed by dropwise addition of phosphoryl chloride (0.28mL, 3.0mmol) and the reaction mixture stirred at 55°C for 1h. The mixture was then concentrated *in vacuo* chromatographed over silica gel eluting with 3% MeOH in DCM, to afford 7-cyclohexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one. ^{1}H NMR (400 MHz – DMSO-d6) δ 1.24 – 1.91 (m, 10H), 3.08 – 3.16 (m, 1H), 7.68 (s, 1H) 7.88 (s, 1H) 11.76 (s, 1H); MS (ES+): m/z: 219.24 (100) [MH+]. HPLC: t_R = 2.44 min (OpenLynx: polar_5 min).

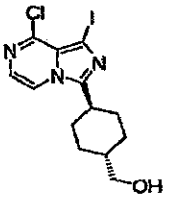
***trans*-[4-(8-Amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol**



[213] *trans*-[4-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol (26.50g, 67.66mmol) was charged in a 400mL steel bomb and was dissolved in 2M NH_3 in isopropanol

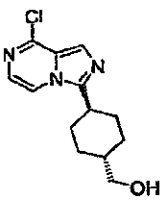
(300mL) and anhydrous THF (10mL). The reaction mixture was cooled to -78°C. Ammonia gas was bubbled vigorously into the solution for 8min; then the bomb was tightly sealed and heated to 120°C for 20h. The crude reaction mixture was concentrated *in vacuo*, then the reaction residue was taken up with MeOH/$CHCl_3$, loaded onto silica gel. The mixture was purified by a silica gel glass column chromatography [eluted with 1:1 CH_2Cl_2/EtOAc to 10% ~7 *N* NH_3 in MeOH/$CHCl_3$] to afford the desired product as a beige cream white solid; MS (ES+): *m/z* 373.01 (100) [MH^+], 373.98 (50) [MH^+2]; t_R(polar-5min/openlynx) 1.57 min.

trans-[4-(8-Chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol



[214] _trans_-[4-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol (18.00g, 67.74mmol) and *N*-iodosuccinimide (19.81g, 88.06mmol) in anhydrous DMF (360mL) were stirred at 60°C under N_2 for 6h. The reaction was diluted with DCM (~600mL), washed with water and brine, dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude material was purified by a silica gel flash chromatography (eluted with 1:2 EtOAc/DCM to 1:1 EtOAc/DCM) to obtain the desired product as a pale yellow solid; By ^1H NMR analysis, the product was contaminated with 0.35eq. of NIS-impurity. The product was carried onto the next reaction without further purification; MS (ES+): *m/z* 391.92 (100) [MH^+], 393.88 (50) [MH^+2], 394.89 (10) [MH^+3]; t_R(polar-5min/openlynx) 2.79 min.

trans-[4-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol



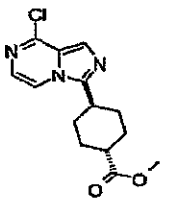
[215] A THF solution (1.00L) of _trans_-methyl 4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate (29.70g, 101.1mmol) was cooled to –78°C and was charged with LAH (1M in THF, 25.3mmol, 25.3mL) dropwise. After 30min., the reaction mixture was charged with additional LAH (25.3mmol) at –78°C and then, allowed to stir at –78°C for 1.5h. The reaction was slowly warmed up to rt and stirred for additional 30min. Ethyl acetate, $Na_2SO_4 \cdot 10H_2O$, and silica gel were added to the reaction mixture and concentrated *in vacuo* to give an orange solid. The crude mixture was purified by a silica gel glass column chromatography (eluted with 2:3 EtOAc/DCM to

100% EtOAc) to obtain the title compound as a slightly yellow-tinted white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14–1.30 (m, 2H), 1.61–1.75 (m_c, 1H), 1.84 (ddd, J = 13.2, 13.2, 13.2, 3.2 Hz, 2H), 1.98–2.13 (m, 4H), 2.19 (s, br, –OH), 2.94 (tt, J = 11.6, 3.2 Hz, 1H), 3.56 (d, J = 6.0 Hz, 2H), 7.31 (d, J = 5.2 Hz, 1H), 7.64 (dd, J = 5.2, 1.2 Hz, 1H), 7.79 (d, J = 0.8 Hz, 1H); MS (ES+): *m/z* 266.21/268.17 (100/89) [MH^+]. HPLC: t_R = 2.38 min (OpenLynx, polar_5min). MS (ES+): *m/z* 266.21 (100) [MH^+], 268.17 (80) [MH^+2}, 289.18 (20) [MH^+3]; t_R(polar-5min/openlynx) 2.36 min.

General procedure for the hydrolysis of carboxylic esters

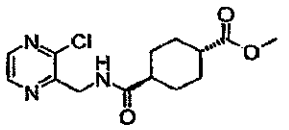
To a solution/slurry of the carboxylic ester (30.17 mmol) in ethanol (200 mL) was added 3.0 M of sodium hydroxide in water (15.1 mL) and the mixture was stirred at 40°C for 4 h. The solvent was removed under reduced pressure at 40 °C and to the residue was added water (10 mL) and ethanol (10 mL) and the slurry was filtered. The filter cake was washed with ethanol (2 x 10 mL) and dried under vacuum to yield the sodium salt. For the isolation of the free acid, water was added to this salt and the slurry was acidified with formic acid, stirred for 10 min at RT and filtered. The filter cake was washed with water followed by ethanol to yield the carboxylic acid.

***trans*-Methyl 4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate**



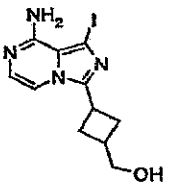
[216] *trans*-Methyl 4-({[(3-chloropyrazin-2-yl)methyl]amino}carbonyl)-cyclohexanecarboxylate (29.00g, 93.02mmol) was dissolved in anhydrous acetonitrile (930mL) and anhydrous DMF (9mL) and heated at 55°C under nitrogen for 3h. The reaction mixture was concentrated *in vacuo*, then, the solid residue was taken up in DCM, then, basified to pH 10 with 2M ammonia in isopropanol. The mixture was concentrated *in vacuo*, re-dissolved in DCM, and then loaded onto TEA-basified silica gel. The crude product was purified by a silica gel column chromatography (eluted with 2:3 EtOAc/DCM) to obtain the title compound as a yellow powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63 (ddd, J = 13.2, 13.2, 13.2, 3.2 Hz, 2H), 1.85 (ddd, J = 13.2, 13.2, 13.2, 2.8 Hz, 2H), 2.10 (dd, J = 14.4, 3.2 Hz, 2H), 2.19 (dd, J = 14.0, 3.2 Hz, 2H), 2.46 (tt, J = 12.4, 3.6 Hz, 1H), 2.96 (tt, J = 11.6, 3.2 Hz, 1H), 3.70 (s, 3H), 7.33 (dd, J = 5.2, 1.2 Hz, 1H), 7.61 (d, J = 4.8 Hz, 1H), 7.79 (s, 1H). MS (ES+): *m/z* 294.17/296.14 (100/86) [MH^+]. HPLC: t_R = 2.85 min (OpenLynx, polar_5min).

***trans*-Methyl 4-({[(3-chloropyrazin-2-yl)methyl]amino}carbonyl)cyclohexanecarboxylate**



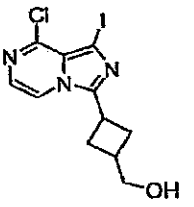
[217] A THF (370mL) solution of 4-(methoxycarbonyl)cyclohexanecarboxylic acid (15.14g, 81.30mmol) and CDI (13.18g, 81.30mmol) was placed under a nitrogen atmosphere and stirred at 60°C for 4h. The reaction mixture was cooled to rt, then, (3-chloropyrazin-2-yl)methylamine bis-hydrochloride salt (16.00g, 73.91mmol) and DIPEA (31.52g, 244.00mmol, 42.5mL) was added. After stirring at 60°C for 20h, the reaction was concentrated *in vacuo*. The crude reaction mixture was purified by a silica gel glass column chromatography (eluted with 3:2 DCM/EtOAc) to obtain the pure desired product as a slightly yellowish creamy white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43–1.65 (m, 4H), 2.01–2.14 (m, 4H), 2.25 (tt, J = 12.0, 3.6 Hz, 1H), 2.34 (tt, J = 11.6, 3.2 Hz, 1H), 3.68 (s, 3H), 4.70 (d, J = 4.4 Hz, 2H), 6.81 (s, br, –NH), 8.32–8.36 (m, 1H), 8.46 (d, J = 2.4 Hz, 1H); MS (ES+): *m/z* 312.17/314.12 (84/32) [MH^+]; HPLC: t_R = 2.44 min (OpenLynx, polar_5min).

[3-(8-Amino-1-iodoimidazo[1,5-a]pyrazin-3-yl)-cyclobutyl]methanol



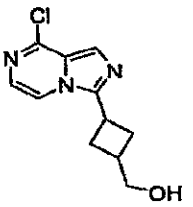
[218] [3-(8-Chloro-1-iodoimidazo[1,5-a]pyrazin-3-yl)cyclobutyl]methanol (6.9g) in *i*-PrOH (200mL) was saturated with $NH_{3(g)}$, by passing a slow a slow stream of ammonia for 10min at -20°C, and then heated in a Parr bomb at 110°C for 2d. The reaction mixture was then cooled to rt, filtered through a sintered glass and the solid residue and the Parr vessel were rinsed with *i*-PrOH several times. The filtrate was concentrated under reduced pressure to provide an orange solid still containing NH_4Cl. The material was taken up into refluxing MeCN (250mL) and filtered hot. The step was repeated with another portion of hot MeCN (200mL). The combined MeCN filtrates were concentrated under reduced pressure to give the title compound as an orange solid; HPLC: (polar5min) 0.53 and 1.51 min; MS (ES+): 345.1 (100, M^++1); ^{1}H NMR (400 MHz,DMSO-*d6*) δ 7.50 (d, J = 5.2 Hz, 1 H), 7.44 (d, J = 5.2 Hz, 0.27 H, *minor isomer*), 6.95 (d, J = 5.2 Hz, 1.29 H *overlapped with the minor isomer*) 6.63 (br, 2H), 4.61 (t, J = 5.2 Hz, 0.27H, *minor isomer*), 4.52 (t, J = 5.2 Hz, 1H), 3.69 (quintet, J = 5.6 Hz,0.32H, *minor isomer*), 3.54 (quintet, J = 5.6 Hz, 1H), 2.52-2.25 (m, 4H), 2.10-2.00 (m, 1H).

[3-(8-Chloro-1-iodo-imidazo[1,5-a]pyrazin-3-yl)-cyclobutyl]-methanol



[219] To a solution of NIS (6.31g, 28.0mmol) in anh DMF (100mL) under Ar was added dry [3-(8-chloroimidazo[1,5-a]pyrazin-3-yl)cyclobutyl]methanol (6.67g) dissolved in anh DMF (30mL). The flask containing [3-(8-chloroimidazo[1,5-a]pyrazin-3-yl)cyclobutyl] methanol was rinsed with another portion of anh DMF (20mL) and the rinse was added to the reaction mixture. The reaction was heated to 60°C (rt → 60°C ~ 30min) and the stirred at this temperature for 3h. The mixture was then cooled to rt, partitioned between 1M aq $Na_2S_2O_3$ (60mL), brine (60mL) and DCM (160mL). The aq layer was extracted with DCM (3x100mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography on SiO_2 (0-8 % MeOH in DCM) to provide a material, homogenous by UV on both TLC and HPLC, still containing DMF. The material was dissolved in DCM (200 mL) and washed with water (3x40 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide the title compound as a pale yellow solid; HPLC (polar5min) 2.52 min; MS (ES+): *m/z* (rel. int.) 364.0 (100, M^++1); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.59 (d, J = 4.8 Hz, 1 H), 7.49 (d, J = 4.8 Hz, 0.22 H, *minor isomer*), 7.29 (d, J = 4.8 Hz, 1 H), 7.28 (d, J = 5.2 Hz, 0.23 H, *minor isomer*), 3.83-3.80 (m, 0.7 H), 3.72-3.62 (m, 3 H), 2.75-2.55 (m, 4 H), 2.42-2.32 (m, 1-2H).

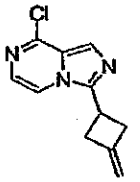
[3-(8-Chloro-imidazo[1,5-a]pyrazin-3-yl)-cyclobutyl]-methanol



[220] To a solution of 8-chloro-3-(3-methylenecyclobutyl)imidazo[1,5-a]pyrazine (4.48g, 20.4mmol) in anh THF (255mL) at –78°C under Ar, 9-BBN (61.2mL, 0.5M in THF, 30.6mmol) was added dropwise over 8min (a suspension). The cooling bath was replaced with ice-H_2O and the reaction was allowed to warm slowly to rt. After being stirred for 17h, H_2O (100mL,) was added followed by, after ~ 5min, $NaBO_3$•H_2O (12.2g, 122.3mmol) added in one lot. The reaction was stirred at rt for 5h and then filtered through Celite. The Celite and residual solids were washed with DCM and EtOAc. The filtrate was concentrated under reduced pressure to yield an aq solution, which was saturated with NaCl and extracted with EtOAc (3x). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield a light yellow oil which was purified by flash chromatography on SiO_2 (9:1 DCM:MeOH) to afford the title compound as a light yellow oil; HPLC:

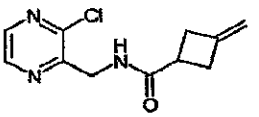
t_R (mass-directed HPLC, polar7min) 2.52min; MS (ES+): 238.0. The addition may be carried out at 0 °C. Suspension quickly clears up after the exchange of cooling baths. The final product contained 1,5-*cis*-octanediol derived from 9-BBN. Based on ^{1}H NMR estimated roughly to be 66 % target material and 33 % of the byproduct. The crude product was taken onto next step crude, stereoselectivity of the product was 4-5:1 as judged by ^{1}H NMR.

(8-Chloro-3- (3-methylene-cyclobutyl)-imidazo[1,5a]pyrazine)



[221] 3-Methylene-cyclobutanecarboxylic acid (3-chloro-pyrazin-2-ylmethyl)-amide (52.1g, 219.2mmol) was dissolved in 1.0L of anhydrous MeCN. Followed by the addition of DMF (1.0mL) and $POCl_3$ (100mL, 1.09mol). The reaction was heated to 55°C for 30min. with a slow N_2 bubbling the reaction. The reaction was then concentrated *in vacuo*, basified with cold 2.0M NH_3 in IPA with CH_2Cl_2. The IPA/CH_2Cl_2 was concentrated *in vacuo* and the salts were dissolved with minimal water and extracted with CH_2Cl_2 (4×). The organic layers where combined and washed with sat. $NaHCO_3$ (1×), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography [eluting with 2:1 Hex: EtOAc] to yield the title compound as a light yellow solid; ^{1}H NMR (400 MHz,$CDCl_3$) δ 3.24–3.30 (4 H, m), 3.78–3.85 (1 H, m), 4.89–4.94 (2 H, m), 7.33 (1 H, d, *J*=4.99 Hz), 7.53 (1 H, d, *J*=5.09 Hz), 7.82 (1 H, s); MS (ES+): *m/z* 220.28/222.30 (100/80) [MH^+]; HPLC: t_R = 2.87 min (OpenLynx, polar_5min).

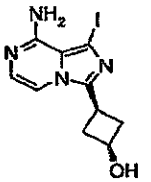
3-Methylene-cyclobutanecarboxylic acid (3-chloropyrazin-2-ylmethyl)amide



[222] *C*-(3-Chloropyrazin-2-yl)-methylamine bis-HCl (1.0g, 4.62mmol), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC) (1.31g, 6.47mmol, 1.4eq.), 4-dimethylamino pyridine (DMAP) (0.141g, 1.15mmol, 0.25eq.), and diisopropylethylamine (DIPEA) (2.42mL, 1.79g, 13.9mmol, 3.0eq.) were dissolved in anhydrous CH_2Cl_2 (25mL). To this solution, a solution of 3-methylenecyclobutanecarboxylic acid (0.622g, 5.54mmol, 1.2eq.) in anhydrous CH_2Cl_2 (25mL) was added under N_2 and the reaction was allowed to stir overnight at rt. Reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc, washed with water (2×), $NaHCO_3$ (1×), water (1×), and brine (1×), dried over Na_2SO_4, filtered, and concentrated *in vacuo*, giving crude title compound, as a brown oil. The crude material was purified by chromatography on

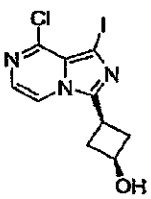
silica gel [Jones Flashmaster, 20g/70mL cartridge, eluting with EtOAc:Hex 10% → 20% → 40% → 70%], affording the title compound as a pale yellow solid. Additionally, the title compound could be prepared by the following route: 1,1'-Carbonyldiimidazole (CDI) (0.824g, 5.08mmol, 1.1eq.) and 3-methylenecyclobutanecarboxylic acid (0.570g, 5.08mmol, 1.1eq.) were dissolved in anhydrous THF (12mL) and allowed to stir at 60°C for 2h. A solution of *C*-(3-chloropyrazin-2-yl)-methylamine bis-HCl (1.0g, 4.62mmol) and diisopropylethylamine (DIPEA) (2.42mL, 1.79g, 13.9mmol, 3.0eq.) in anhydrous CH_2Cl_2 (13mL) was added to the acid mixture and the reaction was allowed to stir at 60°C, under N_2, overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc, washed with $NaHCO_3$ (2×) and brine (1×), dried over Na_2SO_4, filtered, and concentrated *in vacuo*, giving crude title compound, as a brown oil. The crude material was purified by chromatography on silica gel [Jones Flashmaster, 20g/70mL cartridge, eluting with EtOAc:Hex 10% → 20% → 40% → 70%], affording the title compound as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.86–2.96 (m, 2H), 3.03–3.19 (m, 3H), 4.72 (dd, J = 4.4, 0.8 Hz, 2H), 4.79–4.84 (m, 2H), 6.78 (s, –NH), 8.32–8.34 (m, 1H), 8.46 (d, J = 2.8 Hz, 1H); MS (ES+): *m/z* 238.19 (90) [MH^+]; HPLC: t_R = 2.67 min (OpenLynx, polar_7min).

3-(8-Amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanol



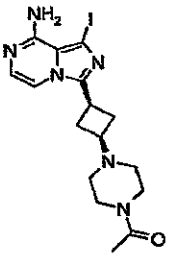
[223] In a Parr pressure reactor 3-(8-chloro-1-iodo-imidazo[1,5-a]pyrazin-3-yl)-cyclobutanol (4.159g, 0.0119mol) was dissolved with 2.0M ammonia in isopropyl alcohol (40mL). The mixture was cooled to -20°C and saturated with ammonia. The reaction was heated at 110°C for 63h at which point it was cooled and concentrated *in vacuo*. The crude product was purified using HPFC Jones 25g silica gel column eluting with 5-8% MeOH: CH_2Cl_2 to yield the title compounds; MS (ES+): *m/z* 330.88 (100) [MH^+], 331.89 (10) [MH^{++}]; HPLC: t_R = 0.48 min (OpenLynx, polar_5min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 - 2.76 (m, 2 H) 3.06 - 3.22 (m, 2 H) 3.32 - 3.50 (m, 1 H) 4.51 - 4.69 (m, 1 H) 6.15 (br. s., 2 H) 7.24 (d, J=5.05 Hz, 1 H) 7.39 (d, J=5.05 Hz, 1 H).

3-(8-Chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanol



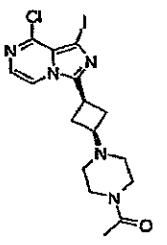
[224] 3-(8-Chloro-1-iodo-imidazo[1,5-a]pyrazin-3-yl)-cyclobutanone (5.0g, 14mmol) was dissolved in a 1:1 mixture of methanol (35.0mL) and CH_2Cl_2 (35.0mL). To the solution mixture sodium tetrahydroborate (560mg, 14.0mmol) was added slowly, gas evolution was observed. After 4.5h at rt under nitrogen, the reaction was concentrated *in vacuo*. The crude mix was dissolved in EtOAc and washed with water. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using HPFC Jones 50 gram silica gel column eluting with 50% EtOAc: Hex to 100% EtOAc, to yield the title compound as a light yellow solid; MS (ES+): *m/z* 349.81 (100) [MH^+], 351.50 (30) [MH^{+++}]; HPLC: t_R = 2.49 min (OpenLynx, polar_5min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 - 2.54 (m, 2 H) 2.78 - 3.05 (m, 1 H) 3.12 - 3.32 (m, 1 H) 4.08 - 4.75 (m, 1 H) 5.30 (s, 1 H) 7.31 (d, *J*=5.05 Hz, 1 H) 7.57 (d, *J*=4.80 Hz, 1 H)

1-{4-[3-(8-Amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutyl]piperazin-1-yl}ethanone



[225] 1-{4-[3-(8-Chloro-1-iodoimidazo[1, 5-*a*]pyrazin-3-yl)cyclobutyl]piperazin-1-yl}ethanone (13.2g, 0.029mol) was dissolved in isopropyl alcohol (100mL) into a Parr pressure reactor. The vessel was cooled to -78°C and saturated with ammonia gas and sealed. The reaction was heated for 19h at 110°C, at which point the reaction was cooled and the solvent concentrated *in vacuo*. The crude product was purified via silica gel chromatography eluting with 5-10% MeOH (7M NH_3): CH_2Cl_2 to yield the title compounds as an off white solid; MS (ES+): *m/z* 440.89 (100) [MH^+], 441.89 (20) [MH^{++}]; HPLC: t_R = 0.46 min (OpenLynx, polar_5min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3 H) 2.28 - 2.48 (m, 6 H) 2.54 - 2.71 (m, 2 H) 2.80 - 2.99 (m, 1 H) 3.27 - 3.43 (m, 1 H) 3.43 - 3.54 (m, 2 H) 3.56 - 3.70 (m, 2 H) 7.02 (d, *J*=5.05 Hz, 1 H) 7.16 (d, *J*=5.05 Hz, 2 H).

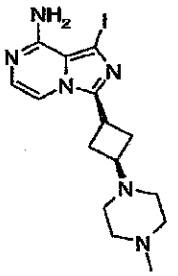
1-{4-[3-(8-Chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutyl]piperazin-1-yl}ethanone



[226] Into a RBF 3-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone (1.00g, 0.0029mol) and sodium triacetoxyborohydride (1.30g, 0.006mol) were dissolved in 1,2-

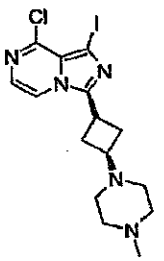
dichloroethane (65.0mL) and a solution of 1-acetylpiperazine (0.39g, 0.003mol) in 1,2-dichloroethane was added to the reaction. The reaction mixture was stirred at rt for 2h. The crude product was concentrated *in vacuo* and the dissolved in CH_2Cl_2 (25.0mL) and washed with saturated $NaHCO_3$ solution (1 x 40mL). The product was dried with sodium sulfate and concentrated *in vacuo* to yield a light yellow solid; MS (ES+): *m/z* 459.84 (100) [MH^+], 461.80 (40) [MH^{+++}]; HPLC: t_R = 1.81 min (OpenLynx, polar_5min); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.04 - 2.15 (m, 3 H) 2.26 - 2.50 (m, 6 H) 2.55 - 2.72 (m, 2 H) 2.83 - 2.99 (m, 1 H) 3.29 - 3.52 (m, 3 H) 3.56 - 3.67 (m, 2 H) 7.29 (d, 1 H) 7.58 (d, 1 H).

(1-Iodo-3-[3-(4-methyl-piperazin-1-yl)-cyclobutyl]-imidazo[1,5-a]pyrazin-8-ylamine)



[227] A solution of 2N ammonia in isopropyl alcohol (350mL) and THF (30mL, 0.4mol) was added to 8-chloro-1-iodo-3-[3-(4-methyl-piperazin-1-yl)-cyclobutyl]-imidazo[1,5-a]pyrazine (19.91g, 0.04612mol) in a Parr bomb and cooled to -78°C. Ammonia was bubbled into the solution for 8-10min. The bomb was sealed, stirred and heated to at 110°C over 3d. The solvent was then evaporated *in vacuo* and purified by flash silica gel chromatography (wetted with $CHCl_3$, dried loaded with silica, and eluted with 8% (7N NH_3) MeOH in $CHCl_3$), which afforded the title compound; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (1 H, d, *J = 5.01*), 7.16 (1 H, d, *J* = 6.25), 5.83 (2 H, s), 3.49 (1 H, m), 3.06 (1 H, m), 2.76 (4 H, m), 2.64 (8 H, m), 2.46 (3H, s); MS (ES+): *m/z* 412.89/413.91 (50/10) [MH^+]; HPLC: t_R = 0.31 min. (OpenLynx, polar_5min.).

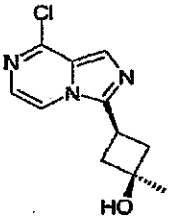
(8-Chloro-1-iodo-3-[3-(4-methylpiperazin-1-yl)cyclobutyl]imidazo[1,5-*a*]pyrazine)



[228] 1-Methyl piperazine (5.75mL, 0.0514mol) in 1,2-dichloroethane (1096.7mL, 13.892mol) was added to 3-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone (17.00g, 0.04892mol) and sodium triacetoxyborohydride (21.8g, 0.0978mol). The reaction stirred at rt for 3h.

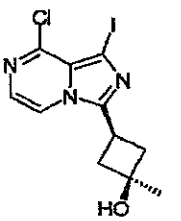
The reaction was concentrated, dissolved in CH_2Cl_2, and then washed with saturated $NaHCO_3$ solution and brine. The product was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The product was flushed through a quick silica gel plug (wetted with 100% $CHCl_3$, eluted with 8% (7N NH_3) MeOH in $CHCl_3$), to afford the title compound; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (1 H, d), 7.30 (1 H, d), 3.42 (1H, m), 2.94 (1H, m), 2.65 (4 H, m), 2.44 (8 H, m), 2.32 (3H, s); MS (ES+): *m/z* 431.85/433.87 (100/45) [MH^+]; HPLC: t_R = 1.82 min. (OpenLynx, polar_5min.).

3-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol



[229] 3-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone (1.95 g, 8.80 mmol) in anhydrous THF (77.78 mL) at -78 °C under an atmosphere of nitrogen was treated slowly with a 3.0 M solution of methylmagnesium chloride in THF (5.9 mL). The solution stirred for 3hr at -78 °C then quenched with 40 mL of semi-saturated aqueous NH_4Cl (NH_4Cl dilution in 1:1 mixture with water) at -78 °C and allowed to warm up to rt. The mixture was then extracted with EtOAc (3 x 40 mL) and the combined extracts washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude solid was purified by chromatography over silica gel eluting with 1:1 EtOAc/DCM to 4% MeOH in (1:1) EtOAc/DCM to afford desired product. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.54 (s, 3 H), 2.74 - 2.60 (m, 4 H), 3.75 – 3.39 (m, 1 H), 7.35 (d, J = 5.04 Hz, 1 H), 7.71 (d, J = 5.00 Hz, 1 H) and 7.86 (s, 1 H). MS (ES+): m/z 238.15 and 240.17 [MH^+].

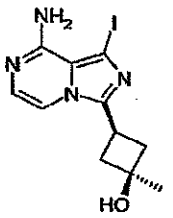
3-(8-Chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol



[230] 3-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol (2.20 g, 9.26 mmol) and NIS (2.71 g, 12.0 mmol) were dissolved in DMF (36.6 mL, 0.472 mol) and stirred at 60 °C for 4 h. The mixture was then concentrated *in vacuo* and the residue reconstituted in EtOAc (100 mL). This solution was washed with sodium bicarbonate (2 x 20 mL) and these washes back-extracted with

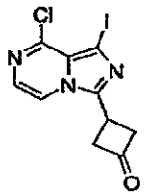
EtOAc (2 x 20 mL). The organic layers were combined, dried with sodium sulfate, filtered and concentrated *in vacuo*. The crude solid was purified by chromatography over silica gel eluting with 1:1 EtOAc:hexanes to afford desired product. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.53 (s, 3 H), 2.72 - 2.59 (m, 4 H), 3.37 – 3.29 (m, 1 H), 7.32 (d, J = 4.91 Hz, 1 H) and 7.60 (d, J = 4.96 Hz, 1 H). MS (ES+): m/z 363.95 and 365.91 [MH^+].

3-(8-Amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol



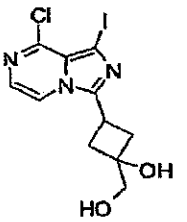
[231] A solution of 2M ammonia in isopropanol (80 mL) and THF (5 mL) was added to 3-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol (2.77 g, 7.62 mmol) in a Parr pressure reactor. The mixtiure was cooled to at -78 °C then ammonia gas was bubbled into the solution for 4-6 min. The reactor was sealed then heated at 110 °C for 15 h. The solvent was then removed *in vacuo* and the residue purified by chromatography over silica gel eluting with 7% MeOH in DCM to afford desired product. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.44 (s, 3 H), 2.32 - 2.51 (m, 4 H), 3.33 - 3.52 (m, 1 H), 6.61 (br.s., 2 H), 7.03 (d, J = 5.05 Hz, 1 H) and 7.62 (d, J = 5.05 Hz, 1 H).

(3-(8-Chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone)



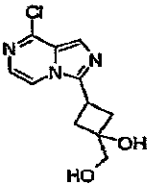
[232] A solution of 3-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)-1-hydroxymethylcyclobutanol (4.08g, 0.011mol) in THF (120mL) and water (40mL) was charged with sodium periodate (2.8g, 0.013mol) at 0°C. The reaction warmed to rt and stirred for 5h. The reaction mixture was diluted with ethyl acetate and then washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (1 H, d, *J* = 4.94), 7.32 (1 H, d, *J* = 4.98), 3.64 (5 H, m); MS (ES+): *m/z* 347.82 and 349.85 [MH^+]; HPLC: t_R = 2.89 min. (OpenLynx, polar_5min.).

3-(8-Chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)-1-hydroxymethylcyclobutanol



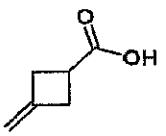
[233] Under inert atmosphere *N*-iodosuccinimide (3.6g, 0.016mol) and 3-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)-1-hydroxymethylcyclobutanol (3.16g, 0.012mol) were dissolved in *N*,*N*-dimethylformamide (30mL) and heated at 60°C for 3.0h. The reaction mixture was then concentrated *in vacuo* to a dark oil and purified by HPFC Jones 20g silica gel column, eluting with 5% MeOH: CH_2Cl_2 to yield a light brown fluffy solid which was triturated with diethyl ether and hexanes to afford the title compound; MS (ES+): *m/z* 379.85 and 381.80 [MH^+]; HPLC: t_R = 2.30 min (OpenLynx, polar_5min).

3-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)-1-hydroxymethylcyclobutanol



[234] To a THF solution (170 mL) of 8-chloro-3-(3-methylenecyclobutyl)imidazo[1,5-*a*]pyrazine (3.1g, 14mmol), water (18mL), 50% *N*-methylmorpholine-*N*-oxide in water (3.2mL) and potassium osmate, dehydrate (200mg, 0.70mmol) were added and the reaction was allowed to stir at rt for 4h. Sodium sulfite (8.0g, 70.0mmol) was added to the reaction mixture and allowed to stir for 30min at which point the reaction was concentrated *in vacuo*. The crude product was extracted from the aqueous with EtOAc. The organics were washed with brine and the combined aqueous washes were back extracted with EtOAc (5 x 50 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the title compounds as a sticky tan/off-white solid; MS (ES+): *m/z* 254.17 (100) [MH^+], 256.19 (50) [MH^{+++}]; HPLC: t_R = 1.95 min (OpenLynx, polar_5min).

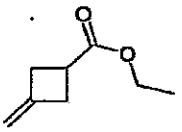
3-Methylene-cyclobutanecarboxylic acid



[235] To a solution of 3-methylenecyclobutanecarbonitrile (100.0 g, 1.042 mol) in ethanol (1.00 L) and water (1.00 L) was added potassium hydroxide (230.0 g, 4.2 mol). The resulting mixture

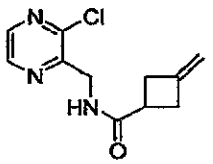
was heated at reflux for 7 hr then the EtOH was removed *in vacuo* and the solution was cooled to 0 °C and acidified with (300.0 mL) of conc. HCl to pH = 1. The mixture was extracted with diethyl ether (4 x 1L) and the combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo* to yield desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.64–3.44 (m, 5H), 4.60–4.98 (m, 2H) and 10.64 (br. s., 1H).

Ethyl 3-methylenecyclobutanecarboxylate



[236] Iodoethane (7.5 mL, 93.0 mol) was added at rt to a mixture of 3-methylenecyclobutanecarboxylic acid (10.0 g, 80.0 mmol) and cesium carbonate (56.0 g, 170.0 mmol) in anhydrous *N,N*-dimethylformamide (500.00 mL) under an atmosphere of nitrogen. The reaction was stirred for 16hr then partitioned between diethyl ether (1L) and brine (1L). The aqueous layer was extracted with diethyl ether (3 x 500 mL) and the combined organic phases washed with water (2 x 1L), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield desired product ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (t, 3H), 2.71–3.27 (m, 5H), 4.15 (q, J=7.07 Hz, 2H) and 4.53–4.96 (m, 2H).

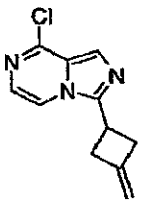
***N*-[(3-chloropyrazin-2-yl)methyl]-3-methylenecyclobutanecarboxamide**



[237] 1,1'-Carbonyldiimidazole (CDI) (8.24 g, 50.81 mmol) and 3-methylenecyclobutanecarboxylic acid (5.70 g, 50.81 mmol) were dissolved in anhydrous THF (100 mL) and allowed to stir at 60 °C for 4 h. A solution of C-(3-Chloropyrazin-2-yl)methylamine bis-hydrochloride (10.0 g, 46.19 mmol) and diisopropylethylamine (DIPEA) (32.30 mL, 184.76 mmol) in anhydrous CH_2Cl_2 (150 mL) was added to the mixture and the reaction was allowed to stir at rt for 24h. The mixture was concentrated *in vacuo*, the residue dissolved in EtOAc and the resulting solution washed with saturated $NaHCO_3$ (aq.) water H_2O and Brine. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude product, which was purified by chromatography over silica gel eluting with 50-70% EtOAc/hexane to yield desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.92–2.94 (2 H, m), 3.05–3.14 (2 H, m), 4.60 (2 H, d,

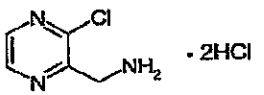
J=4.24 Hz), 4.80–4.84 (2 H, m), 6.75 (1 H, brs), 8.33 (1 H, d, J=4.22 Hz) and 8.45 (1 H, d, J=2.54 Hz). MS (ES+): m/z 238 and 240 [MH+].

8-Chloro-3-(3-methylenecyclobutyl)imidazo[1,5-*a*]pyrazine



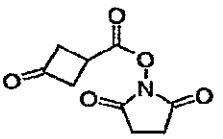
[238] *N*-[(3-Chloropyrazin-2-yl)methyl]-3-methylenecyclobutanecarboxamide (52.1 g, 219.2 mmol) in anhydrous MeCN (1.0 L) was treated with DMF (1.0 mL) and $POCl_3$ (100 mL, 1.09 mol) and the mixture was stirred at 55°C for 30 min. under a gentle stream of N_2. The reaction was then concentrated *in vacuo* and the residue reconstituted in CH_2Cl_2 and treated with cold 2.0 M NH_3 in IPA. This mixture was concentrated *in vacuo*, water added to dissolve the salts, and then extracted with CH_2Cl_2 (4× 60mL). The organic layers where combined and washed with sat. $NaHCO_3$ (1× 70mL) dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by chromatography over silica gel eluting with 2:1 hexane: EtOAc to yield desired product. ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm 3.24–3.30 (4 H, m), 3.78–3.85 (1 H, m), 4.89–4.94 (2 H, m), 7.33 (1 H, d, J=4.99 Hz), 7.53 (1 H, d, J=5.09 Hz) and 7.82 (1 H, s). MS (ES+): m/z 220.28 and 222.30 [MH+].

C-(3-Chloropyrazin-2-yl)methylamine bis-hydrochloride



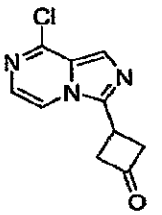
[239] A solution of 2-(3-chloropyrazin-2-ylmethyl)-isoindole-1,3-dione (10.0g, 36.5mmol) in anhydrous CH_2Cl_2 (200mL) was charged with hydrazine (2.87mL, 2.93g, 91.3mmol, 2.5eq.) at rt, under N_2 atmosphere. After 2.5h, MeOH (300mL) was added and the reaction was heated until the solution was homogenous. The reaction mixture was allowed to stir for 19h. The white ppt that had formed (2,3-dihydrophthalazine-1,4-dione byproduct), was filtered off and washed several times with ether. The clear filtrate was concentrated *in vacuo* and the concentrate was dissolved in EtOAc and filtered again to remove white ppt. All solvent was removed, giving a yellow oil, which was dissolved into EtOAc and ether and charged with HCl (g). The title compound, a pale yellow solid, instantly precipitated. The title compound was dried in a 40 °C oven for 72h, affording the title compound, as a dark yellow solid; ^{1}H NMR (400 MHz, CD_3OD) δ 4.55 (2 H, s), 8.27 (1 H, d, *J*=2.52 Hz), 8.54 (1 H, d, *J*=2.56 Hz); MS (ES+): *m/z* 143.96/145.96 (100/60) [MH^+]; HPLC: t_R = 0.41 min (OpenLynx, polar_7min).

1-{[(3-Oxocyclobutyl)carbonyl]oxy}pyrrolidine-2,5-dione



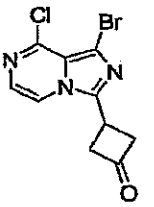
[240] Into a 5L reactor equipped with a nitrogen flow and an overhead stirrer was added *N*-hydroxysuccinimide (250.0 g, 2.172 mol) and 3-oxo-cyclobutanecarboxylic acid (248 g, 2.17 mol). Ethyl acetate (3.4 L) was added and the reaction was cooled to 16 °C. A solution of 25% DCC in EtOAc (2.17 mol) was added slowly via an addition funnel to the reaction mixture over 7 minutes then the mixture was then heated at 45 °C. After 2h, the mixture was filtered and the filtrate was washed once with EtOAc (1L x 1) and evaporated to dryness *in vacuo* to afford the desired product. ^{1}H NMR (400 MHz, DMSO-d6) δ 2.83 (bs, 4H), 3.30–3.39 (m, 2H), 3.52–3.60 (m, 2H) and 3.67–3.73 (m, 1H).

3-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone



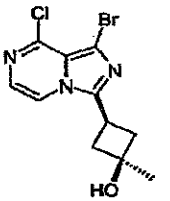
[241] Into a round bottom 1-neck flask (5L), 3-oxo-cyclobutanecarboxylic acid 2,5-dioxo-pyrrolidin-1-yl ester (217.2g, 0.937 mol), C-(3-chloro-pyrazin-2-yl)-methylamine hydrochloride salt (153.3 g, 0.852 mol), and THF (760 mL) were added. A solution of 10% NaHCO3 (1.07 kg) was then added and after 20 min, the layers were allowed to separate and the aqueous layer was removed. The aqueous layer was back extracted with EtOAc (1x700 mL, 1x300 mL). The combined organics were washed with brine (350 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide the title compound. This solid was resuspended in ethyl acetate (915 mL) and DMF (132 mL) and the solution was put under an atmosphere of nitrogen and cooled to 10.5 °C. Phosphorus oxychloride (159 mL, 1.70 mol) was then added over 15 minutes and the reaction was allowed to stir for 45 min. The reaction solution was then poured slowly into a 22% aqueous Na_2CO_3 solution at 10°C. Water (1 L) was added and the layers were allowed to separate. The organic layer was removed and the aqueous was back extracted with EtOAc (1x1L, 1x0.5L). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo* until about 0.5 L of solvent remained. Heptane was added and the slurry was concentrated *in vacuo* until most of the EtOAc was removed. The resultant slurry was filtered to give desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59–3.68 (m, 2H), 3.72–3.79 (m, 2H), 3.86–3.94 (m, 1H), 7.40 (d, 1H, J = 5.2 Hz), 7.60 (d, 1H, J = 5.2 Hz) and 7.85 (s, 1H).

3-(1-Bromo-8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone



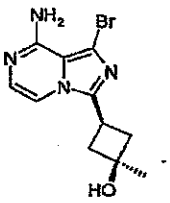
[242] 3-(8-Chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone (47.7 g, 215 mmol) was dissolved in DMF (200 mL) under an atmosphere of nitrogen and cooled to –4 °C. *N*-Bromosuccinimide (40.3 g, 226 mmol) was dissolved in DMF (140 mL) and slowly added to the reaction mixture. After 5 min, water (400 mL) was added and the resulting solid isolated by filtration and washed with solid with water to give the title compound. ^{1}H NMR (DMSO-d6, 400 MHz): δ 3.45–3.53 (m, 2H), 3.58–3.67 (m, 2H), 4.08–4.16 (m, 1H), 7.45 (d, 1H, J = 5.2 Hz) and 8.30 (d, 1H, J = 4.8 Hz).

3-(1-Bromo-8-chloroimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol



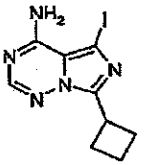
[243] 3-(1-Bromo-8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone (51.988 g, 0.17 mol) in anhydrous THF (550 g, 620 mL) under nitrogen at -78 °C was treated with a 3.0 M solution of methyl magnesium chloride in THF (130 mL, 0.38 mol) over 30 min. The mixture was stirred at -78 °C for 30 min and then the cooling bath was removed and the mixture quenched with 14% NH_4Cl (132 g). EtOAc was added to the aqueous phase and the pH was adjusted to ~5 with 20% HCl and the layers separated. The combined organic phases were concentrated *in vacuo* to a slurry and 0.5 L of toluene was added and the mixture concentrated *in vacuo* until the EtOAc was removed. The slurry was heated at reflux until homogeneous then allowed to cool to provide desired product, which was isolated by filtration and dried *in vacuo*. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.37 (s, 3H), 2.35–2.49 (m, 4H), 3.52 (dddd, 1H, *J* = 9.6, 9.6, 9.6, 9.6 Hz), 5.18 (bs, 1H), 7.37 (d, 1H, *J* = 5.2 Hz) and 8.26 (d, 1H, *J* = 5.2 Hz).

3-(8-Amino-1-bromoimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol



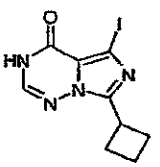
[244] A 35% ammonia solution (132ml, 2.9 moles) was added to a suspension of 3-(1-bromo-8-chloroimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol (22.0g, 0.06463 mol) in 2-butanol (81ml). The mixture was heated at 90 °C in a pressure vessel for 15hr then concentrated to ~130ml, cooled to room temperature and the solid collected by filtration. This material was washed with water (3 x 22mL) and dried at 40 °C under vacuum. To afford the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.5 (d, 1H), 7.0 (d, 1H), 6.6 (bs, 2H), 5.1 (s, 1H), 3.4 (pentet, 1H), 2.3-2.4 (m, 4H) and 1.4 (s, 3H).

7-Cyclobutyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-ylamine



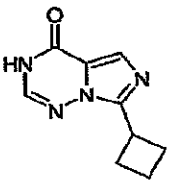
[245] To a solution of 1,2,4-triazole (1.28g, 18.59mmol) in anhydrous pyridine (10mL) was added phosphorus oxychloride ($POCl_3$) (0.578mL, 6.20mmol) and stirred at rt for 15min. This mixture was dropwise charged (3.5min) with a solution of 7-cyclobutyl-5-iodo-3H imidazo[5,1f][1,2,4]triazin-4-one (0.653mg, 2.07mmol) in anhydrous pyridine (14mL) and stirred for 1.5h. The reaction mixture was cooled to 0°C quenched with 2M NH_3 in isopropanol (IPA) until basic then allowed to reach rt and stirred for an additional 2h. The reaction mixture was filtered through a fritted Buchner funnel and washed with DCM. The filtrate was concentrated *in vacuo* and purified by chromatography on silica gel [eluting with 30% EtOAc in DCM] resulting in the title compound as an off-white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93–2.04 (m, 1H), 2.05–2.18 (m, 1H), 2.35–2.45 (m, 2H), 2.49-2.62 (m, 2H), 4.00-4.12 (m, 1H), 7.82 (s, 1H); MS (ES+): *m/z* 316.08 (100) [MH^+], HPLC: t_R = 2.59 min (MicromassZQ, polar_5min).

7-Cyclobutyl-5-iodo-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one



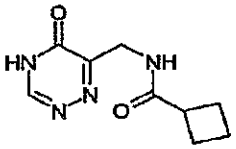
[246] A solution of 7-cyclobutyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (789mg, 4.15mmol) and *N*-iodosuccinimide (NIS, 933mg, 4.15mmol) in anhydrous DMF (40mL) was stirred overnight at rt. An additional 4eq. of NIS was added and reaction was heated to 55°C for 6h. The reaction mixture was concentrated *in vacuo* and partitioned between DCM and H_2O and separated. The aqueous layer was washed with DCM (3X) and the combined organic fractions were washed with 1M sodium thiosulfate ($Na_2S_2O_3$) (1X), brine (1X), dried over sodium sulfate (Na_2SO_4), filtered, and concentrated *in vacuo*. The solid was triturated with 20 % EtOAc in DCM and filtered through a fritted Buchner funnel resulting in the title compound as an off-white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.84–1.96 (m, 1H), 1.98–2.13 (m, 1H), 2.25–2.43 (m, 4H), 3.84–3.96 (m, 1H), 7.87 (s, 1H); MS (ES+): *m/z* 317.02 (100) [MH^+], HPLC: t_R = 2.62 min (MicromassZQ, polar_5min).

7-Cyclobutyl-3H-imidazo[5,1-*f*][1,2,4]triazin-4-one



[247] A crude solution of cyclobutanecarboxylic acid (5-oxo-4,5-dihydro-[1,2,4]triazin-6-ylmethyl)amide (1.33g, 6.39mmol) in phosphorus oxychloride ($POCl_3$) (10mL) was heated to 55°C. The reaction was heated for 2h then concentrated *in vacuo* and the crude oil was cooled to 0°C in an ice-bath and quenched with 2M NH_3 in ispropanol (IPA) until slightly basic. This crude reaction mixture was concentrated *in vacuo* and was partitioned between DCM and H_2O and separated. The aqueous layer was extracted with DCM (3X) and the combined organic fractions were dried over sodium sulfate (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel [eluting with 5% MeOH in DCM], resulting in the title compound as an off-white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86–1.96 (m, 1H), 2.00–2.13 (m, 1H); 2.26–2.46 (m, 4H); 3.87–4.00 (m, 1H); 7.71 (s, 1H); 7.87 (d, J = 3.6 Hz, 1H); 11.7 (brs, 1H); MS (ES+): *m/z* 191.27 (100) [MH^+], HPLC: t_R = 2.06 min (MicromassZQ, polar_5min).

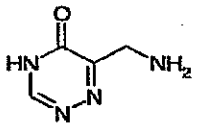
Cyclobutanecarboxylic acid (5-oxo-4,5-dihydro-[1,2,4]triazin-6-ylmethyl)amide



[248] To a solution of 6-aminomethyl-4*H*-[1,2,4]triazin-5-one (500mg, 3.96mmol) and N,N-diisopropylethylamine (DIEA) (0.829mL, 4.76mmol) in anhydrous N,N-dimethylforamide (DMF) (20mL) and anhydrous pyridine (2mL) was dropwise charged with cyclobutanecarbonyl

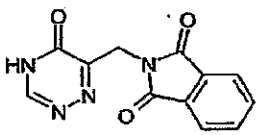
chloride (0.451mL, 3.96mmol) at 0°C then warmed to rt and stirred for an additional 1.5h. The reaction mixture was quenched with H_2O (2mL) and concentrated *in vacuo* and was purified by chromatography on silica gel [eluting with 5% MeOH in DCM (200 mL) → 10% MeOH in DCM (800mL)], affording the title compound; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.7–1.82 (m, 1H), 1.70–1.92 (m, 1H); 1.97–2.07 (m, 2H); 2.07–2.19 (m, 2H); 3.55–3.67 (m, 1H); 4.19 (d, 2H); 7.97 (brt, J = 5.6 Hz, 1H); 8.67 (s, 1H); MS (ES+): *m/z* 209.25 (100) [MH$^+$], HPLC: t_R = 1.56 min (MicromassZQ, polar_5min).

6-Aminomethyl-4*H*-[1,2,4]triazin-5-one



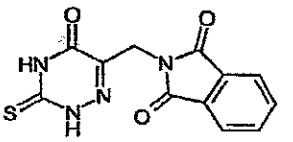
[249] A slurry of 2-(5-oxo-4,5-dihydro-[1,2,4]triazin-6-ylmethyl)isoindole-1,3-dione (4g, 15.6mmol) in DCM/EtOH (1:1) (150mL) was charged with anhydrous hydrazine (1.23mL, 39.0mmol) and stirred at rt for 18h. The reaction mixture was concentrated *in vacuo* and the off-white solid was triturated with warm $CHCl_3$ and filtered through a fritted funnel. The solid was then triturated with hot boiling methanol (MeOH) and filtered through a fritted funnel resulting in an off-white solid. The material was triturated a second time as before and dried overnight resulting in the title compound as a white solid, which was taken on to the next step without further purification; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.88(s, 2H), 8.31 (2, 1H); MS (ES+): *m/z* 127.07 (100) [MH$^+$], HPLC: t_R = 0.34 min (MicromassZQ, polar_5min).

2-(5-Oxo-4,5-dihydro-[1,2,4]triazin-6-ylmethyl)isoindole-1,3-dione



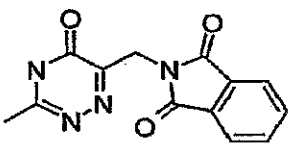
[250] A slurry of 2-(5-oxo-3-thioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylmethyl)isoindole-1,3-dione (1.0g, 3.47mmol) in EtOH (40mL) was charged with excess Raney Ni (3 spatula) and heated to reflux for 2h. The reaction mixture was filtered hot through a small pad of celite and washed with a hot mixture of EtOH/THF (1:1) (100mL) and the filtrate was concentrated *in vacuo* resulting in the title compound as an off-white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.75 (s, 2H), 7.84-7.98 (m, 4H), 8.66 (s, 1H); MS (ES+): *m/z* 257.22 (100) [MH$^+$].

2-(5-Oxo-3-thioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-ylmethyl)indan-1,3-dione



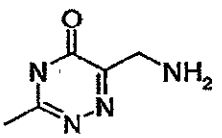
[251] A slurry of 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-oxo-propionic acid ethyl ester (20g, 76.6mmol) in anhydrous EtOH (300mL) was charged with thiosemicarbazide (6.98 g, 76.6mmol) in one portion and heated to 80°C for 2h. The reaction mixture was charged with N,N-diisopropylethylamine (DIEA) (26.7mL, 76.56mmol) and heated to 40°C for 6h then stirred at rt for an additional 10h. The reaction mixture was concentrated *in vacuo* and solid was triturated with hot EtOH/EtOAc filtered and washed with EtOAc. The solid was dried overnight in a vacuum oven (40°C) resulting in the title compound as an off-white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.68 (s, 2H), 7.85-7.95 (m, 4H); MS (ES+): *m/z* 289.2 (100) [MH$^+$].

2-[(3-Methyl-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione



[252] A solution of ethyl 3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-oxopropanoate [*J.Org.Chem.*, (1985), **50** (1), 91] (4.29 g, 16.4 mmol), acetamidrazone hydrochloride (1.80 g, 16.4 mmol) in anhydrous EtOH (85.8 mL) was heated to 80 °C for 3 h then cooled to rt and stirred for an additional 16 h. The reaction mixture was filtered through a fritted funnel resulting in 3.28 g, (73 % yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.28 (s, 3H), 4.73 (s, 2H) and 7.74 - 8.12 (m, 4H); MS (ES+): m/z 271.08 [MH+].

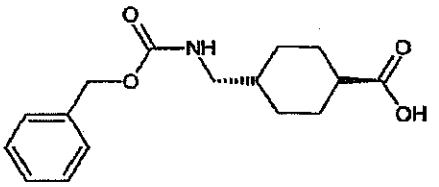
6-(Aminomethyl)-3-methyl-1,2,4-triazin-5(4*H*)-one



[253] A solution of 2-[(3-methyl-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (2.00 g, 7.40 mmol) in DCM (10.0 mL) and EtOH (10.0 mL) was charged with hydrazine (0.58 mL, 18.5 mmol) and stirred at rt for 8 h, then heated to 45 °C for an additional 16 h. The reaction was charged with an additional 0.5 equiv of hydrazine (0.116 mL, 3.70 mmol) and heated to 45 °C for 4 h. The reaction mixture was allowed to cool to rt then filtered through a fritted funnel and the cake was washed with 2 portions of cold 1:1 EtOH/DCM (75 mL) and the filtrate was

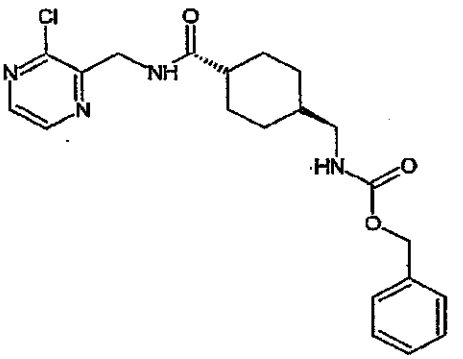
concentrated resulting in 622 mg of a pale yellow solid which was taken on to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3H), 3.72 (s, 2H); MS (ES+): m/z 141.06 [MH+].

trans-4-({[(Benzyloxy)carbonyl]amino}methyl)cyclohexanecarboxylic acid



[254] *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid (10.00 g, 0.06361 mol), in a 10% aq solution of NaOH (5.60g in 55 mL) was cooled to 0°C and treated over 15 min with vigorous stirring, with benzyl chloroformate (11 mL, 0.076 mol). After one hour the solution was acidified (1M HCl(aq)) and the resulting the white precipitate collected by filtration, washed with water and hexane then dried *in vacuo* oven overnight to afford 17.23g of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93-0.99 (m, 2H), 1.38-1.46 (m, 2H), 1.82-1.85 (m, 2H), 2.03-2.06 (m, 2H), 2.25 (m, 1H), 3.06 (t, J = 5.6 Hz, 2H), 4.83 (m, 1H), 5.09 (s, 2H), 7.31-7.36 (m, 5H). MS (ES+): m/z 292 [MH+].

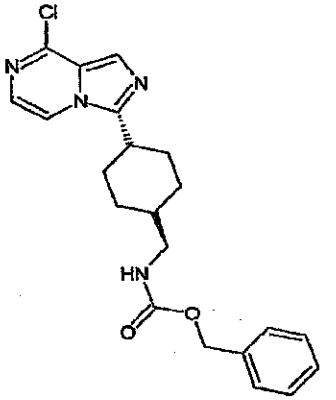
Benzyl [(trans-4-{[(3-chloropyrazin-2-yl)methyl]carbamoyl}cyclohexyl)methyl]carbamate



[255] To a solution of C-(3-chloropyrazin-2-yl)methylamine hydrochloride salt (0.100 g, 0.533 mmol) in DCM (1.35 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.16 g, 0.83 mmol), *N,N*-diisopropylethylamine (0.14 mL, 0.83 mmol), 1-hydroxybenzotriazole (0.075 g, 0.56 mmol) and *trans*-4-({[(benzyloxy)carbonyl]amino}methyl)cyclohexanecarboxylic acid (0.21 g, 0.70 mmol). The reaction was stirred at rt overnight then diluted with DCM, washed with sat. $NaHCO_3$ (aq) and brine, then dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue thus isolated was chromatographed over silica gel eluting with EtOAc/hexane (1:1) to afford 0.173g of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00-1.03 (m, 2H), 1.45-1.51 (m, 2H), 1.83-1.89 (m, 2H), 1.99-2.03 (m, 2H), 2.20 (m, 1H), 3.05-3.12 (m, 3H), 4.68 (d, J = 4.4 Hz, 2H), 4.79 (br, 1H), 5.10 (s,

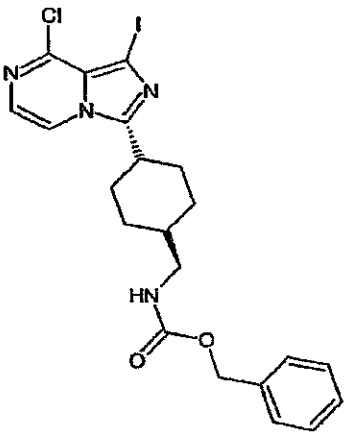
2H), 6.79 (br, 1H), 7.31-7.37 (m, 5H), 8.33 (d, J = 2.8 Hz, 1H), 8.46 (d, J = 2.8 Hz, 1H). MS (ES+): m/z 417.14 [MH+].

Benzyl {[*trans*-4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate



[256] To a suspension of benzyl {(*trans*-4-{[(3-chloropyrazin-2-yl)methyl]carbamoyl}cyclohexyl)methyl]carbamate (0.100 g, 0.220 mmol) in EtOAc (0.9 mL) and DMF (0.068 mL) at 0 °C was added slowly $POCl_3$ (0.082 mL, 0.88 mmol). After stirring at rt for an hour, the mixture was cooled to 0°C and solid $NaHCO_3$ was added. After a further 10min at 0°C and 20min at rt, the mixture was re-cooled to 0°C and water (20mL) was added. The reaction mixture was extracted with EtOAc (3 x 20mL) and the extracts washed with water (2 x 30 mL) and brine (30 mL) and then dried over Na_2SO_4 and concentrated *in vacuo* to afford 0.096g of the title compound. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15-1.19 (m, 2H), 1.76-1.87 (m, 3H), 1.93-2.00 (m, 2H), 2.04-2.08 (m, 2H), 3.07 (m, 1H), 3.15 (t, J = 6.4 Hz, 2H), 4.84 (br, 1H), 5.09 (s, 2H), 7.31-7.40 (m, 6H), 7.61 (d, J = 4.8 Hz, 1H), 7.79 (s, 1H). MS (ES+): m/z 399.26 [MH+].

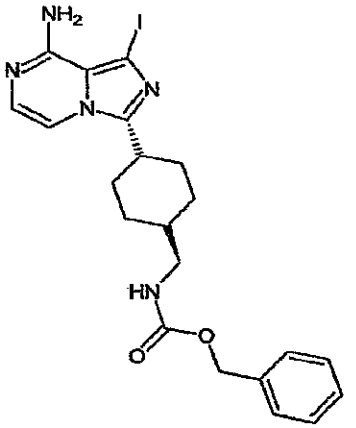
Benzyl {[*trans*-4-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate



[257] To a solution of benzyl {[*trans*-4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate (1.49 g, 0.00374 mol) in DMF (0.6 mL) was added NIS (1.0g,

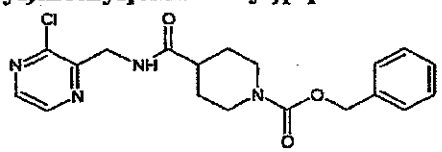
0.0045 mol). The reaction mixture was stirred at 55 °C overnight then diluted with EtOAc (20mL), washed with water (2 x 40 mL) and brine (20mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture thus isolated was chromatographed over silica gel eluting with hexane → hexane:EtOAc 1:1 to afford 1.7g of the title compound.
MS (ES+): m/z 525.01 [MH+].

Benzyl {[*trans*-4-(8-amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate



[258] A solution of benzyl {[*trans*-4-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate (1.70 g, 0.00324 mol) in IPA (30 mL) was cooled to -78 °C, treated with a stream of ammonia gas over 3 min. and then heated at 110 °C in a Parr vessel overnight. The reaction solution was concentrated *in vacuo* and residue washed with water to afford 1.37g of desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08-1.17 (m, 2H), 1.88 (m, 1H), 1.71-1.81 (m, 2H), 1.91-1.94 (m, 2H), 2.00-2.04 (m, 2H), 2.90 (m, 1H), 3.13 (t, J = 6.4 Hz, 2H), 4.86 (br, 1H), 5.11 (s, 2H), 5.76 (br, 2H), 7.00 (d, J = 5.2 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.31-7.37 (m, 5H). MS (ES+): m/z 5.7.36 [MH+].

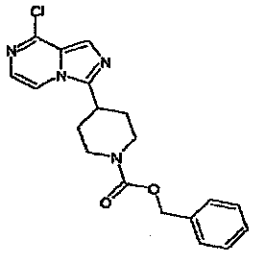
Benzyl 4-{[(3-chloropyrazin-2-yl)methyl]carbamoyl}piperidine-1-carboxylate



[259] A solution of C-(3-Chloropyrazin-2-yl)methylamine bis-hydrochloride (2.00 g, 0.0107 mol) and *N,N*-diisopropylethylamine (2.2 g, 0.017 mol) in DCM (27.0 mL) was treated with and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (3.2 g, 0.017 mol), 1-hydroxybenzotriazole (1.5 g, 0.011 mol) and 1-[(benzyloxy)carbonyl]-4-piperidine carboxylic acid (3.8 g, 0.014 mol). The mixture was stirred at rt overnight then diluted with DCM (30mL), washed with sat. $NaHCO_3$ (20mL) and brine (20mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material thus obtained was chromatographed over silica gel eluting with EtOAc:hexane 1:1

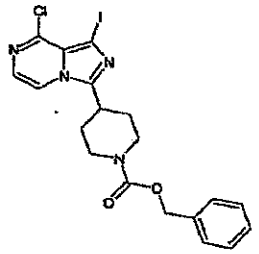
yielding 3.38g of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68-1.78 (m, 2H), 1.91-1.94 (m, 2H), 2.44 (m, 1H), 2.89-2.92 (m, 2H), 4.24-4.26 (m, 2H), 4.70 (d, J = 4.8 Hz, 2H), 5.14 (s, 2H), 6.85 (br, 1H), 7.30-7.37 (m, 5H), 8.34 (d, J = 2.8 Hz, 1H), 8.45 (d, J = 2.8 Hz, 1H). MS (ES+): m/z 389.17 [MH+].

Benzyl 4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate



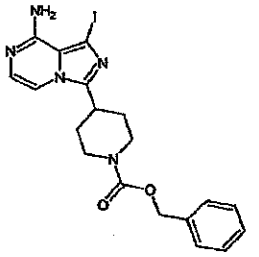
[260] To a suspension of benzyl 4-{[(3-chloropyrazin-2-yl)methyl]carbamoyl}piperidine-1-carboxylate (0.100 g, 0.220 mmol) in EtOAc (0.9 mL) and DMF (0.068 mL) at 0 °C was slowly added $POCl_3$ (0.082 mL, 0.88 mmol). After stirring at rt for an hour the mixture was cooled to 0°C then treated with solid $NaHCO_3$. The mixture was stirred for 20min at rt, diluted with water and extracted with EtOAc (3 x 20mL). The combined extracts were washed with water (2 x 30 mL) and brine (30 mL), then dried over Na_2SO_4, and concentrated *in vacuo* to yield 2.07 g of desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98-2.04 (m, 4H), 3.03-3.20 (m, 3H), 4.30-4.33 (m, 2H), 5.16 (s, 2H), 7.33 (d, J = 5.2 Hz, 1H), 7.35-7.38 (m, 5H), 7.26 (d, J = 4.4 Hz, 1H), 7.79 (s, 1H). MS (ES+): m/z 371.22 [MH+].

Benzyl 4-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate



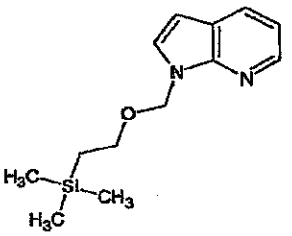
[261] To a solution of benzyl 4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate (1.31 g, 0.00354 mol) in DMF (0.6 mL) was added NIS (1.6 g, 0.0071 mol). The reaction mixture was left to stir at 55 °C for 20 h. then the mixture was diluted with EtOAc (20mL), washed with water (2 x 40 mL) and brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was chromatographed over silica gel eluting with hexane→ hexane:EtOAc 1:1 yielding 1.63g of desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95-2.04 (m, 4H), 3.02-3.15 (m, 3H), 4.29-4.32 (m, 2H), 5.15 (s, 2H), 7.32 (d, J = 5.2 Hz, 1H), 7.34-7.37 (m, 5H), 7.66 (d, J = 5.2 Hz, 1H). MS (ES+): m/z 497.03 [MH+].

Benzyl 4-(8-amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate



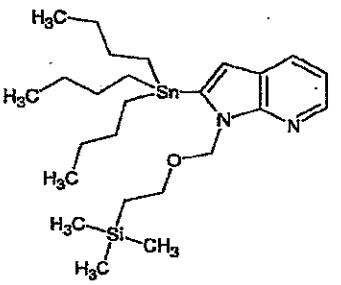
[262] A mixture of benzyl 4-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate (0.500 g, 0.00101 mol) in IPA (20 mL) was cooled to at -78 °C and treated with a stream of ammonia gas over 3 minutes. The resulting solution was heated at 110 °C in a Parr vessel prior to concentration *in vacuo*, suspension in DCM and filtration through a bed of Celite. The filtrate was concentrated *in vacuo* to afford 0.504 g of desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88-2.02 (m, 2H), 2.99-3.10 (m, 3H), 4.24-4.41 (m, 2H), 5.15 s, 2H), 6.03 (br, 2H), 7.03 (d, J = 4.8 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 7.31-7.40 (m, 5H). MS (ES+): m/z 479.33 [MH+].

1-(2-Trimethylsilylethoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine



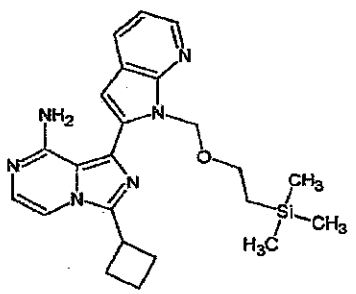
[263] To a suspension of sodium hydride (934 mg, 0.0358 mol) in DMF (57 mL) was added dropwise under N_2, a solution of 1H-pyrrolo[2,3-*b*]pyridine (3.00 g, 0.0254 mol) in DMF (20 mL). The mixture was stirred at r.t. for 45 min. then cooled to 0°C and treated dropwise with [2-(trimethylsilyl)ethoxy]methyl chloride (6.32 mL, 0.0357 mol). The mixture was stirred at rt for 12h. then poured into water (10 mL), stirred for 30 min. and extracted with Et2O (4 x 10mL). The combined extracts were washed with brine (20mL), dried over sodium sulfate, and concentrated *in vacuo* to give the crude product which was chromatographed over silica gel eluting with hexane → 1:9 Et_2O: hexane to afford 6 g desired product.

***N*-(2-Trimethylsilyl-1-ethoxymethyl)-2-(tributylstannyl)-1*H*-pyrrolo[2,3-*b*]pyridine**



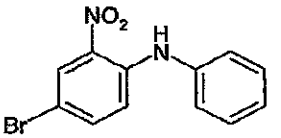
[264] To a solution of 1-(2-trimethylsilylethoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 0.0020129 mol) in THF (5 mL) at -10°C was added a 2.0 M of n-BuLi in cyclohexane (1.2 mL). After 10 min at -10 °C, the mixture was cooled to -20 °C and tributyltin chloride (0.65 mL, 0.0024 mol) was added. The mixture was stirred at rt for 1 h, the poured into a 5% aqueous ammonium chloride (20mL), extracted with EtOAc (3 x 20mL) and the combined extracts dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The material thus obtained was chromatographed over silica gel eluting with 1:9 EtOAc: hexane to afford 0.7g of the title compound. ^{1}H NMR (400 MHz DMSO-d6) δ 0.01 (s, 9H), 0.10 (s, 2H), 0.92 - 0.94 (m, 9H), 1.14 - 1.27 (m, 6H), 1.37 -1.46 (m, 6H), 1.60 - 1.72 (m, 6H), 3.48 - 3.52 (m, 2H), 5.71 (s, 2H), 6.74 (s, 1H), 7.16 - 7.19 (m, 1H), 8.02 (dd, J = 1.6, 7.6 Hz, 1H) and 8.31 (dd, J = 1.6, 4.4 Hz, 1H).

3-Cyclobutyl-1-[1-(2-trimethylsilylethoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]imidazo[1,5-*a*]pyrazin-8-amine



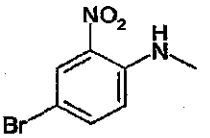
[265] A mixture of *N*-(2-trimethylsilyl-1-ethoxymethyl)-2-(tributylstannyl)-1*H*-pyrrolo[2,3-*b*]pyridine (110 mg, 0.20 mmol), 3-cyclobutyl-1-iodoimidazo[1,5-*a*]pyrazin-8-amine (50 mg, 0.1592 mmol) and bis(triphenylphosphine)palladium(II) chloride (10 mg, 0.02 mmol) in ethanol (2 mL) was heated at reflux for 48 h. The mixture was then cooled to rt, filtered through a pad of Celite and concentrated *in vacuo*. The residue thus obtained was chromatographed over silica gel eluting with hex :EtOAc to afford 17.2mg of the title compound. ^{1}H NMR (400 MHz CDCl3) δ 0.22 (s, 9H), 0.70 (t, 2H), 1.87 - 2.19 (m, 2H), 2.49 - 2.64 (m, 4H), 3.37 (t, 2H), 3.81 - 3.86 (m, 1H), 5.51 (bs, 2H), 6.07 (s, 2H), 6.67 (s, 1H), 7.10 - 7.16 (m, 3H), 7.93 (dd, J = 1.6, 8.0 Hz, 1H) and 8.41 (dd, J = 1.6, 4.8 Hz, 1H). MS (ES+): m/z: 435.21 [MH+].

4-Bromo-2-nitro-*N*-phenylaniline



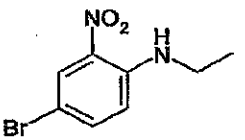
[266] A mixture of 1-bromo-4-fluoro-3-nitrobenzene (2270 mg, 10.01 mmol), aniline (3 ml) and DMF (20 ml) was heated at 100 °C under an atmosphere of Nitrogen for 7 h. The mixture was then concentrated in vacuo, and the residue triturated with heptane (30 ml) to give the desired product. 1H NMR (400 MHz, CDCl3) δ = 7.11 (d, 1 H, J = 9.2 Hz), 7.25 – 7.29 (m, 3 H), 7.40 – 7.45 (m, 3 H), 8.35 (d, 1 H, J = 2.4 Hz) and 9.45 (brs, 1 H).

4-Bromo-*N*-methyl-2-nitroaniline



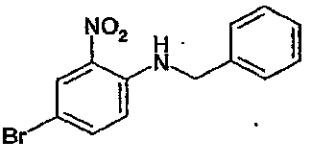
[267] Prepared according to a procedure analogous to that described for 4-bromo-2-nitro-*N*-phenylaniline. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.02 (d, 3 H, J = 5.2 Hz), 6.76 (d, 1 H, J = 9.6 Hz), 7.51 – 7.54 (m, 1 H), 8.02 (brs, 1 H) and 8.32 (d, 1 H, J = 2.8 Hz). MS(ES+): m/z 231.05 and 233.08[MH+].

4-Bromo-*N*-ethyl-2-nitroaniline



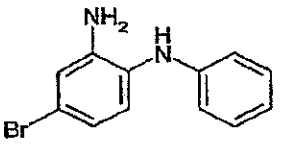
[268] Prepared according to a procedure analogous to that described for 4-bromo-2-nitro-N-phenylaniline. ^{1}H NMR (400 MHz, CDCl3) δ = 1.37 (t, 3 H, J = 7.2 Hz), 3.31 – 3.37 (m, 2 H), 6.76 (d, 1 H, J = 8.8 Hz), 7.48 – 7.51 (m, 1 H), 7.95 (brs, 1 H) and 8.31 (d, 1 H, J = 2.4 Hz). MS(ES+): m/z 245.07 and 247.11 [MH+].

***N*-Benzyl-4-bromo-2-nitroaniline**



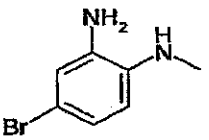
[269] Prepared according to a procedure analogous to that described for 4-bromo-2-nitro-N-phenylaniline. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.54 (d, 2 H, J = 5.6 Hz), 6.72 (d, 1 H, J = 9.2 Hz), 7.30 – 7.40 (m, 5 H), 7.44 (ddd, 1 H, J = 0.4 & 2.4 & 9.2 Hz), 8.34 (d, 1 H, J = 2.4 Hz) and 8.41 (brs, 1 H). MS(ES+): m/z 245.07 and 247.11[MH+].

4-Bromo-N^1-phenylbenzene-1,2-diamine



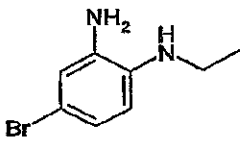
[270] Prepared according to a procedure analogous to that described for 4-bromo-2-nitro-N-phenylaniline. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.80 (brs, 2 H), 5.07 (br, s, 1 H), 6.70 – 6.75 (m, 2 H), 6.82 – 6.86 (m, 2 H), 6.93 (d, 1 H, J = 2.4 Hz), 6.97 (d, 1 H, J = 8.0 Hz) and 7.17 – 7.24 (m, 2 H). MS(ES+): m/z 263.17 and 265.20 [MH+].

4-Bromo-N^1-methylbenzene-1,2-diamine



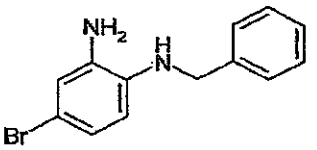
[271] A suspension of 4-bromo-*N*-methyl-2-nitroaniline (5328 mg, 22.04 mmol) in EtOH (100 ml) was treated with $SnCl_2 \cdot 2H_2O$ (25.61 g, 110.2 mmol) and the resulting mixture heated at 70 °C under an atmosphere of Nitrogen for 5 h. The reaction mixture was then cooled to rt and treated with ice-water (50 ml) followed by aqueous NaOH (4 N) until pH > 8. This basic mixture was then extracted with EtOAc (3 × 150 ml) and the combined extracts washed with brine (3 × 100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 2.68 (s, 3 H), 4.74 (brs, 3 H), 6.27 (d, 1 H, J = 8.4 Hz), 6.61 (dd, 1 H, J = 2.0 & 8.4 Hz) and 6.66 (d, 1 H, J = 2.0 Hz). MS(ES+): m/z 201.10 and 203.12[MH+].

4-Bromo-N^1-ethylbenzene-1,2-diamine



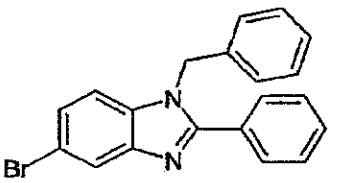
[272] Prepared according to a procedure analogous to that described for 4-bromo-N^1-methylbenzene-1,2-diamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (t, 3 H, J = 6.8 Hz), 3.01 (quartet, 2 H, J = 6.8 Hz), 4.46 (brs, 1 H), 4.81 (brs, 2 H), 6.30 (d, 1 H, J = 8.4 Hz), 6.58 (dd, 1 H, J = 2.4 & 8.4 Hz) and 6.66 (d, 1 H, J = 2.0 Hz). MS(ES+): m/z 215.07 and 217.16 [MH+].

N^1-Benzyl-4-bromobenzene-1,2-diamine



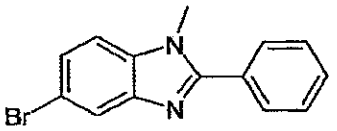
[273] Prepared according to a procedure analogous to that described for 4-bromo-N^1-methylbenzene-1,2-diamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.39 (brs, 2 H), 3.61 (brs, 1 H), 4.28 (s, 2 H), 6.51 (d, 1 H, J = 8.4 Hz), 6.85 – 6.89 (m, 2 H) and 7.27 – 7.38 (m, 5 H). MS(ES+): m/z 277.20 and 279.20 [MH+].

1-Benzyl-5-bromo-2-phenyl-1*H*-benzimidazole



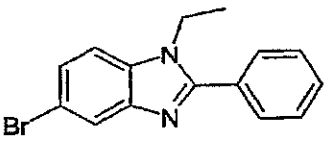
[274] *p*-TsOH·H_2O (311.7 mg, 1.606 mmol) was added to a DCM (50 ml) solution of N^1-benzyl-4-bromobenzene-1,2-diamine (4451 mg, 16.06 mmol) and trimethyl orthobenzoate (3096 µl, 17.66 mmol) and the resulting mixture was stirred at rt under an atmosphere of Nitrogen for 40 h. The reaction mixture was then concentrated *in vacuo* to give a yellow solid which was triturated with 40%MeOH/water (375 mL), filtered, washed with saturated $NaHCO_3$ (20 ml)+H_2O (80 ml) twice and 40% MeOH/H_2O (2 × 50 ml), and dried to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 5.44 (s, 2 H), 7.05 – 7.08 (m, 3 H), 7.30 – 7.36 (m, 4 H), 7.44 – 7.50 (m, 3 H), 7.66 – 7.68 (m, 2 H) and 7.99 (dd, 1 H, J =0.4 & 1.6 Hz). MS(ES+): m/z 363.20 and 365.26[MH+].

5-Bromo-1-methyl-2-phenyl-1*H*-benzimidazole



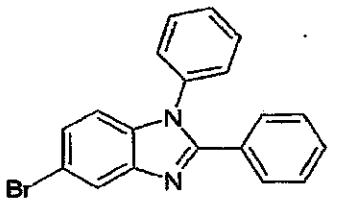
[275] Prepared according to a procedure analogous to that described for 1-benzyl-5-bromo-2-phenyl-1*H*-benzimidazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.86 (s, 3 H), 7.26 – 7.29 (m, 1 H), 7.42 (dd, 1 H, J = 2.0 & 8.4 Hz), 7.53 – 7.56 (m, 3 H), 7.74 – 7.76 (m, 2 H) and 7.95 (dd, 1 H, J = 0.4 & 1.6 Hz). MS(ES+): m/z 287.18 and 289.14 [MH+].

5-Bromo-1-ethyl-2-phenyl-1*H*-benzimidazole



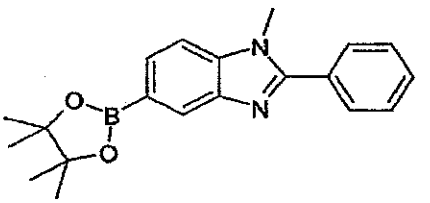
[276] Prepared according to a procedure analogous to that described for 1-benzyl-5-bromo-2-phenyl-1*H*-benzimidazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.46 (t, 3 H, J = 7.2 Hz), 4.27 (quartet, 2 H, J = 7.2 Hz), 7.27 (m, 1 H), 7.30 (dd, 1 H, J = 0.4 & 8.8 Hz), 7.42 (dd, 1 H, J = 1.6 & 8.8 Hz), 7.53 – 7.55 (m, 3 H), 7.70 – 7.72 (m, 2 H) and 7.96 (dd, 1 H, J = 0.4 & 1.6 Hz). MS(ES+): m/z 301.18 and 303.11 [MH+].

5-Bromo-1,2-diphenyl-1*H*-benzimidazole



[277] Prepared according to a procedure analogous to that described for 1-benzyl-5-bromo-2-phenyl-1*H*-benzimidazole. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, 1 H, J = 0.4 & 8.4 Hz), 7.27 – 7.39 (m, 6 H), 7.48 – 7.56 (m, 5 H) and 8.01 (dd, 1H, J =0.4 & 1.6 Hz). MS(ES+): m/z 349.20 and 351.22 [MH+].

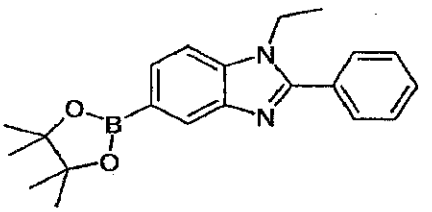
1-Methyl-2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzimidazole



[278] A mixture of 5-bromo-1-methyl-2-phenyl-1*H*-benzimidazole (616 mg, 2.14 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (52.6 mg, 0.0644 mmol), bis(pinacolato)diboron (667 mg, 2.57 mmol), 1,1'-bis(diphenylphosphino)ferrocene (36.8 mg, 0.0644 mmol) and AcOK (638 mg, 6.44 mmol) in 1,4-dioxane (10 ml) was purged with N_2 for 5 min, and was then heated at 100 °C under an atmosphere of Nitrogen for 16 h. The mixture was then treated with saturated NH_4Cl (20 ml), extracted with EtOAc (3 × 20 ml) and the combined extracts washed with brine (3 × 20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford crude product which was purified by chromatography over silica gel eluting with 30% (250 ml) and 40% (250 ml) EtOAc/Heptane to give a white solid that was triturated

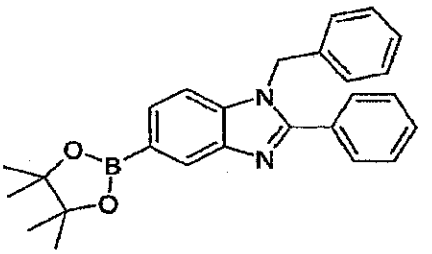
with 50% EtOAc/Heptane (10 ml) to yield the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.38 (s, 12 H), 3.86 (s, 3 H), 7.39 (dd, 1 H, J = 1.2 & 8.0 Hz), 7.50 – 7.55 (m, 3H), 7.76 – 7.79 (m, 3H) and 8.29 (d, 1 H, J = 0.8 Hz). MS(ES+): m/z 335.29 (100) [MH+].

1-Ethyl-2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzimidazole



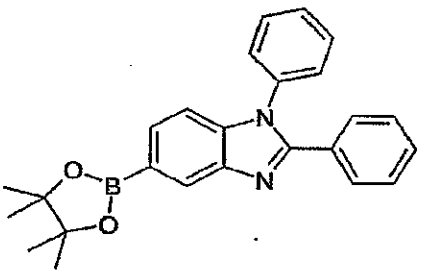
[279] Prepared according to a procedure analogous to that described for 1-Methyl-2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzimidazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.38 (s, 12 H), 1.45 (t, 3 H, J = 7.2 Hz), 4.28 (quartet, 2 H, J = 7.2 Hz), 7.42 (dd, 1 H, J = 0.8 & 8.0 Hz), 7.51– 7.54 (m, 3H), 7.71 – 7.74 (m, 2H), 7.77 (dd, 1 H, J = 0.8 & 8.0 Hz) and 8.31 (s, 1 H). MS(ES+): m/z 349.33 [MH+].

1-Benzyl-2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*- benzimidazole



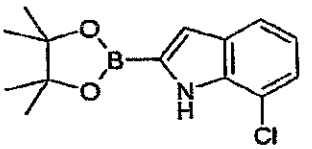
[280] Prepared according to a procedure analogous to that described for 1-Methyl-2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzimidazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.36 (s, 12 H), 5.45 (s, 2 H), 7.05 – 7.08 (m, 1 H), 7.21 (dd, 1 H, J = 0.8 & 8.0 Hz), 7.26 – 7.31 (m, 3H), 7.44 – 7.48 (m, 3H), 7.66 – 7.71 (m, 3H) and 8.36 (m, 1 H). MS(ES+): m/z 411.42 [MH+].

1,2-Diphenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzimidazole



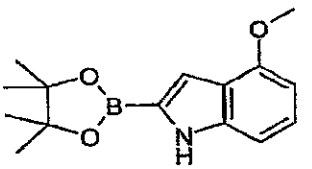
[281] Prepared according to a procedure analogous to that described for 1-Methyl-2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzimidazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.38 (s, 12 H), 7.22 (dd, 1 H, J = 0.8 & 8.0 Hz), 7.29 – 7.35 (m, 5 H), 7.47 – 7.50 (m, 3 H), 7.55 – 7.57 (m, 2 H) and 7.71 (dd, 1 H, J = 0.8 & 8.0 Hz), 8.38 (m, 1 H). MS(ES+): m/z 397.43 [MH+].

7-Chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



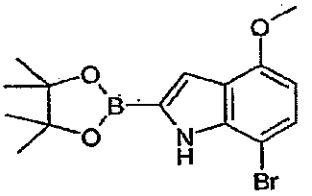
[282] A flask containing $Ir(Ome)_2(COD)_2$ [*Inorganic Syntheses* (1985), **23**, 126] (850 mg, 0.0013 mol), 4,4'-di-tert-butyl-[2,2']bipyridinyl (686 mg, 0.00256 mol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (15.2 g, 0.0600 mol) was evacuated and refilled with Ar (3x), then charged with anhydrous DME (400 mL, 3 mol) and a solution of 7-chloro-1*H*-indole (0.086 mol) in DME (10 mL). The resulting mixture was stirred under Ar for 16h then concentrated and chromatographed over silica gel eluting with 10% EtOAc/Heptane to afford the desired product as a waxy solid in a 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.39 (s, 12 H), 7.04 (t, J=7.71 Hz, 1 H), 7.15 (d, J=2.27 Hz, 1 H), 7.21 - 7.30 (m, 1 H), 7.58 (d, J=8.08 Hz, 1 H) and 8.72 (br. s., 1 H).

4-Methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



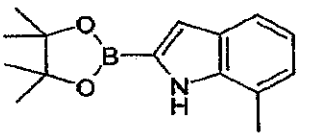
[283] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 4-methoxy-1*H*-indole.

7-Bromo-4-methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



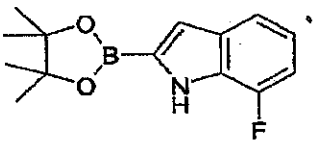
[284] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-bromo-4-methoxy-1*H*-indole.

7-Methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



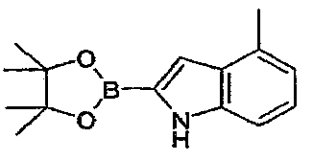
[285] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-methyl-1*H*-indole.

7-Fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



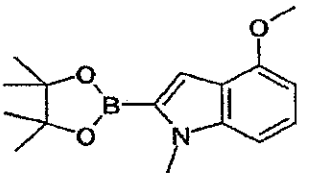
[286] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-fluoro-1*H*-indole.

4-Methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



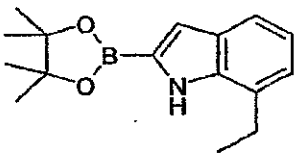
[287] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 4-methyl-1*H*-indole.

4-Methoxy-1-methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



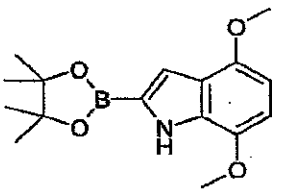
[288] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 4-methoxy-1-methyl-1*H*-indole.

7-Ethyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



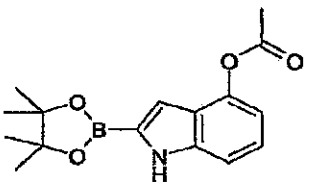
[289] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-ethyl-1*H*-indole.

4,7-Dimethoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



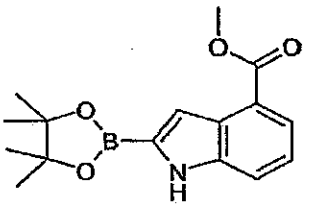
[290] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 4,7-dimethoxy-1*H*-indole.

2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indol-4-yl acetate



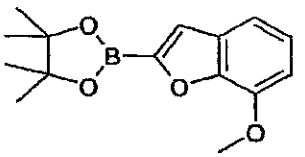
[291] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 1*H*-indol-4-yl acetate.

2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole-4-carboxylic acid, methyl ester



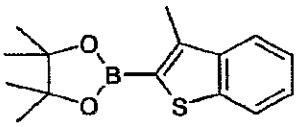
[292] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 1*H*-indole-4-carboxylic acid, methyl ester.

7-Methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzofuran



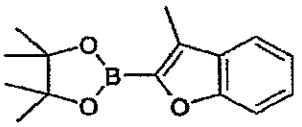
[293] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-methoxy-benzofuran.

4,4,5,5-Tetramethyl-2-(3-methyl-benzo[*b*]thiophen-2-yl)-[1,3,2]dioxaborolane



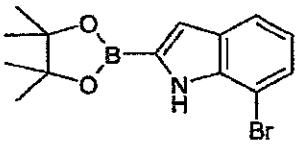
[294] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 3-methyl-benzo[*b*]thiophene.

3-Methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzofuran



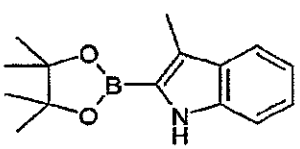
[295] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 3-methyl-benzofuran.

7-Bromo-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



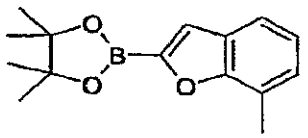
[296] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-bromo-1*H*-indole.

3-Methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



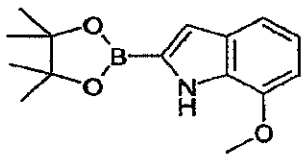
[297] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 3-methyl-1*H*-indole.

7-Methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzofuran



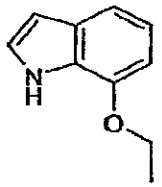
[298] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-methyl-benzofuran.

7-Methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



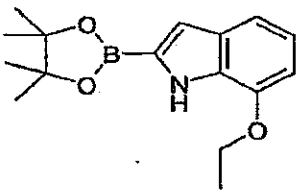
[299] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-methoxy-1*H*-indole.

7-Ethoxy-1*H*-indole



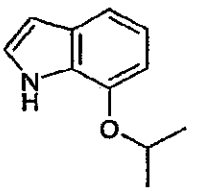
[300] To a stirred solution of 1*H*-indol-7-ol (500 mg, 3.75 mmol) in acetone (10 mL) at r.t. was added potassium carbonate (3.11 g, 22.5 mmol), followed by iodoethane (0.45 mL, 5.63 mol). The mixture was stirred at r.t. for 16h then solvent removed under reduced pressure. The crude product thus obtained was purified by chromatography over silica gel to afford 7-ethoxy-1*H*-indole: ^{1}H NMR (400 MHz, MeOD) δ ppm 1.51 (t, J=6.95 Hz, 3 H), 4.22 (q, J=6.91 Hz, 2 H), 6.42 (d, J=3.03 Hz, 1H), 6.63 (d, J=7.58 Hz, 1 H), 6.92 (t, J=7.83 Hz, 1 H), 7.04 - 7.23 (m, 2 H); MS (ES+): m/z 162.20 (MH+).

7-Ethoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



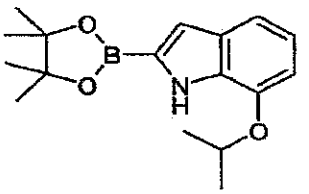
[301] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-ethoxy-1*H*-indole.

7-Isopropoxy-1*H*-indole



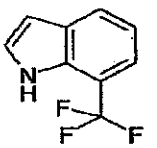
[302] Made according to the procedure described for 7-ethoxy-1*H*-indole using 2-iodopropane.

7-Isopropoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



[303] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-isopropoxy-1*H*-indole.

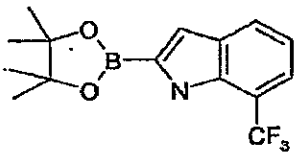
7-Trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



[304] To a stirred mixture of 7-trifluoromethyl-1*H*-indole-2,3-dione (116 mg) in THF (5.00 mL) was added boron trifluoride etherate (0.205 mL, 1.62 mmol) followed by sodium borohydride (71.4 mg, 1.88 mmol). The resulting mixture was stirred at -20 °C for 2hrs, then water (1 mL) was added and the mixture was stirred at 0 °C for 10min. The solution was acidified to pH = 1 with 2N HCl, warmed to r.t. and stirred at r.t. for 20min prior to extraction with EtOAc. The extracts were dried over magnesium sulphate, concentrated in vacuo and the residue purified by chromatography over silica gel eluting with hexane to give 7-trifluoromethyl-1*H*-indole. ^{1}H NMR (400 MHz, $CDCl_3$) δ

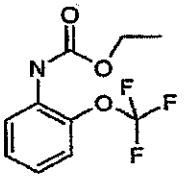
ppm 6.63 - 6.68 (1 H, m), 7.20 (1 H, t, J=7.71 Hz), 7.30 - 7.35 (1 H, m), 7.47 (1 H, d, J=7.33Hz), 7.83 (1 H, d, J=8.08 Hz), and 8.56 (1 H, br. s.).

7-Trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



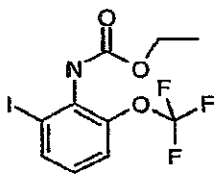
[305] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-trifluoromethyl-1*H*-indole.

Ethyl *N*-[2(trifluoromethoxy)phenyl]carbamate



[306] Ethyl chloroformate (4.4 mL, 0.046 mol) was added to a mixture of 2-(trifluoromethoxy)aniline (8.25 g, 0.0466 mol), sodium carbonate (15 g, 0.14 mol), 1,4-dioxane (70 mL) and water (70 mL) at 0 °C and the the reaction mixture stirred at room temperature overnight. The reaction mixture was then washed with ether, acidified (pH 3) and the product extracted into EtOAc (3 x 40mL). The combined extracts were washed with water (40mL) and brine (40mL), dried over Na2SO4 and the solvent removed in vacuo to give the desired product in a 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, J = 5.2 Hz, 3H), 4.25 (q, J = 6.8 Hz, 2H), 6.91 (br, 1H), 7.04 (m, 1H), 7.23 (m, 1H), 7.28 (m, 1H) and 8.2 (m, 1H). MS (ES+): m/z 250.12 [MH+].

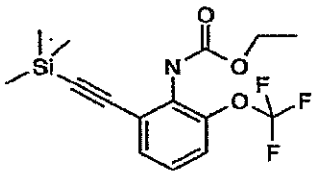
Ethyl [2-iodo-6-(trifluoromethoxy)phenyl]carbamate



[307] A 1.4 M solution of sec-butyllithium in cyclohexane (3.0 mL) was added drop-wise to a solution of ethyl *N*-[2-(trifluoromethoxy)phenyl]carbamate (0.5000 g, 0.002006 mol) in THF (9 mL) at -70 °C. After stirring for 1 hour a solution of iodine (0.51g, 0.002 mol) in THF (1.0 mL) was added drop-wise at -70 °C. Stirring was continued for another 1 hour then the mixture was quenched

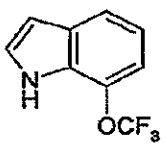
with saturated ammonium chloride solution. Water (50mL) was added and the mixture extracted with diethyl ether (3 x 40mL). The combined organic phases was washed with 40% sodium meta-bisulfite solution, water and brine, then dried over Na2SO4 and the solvent removed in vacuo to give the desired product in a 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.36 (m, 3H), 4.21-4.28 (m, 2H), 6.21 (br, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.30 (m, 1H) and 7.80 (dd, J = 6.8, 1.2 Hz, 1H). MS (ES+): m/z 375.78 [MH+].

Ethyl [2-trifluoromethoxy-6-(trimethylsilanylethynylphenyl)]carbamate



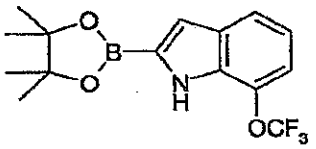
[308] A mixture of Pd(PPh3)2Cl2 (83 mg, 0.00012 mol) and copper (I) iodide (23 mg, 0.00012 mol) in triethylamine (44 mL, 0.32 mol) was heated at 40 °C for 20 min then cooled to rt and ethyl [2-iodo-6-(trifluoromethoxy)phenyl]carbamate (4.50 g, 0.0120 mol) was added in one portion. The mixture was stirred at room temperature for 30 min, then (trimethylsilyl)acetylene (1.6 mL, 0.011 mol) was added and the mixture stirred for a further 2 hours. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether (60mL of each). The organic was washed wtih 1N HCl and brine, then dried over Na2SO4 then the solvent removed in vacuo. The reaction was chromatographed over silica gel eluting with 20% EtOAc/hexane to afford the desired product in 80% yield. MS (ES+): m/z 345.99 [MH+].

7-Trifluoromethoxy-1*H*-indole



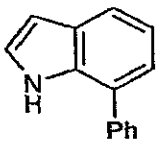
[309] Sodium ethoxide (0.65 mL, 0.0017 mol, 2.6M) was added to a solution of ethyl [2-trifluoromethoxy-6-(trimethylsilanylethynylphenyl)]carbamate in EtOH (5.0 mL) and the mixture stirred at 72 °C for 14 hours. The solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and water (30mL of each). The ether phase was washed with brine and dried over Na_2SO_4 yielding the desired compound in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60-6.61 (m, 1H), 7.07-7.09 (m, 2H), 7.25 (d, *J* = 5.6 Hz, 1H), 7.55-7.57 (m, 1H) and 8.42 (br, 1H). MS (ES+): m/z 202.18 [MH+].

7-Trifluoromethoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



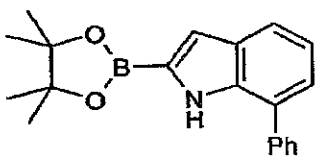
[310] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-trifluoromethoxy-1*H*-indole.

7-Phenyl-1*H*-indole



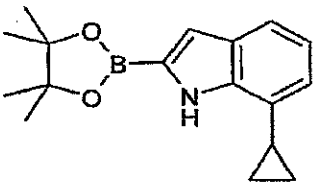
[311] To a suspension of 7-bromo-1*H*-indole (196 mg, 0.00100 mol) in 1,4-dioxane (4 mL) and water (1 mL) was added phenylboronic acid (146 mg, 0.00120 mol), potassium carbonate (414 mg, 0.00300 mol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II),complex with dichloromethane (1:1) (82 mg, 0.00010 mol). The flask was evacuated and refilled with nitrogen, three times then the mixture was heated at 100 °C overnight. The mixture was diluted with EtOAc (30 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), then dried over anhydrous sodium sulfate and the solvent removed *in vacuo*. The crude material was purified by chromatography over silica gel eluting with hexane/EtOAc to give the title compound (180 mg, 93% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (dd, J = 3.0, 2.0 Hz, 1H), 7.18-7.26 (m, 3H), 7.41 (t, J = 7.5 Hz, 1H), 7.48-7.57 (m, 2H), 7.61-7.70 (m, 3H) and 8.43 (br s, 1H) ppm. LC-MS (ES+.): 194 [MH^+].

7-Phenyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



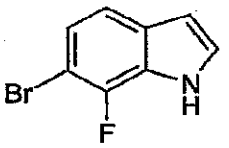
[312] Prepared according to a procedure analogous to that described for 7-chloro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using 7-phenyl-1*H*-indole.

7-Cyclopropyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



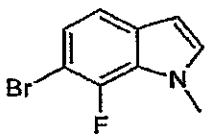
[313] Prepared according to the procedures described above for 7-phenyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole using cyclopropylboronic acid in place of phenylboronic acid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75-0.82 (m, 2H), 0.95-1.04 (m, 2H), 2.08 (m, 1H), 6.59 (dd, J = 3.0, 2.0 Hz, 1H), 6.96 (d, J = 7.1 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.25 (m, 1H), 7.52 (d, J = 7.8 Hz, 1H) and 8.39 (br s, 1H) ppm. LC-MS (ES, Pos.): 158 [MH^+].

6-Bromo-7-fluoro-1*H*-indole



[314] To a solution of 1-bromo-2-fluoro-3-nitrobenzene (2.5 g, 11.3 mmol) in THF (25 mL) at –50 °C was added vinyl magnesium bromide (34 mL, 34 mmol) and the mixture was stirred at –40 °C for 1 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield a gum, which was purified by column chromatography over silica gel eluting with EtOAc/hexane to afford pure 6-bromo-7-fluoro-1H-indole. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.53–6.62 (m, 1H), 7.16–7.25 (m, 2H), 7.29 (d, J = 8.34 Hz, 1H) and 8.36 (br. s., 1H); MS (ES+): m/z 214.08 [MH+].

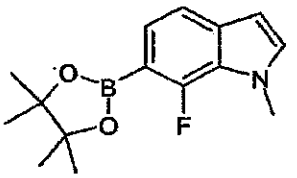
6-Bromo-7-fluoro-1-methyl-1*H*-indole



[315] To a solution of 6-bromo-7-fluoro-1*H*-indole (470 mg, 2.19 mmol) in THF (7 mL) at -10 °C was added sodium hydride (175 mg, 4.39 mmol, 60% dispersion) and the mixture was stirred at 0 °C for 30 min. Methyl iodide was added at 0 °C and the reaction was allowed to warm to at 10 °C and stirred for 2h. The reaction was quenched with saturated ammonium chloride and extracted with DCM. The DCM extract was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with EtOAc/hexane to afford 6-bromo-7-fluoro-1-methyl-1*H*-indole. ^{1}H NMR (400

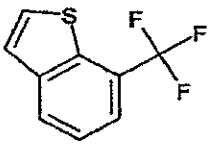
MHz, $CDCl_3$) δ = 3.95 (d, J = 2.00 Hz, 1H), 6.42 (t, J = 2.78 Hz, 1H), 6.94 (d, J = 3.03 Hz, 1H), 7.09–7.15 (m, 1H) and 7.20 (d, J = 8.34 Hz, 1H); MS (ES+): m/z 228.04 [MH+].

7-Fluoro-1-methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole



[316] To a mixture of 6-bromo-7-fluoro-1-methyl-1*H*-indole (420 mg, 1.84 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (514 mg, 2.02 mmol), potassium acetate (542 mg, 5.52 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1 complex, 150 mg, 0.184 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (102 mg, 0.184 mmol) was added dioxane (10 mL) and the mixture was degassed by bubbling through with nitrogen for 3 min. The reaction mixture was heated at 100 °C overnight then the dioxane was removed under reduced pressure and the residue was dissolved in DCM and filtered to remove inorganics. The filtrate was concentrated and the crude product was purified by column chromatography over silica gel eluting with EtOAc/hexane to afford pure 7-fluoro-1-methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indole. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.41 (s, 12H), 4.02 (d, J = 2.02 Hz, 3H), 6.46 (t, J = 2.65 Hz, 1H), 7.03 (d, J = 3.03 Hz, 1H) and 7.28–7.47 (m, 2 H); MS (ES+): m/z 276.03 [MH+].

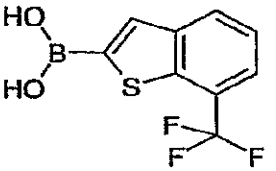
7-Trifluoromethyl-benzo[*b*]thiophene



[317] To a stirred solution of 2-(trifluoromethyl)benzenethiol (5.000 g, 0.028 mol) in acetone (50 mL) was added 2-bromo-1,1-diethoxyethane (6.08 g, 0.030 mol) and potassium carbonate (7.757 g, 0.056 mol). The resulting mixture was then stirred at 45 °C for 2 hours prior to removal of the solvent *in vacuo* and suspension of the residue in EtOAc. The inorganic salts were filtered off and the organic phase was concentrated to give crude product, which was used in next step without further purification. This residue was dissolved in toluene (50mL), and to this solution was added PPA (10g) and the resulting mixture stirred at 95-100 °C for 2 hours. The mixture was allowed to cool to rt, was poured into ice-water, then extracted with EtOAc (3 x 50mL). The combined extracts were washed with aqueous sodium bicarbonate followed by brine, then dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield an oil. This was purified by column chromatography over

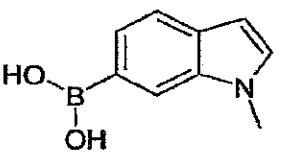
silica gel eluting with hexane to give 7-trifluoromethyl-benzo[*b*]thiophene. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.49 - 7.57 (m, 2H), 7.70 (d, *J*=7.33 Hz, 1H), 7.74 (d, *J*=5.56 Hz, 1H) and 8.10 (d, *J*=8.08 Hz, 1H).

7-Trifluoromethylbenzo[*b*]thiophene-2-boronic acid



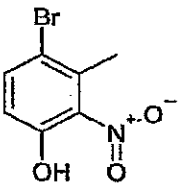
[318] To a solution of 7-trifluoromethyl-benzo[*b*]thiophene (0.52 g, 0.0026 mol) in THF (30 mL) at -78 °C was added 2.5 M of *n*-BuLi in hexane (1.4 mL). The reaction was then slowly warmed up to -30 °C over 30 min. and stirred at this temperature for 10min prior to recooling to -78 °C and treatement with triisopropyl borate (0.7255 g, 0.0038 mol). The reaction was then slowly warmed up to 0 °C then was quenched with saturated ammonium chloride and the solvent removed *in vacuo*. To the residue was added aqueous sodium hydroxide (10 mL, 2N solution) followed by water (30 mL) then this mixture was extracted with DCM. The aqueous solution was acidified using dilute sulfuric acid (2N solution), filtered and the residue dried *in vacuo* to yield 7-trifluoromethylbenzo[*b*]thiophen-2-boronic acid. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.55 (1 H, t, *J*=7.45 Hz), 7.75 (1 H, d, *J*=7.07 Hz), 8.02 (1 H, s) and 8.17 (1 H, d, *J*=7.83 Hz).

***N*-Methylindole-6-boronic acid**



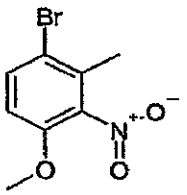
[319] A mixture of indole-6-boronic acid (0.100g, 0.615 mmol), sodium hydride (0.07g, 20 mmol) and THF (5 mL, 60 mmol) was stirred at rt for 20 min. then methyl iodide (100 uL, 20 mmol) was added and the mixture was allowed ro stir at rt for 3 hours. The reaction was quenched with sat. NH_4Cl solution, washed with brine and dried over Na_2SO4, then the solvent was removed in vacuo. The crude product was purified by chromatography over silica gel eluting with 1:9 EtOAc/hexane and 1% MeOH, yielding the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.99 (s, 3H), 6.58 (m, 1H). 7.23 (m, 1H), 7.81 (m, 1H), 8.08 (m, 1H) and 8.34 (m, 1H). MS (ES+): m/z 176.15 [MH+].

4-Bromo-3-methyl-2-nitrophenol



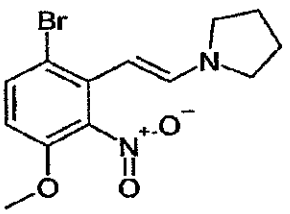
[320] To a solution of 3-methyl-2-nitrophenol (2.0 g, 13.06 mmol) in acetic acid (40 mL) was added bromine (0.70 mL, 13.71 mmol) and the mixture was stirred at RT for 5 h. The reaction was poured in to ice water and the yellow precipitate formed was filtered and washed with water and dried *in vacuo* to yield 4-bromo-3-methyl-2-nitrophenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.61 (s, 3H), 2.62 (s, 5H), 6.92 (d, J = 8.84 Hz, 1H), 7.66 (d, J = 9.09 Hz, 1H) and 9.28 (s, 1 H); MS (ES+): m/z 215.00 [M-17].

1-Bromo-4-methoxy-2-methyl-3-nitrobenzene



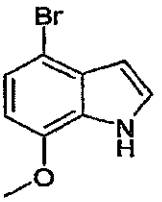
[321] To a solution of 4-bromo-3-methyl-2-nitrophenol (2.200 g, 9.48 mmol) in acetone (35 mL) was added potassium carbonate (3.276 g, 23.70 mmol) and methyl iodide (1.47 mL, 23.70 mmol) and the mixture was heated to reflux for 4 h. The reaction was cooled to rt, filtered and the filtrate was evaporated under reduced pressure to afford the crude product. Purification of the crude product by column chromatography over silica gel eluting with EtOAc/hexane afforded pure 1-bromo-4-methoxy-2-methyl-3-nitrobenzene as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.33 (s, 2H), 3.87 (s, 3H), 6.78 (d, *J* = 8.84 Hz, 1H) and 7.58 (d, *J* = 8.84 Hz, 1H); MS (ES+): *m/z* 247.26 [MH+].

1-[(*E*)-2-(6-bromo-3-methoxy-2-nitrophenyl)vinyl]pyrrolidine



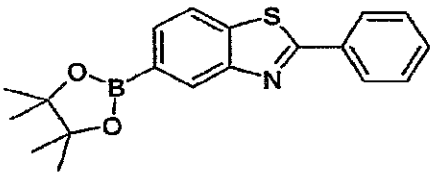
[322] To a solution of 1-bromo-4-methoxy-2-methyl-3-nitrobenzene (1.400 g, 5.68 mmol) and 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (0.884 mL, 6.657 mmol) in DMF (10.0 mL) was added pyrrolidine (0.555 mL, 6.656 mmol) and the mixture was heated to at 110 °C for 4 h. The DMF was removed and the residue was recrystallized from DCM:methanol (1:6) mixture to afford 1-[(*E*)-2-(6-bromo-3-methoxy-2-nitrophenyl)vinyl]pyrrolidine.

4-Bromo-7-methoxy-1*H*-indole



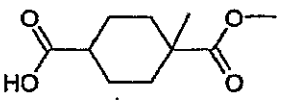
[323] To a solution of 1-[(*E*)-2-(6-bromo-3-methoxy-2-nitrophenyl)vinyl]pyrrolidine (1.3 g, 3.97 mmol) in THF (6 mL) and methanol (6 mL) was added Raney Ni (≈ 500 mg) followed by hydrazine (0.19 mL). (CAUTION: Exothermic reaction with vigorous gas evolution). Hydrazine (0.19 mL) was added again, two times, after 30 min and 1 h. The reaction was stirred at 45 °C for 2 h, filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue purified by chromatography over silica gel eluting with EtOAc/hexane to afford pure 4-bromo-7-methoxy-1*H*-indole. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.94 (s, 3H), 6.52 (d, *J* = 8.08 Hz, 1H), 6.56 (dd, *J* = 3.16, 2.40 Hz, 1H), 7.17 (d, *J* = 8.08 Hz, 1H), 7.22 (t, *J* = 2.78 Hz, 1H) and 8.47 (br. s., 1H); MS (ES+): *m/z* 226.12 [MH+].

2-Phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-benzothiazole



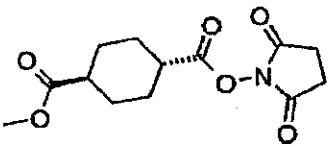
[324] A stirred solution of 5-bromo-2-phenylbenzothiazole (0.500 g, 0.00172 mol), bis(pinacolato)diboron (0.508 g, 0.00200 mol), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene hydrochloride (0.044 g, 0.10 mmol), Pd(OAc)2 (0.019 g, 0.086 mmol) and AcOK (0.423 g, 0.00431 mol) in anhydrous THF (9.78 mL, 0.121 mol) was heated at 72 °C under Argon for 29 h. The mixture was filtered through a multi-layered pad of anhydrous sodium sulfate, silica gel and celite and the filtrate was concentrated *in vacuo* and the solids triturated multiple times with hexanes to give the title compound. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm = 1.39 (s, 12 H), 7.49 - 7.56 (m, 3 H), 7.83 (dd, J = 8.08, 1.01 Hz, 1 H), 7.92 (d, J = 7.33 Hz, 1 H), 8.12 - 8.18 (m, 2 H) and 8.60 (s, 1 H); MS (ES+): m/z 337.91 [MH+].

4-(Methoxycarbonyl)-4-methylcyclohexanecarboxylic acid



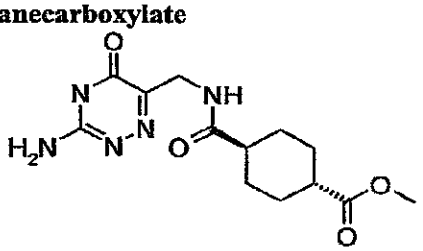
[325] *N,N*-Diisopropylamine (1.18mL, 8.35mmol) was added dropwise to a 2M solution of ^{n}butyllithium (4.18mL, 8.4mmol) at -78^{0}C under nitrogen. After 15min at this temperature the solution was raised to and held at 0^{0}C for 15 min prior to re-cooloing to -78^{0}C and treatment with a solution of 4-(methoxycarbonyl)cyclohexanecarboxylic acid (0.62g, 3.34mmol) in THF (8 mL). After 30min., iodomethane (0.31 mL, 5mmol) was added dropwise and the mixture was allowed to warm to rt over 2hr. The mixture was cooled to at 0 °C, quenched with 2 N HCl (10 mL) then was extracted with EtOAc (2 x 10 mL), washed with brine (3 x 15 mL), and dried over anhydrous magnesium sulfate. Concentration of the combined organic extracts afforded a yellow solid. NMR ($CDCl_3$) consistent with crude, desired product.

Methyl *trans*-4-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}cyclohexanecarboxylate



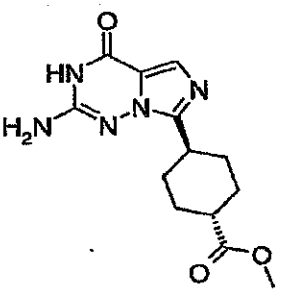
[326] A solution of *N*-hydroxysuccinimide (6.18 g, 0.0537 mol) and *trans*-4-(methoxycarbonyl)cyclohexanecarboxylic acid (10.00 g, 0.05370 mol) in THF (100.00 mL) was charged with (*N,N'*-dicyclohexylcarbodiimide (11.08 g, 0.0537 mol) in THF (16 mL). This reaction was stirred at rt for an additional 16 h then stirred at 45 °C for 1 h. The reaction mixture was filtered while still warm through a fritted funnel. The cake was washed with 3 more portions of THF and the filtrate was concentrated *in vacuo* and was crystallized from i-PrOH (300 mL) and filtered through a fritted funnel resulting in 11.8 g, (78% yield) of the title compound as a white crystals. ^{1}H NMR (400 MHz, CDCl3) δ ppm 1.45-1.69 (m, 4H), 2.07 - 2.16 (m, 2H), 2.18- 2.28 (m, 2H), 2.29 - 2.39 (m, 1H), 2.59 - 2.71 (m, 1H) 2.84 (br. s., 4H) and 3.68 (s, 3H); MS (ES+): m/z 284.09 [MH+].

Methyl *trans*-4-{[(3-amino-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl]carbamoyl}cyclohexanecarboxylate



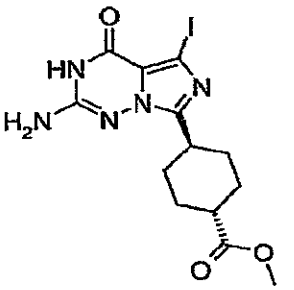
[327] A solution of 3-amino-6-(aminomethyl)-1,2,4-triazin-5(4*H*)-one [*J.Heterocyclic Chem.*, (1984), 21 (3), 697] (2.00 g, 0.0113 mol) in H_2O (60.0 mL, 3.33 mol) was cooled to 0 °C and drop wise charged with 1.00 M of $NaHCO_3$ in H_2O (22.5 mL) and allowed to warm to rt. This mixture was charged with methyl *trans*-4-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}cyclohexanecarboxylate (3.8 g, 0.012 mol) in 1:1 THF/MeCN (40 mL). After 30 min a precipitate began to form in the reaction. This was allowed to stir at rt for an additional 16 h and was filtered through a fritted funnel and washed with H_2O (2x), diethyl ether (2x), and dried *in vacuo* resulting in the title compound 2.92g, (84 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 - 1.55 (m, 4H), 1.83 (s, 2H), 1.98 (d, J = 10.61 Hz, 2H), 2.27 (s, 2H), 3.64 (s, 3H), 4.10 (d, J = 5.81 Hz, 2H), 6.81 (br. s., 2H), 7.91 (t, J = 5.56 Hz, 1H) and 11.98 (br. s., 1H); MS (ES+): m/z 310.05 [MH+].

Methyl *trans*-4-(2-amino-4-oxo-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate



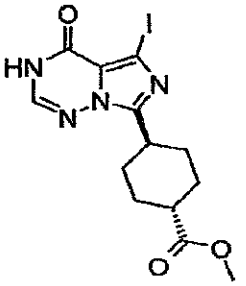
[328] A solution of methyl *trans*-4-{[(3-amino-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl]carbamoyl}cyclohexanecarboxylate (2.00 g, 0.00646 mol) in 1,2-dichloroethane (130 mL) was charged with $POCl_3$ (4.2 mL, 0.045 mol) and heated to reflux for 3 h. The reaction mixture was concentrated *in vacuo* then partitioned between EtOAc and sat. $NaHCO_3$ and separated. The aqueous was re-extracted with EtOAc (3x) and the combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* resulting in 1.43 g, (76 % yield) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 (q, J = 11.79 Hz, 2H), 1.61 (q, J = 12.55 Hz, 2H), 1.85 - 2.11 (m, 4H), 2.38 (t, J = 11.87 Hz, 1H), 2.98 (t, J = 11.75 Hz, 1H), 3.61 (s, 3 H), 6.17 (br. s., 2 H), 7.49 (s, 1H) and 10.90 (br. s., 1H); MS (ES+): m/z 292.25 [MH+].

Methyl *trans*-4-(2-amino-5-iodo-4-oxo-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate



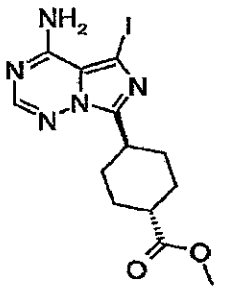
[329] A solution of methyl *trans*-4-(2-amino-4-oxo-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate (0.200 g, 0.000686 mol) and *N*-iodosuccinimide (0.278 g, 0.00124 mol) in anhydrous DMF (4.0 mL) was stirred at rt for 48 h. The reaction was concentrated *in vacuo* then partitioned between H_2O and EtOAc. The aqueous material was re-extracted with EtOAc (3x) and the combined organic fractions were washed with H_2O (2x), $Na_2S_2O_3$ (2x) and brine (1x). The aqueous was re-extracted with $CHCl_3$ and combined with the EtOAc fractions dried over Na_2SO_4, filtered and concentrated *in vacuo* resulting in 229 mg, (79.9 % yield) of the title compound as a light orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.65 (m, 4H), 1.88 - 2.06 (m, 4H), 2.33 - 2.45 (m, 1H), 2.91 - 3.01 (m, 1H), 3.61 (s, 3H), 6.17 (s, 2H) and 10.82 (br. s., 1H); MS (ES+): m/z 417.82 [MH+].

Methyl *trans*-4-(5-iodo-4-oxo-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate



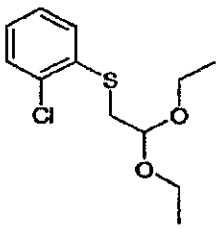
[330] A solution of methyl *trans*-4-(2-amino-5-iodo-4-oxo-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate (0.880 g, 0.00211 mol) in anhydrous THF (74 mL) and DMF (13.2 mL) was charged with tert-butyl nitrite (1.2 mL, 0.010 mol) and stirred at rt for 2 h. The reaction was concentrated *in vacuo* and was purified by chromatography over silica gel [eluting with 5% MeOH in $CHCl_3$] resulting in 570 mg, (67% yield) of the title compound as a pale orange solid. (^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 - 1.54 (m, 2H), 1.56 - 1.69 (m, 2H), 1.92 - 2.06 (m, 4H), 2.36 - 2.46 (m, 1H), 3.02 - 3.14 (m, 1H), 3.61 (s, 3H), 7.89 (d, J = 3.28 Hz, 1 H) and 11.79 (br. s., 1H); MS (ES+): m/z 402.86 [MH+].

Methyl *trans*-4-(4-amino-5-iodoimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate



[331] A solution of 1*H*-1,2,4-triazole (0.881 g, 0.0128 mol) in pyridine (3.00 mL) was charged with $POCl_3$ (0.396 mL, 0.00425 mol) and stirred at rt for 15 min. To this mixture was drop wise added methyl *trans*-4-(5-iodo-4-oxo-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-7-yl)cyclohexanecarboxylate (0.570 g, 0.00142 mol) in pyridine (6.00 mL) and stirred at rt for an additional 2.45 h. The reaction was quenched with excess 2 M of NH_3 in *i*-PrOH (40.00 mL) at 0 °C and allowed to stir at rt for an additional 3 h. The reaction was concentrated *in vacuo* and partitioned between EtOAc and sat. $NaHCO_3$ and separated. The aqueous was washed with EtOAc (3x) and the combined organic fractions were washed with brine (1x). The aqueous was re-extracted with $CHCl_3$ (3x) and the organic was added to the EtOAc fractions. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude brown/red solid was purified by chromatography over silica gel [eluting with 5% MeOH in $CHCl_3$] resulting in 438 mg, (76% yield) of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.54 (m, 2H), 1.55 - 1.71 (m, 2H), 1.92 - 2.07 (m, 4H), 2.35 - 2.46 (m, 1H), 3.06 - 3.19 (m, 1H), 3.61 (s, 3H), 6.77 (br. s., 1H) 7.86 (s, 1H) and 8.44 (br. s., 1H); MS (ES+): m/z 401.85 [MH+].

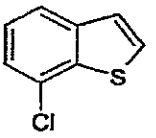
1-Chloro-2-[(2,2-diethoxyethyl)thio]benzene



[332] To a solution of 2-chlorobenzenethiol (5.0 g, 34.5 mmol) in acetone (35 mL) was added 2-bromo-1,1-diethoxyethane (7.15 g, 36.3 mmol) followed by potassium carbonate (9.55 g, 69.1 mmol). The mixture was heated at reflux for 3 h. then cooled to rt, filtered and the filtrate evaporated under reduced pressure to yield the crude product. This material was purified by chromatography over silica gel eluting with ethyl acetate in hexanes (0→2%) to afford pure 1-chloro-2-(2,2-diethoxyethylsulfanyl)benzene (7.3, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.20 (t, *J* = 7.07 Hz, 6H), 3.15 (d, *J* = 5.56 Hz, 2H), 3.51–3.61 (m, 2H), 3.63–3.74 (m, 2H), 4.69 (t, *J* = 5.56 Hz, 1H),

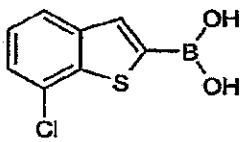
7.12 (td, J = 7.58, 1.52 Hz, 1H), 7.20 (td, J = 7.58, 1.52 Hz, 1H), 7.36 (dd, J = 7.83, 1.52 Hz, 1H), 7.39 (dd, J = 8.08, 1.52 Hz, 1H); MS (ES+): *m/z* 187.17 [M-74].

7-Chlorobenzo[*b*]thiophene



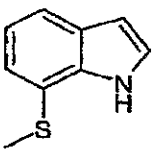
[333] To a solution of 1-chloro-2-(2,2-diethoxyethylsulfanyl)benzene (3.95 g, 15.14 mmol) in toluene (40 mL) was added polyphosphoric acid (15 g, 137.5 mmol). The mixture was heated at reflux for 4 h. then was poured in to ice water, stirred for 30 min and extracted with toluene. The combined toluene extracts were washed with aqueous sodium bicarbonate followed by brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield the crude product. This material was purified by chromatography over silica gel eluting with hexane to afford pure 7-chlorobenzo[*b*]thiophene (1.72 g, 67.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13–7.30 (m, 3H), 7.38 (d, J = 5.31 Hz, 1H), 7.62 (dd, J = 7.33, 1.52 Hz, 1H); MS (ES+): *m/z* 169.06 [MH+].

7-Chlorobenzo[*b*]thiophene-2-boronic acid



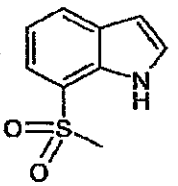
[334] To a solution of 7-chlorobenzo[*b*]thiophene (1.0 g, 5.92 mmol) in THF (25 mL) at –78 °C was added "butyllithium (7.41 mL, 11.8 mmol, 1.6 M solution). The reaction was allowed to warm to –30 °C then was cooled back to –78 °C and triisopropyl borate (2.23 g, 11.8 mmol) was added. The mixture was allowed to warm to 0 °C, saturated ammonium chloride added and the organic phase separated off and concentrated *in vacuo*. To the residue was added aqueous sodium hydroxide (10 mL, 2N solution) followed by water (30 mL) and the mixture was washed with DCM. The aqueous phase was acidified with 2N sulfuric acid, and the resulting precipitate isolated by filtration and dried under vacuum to yield 7-chlorobenzo[*b*]thiophene-2-boronic acid (1.21 g, 96%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (t, J = 7.70 Hz, 1H), 7.50 (d, J = 7.70 Hz, 1H), 7.91 (d, J = 7.70 Hz, 1H), 8.03 (s, 1H), 8.63 (s, 2H); MS (ES+): *m/z* 211.86 [M+].

7-(methylthio)-1*H*-indole



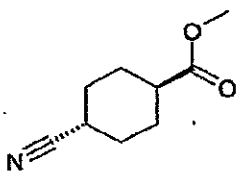
[335] To a solution of 7-bromo-1*H*-indole (3.0 g, 15.3 mmol) in THF (60 mL) at –78 °C was added ^{t}BuLi (1.7 M, 33.8 mL, 57.4 mmol) and the mixture was allowed to warm to 0 °C. The reaction was re-cooled to –78 °C and a solution of dimethyl disulfide (2.0 mL, 22.9 mmol) was added and the reaction was allowed to warm to 0 °C. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield the crude product. This material was purified by chromatography over silica gel eluting with ethyl acetate in hexanes (0→2%) to afford pure 7-(methylthio)-1*H*-indole (1.4 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.50 (s, 3 H), 6.58 (dd, *J* = 3.03, 2.02 Hz, 1H), 7.09 (t, *J* = 7.58 Hz, 1H), 7.18–7.31 (m, 2H), 7.56 (d, *J* = 7.83 Hz, 1H), 8.45 (br. s., 1 H); MS (ES+): *m/z* 164.15 [MH+].

7-(Methylsulfonyl)-1*H*-indole



[336] To a solution of 7-(methylthio)-1*H*-indole (1.1 g, 6.7 mmol) in DCM (25 ml) at –40 °C was added *m*-chloroperbenzoic acid (3.02 g, 13.4 mmol) and the reaction was stirred at –40 °C for 30 min. The reaction mixture was then quenched with saturated sodium bicarbonate and extracted with DCM. The DCM extracts was washed with water, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield the crude product. This material was purified by chromatography over silica gel eluting with hexanes (0→10%) to afford pure 7-(methylsulfonyl)-1*H*-indole (987 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.12 (s, 1H), 6.66 (d, *J* = 2.53 Hz, 1H), 7.24 (t, *J* = 7.71 Hz, 1H), 7.35 (d, *J* = 1.77 Hz, 1H), 7.68 (d, *J* = 7.07 Hz, 1H), 7.90 (d, *J* = 7.83 Hz, 1H), 9.68 (br. s., 1H); MS (ES+): *m/z* 196.08 [MH+].

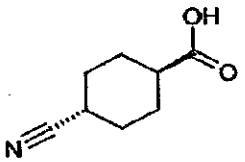
Methyl *trans*-4-cyanocyclohexanecarboxylate



[337] Chlorosulfonyl isocyanate (1.0 mL, 0.012 mol) was added to a solution of *trans*-4-(methoxycarbonyl)cyclohexanecarboxylic acid (2.00 g, 0.0107 mol) in DCM cooled to 0 °C. The

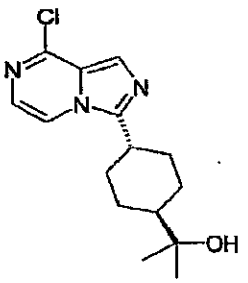
resulting solution was heated at reflux for 15 minutes and then cooled 0 °C and treated dropwise with DMF. The mixture was stirred at room temperature overnight then poured onto ice water and the organic phase separated and washed with a saturated solution of sodium bicarbonate. The solvent was removed *in vacuo* and the crude material was taken up in ethyl acetate, washed with 1N aq. NaOH (10mL) and the ethyl acetate removed *in vacuo*. The resulting crude product was used in subsequent steps without further purification. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.36 - 1.70 (4 H, m), 2.01 - 2.18 (4 H, m), 2.24 - 2.54 (2 H, m) and 3.68 (3 H, s).

Trans-4-cyanocyclohexanecarboxylic acid



[338] To a solution of methyl *trans*-4-cyanocyclohexanecarboxylate (996 mg, 5.96 mmol) in THF (37 mL) was added a solution of 0.5 M lithium hydroxide in water (20 mL). The mixture was stirred overnight then the THF was removed *in vacuo* and the residual aqueous solution acidified to pH 4. The resulting mixture was extracted with ether (2 x 30 mL), EtOAc (2 x 30 mL) and $CHCl_3$ (2 x 30 mL) then the combined extracts, dried over anhydrous sodium sulfate and concentrated *in vacuo*. This material was taken to the next step without any purification. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 - 1.73 (4 H, m), 2.05 - 2.22 (4 H, m) and 2.36 - 2.59 (2 H, m).

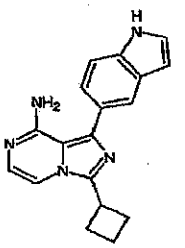
2-[T*rans*-4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]propan-2-ol



[339] A solution of methyl *trans*-4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate (4.0 g, 0.014 mol) in toluene (300 mL) and THF (70 mL) was cooled to 0 °C and treated with a 3.0 M solution of methylmagnesium bromide in ether (14 mL) mantaining the temperature at 0 °C. The mixture was stirred at rt for 1.5 hours then cooled to 0 °C and an addtional 3 eq of 3.0 M of methylmagnesium bromide in ether was added. The mixture was stirred at rt for 15

minutes then cooled to 0 °C and quenched with 1:1 NH_4Cl sat. : H_2O (50 mL total volume). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* and the crude product thus obtained, chromatographed over silica gel eluting with EtOAc to afford desired 2-[*trans*-4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]propan-2-ol. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.14 - 1.39 (m, 8 H), 1.41 - 1.60 (m, 1 H), 1.77 - 1.98 (m, 2 H), 2.01 - 2.20 (m, 4 H), 2.78 - 3.06 (m, 1 H), 7.35 (d, J=5.05 Hz, 1 H), 7.64 (d, J=5.05 Hz, 1 H) and 7.83 (s, 1 H).

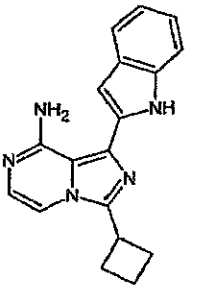
EXAMPLE 1



3-Cyclobutyl-1-(1*H*-indol-5-yl)imidazo[1,5-*a*]pyrazin-8-amine

[340] A dry mixture of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine (30mg, 0.096mmol), cesium carbonate (38mg, 0.117mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (26mg, 0.107mmol) was purged with Argon 3 times prior to the addition of tetrakistriphenylphosphino palladium (0) (6mg, 0.005mmol). The mixture was purged twice more and then treated with a degassed mixture of DME:water (5:1, 2mL). The resulting solution was degassed twice more and then heated at 80°C overnight. The resulting reaction mixture was concentrated *in vacuo*, the residue dissolved in 1:1 MeCN:MeOH (1.5mL) and purified by mass directed preparative HPLC to afford 3-cyclobutyl-1-(1*H*-indol-5-yl)imidazo[1,5-*a*]pyrazin-8-amine. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 1.82 - 1.92 (1 H, m) 1.95 - 2.08 (1 H, m) 2.32 - 2.41 (4 H, m) 3.82 - 3.93 (1 H, m) 5.91 (2 H, br. s.) 6.45 (1 H, d, *J*=3.03 Hz) 6.90 (1 H, d, *J*=5.05 Hz) 7.26 (1 H, dd, *J*=8.34, 1.52 Hz) 7.34 (1 H, d, *J*=5.05 Hz) 7.35 - 7.39 (1 H, m) 7.45 (1 H, d, *J*=8.34 Hz) 7.64 - 7.68 (1 H, m) 11.20 (1 H, br. s.); MS (ES+): m/z 304.15 [MH+]. HPLC: t_R 6.18min (XTerra C18 5uM, 4.6 x 15mm, A: MeCN & B:10mmol NH_4OAc in 0.05% HOAc/aq., method Polar15).

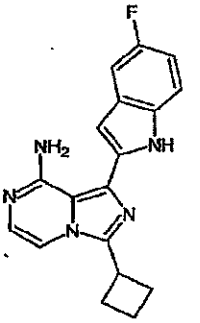
EXAMPLE 2



3-Cyclobutyl-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[341] Prepared as described above for **EXAMPLE 1** using 1-(*tert*-butoxycarbonyl)-1*H*-indole-2-boronic acid in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. The reaction conditions used effected significant cleavage of the *N*-(*tert*-butoxycarbamoyl) functionality. MS (ES+): m/z 304.10 [MH+].

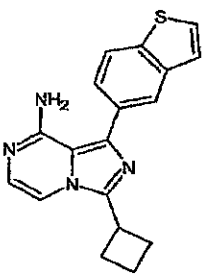
EXAMPLE 3



3-Cyclobutyl-1-(5-fluoro-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[342] Prepared as described above for **EXAMPLE 1** using 1-(*tert*-butoxycarbonyl)-5-fluoro-1*H*-indole-2-boronic acid in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. The reaction conditions used effected significant cleavage of the *N*-(*tert*-butoxycarbamoyl) functionality. MS (ES+): m/z 322.06 [MH+].

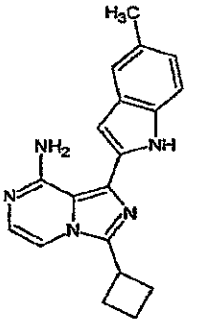
EXAMPLE 4



1-(1-Benzothien-5-yl)-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine

[343] Prepared as described above for **EXAMPLE 1** using 2-(1-benzothiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. MS (ES+): m/z 321.10 [MH+].

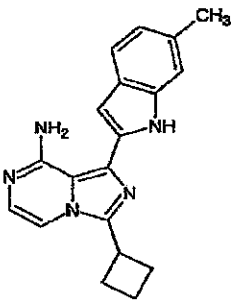
EXAMPLE 5



3-Cyclobutyl-1-(5-methyl-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[344] Prepared as described above for **EXAMPLE 1** using 1-(*tert*-butoxycarbonyl)-5-methyl-1*H*-indole-2-boronic acid in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. MS (ES+): m/z 318.05 [MH+].

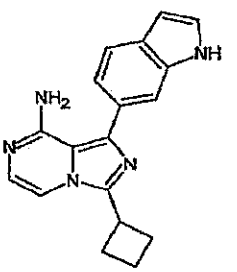
EXAMPLE 6



3-Cyclobutyl-1-(6-methyl-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[345] Prepared as described above for **EXAMPLE 1** using 1-(*tert*-butoxycarbonyl)-6-methyl-1*H*-indole-2-boronic acid in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. MS (ES+): m/z 318.05 [MH+].

EXAMPLE 7

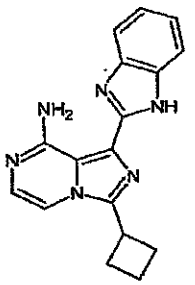


3-Cyclobutyl-1-(1*H*-indol-6-yl)imidazo[1,5-*a*]pyrazin-8-amine

[346] A mixture of 6-bromo-1*H*-indole (2g, 10.00mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.00g, 7.87mmol) and potassium acetate (3.0g, 31.00mmol) was degassed three times, treated with (1,1'-bis(diphenylphosphino)ferrocene) palladium dichloride (0.20g, 0.28mmol) and degassed twice more. 1,2-dimethoxyethane (28mL) was added and the mixture was heated at 75°C overnight. The cooled reaction mixture was then diluted with water, extracted with EtOAc and the extracts washed with water and brine, then dried over magnesium sulphate, and concentrated *in vacuo* to afford a brown/black semi-solid. This was triturated with ether to afford a brown powder, which was identified by LCMS to be desired indole-6-boronic acid, pinacol ester. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.37 (s, 12 H), 6.54 - 6.58 (m, 1 H), 7.26 - 7.28 (m, 1 H), 7.55 (dd, *J*=7.83, 1.01 Hz, 1 H), 7.62 - 7.68 (m, 1 H),7.90 (s, 1 H), 8.19 (br. s., 1 H); MS (ES+): *m/z* 244.25 [MH$^+$]; HPLC: t_R = 3.52 min (OpenLynx, polar_5min).

[347] This material was used in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole under the conditions described in **EXAMPLE 1** to afford 3-cyclobutyl-1-(1*H*-indol-6-yl)imidazo[1,5-*a*]pyrazin-8-amine. MS (ES+): m/z 304.15 [MH+].

EXAMPLE 8



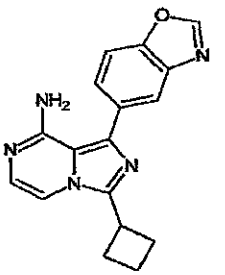
1-(1*H*-Benzimidazol-2-yl)-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine

[348] 3-Cyclobutyl-1-iodoimidazo[1,5-*a*]pyrazin-8-amine (500mg, 2mmol) and tetrakis(triphenylphosphine)palladium(0) (100mg, 0.1mmol) was degassed dry three times then treated with methanol (20mL) and *N,N*-diisopropylethylamine (0.7mL, 4.0mmol) and the mixture heated at 70°C under an atmosphere of carbon monoxide, with intermittent bubbling of this gas under the surface of the reaction mixture. After 3d heating with extensive bubbling through of the solution with carbon monoxide and some addition of fresh catalyst after day 2, TLC (10% MeOH/DCM) indicated the reaction to be complete. The reaction mixture was diluted with water, extracted with DCM and the extracts washed with water and brine, then dried over magnesium sulphate, and concentrated *in vacuo* to afford an orange solid which was recrystallised from acetonitrile to afford methyl 8-amino-3-cyclobutylimidazo[1,5-*a*]pyrazine-1-carboxylate. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.97 - 2.06 (m, 1 H), 2.10 - 2.26 (m, 1 H), 2.43 - 2.54 (m, 2 H), 2.53 - 2.68 (m, 2 H), 3.78 (dd, *J*=9.09, 8.08 Hz, 1 H), 4.01 (s, 3 H), 7.08 (d, *J*=4.80 Hz, 1 H), 7.22 (d, *J*=4.80 Hz, 1 H), 7.38 (br. s., 1 H), 7.69 (br. s., 1 H).

[349] A suspension of 1,2-phenylenediamine (60mg, 0.6mmol) in toluene (2.0mL) was treated with a 2M solution of trimethylaluminum in toluene (0.5mL) effecting the formation of a pink solution. After 5min this solution was treated with solid methyl 8-amino-3-cyclobutylimidazo[1,5-*a*]pyrazine-1-carboxylate (30mg, 0.1mmol) and the mixture heated at 120°C for 30min then stirred at rt overnight. The mixture was then partitioned between 2M NaOH (10mL) & EtOAc (10mL) and stirred for 15min. The organic layer was separated and the aqueous layer extracted further with EtOAc (3 x 10mL). The combined organics were washed with brine, dried and concentrated *in vacuo* to give ~85% pure 8-amino-*N*-(2-aminophenyl)-3-cyclobutylimidazo[1,5-*a*]pyrazine-1-carboxamide which was used without purification.

[350] A solution of 8-amino-*N*-(2-aminophenyl)-3-cyclobutylimidazo[1,5-*a*]pyrazine-1-carboxamide (40.0mg, 0.124mmol) in acetic acid (1.2mL) was microwaved at 120°C for 10min (300W). The resulting solution was purified mass directed preparative HPLC to afford 1-(1*H*-benzimidazol-2-yl)-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.92 - 2.05 (m, 1 H) 2.07 - 2.21 (m, 1 H) 2.53 - 2.59 (m, 4 H) 3.91 - 4.06 (m, 1 H) 7.08 (d, J=4.80 Hz, 1 H) 7.16 - 7.26 (m, 2 H) 7.38 (d, J=4.80 Hz, 1 H) 7.44 (br. s., 1 H) 7.55 (d, J=8.08 Hz, 1 H) 7.62 (d, J=6.82 Hz, 1 H) 10.49 (br. s., 1 H) 12.76 (s, 1 H); MS (ES+): *m/z* 305.15 [MH^+].

EXAMPLE 9

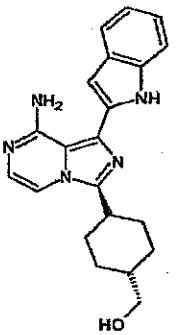


1-(1,3-Benzoxazol-5-yl)-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine

[351] A mixture of 5-chlorobenzoxazole (0.129g, 0.84mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (0.4956g, 1.95mmol), potassium acetate (0.41g, 4.2mmol), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene hydrochloride (43mg, 0.10mmol) and palladium acetate (11mg, 0.05mmol) was degassed, treated with tetrahydrofuran (10mL) and the resulting mixture heated at 80°C overnight. The mixture was diluted with water (100mL), acidified to pH 6 and extracted with EtOAc (3 x 40mL). The extracts were washed with water, dried and concentrated *in vacuo*. The residue so obtained was purified by chromatography over silica gel eluting with DCM to 10% MeCN/DCM to afford 1,3-benzoxazole-5-boronic acid, pinacol ester. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.37 - 1.39 (m, 12 H) 7.59 (d, *J*=8.34 Hz, 1 H) 7.86 (dd, *J*=8.08, 1.01 Hz, 1 H) 8.10 (s, 1 H) 8.26 (s, 1 H); MS (ES+): *m/z* 246.23 [MH^+].

[352] This material was used in place of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole under the conditions described in example 1 to afford 1-(1,3-benzoxazol-5-yl)-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine MS (ES+): m/z 306.16 [MH+].

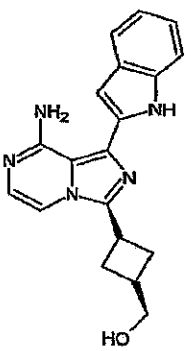
EXAMPLE 10



{*trans*-4-[8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methanol

[353] Prepared according to the procedure described in EXAMPLE 2 using *trans*-[4-(8-amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.12–1.23 (m,), 1.38-1.54 (m, 1H); 1.58-1.78 (m, 2H); 1.82-1.92 (m, 2H); 1.96-2.06 (m, 2H); 3.03-3.16 (m, 1H); 3.29 (t, J = 5.6 Hz, 2H); 4.46 (t, J = 5.3 Hz, 1H); 6.45 (brs, 2H); 6.63 (d, J = 1.38 Hz, 1H); 7.02 (t, J = 7.50 Hz, 1H); 7.06 (d, J = 4.99 Hz, 1H); 7.12 (t, J = 7.52, 1H), 7.46 (d, J = 8.02 Hz, 1H), 7.58 (d, J = 7.83 Hz, 1H), 7.66 (d, J = 5.06 Hz, 1H), 11.43 (s, 1H); MS (ES+): m/z 362.07 (100) [MH+], HPLC: *t*R = 1.97 min (MicromassZQ, polar_5min).

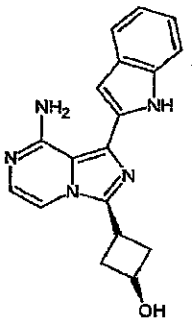
EXAMPLE 11



{*cis*-3-[8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclobutyl}methanol

[354] Prepared according to the procedure described in EXAMPLE 2 using [3-(8-chloro-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclobutyl]methanol in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. MS (ES+): m/z 334.10 [MH+].

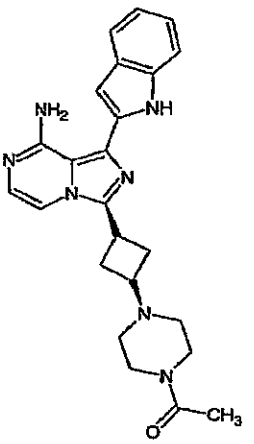
EXAMPLE 12



cis-3-[8-Amino-1-(1_H_-indol-2-yl)imidazo[1,5-_a_]pyrazin-3-yl]cyclobutanol

[355] Prepared according to the procedure described in EXAMPLE 2 using 3-(8-amino-1-iodoimidazo[1,5-_a_]pyrazin-3-yl)cyclobutanol in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-_a_]pyrazine. MS (ES+): m/z 320.03 [MH+].

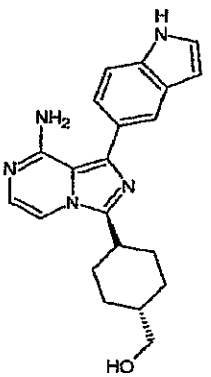
EXAMPLE 13



3-[_cis_-3-(4-Acetylpiperazin-1-yl)cyclobutyl]-1-(1_H_-indol-2-yl)imidazo[1,5-_a_]pyrazin-8-amine

[356] Prepared according to the procedure described in EXAMPLE 2 using 1-{4-[3-(8-amino-1-iodoimidazo[1,5-_a_]pyrazin-3-yl)cyclobutyl]piperazin-1-yl}ethanone in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-_a_]pyrazine. MS (ES+): m/z 430.08 [MH+].

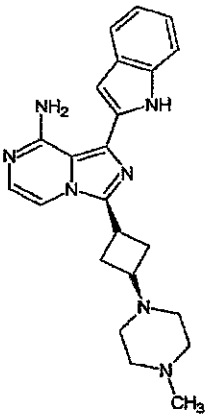
EXAMPLE 14



{*trans*-4-[8-Amino-1-(1*H*-indol-5-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methanol

[357] Prepared according to the procedure described in EXAMPLE 1 using *trans*-[4-(8-amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methanol in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. MS (ES+): m/z 362.07 [MH+].

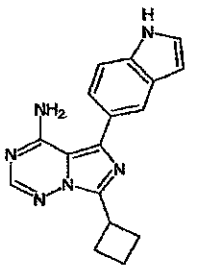
EXAMPLE 15



1-(1*H*-Indol-2-yl)-3-[*cis*-3-(4-methylpiperazin-1-yl)cyclobutyl]imidazo[1,5-*a*]pyrazin-8-amine

[358] Prepared according to the procedure described in EXAMPLE 2 using 1-iodo-3-[3-(4-methyl-piperazin-1-yl)cyclobutyl]imidazo[1,5-*a*]pyrazin-8-ylamine in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. MS (ES+): m/z 402.10 [MH+].

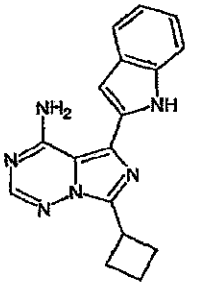
EXAMPLE 16



7-Cyclobutyl-5-(1*H*-indol-5-yl)imidazo[5,1-*f*][1,2,4]triazin-4-amine

[359] Prepared according to the procedure described in EXAMPLE 1 using 7-cyclobutyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-ylamine in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. MS (ES+): m/z 305.16 [MH+].

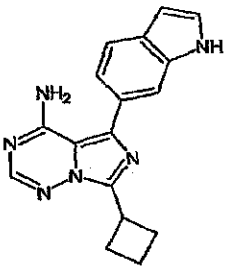
EXAMPLE 17



7-Cyclobutyl-5-(1*H*-indol-2-yl)imidazo[5,1-*f*][1,2,4]triazin-4-amine

[360] Prepared according to the procedure described in EXAMPLE 2 using 7-cyclobutyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-ylamine in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. MS (ES+): m/z 305.07 [MH+].

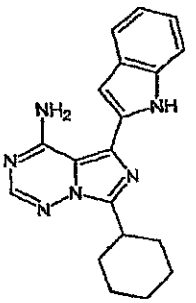
EXAMPLE 18



7-Cyclobutyl-5-(1*H*-indol-6-yl)imidazo[5,1-*f*][1,2,4]triazin-4-amine

[361] Prepared according to the procedure described in EXAMPLE 7 using 7-cyclobutyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-ylamine in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. MS (ES+): m/z 305.07 [MH+].

EXAMPLE 19

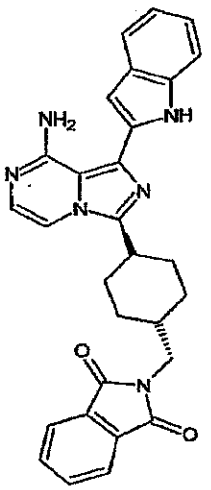


7-Cyclohexyl-5-(1*H*-indol-2-yl)imidazo[5,1-*f*][1,2,4]triazin-4-amine

[362] Prepared according to the procedure described in EXAMPLE 2 using 7-cyclohexyl-5-iodoimidazo[5,1-*f*][1,2,4]triazin-4-amine in place of 8-amino-3-cyclobutyl-1-iodoimidazo[3,4-*a*]pyrazine. ^{1}H NMR (400 MHz – DMSO-d6) δ 1.40 – 1.54 (m, 4H), 1.72 – 1.82 (m, 2H), 1.87 – 1.92 (m, 2H), 2.02 – 2.09 (m, 2H) 3.31 – 3.38 (m, 1H) 6.26 (bs, 2H) 6.73 – 6.74 (m, 1H), 7.13 – 7.17 (m,

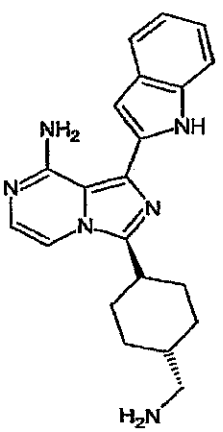
1H), 7.22 – 7.25 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H) 7.64 (d, J =8.0 Hz, 1H), 7.91 (s, 1H), 9.18 (s, 1H). MS (ES+): m/z: 333.16 (100) [MH+]. HPLC: t_R = 3.46 min (OpenLynx: polar_5 min).

EXAMPLE 20



[363] A mixture of {*trans*-4-[8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methanol (400mg, 0.001mol), phthalimide (211.7mg, 0.001439mol), and triphenylphosphine resin (2.14mmol/g loading; 1.03g, 0.00221mol; Argonaut) in THF (22mL, 0.27mol; Aldrich) was placed under nitrogen atmosphere and charged dropwise with diisopropyl azodicarboxylate (290.9mg, 0.001439mol). After 16h, the resin was filtered off, washed with chloroform (5 x 20mL) and the filtrate concentrated *in vacuo* to yield an orange oil which was chromatographed over silica gel eluting with chloroform → 5% MeOH/chloroform to afford the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.85 (m, 2H), 7.77-7.70 (m, 2H), 7.64 (m, 1H), 7.43 (dd, J = 8.0, 0.8 Hz, 1H), 7.27-7.15 (m, 2H), 7.14 (m, 1H), 7.09 (d, J = 4.8 Hz, 1H), 6.77 (br s, 1H), 3.64 (d, J = 6.4 Hz, 2H), 2.91 (m, 1H), 2.09 (m, 2H), 2.25-1.90 (m, 4H), 1.80 (ddd, J = 13.2, 12,4, 2,4 Hz, 2H), 1.27 (ddd, J = 13.2, 12,4, 2,4 Hz, 2H). MS (ES+): m/z 491.09 [MH+].

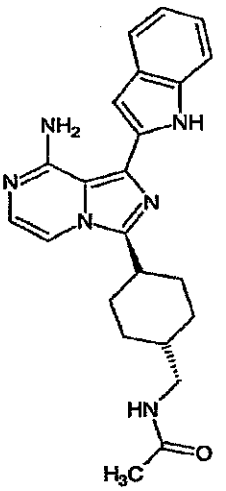
EXAMPLE 21



1-{*trans*-4-[8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methanamine

[364] A solution of benzyl {[*trans*-4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate (0.163 g, 0.330 mmol) in conc. HCl (5 ml) was stirred at rt overnight. The reaction mixture was diluted with H_2O (20mL), washed with Et_2O (30mL), then basified with 1N NaOH (aq) and extracted with DCM (3 x 20mL). The combined extracts were washed with water then dried over Na_2SO_4 and concentrated *in vacuo* To afford 0.085g of desired compound. MS (ES+): m/z 361.30 [MH+].

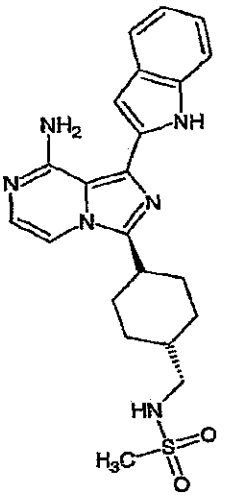
EXAMPLE 22



***N*-({*trans*-4-[8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methyl)acetamide**

[365] To a suspension of 1-{*trans*-4-[8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methanamine (100.00 mg, 0.27 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.0798 g, 0.416 mmol), *N,N*-diisopropylethylamine (0.097 mL, 0.55 mmol), 1-hydroxbenzotriaxole Hydrate (0.0425 g, 0.277 mmol), and DMF (600 uL) in DCM (5 mL) was added AcOH (24 uL). The mixture was stirred at rt for 3 h under an atmosphere of nitrogen then diluted with DCM (20mL), washed with saturated $NaHCO_3$ (aq) (2 x 25mL) and brine (2 x 25mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with DCM → 2% 2M NH_3 in MeOH/DCM to afford 0.02g of the title compound. MS (ES+): m/z 403.31 [MH+]. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12-1.31 (m, 3H), 1.79-1.86 (m, 2H), 1.94-1.97 (m, 2H), 2.02 (s, 3H), 2.04-2.09 (m, 2H), 2.91 (m, 1H), 3.20 (t, J = 6.4 Hz, 2H), 5.51 (br, 1H), 5.66 (br, 2H), 6.79 (s, 1H), 7.10-7.16 (m, 2H), 7.20-7.25 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 9.07 (br, 1H).

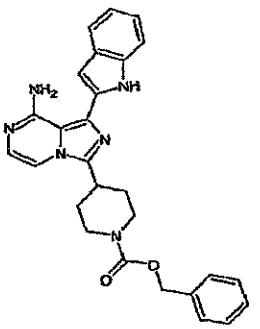
EXAMPLE 23



***N*-({4-[8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methyl)methanesulfonamide**

[366] Methanesulfonyl chloride (4.40μL, 0.057 mmol was added to a mixture of 1-{*trans*-4-[8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexyl}methanamine (20.5mg, 0.057mol) and PS-DIEA (3.90mmol/g loading; 60mg, 0.2mmol) in DCM (1.14mL). The reaction mixture was stirred for 30min at r.t. for 18h. The crude reaction mixture was then concentrated and residue purified by mass directed preparative HPLC to afford 4mg of desired product. MS (ES+): m/z 439.10 (100) [MH+]. ^{1}H NMR (CD3OD, 400 MHz): δ 8.24 (br s, 2H), 7.61 (m, 2H), 7.46 (dd, J = 8.4, 0.8 Hz, 1H), 7.19 (ddd, J = 7.2, 1.2, 1.2 Hz, 1H), 7.08 (ddd, J = 7.2, 1.2, 1.2 Hz, 1H), 6.75 (d, J = 0.8 Hz, 1H), 3.14 (m, 1H), 2.07 (m, 4H), 1.85 (m, 2H), 1.64 (m, 1H), 1.26 (m, 2H).

EXAMPLE 24

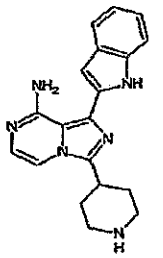


Benzyl 4-[8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]piperidine-1-carboxylate

[367] A mixture of benzyl 4-(8-amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate (1.149g, 0.002191mol), 1-(*tert*-butoxycarbonyl)-1*H*-indole-2-boronic acid (0.629g, 0.00241mol), 1,2-dimethoxyethane (9.3mL), water (1.8mL) and cesium carbonate (1.43g, 0.00438mol) was degassed three times and then treated with tetrakis(triphenyl phosphine)palladium(0) (200mg, 0.0002mol). The mixture was once more degassed and then heated

at 100 °C overnight. The resulting reaction mixture was diluted with EtOAc (30mL) then washed with water (2 x 30mL) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was chromatographed over silica gel eluting with hexane → EtOAc:hexane 1:1:0.05 2M NH_3/MeOH to afford the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02-2.06 (m, 4H), 3.03-3.17 (m, 3H), 4.29-4.33 (m, 2H), 5.16 (s, 2H), 5.66 (br, 2H), 6.79-6.80 (m, 1H), 7.11-7.16 (m, 2H), 7.20-7.25 (m, 2H), 7.31-7.45 (m, 5H), 7.44 (m, 1H), 7.64 (d, J = 7.6 Hz, 1H), 8.96 (br, 1H). MS (ES+): m/z 467.12 [MH+].

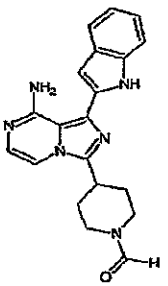
EXAMPLE 25



1-(1*H*-Indol-2-yl)-3-piperidin-4-ylimidazo[1,5-*a*]pyrazin-8-amine

[368] A solution of benzyl 4-[8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]piperidine-1-carboxylate (3.61 g, 0.00774 mol) in conc. HCl (100 ml) was stirred at rt overnight. The mixture was then diluted with water (200mL), washed with Et_2O (2 x 30mL) then the aqueous layer concentrated *in vacuo* yielding 2.62 g of desired product as the trihydrochloride salt. ^{1}H NMR (400 MHz, MeOD): δ 2.19-2.32 (m, 4H), 3.26-3.30 (m, 2H), 3.53-3.36 (m, 2H), 3.70 (m, 1H), 7.06 (d, J = 5.6 Hz, 1H), 7.10-7.14 (m, 1H), 7.23-7.26 (m, 2H), 7.50-7.52 (m, 1H), 7.67 (m, 1H), 7.93 (m, 1H). MS (ES+): m/z 333.27 [MH+].

EXAMPLE 26

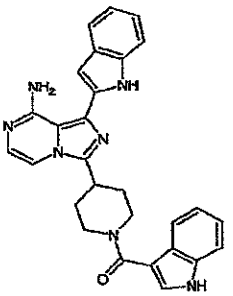


4-[8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]piperidine-1-carbaldehyde

[369] To a solution of 1-(1*H*-Indol-2-yl)-3-piperidin-4-ylimidazo[1,5-*a*]pyrazin-8-amine hydrochloride (30.00 mg, 0.0068 mmol) in DCM (0.5 mL, 0.008 mol) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.0195 g, 0.102 mmol), *N,N*-diisopropylethylamine (0.047 mL), 1-hydroxbenzotriaxole hydrate (0.0104 g, 0.0679 mmol) and formic acid (4.7 mg, 0.10 mmol). The reaction was stirred at rt overnight then diluted with DCM, washed with saturated $NaHCO_3$ (2 x 25mL) and brine (2 x 25), then dried over Na_2SO_4 and

concentrated *in vacuo*. The material thus isolated was crystallized from EtOAc to afford 10.6 mg of desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04-2.12 (m, 4H), 2.99-3.00 (m, 1H), 3.27-3.32 (m, 2H), 3.85 (m, 1H), 4.49 (m, 1H), 5.70 (br, 2H), 6.80 (s, 1H), 7.13-7.24 (m, 4H), 7.45 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 8.10 (s, 1H), 8.97 (br, 1H). MS (ES+): m/z 361.16 [MH+].

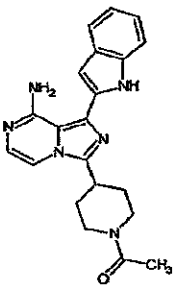
EXAMPLE 27



3-[1-(1*H*-Indol-3-ylcarbonyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[370] Prepared according to the procedure described above for EXAMPLE 26, except using indole-3-carboxylic acid in place of formic acid. MS (ES+): m/z 476.18 [MH+].

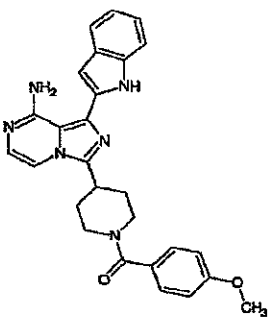
Example 28



3-(1-Acetylpiperidin-4-yl)-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[371] Prepared according to the procedure described above for EXAMPLE 26, except using acetic acid in place of formic acid. MS (ES+): m/z 375.17 [MH+].

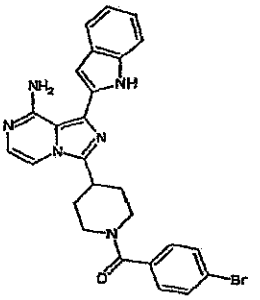
EXAMPLE 29



3-[1-(4-Methoxybenzoyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[372] Prepared according to the procedure described above for EXAMPLE 26, except using 4-methoxybenzoic acid in place of formic acid. MS (ES+): m/z 467.27 [MH+].

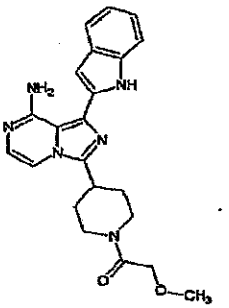
EXAMPLE 30



3-[1-(4-Bromobenzoyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[373] Prepared according to the procedure described above for EXAMPLE 26, except using 4-methoxybenzoic acid in place of formic acid. MS (ES+): m/z 515.17 & 517.17 [MH+].

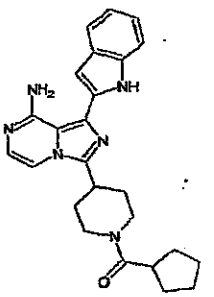
EXAMPLE 31



1-(1*H*-Indol-2-yl -3-[1-(methoxyacetyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[374] Prepared according to the procedure described above for **EXAMPLE 26**, except using 2-methoxyacetic acid in place of formic acid. MS (ES+): m/z 405.10 [MH+].

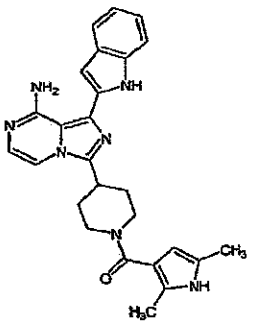
EXAMPLE 32



3-[1-(Cyclopentylcarbonyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[375] Prepared according to the procedure described above for **EXAMPLE 26**, except using cyclopentanecarboxylic acid in place of formic acid. MS (ES+): m/z 429.07 [MH+].

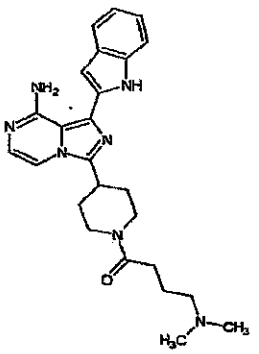
EXAMPLE 33



3-{1-[(2,5-Dimethyl-1*H*-pyrrol-3-yl)carbonyl]piperidin-4-yl}-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[376] Prepared according to the procedure described above for **EXAMPLE 26**, except using 2,5-dimethylpyrrolecarboxylic acid in place of formic acid. MS (ES+): m/z 454.19 [MH+].

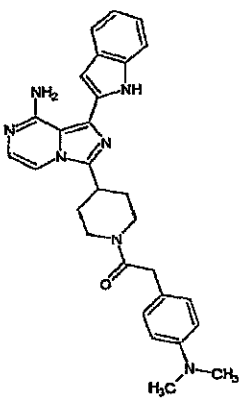
EXAMPLE 34



3-{1-[4-(Dimethylamino)butanoyl]piperidin-4-yl}-1-(1*H*-indol-2-yl) imidazo[1,5-*a*]pyrazin-8-amine

[377] Prepared according to the procedure described above for **EXAMPLE 26**, except using 4-(dimethylamino)butanoic acid in place of formic acid. MS (ES+): m/z 446.22 [MH+].

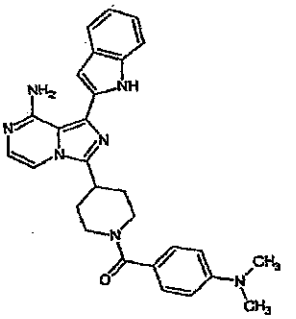
EXAMPLE 35



3-{1-[4-(Dimethylamino)phenacyl]piperidin-4-yl}-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[378] Prepared according to the procedure described above for **EXAMPLE 26**, except using 4-(dimethylamino)phenylacetic acid in place of formic acid. MS (ES+): m/z 480.22 [MH+].

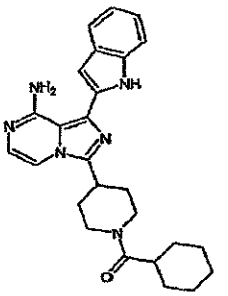
Example 36



3-{1-[4-(Dimethylamino)benzoyl]piperidin-4-yl}-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[379] Prepared according to the procedure described above for **EXAMPLE 26**, except using 4-(dimethylamino)benzoic acid in place of formic acid. MS (ES+): m/z 480.22 [MH+].

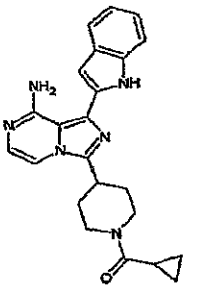
EXAMPLE 37



3-[1-(Cyclohexylcarbonyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[380] Prepared according to the procedure described above for **EXAMPLE 26**, except using cyclohexanecarboxylic acid in place of formic acid. MS (ES+): m/z 443.20 [MH+].

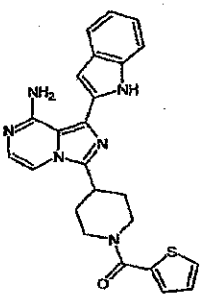
EXAMPLE 38



3-[1-(Cyclopropylcarbonyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[381] Prepared according to the procedure described above for **EXAMPLE 26**, except using cyclopropanecarboxylic acid in place of formic acid. MS (ES+): m/z 401.19 [MH+].

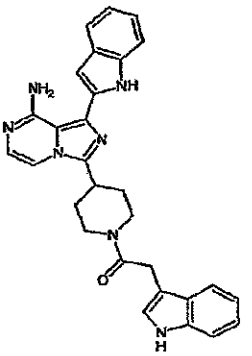
EXAMPLE 39



1-(1*H*-Indol-2-yl)-3-[1-(2-thienylcarbonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[382] Prepared according to the procedure described above for **EXAMPLE 26**, except using thiophene-2-carboxylic acid in place of formic acid. MS (ES+): m/z 443.22 [MH+].

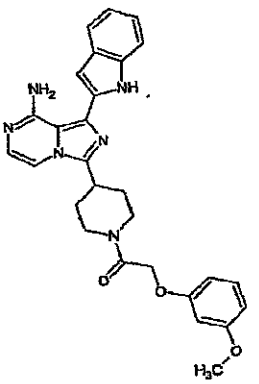
EXAMPLE 40



3-[1-(1*H*-Indol-3-ylacetyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[383] Prepared according to the procedure described above for **EXAMPLE 26**, except using indole-3-acetic acid in place of formic acid. MS (ES+): m/z 490.10 [MH+].

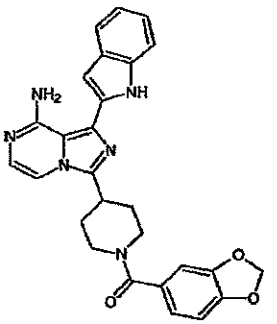
EXAMPLE 41



1-(1*H*-Indol-2-yl)-3-{1-[(3-methoxyphenoxy)acetyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[384] Prepared according to the procedure described above for **EXAMPLE 26**, except using (3-methoxyphenoxy)acetic acid in place of formic acid. MS (ES+): m/z 497.11 [MH+].

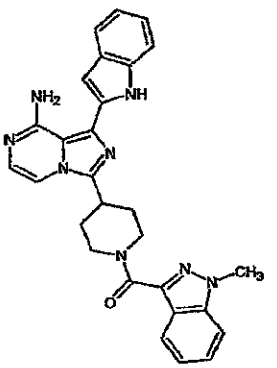
EXAMPLE 42



3-[1-(1,3-Benzodioxol-5-ylcarbonyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[385] Prepared according to the procedure described above for **EXAMPLE 26**, except using 1,3-benzodioxole-5-carboxylic acid in place of formic acid. MS (ES+): m/z 481.05 [MH+].

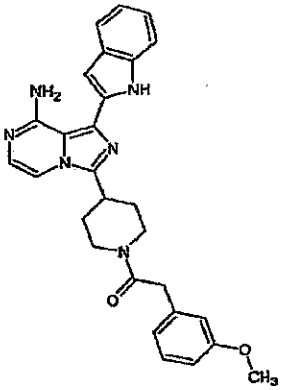
EXAMPLE 43



1-(1*H*-Indol-2-yl)-3-{1-[(1-methyl-1*H*-indazol-3-yl)carbonyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[386] Prepared according to the procedure described above for **EXAMPLE 26**, except using 1-methyl-1*H*-indazole-3-carboxylic acid in place of formic acid. MS (ES+): m/z 491.04 [MH+].

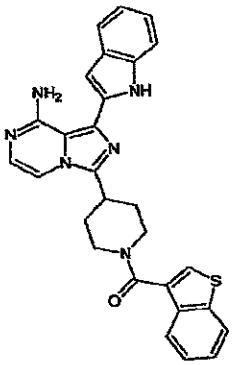
EXAMPLE 44



1-(1*H*-Indol-2-yl)-3-{1-[(3-methoxyphenyl)acetyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[387] Prepared according to the procedure described above for **EXAMPLE 26**, except using 3-methoxyphenylacetic acid in place of formic acid. MS (ES+): m/z 481.09 [MH+].

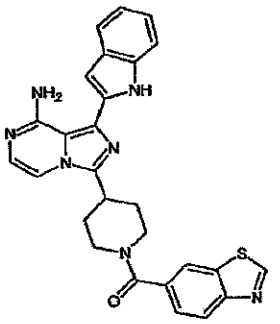
EXAMPLE 45



3-[1-(1-Benzothien-3-ylcarbonyl)piperidin-4-yl]-1-iodoimidazo[1,5-*a*]pyrazin-8-amine

[388] Prepared according to the procedure described above for **EXAMPLE 26**, except using benzothiophene-3-carboxylic acid in place of formic acid. MS (ES+): m/z 493.01 [MH+].

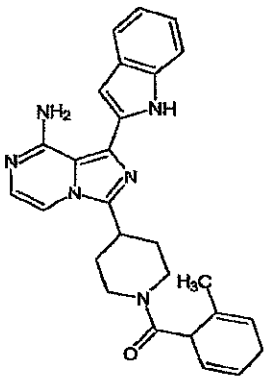
EXAMPLE 46



3-[1-(1,3-Benzothiazol-6-ylcarbonyl)piperidin-4-yl]-1-iodoimidazo[1,5-*a*]pyrazin-8-amine

[389] Prepared according to the procedure described above for **EXAMPLE 26**, except using benzothiazole-6-carboxylic acid in place of formic acid. MS (ES+): m/z 494.01 [MH+].

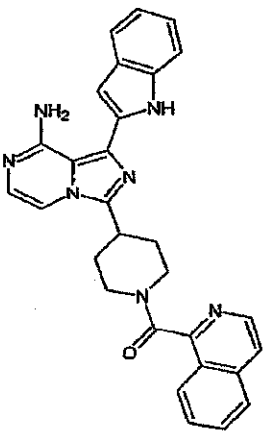
EXAMPLE 47



1-(1*H*-Indol-2-yl)-3-{1-[(2-methylcyclohexa-2,5-dien-1-yl)carbonyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[390] Prepared according to the procedure described above for **EXAMPLE 26**, except using 2-methylcyclohexa-2,5-diene-1-carboxylic acid in place of formic acid. MS (ES+): m/z 453.08 [MH+].

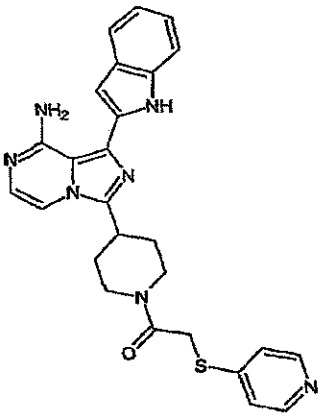
EXAMPLE 48



1-(1*H*-Indol-2-yl)-3-[1-(isoquinolin-1-ylcarbonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[391] Prepared according to the procedure described above for **EXAMPLE 26**, except using isoquinoline-1-carboxylic acid in place of formic acid. MS (ES+): m/z 488.01 [MH+].

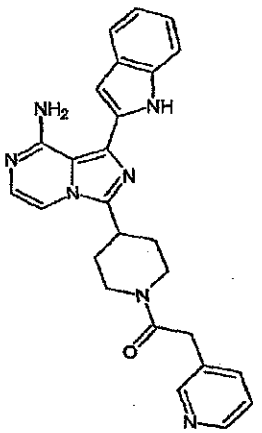
EXAMPLE 49



1-(1*H*-Indol-2-yl)-3-{1-[(pyridin-4-ylthio)acetyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[392] Prepared according to the procedure described above for **EXAMPLE 26**, except using (pyridin-4-ylthio)acetic acid in place of formic acid. MS (ES+): m/z 484.04 [MH+].

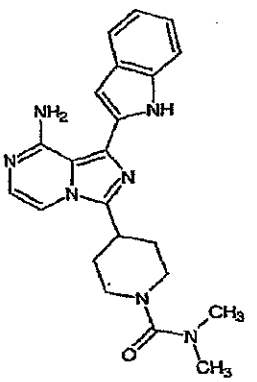
EXAMPLE 50



1-(1*H*-Indol-2-yl)-3-[1-(pyridin-3-ylacetyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[393] Prepared according to the procedure described above for **EXAMPLE 26**, except using pyridin-3-ylacetic acid in place of formic acid. MS (ES+): m/z 452.07 [MH+].

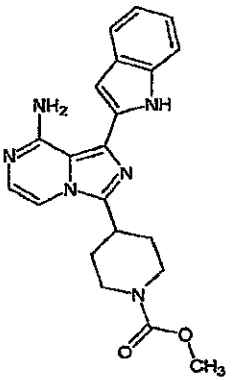
EXAMPLE 51



4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*,*N*-dimethylpiperidine-1-carboxamide

[394] A mixture of 1-(1*H*-indol-2-yl)-3-piperidin-4-ylimidazo[1,5-*a*]pyrazin-8-amine hydrochloride (30.0mg, 0.0679mmol), *N*,*N*-diisopropylethylamine (59.1μL, 0.340mmol) and DMF (1.00mL) was treated with *N*,*N*-dimethylcarbamoyl chloride (6.23μL, 0.0679mmol) and stirred at rt for 1h prior to semi-preparative HPLC to afford the isolated title compound. ^{1}H NMR (400 MHz, CD_3OD) ppm: 8.32 (br. s., 1H), 7.59-7.66 (m, 2H), 7.46 (d, 1H, J = 8.3 Hz), 7.15-7.22 (m, 1H), 7.01-7.10 (m, 2H), 6.74 (s, 1H), 3.82 (d, 2H, J = 12.6 Hz), 3.34-3.42 (m, 1H), 2.97-3.09 (m, 2H), 2.87 (s, 6H), 1.95-2.09 (m, 4H); MS (ES+): m/z 404.14 [MH+].

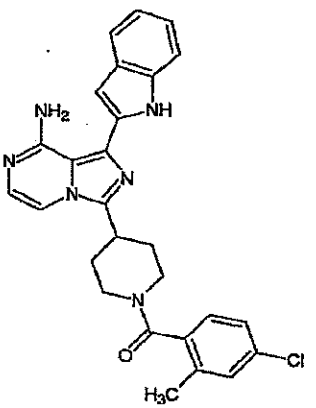
EXAMPLE 52



Methyl 4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)piperidine-1-carboxylate

[395] A mixture of 1-(1*H*-indol-2-yl)-3-piperidin-4-ylimidazo[1,5-*a*]pyrazin-8-amine hydrochloride (30.0mg, 0.0679mmol), *N*,*N*-diisopropylethylamine (59.1μL, 0.340mmol) and DMF (1.00mL) was treated with methyl chloroformate (5.25μL, 0.0679mmol) and stirred at rt for 1h prior to semi-preparative HPLC to afford the isolation of the title compound. ^{1}H NMR (400 MHz, CD_3OD) ppm: 8.32 (br. s., 1H), 7.58-7.66 (m, 2H), 7.46 (d, 1H, J = 8.1 Hz), 7.14-7.22 (m, 1H), 7.00-7.12 (m, 2H), 6.73 (s, 1H), 4.26 (d, 2H, J = 12.9 Hz), 3.71 (s, 3H), 3.33-3.37 (m, 1H), 2.9-3.17 (m, 2H), 1.85-2.06 (m, 4H); MS (ES+): m/z 391.06 [MH+].

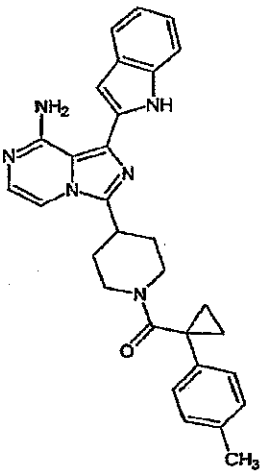
EXAMPLE 53



3-[1-(4-Chloro-2-methylbenzoyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[396] Prepared according to the procedure described above for **EXAMPLE 26**, except using 4-chloro-2-methylbenzoic acid in place of formic acid. MS (ES+): m/z 485.05 [MH+].

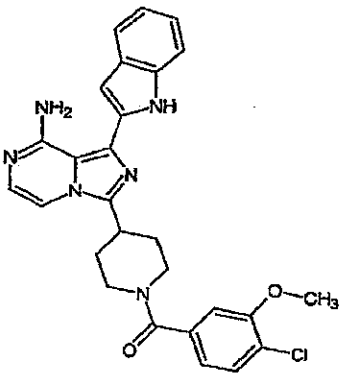
EXAMPLE 54



1-(1*H*-Indol-2-yl)-3-(1-{[1-(4-methylphenyl)cyclopropyl]carbonyl}piperidin-4-yl)imidazo[1,5-*a*]pyrazin-8-amine

[397] Prepared according to the procedure described above for **EXAMPLE 26**, except using 1-(4-methylphenyl)cyclopropanecarboxylic acid in place of formic acid. MS (ES+): m/z 491.11 [MH+].

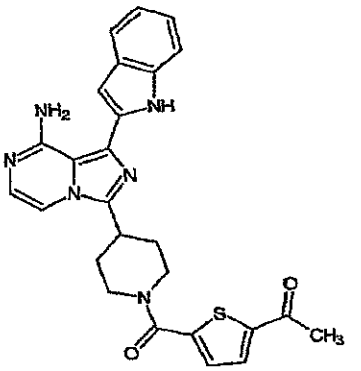
EXAMPLE 55



3-[1-(4-Chloro-3-methoxybenzoyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[398] Prepared according to the procedure described above for **EXAMPLE 26**, except using 4-chloro-3-methoxybenzoic acid in place of formic acid. MS (ES+): m/z 501.04 [MH+].

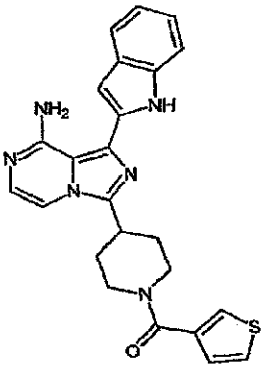
EXAMPLE 56



1-(5-{[4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)piperidin-1-yl]carbonyl}-2-thienyl)ethanone

[399] Prepared according to the procedure described above for **EXAMPLE 26**, except using 5-acetylthiophene-2-carboxylic acid in place of formic acid. MS (ES+): m/z 485.04 [MH+].

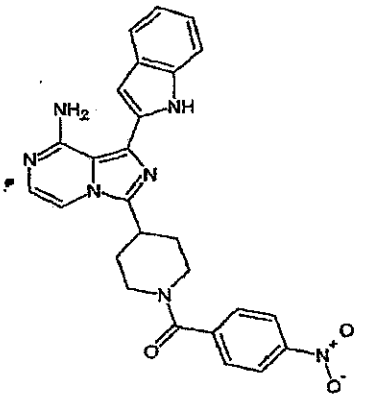
EXAMPLE 57



1-(1*H*-Indol-2-yl)-3-[1-(3-thienylcarbonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[400] Prepared according to the procedure described above for **EXAMPLE 26**, except using thiophene-3-carboxylic acid in place of formic acid. MS (ES+): m/z 443.04 [MH+].

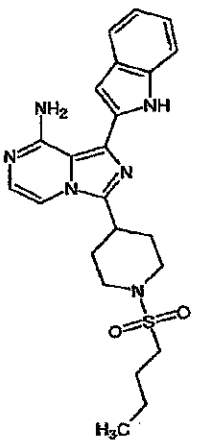
EXAMPLE 58



1-(1*H*-Indol-2-yl)-3-[1-(4-nitrobenzoyl)piperidin-4-yl]-imidazo[1,5-*a*]pyrazin-8-amine

[401] Prepared according to the procedure described above for **EXAMPLE 26**, except using 4-nitrobenzoic acid in place of formic acid. MS (ES+): m/z 482.07 [MH+].

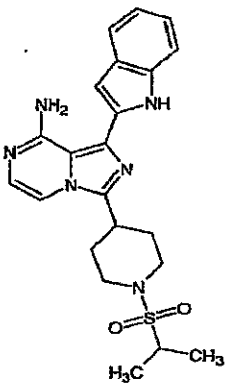
EXAMPLE 59



3-[1-(Butylsulfonyl)piperidin-4-yl]-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[402] A solution of 1-(1*H*-indol-2-yl)-3-piperidin-4-ylimidazo[1,5-*a*]pyrazin-8-amine hydrochloride (33.23mg, 0.075mmol) in DMF (1mL) was treated with *N*,*N*-diisopropylethylamine (0.05mL, 0.3mmol) and a solution of ^{n}butanesulfonyl chloride (9.42mg, 0.0602mmol) in 1mL of DMF. The mixture was left to stir at rt for 1h and then subjected to mass-directed preparative HPLC to afford the title compound. ^{1}H NMR (400 MHz – DMSO-d6) δ 0.91 (t, 3H), 1.40 – 1.45 (m, 2H), 1.66 – 1.69 (m, 2H), 1.86 – 1.90 (m, 2H) 2.04 – 2.09 (m, 2H) 3.02 – 3.11 (m, 5H) 3.73 – 3.77 (m, 2H), 6.47 (bs, 2H), 6.64 (s, 1H), 7.00 – 7.05 (m, 1H) 7.09 – 7.12 (m, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 5.2 Hz, 1H). MS (ES+): m/z: 453.24 [MH+].

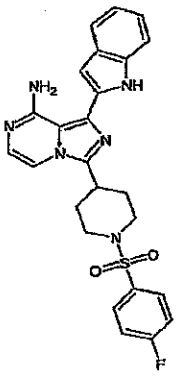
EXAMPLE 60



1-(1*H*-Indol-2-yl)-3-[1-(isopropylsulfonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[403] Prepared according to the procedure described above for **EXAMPLE 59**, except using isopropane-2-sulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 439.27 [MH+].

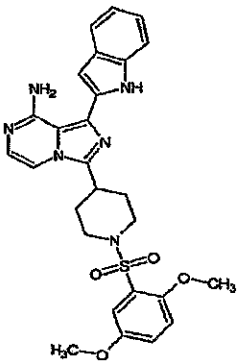
EXAMPLE 61



3-{1-[(4-Fluorophenyl)sulfonyl]piperidin-4-yl}-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[404] Prepared according to the procedure described above for **EXAMPLE 59**, except using 4-fluorobenzenesulfonyl chloride in place of "butanesulfonyl chloride. MS (ES+): m/z 491.15 [MH+].

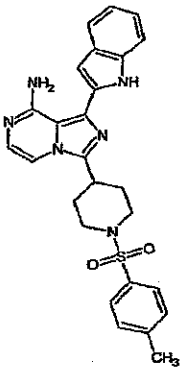
EXAMPLE 62



3-{1-[(2,5-Dimethoxyphenyl)sulfonyl]piperidin-4-yl}-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[405] Prepared according to the procedure described above for **EXAMPLE 59**, except using 2,5-dimethoxybenzenesulfonyl chloride in place of "butanesulfonyl chloride. MS (ES+): m/z 533.17 [MH+].

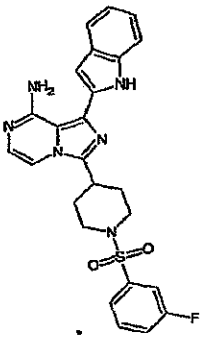
EXAMPLE 63



1-(1*H*-Indol-2-yl)-3-{1-[(4-methylphenyl)sulfonyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[406] Prepared according to the procedure described above for **EXAMPLE 59**, except using 4-methylbenzenesulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 487.94 [MH+].

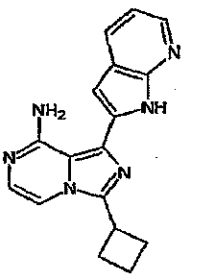
EXAMPLE 64



3-{1-[(3-Fluorophenyl)sulfonyl]piperidin-4-yl}-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[407] Prepared according to the procedure described above for **EXAMPLE 59**, except using 3-fluorobenzenesulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 491.92 [MH+].

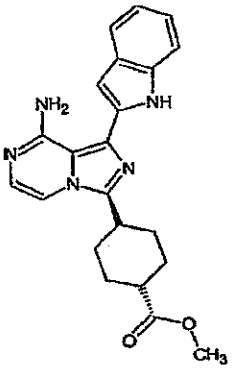
EXAMPLE 65



3-Cyclobutyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)imidazo[1,5-*a*]pyrazin-8-amine

[408] 3-Cyclobutyl-1-[1-(2-trimethylsilylethoxymethyl)-1H-pyrrolo[2,3-*b*]pyridin-2-yl]imidazo[1,5-*a*]pyrazin-8-amine (35mg, 0.08mmol) was stirred with concentrated HCl for 15min. The mixture was then concentrated *in vacuo* and purified via mass directed preparative HPLC to afford the title compound. ^{1}H NMR (400 MHz DMSO-d6) δ 1.92 – 2.00 (m, 1H), 2.07 – 2.14 (m, 1H), 2.43 – 2.47 (m, 4H), 3.93 – 4.01 (m, 1H), 6.35 – 6.49 (bs, 2H), 6.64 – 6.70 (m, 1H), 7.03 – 7.10 (m, 2H), 7.39 – 7.49 (m, 1H), 7.95 – 8.00 (m, 1H), 8.18 – 8.23 (m, 1H), 11.91 (bs, 1H). MS (ES+): m/z: 305.17 [MH+].

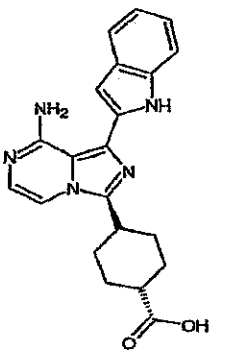
EXAMPLE 66



Methyl *trans*-4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate

[409] Starting from *trans*-methyl 4-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate, the title compound was prepared according to procedures analogous to those described for **EXAMPLE 10**. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 11.42 (br s, 1H), 7.70 (d, J = 4.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.30–6.90 (m, 3H), 6.63 (br s, 1H), 6.44 (br s, 1H), 3.64 (s, 3H), 3.18 (m, 1H), 2.44 (m, 1H), 2.03 (m, 4H), 1.80–1.50 (m, 4H). MS (ES+): m/z 390.28 [MH+].

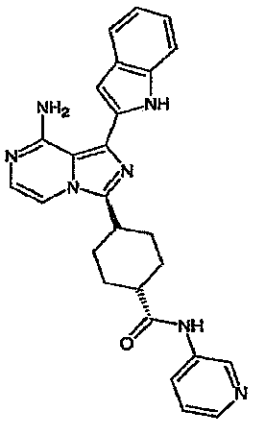
EXAMPLE 67



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylic acid**

[410] A mixture of 37% HCl (30 mL) and methyl *trans*-4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate (500.0mg, 1.28mmol) was stirred for 18h at rt. The reaction mixture was then concentrated *in vacuo*, and the residue washed with diethyl ether (3 x 10mL) and ethyl acetate (2 x 10mL), then with ice-cold acetonitrile (10mL) to afford 0.3g of the desired product. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 12.15 (br s, 1H), 11.69 (s, 1H), 8.45 (br s, 2H), 7.97 (d, J = 6.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 8.0, 0.4 Hz, 1H), 7.19 (m, 1H), 7.13 (d, J = 6.0 Hz, 1H), 7.06 (m, 1H), 6.83 (d, J = 1.6 Hz, 1H), 3.27 (td, J = 11.6, 3.2, 3.2 Hz, 1H), 2.33 (td, J = 10.8, 3.2, 3.2 Hz, 1H), 2.05 (m, 4H), 1.73 (m, 2H) and 1.58 (mz, 2H). MS (ES+): m/z 376.05 [MH+].

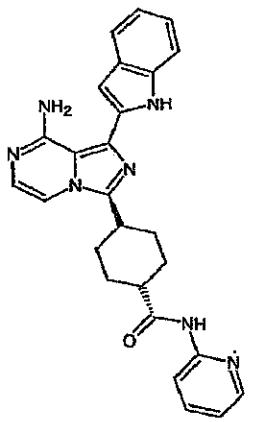
EXAMPLE 68



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-pyridin-3-ylcyclohexanecarboxamide**

[411] A suspension of 3-aminopyridine (40mg, 0.43mmol) in toluene (1.3mL) was treated with a 2M toluene solution of trimethylaluminum (0.3mL, 0.60mmol). After 25min, the resulting solution was treated with methyl *trans*-4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylate (30mg, 0.08mol) and the mixture stirred at rt overnight. The mixture was then stirred with 2M NaOH (20 mL) and ethyl acetate (20mL) for 10min., then the organic phase was separated and the aqueous extracted EtOAc (3×15mL). The combined organic extracts were washed with water (20mL) and brine (20mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give crude product which was subjected to mass-directed preparative HPLC to afford pure desired product. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 11.45 (br s, 1H), 10.12 (s, 1H), 8.77 (d, J = 2.4 Hz, 1H), 8.25 (d, J = 4.8 Hz, 1H), 8.14 (s, 1H), 8.08 (dd, J = 8.0, 1.6 Hz, 1H), 7.71 (d, J = 5.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.34 (m, 1H), 7.15–7.00 (m, 3H), 6.65 (s, 1H), 6.42 (br s, 2H), 3.22 (m, 1H), 2.47 (m, 1H), 2.15–1.95 (m, 4H), and 1.85–1.65 (m, 4H). MS (ES+): *m/z* 452.17 [MH+].

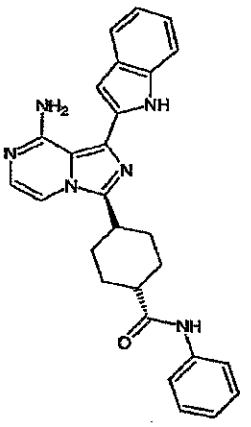
EXAMPLE 69



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-pyridin-2-ylcyclohexanecarboxamide**

[412] Prepared according to the procedure described above for **EXAMPLE 68**, except using 2-aminopyridine in place of 3-aminopyridine. MS (ES+): m/z 452.17 [MH+].

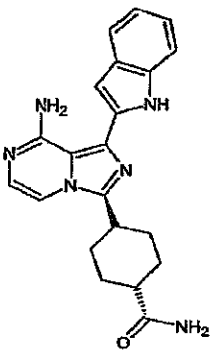
EXAMPLE 70



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-phenylcyclohexane carboxamide**

[413] Prepared according to the procedure described above for **EXAMPLE 68**, except using aniline in place of 3-aminopyridine. MS (ES+): m/z 451.16 [MH+].

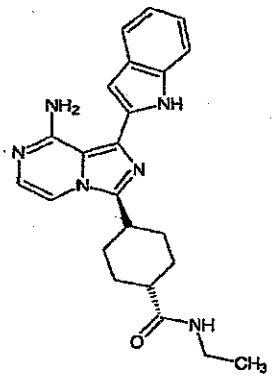
EXAMPLE 71



***trans*-4-[8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexanecarboxamide**

[414] *trans*-4-(8-Amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxamide (40mg, 0.10mmol), 1-(*tert*-butoxycarbonyl)-1*H*-indole-2-boronic acid (33mg, 0.12mmol), and sodium carbonate (33mg, 0.31mmol) were added to DME:Water (5:1) (2mL) and the mixture degassed with Argon for 10min. Tetrakis(triphenylphosphine)palladium(0) (8.0mg, 0.007mmol) was then added and the reaction mixture microwaved at 110°C for 1h, The mixture was concentrated *in vacuo*, taken up in DMSO, and purified by mass-directed preparative HPLC to afford desired product. ^{1}H NMR (d_6-DMSO, 400 MHz): □ 11.50 (br s, 1H), 7.72 (m, 1H), 7.58 (m, 1H), 7.46 (dd, J = 7.6, 0.4 Hz, 1H), 7.25 (br s, 1H), 7.13 (m, 1H), 7.08–7.00 (m, 2H), 6.70 (br s, 1H), 6.69 (br s, 1H), 3.16 (m, 1H), 2.20 (m, 1H), 2.10–1.80 (m, 4H) and 1.65 (m, 4H). MS (ES+): m/z 375.17 [MH+].

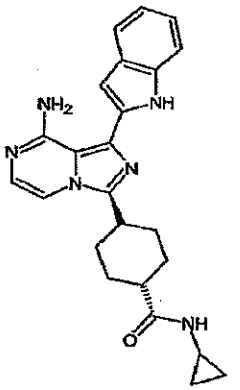
EXAMPLE 72



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-ethylcyclohexanecarboxamide**

[415] Ethylamine hydrochloride (30 mg, 0.37mmol), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (35mg, 0.11mmol), and *N,N*-diisopropylethylamine (80μL, 0.53mmol) were added to a solution of *trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexanecarboxylic acid (25mg, 0.07mmol) in anhydrous DMF (2mL). Upon completion of reaction (as monitored by LCMS), the mixture was added to a saturated aqueous sodium bicarbonate solution (10mL). The resulting precipitate was collected by filtration and washed with cold acetonitrile (3 x 10mL) to afford 13mg of the desired product. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 11.41 (br s, 1H), 7.75 (dd, J = 4.0, 4.0Hz, 1H), 7.69 (d, J = 4.0Hz, 1H), 7.58 (d, J = 8.0, 4.0Hz, 1H), 7.45 (d, J = 4.0, 4.0Hz, 1H), 7.12 (dd, J = 8.0, 8.0 Hz, 1H), 7.08–7.00 (m, 2H), 6.63 (m, 1H), 6.43 (br s, 2H), 3.16 (m, 1H), 3.07 (m, 2H), 2.18 (m, 1H), 2.02 (m, 2H), 1.84 (m, 2H), 1.66 (m, 4H) and 1.02 (t, J = 4.0 Hz, 3H). MS (ES+): m/z 403.09 [MH+].

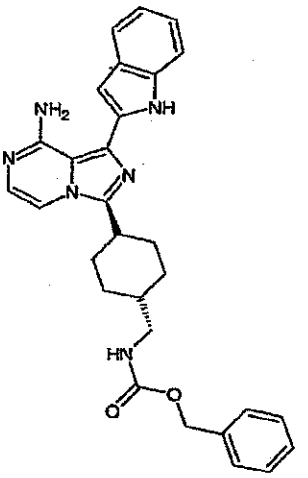
EXAMPLE 73



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-cyclopropylcyclo hexanecarboxamide**

[416] Prepared according to the procedure described above for **EXAMPLE 72**, except using cyclopropylamine in place of ethylamine. MS (ES+): m/z 415.22 [MH+].

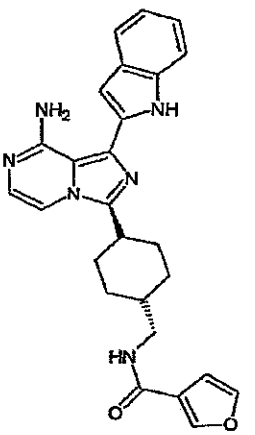
EXAMPLE 74



Benzyl {[*trans*-4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl] methyl}carbamate

[417] A mixture of benzyl {[*trans*-4-(8-amino-1-iodoimidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}carbamate (1.00g, 0.00180mol), 1-(*tert*-butoxycarbonyl)-1*H*-indole-2-boronic acid (0.517g, 0.00198mol), 1,2-dimethoxyethane (7.7mL), water (1.4mL, 0.081mol) and Cesium Carbonate (1.17g, 0.00360mol) degassed three times, treated with tetrakis (triphenylphosphine)palladium(0) (200mg, 0.0002mol) and degassed once more. The resulting mixture was heated at 100°C overnight before being diluted with EtOAc (40mL), washed with water (2 X 30mL) and brine (20mL) then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product thus isolated was chromatographed over silica gel eluting with hexane → EtOAc: hexane: 5% 2M NH_3 in MeOH 1:1:0.05 to afford the title compound. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13-1.22 (m, 2H), 1.75-1.86 (m, 2H), 1.94-1.97 (m, 2H), 2.11-2.13 (m, 2H), 2.86 (m, 1H), 3.12-3.16 (m, 2H), 4.82 (m, 1H), 5.12 (s, 2H), 5.69 (br, 2H), 6.78 (s, 1H), 7.13-7.15 (m, 2H), 7.19-7.25 (m, 2H), 7.32-7.38 (m, 5H), 7.42 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 9.09 (br, 1H). MS (ES+): m/z 495 [MH+].

EXAMPLE 75

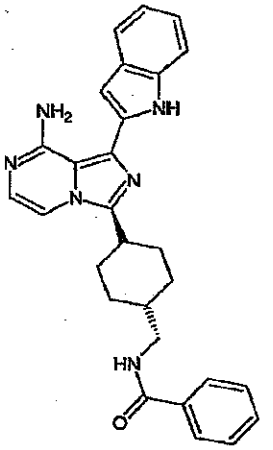


***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}-3-**

furamide

[418] Prepared according to the procedure described above for **EXAMPLE 22**, except using 2-furoic acid in place of acetic acid. MS (ES+): m/z 455.20 [MH+].

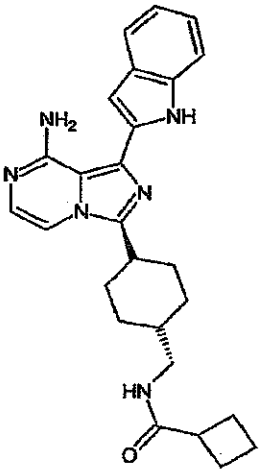
EXAMPLE 76



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}benzamide**

[419] Prepared according to the procedure described above for **EXAMPLE 22**, except using benzoic acid in place of acetic acid. MS (ES+): m/z 465.25 [MH+].

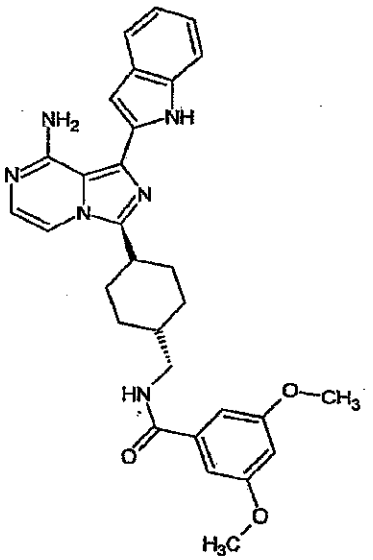
EXAMPLE 77



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}cyclobutanecarboxamide**

[420] Prepared according to the procedure described above for **EXAMPLE 22**, except using cyclobutanecarboxylic acid in place of acetic acid. MS (ES+): m/z 443.25 [MH+].

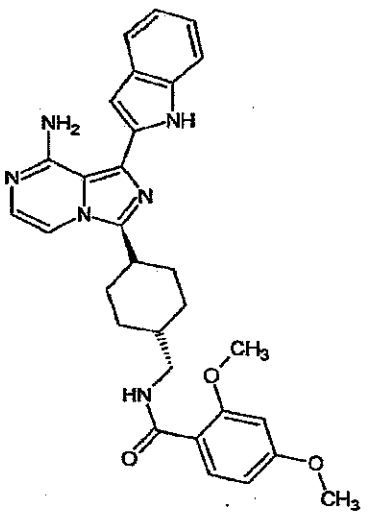
EXAMPLE 78



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}-3,5-dimethoxybenzamide**

[421] Prepared according to the procedure described above for **EXAMPLE 22**, except using 3,5-dimethoxybenzoic acid in place of acetic acid. MS (ES+): m/z 525.35 [MH+].

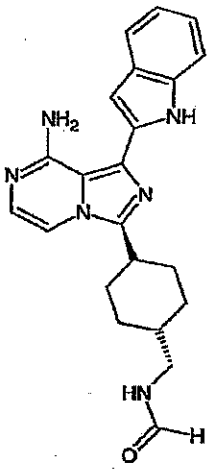
EXAMPLE 79



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}-2,4-dimethoxybenzamide**

[422] Prepared according to the procedure described above for **EXAMPLE 22**, except using 2,4-dimethoxybenzoic acid in place of acetic acid. MS (ES+): m/z 525.33 [MH+].

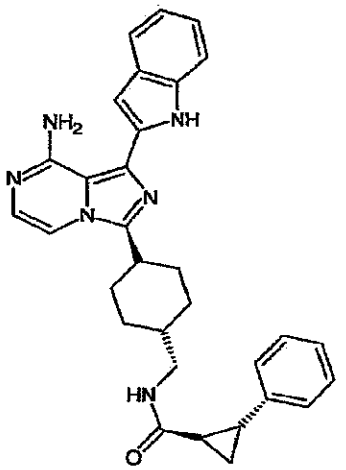
EXAMPLE 80



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}formamide**

[423] Prepared according to the procedure described above for **EXAMPLE 22**, except using formic acid in place of acetic acid. MS (ES+): m/z 389.10 [MH+].

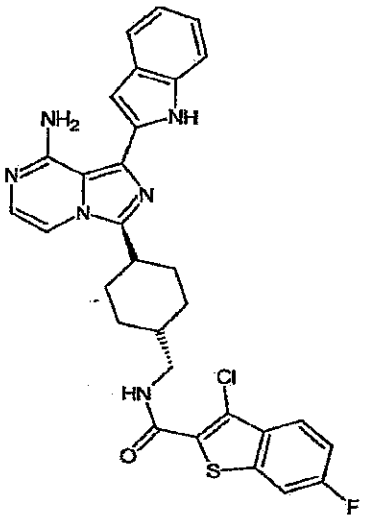
EXAMPLE 81



(1R,2R)-*N*-{[*trans*-4-(8-amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}-2-phenylcyclopropanecarboxamide

[424] Prepared according to the procedure described above for **EXAMPLE 22**, except using (1R,2R)-2-phenylcyclopropanecarboxylic acid in place of acetic acid. MS (ES+): m/z 505.30 [MH+].

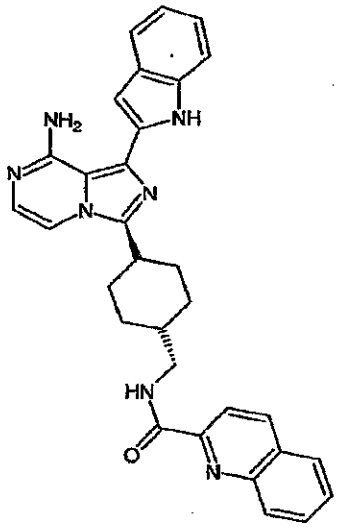
EXAMPLE 82



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}-3-chloro-6-fluorobenzo[*b*]thiophene-2-carboxamide**

[425] Prepared according to the procedure described above for **EXAMPLE 22**, except using 3-chloro-6-fluorobenzo[*b*]thiophene-2-carboxylic acid in place of acetic acid. MS (ES+): m/z 573.35 & 575.31 [MH+].

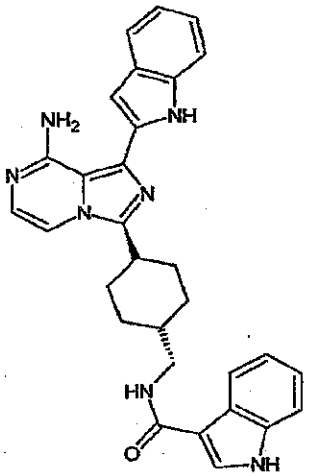
EXAMPLE 83



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}isoquinoline-2-carboxamide**

[426] Prepared according to the procedure described above for **EXAMPLE 22**, except using isoquinoline-2-carboxylic acid in place of acetic acid. MS (ES+): m/z 516.40 [MH+].

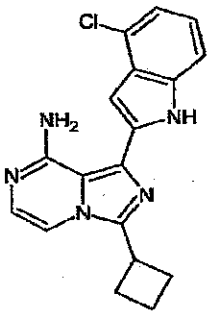
EXAMPLE 84



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl} indole-3-carboxamide**

[427] Prepared according to the procedure described above for **EXAMPLE 22**, except using indole-3-carboxylic acid in place of acetic acid. MS (ES+): m/z 505.46 [MH+].

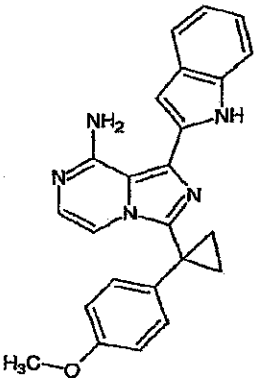
EXAMPLE 85



1-(4-Chloro-1*H*-indol-2-yl)-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine

[428] Prepared according to the procedure described above for **EXAMPLE 2**, except using 1-(*tert*-butoxycarbonyl)-4-chloro-1*H*-indole-2-boronic acid in place of 1-(*tert*-butoxycarbonyl)-1*H*-indole-2-boronic acid. ^{1}H NMR (400 MHz – DMSO-d6) δ 1.91 – 1.98 (m, 1H), 2.08 – 2.15 (m, 1H), 2.42 – 2.46 (m, 4H), 3.97 – 4.00 (m, 1H), 6.42 (bs, 2H), 6.67 (s, 1H), 7.09 – 7.14 (m, 3H), 7.43 – 7.47 (m, 2H) and 11.83 (bs, 1H). MS (ES+): m/z 338.26 [MH+].

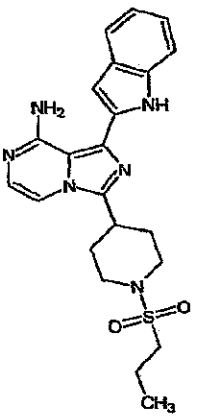
EXAMPLE 86



1-(1*H*-Indol-2-yl)-3-[1-(4-methoxyphenyl)cyclopropyl]imidazo[1,5-*a*]pyrazin-8-amine

[429] Prepared according to the procedure described above for **EXAMPLE 2**, except using 4-methoxyphenylcyclopropanecarboxylic acid in place of cyclobutanecarboxylic acid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.46 (s, 2 H), 1.58 (s, 2 H), 3.76 (s, 3 H), 6.78 (d, J=8.80 Hz, 2 H), 6.77 (s, 1 H), 6.82 (s, 1 H), 6.98 (d, J=5.13 Hz, 1 H), 7.03 (d, J=8.80 Hz, 2 H), 7.15 (t, J=7.52 Hz, 1 H), 7.23 (s, 2 H), 7.44 (d, J=8.07 Hz, 1 H), 7.65 (d, J=8.07 Hz, 1 H) and 9.36 (br. s., 1 H). MS (ES+): m/z 396.15 [MH+].

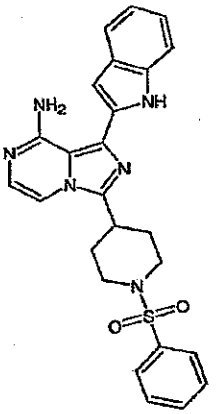
EXAMPLE 87



1-(1*H*-Indol-2-yl)-3-[1-(propylsulfonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[430] Prepared according to the procedure described above for **EXAMPLE 59**, except using propane-2-sulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 439.06 [MH+].

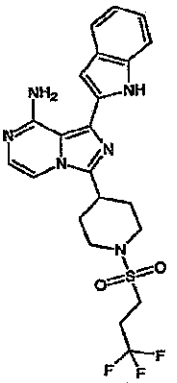
EXAMPLE 88



1-(1*H*-Indol-2-yl)-3-[1-(phenylsulfonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[431] Prepared according to the procedure described above for **EXAMPLE 59**, except using benzenesulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 473.29 [MH+].

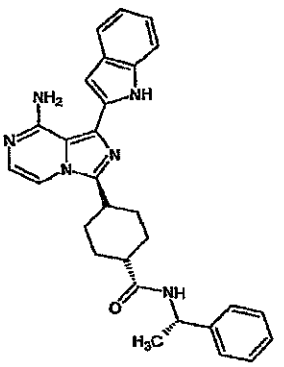
EXAMPLE 89



1-(1*H*-Indol-2-yl)-3-{1-[(3,3,3-trifluoropropyl)sulfonyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[432] Prepared according to the procedure described above for **EXAMPLE 59**, except using 3,3,3-trifluoropropane-1-sulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 493.19 [MH+].

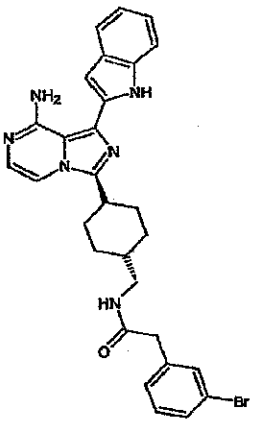
EXAMPLE 90



***trans*-3-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-[(1S)-1-phenylethyl] cyclohexanecarboxamide**

[433] Prepared according to the procedure described above for **EXAMPLE 72**, except using (1S)-1-phenylethanamine in place of cyclopropylamine. MS (ES+): m/z 479.11 [MH+].

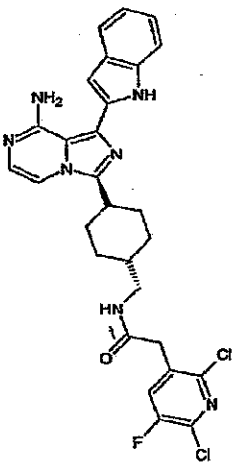
EXAMPLE 91



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}(3-bromophenyl)acetamide**

[434] Prepared according to the procedure described above for **EXAMPLE 22**, except using 3-bromophenylacetic acid in place of acetic acid. MS (ES+): m/z 557.21 and 559.20 [MH+].

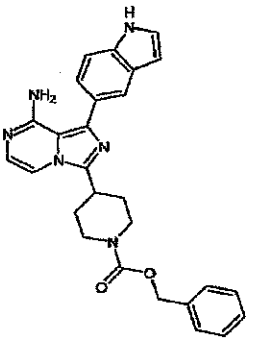
EXAMPLE 92



***N*-{[*trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)cyclohexyl]methyl}(2,6-dichloro-5-fluoropyridin-3-yl)acetamide**

[435] Prepared according to the procedure described above for **EXAMPLE 22**, except using (2,6-dichloro-5-fluoropyridin-3-yl)acetic acid in place of acetic acid. MS (ES+): m/z 522.21 [MH+].

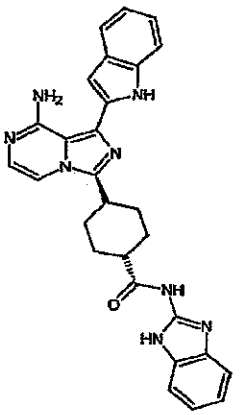
EXAMPLE 93



Benzyl 4-[8-amino-1-(1*H*-indol-5-yl)imidazo[1,5-*a*]pyrazin-3-yl]piperidine-1-carboxylate

[436] Prepared according to the procedure described above for **EXAMPLE 24**, except using indole-5-boronic acid in place of 1-(*tert*-butoxycarbonyl)-1*H*-indole-2-boronic acid. MS (ES+): m/z 494.97 [MH+].

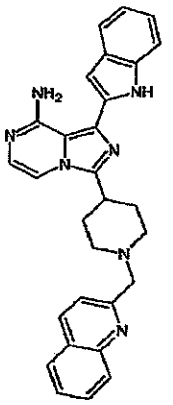
EXAMPLE 94



***trans*-4-(8-Amino-1-(1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl)-*N*-benzimidazol-2-ylcyclohexanecarboxamide**

[437] Prepared according to the procedure described above for **EXAMPLE 68**, except using 2-aminobenzimidazole in place of 3-aminopyridine. MS (ES+): m/z 490.97 [MH+].

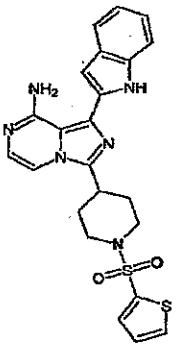
EXAMPLE 95



1-(1*H*-Indol-2-yl)-3-[1-(quinolin-2-ylmethyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[438] A solution of 1-(1*H*-Indol-2-yl)-3-piperidin-4-ylimidazo[1,5-*a*]pyrazin-8-amine hydrochloride (30mg, 0.09mmol), 2-formylquinoline (17mg, 0.11mmol) and triethylamine (0.019mL, 0.14mmol) in 1,4-dioxane (1mL) was treated with sodium cyanoborohydride (5.7mg, 0.090mmol) and microwaved at 300 watts, 120°C for 20min. The mixture was concentrated in vacuo, the residue was dissolved in methanol loaded onto an SCX ion exchange cartridge, and then eluted with 1M NH_4OH in methanol. The semi-pure material thus obtained was then subjected to semi-preparative HPLC to afford desired product. ^1H NMR (400 MHz, MeOD) δ ppm 2.13 - 2.33 (m, 4 H), 2.90 (t, J=10.86, 9.60 Hz, 2 H), 3.47 (d, J=10.11 Hz, 2 H), 4.29 (s, 2 H), 6.74 (s, 1 H), 7.02 - 7.11 (m, 2 H), 7.19 (t,J=8.08, 7.07 Hz, 1 H), 7.47 (d, J=9.09 Hz, 1 H), 7.58 - 7.65 (m, 3 H), 7.69 (d, J=8.59 Hz, 1 H), 7.80 (t, J=8.34, 6.82 Hz, 1 H), 7.96 (d, J=7.33 Hz, 1 H), 8.08 (d, J=8.34 Hz, 1H) and 8.39 (d, J=8.59 Hz, 1 H). MS (ES+): m/z 474.23 [MH+].

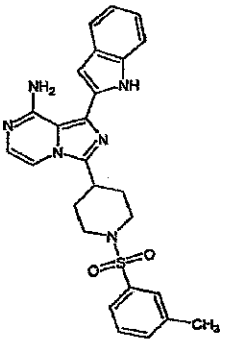
EXAMPLE 96



1-(1*H*-Indol-2-yl)-3-[1-(2-thienylsulfonyl)piperidin-4-yl]imidazo[1,5-*a*]pyrazin-8-amine

[439] Prepared according to the procedure described above for **EXAMPLE 59**, except using thiophene-2-sulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 479.16 [MH+].

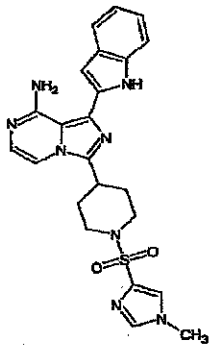
EXAMPLE 97



1-(1*H*-Indol-2-yl)-3-{1-[(3-methylphenyl)sulfonyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

[440] Prepared according to the procedure described above for **EXAMPLE 59**, except using 3-methylbenzenesulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 487.94 [MH+].

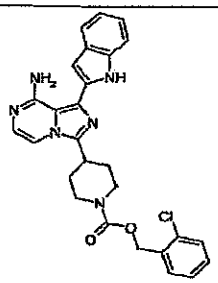
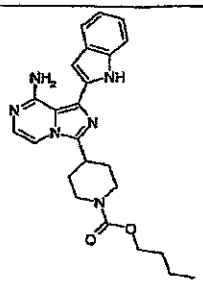
EXAMPLE 98

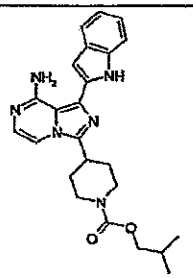
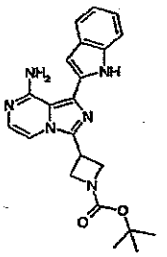
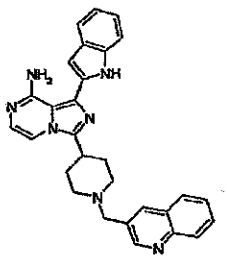
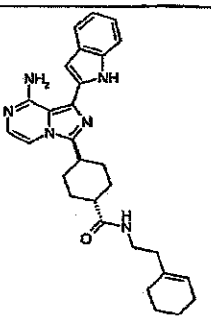
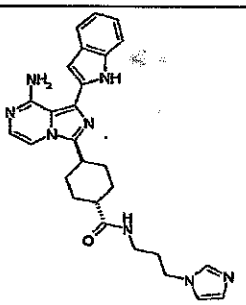
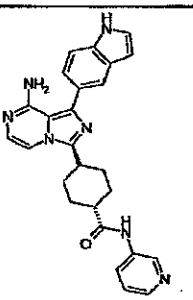
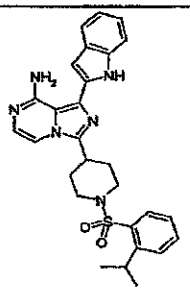
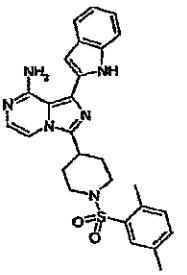
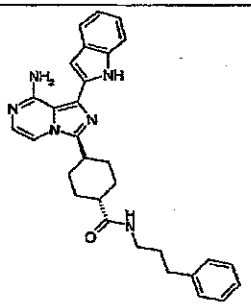
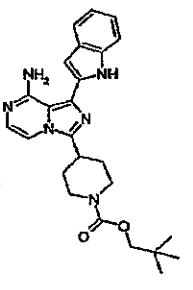


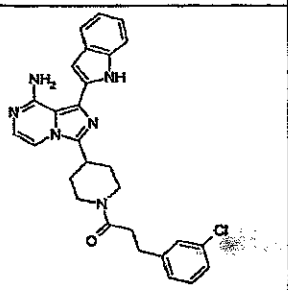
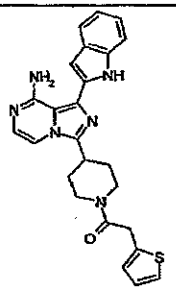
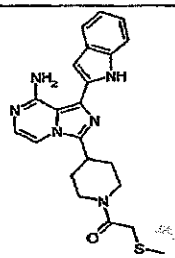
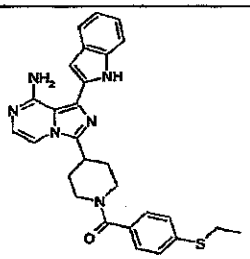
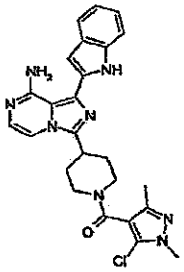
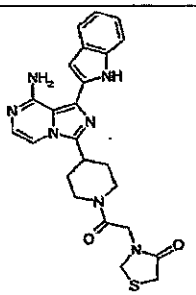
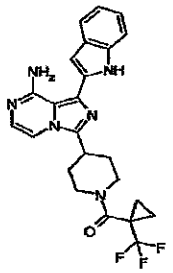
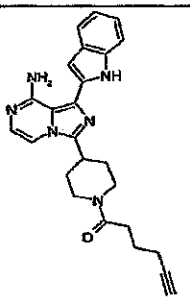
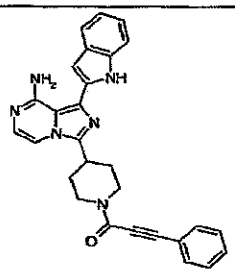
1-(1*H*-Indol-2-yl)-3-{1-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]piperidin-4-yl}imidazo[1,5-*a*]pyrazin-8-amine

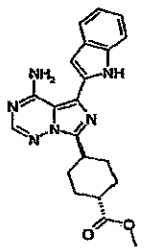
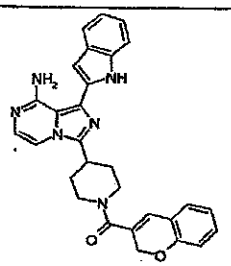
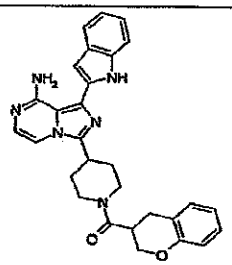
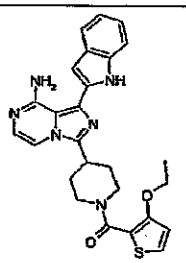
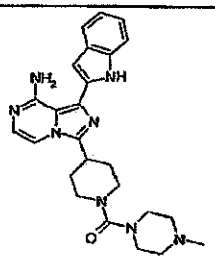
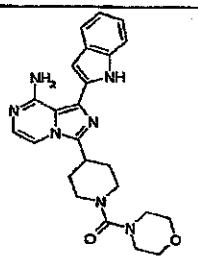
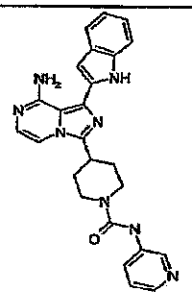
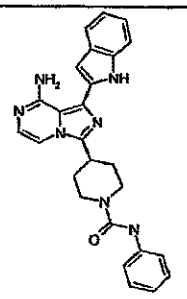
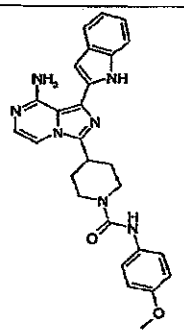
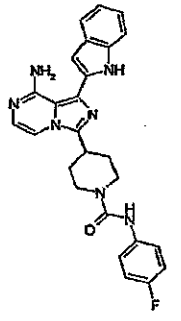
[441] Prepared according to the procedure described above for **EXAMPLE 59**, except using 1-methyl-1H-imidazole-4-sulfonyl chloride in place of ^{n}butanesulfonyl chloride. MS (ES+): m/z 477.20 [MH+].

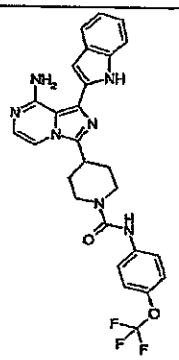
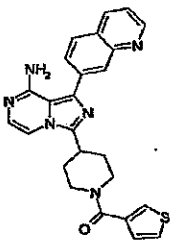
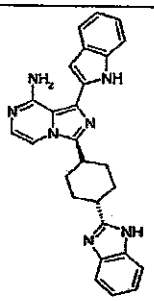
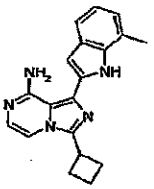
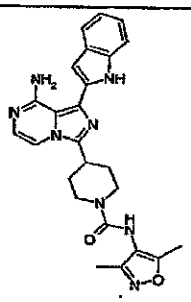
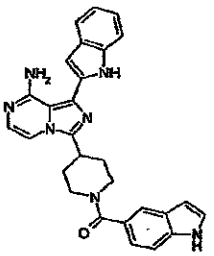
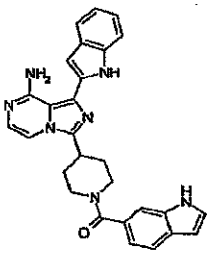
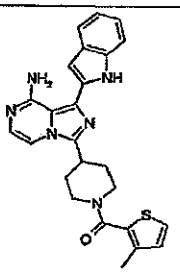
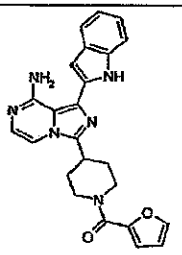
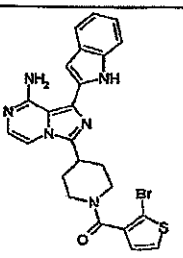
[442] The following examples were prepared according to procedures analogous to those described above, utilizing where necessary known literature chemistries.

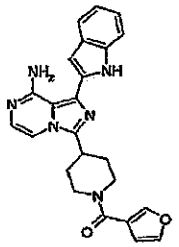
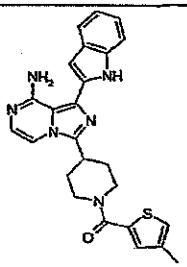
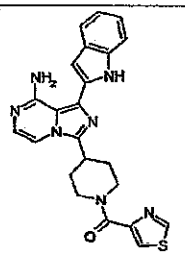
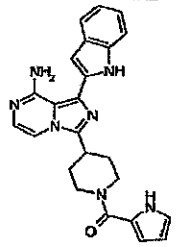
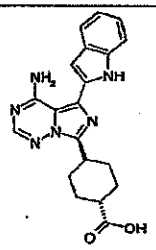
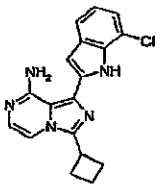
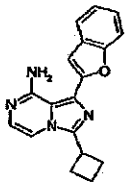
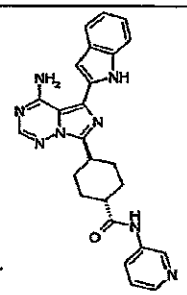
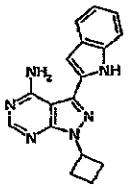
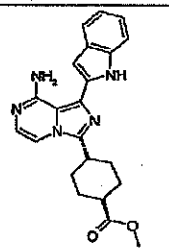
Ex #	Structure	MH+	Ex #	Structure	MH+
99		500.93 502.91	100		433.06

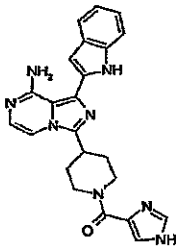
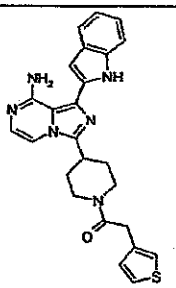
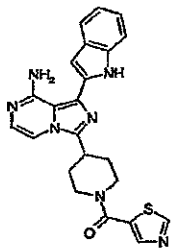
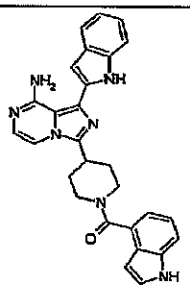
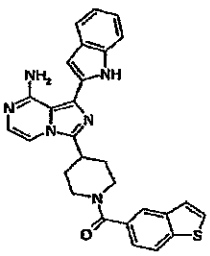
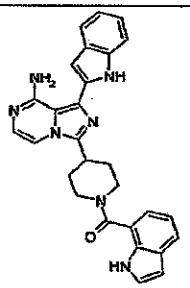
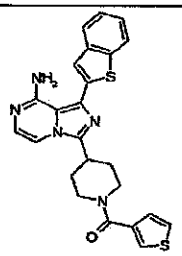
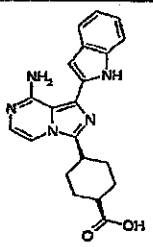
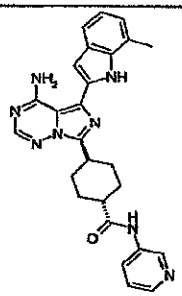
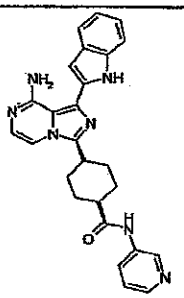
Ex #	Structure	MH+	Ex #	Structure	MH+
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103		474.23	104		483.00
105		483.27	106		452.04
107		514.92	108		500.89
109		492.92	110		447.01

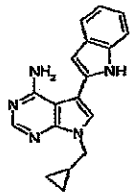
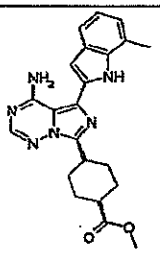
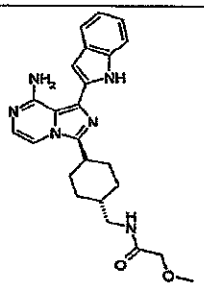
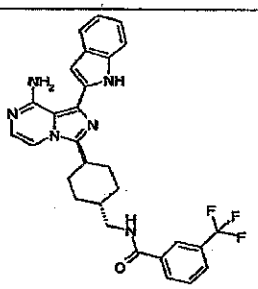
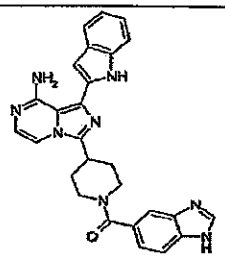
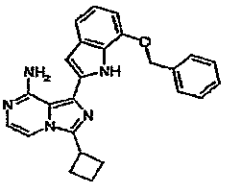
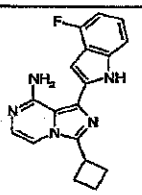
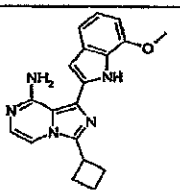
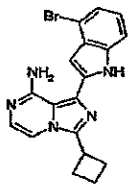
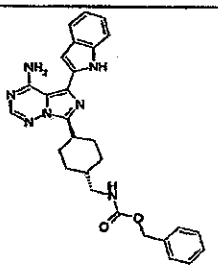
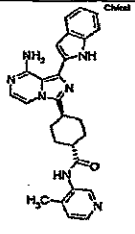
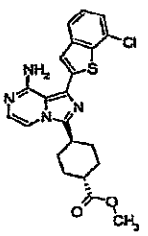
Ex #	Structure	MH+	Ex #	Structure	MH+
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113		420.97	114		496.91
115		488.91	116		475.91
117		468.84	118		426.99
119		461.00	120		320.86

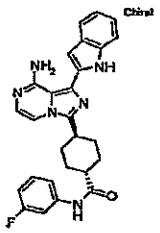
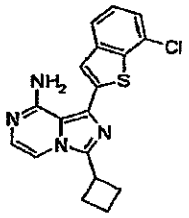
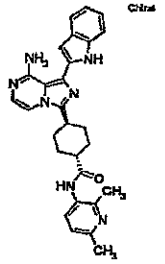
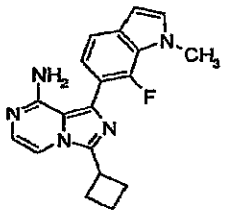
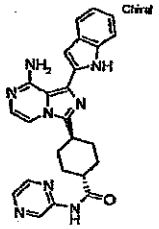
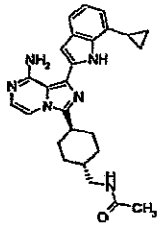
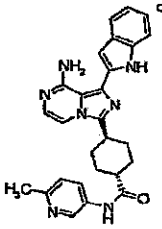
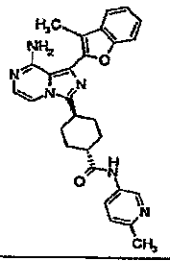
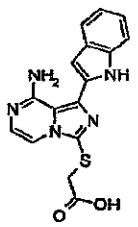
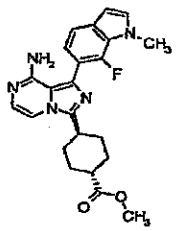
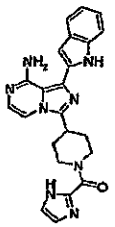
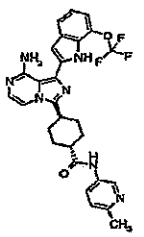
Ex #	Structure	MH+	Ex #	Structure	MH+
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123		493.18	124		487.09
125		459.01	126		446.15
127		452.98	128		451.97
129		481.95	130		470.00

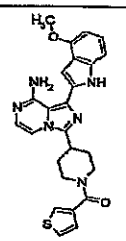
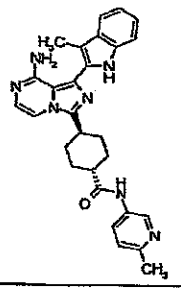
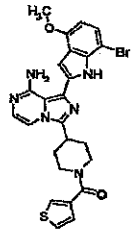
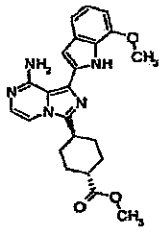
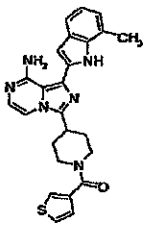
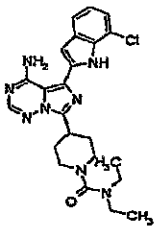
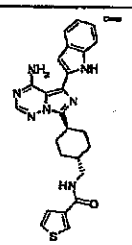
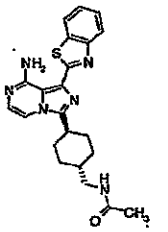
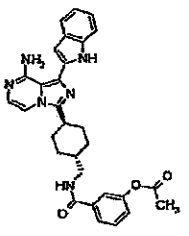
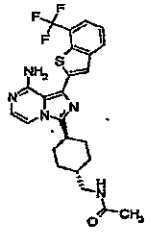
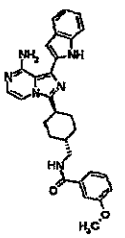
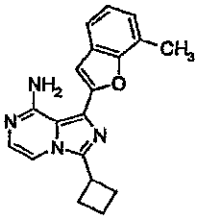
Ex #	Structure	MH+	Ex #	Structure	MH+
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133		448.02	134		318.03
135		470.96	136		475.92
137		475.92	138		457.08
139		426.92	140		521.03 523.08

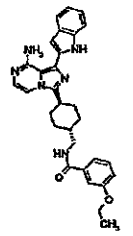
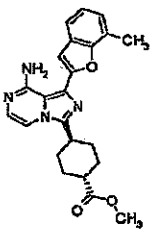
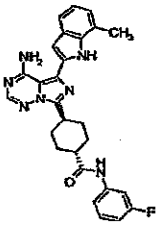
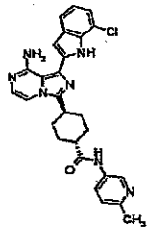
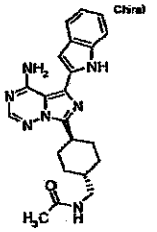
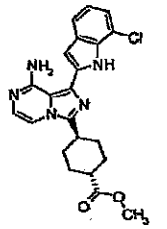
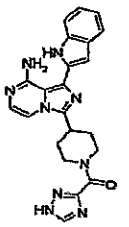
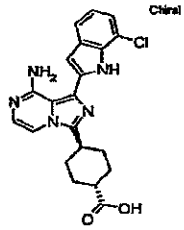
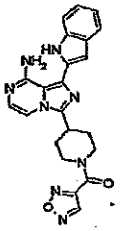
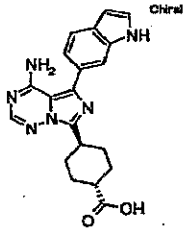
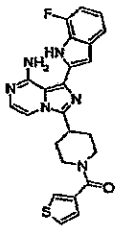
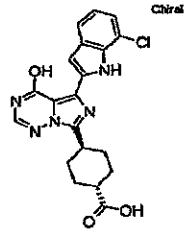
Ex #	Structure	MH+	Ex #	Structure	MH+
141		427.05	142		457.02
143		444.20	144		425.91
145		376.98	146		337.97 339.92
147		304.95	148		452.95
149		305.20	150		389.83

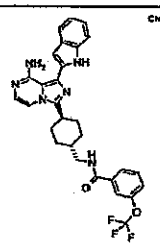
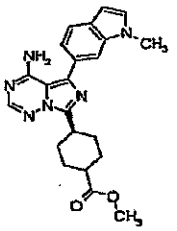
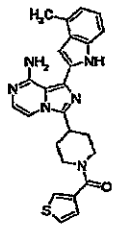
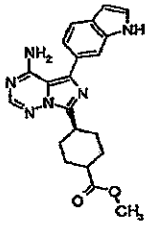
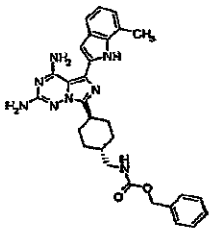
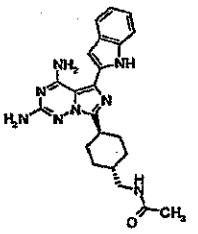
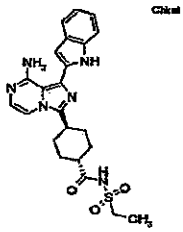
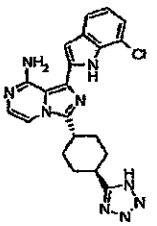
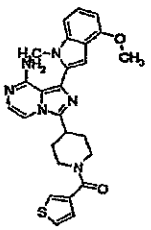
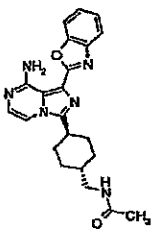
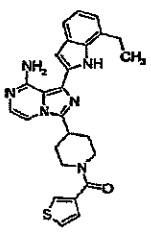
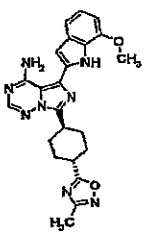
Ex #	Structure	MH+	Ex #	Structure	MH+
151		426.97	152		456.79
153		443.97	154		475.94
155		492.76	156		475.85
157		460.13	158		375.98
159		466.97	160		451.98

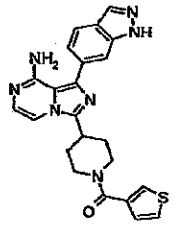
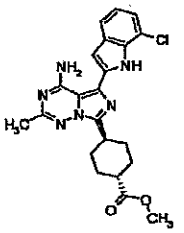
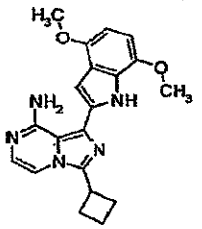
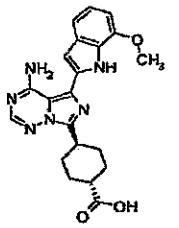
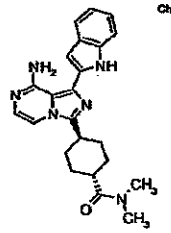
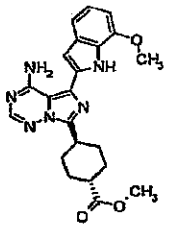
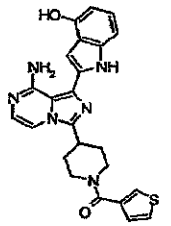
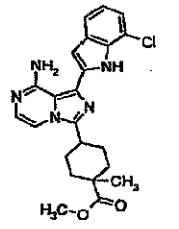
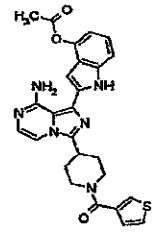
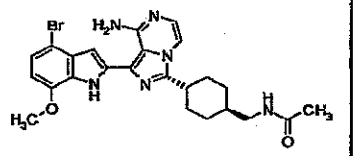
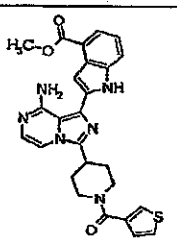
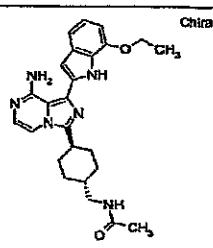
Ex #	Structure	MH+	Ex #	Structure	MH+
161		304.19	162		405.02
163		433.18	164		532.90
165		476.95	166		410.02
167		321.92	168		333.87
169		381.83 383.72	170		495.97
171		465.96	232		440.89 442.86

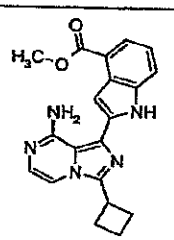
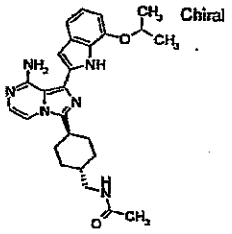
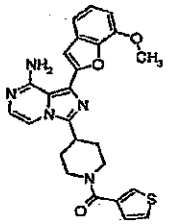
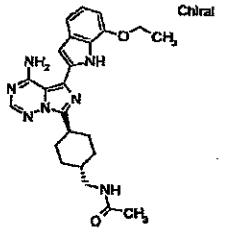
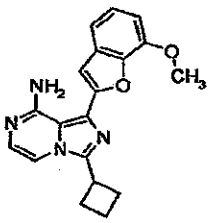
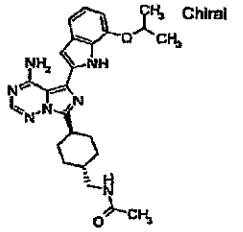
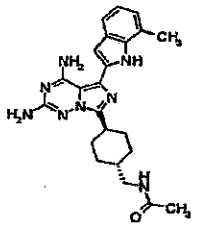
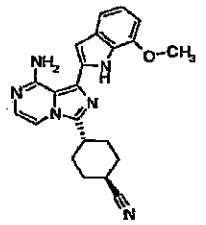
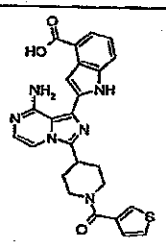
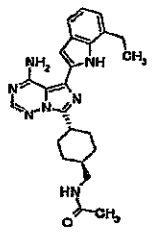
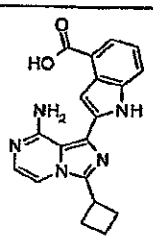
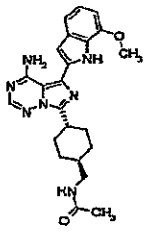
Ex #	Structure	MH+	Ex #	Structure	MH+
172		468.84 470.50	233		354.74 356.98
173		480.20	234		335.84
174		452.97	235		442.96
175		466.20	236		480.98
176		339.92	237		421.83
177		426.91	238		549.91

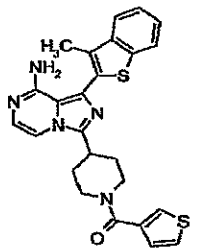
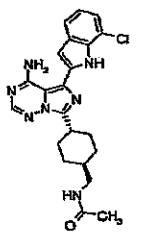
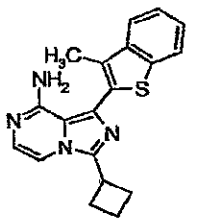
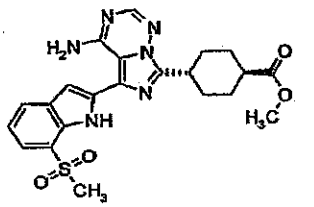
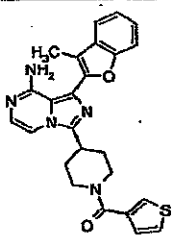
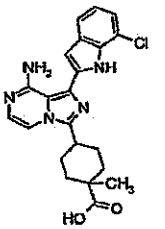
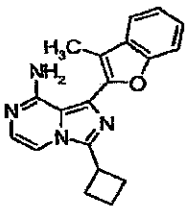
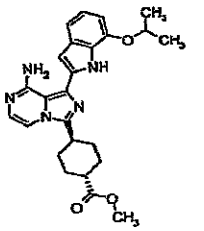
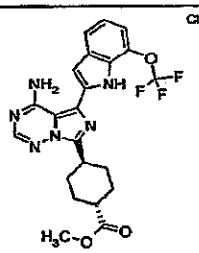
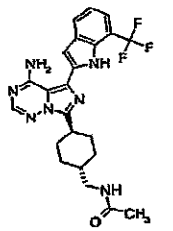
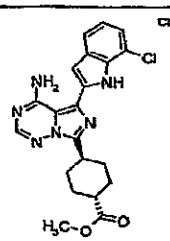
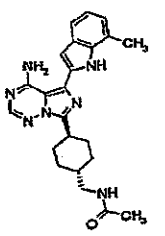
Ex #	Structure	MH+	Ex #	Structure	MH+
178		472.62	239		480.02
179		550.68 552.50	240		419.89
180		456.63	241		467.92
181		471.89	242		420.97
182		523.93	243		487.97
183		496.05	244		319.00

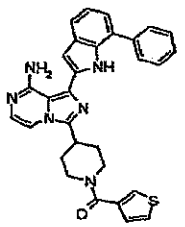
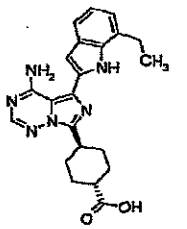
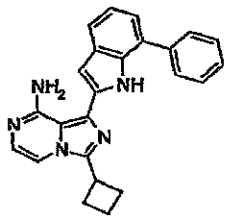
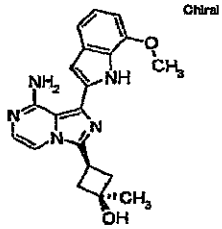
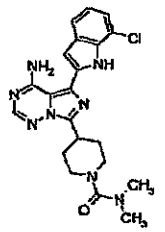
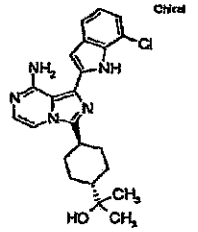
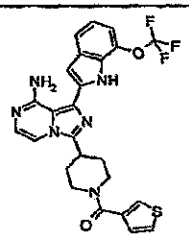
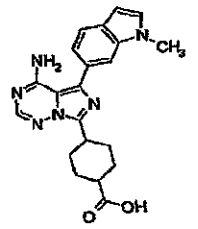
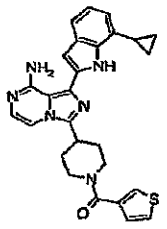
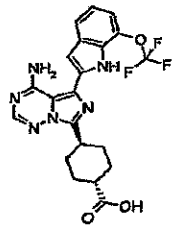
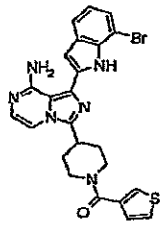
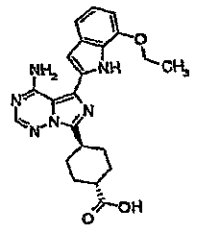
Ex #	Structure	MH+	Ex #	Structure	MH+
184		510.00	245		405.03
185		483.89	246		499.95 501.96
186		404.18	247		423.83 425.93
187		427.93	248		409.95 411.90
188		428.88	249		376.99
189		460.66	250		412.06 414.03

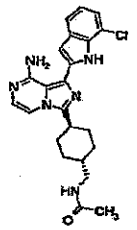
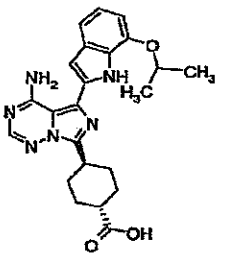
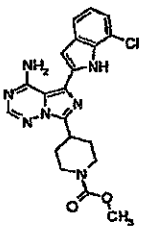
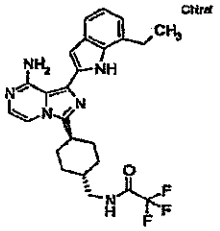
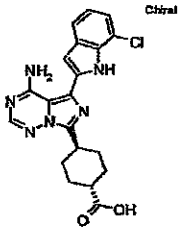
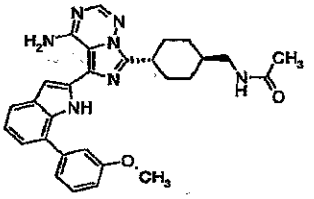
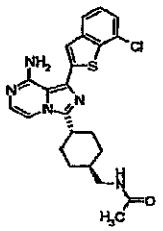
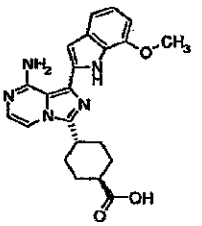
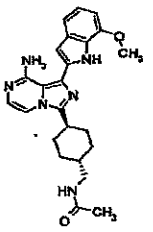
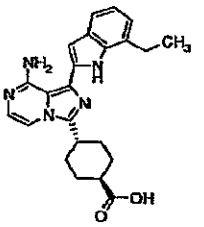
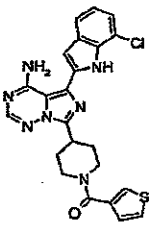
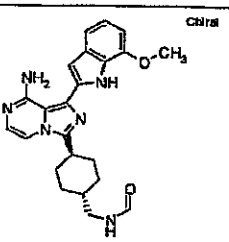
Ex #	Structure	MH+	Ex #	Structure	MH+
191		548.72	251		404.96
192		456.86	252		391.01
193		525.25	253		419.12
194		467.21	254		434.04
195		486.96	255		405.03
196		470.97	256		445.01

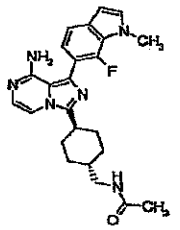
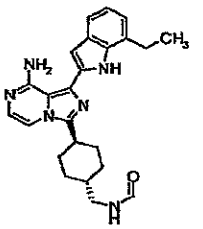
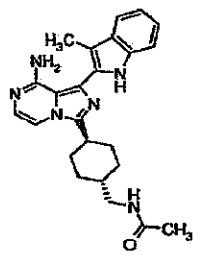
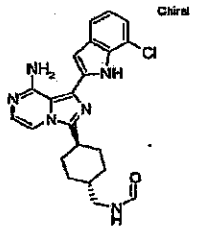
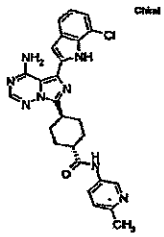
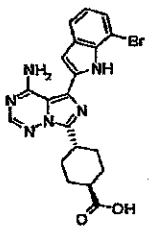
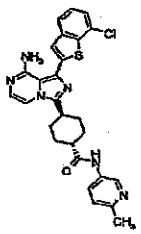
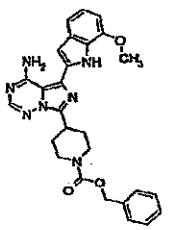
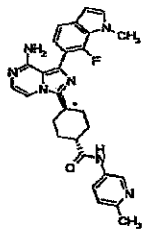
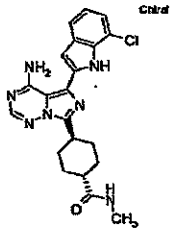
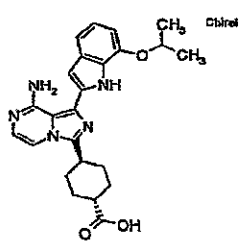
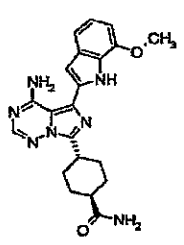
Ex #	Structure	MH+	Ex #	Structure	MH+
197		444.00	257		438.94 440.89
198		363.89	258		406.98 406.99
199		403.07	259		421.00
200		458.97	260		437.93 439.95
201		500.96	261		511.21 513.14
202		500.94	262		447.03

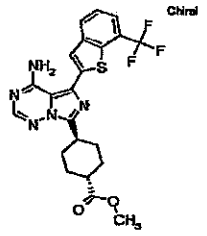
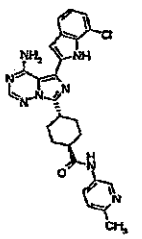
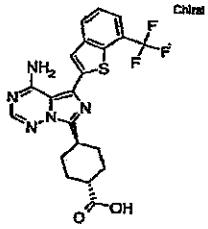
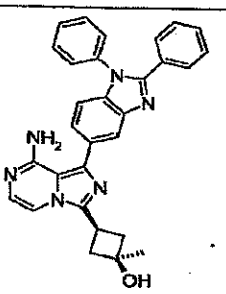
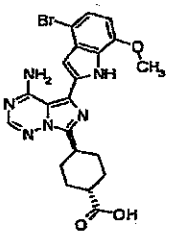
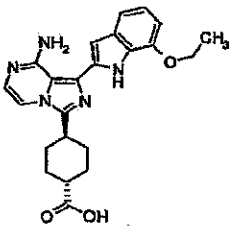
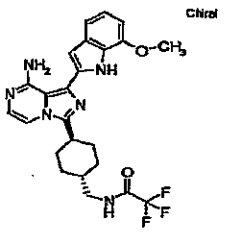
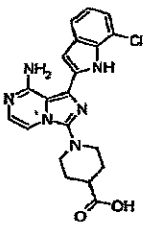
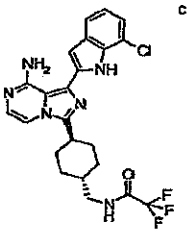
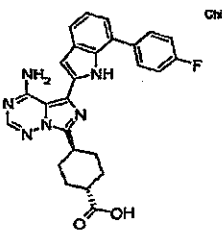
Ex #	Structure	MH+	Ex #	Structure	MH+
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204		473.95	264		447.99
205		335.06	265		462.00
206		433.07	266		387.20
207		486.96	267		432.06
208		348.02	268		434.02 434.06

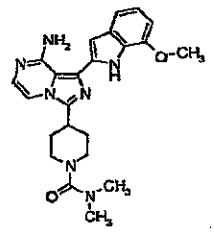
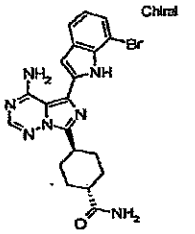
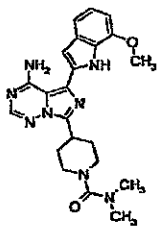
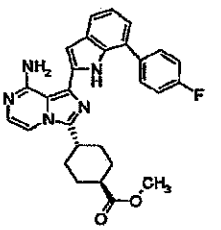
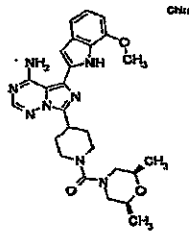
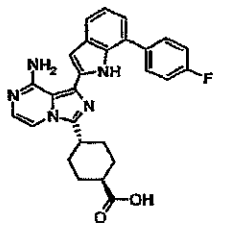
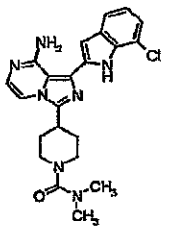
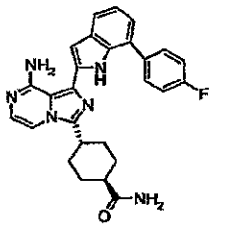
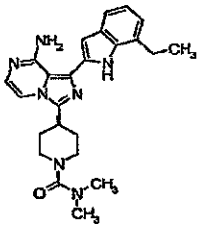
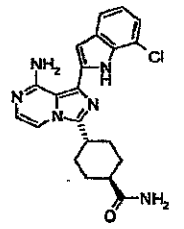
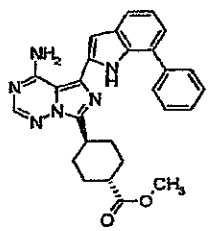
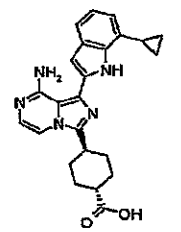
Ex #	Structure	MH+	Ex #	Structure	MH+
209		473.87	269		437.97 439.95
210		334.88	270		468.95
211		457.95	271		423.97 425.93
212		318.92	272		448.05
213		475.02	273		471.98
214		425.17 427.06	274		418.09

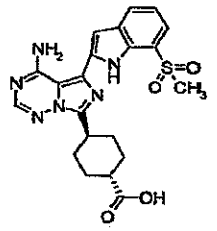
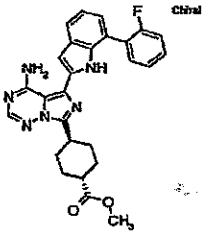
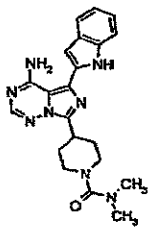
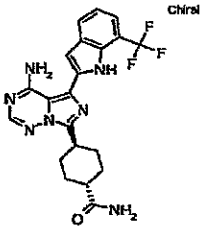
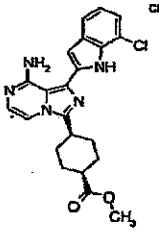
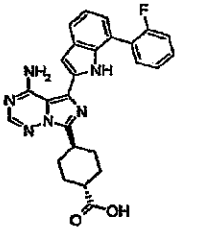
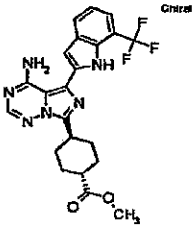
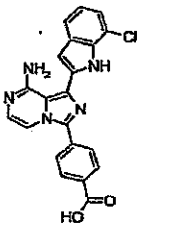
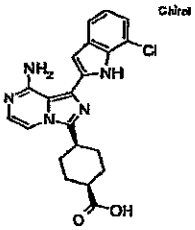
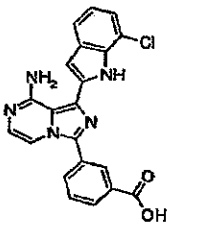
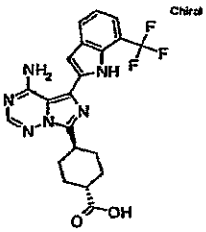
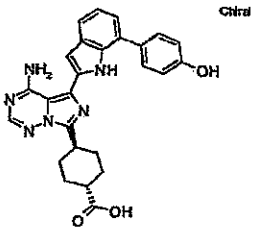
Ex #	Structure	MH+	Ex #	Structure	MH+
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216		379.87	276		363.98
217		439.19	277		423.97 425.99
218		526.77	278		391.01
219		483.04	279		460.94
220		520.89	280		421.00

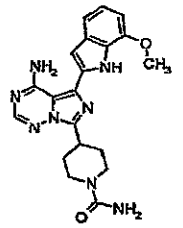
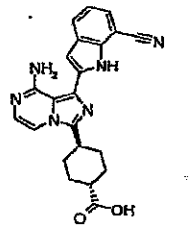
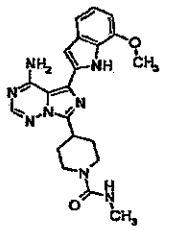
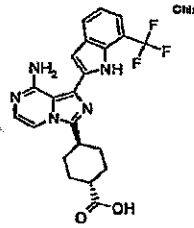
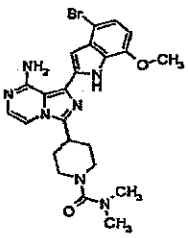
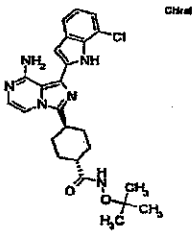
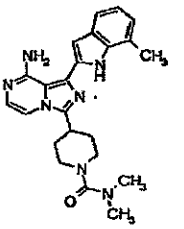
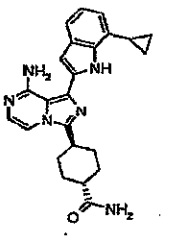
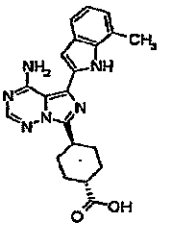
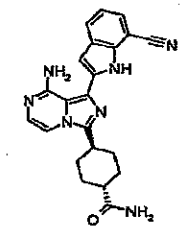
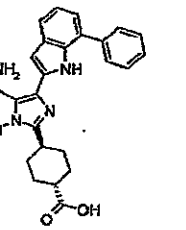
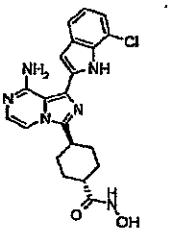
Ex #	Structure	MH+	Ex #	Structure	MH+
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222		425.93	282		485.32
223		411.13 413.02	283		510.38
224		453.99	284		406.29
225		433.02	285		404.21
226		479.85	286		420.53

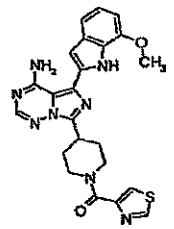
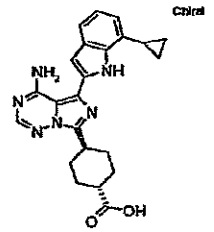
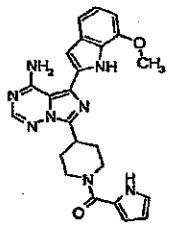
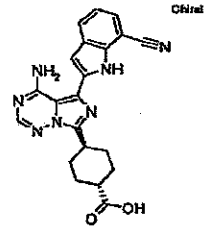
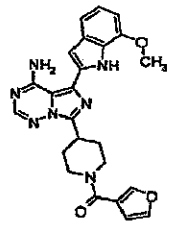
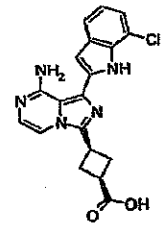
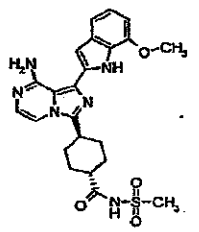
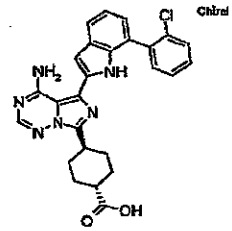
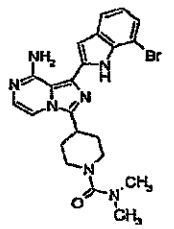
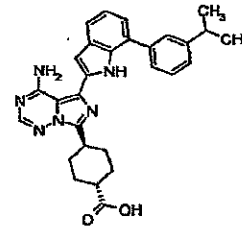
Ex #	Structure	MH+	Ex #	Structure	MH+
227		434.95	287		417.29
228		417.21	288		423.29
229		500.99 502.88	289		455.11 457.09
230		516.91 518.90	290		497.93
231		498.02	291		424.04 425.99
292		434.08	333		406.35 406.42

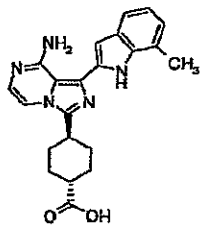
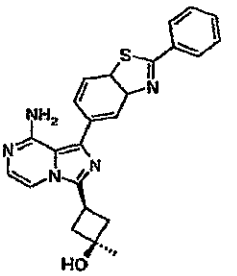
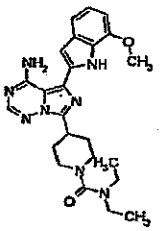
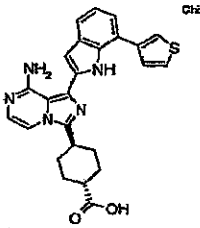
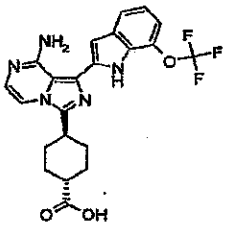
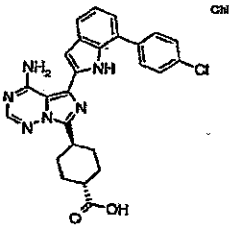
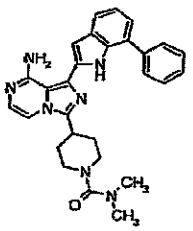
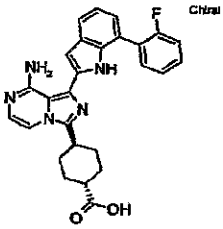
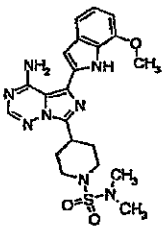
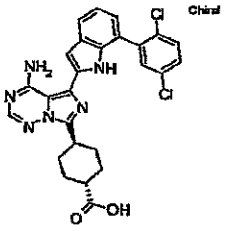
Ex #	Structure	MH+	Ex #	Structure	MH+
293		475.89	334		501.31
294		461.94	335		487.44
295		485.14 487.10	336		420.15 420.18
296		491.18	337		411.06 413.07
297		488.63	338		471.35

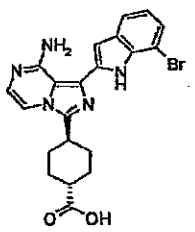
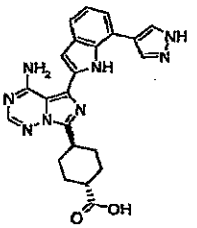
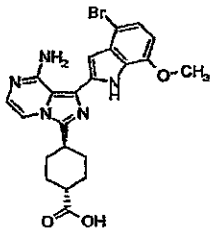
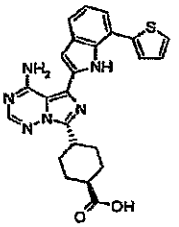
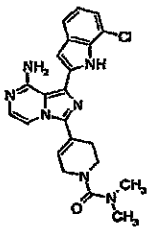
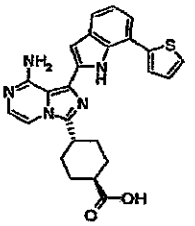
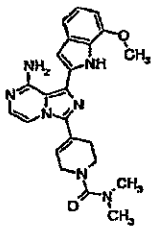
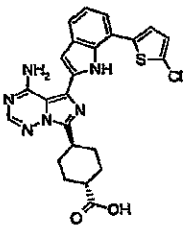
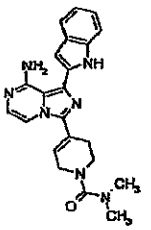
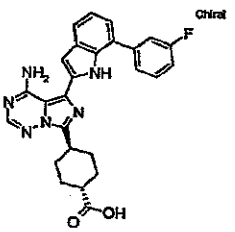
Ex #	Structure	MH+	Ex #	Structure	MH+
298		434.08	339		454.07 456.03
299		435.10	340		484.44
300		505.10	341		470.41
301		438.00	342		469.46
302		432.02	343		409.35
303		467.30	344		416.17

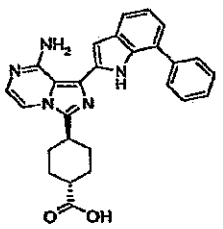
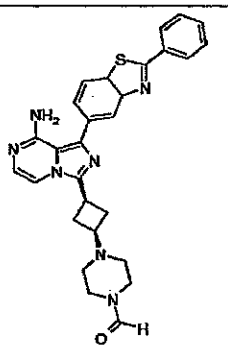
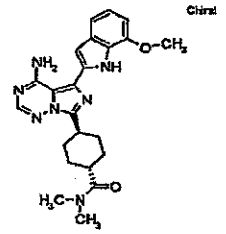
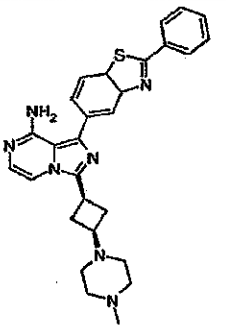
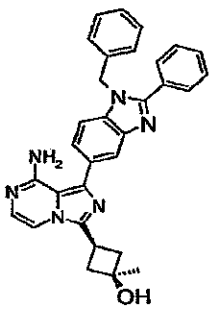
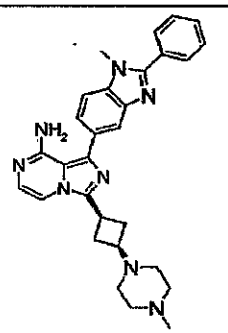
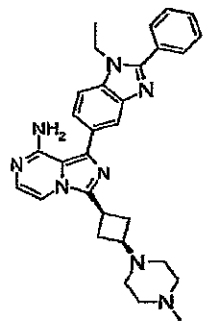
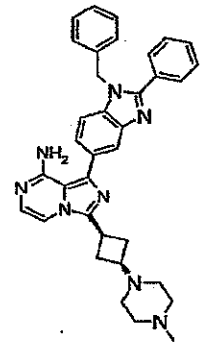
Ex #	Structure	MH+	Ex #	Structure	MH+
304		455.23	345		485.39
305		405.09	346		444.10
306		424.13 426.23	347		471.41
307		458.99	348		404.04 406.06
308		409.97 411.96	349		404.27 406.29
309		445 445.1	350		469.39

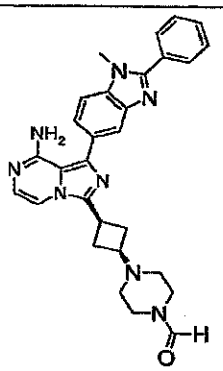
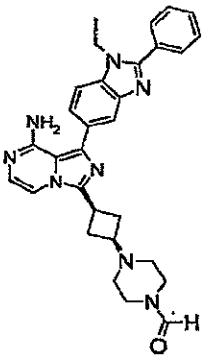
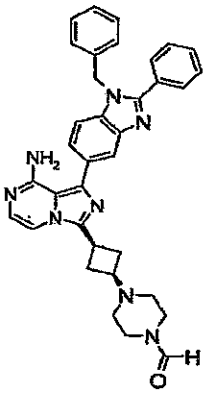
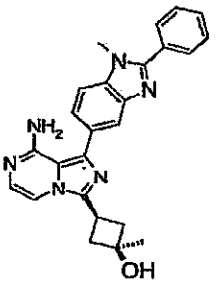
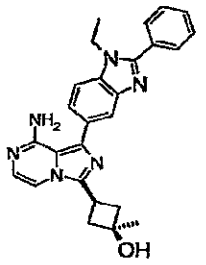
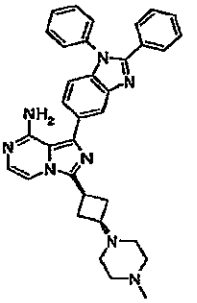
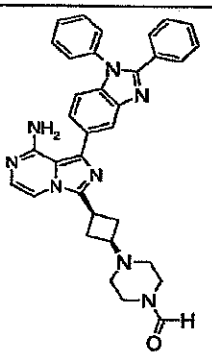
Ex #	Structure	MH+	Ex #	Structure	MH+
310		407.05	351		401.39
311		421.00	352		444.16
312		512.40	353		481.12 483.14
313		418.03	354		415.17
314		391.06	355		400.09
315		453.04 453.17 453.39	356		425.34 427.33

Ex #	Structure	MH+	Ex #	Structure	MH+
316		474.95	357		417.36
317		457.08	358		402.33
318		457.95	359		381.96 384.01
319		482.96	360		487.01 489.03
320		483.90	361		495.03

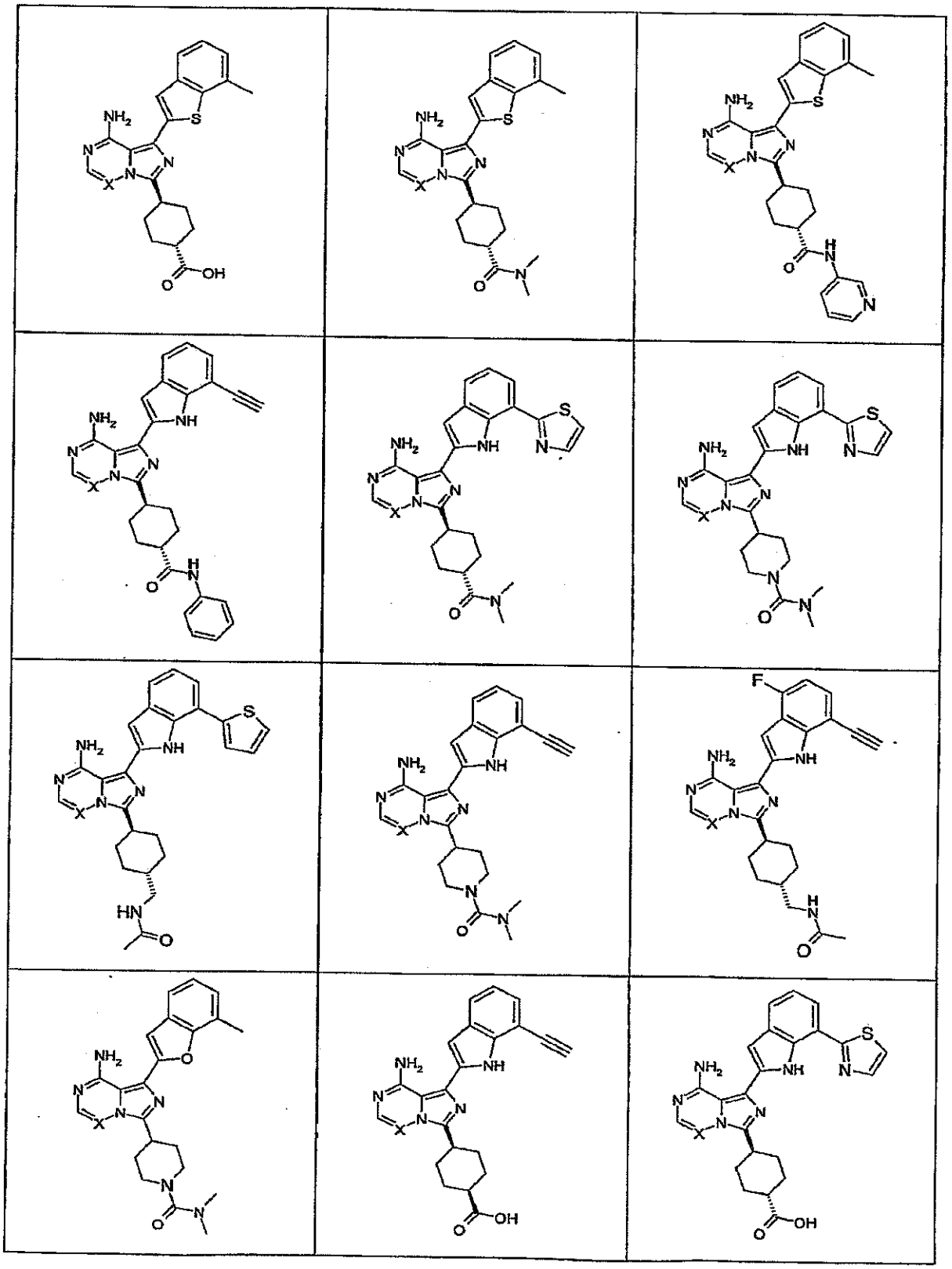
Ex #	Structure	MH+	Ex #	Structure	MH+
321		390.02	362		428.02
322		463.08	363		458.32
323		460.09	364		487.01 488.90
324		480.21	365		470.37
325		471.11	366		521.27 523.27

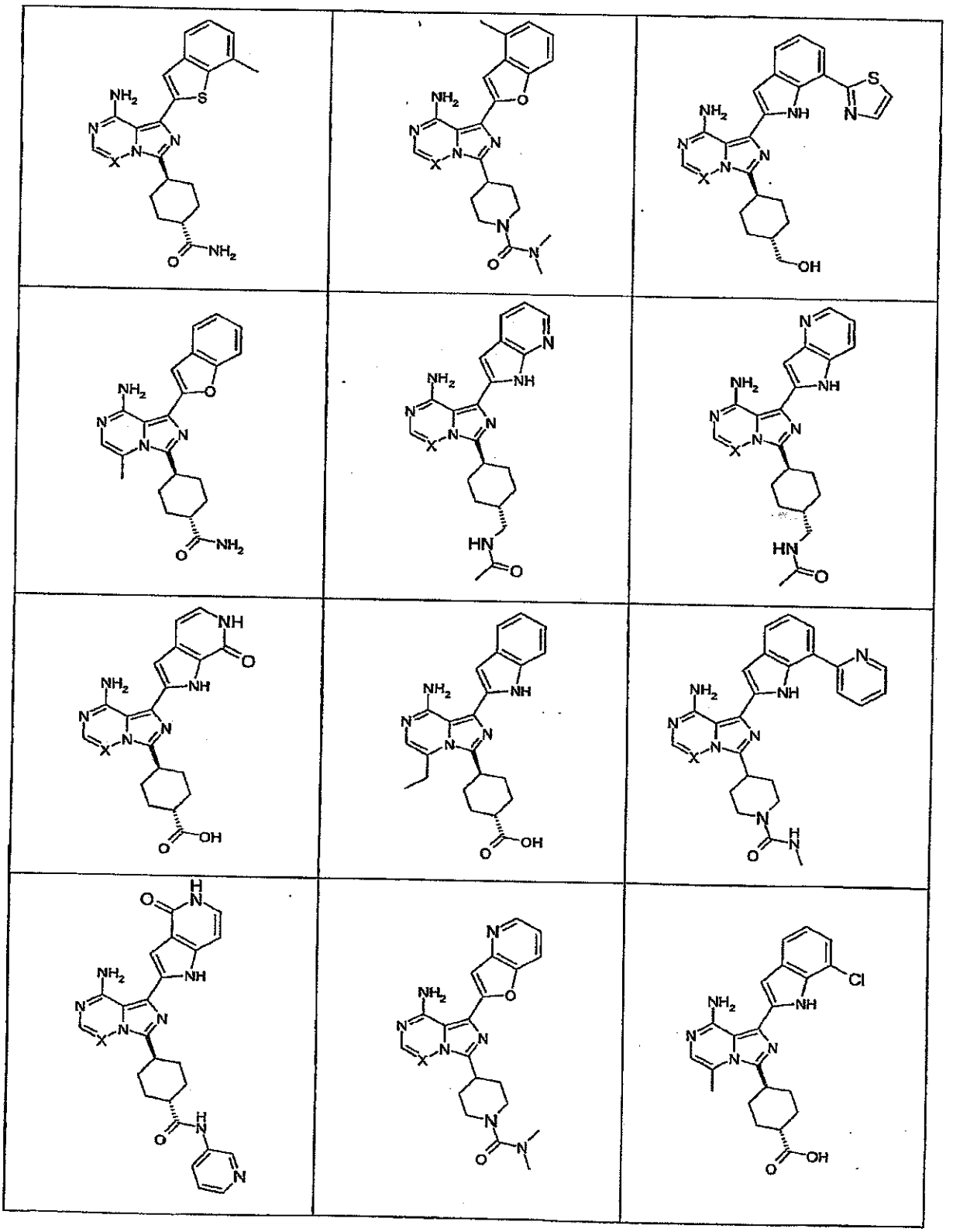
Ex #	Structure	MH+	Ex #	Structure	MH+
326		455.94	367		443.22
327		486.20	368		459.28
328		436.23 438.26	369		458.37
329		432.02	370		493.22 495.18
330		402.06	371		471.03

Ex #	Structure	MH+	Ex #	Structure	MH+
331		452.12	372		510.03
332		434.25	373		496.06
374		501.45	375		493.49
376		507.46	377		569.56

Ex #	Structure	MH+	Ex #	Structure	MH+
378		507.46	379		521.50
380		583.53	381		425.39
382		439.42	383		555.55
384		569.55			

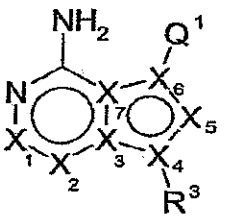
[443] The following compounds are expected to be active as inhibitors of mTOR. Where shown, X can be N or CH.





WHAT IS CLAIMED IS:

Claim 1. A compound represented by Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X_1, and X_2 are each independently N or C–$(E^1)_{aa}$;

X_5 is N, C–$(E^1)_{aa}$, or N–$(E^1)_{aa}$;

X_3, X_4, X_6, and X_7 are each independently N or C;

wherein at least one of X_3, X_4, X_5, X_6, and X_7 is independently N or N–$(E^1)_{aa}$;

R^3 is $C_{0\text{-}10}$alkyl, cyclo$C_{3\text{-}10}$alkyl, aminomethylcyclo$C_{3\text{-}10}$alkyl, bicyclo$C_{5\text{-}10}$alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl or heterobicyclo$C_{5\text{-}10}$alkyl any of which is optionally substituted by one or more independent G^{11} substituents;

Q^1 is $–A(R^1)_mB(W)_n$ or $–B(G^{11})_nA(Y)_m$;

A and B are respectively, 5 and 6 membered aromatic or heteroaromatic rings, fused together to form a 9-membered heteroaromatic system excluding 5-benzo[*b*]furyl and 3-indolyl; and excluding 2-indolyl, 2-benzoxazole, 2-benzothiazole, 2-benzimidazolyl, 4-aminopyrrolopyrimidin-5-yl, 4 -aminopyrrolopyrimidin-6-yl, and 7-deaza-7-adenosinyl derivatives when X_1 and X_5 are CH, X_3, X_6 and X_7 are C, and X_2 and X_4 are N;

or Q^1 is $–A(R^1)_mA(Y)_m$, wherein each A is the same or different 5-membered aromatic or heteroaromatic ring, and the two are fused together to form an 8-membered heteroaromatic system;

R^1 is independently, hydrogen, $–N(C_{0\text{-}8}alkyl)(C_{0\text{-}8}alkyl)$, hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), $C_{1\text{-}6}$alkyl, $–C_{0\text{-}8}alkylC_{3\text{-}8}cycloalkyl$, $–C_{0\text{-}8}alkyl\text{-}NR^{311}S(O)_{0\text{-}2}R^{321}$, $–C_{0\text{-}8}alkyl\text{-}NR^{311}S(O)_{0\text{-}2}NR^{321}R^{331}$, $–C_{0\text{-}8}alkyl\text{-}S(O)_{0\text{-}2}NR^{311}R^{321}$, $–C_{0\text{-}8}alkyl\text{-}NR^{311}COR^{321}$, $–C_{0\text{-}8}alkyl\text{-}NR^{311}CO_2R^{321}$, $–C_{0\text{-}8}alkyl\text{-}NR^{311}CONR^{321}R^{331}$, $–C_{0\text{-}8}alkyl\text{-}CONR^{311}R^{321}$, $–C_{0\text{-}8}alkyl\text{-}CON(R^{311})S(O)_{0\text{-}2}R^{321}$, $–C_{0\text{-}8}alkyl\text{-}CO_2R^{311}$, $-C_{0\text{-}8}alkyl\text{-}S(O)_{0\text{-}2}R^{311}$, $–C_{0\text{-}8}alkyl\text{-}O\text{-}C_{1\text{-}8}alkyl$, $–C_{0\text{-}8}alkyl\text{-}O\text{-}C_{0\text{-}8}alkylC_{3\text{-}8}cycloalkyl$, $–C_{0\text{-}8}alkyl\text{-}O\text{-}C_{0\text{-}8}alkylheterocyclyl$, $–C_{0\text{-}8}alkyl\text{-}O\text{-}C_{0\text{-}8}alkylaryl$, $–C_{0\text{-}8}alkylaryl$, $–C_{0\text{-}8}alkylhetaryl$, $–C_{0\text{-}8}alkylheterocyclyl$, $–C_{0\text{-}8}alkyl\text{-}O\text{-}C_{0\text{-}8}alkylhetaryl$, $–C_{0\text{-}8}alkyl\text{-}S\text{-}C_{0\text{-}8}alkyl$, $–C_{0\text{-}8}alkyl\text{-}S\text{-}C_{0\text{-}8}alkylC_{3\text{-}8}cycloalkyl$, $–C_{0\text{-}8}alkyl\text{-}S\text{-}C_{0\text{-}8}alkylheterocyclyl$, $-C_{0\text{-}8}alkyl\text{-}S\text{-}C_{0\text{-}8}alkylaryl$, $–C_{0\text{-}8}alkyl\text{-}S\text{-}C_{0\text{-}8}alkylhetaryl$, $–C_{0\text{-}8}alkyl\text{-}N(R^{311})\text{-}C_{0\text{-}8}alkyl$, $–C_{0\text{-}8}alkyl\text{-}N(R^{311})\text{-}C_{0\text{-}8}alkylC_{3\text{-}8}cycloalkyl$, $–C_{0\text{-}8}alkyl\text{-}N(R^{311})\text{-}C_{0\text{-}8}alkylheterocyclyl$, $–C_{0\text{-}8}alkyl\text{-}N(R^{311})\text{-}C_{0\text{-}8}alkylaryl$, $–C_{0\text{-}8}alkyl\text{-}N(R^{311})\text{-}C_{0\text{-}8}alkylhetaryl$, –

C_{0-8}alkyl-$NR^{311}R^{321}$, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not N-methyl-2-indolyl, N-(phenylsulfonyl)-2-indolyl, or N-tert-butoxycarbonyl;

W is independently, hydrogen, $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{1-6}alkyl, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-NR^{312}S(O)_{0-2}R^{322}$, $-C_{0-8}alkyl-NR^{311}S(O)_{0-2}NR^{321}R^{331}$, $-C_{0-8}alkyl-NR^{311}CO_2R^{321}$, $-C_{0-8}alkyl-CON(R^{311})S(O)_{0-2}R^{321}$, $-C_{0-8}alkyl-S(O)_{0-2}NR^{312}R^{322}$, $-C_{0-8}alkyl-NR^{312}COR^{322}$, $-C_{0-8}alkyl-NR^{312}CONR^{322}R^{332}$, $-C_{0-8}alkyl-CONR^{312}R^{322}$, $-C_{0-8}alkyl-CO_2R^{312}$, $-C_{0-8}alkylS(O)_{0-2}R^{312}$, $-C_{0-8}alkyl-O-C_{1-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylcyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, $-C_{0-8}alkylaryl$, $-C_{0-8}alkylhetaryl$, $-C_{0-8}alkylheterocyclyl$, -Oaryl, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(R^{312})-C_{0-8}alkylhetaryl$, $C_{0-8}alkyl-NR^{312}R^{322}$, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not 4-benzyloxy-2-indolyl;

Y is independently, hydrogen, $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl(optionally substituted with 1 or more R^{31} groups), hetaryl(optionally substituted with 1 or more R^{31} groups), C_{0-6}alkyl, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-NR^{311}S(O)_{0-2}R^{321}$, $-C_{0-8}alkyl-NR^{311}S(O)_{0-2}NR^{321}R^{331}$, $-C_{0-8}alkyl-NR^{311}CO_2R^{321}$, $-C_{0-8}alkyl-CON(R^{311})S(O)_{0-2}R^{321}$, $-C_{0-8}alkyl-S(O)_{0-2}NR^{311}R^{321}$, $-C_{0-8}alkyl-NR^{311}COR^{321}$, $-C_{0-8}alkyl-NR^{311}CONR^{321}R^{331}$, $-C_{0-8}alkyl-CONR^{311}R^{321}$, $-C_{0-8}alkyl-CO_2R^{311}$, $-C_{0-8}alkylS(O)_{0-2}R^{311}$, $-C_{0-8}alkyl-O-C_{1-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, $-C_{0-8}alkylaryl$, $-C_{0-8}alkylhetaryl$, $-C_{0-8}alkylheterocyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(R^{311})-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-NR^{311}R^{321}$, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$; provided that Q^1 is not 2-carboxy-5-benzo[*b*]thiophenyl;

G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{312}$, $-NR^{312}R^{322}$, $-C(O)R^{312}$, $-C(O)C_{3-8}$cycloalkyl, $-CO_2C_{3-8}$cycloalkyl, $-CO_2R^{312}$, $-C(=O)NR^{312}R^{322}$, $-NO_2$, $-CN$, $-S(O)_{0-2}R^{312}$, $-SO_2NR^{312}R^{322}$, $NR^{312}(C=O)R^{322}$, $NR^{312}C(=O)OR^{322}$, $NR^{312}C(=O)NR^{322}R^{332}$, $NR^{312}S(O)_{0-2}R^{322}$, $-C(=S)OR^{312}$, $-C(=O)SR^{312}$, $-NR^{312}C(=NR^{322})NR^{332}R^{341}$, $-NR^{312}C(=NR^{322})OR^{332}$, $-NR^{312}C(=NR^{322})SR^{332}$, $-OC(=O)OR^{312}$, $-OC(=O)NR^{312}R^{322}$, $-OC(=O)SR^{312}$, $-SC(=O)OR^{312}$, $-SC(=O)NR^{312}R^{322}$, $-P(O)OR^{312}OR^{322}$, C_{1-10}alkylidene, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $-C_{1-10}alkoxyC_{1-10}alkyl$, $-C_{1-10}alkoxyC_{2-10}alkenyl$, $-C_{1-10}alkoxyC_{2-10}alkynyl$, $-C_{1-10}alkylthioC_{1-10}alkyl$, $-C_{1-10}alkylthioC_{2-10}alkenyl$, $-C_{1-10}alkylthioC_{2-10}alkynyl$, $cycloC_{3-8}$alkyl, $cycloC_{3-8}$alkenyl, $-cycloC_{3-8}alkylC_{1-10}alkyl$, $-cycloC_{3-}$

$_{8}$alkenylC_{1-10}alkyl, –cycloC_{3-8}alkylC_{2-10}alkenyl, –cycloC_{3-8}alkenylC_{2-10}alkenyl, –cycloC_{3-8}alkylC_{2-10}alkynyl, –cycloC_{3-8}alkenylC_{2-10}alkynyl, –heterocyclyl–C_{0-10}alkyl, –heterocyclyl–C_{2-10}alkenyl, or –heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{313}$, $–NR^{313}R^{323}$, $–C(O)R^{313}$, $–CO_2R^{313}$, $–C(=O)NR^{313}R^{323}$, $–NO_2$, –CN, $–S(O)_{0-2}R^{313}$, $–SO_2NR^{313}R^{323}$, $–NR^{313}C(=O)R^{323}$, $–NR^{313}C(=O)OR^{323}$, $–NR^{313}C(=O)NR^{323}R^{333}$, $–NR^{313}S(O)_{0-2}R^{323}$, $–C(=S)OR^{313}$, $–C(=O)SR^{313}$, $–NR^{313}C(=NR^{323})NR^{333}R^{342}$, $–NR^{313}C(=NR^{323})OR^{333}$, $–NR^{313}C(=NR^{323})SR^{333}$, $–OC(=O)OR^{333}$, $–OC(=O)NR^{313}R^{323}$, $–OC(=O)SR^{313}$, $–SC(=O)OR^{313}$, $–P(O)OR^{313}OR^{323}$, or $–SC(=O)NR^{313}R^{323}$ substituents;

or G^{11} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, where the attachment point is from either the left or right as written, where any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, $–OR^{313}$, $–NR^{313}R^{323}$, $–C(O)R^{313}$, $–CO_2R^{313}$, $–C(=O)NR^{313}R^{323}$, $–NO_2$, –CN, $–S(O)_{0-2}R^{313}$, $–SO_2NR^{313}R^{323}$, $–NR^{313}C(=O)R^{323}$, $–NR^{313}C(=O)OR^{323}$, $–NR^{313}C(=O)NR^{323}R^{333}$, $–NR^{313}S(O)_{0-2}R^{323}$, $–C(=S)OR^{313}$, $–C(=O)SR^{313}$, $–NR^{323}C(=NR^{313})NR^{333}R^{342}$, $–NR^{313}C(=NR^{323})OR^{333}$, $–NR^{313}C(=NR^{323})SR^{333}$, $–OC(=O)OR^{313}$, $–OC(=O)NR^{313}R^{323}$, $–OC(=O)SR^{313}$, $–SC(=O)OR^{313}$, $–P(O)OR^{313}OR^{323}$, or $–SC(=O)NR^{313}R^{323}$ substituents; provided that G^{11} is not *N*-CH_2CO_2H when R^3 is 4-piperidinyl;

R^{31}, R^{32}, R^{33}, R^{311}, R^{321}, R^{331}, R^{312}, R^{322}, R^{332}, R^{341}, R^{313}, R^{323}, R^{333}, and R^{342}, in each instance, is independently

C_{0-8}alkyl optionally substituted with an aryl, heterocyclyl or hetaryl substituent, or C_{0-8}alkyl optionally substituted with 1-6 independent halo, -CON(C_{0-8}alkyl)(C_{0-8}alkyl), -CO(C_{0-8}alkyl), -OC_{0-8}alkyl, -Oaryl, -Ohetaryl, -Oheterocyclyl, -S(O)$_{0-2}$aryl, -S(O)$_{0-2}$hetaryl, -S(O)$_{0-2}$heterocyclyl, -S(O)$_{0-2}C_{0-8}$alkyl, -N(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CO(C_{1-8}alkyl), -N(C_{0-8}alkyl)CO(C_{3-8}cycloalkyl), -N(C_{0-8}alkyl)CO_2(C_{1-8}alkyl), S(O)$_{1-2}$N(C_{0-8}alkyl)(C_{0-8}alkyl), $-NR^{11}$S(O)$_{1-2}$(C_{0-8}alkyl), -CON(C_{3-8}cycloalkyl)(C_{3-8}cycloalkyl), -CON(C_{0-8}alkyl)(C_{3-8}cycloalkyl), -N(C_{3-8}cycloalkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl), -N(C_{3-8}cycloalkyl)CON(C_{3-8}cycloalkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CON(C_{3-8}cycloalkyl)(C_{0-8}alkyl), -N(C_{0-8}alkyl)CO_2(C_{3-8}cycloalkyl), -N(C_{3-8}cycloalkyl)CO_2(C_{3-8}cycloalkyl), S(O)$_{1-2}$N(C_{0-8}alkyl)(C_{3-8}cycloalkyl), $-NR^{11}$S(O)$_{1-2}$(C_{3-8}cycloalkyl), C_{2-8}alkenyl, C_{2-8}alkynyl, CN, CF_3, OH, or optionally substituted aryl substituents; such that each of the above aryl, heterocyclyl, hetaryl, alkyl or cycloalkyl groups may be optionally, independently substituted with –N(C_{0-8}alkyl)(C_{0-8}alkyl), hydroxyl, halogen, oxo, aryl, hetaryl, C_{0-6}alkyl, –C_{0-8}alkylcyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)–S(O)$_{0-2}$–(C_{0-8}alkyl), –C_{0-8}alkyl-S(O)$_{0-2}$–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{0-8}alkyl–N(C_{0-8}alkyl)CO(C_{0-8}alkyl), –C_{0-8}alkyl–N(C_{0-8}alkyl)CO–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{0-8}alkyl-CO–N(C_{0-8}alkyl)(C_{0-8}alkyl), –C_{1-8}alkyl-CO_2–(C_{0-8}alkyl), –C_{0-8}alkylS(O)$_{0-2}$–(C_{0-8}alkyl), –C_{0-8}alkyl-O-C_{1-8}alkyl, –C_{0-8}alkyl-O-C_{0-8}alkylcyclyl, –C_{0-8}alkyl-O-C_{0-8}alkylheterocyclyl, –C_{0-}

$_{8}$alkyl-O-C_{0-8}alkylaryl, –C_{0-8}alkyl-O-C_{0-8}alkylhetaryl, –C_{0-8}alkyl-S-C_{0-8}alkyl, –C_{0-8}alkyl-S-C_{0-8}alkylcyclyl, –C_{0-8}alkyl-S-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl-S-C_{0-8}alkylaryl, –C_{0-8}alkyl-S-C_{0-8}alkylhetaryl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylcyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylheterocyclyl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylaryl, –C_{0-8}alkyl–N(C_{0-8}alkyl)-C_{0-8}alkylhetaryl, –C_{2-8}alkenyl, –C_{2-8}alkynyl, NO_2, CN, CF_3, OCF_3, $OCHF_2$,

–C_{0-8}alkyl–C_{3-8}cycloalkyl,

-C_{0-8}alkyl-O-C_{0-8}alkyl,

–C_{0-8}alkyl-N(C_{0-8}alkyl)(C_{0-8}alkyl),

–C_{0-8}alkyl-S(O)$_{0-2}$-C_{0-8}alkyl, or

heterocyclyl optionally substituted with 1-4 independent C_{0-8}alkyl, cyclyl, or substituted cyclyl substituents;

E^1 in each instance is independently halo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^{31}R^{32}$, $-C(=O)R^{31}$, $-CO_2R^{31}$, $-CONR^{31}R^{32}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-S(O)_{0-2}NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{31})SR^{31}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-SC(=O)NR^{31}R^{32}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, –C_{1-10}alkoxyC_{1-10}alkyl, –C_{1-10}alkoxyC_{2-10}alkenyl, –C_{1-10}alkoxyC_{2-10}alkynyl, –C_{1-10}alkylthioC_{1-10}alkyl, –C_{1-10}alkylthioC_{2-10}alkenyl, –C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, –cycloC_{3-8}alkylC_{1-10}alkyl, –cycloC_{3-8}alkenylC_{1-10}alkyl, –cycloC_{3-8}alkylC_{2-10}alkenyl, –cycloC_{3-8}alkenylC_{2-10}alkenyl, –cycloC_{3-8}alkylC_{2-10}alkynyl, –cycloC_{3-8}alkenylC_{2-10}alkynyl, –heterocyclyl–C_{0-10}alkyl, –heterocyclyl–C_{2-10}alkenyl, or –heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(=O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $-S(=O)_{0-2}R^{31}$, $-SO_2NR^{31}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{31}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{31}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, or $-SC(=O)NR^{31}R^{32}$ substituents;

or E^1 in each instance is independently aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, where the attachment point is from either the left or right as written, where any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-S(O)_{0-2}NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{31}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{31}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, or $-SC(=O)NR^{31}R^{32}$ substituents;

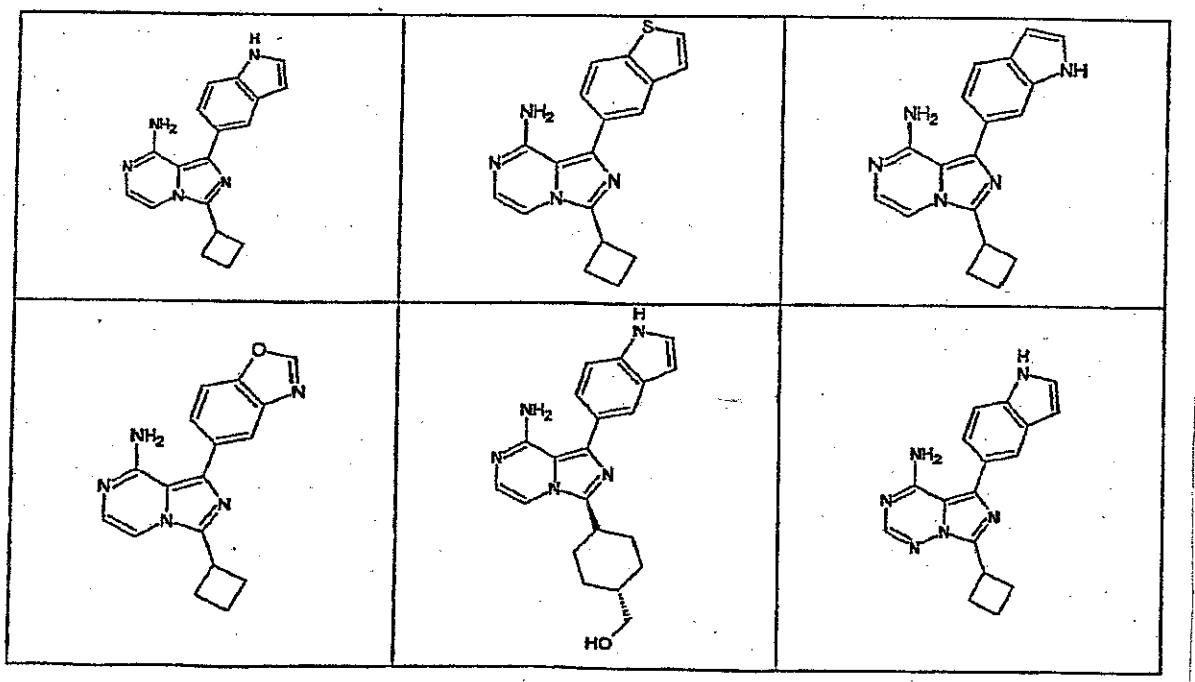
in the cases of $-NR^{31}R^{32}$, $-NR^{311}R^{321}$, $-NR^{312}R^{322}$, $-NR^{332}R^{341}$, $-NR^{313}R^{323}$, and $-NR^{323}R^{333}$, the respective R^{31} and R^{32}, R^{311} and R^{321}, R^{312} and R^{322}, R^{331} and R^{341}, R^{313} and R^{323}, and R^{323} and R^{333} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring in each instance independently is optionally substituted by one or more independent $-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, hydroxyl, halogen, oxo, aryl, hetaryl, $C_{0-6}alkyl$, $-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)S(O)_{0-2}C_{0-8}alkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)S(O)_{0-2}N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CO_2(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CON((C_{0-8}alkyl))S(O)_{0-2}(C_{0-8}alkyl)$, $-C_{0-8}alkyl-S(O)_{0-2}N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CO(C_{0-8}alkyl)$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)CON(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CON(C_{0-8}alkyl)(C_{0-8}alkyl)$, $-C_{0-8}alkyl-CO_2(C_{0-8}alkyl)$, $-C_{0-8}alkylS(O)_{0-2}(C_{0-8}alkyl)$, $-C_{0-8}alkyl-O-C_{0-8}alkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylcyclyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-O-C_{0-8}alkylaryl$, -Oaryl, $-C_{0-8}alkyl-O-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-S-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-S-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylC_{3-8}cycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylheterocycloalkyl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)-C_{0-8}alkylhetaryl$, $-C_{0-8}alkyl-N(C_{0-8}alkyl)(C_{0-8}alkyl)$, $C_{2-8}alkenyl$, $C_{2-8}alkynyl$, NO_2, CN, CF_3, OCF_3, or $OCHF_2$ substituents; wherein said ring in each instance independently optionally includes one or more heteroatoms other than the nitrogen;

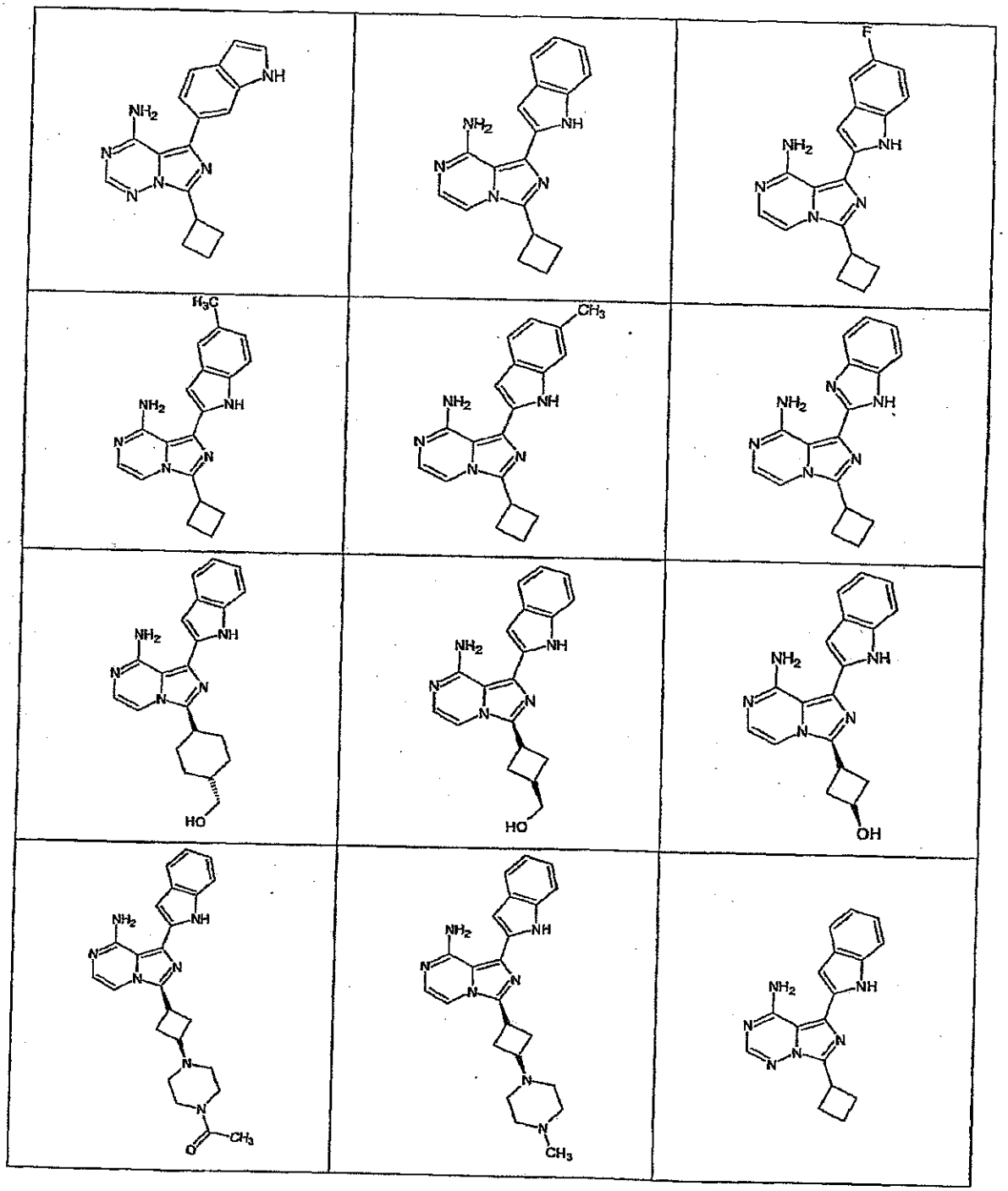
m is 0, 1, 2, or 3;

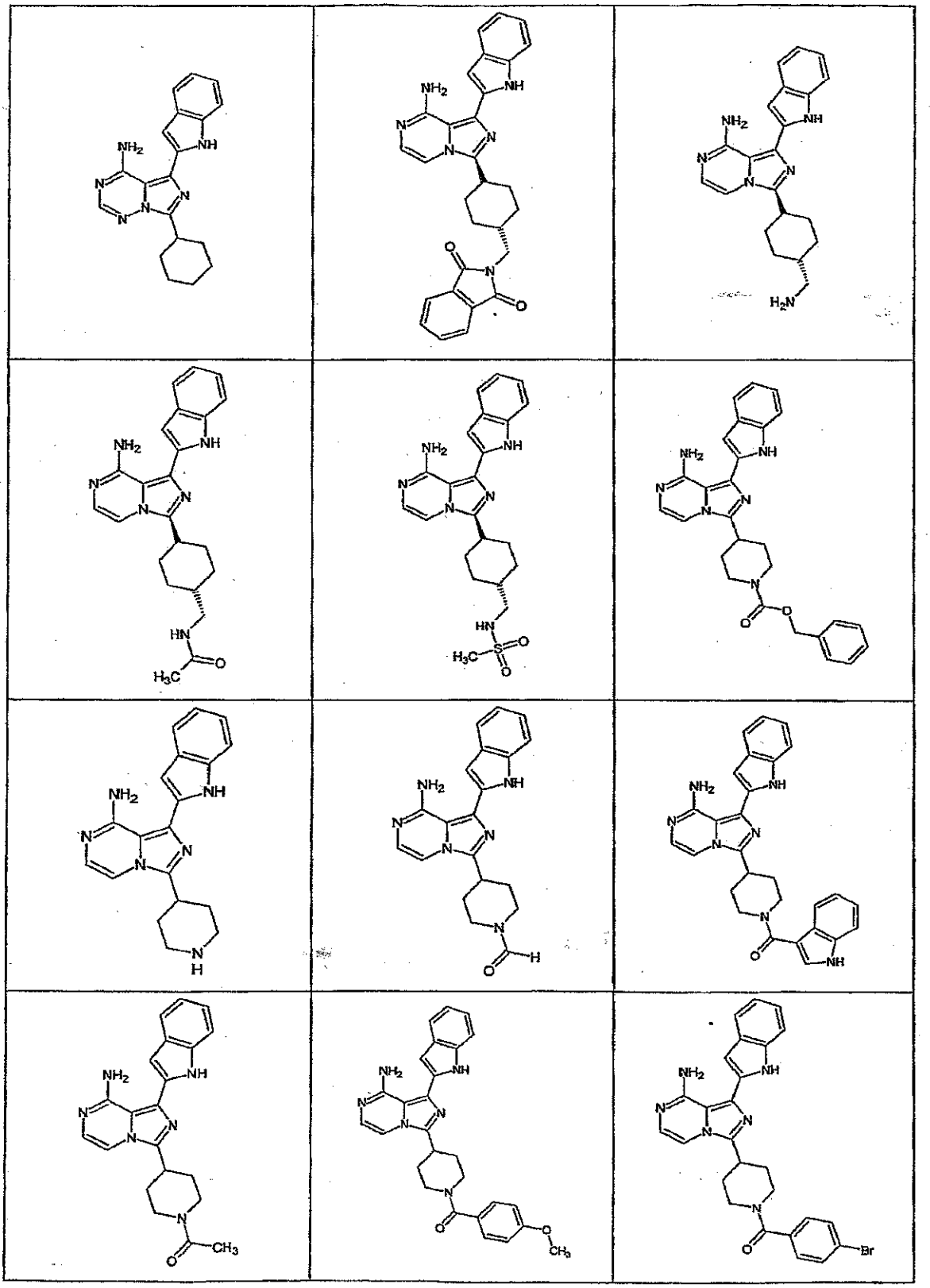
n is 0, 1, 2, 3, or 4; and

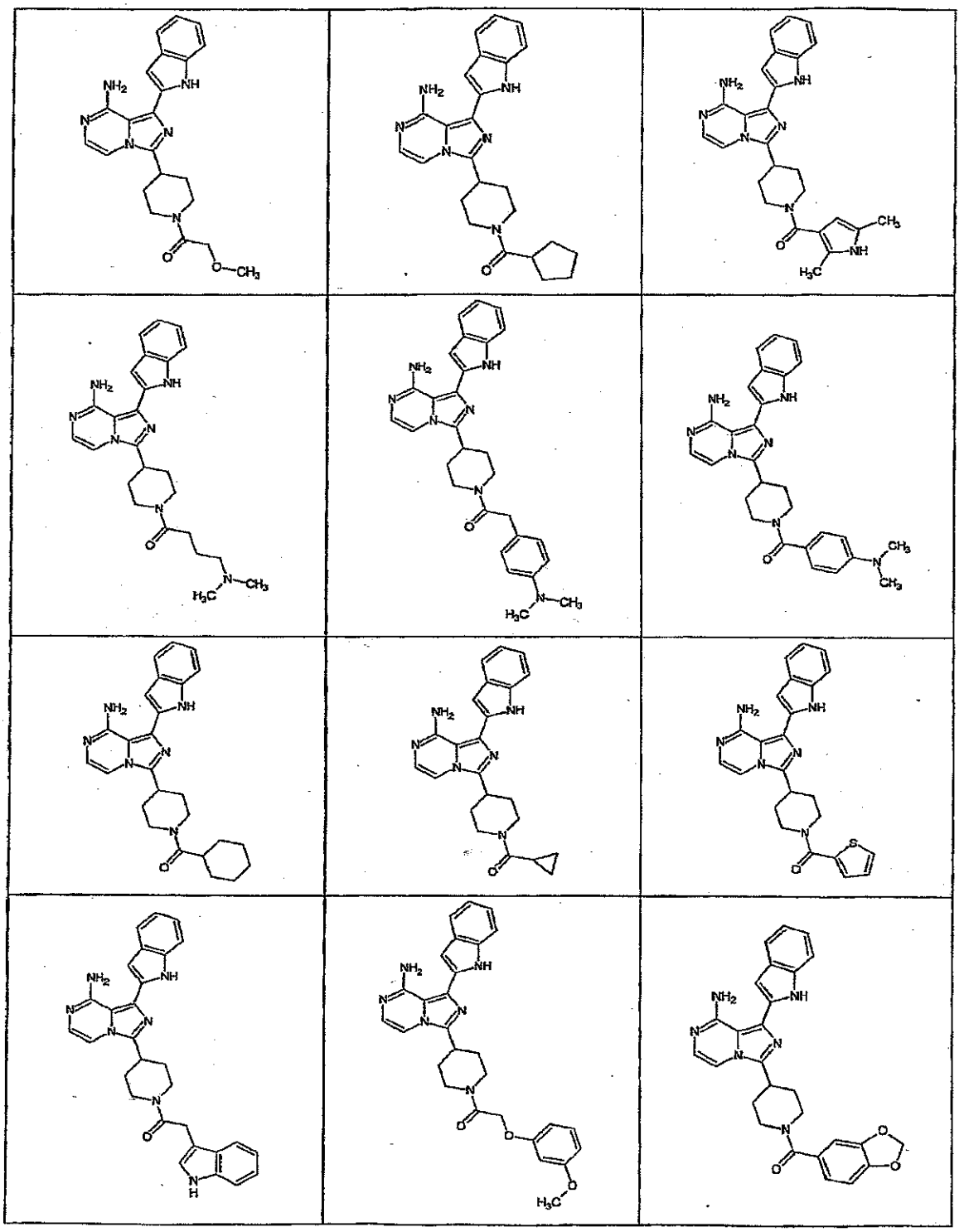
aa is 0 or 1; and provided that the compound is not *trans*-4-[8-amino-1-(7-chloro-4-hydroxy-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclohexanecarboxylic acid, *cis*-3-[8-amino-1-(7-chloro-1*H*-indol-2-yl)imidazo[1,5-*a*]pyrazin-3-yl]cyclobutanecarboxylic acid, *trans*-4-{8-amino-1-[7-(3-isopropyl)phenyl-1*H*-indol-2-yl]imidazo[1,5-*a*]pyrazin-3-yl}cyclohexanecarboxylic acid, or *trans*-4-{8-amino-1-[7-(2,5-dichloro)phenyl-1*H*-indol-2-yl]imidazo[1,5-*a*]pyrazin-3-yl}cyclohexane carboxylic acid,

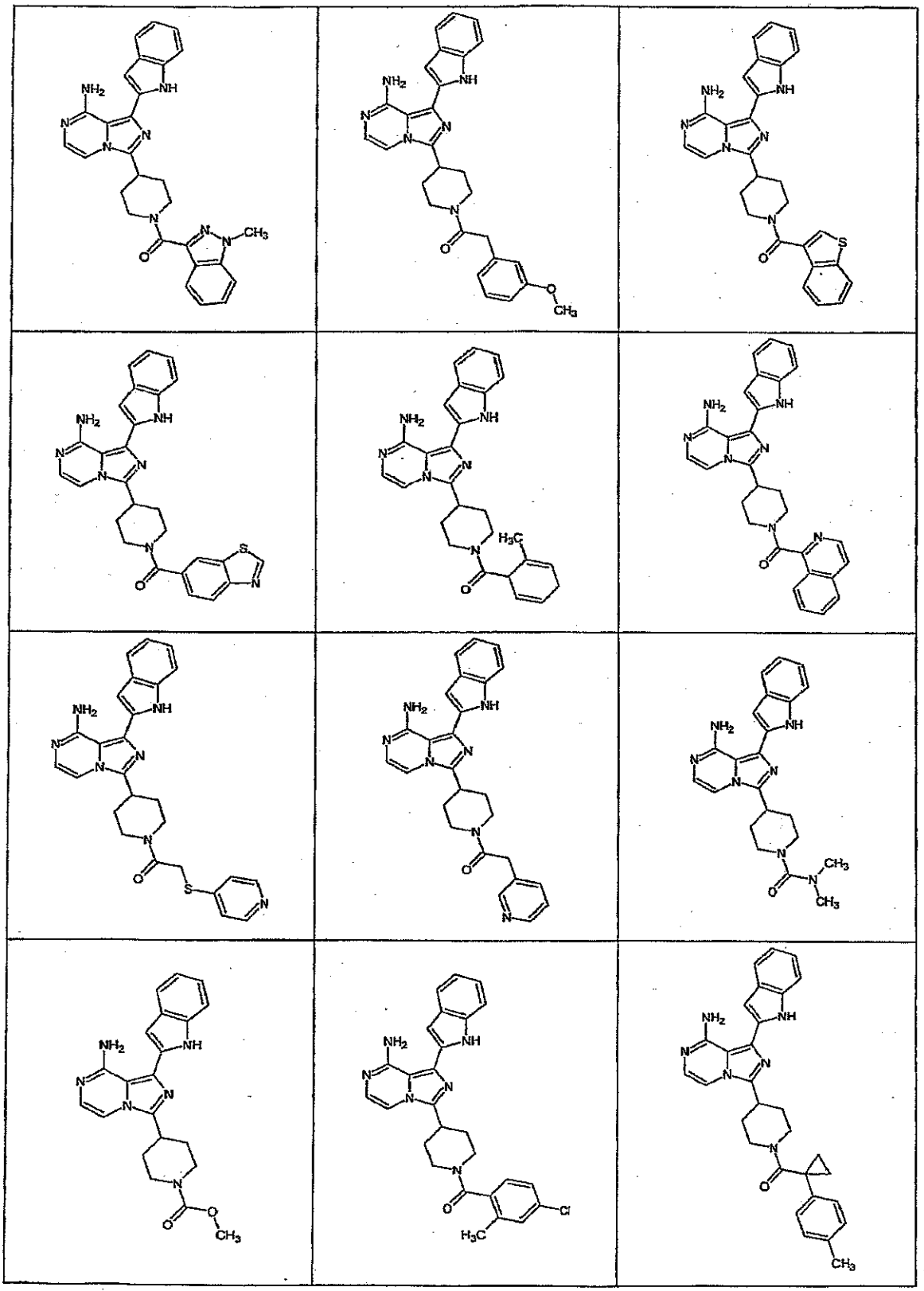
wherein the compound is selected from any one of the following structures

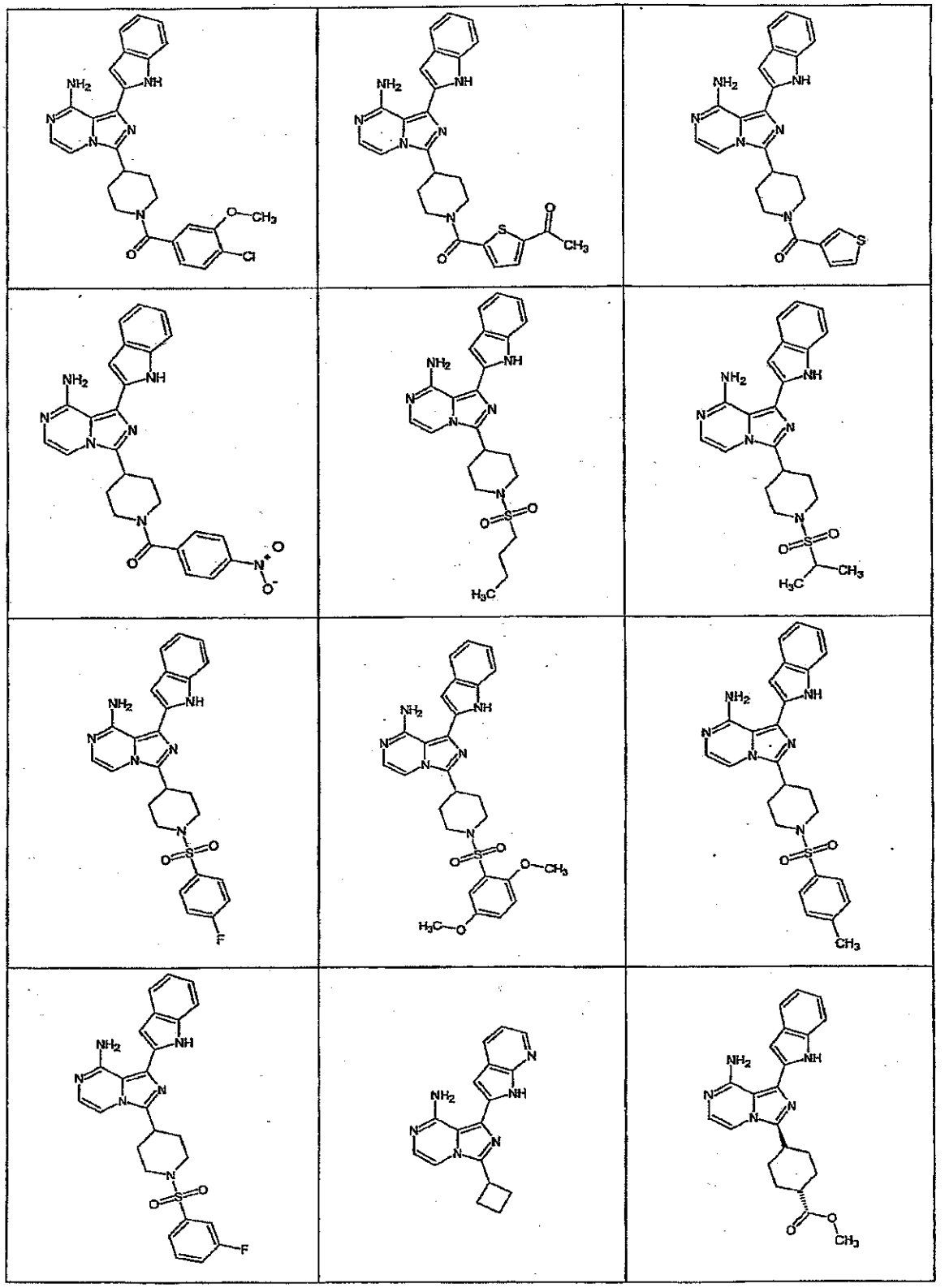


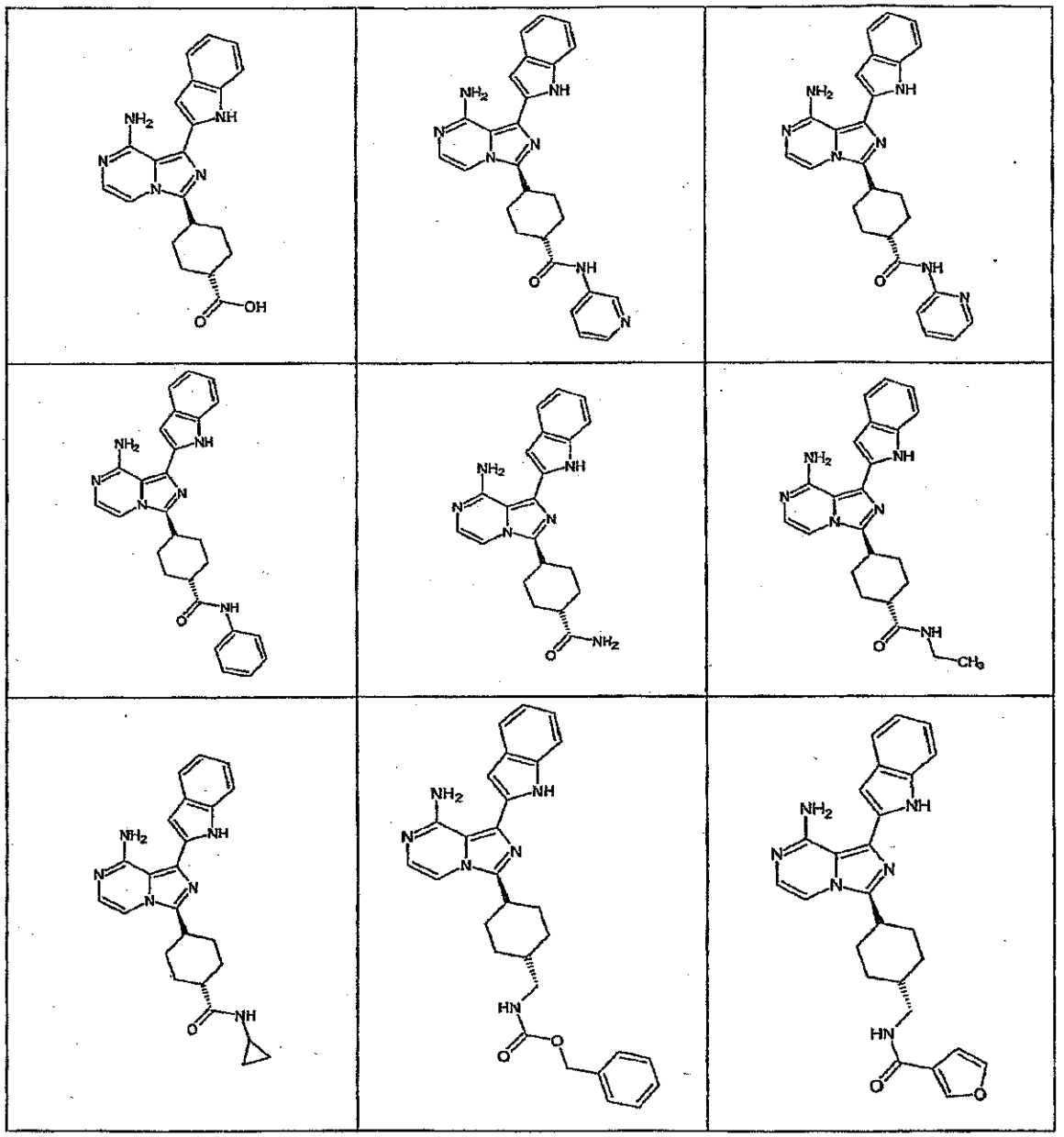


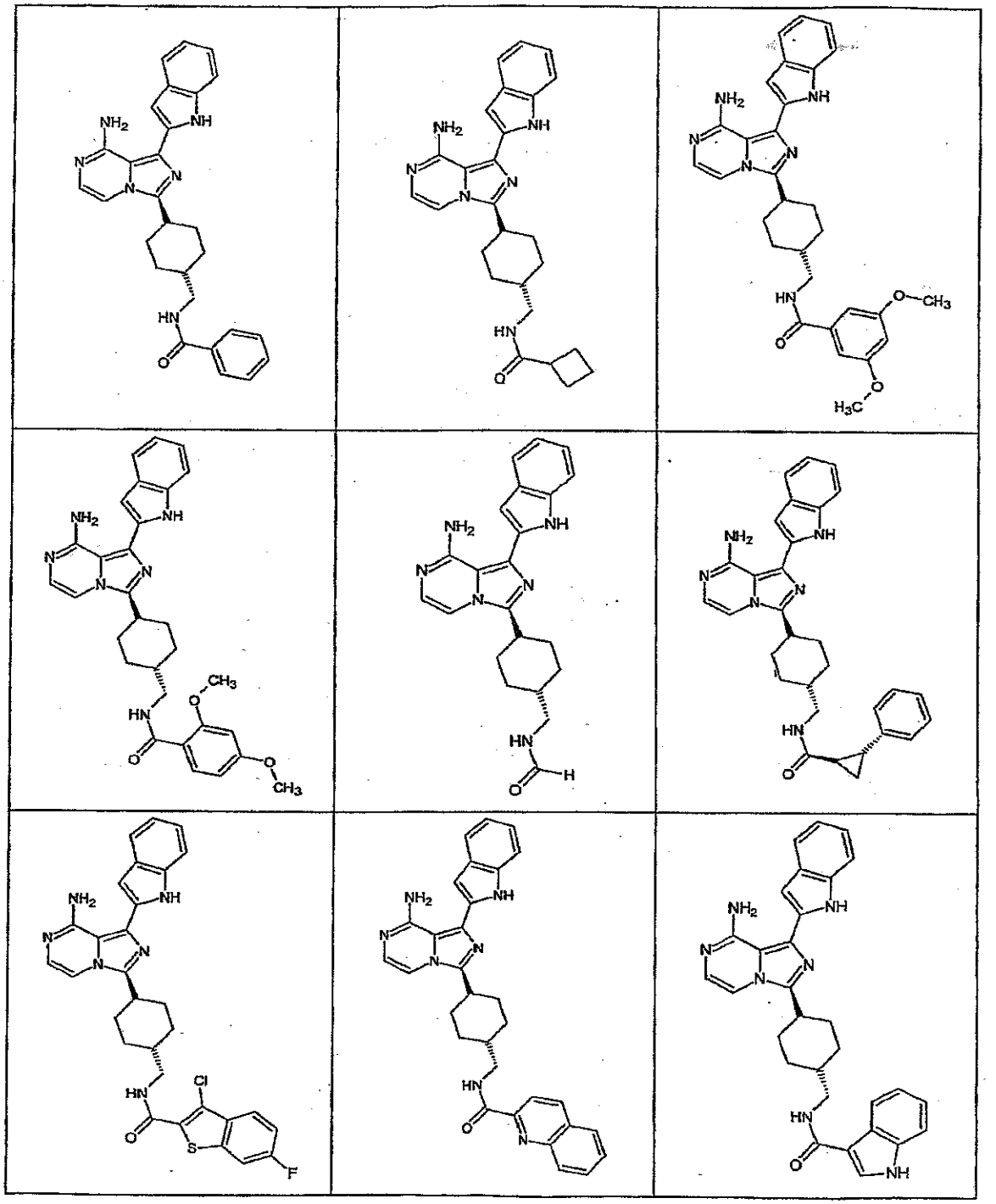


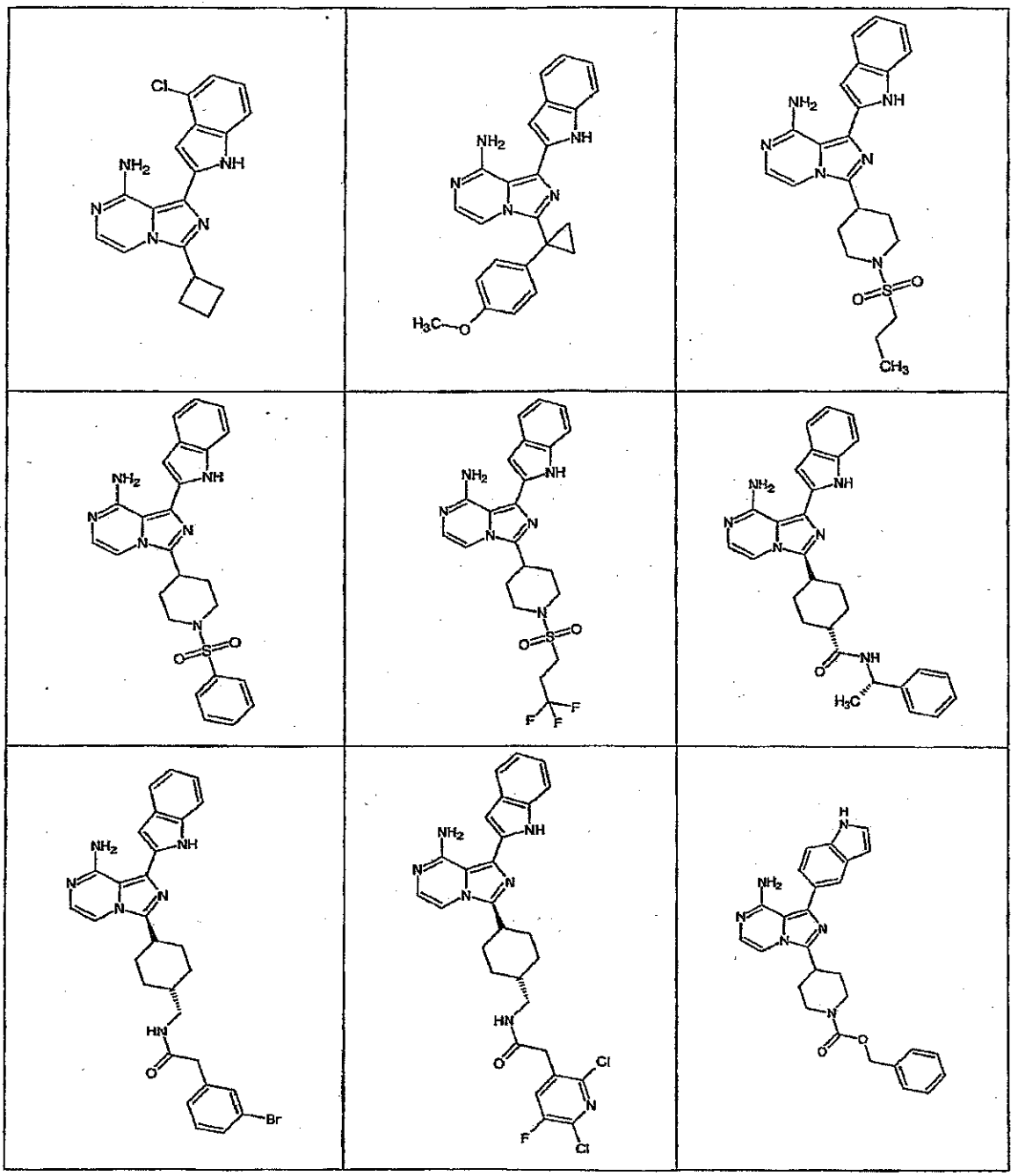


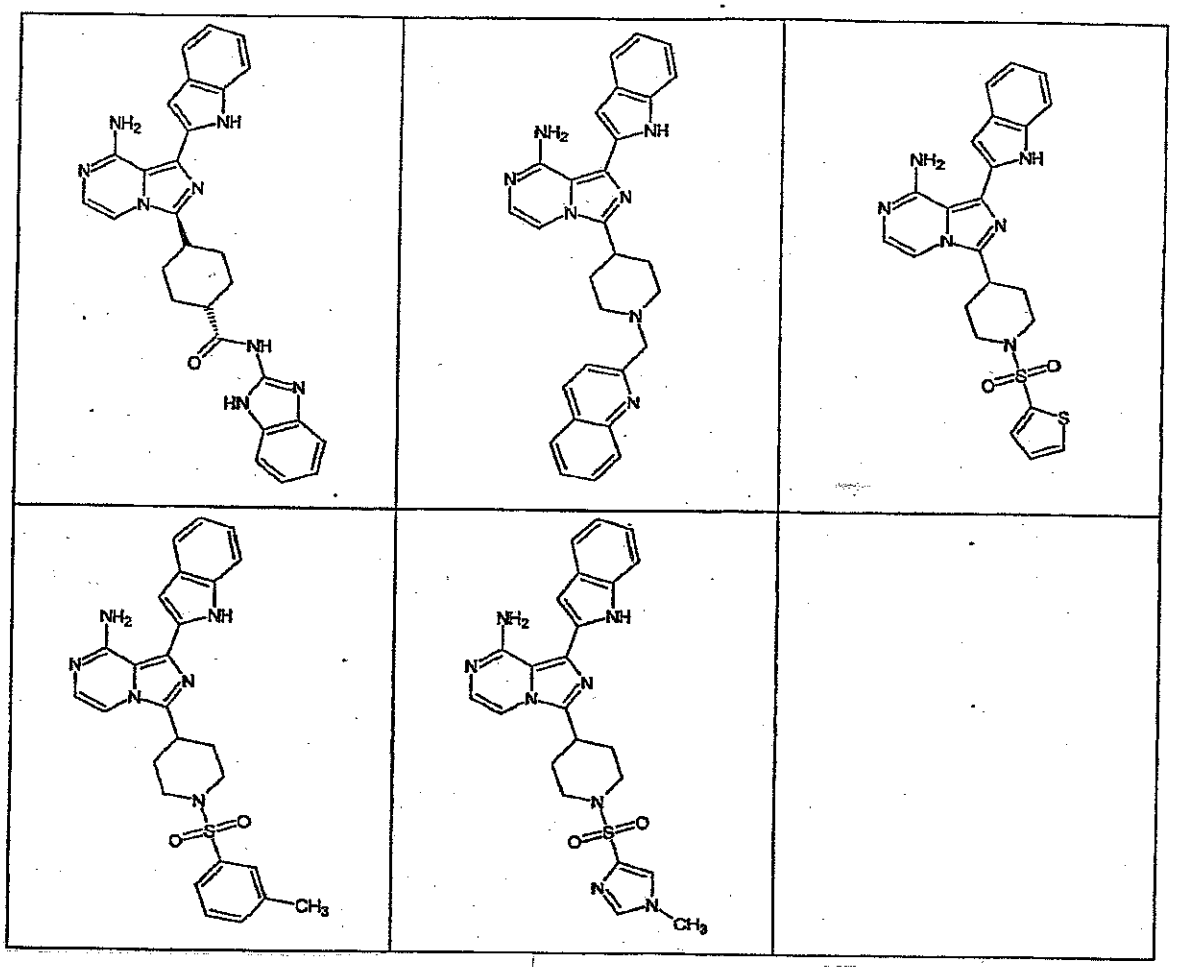


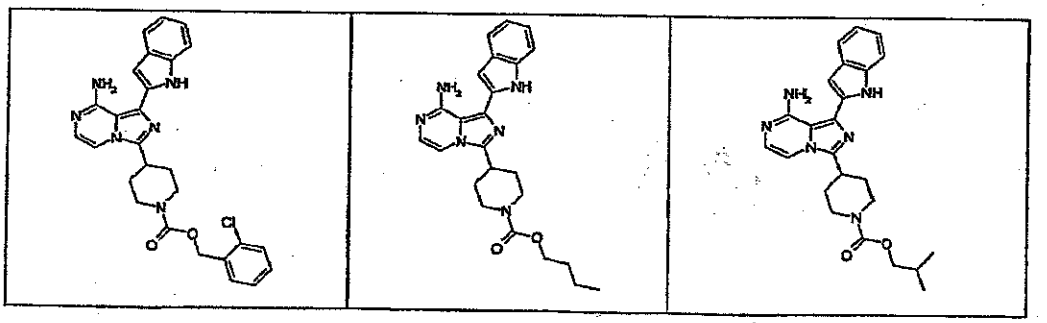


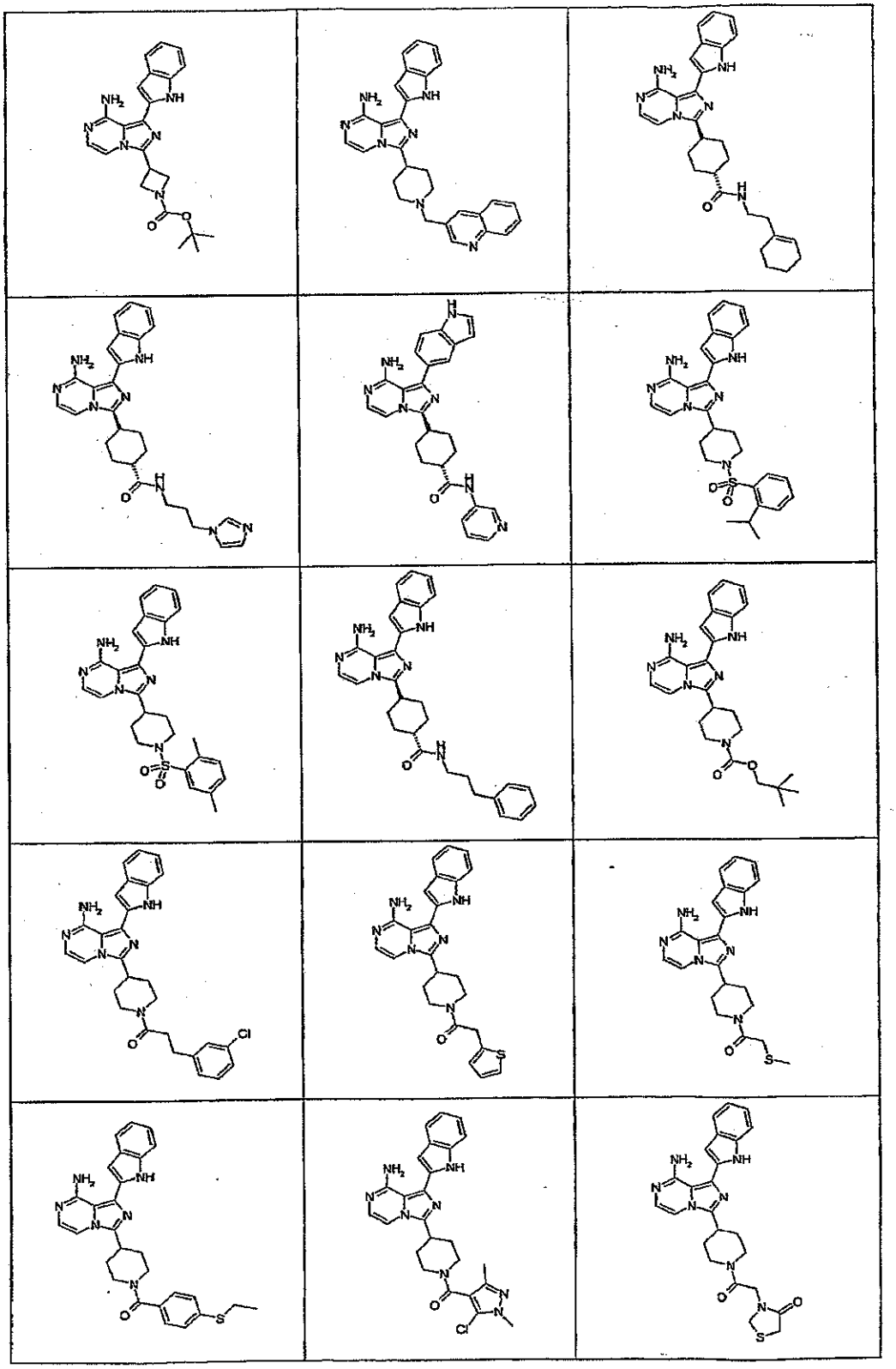


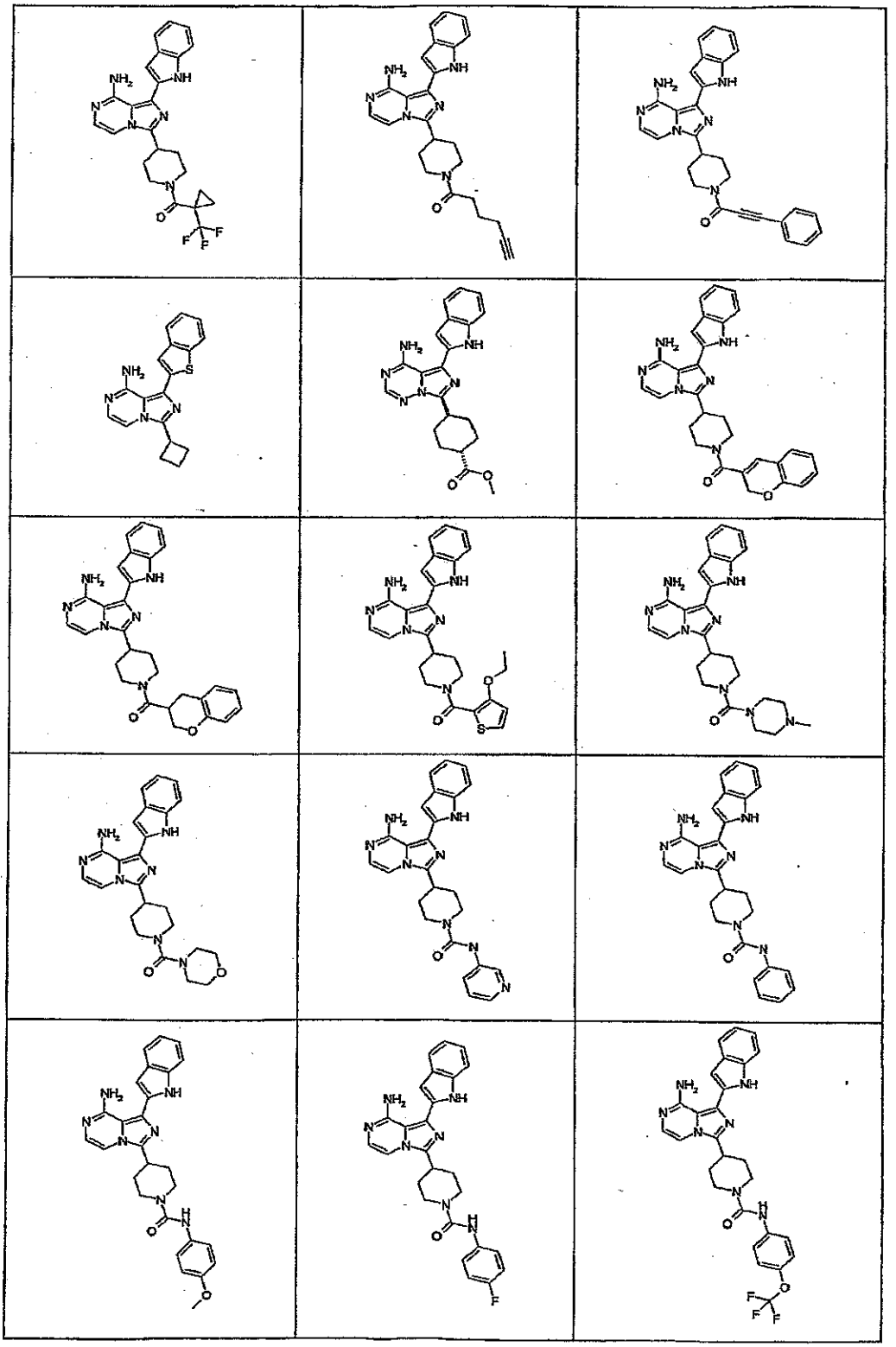


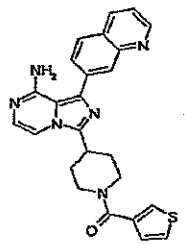
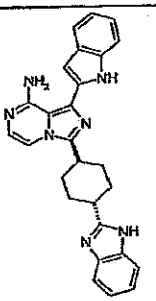
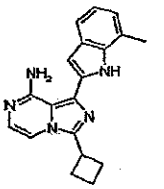
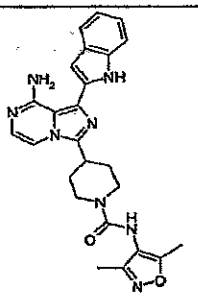
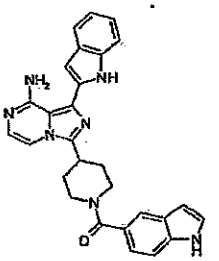
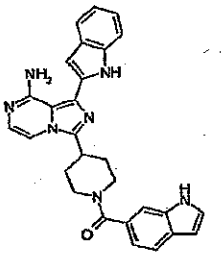
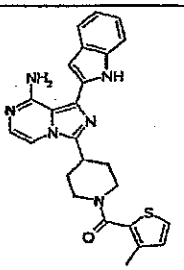
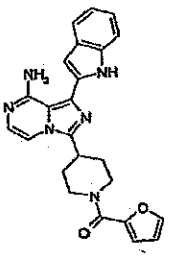
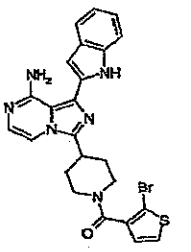
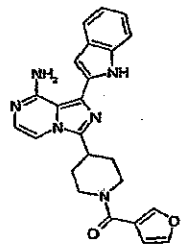
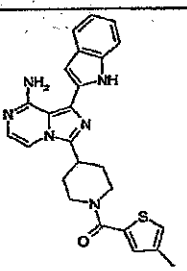
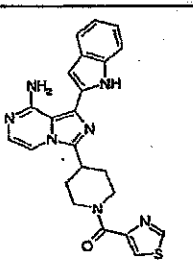
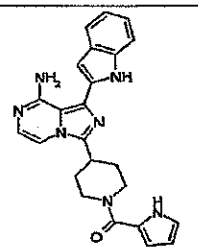
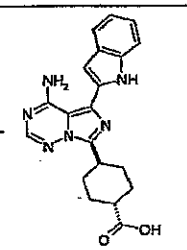
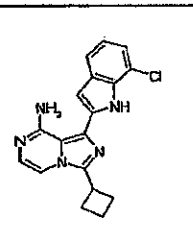


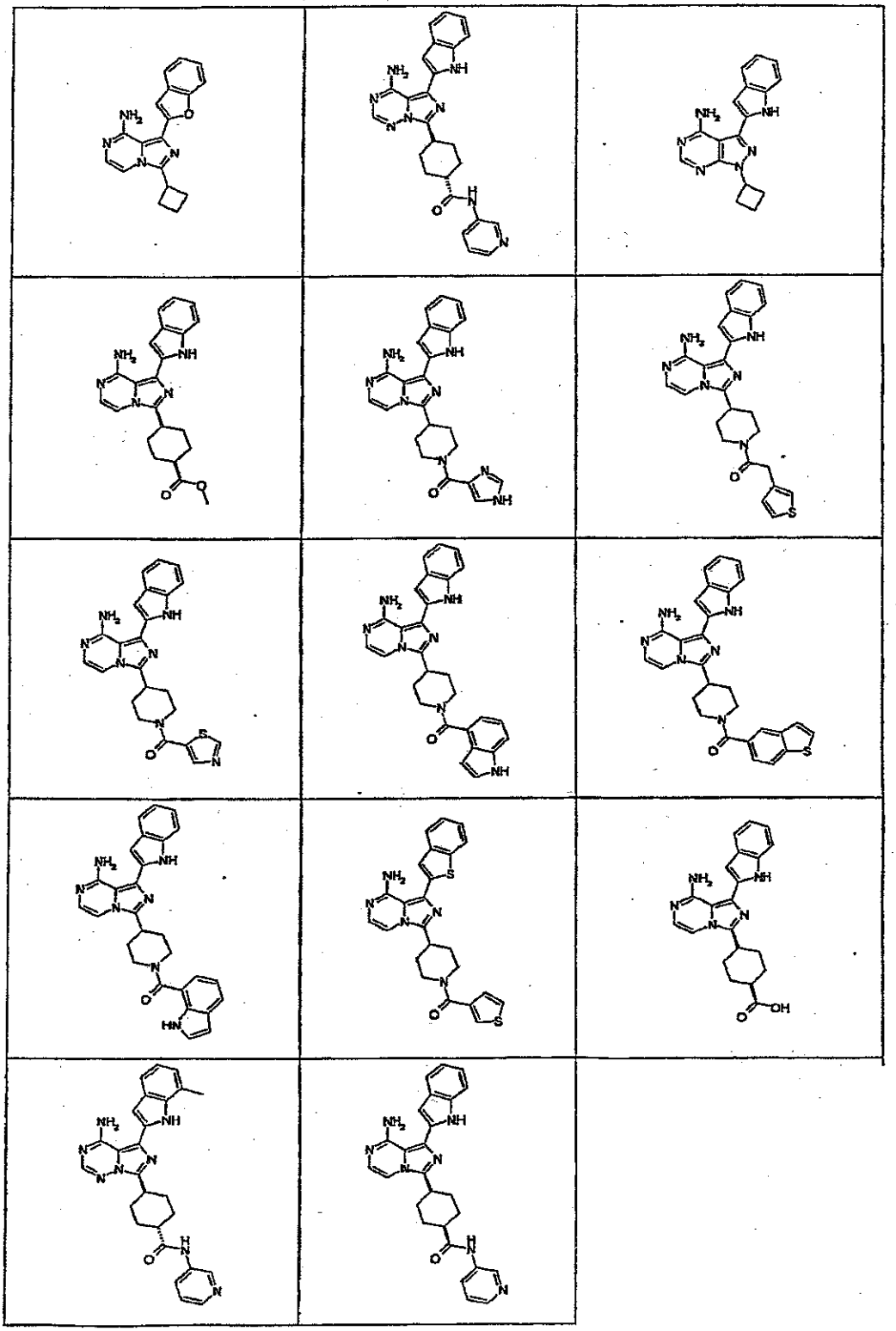


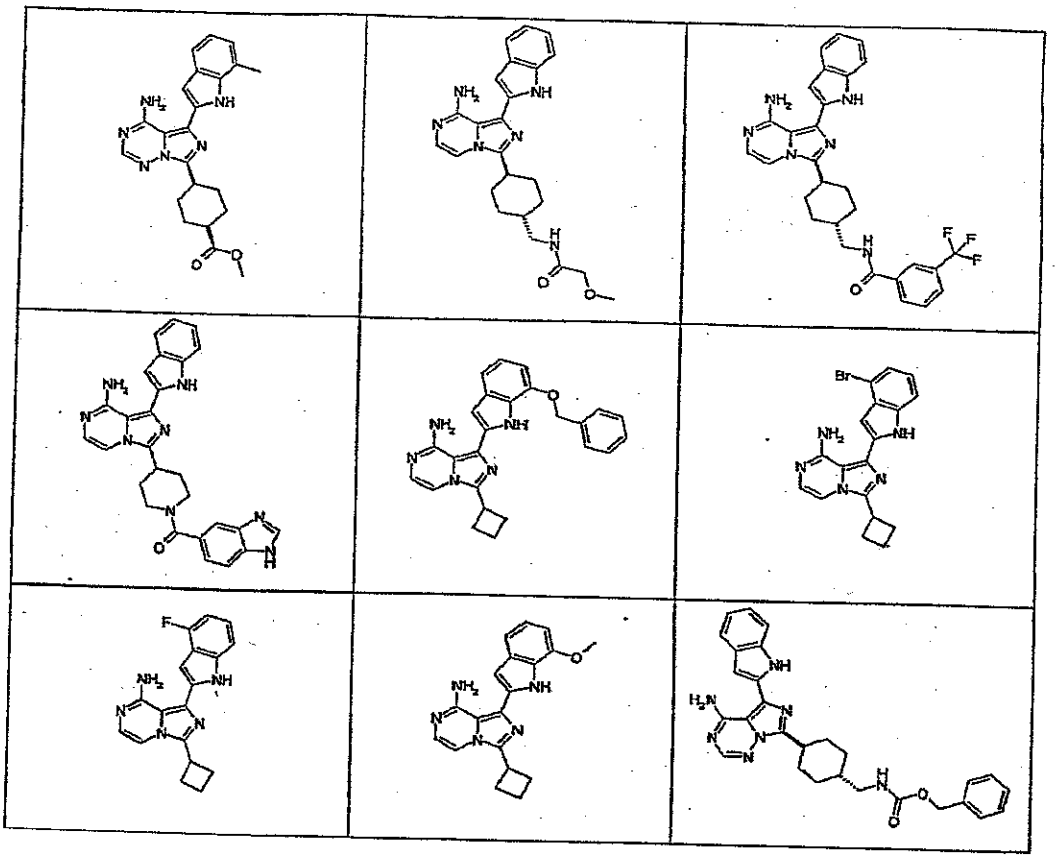


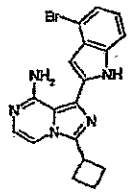
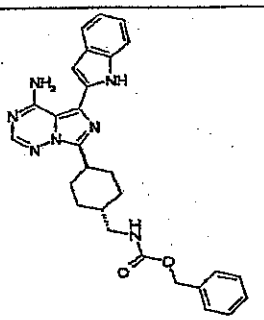
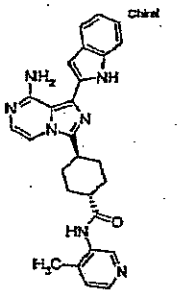
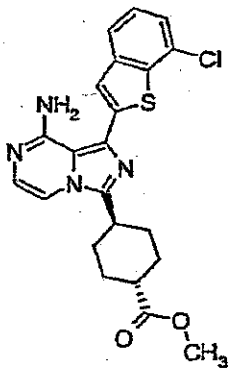
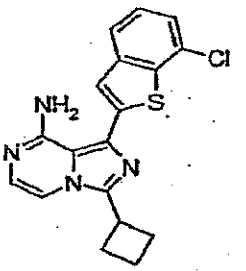
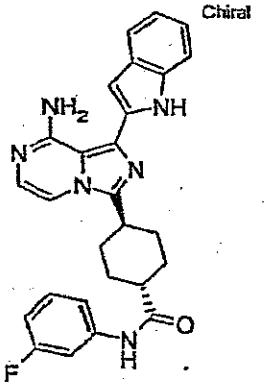
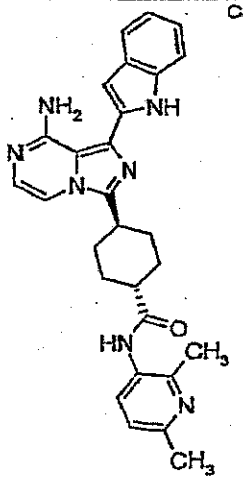
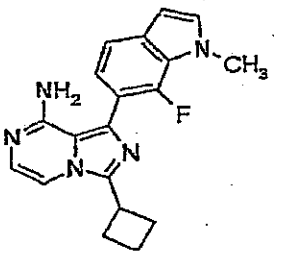
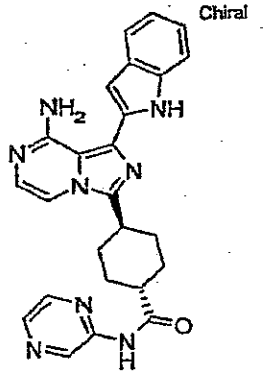


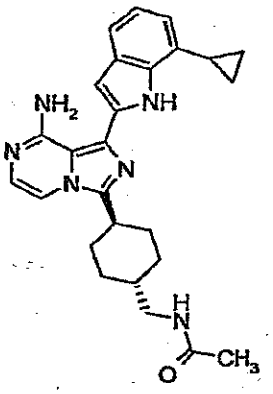
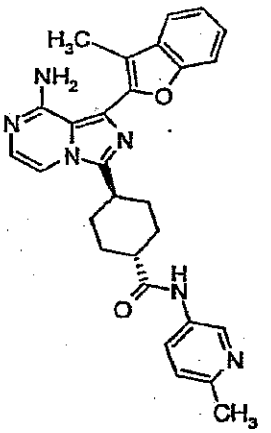
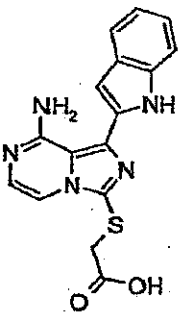
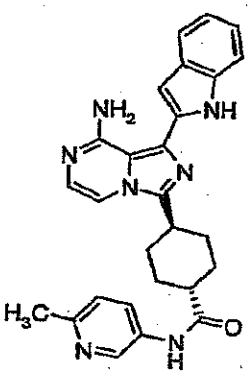
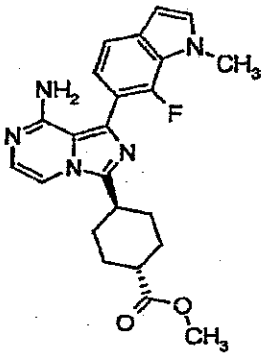
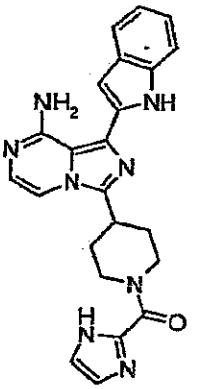
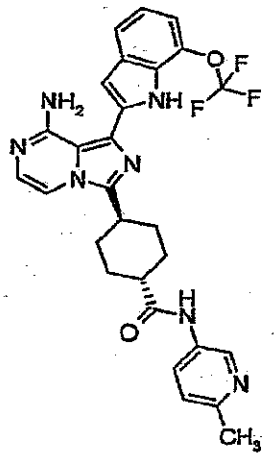


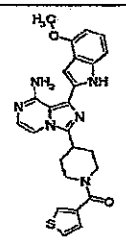
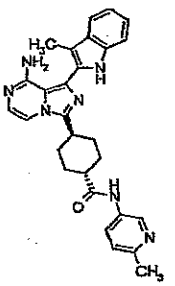
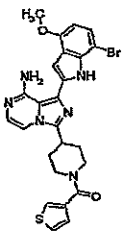
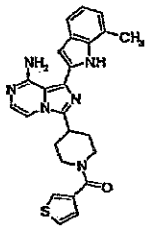
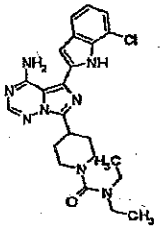
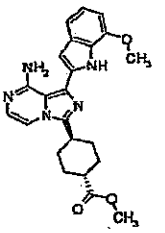
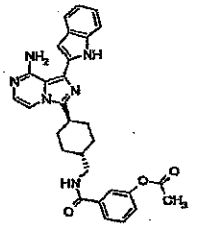
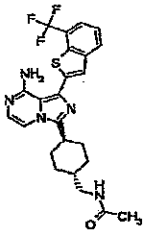
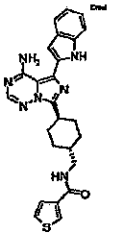
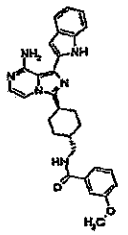
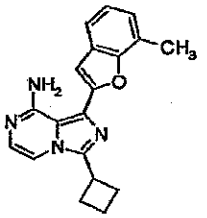
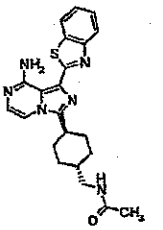
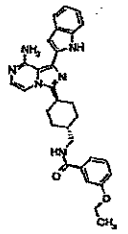
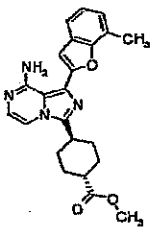
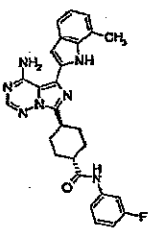
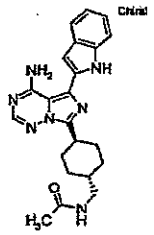
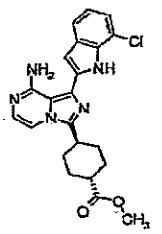
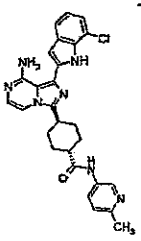
		
		
		
		
		

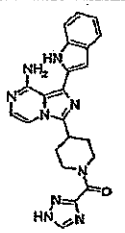
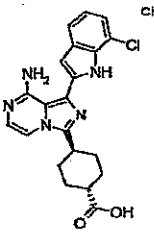
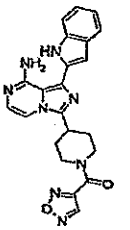
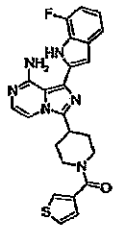
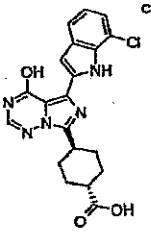
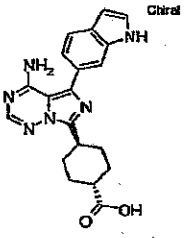
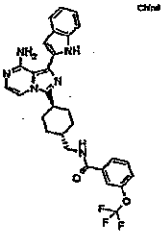
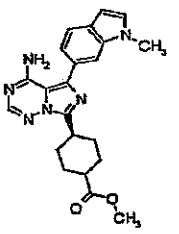
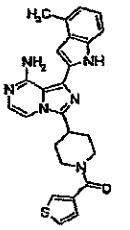
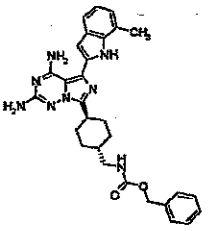
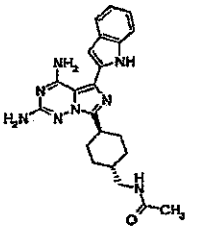
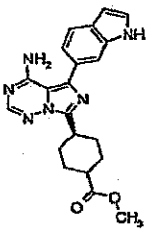
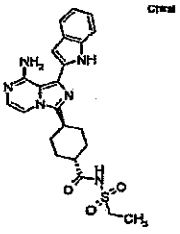
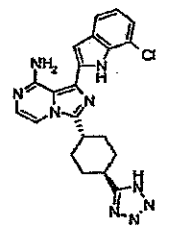
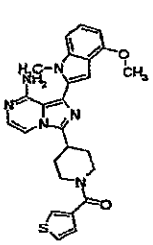
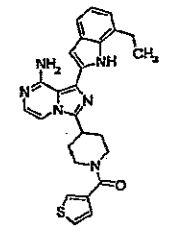
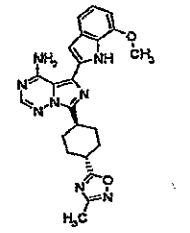
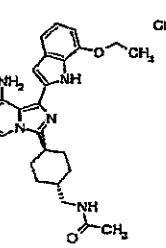


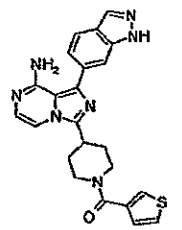
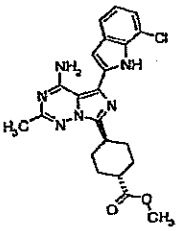
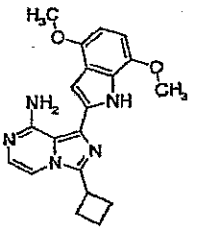
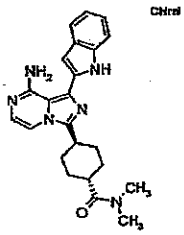
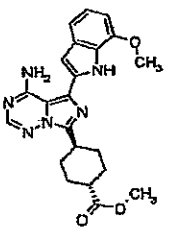
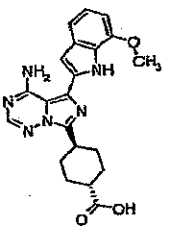
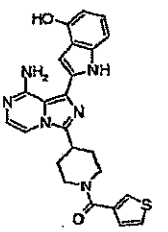
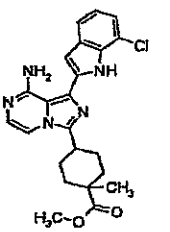
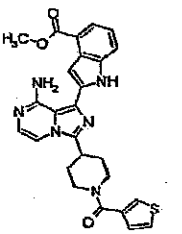
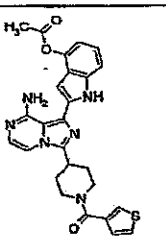
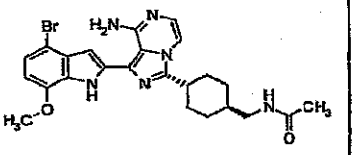
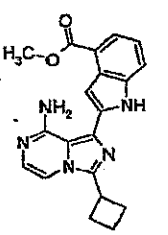
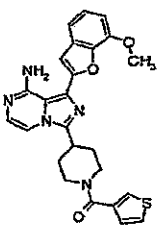
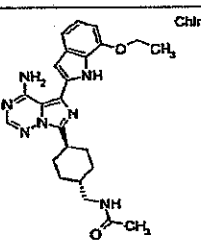
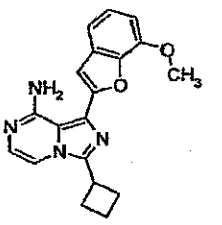
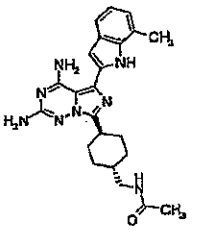
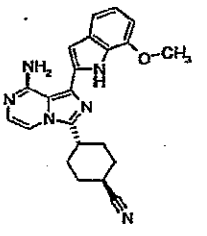
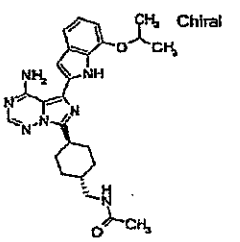


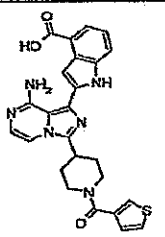
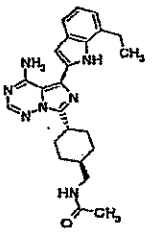
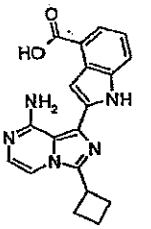
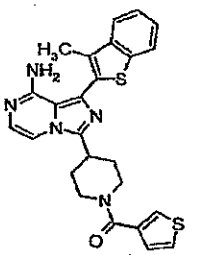
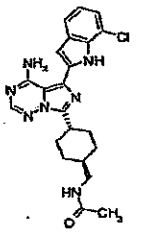
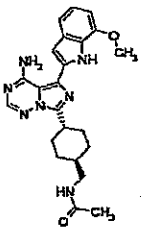
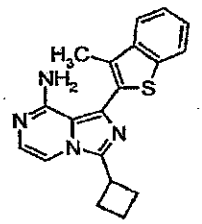
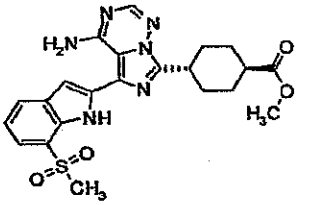
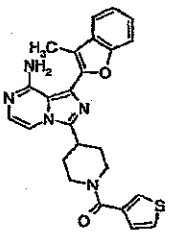
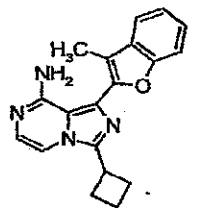
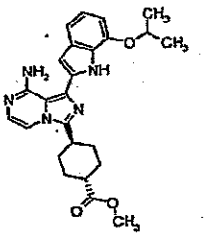
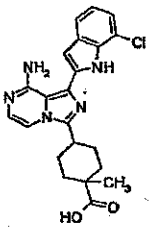
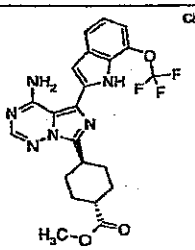
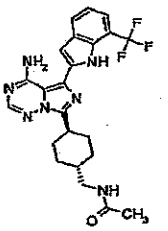
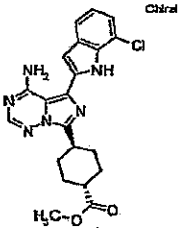
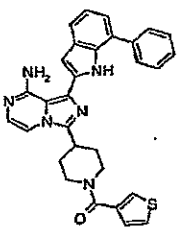
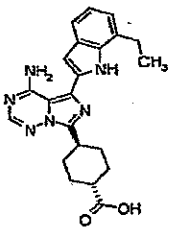
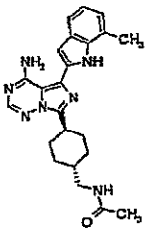
		
		
		

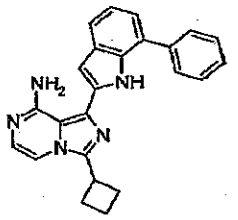
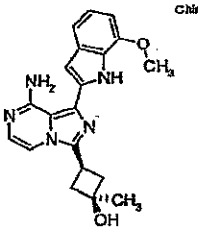
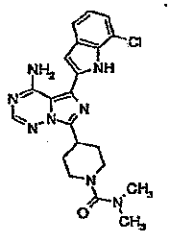
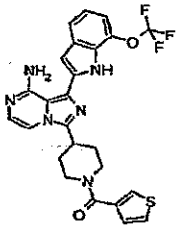
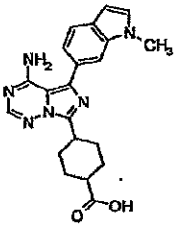
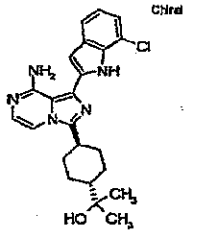
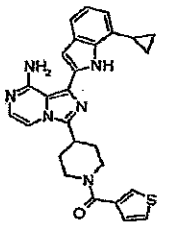
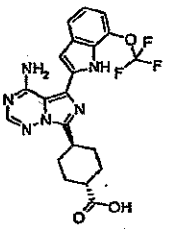
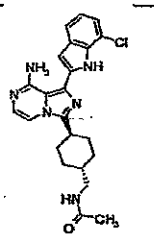
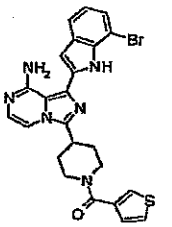
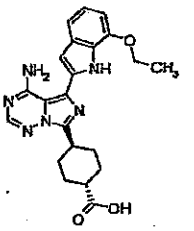
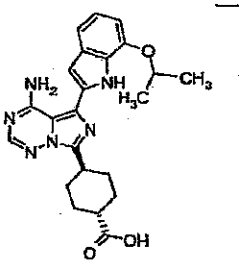
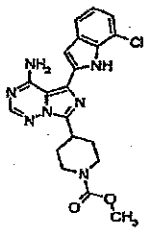
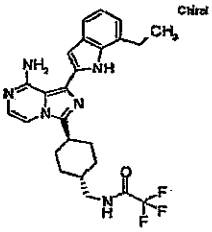
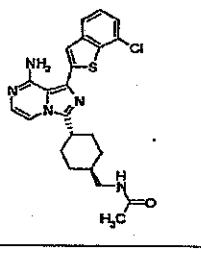
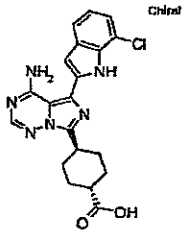
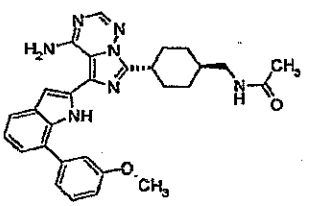
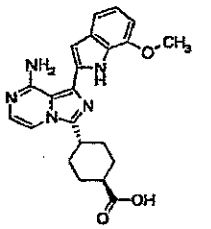
		
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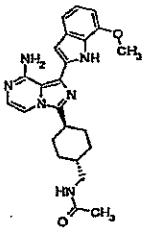
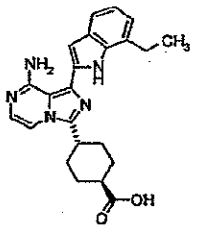
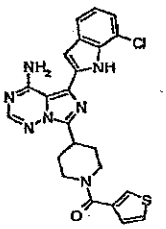
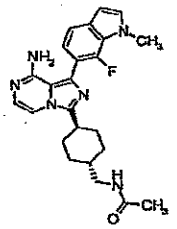
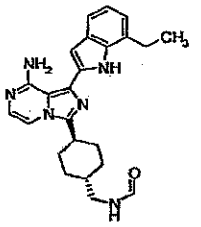
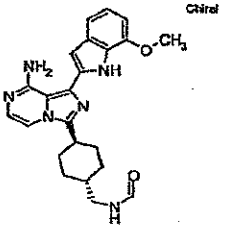
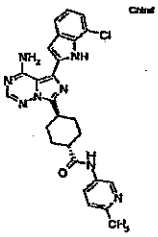
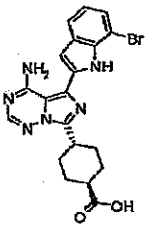
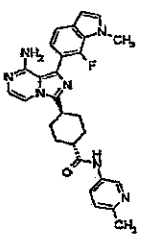
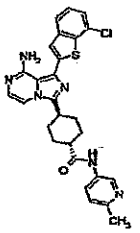
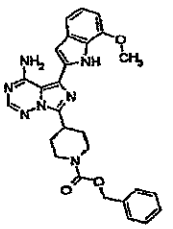
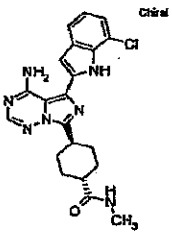
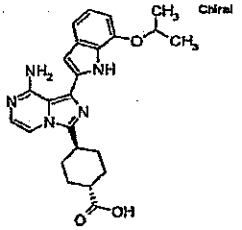
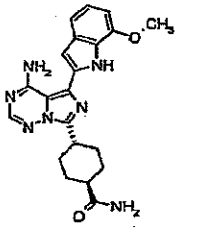
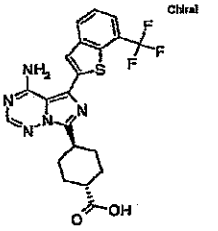
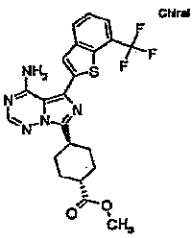
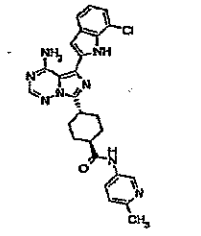
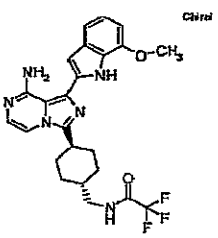
		
		
		
		
		
		

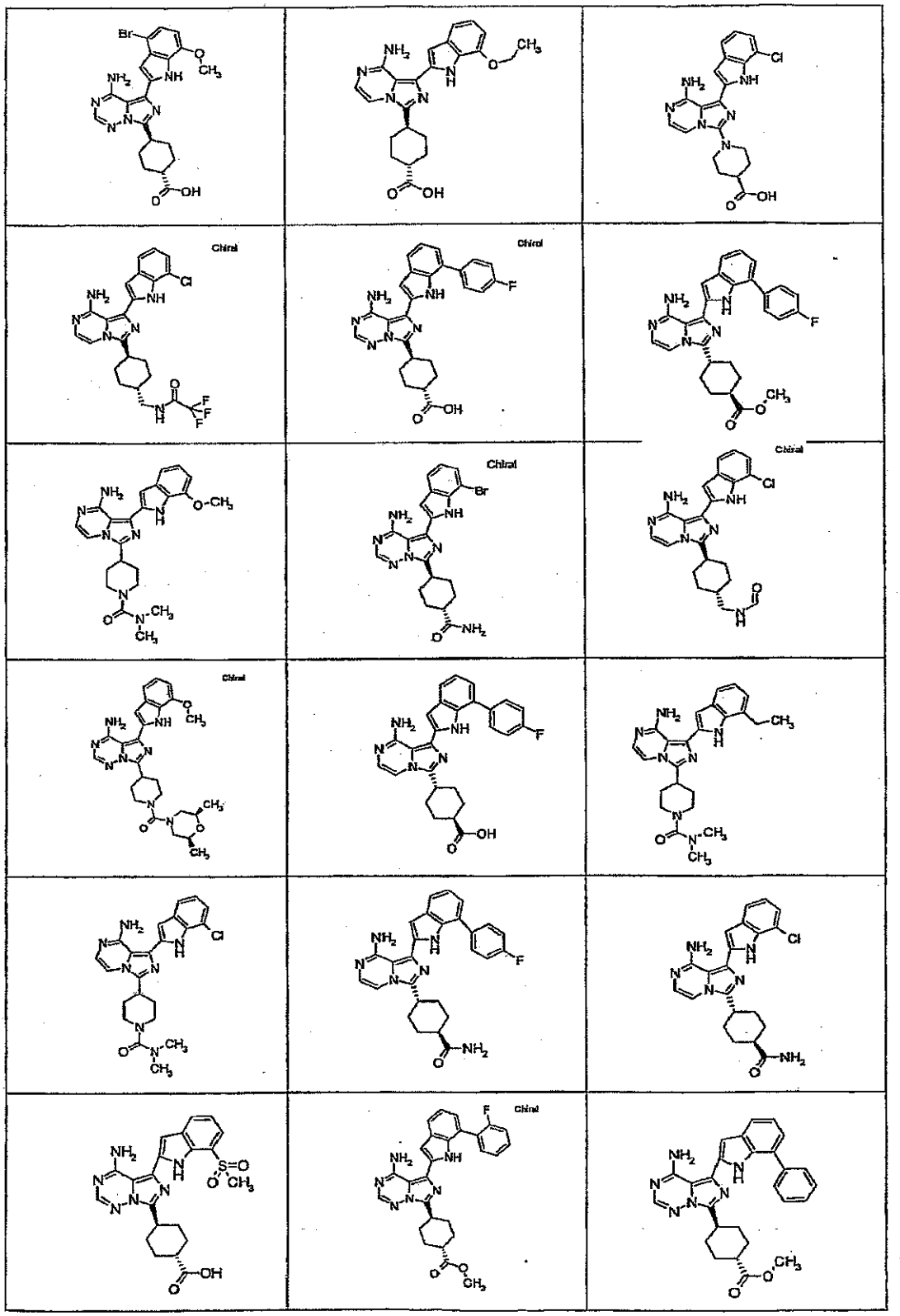
		
		
		
		
		
		
		

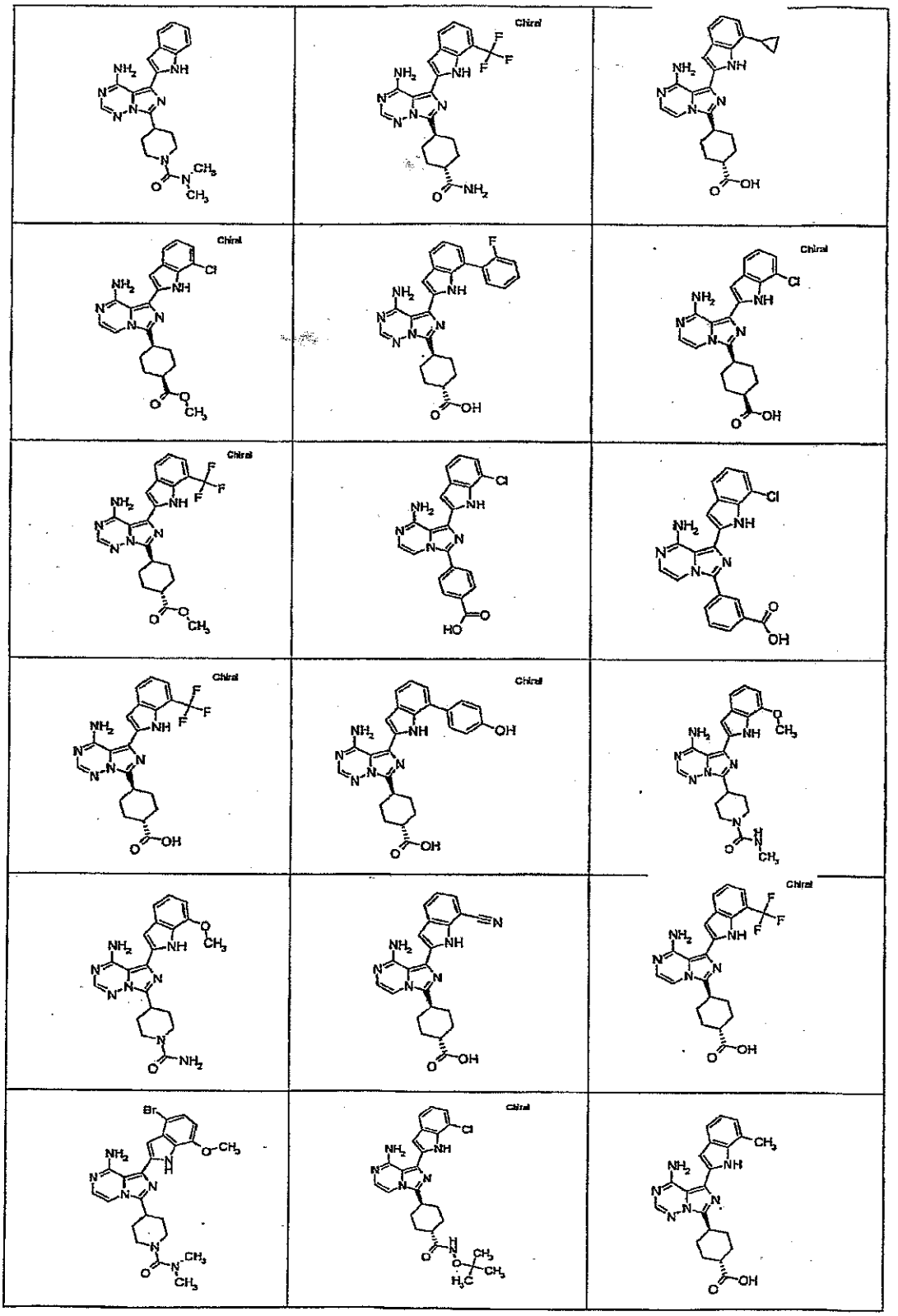
		
		
		
		
		
		

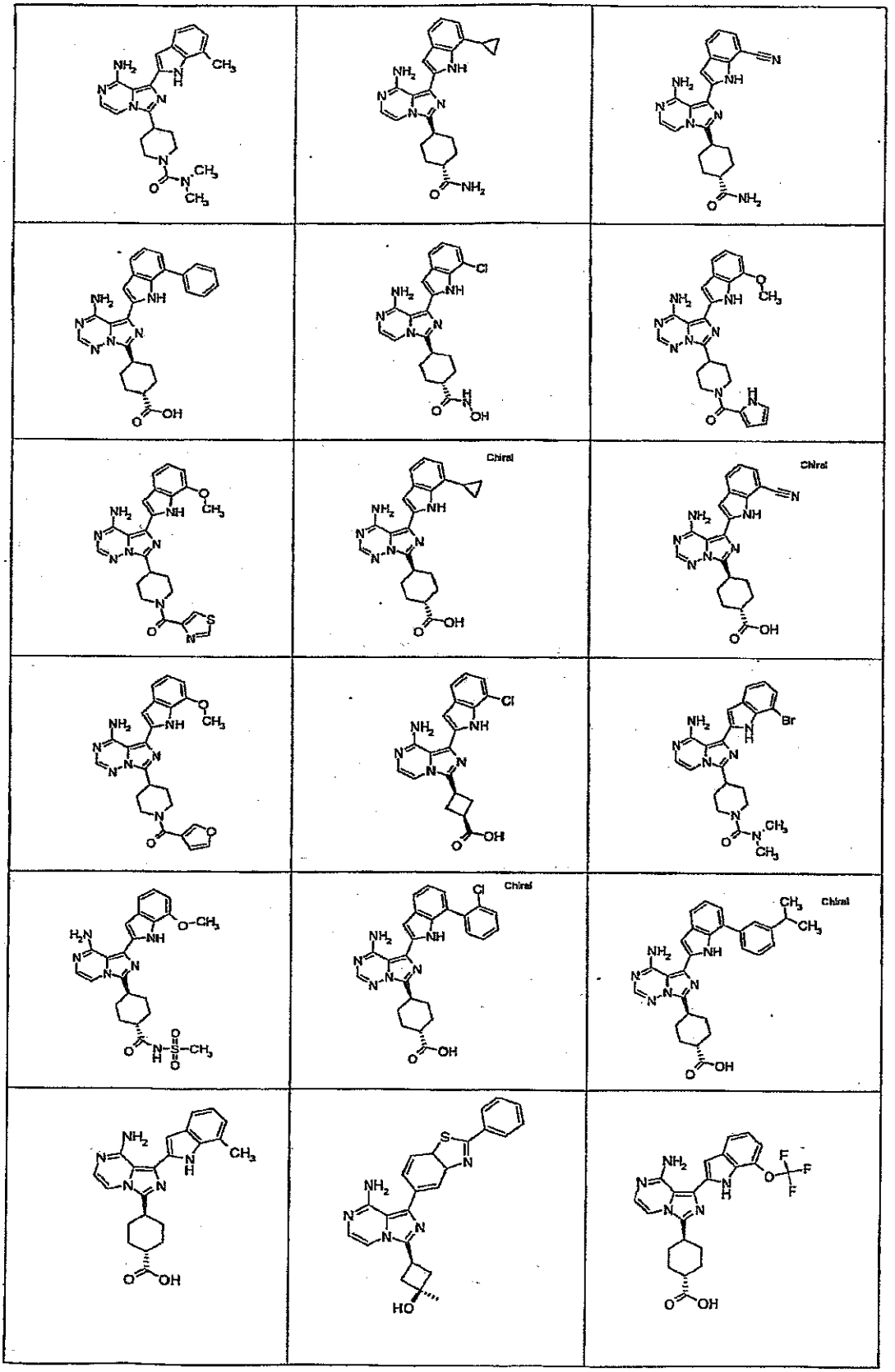
		
		
		
		
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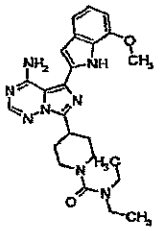
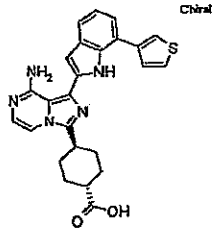
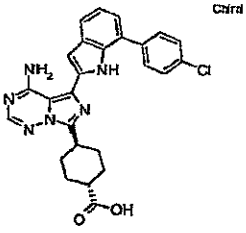
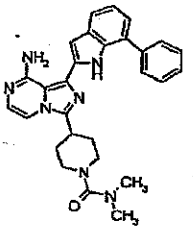
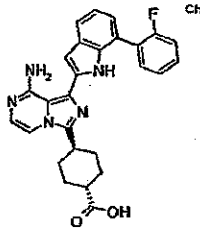
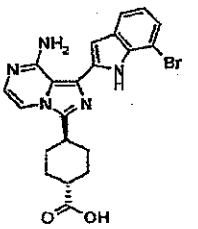
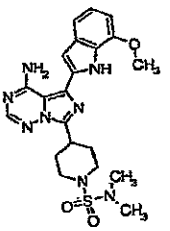
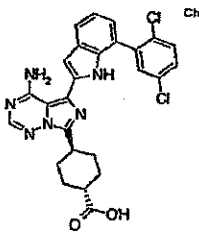
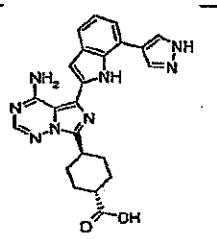
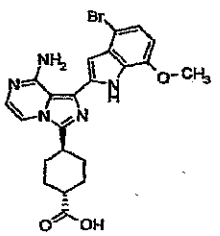
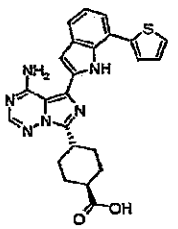
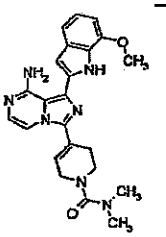
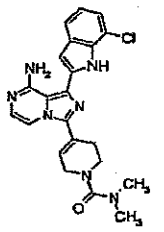
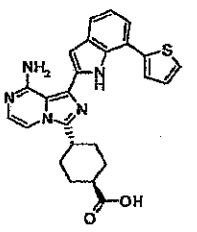
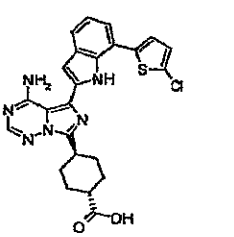
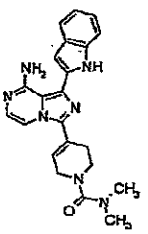
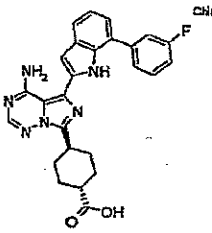
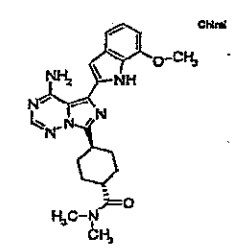
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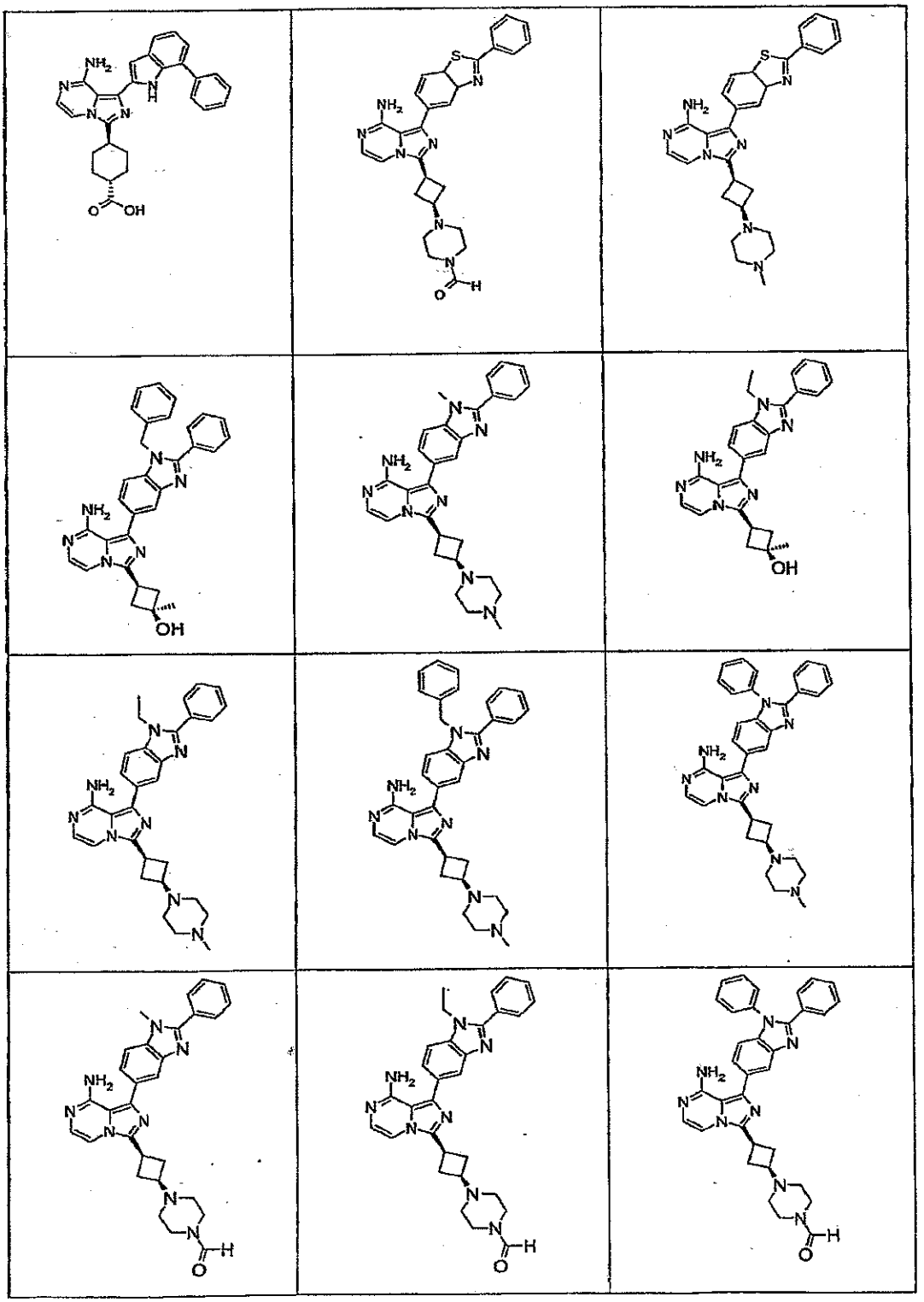
		
		
		
		
		
		

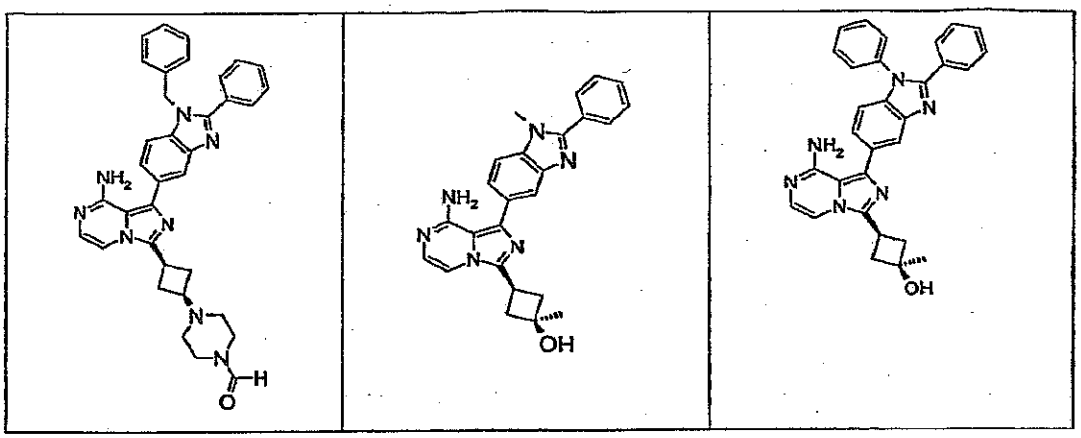


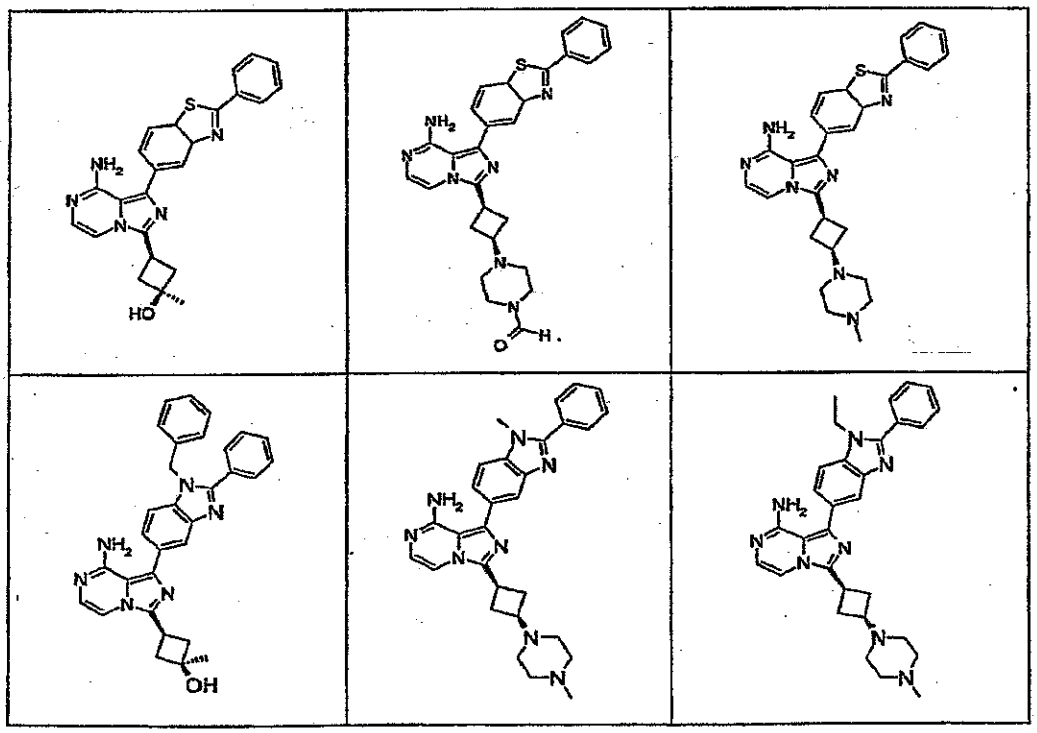


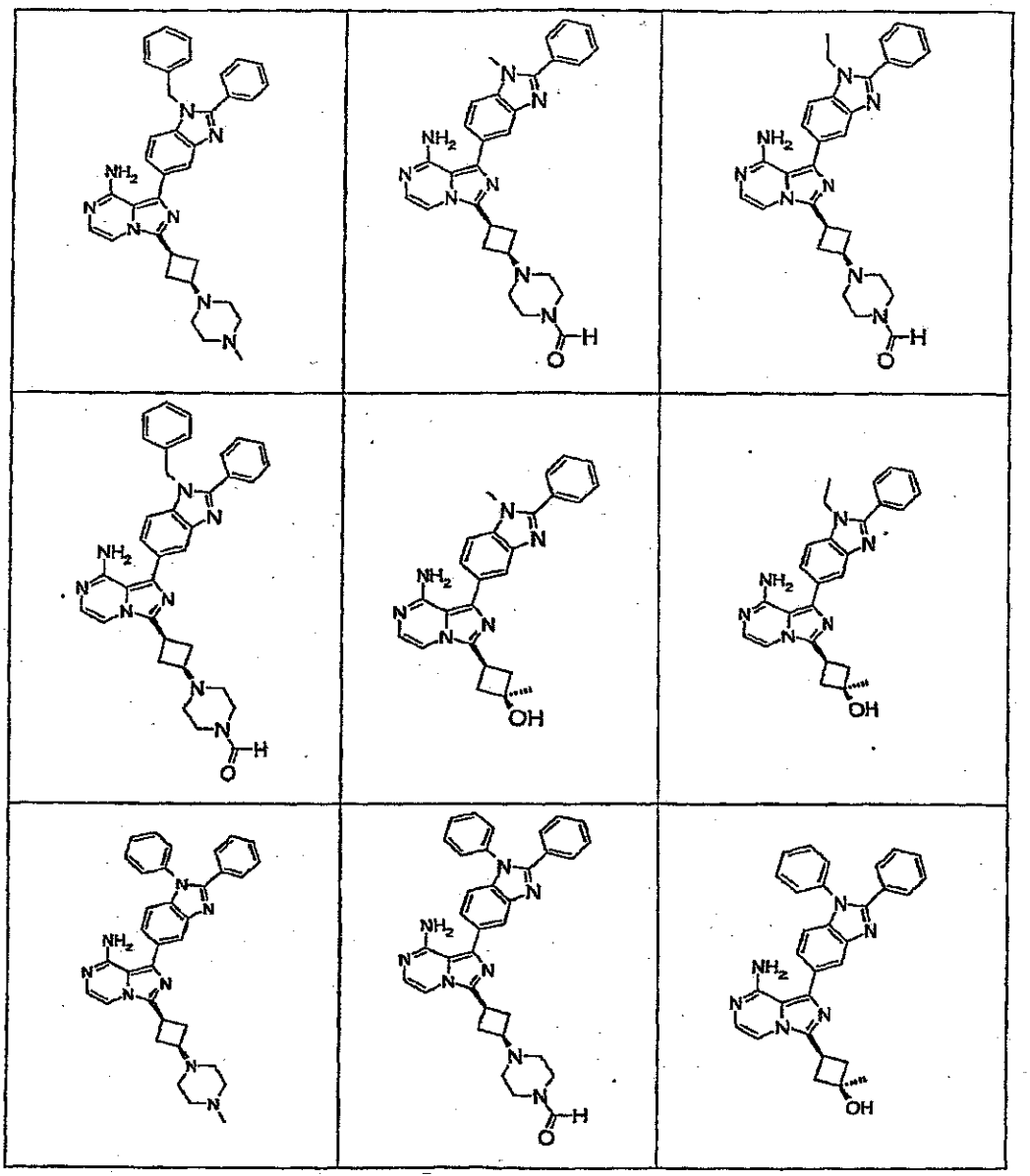


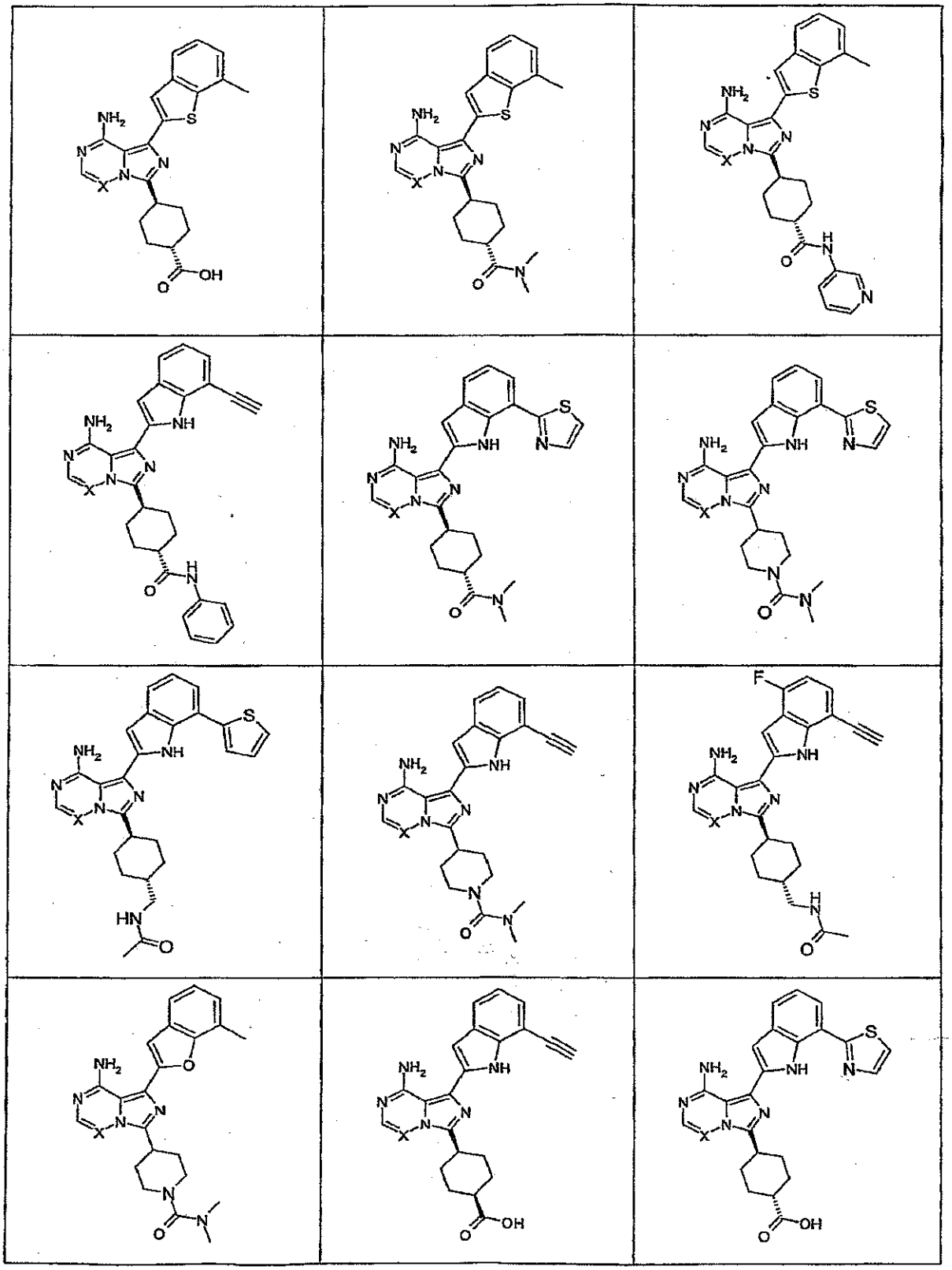
		
		
		
		
		
		

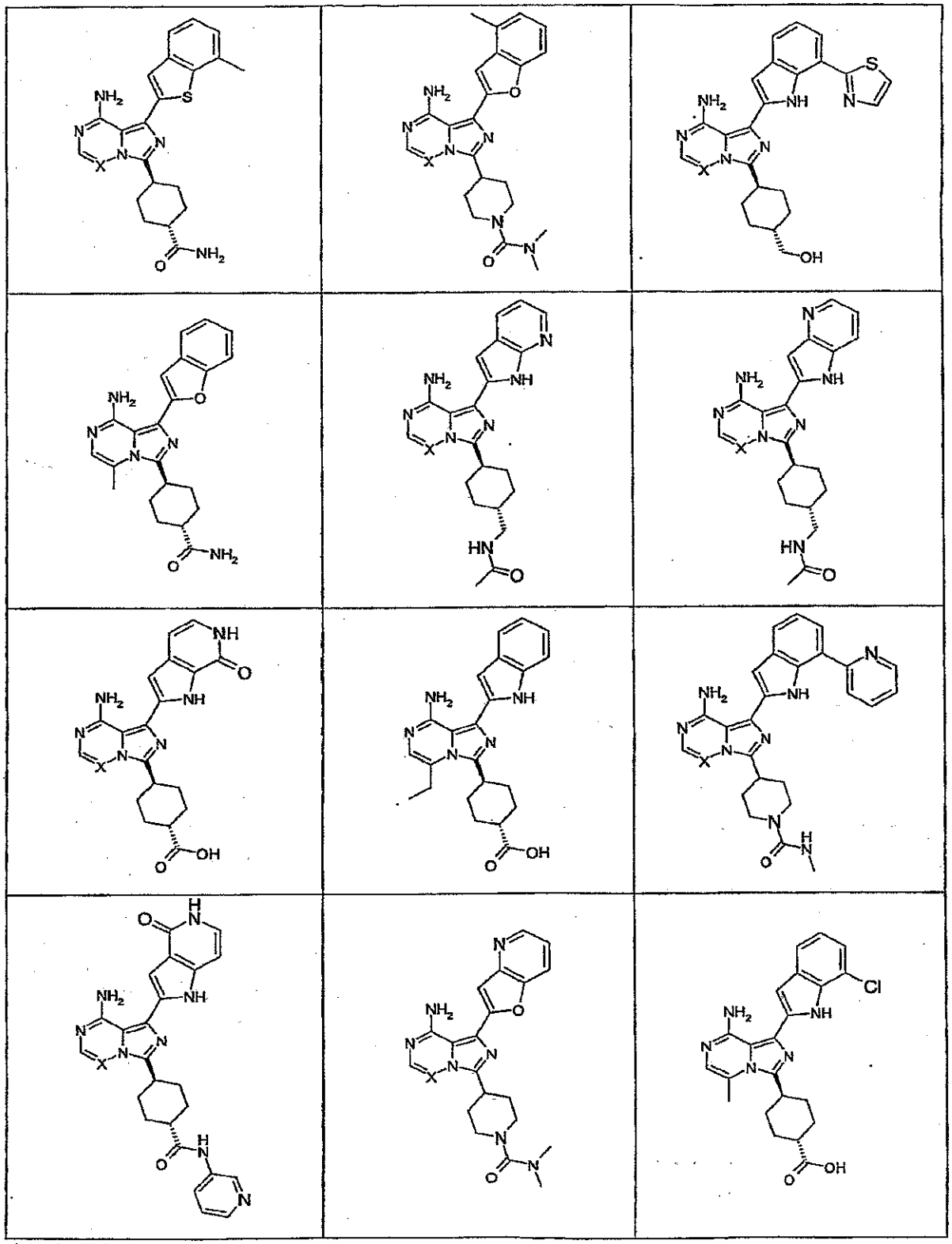








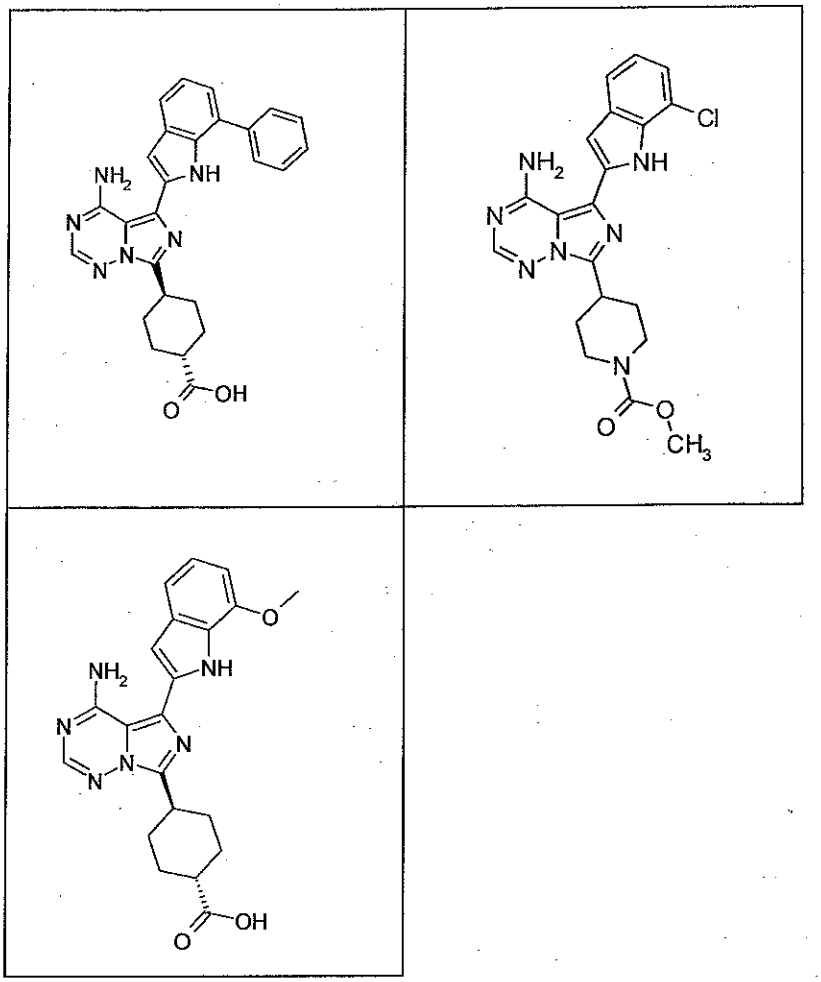




wherein X is N or CH;

or a pharmaceutically acceptable salt thereof.

Claim 2. The compound according to claim 1, consisting of any one of the following structures



or a pharmaceutically acceptable salt thereof.

Claim 3. A composition comprising a compound according to any one of claims 1 and 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Claim 4. Use of the compound according to any one of claims 1 and 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of hyperproliferative disorder.

Claim 5. The use according to claim 4, wherein the hyperproliferative disorder is breast cancer, lung cancer, non-small cell lung cancer, kidney cancer, renal cell carcinoma, prostate cancer, cancer of the blood, liver cancer, ovarian cancer, thyroid cancer, cancer of the GI tract, lymphoma, mantle cell lymphoma, or endometrial cancer.