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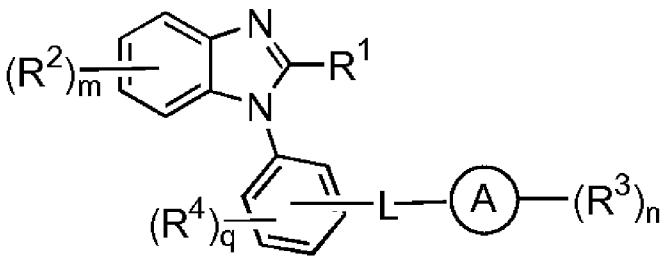
(54) **Title**: SUBSTITUTED BENZIMIDAZOLE COMPOUNDS AS COT KINASE INHIBITORS



(I)

(57) **Abstract**: Substituted benzimidazole compounds or pharmaceutically acceptable salts thereof are provided, which are useful for treating or preventing diseases, conditions and/or disorders such as asthma, osteoarthritis, rheumatoid arthritis, pain and neurodegenerative diseases by inhibiting Cancer Osaka Thyroid kinase.

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SUBSTITUTED BENZIMIDAZOLE COMPOUNDS AS COT KINASE INHIBITORS

This application claims benefit of Indian provisional application No(s). 943/MUM/2011 filed on March 28, 2011; 1952/MUM/2011 filed on July 06, 2011; and US provisional application No(s). 61/470,583 filed on April 01, 2011; 61/509,214 filed on July 19, 201; all of which are hereby incorporated by reference in their entirety.

Technical Field

The present patent application relates to substituted benzimidazole compounds and their use in treating or preventing diseases, conditions and/or disorders by inhibiting Cancer Osaka Thyroid kinase (COT-kinase).

Background of the Invention

Cancer Osaka Thyroid (COT) kinase is a protein serine/threonine kinase which phosphorylates the OH group of serine or threonine. It is classified as mitogen-activated protein (MAP) kinase kinase kinase 8 belonging to the MAP kinase kinase kinase family of enzymes. In humans it is encoded by the MAP3K8 gene. COT was originally identified as an oncogene during SHOK cell transfection of human genomic DNA [*Proc. Natl. Acad. Sci. U. S. A.* (1990), 87, 2409-2413 and *Mol. Cell. Biol.* (1991), 11, 4088-4096]. Subsequently its murine homologue, called Tpl2 (Tumor Progression Locus), was identified as a target for proviral integration in MoMuLV-induced rat T cell lymphomas and MMTV-induced mammary carcinomas [*Proc. Natl. Acad. Sci. USA* 1993, 90, 2251-2255]. It was later implicated in T lymphocyte activation [*J. Biol. Chem* (1998), 273, 14099-14106]. COT/Tpl2 that belongs to the MAP3K8 family can activate both the extracellular signal–regulated kinase (ERK) and the c-jun N-terminal kinase (JNK) signaling pathways. It has been implicated in NF-κB activation through IκB kinase complex or degradation of the inhibitory p105 protein. Tsichlis and colleagues reported that the COT/Tpl2 kinase plays an important role in LPS signaling [*Cell.* (2000), 103, 1071-1083., and *EMBO J.* (2002), 21, 4831-4840].

COT/Tpl2 is expressed primarily in spleen, thymus, and lung tissue and is a key component in activation of T cells and macrophages, resulting in TNF-α production from these cell types. COT/Tpl-2$^{-/-}$ macrophages have a specific defect in

LPS stimulated activation of the ERK1/2 mitogen activated protein kinase (MAPK) pathway that affects TNF-α production. As a consequence of this, COT/Tpl-2 knockout animals are resistant to LPS/D-Galactosamine-Induced Endotoxin Shock [*Cell* (**2000**), *103*, 1071-1083].

In rheumatoid arthritis fibroblast-like synoviocytes, COT/Tpl-2 modulates cyclooxygenase-2 expression and the production of IL-6, IL-8, and the matrix metalloproteinases MMP-1 and MMP-3. Inhibition of COT/Tpl2 in primary human cell types can decrease the production of TNF-α and other pro-inflammatory mediators during inflammatory events [*J. Biol. Chem.* (2007), 282, pp. 33295–33304]

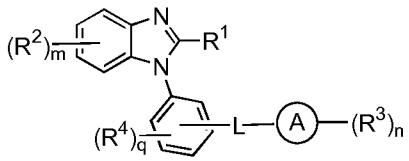
TNF-α is believed to be responsible for initiation of inflammation and maintenance of the disease development through induction of effector proteins such as adhesion molecules and matrix metalloproteinases (MMPs) that contributes to cartilage breakdown and bone erosion. The control of TNF-α, therefore, is a major goal in treating the progression of Rheumatoid Arthritis [*J. Med.* (2001), 344, 907., Ann. *Rev. Immunol* (2001), 19, 163., *Curr. Dir. Autoimmun* (2001), 3, 188].

COT/tpl-2 is considered to be a promising target to develop new and improved anti-inflammatory drugs [Curr Opin Cell Biol. (2009), 21, 317-324, and Curr Med Chem (2007), 14, 2214-2234]. So far, there are a few biologics which targeted TNF-α in man, such as adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade) have demonstrated significant efficacy in the treatment of rheumatoid arthritis. However these agents require administration via injection or infusion hence, identification of an orally available small molecule (chemical) therapy would be desirable. Identification of an inhibitor for COT kinase, which would potentially alter the production of pro-inflammatory cytokines for example TNF-α, have a potential to be a novel and effective small molecule therapy for the treatment of various inflammatory diseases.

PCT publication numbers WO2005110410, WO2006124692, WO2006124944 & WO2007117465 disclose various classes of heterocyclic compounds which are shown to be COT kinase inhibitors and may be useful for the treatment of various diseases such as rheumatoid arthritis.

Summary of the Invention

The present invention relates to compound of formula (I):



(I)

or pharmaceutically acceptable salt thereof,

wherein,

A is aryl, heteroaryl, cycloalkyl or heterocyclyl;

'L' is a bond or selected from –O-, -C(O)-, -O-$(CH_2)_p$-, -$(CH_2)_p$-O-, and -$(CH_2)_p$-;

R^1 is selected from hydrogen, halogen, nitro, cyano, hydroxyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, -$C(O)R^a$, -$C(O)NR^aR^b$, -$C(O)OR^a$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)NR^bR^c$, -$NR^aC(O)OR^b$, -$N(R^a)SO_2R^b$, -$OC(O)R^a$, -$OC(O)OR^a$ and -$OC(O)NR^aR^b$;

R^2, at each occurrence, is independently selected from cyano, halogen, -COOH, -$C(O)NR^aR^b$, -$C(O)N(R^a)SO_2R^b$, -$N(R^a)SO_2R^b$, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^3, at each occurrence, is independently selected from halogen, nitro, cyano, hydroxyl, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, -$C(O)R^a$, -$C(O)NR^aR^b$, -$C(O)OR^a$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)NR^bR^c$, -$NR^aC(O)OR^b$, -$N(R^a)SO_2R^b$, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$,-$OC(O)NR^aR^b$ and $SO_2NR^aR^b$;

R^4, at each occurrence, is independently selected from halogen, nitro, cyano, hydroxyl and substituted or unsubstituted alkyl;

R^a, R^b and R^c, which may be the same or different, are independently selected from hydrogen, halogen, hydroxyl, cyano, amino, substituted or unsubstituted alkyl,

substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocyclyl; or R^a and R^b or R^b and R^c together with the atom to which they are attached, may form cyclic ring, which may be monocyclic, bicyclic or tricyclic rings; substituted or unsubstituted; the cyclic ring may optionally contain one or more hetero atoms selected from O, N or S;

'm' is an integer ranging from 1 to 4, both inclusive;

'n' is an integer ranging from 0 to 5, both inclusive;

'p' is an integer ranging from 1 to 2, both inclusive; and

'q' is an integer ranging from 0 to 4, both inclusive.

The compounds of formula (I) may involve one or more embodiments. Embodiments of formula (I) include compounds of formula (II), as described hereinafter. It is to be understood that the embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified. It is also to be understood that the embodiments defined herein may be used independently or in conjunction with any definition, claim or any other embodiment defined herein. Thus the invention contemplates all possible combinations and permutations of the various independently described embodiments.

According to one embodiment, specifically provided are compounds of formula (I), in which A is aryl, preferably phenyl.

According to another embodiment, specifically provided are compounds of formula (I), in which A is heteroaryl, preferably pyrazolyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which A is heterocyclic ring, preferably piperidinyl.

According to yet another embodiment, specifically provided are compounds of formula (I) in which L is a bond.

According to yet another embodiment, specifically provided are compounds of the formula (I) in which L is –O- .

According to yet another embodiment, specifically provided are compounds of formula (I) in which L is -C(O)-.

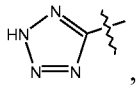
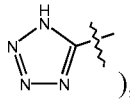
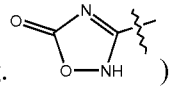
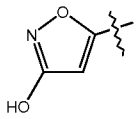
According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is –COOH.

According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is $-C(O)NR^aR^b$, wherein R^a is hydrogen and R^b is hydrogen or hydroxyl.

According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is $-C(O)N(R^a)SO_2R^b$, wherein R^a is hydrogen and R^b is alkyl (e.g. methyl), haloalkyl (e.g. trifluoromethyl) or aryl (e.g. phenyl).

According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is $N(R^a)SO_2R^b$, wherein R^a is hydrogen and R^b is $C_{1\text{-}8}$alkyl (e.g. methyl or isopropyl).

According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is substituted aryl, preferably hydroxyl substituted phenyl.

According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is substituted or unsubstituted heteroaryl or heterocyclic ring wherein heterocyclic or heteroaryl ring is selected from tetrazolyl (e.g.  , ), oxadiazolyl (e.g. ) and hydroxyl substituted isoxazolyl (e.g. )

According to yet another embodiment, specifically provided are compounds of formula (I) in which R^2 is halogen, preferably fluorine.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^3 is same or different at each occurrence and independently selected from halogen (e.g. F, Cl, Br or I), cyano, $CONH_2$, $COCH_3$, SO_2NH_2, alkyl (e.g. methyl), alkoxy (e.g. methoxy, ehthoxy, propran-2-yloxy), haloalkyl (e.g. trifluoromethyl), and haloalkoxy (e.g. trifluoromethoxy).

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^3 is OR^a, wherein R^a is hydrogen or cycloalkyl (e.g. cyclopentyl).

According to yet another embodiment specifically provided are compounds of formula (I), in which R^4 is selected from halogen (e.g. F, Cl, Br or I).

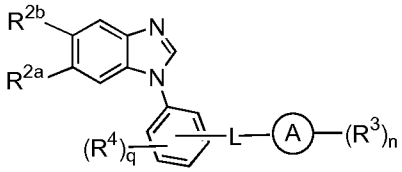
According to yet another embodiment specifically provided are compounds of formula (I), in which m is 1 or 2.

According to yet another embodiment specifically provided are compounds of formula (I), in which n is 0, 1 or 2.

According to yet another embodiment, specifically provided are compounds of formula (I), in which q is 0 or 1

The invention also provides a compound of formula (II), which is an embodiment of a compound of formula (I).

Accordingly, the invention provides the compound of formula (II);



(II)

or pharmaceutically acceptable salt thereof,

wherein,

'A' is C_{6-14} aryl, 5-14 membered heteroaryl or 3-15 membered heterocyclyl;

'L' is a bond or selected from -O- and -C(O)-;

R^{2a} is independently selected from -COOH, $-C(O)NR^aR^b$, $-C(O)N(R^a)SO_2R^b$, $-N(R^a)SO_2R^b$, substituted or unsubstituted C_{6-14}aryl, substituted or unsubstituted 3-15 membered heterocyclyl ring and substituted or unsubstituted 5-14 membered heteroaryl;

R^{2b} is selected from hydrogen, halogen, nitro, cyano, hydroxyl and substituted or unsubstituted C_{1-8}alkyl;

R^3, at each occurrence, is independently selected from halogen, cyano, hydroxyl, $-C(O)R^a$, $-C(O)NR^aR^b$, $-C(O)OR^a$, $-NR^aR^b$, $-NR^aC(O)R^b$, $N(R^a)SO_2R^b$, $-OR^a$, and $SO_2NR^aR^b$, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{1-8}alkoxy, substituted or unsubstituted haloC_{1-8}alkyl, substituted or unsubstituted haloC_{1-8}alkoxy and substituted or unsubstituted C_{3-12}cycloalkyl;

R^4, at each occurrence, is independently selected from halogen, cyano, hydroxyl and substituted or unsubstituted C_{1-8}alkyl;

R^a and R^b, which may be the same or different, are independently selected from hydrogen, hydroxyl, substituted or unsubstituted C_{1-8}alkyl, substituted or

unsubstituted C_{1-8}alkoxy, substituted or unsubstituted haloC_{1-8}alkyl, substituted or unsubstituted haloC_{1-8}alkoxy, substituted or unsubstituted C_{3-12}cycloalkyl, substituted or unsubstituted C_{6-14}aryl, substituted or unsubstituted 3-15 membered heterocyclyl, substituted or unsubstituted 5-14 membered heteroaryl and; or R^a and R^b together with the atom to which they are attached, may form cyclic ring, which may be monocyclic, bicyclic or tricyclic rings; substituted or unsubstituted; the cyclic ring may optionally contain one or more hetero atoms selected from O, N or S;

'n' is an integer ranging from 0 to 5, both inclusive; and

'q' is an integer ranging from 0 to 4, both inclusive.

The compound of formula (II) may involve one or more embodiments. It is to be understood that the embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified.

According to one embodiment, specifically provided are compounds of formula (II), in which A is C_{6-14}aryl, preferably phenyl.

According to another embodiment, specifically provided are compounds of formula (II), in which A is 5-14 membered heteroaryl, preferably pyrazolyl.

According to yet another embodiment, specifically provided are compounds of formula (II), in which A is 3-15 membered heterocyclic ring, preferably piperidinyl.

According to yet another embodiment, specifically provided are compounds of formula (II) in which L is a bond.

According to yet another embodiment, specifically provided are compounds of the formula (II) in which L is –O- .

According to yet another embodiment, specifically provided are compounds of formula (II) in which L is -C(O)-.

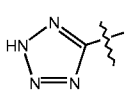
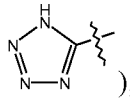
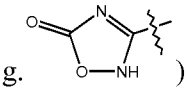
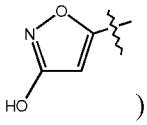
According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2a} is –COOH.

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2a} is -C(O)NR^aR^b, wherein R^a is hydrogen and R^b is hydrogen or hydroxyl.

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2a} is -C(O)N(R^a)SO_2R^b, wherein R^a is hydrogen and R^b is C_{1-8}alkyl (e.g. methyl), halo C_{1-8}alkyl (e.g. trifluoromethyl) or C_{6-14}aryl (e.g. phenyl).

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2a} is $N(R^a)SO_2R^b$, wherein R^a is hydrogen and R^b is C_{1-8}alkyl (e.g. methyl or isopropyl).

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2a} is substituted C_{6-14}aryl, preferably hydroxyl substituted phenyl.

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2a} is substituted or unsubstituted 5-14 membered heteroaryl or 3 – 15 membered heterocyclic ring wherein heterocyclic or heteroaryl ring is selected from tetrazolyl (e.g.  , ), oxadiazolyl (e.g. ) and hydroxyl substituted isoxazolyl (e.g. )

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2b} is hydrogen.

According to yet another embodiment, specifically provided are compounds of formula (II) in which R^{2b} is halogen, preferably fluorine.

According to yet another embodiment, specifically provided are compounds of formula (II), in which R^3 is same or different at each occurrence and independently selected from halogen (e.g. F, Cl, Br or I), cyano, $CONH_2$, $COCH_3$, SO_2NH_2, C_{1-8}alkyl (e.g. methyl), C_{1-8}alkoxy (e.g. methoxy, ehthoxy, propran-2-yloxy), haloC_{1-8}alkyl (e.g. trifluoromethyl), and haloC_{1-8}alkoxy (e.g. trifluoromethoxy).

According to yet another embodiment, specifically provided are compounds of formula (II), in which R^3 is OR^a, wherein R^a is hydrogen or C_{3-12}cycloalkyl (e.g. cyclopentyl).

According to yet another embodiment specifically provided are compounds of formula (II), in which R^4 is selected from halogen (e.g. F, Cl, Br or I).

According to yet another embodiment specifically provided are compounds of formula (II), in which n is 0, 1 or 2.

According to yet another embodiment, specifically provided are compounds of formula (II), in which q is 0 or 1

According to yet another embodiment, specifically provided are compound of formula (I) and/or (II) with an IC_{50} value of less than 500 nM, preferably, less than 250 nM, more preferably, less than 100 nM with respect to COT kinase activity as measured by method described in the present patent application.

According to yet another embodiment specifically provided are compounds of formula (I) and/or (II) with an IC_{50} value of less than 1000 nM, preferably, less than 500 nM, with respect to COT kinase activity as measured by method described in the present patent application.

It should be understood that the formulas (I) and/or (II) structurally encompasses *N*-oxide, all tautomers, geometrical isomers, stereoisomers, including enantiomers and diastereomers and pharmaceutically acceptable salts that may be contemplated from the chemical structure of the genera described herein.

The present invention also provides a pharmaceutical composition that includes at least one compound described herein and at least one pharmaceutically acceptable excipient, such as a pharmaceutically acceptable carrier or diluent. Preferably, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound described herein. The compounds described in the present patent application may be associated with a pharmaceutically acceptable excipient, such as a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

The compounds and pharmaceutical compositions of the present invention are useful for inhibiting COT kinase, which is related to a variety of disease states.

The present invention further provides a method of inhibiting COT kinase receptors in a subject in need thereof by administering to the subject one or more compounds described herein in an amount effective to cause inhibition of such receptor.

Detailed Description of the Invention

Definitions

The invention is defined by the claims and not limited by the description provided herein below. The terms used in the appended claims are defined herein in this glossary section, with the proviso that the claim terms may be used in a different manner if so defined by express recitation.

The terms "halogen" or "halo" means fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo).

The term "alkyl" refers to a hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, containing no unsaturation, having from one to eight carbon atoms (i.e. C_{1-8}alkyl), and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). The term "C_{1-6} alkyl" refers to an alkyl chain having 1 to 6 carbon atoms. The term "C_{1-4} alkyl" refers to an alkyl chain having 1 to 4 carbon atoms. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkenyl" refers to a hydrocarbon chain containing from 2 to 10 carbon atoms (i.e. C_{2-10}alkenyl) and including at least one carbon-carbon double bond. Non-limiting examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkynyl" refers to a hydrocarbyl radical having at least one carbon-carbon triple bond, and having 2 to about 12 carbon atoms (with radicals having 2 to about 10 carbon atoms being preferred i.e. C_{2-10}alkynyl). Non-limiting examples of alkynyl groups include ethynyl, propynyl, and butynyl. Unless set forth or recited to the contrary, all alkynyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkoxy" denotes an alkyl group attached via an oxygen linkage to the rest of the molecule (i.e. C_{1-8} alkoxy). Representative examples of such groups are $-OCH_3$ and $-OC_2H_5$. Unless set forth or recited to the contrary, all alkoxy groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkoxyalkyl" or "alkyloxyalkyl" refers to an alkoxy or alkyloxy group as defined above directly bonded to an alkyl group as defined above (i.e. C_{1-8}alkoxyC_{1-8}alkyl or C_{1-8}alkyloxyC_{1-8}alkyl). Example of such alkoxyalkyl moiety includes, but are not limited to, $-CH_2OCH_3$ and $-CH_2OC_2H_5$. Unless set forth or

recited to the contrary, all alkoxyalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkyl" refers to at least one halo group (selected from F, Cl, Br or I), linked to an alkyl group as defined above (i.e.haloC_{1-8}alkyl). Examples of such haloalkyl moiety include, but are not limited to, trifluoromethyl, difluoromethyl and fluoromethyl groups. Unless set forth or recited to the contrary, all haloalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkoxy" refers to an alkoxy group substituted with one or more halogen atoms (i.e.haloC_{1-8}alkoxy). Examples of "haloalkoxy" include but are not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, pentachloroethoxy, chloromethoxy, dichlorormethoxy, trichloromethoxy and 1-bromoethoxy. Unless set forth or recited to the contrary, all haloalkoxy groups described herein may be straight chain or branched, substituted or unsubstituted.

The term "hydroxyalkyl" refers to an alkyl group as defined above wherein one to three hydrogen atoms on different carbon atoms is/are replaced by hydroxyl groups (i.e. hydroxyC_{1-8}alkyl). Examples of hydroxyalkyl moiety include, but are not limited to -CH_2OH, -C_2H_4OH and –$CH(OH)C_2H_4OH$.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, for example C_{3-12}cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups or spirobicyclic groups, e.g., spiro(4,4)non-2-yl. The term "C_{3-6} cycloalkyl" refers to the cyclic ring having 3 to 6 carbon atoms. Unless set forth or recited to the contrary, all cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms directly attached to an alkyl group, for example C_{3-8}cycloalkylC_{1-8}alkyl. The cycloalkylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl. Unless set forth or recited to the contrary, all cycloalkylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkenyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, for example C_{3-8}cycloalkenyl, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl. Unless set forth or recited to the contrary, all cycloalkenyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkenylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, directly attached to an alkyl group, for example C_{3-8}cycloalkenylC_{1-8}alkyl. The cycloalkenylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all cycloalkenylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms (i.e. C_{6-14}aryl), including monocyclic, bicyclic and tricyclic aromatic systems, such as phenyl, naphthyl, tetrahydronapthyl, indanyl, and biphenyl. Unless set forth or recited to the contrary, all aryl groups described or claimed herein may be substituted or unsubstituted.

The term "aryloxy" refers to an aryl group as defined above attached via an oxygen linkage to the rest of the molecule (i.e. C_{6-14}aryloxy). Examples of aryloxy moiety include, but are not limited to phenoxy and naphthoxy. Unless set forth or recited to the contrary, all aryloxy groups described herein may be substituted or unsubstituted.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, i.e. C_{6-14}arylC_{1-8}alkyl, such as $-CH_2C_6H_5$ and $-C_2H_4C_6H_5$. Unless set forth or recited to the contrary, all arylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclic ring" or "heterocyclyl" unless otherwise specified refers to substituted or unsubstituted non-aromatic 3 to 15 membered ring radical which consists of carbon atoms and from one to five hetero atoms selected from nitrogen, phosphorus, oxygen and sulfur. The heterocyclic ring radical may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the

heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; also, unless otherwise constrained by the definition the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s). Examples of such heterocyclic ring radicals include, but are not limited to azepinyl, azetidinyl, benzodioxolyl, benzodioxanyl, chromanyl, dioxolanyl, dioxaphospholanyl, decahydroisoquinolyl, indanyl, indolinyl, isoindolinyl, isochromanyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxazolinyl, oxazolidinyl, oxadiazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, octahydroindolyl, octahydroisoindolyl, perhydroazepinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, piperidinyl, phenothiazinyl, phenoxazinyl, quinuclidinyl, tetrahydroisquinolyl, tetrahydrofuryl, tetrahydropyranyl, thiazolinyl, thiazolidinyl, thiamorpholinyl, thiamorpholinyl sulfoxide and thiamorpholinyl sulfone. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclyl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclylalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group (i.e. heterocyclylC_{1-8}alkyl). The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heteroaryl" unless otherwise specified refers to substituted or unsubstituted 5 to 14 membered aromatic heterocyclic ring radical with one or more heteroatom(s) independently selected from N, O or S. The heteroaryl may be a mono-, bi- or tricyclic ring system. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Examples of such heteroaryl ring radicals include, but are not limited to oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, triazolyl, triazinyl, tetrazoyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzopyranyl, carbazolyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, naphthyridinyl, pteridinyl, purinyl, quinoxalinyl, quinolyl, isoquinolyl,

thiadiazolyl, indolizinyl, acridinyl, phenazinyl and phthalazinyl. Unless set forth or recited to the contrary, all heteroaryl groups described or claimed herein may be substituted or unsubstituted.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group (i.e. heterarylC_{1-8}alkyl). The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heteroarylalkyl groups described or claimed herein may be substituted or unsubstituted.

Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyl alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstiuted guanidine, $-COOR^{x'}$, $-C(O)R^{x'}$, $-C(S)R^{x'}$, $-C(O)NR^{x'}R^{y'}$, $-C(O)ONR^{x'}R^{y'}$, $-NR^{x'}CONR^{y'}R^{z'}$, $-N(R^{x'})SOR^{y'}$, $-N(R^{x'})SO_2R^{y'}$, $-(=N-N(R^{x'})R^{y'})$, $-NR^{x'}C(O)OR^{y'}$, $-NR^{x'}R^{y'}$, $-NR^{x'}C(O)R^{y'}$, $-NR^{x'}C(S)R^{y'}$, $-NR^{x'}C(S)NR^{y'}R^{z'}$, $-SONR^{x'}R^{y'}$, $-SO_2NR^{x'}R^{y'}$, $-OR^{x'}$, $-OC(O)NR^{y'}R^{z'}$, $-OC(O)OR^{y'}$, $-OC(O)R^{x'}$, $-OC(O)NR^{x'}R^{y'}$, $-SR^{x'}$, $-SOR^{x'}$, $-SO_2R^{x'}$, and $-ONO_2$, wherein $R^{x'}$, $R^{y'}$ and $R^{z'}$ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, and substituted or unsubstituted heterocyclic ring. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted

aryl", the substituent on "substituted aryl" can be unsubstituted alkenyl but cannot be "substituted alkenyl".

The term "pharmaceutically acceptable salt" includes salts prepared from pharmaceutically acceptable bases or acids including inorganic or organic bases and inorganic or organic acids. Examples of such salts include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate, diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Examples of salts derived from inorganic bases include, but are not limited to, aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, and zinc.

The term "treating" or "treatment" of a state, disorder or condition includes: (a) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (b) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; or (c) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

The term "acute pain" is usually self-limiting. The sensation of pain can be triggered by any number of physical or chemical stimuli and the sensory neurons which mediate the response to this harmful stimulus are termed as "nociceptors". Nociceptors are primary sensory afferent (C and Aδ fibers) neurons that are activated by a wide variety of noxious stimuli including chemical, mechanical, thermal, and proton (pH<6) modalities. Nociceptors are the nerves which sense and respond to parts of the body which suffer from damage. They signal tissue irritation, impending injury, or actual injury. When activated, they transmit pain signals (via the peripheral nerves as well as the spinal cord) to the brain.

The term "chronic pain" usually refers to pain which persists for 3 months or longer and can lead to significant changes in a patient's personality; lifestyle, functional ability and overall quality of life. Chronic pain can be classified as either nociceptive or neuropathic. Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that associated with arthritis. Neuropathic pain is caused by damage to the sensory nerves of the peripheral or central nervous system and is maintained by aberrant somatosensory processing. The pain is typically well localized, constant, and often with an aching or throbbing quality. Visceral pain is the subtype of nociceptive pain that involves the internal organs. It tends to be episodic and poorly localized. Nociceptive pain is usually time limited, meaning when the tissue damage heals, the pain typically resolves (arthritis is a notable exception in that it is not time limited).

The compound described in the present patent application may form salts. Non-limiting examples of pharmaceutically acceptable salts forming part of this patent application include salts derived from inorganic bases salts of organic bases salts of chiral bases, salts of natural amino acids and salts of non-natural amino acids. Certain compounds of present patent application are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers). With respect to the overall compounds described by the general formula (I) the present patent application extends to these stereoisomeric forms and to mixtures thereof. To the extent prior art teaches synthesis or separation of particular stereoisomers, the different stereoisomeric forms of the present patent application may be separated from one another by the method known in the art, or a given isomer may be obtained by stereospecific or asymmetric synthesis. Tautomeric forms and mixtures of compounds described herein are also contemplated. It is also to be understood that compounds of

the invention may exist in solvated forms (such as hydrates) as well as unsolvated forms, and that the invention encompasses all such forms.

Pharmaceutical Compositions

The present invention also relates to a pharmaceutical composition that comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents, solvents and the like.

The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide desired release profile.

The pharmaceutical compositions can be suitable for administration by various routes, which include, but are not limited to, oral, pulmonary, buccal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic or topical.

The pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g., as described in *Remington: The Science and Practice of Pharmacy,* 20th Ed., 2003 (Lippincott Williams & Wilkins).

Methods of Treatment

Compounds of the present invention are particularly useful because they may selectively inhibit the activity of COT kinase, i.e. they prevent the action of COT kinase or a complex of which the COT kinase forms a part, and/or may elicit COT kinase modulating effect. Compounds of the invention may thus be useful in the treatment of those conditions in which inhibition of COT kinase is required.

Compounds of the invention are thus expected to be useful in the treatment of inflammation. The term “inflammation” will be understood by those skilled in the art to include any condition characterized by a localized or a systemic protective response, which may be elicited by physical trauma, infection, chronic diseases, such as those mentioned hereinbefore, and/or chemical and/or physiological reactions to

external stimuli (e.g. as part of an allergic response). Any such response, which may serve to destroy, dilute or sequester both the injurious agent and the injured tissue, may be manifest by, for example, heat, swelling, pain, redness, dilation of blood vessels and/or increased blood flow, invasion of the affected area by white blood cells.

The term "inflammation" is also understood to include any inflammatory disease, disorder or condition per se, any condition that has an inflammatory component associated with it, and/or any condition characterized by inflammation as a symptom, including inter alia acute, chronic, ulcerative, specific, allergic, infection by pathogens, immune reactions due to hypersensitivity, autoimmune response, entering foreign bodies, physical injury, and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

The compounds of the present invention may also be useful in the treatment of asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, inflammatory pain, chronic pain, acute pain, neuropathic pain, bone cancer pain and pain due to endometriosis, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections {e.g. influenza, common cold, herpes zoster, hepatitis C and AIDS), bacterial infections, fungal infections, dysmenorrhea, endometriosis, burns, surgical or dental procedures, malignancies {e.g. breast cancer, colon cancer, and prostate cancer), hyperprostaglandin E syndrome, classic Bartter syndrome, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, neurodegenerative and neuroinflammatory disorders such as Alzheimer's disease Parkinson's, Huntington's, Amyotrophic lateral sclerosis (ALS) and multiple sclerosis, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, sarcoidosis and any other disease with an inflammatory component.

Compounds of the invention may also have effects that are not linked to inflammatory mechanisms, such as in the reduction of bone loss in a subject.

Conditions that may be mentioned in this regard include osteoporosis, osteoarthritis, Paget's disease and/or periodontal diseases.

By virtue of the COT kinase inhibitory activity of compounds of the present invention, the compounds of Formula I are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, migraine (acute and prophylactic treatment), toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, juvenile rheumatoid arthritis, degenerative joint diseases (osteoarthritis), acute gout and ankylosing spondylitis, acute, subacute and chronic musculoskeletal pain syndromes such as bursitis, burns, injuries, and pain following surgical and dental procedures as well as the preemptive treatment of surgical pain. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compounds of Formula I may also be useful for the treatment or prevention of endometriosis, hemophilic arthropathy and Parkinson's disease.

Compounds of the invention may also be useful for the treatment of cancer. "Treatment", as used herein, refers to either reducing the risk of mortality, improving the quality of life or retarding the progression of the cancer.

Cancers include but not limited to lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cancers of the tongue, mouth, pharynx, and oral cavity, melanoma, cutaneous or intraocular melanoma, BRAF resistant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lynphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem glioma or pituitary adenomas), cancers of the bloodsuch as acute myeloid leukemia, chronic mueloid leukemia.

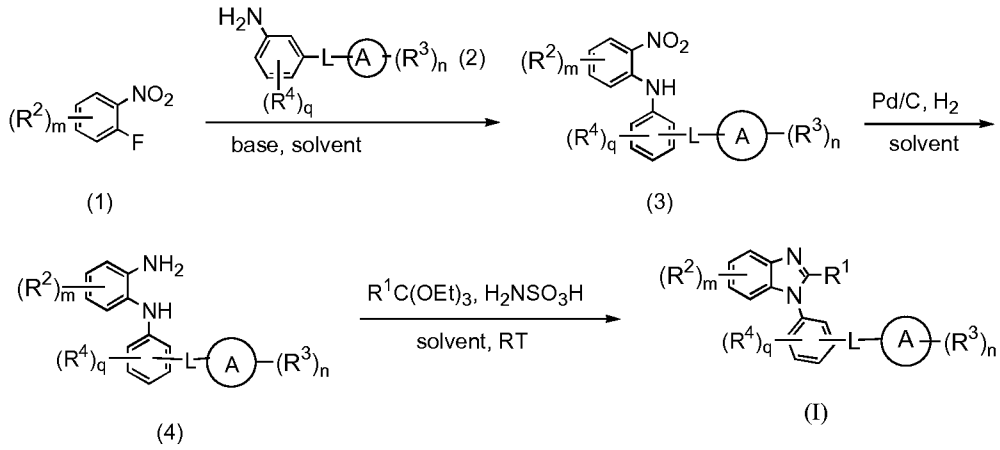
Compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions. For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

General Methods of Preparation

The compounds described represented by the general formula (I) and (II) can be prepared by methods depicted in the Schemes provided below as well as by other methods. Furthermore, in the following schemes, where specific acids, bases, reagents, coupling agents, solvents, etc. are mentioned, it is understood that other suitable acids, bases, reagents, coupling agents etc. may be used and are included within the scope of the present invention. Modifications to reaction conditions, for example, temperature, duration of the reaction or combinations thereof are envisioned as a part of the present invention. The compounds obtained by using the general reaction schemes may be of insufficient purity. These compounds can be purified by any of the methods for purification of organic compounds known in the art, for example, crystallization or silica gel or alumina column chromatography using different solvents in suitable ratios.

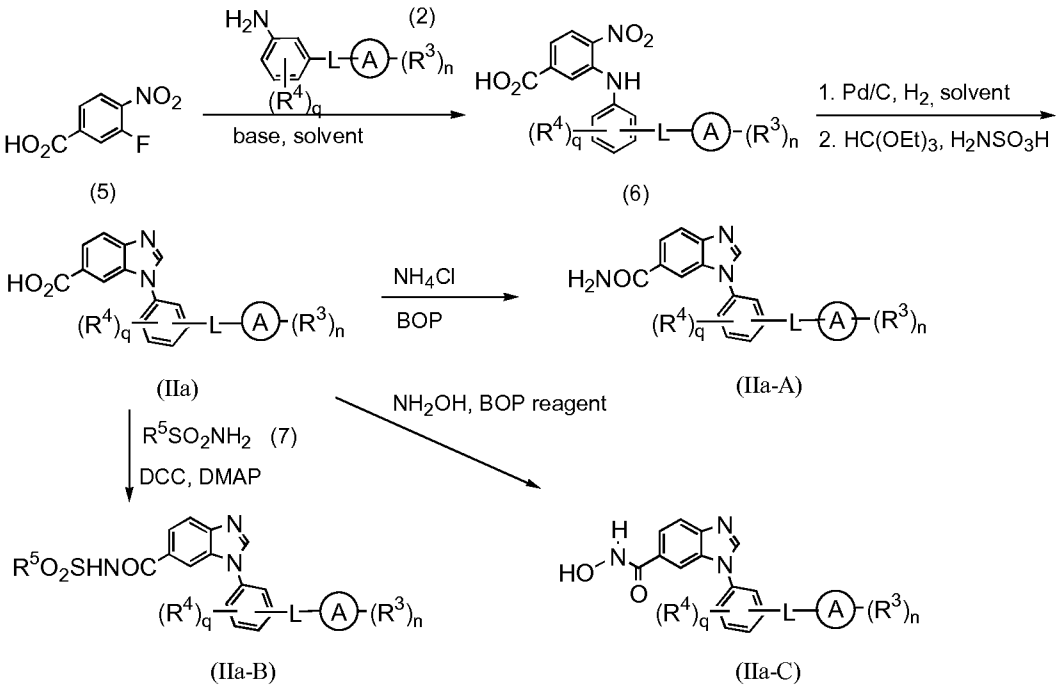
The benzimidazole derivatives of the general formula (I), wherein A, L, R^1, R^2, R^3, R^4, 'm', 'n' and 'q' are as defined above, can be prepared as per the process outlined in Scheme 1. Coupling reaction of substituted *o*-fluoronitrobenzene of general formula (1) with an aromatic amine of the formula (2) in presence of suitable base such as sodium hydride in a polar aprotic solvent such as *N*,*N*-dimethylacetamide affords the o-nitroaniline derivative (3). Palladium catalyzed reduction of nitro group affords the diamine derivative (4). The diamine intermediate (4) on reaction with an ester of formula $R^1C(OEt)_3$, in the presence of sulfamic acid in a suitable solvent such as methanol furnishes *N*-substituted benzimidazole derivatives of general formula (I). Similar approach is reported by Zhan-Hui Z., *et al.*, in *Monatshefte fuer Chemie*, 2007, 138, 89 – 94.

Scheme 1



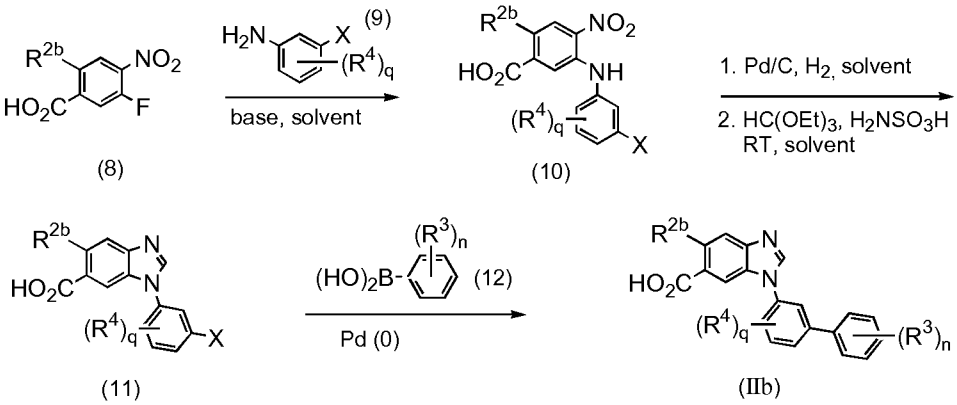
A general approach for synthesis of benzimidazole carboxylic acid of general formula (IIa), and benzimidazole derivatives of formula (IIa-A), (IIa-B), (IIa-C) wherein A, L, R^3, R^4, 'q' and 'n' are as described above and R^5 is alkyl (e.g. methyl), haloalkyl (e.g. trifluoromethyl) or aryl (e.g. phenyl), is depicted in Scheme 2. The coupling reaction of 3-fluoro-4-nitrobenzoic acid (5) with substituted aromatic amine of formula (2) gives the nitroaniline derivative of formula (6). Compound of formula (6) on nitro group reduction and subsequent reaction with triethyl orthoformate yields benzimidazole carboxylic acids of general formula (IIa). Reaction of benzimidazole carboxylic acid (IIa) with ammonium chloride in the presence of BOP reagent furnishes the benzimidazole amides of formula (IIa-A). Also, reaction of benzimidazole carboxylic acid (IIa) with substituted sulfonamide of formula (7) in the presence of N,N'-dicyclohexylcarbodiimide furnishes the sulfonyl carboxamide benzimidazole of formula (IIa-B). Again, reaction of benzimidazole carboxylic acid (IIa) with hydroxylamine hydrochloride in the presence of BOP reagent gives hydroxamic acid derivative of formula (IIa-C).

Scheme 2



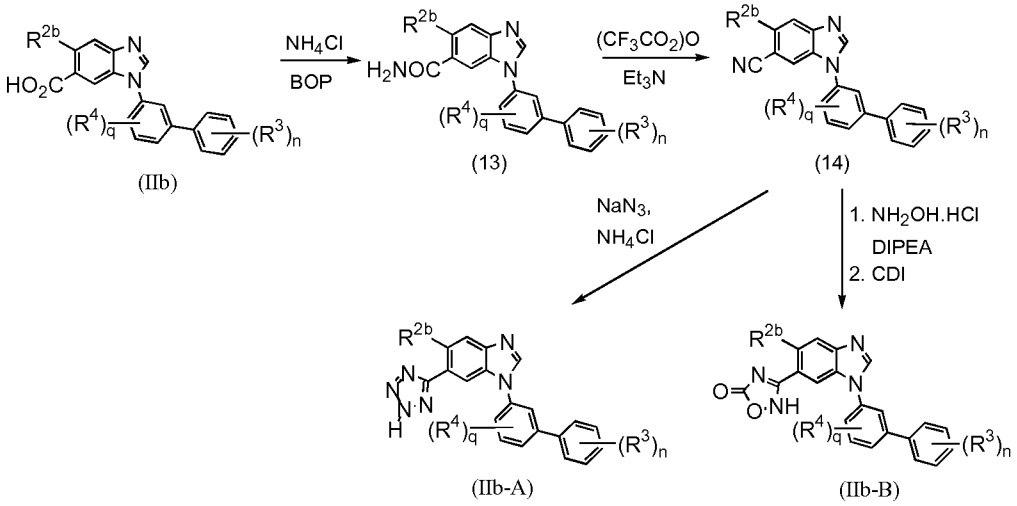
An approach for synthesis of benzimidazole carboxylic acid of the general formula (IIb), wherein R^{2b} can be fluorine or hydrogen is described in Scheme 3. Thus, fluoro nitrobenzoic acid derivative (8) is coupled with 3-haloaniline of formula (9) (where X = Cl, Br or I) to give the nitro intermediate of formula (10). Intermediate (10) on nitro group reduction gives the diamine, which on reaction with triethyl orthoformate affords the benzimidazole carboxylic acid (11). Compound of formula (11) undergoes Suzuki coupling with substituted phenylboronic acid (12) to afford benzimidazole carboxylic acid of formula (IIb).

Scheme 3



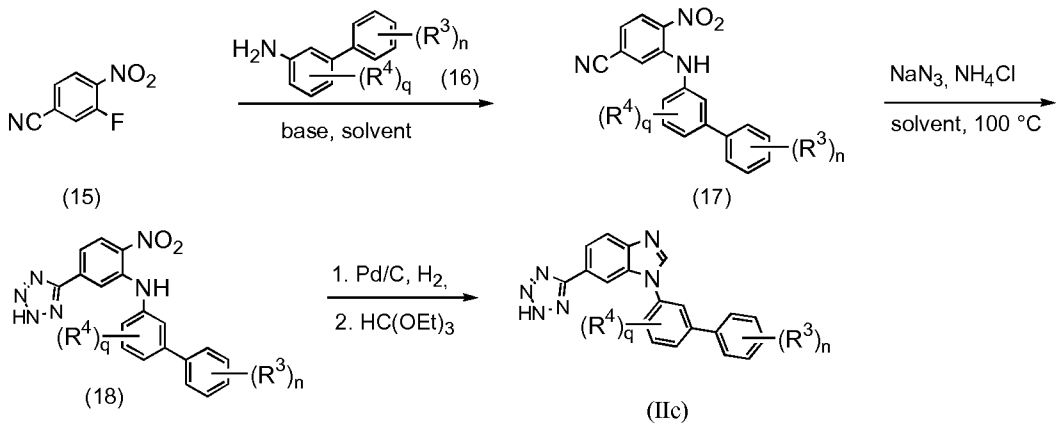
An approach for synthesis of benzimidazole derivatives of formula (IIb-A) and (IIb-B), wherein R^{2b} is fluorine or a suitable aryl substituent, is described in Scheme 4. Thus, benzimidazole carboxylic acid of formula (IIb) on amidation with ammonium chloride in presence of BOP reagent and suitable base such as DIPEA afford the corresponding amide of formula (13). Conversion of amide (13) to nitrile (14) is achieved using trifluoroacetic anhydride in presence of triethylamine. Nitrile (14) undergoes reaction with sodium azide in presence of ammonium chloride to furnish the tetrazole derivative (IIb-A). Also, reaction of intermediate (14) with hydroxylamine hydrochloride in presence of suitable base gives the N-hydroxy aryl imidamide, which on reaction with 1,1'-carbonyldiimidazole (CDI) furnishes the benzimidazoles of formula (IIb-B) bearing an oxadiazolone group.

Scheme 4



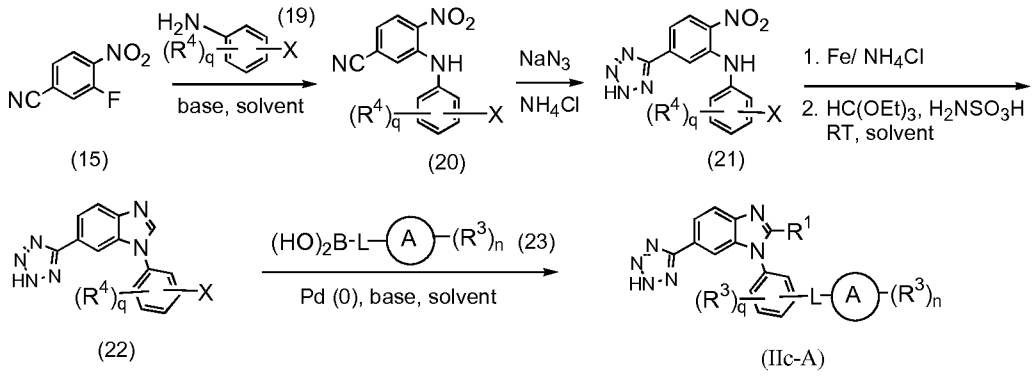
A general approach for synthesis of 6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole derivative of formula (IIc), wherein R^3, R^4, 'q' and 'n' are described above, is depicted in Scheme 5. Coupling reaction of 3-fluoro-4-nitrobenzonitrile (15) with optionally substituted biphenylamine of formula (16) gives the nitroaniline derivative of formula (17). The cyano group of formula (17) is converted to a tetrazole derivative of formula (18) using sodium azide in the presence of ammonium chloride in a suitable solvent such as toluene or dimethyl formamide at elevated temperature. Analogous procedure is reported by Dawn, G., *et al.*, in *Bioorganic and Medicinal Chemistry Letters,* 2008, 18, 4952 – 4955. Compound of formula (18) on nitro group reduction followed by reaction with triethyl orthoformate yields 6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole derivative of the formula (IIc).

Scheme 5



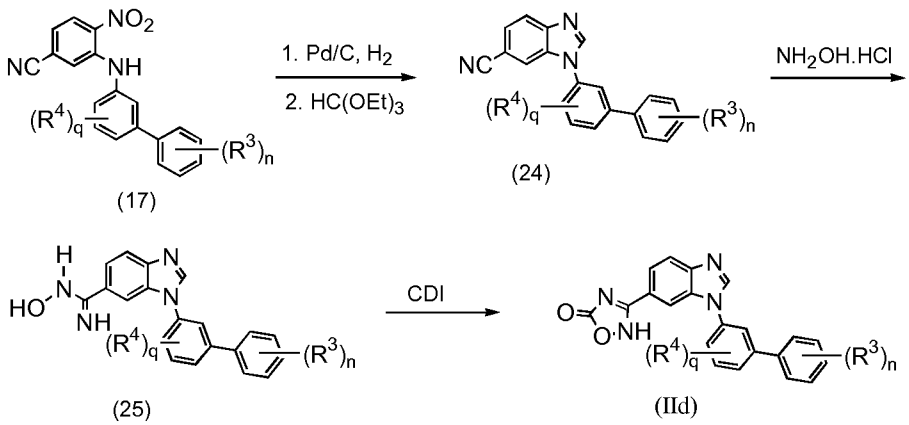
An approach for synthesis of 6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole of the formula (IIc-A) is described in Scheme 6. The coupling reaction of 3-fluoro-4-nitrobenzonitrile (15) with aromatic amine of formula (19), wherein X is a halogen, gives the amine derivative of formula (20). The cyano group of intermediate (20) is converted to a tetrazole derivative (21) using sodium azide in the presence of ammonium chloride in suitable solvent such as toluene or dimethyl formamide at elevated temperature. Similar approach was reported by Dawn, G., *et al.*, in *Bioorganic and Medicinal Chemistry Letters,* 2008, 18, 4952 – 4955. Compound of formula (21) undergoes nitro group reduction and the diamine thus formed on reaction with triethyl orthoformate yields benzimidazole derivatives (22). The benzimidazole (22) on Suzuki coupling with substituted phenylboronic acid (23) using palladium catalyst in presence of suitable base such as potassium carbonate in a suitable solvent affords compounds of formula (IIc-A).

Scheme 6



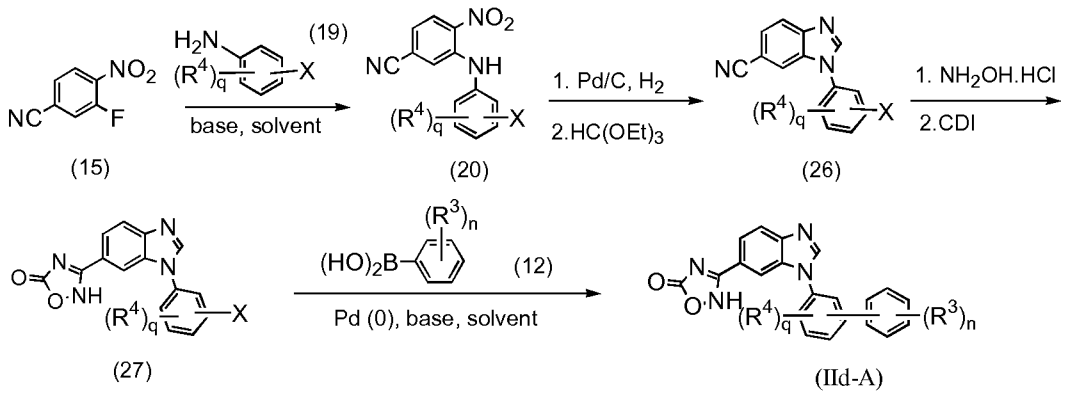
A general approach for synthesis of oxadiazolone substituted benzimidazole derivative of the formula (IId), wherein R^3, R^4, 'q' and 'n' are as described above, is described in Scheme 7. Thus, nitroaniline derivative of formula (17) undergoes palladium catalysed nitro group reduction, followed by reaction with triethyl orthoformate to afford benzimidazole derivative (24). Compound of formula (24) on reaction with hydroxylamine hydrochloride in presence of suitable base such as N,N-diisopropylethylamine forms the N-hydroxy aryl imidamide (25), which undergoes reaction with 1,1'-carbonyldiimidazole (CDI) in presence of suitable solvent such as N,N-dimethylformamide at elevated temperature furnishes the oxadiazolone derivative of formula (IId). Analogous approaches are reported in WO2005/11410A2 and *Bioorganic and Medicinal Chemistry Letters*, Dawn, G., *et al.*, **2008,** 18, 4952-4955.

Scheme 7



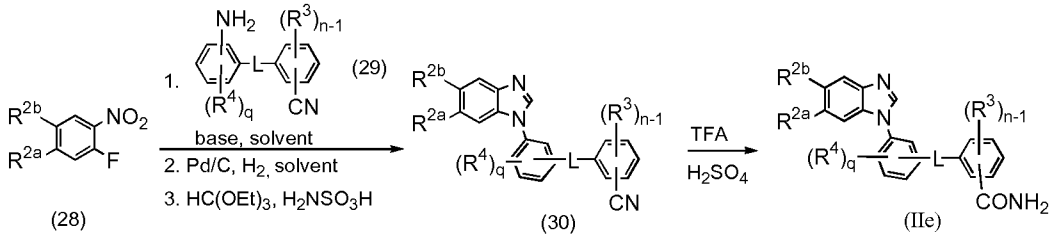
An approach for synthesis of oxadiazolone substituted benzimidazole derivative of the formula (IId-A), is described in Scheme 8. Thus, coupling reaction of 3-fluoro-4-nitrobenzonitrile (15) halosubstituted aromatic amine of formula (19) gives intermediate of formula (20). Intermediate (20) on nitro group reduction and subsequent reaction with triethyl orthoformate gives benzimidazole derivatives of formula (26). The benzimidazole derivative of formula (26) on reaction with hydroxylamine hydrochloride, followed by reaction with 1,1'-carbonyldiimidazole (CDI) furnishes the oxadiazolone derivative of formula (27). Compound of formula (27) on Suzuki coupling reaction with substituted phenylboronic acid (12) furnishes oxadiazolones (IId-A).

Scheme 8



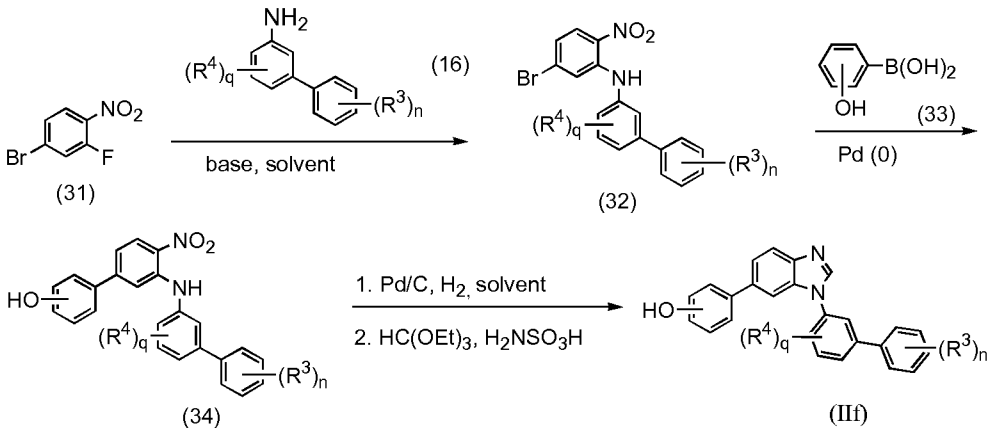
A general approach for the synthesis of benzimidazole amides of the formula (IIe), wherein R^{2a}, R^{2b}, R^3, R^4, L, 'q' and 'n' are as described above, is described in Scheme 9. Thus, substituted fluoro nitrobenzene of formula (28) undergoes reaction with aromatic amine of the formula (29) in presence of suitable base and solvent gives the amino nitro intermediate, which undergoes reduction and cyclization with orthoformate to afford compound of formula (30). The nitrile group of formula (30) undergoes partial hydrolysis using mixture of trifluoroacetic acid and sulfuric acid to afford benzimidazole amide of formula (IIe).

Scheme 9



An approach for synthesis of compounds of the formula (IIf), wherein R^3, R^4, 'q and 'n' are as described above, is described in Scheme 10. Thus, coupling reaction of 4-bromo-2-fluoronitrobenzene (31) with substituted aromatic amine of formula (16) gives the nitro intermediate of formula (32). Intermediate of formula (32) undergoes Suzuki coupling with hydroxyphenylboronic acid (33) in presence of palladium catalyst to give the phenol derivative (34). Nitro group reduction of intermediate (34), followed by reaction with triethyl orthoformate affords the benzimidazoles derivatives (IIf).

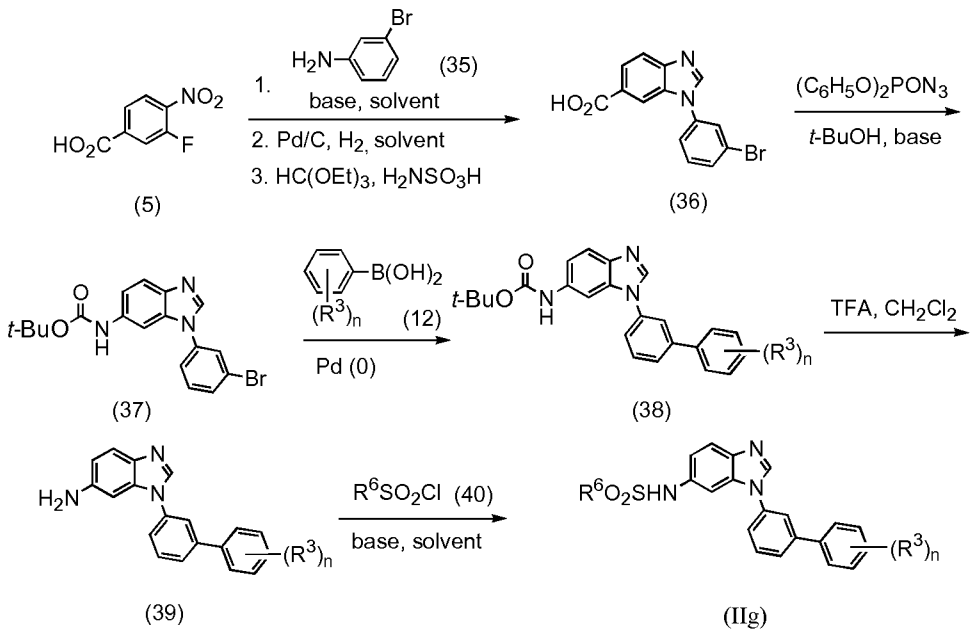
Scheme 10



An approach for synthesis of sulfonamide derivatives of the formula (IIg), where R^3 and 'n' are as described above and R^6 is C_{1-8} alkyl (e.g. methyl, isopropyl), is described in Scheme 11. Thus, 3-fluoro-4-nitrobenzoic acid of formula (5) is first coupled with 3-bromoaniline (35) which undergoes nitro group reduction followed by reaction with triethyl orthoformate to afford the benzimidazoles derivative of formula (36). Intermediate (36) undergoes reaction with diphenylphosphorylazide in *tert*-butanol in presence of suitable base such as triethylamine to give the corresponding carbamate (urethane) (37) via the acyl azide intermediate. Intermediate (37) undergoes Suzuki coupling reaction with substituted phenylboronic acid of formula

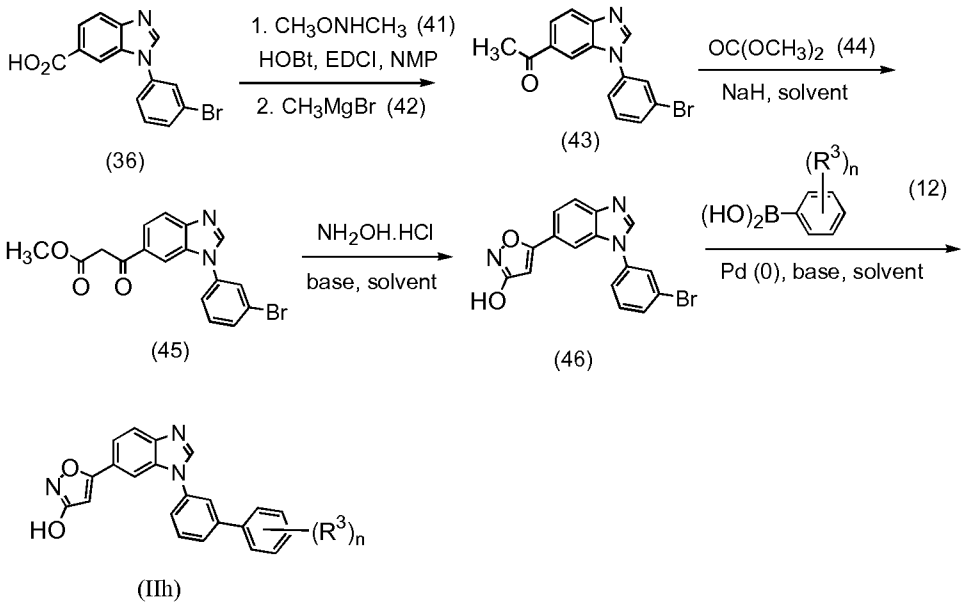
(12) to give intermediate of formula (38). Hydrolysis of compound of formula (38) using trifluoroacetic acid in dichloromethane gives amino benzimidazole derivative of formula (39). The reaction of intermediate of formula (39) with substituted sulfonylchloride (40) furnishes the benzimidazoles of formula (IIg) bearing a sulfonamide group.

Scheme 11



A general approach for synthesis of benzimidazole derivative of the formula (IIh), wherein R^3 and 'n' are as described above, is depicted in Scheme 12. The benzimidazole carboxylic acid of formula (36) undergoes reaction with *N,O*-dimethylhydroxylamine hydrochloride (41) using EDCI affords the corresponding Weinreb amide which further undergoes Grignard reaction with methyl magnesium bromide (42) in presence of suitable solvent such as tetrahydrofuran to form the corresponding ketone of formula (43). The ketone intermediate (43) on reaction with dimethyl carbonate (44) in presence of a suitable base gives the β-ketoester (45). The ketoester undergoes reaction with hydroxylamine hydrochloride to afford the 1,2-oxazol-3-ol derivative of formula (46). Intermediate (46) undergoes Suzuki coupling reaction with substituted phenylboronic acid (12) using palladium catalyst in presence of suitable base and solvent to furnish compounds of the formula (IIh).

Scheme 12



Experimental

The intermediates required for the synthesis are commercially available or alternatively, these intermediates can be prepared using known literature methods. The invention is described in greater detail by way of specific examples. However, the following examples are illustrative and are not intended to limit the broad scope of the invention. The persons skilled in the art can readily recognize a variety of non-critical parameters which can be modified or altered to yield similar results. The Examples described below were prepared using different approaches discussed above.

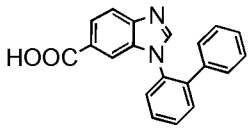
Unless otherwise stated, work-up includes distribution of the reaction mixture between the organic and aqueous phase indicated within parentheses, separation of layers and drying the organic layer over sodium sulphate, filtration and evaporation of the solvent. Purification, unless otherwise mentioned, includes purification by silica gel chromatographic techniques, generally using ethyl acetate/petroleum ether mixture of a suitable polarity as the mobile phase. Use of a different eluent system is indicated within parentheses. The following abbreviations are used in the text: DMSO-d_6: Hexadeuterodimethyl sulfoxide; DMF: *N,N*-dimethyl formamide, *J*: Coupling constant in units of Hz; RT or rt: room temperature (22-26°C). Aq.: aqueous; equiv. or eq.: equivalents; IPA: isopropanol; BOP: Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; TFA: trifluoroacetic acid; DIPEA: N,N-diisopropylethylamine; DMAP: N,N-dimethylaminopyridine; DCC: N,N'-Dicyclohexylcarbodiimide; EDCI. HCl: N-(3-Dimethylaminopropyl)-N′-

ethylcarbodiimide hydrochloride; CDI: 1,1'-carbonyldiimidazole; HOBt: hydroxybenzotriazole; THF: tetrahydrofuran; TEA: triethylamine.

The invention is described in detail by the examples, given below, which are provided by way of illustration only and therefore should not be construed to limit the scope of the present invention.

Example 1

1-(Biphenyl-2-yl)-1*H*-benzimidazole-6-carboxylic acid



Step 1: 3-(Biphenyl-2-ylamino)-4-nitrobenzoic acid: To a well-stirred solution of biphenyl-2-amine (200 mg, 1.18 mmol) in anhydrous DMSO (3 ml) was added sodium hydride (110 mg, 2.67 mmol) in portions for 15 min at room temperature and stirred for further 30 min at room temperature. The reaction mixture was cooled to 0 °C and solution of 3-fluoro-4-nitrobenzoic acid (200 mg, 1.07 mmol) in anhydrous DMSO (3 ml) was added drop-wise over 30 min. The resultant mixture was stirred at 50 °C for 18 h. The reaction mixture was cooled to room temperature and quenched with saturated aqueous solution of NH_4Cl (20 ml). The mixture was extracted with 20% IPA in $CHCl_3$ (2 x 100 ml). The combined organic layer was washed with brine (50 ml), dried (Na_2SO_4) and concentrated under reduced pressure to yield crude residue, which was purified by column chromatography to yield 180 mg of product as an orange solid.

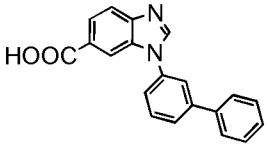
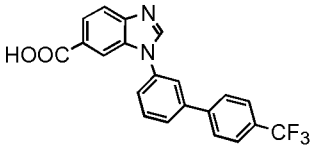
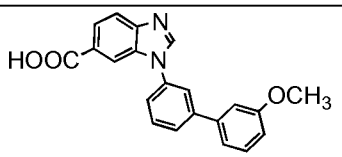
Step 2: 4-Amino-3-(biphenyl-2-ylamino)benzoic acid: To a stirred solution of Step 1 intermediate (175 mg, 0.284 mmol) in methanol (6 ml) was added 10 % Pd/C (50 mg) and stirred at room temperature under hydrogen atmosphere for 2 h. The reaction mixture was filtered through celite bed and washed with methanol (10 ml). The filtrate was evaporated under reduced pressure and triturated with diethyl ether (50 ml) to give 115 mg of product as an off-white solid.

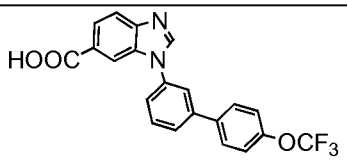
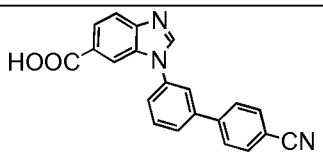
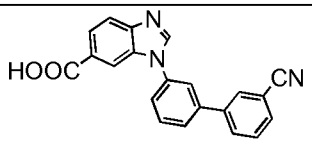
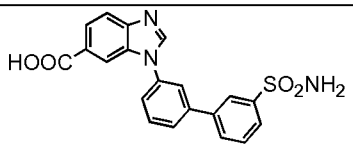
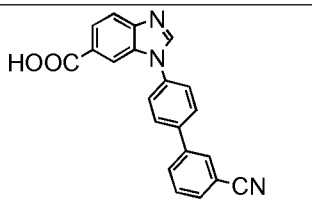
Step 3: To a well stirred mixture of Step 2 intermediate (200 mg, 0.60 mmol) and sulphamic acid (6 mg, 0.06 mmol) in methanol (8 ml) was added triethyl orthoformate (0.2 ml, 1.20 mmol) and stirred at room temperature under nitrogen atmosphere

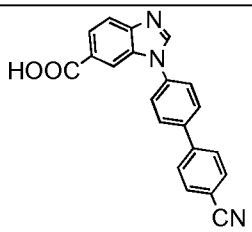
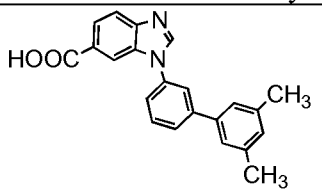
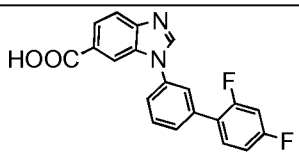
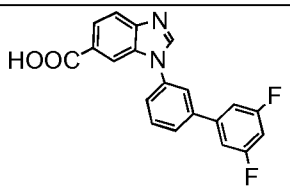
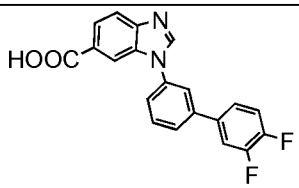
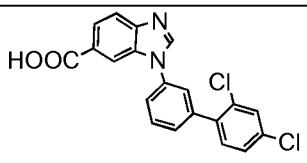
overnight. The reaction mixture was concentrated under reduced pressure to give crude solid. The crude residue was purified by column chromatography to yield 80 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.00-7.09 (m, 2H), 7.13-7.20 (m, 4H), 7.65-7.81 (m, 6H), 8.34 (s, 1H), 12.81 (br s, 1H); ESI (*m/z*) 315 $(M+H)^+$.

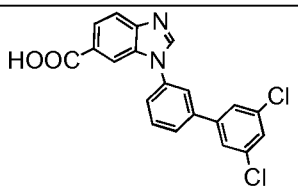
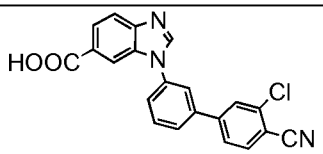
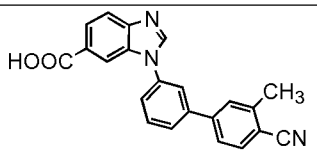
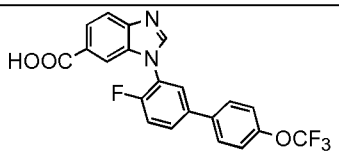
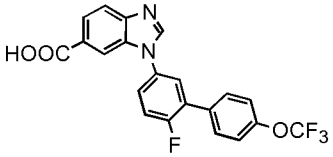
Examples 2-32 described below were prepared in three steps as described in Example 1 using 3-fluoro-4-nitrobenzoic acid and appropriate aryl amines.

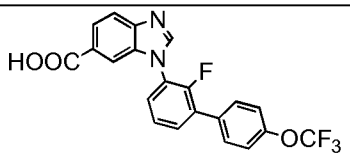
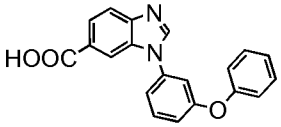
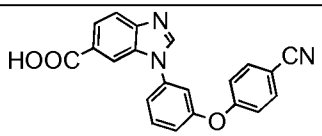
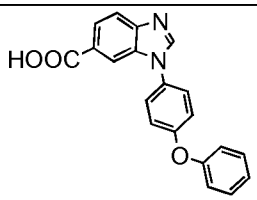
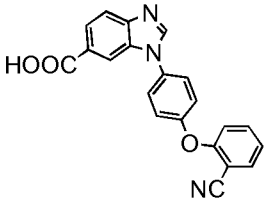
Table 1: Chemical structure, name and analytical data of Examples 2 – 32

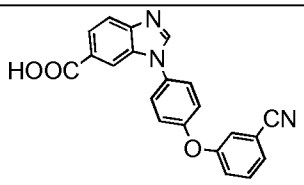
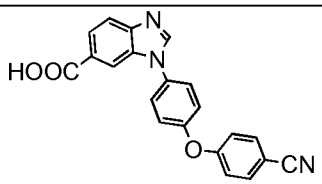
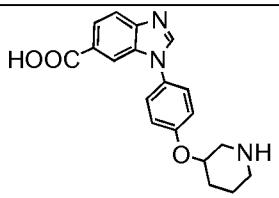
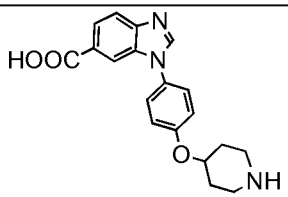
Example no.	Structure & nomenclature	Analytical Data
2	 1-(Biphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42-7.52 (m, 4H), 7.73-7.84 (m, 4H), 7.87-7.99 (m, 3H), 8.17 (s, 1H), 8.88 (s, 1H), 12.95 (br s, 1H); ESI (*m/z*) 315 $(M+H)^+$.
3	 1-[4'-(Trifluoromethyl)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80-7.86 (m, 3H), 7.88-7.93 (m, 4H), 8.04-8.09 (m, 3H), 8.16 (s, 1H), 8.89 (s, 1H), 12.97 (br s, 1H); ESI (*m/z*) 381 $(M-H)^-$.
4	 1-(3'-Methoxybiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.99 (d, J = 7.5 Hz, 1H), 7.35-7.45 (m, 3H), 7.71-7.79 (m, 2H), 7.88-7.96 (m, 3H), 8.00 (s, 1H), 8.17 (s, 1H), 8.87 (s, 1H), 12.95 (br s, 1H); ESI (*m/z*) 345 $(M+H)^+$.

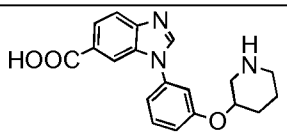
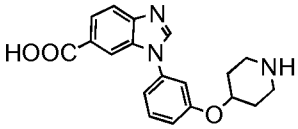
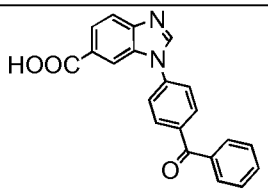
5	 1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 8.1 Hz, 2H), 7.74-7.82 (m, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.97 (t, J = 8.4 Hz, 3H), 8.03 (s, 1H), 8.13 (s, 1H), 8.88 (s, 1H), 12.88 (br s, 1H); ESI (*m/z*) 399 $(M+H)^+$.
6	 1-(4'-Cyanobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82-7.89 (m, 2H), 7.92-8.04 (m, 7H), 8.06-8.17 (m, 2H), 8.89 (s, 1H), 12.95 (br s, 1H); APCI (*m/z*) 338 $(M-H)^-$.
7	 1-(3'-Cyanobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69-7.80 (m, 3H), 7.83-7.95 (m, 4H), 8.12-8.21 (m, 3H), 8.37 (s, 1H), 8.87 (s, 1H), 13.03 (br s, 1H); ESI (*m/z*) 338 $(M-H)^-$.
8	 1-(3'-Sulfamoylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42 (s, 2H), 7.71 (t, J = 7.8 Hz, 1H), 7.80-7.85 (m, 3H), 7.88-7.95 (m, 3H), 8.04 (br s, 2H), 8.15 (s, 1H), 8.24 (s, 1H), 8.87 (s, 1H), 13.31 (br s, 1H); APCI (*m/z*) 394 $(M+H)^+$.
9	 1-(3'-Cyanobiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70-7.78 (m, 1H), 7.87-7.95 (m, 5H), 8.06 (d, J = 7.8 Hz, 2H), 8.13-8.21 (m, 2H), 8.30 (s, 1H), 8.83 (s, 1H), 12.95 (br s, 1H); ESI (*m/z*) 338 $(M-H)^-$.

10	 1-(4'-Cyanobiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85-7.94 (m, 4H), 7.99-8.08 (m, 6H), 8.20 (s, 1H), 8.83 (s, 1H), 12.93 (br s, 1H); ESI (*m/z*) 338 $(M-H)^-$.
11	 1-(3',5'-Dimethylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 6H), 7.05 (s, 1H), 7.42 (s, 2H), 7.70-7.77 (m, 2H), 7.79-7.86 (m, 2H), 7.88-7.96 (m, 2H), 8.15 (s, 1H), 8.87 (s, 1H), 12.82 (br s, 1H); APCI (*m/z*) 343 $(M+H)^+$.
12	 1-(2',4'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 9.3 Hz, 1H), 7.70-7.78 (m, 4H), 7.84-7.95 (m, 3H), 8.17 (s, 1H), 8.83 (s, 1H), 12.94 (br s, 1H); ESI (*m/z*) 349 $(M-H)^-$.
13	 1-(3',5'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.31 (t, *J* = 9.3 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.75-7.82 (m, 2H), 7.86-7.96 (m, 3H), 8.10-8.17 (m, 2H), 8.89 (s, 1H), 12.98 (br s, 1H); ESI (*m/z*) 351 $(M+H)^+$.
14	 1-(3',4'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56-7.70 (m, 1H), 7.72-7.79 (m, 3H), 7.85-7.96 (m, 2H), 7.97-8.03 (m, 2H), 8.05 (s, 1H), 8.16 (s, 1H), 8.88 (s, 1H), 12.97 (s, 1H); APCI (*m/z*) 351 $(M+H)^+$.
15		^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56-7.63 (m, 3H), 7.78-7.88 (m, 4H), 7.90-7.97 (m, 2H), 8.23 (s,

	1-(2',4'-Dichlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	1H), 8.82 (s, 1H), 12.95 (br s, 1H); ESI (*m/z*) 383 $(M)^+$.
16	 1-(3',5'-Dichlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.75-7.782 (m, 2H), 7.87-7.94 (m, 5H), 8.14 (d, *J* = 10.2 Hz, 2H), 8.89 (s, 1H), 12.96 (br s, 1H); ESI (*m/z*) 381 $(M)^-$.
17	 1-(3'-Chloro-4'-cyanobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79-7.89 (m, 3H), 7.92-8.05 (m, 3H), 8.11-8.18 (m, 3H), 8.28 (s, 1H), 8.89 (s, 1H), 12.98 (br s, 1H); ESI (*m/z*) 374 $(M+H)^+$.
18	 1-(4'-Cyano-3'-methylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 3H), 7.73-7.78 (m, 4H), 7.81-7.86 (m, 3H), 7.99 (br s, 2H), 8.28 (s, 1H), 8.41 (s, 1H), 11.37 (br s, 1H); ESI (*m/z*) 352 $(M-H)^-$.
19	 1-[4-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.74 (t, *J* = 9.3 Hz, 1H), 7.87-7.90 (m, 3H), 7.91-7.96 (m, 3H), 8.15 (d, *J* = 5.1 Hz, 1H), 8.79 (s, 1H), 12.96 (br s, 1H); ESI (*m/z*) 417 $(M+H)^+$.
20	 1-[6-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 9.3 Hz, 1H), 7.82-7.87 (m, 3H), 7.90-7.96 (m, 3H), 8.12 (s, 1H), 8.81 (s, 1H), 12.97 (br s, 1H); APCI (*m/z*) 415 $(M-H)^-$.

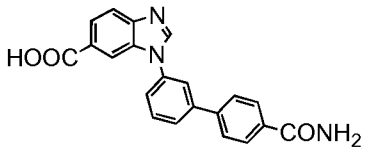
21	 1-[2-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53-7.62 (m, 3H), 7.78-7.86 (m, 4H), 7.89-7.96 (m, 3H), 8.77 (s, 1H), 12.96 (br s, 1H); APCI (*m/z*) 417 $(M+H)^+$.
22	 1-(3-Phenoxyphenyl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.10-7.23 (m, 4H), 7.40-7.51 (m, 4H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.88 (dd, *J* = 8.1 Hz, 21.3 Hz, 2H), 8.14 (s, 1H), 8.79 (s, 1H), 13.03 (br s, 1H); ESI (*m/z*) 331 $(M+H)^+$.
23	 1-[3-(4-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.24-7.31 (m, 3H), 7.58-7.64 (m, 2H), 7.69-7.78 (m, 1H), 7.85-7.93 (m, 4H), 8.16 (s, 1H), 8.78 (s, 1H), 13.03 (br s, 1H); ESI (*m/z*) 354 $(M-H)^-$.
24	 1-(4-Phenoxyphenyl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.12-7.19 (m, 2H), 7.21-7.29 (m, 3H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.88 (dd, *J* = 9.0 Hz, 19.8 Hz, 2H), 8.09 (s, 1H), 8.71 (s, 1H), 12.96 (s, 1H); APCI (*m/z*) 331 $(M+H)^+$.
25	 1-[4-(2-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.18 (d, *J* = 8.4 Hz, 1H), 7.33-7.45 (m, 3H), 7.70-7.78 (m, 1H), 7.80-7.88 (m, 2H), 7.90-7.98 (m, 3H), 8.13 (s, 1H), 8.76 (s, 1H), 13.00 (br s, 1H); ESI (*m/z*) 354 $(M-H)^-$.

26	 1-[4-(3-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.36 (d, J = 8.4 Hz, 2H), 7.44-7.51 (m, 1H), 7.60-7.67 (m, 3H), 7.77 (d, J = 7.8 Hz, 2H), 7.89 (dd, J = 8.4 Hz, 20.7 Hz, 2H), 8.12 (s, 1H), 8.73 (s, 1H), 12.79 (br s, 1H); ESI (m/z) 356 $(M+H)^+$.
27	 1-[4-(4-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.23 (d, J = 6.6 Hz, 2H), 7.43 (d, J = 6.6 Hz, 2H), 7.81-7.93 (m, 6H), 8.13 (s, 1H), 8.74 (s, 1H), 12.94 (s, 1H); ESI (m/z) 356 $(M+H)^+$.
28	 1-[4-(Piperidin-3-yloxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, J = 6.9 Hz, 1H), 1.70 (br s, 1H), 1.92 (br s, 2H), 3.08-3.18 (m, 2H), 3.32-3.43 (m, 2H), 4.84 (br s, 1H), 7.30 (d, J = 11.4 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.4 Hz, 20.4 Hz, 1H), 8.05 (s, 1H), 8.59-8.66 (m, 1H), 8.73 (s, 1H), 8.75-8.81 (m, 1H), 12.95 (br s, 1H); ESI (m/z) 338 $(M+H)^+$.
29	 1-[4-(Piperidin-4-yloxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84-1.92 (m, 2H), 2.23-2.30 (m, 2H), 3.11-3.22 (m, 3H), 4.72-4.80 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.83-7.94 (m, 2H), 8.04 (s, 1H), 8.50-8.60 (m, 1H), 8.73 (s, 1H), 8.75-8.81, 13.17 (br s, 1H); ESI (m/z) 338 $(M+H)^+$.

30	 1-[3-(Piperidin-3-yloxy)phenyl]-1H-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, J = 6.9 Hz, 1H), 1.70 (br s, 1H), 1.92 (br s, 2H), 3.08-3.18 (m, 2H), 3.32-3.43 (m, 2H), 4.84 (br s, 1H), 7.30 (d, J = 11.4 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.89 (dd, J = 8.4 Hz, 20.4 Hz, 1H), 8.05 (s, 1H), 8.59-8.66 (m, 1H), 8.73 (s, 1H), 8.75-8.81 (m, 1H), 12.95 (br s, 1H); ESI (m/z) 338 $(M+H)^+$.
31	 1-[3-(Piperidin-4-yloxy)phenyl]-1H-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (br s, 1H), 1.83-1.90 (m, 1H), 2.00-2.17 (m, 2H), 3.04-3.12 (m, 1H), 3.25-3.38 (m, 2H), 4.75-4.84 (m, 1H), 7.15-7.23 (m, 1H), 7.30-7.39 (m, 1H), 7.56-7.66 (m, 1H), 7.90-7.99 (m, 2H), 8.13-8.20 (m, 1H), 8.54-8.62 (m, 1H), 8.79-8.86 (m, 1H), 10.31 (br s, 1H), 11.10 (br s, 1H), 12.94 (br s, 1H); ESI (m/z) 338 $(M+H)^+$.
32	 1-[4-(Phenylcarbonyl)phenyl]-1H-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58-7.65 (m, 2H), 7.69-7.75 (m, 1H), 7.81-7.87 (m, 2H), 7.90-7.97 (m, 4H), 8.02 (d, J = 8.4 Hz, 2H), 8.26 (s, 1H), 8.88 (s, 1H), 13.03 (br s, 1H); APCI (m/z) 343 $(M+H)^+$.

Example 33

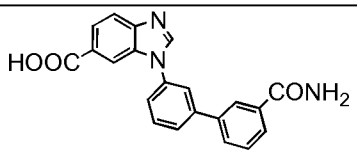
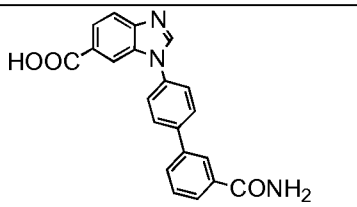
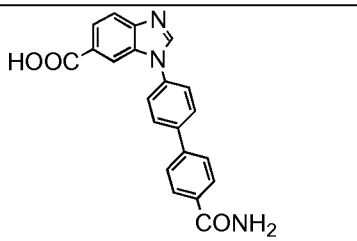
1-(4'-Carbamoylbiphenyl-3-yl)-1H-benzimidazole-6-carboxylic acid

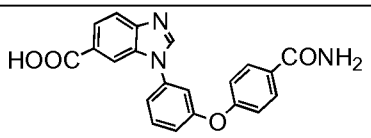
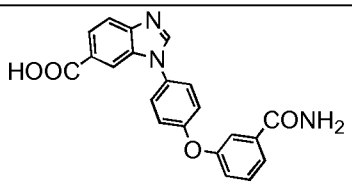
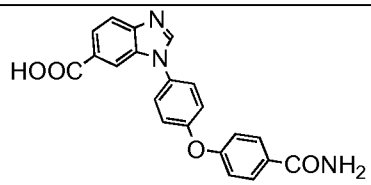


To a well-stirred, 4:1 mixture of TFA and sulfuric acid (0.33 ml) was added Example 6 (0.04 g, 0.1179 mmol) and was stirred at 50 °C overnight. The reaction mixture was cooled at room temperature and poured on crushed ice. The mixture was extracted with 5% ethanol in chloroform (2 x 75 ml), washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography to yield 18 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.77-7.83 (m, 2H), 7.90-7.96 (m, 7H), 8.00-8.10 (m, 2H), 8.18 (s, 1H), 9.08 (s, 1H); 12.85 (br s, 1H); ESI (*m/z*) 358 $(M+H)^+$.

Examples 34-39 given below were prepared from the corresponding nitriles by partial hydrolysis of the cyano group using TFA and H_2SO_4 as described above.

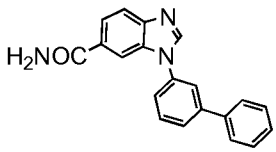
Table 2: Chemical structure, name and analytical data of Examples 34 – 39

Example no.	Structure & nomenclature	Analytical Data
34	 1-(3'-Carbamoylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.75-7.86 (m, 2H), 7.89-8.00 (m, 5H), 8.07-8.17 (m, 3H), 8.28 (s, 1H), 8.88 (s, 1H), 12.82 (br s, 1H); ESI (*m/z*) 358 $(M+H)^+$.
35	 1-(3'-Carbamoylbiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46-7.52 (m, 1H), 7.56-7.63 (m, 1H), 7.80-7.87 (m, 3H), 7.90-7.98 (m, 3H), 8.01-8.08 (m, 2H), 8.20-8.29 (m, 3H), 8.74-8.81 (m, 1H), 12.95 (br s, 1H); ESI (*m/z*) 358 $(M+H)^+$.
36	 1-(4'-Carbamoylbiphenyl-4-yl)-1*H*-	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 (br s, 1H), 7.82-7.93 (m, 6H), 8.00-8.09 (m, 5H), 8.19 (s, 1H), 8.82 (s, 1H), 12.41 (br s, 1H); ESI (*m/z*) 358 $(M+H)^+$.

	benzimidazole-6-carboxylic acid	
37	 1-[3-(4-Carbamoylphenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15-7.26 (m, 3H), 7.35 (br s, 1H), 7.51-7.61 (m, 2H), 7.67-7.74 (m, 1H), 7.86-7.96 (m, 5H), 8.17 (s, 1H), 8.99 (s, 1H), 12.95 (br s, 1H); ESI (*m/z*) 374 $(M+H)^+$.
38	 1-[4-(3-Carbamoylphenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32 (d, *J* = 9.0 Hz, 3H), 7.47-7.55 (m, 2H), 7.62 (s, 1H), 7.70-7.79 (m, 3H), 7.86-7.98 (m, 2H), 8.05-8.12 (m, 2H), 8.93 (br s, 1H), 12.95 (br s, 1H); ESI (*m/z*) 374 $(M+H)^+$.
39	 1-(4'-Carbamoylbiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.17 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 3H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.91-8.03 (m, 5H), 8.14 (s, 1H), 9.12 (s, 1H), 13.25 (br s, 1H); ESI (*m/z*) 374 $(M+H)^+$.

Example 40

1-(Biphenyl-3-yl)-1*H*-benzimidazole-6-carboxamide

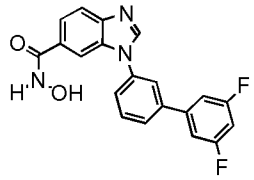


To a well stirred solution of Example 2 (25 mg, 0.0796 mmol), *N*,*N*-diisopropylethylamine (40 µl, 0.2388 mmol) and ammonium chloride (12.77 mg, 0.2388 mmol) in DMSO (5 ml), was added BOP reagent (53.0 mg, 3.182 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with water (50 ml). The aqueous layer was separated and extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with water (25 ml), brine (25 ml), dried (Na_2SO_4) and concentrated under reduced pressure to yield 22 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34-7.43 (m, 2H), 7.46-7.54 (m, 2H),

7.71-7.82 (m, 7H), 7.95 (s, 1H), 8.09 (br s, 1H), 8.17 (s, 1H), 8.79 (s, 1H); ESI (*m/z*) 314 $(M+H)^+$.

Example 41

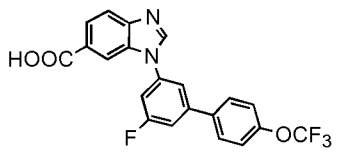
1-(3',5'-Difluorobiphenyl-3-yl)-*N*-hydroxy-1*H*-benzimidazole-6-carboxamide



To a well stirred solution of 1-(3',5'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid (Example 13) (60 mg, 0.177 mmol) in DMSO (4 ml) were added hydroxylamine.hydrochloride (37 mg, 0.531 mmol), BOP (Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; 118 mg, 0.265 mmol) and DIPEA (*N*,*N*-diisopropylethylamine; 0.09 ml, 0.531 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (20 ml). The product was extracted with ethyl acetate (2 x 25 ml). The combined organic layer was washed with brine (25 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product obtained was purified by silica gel column chromatography to yield 50 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.27 (t, J = 8.1 Hz, 1H), 7.44 (d, J = 9.3 Hz, 1H), 7.71-7.79 (m, 3H), 7.82-7.87 (m, 4H), 8.06 (s, 1H), 8.77 (s, 1H), 9.03 (br s, 1H), 11.30 (br s, 1H); APCI (*m/z*) 366 $(M+H)^+$.

Example 42

1-[5-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid



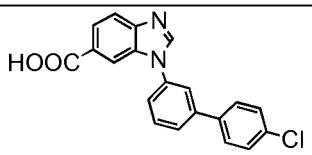
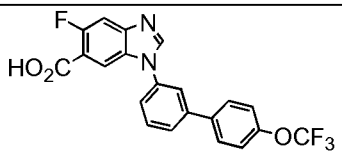
Step 1: 1-(3-Bromo-5-fluorophenyl)-1*H*-benzimidazole-6-carboxylic acid: This intermediate was prepared by reacting 3-bromo-5-fluoroaniline (276 mg, 1.491 mmol) and 3-fluoro-4-nitrobenzoic acid (276 mg, 1.789 mmol) which yielded the amino nitro intermediate, which on further reduction followed by cyclization using triethyl orthoformate as described in Example 1 afforded 140 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.76-7.83 (m, 2H), 7.86-7.95 (m, 1H), 8.14 (s, 1H), 8.77 (s, 1H).

Step 2: To the well stirred solution of Step 1 intermediate (70 mg, 0.208 mmol) in DMF (4 ml) were added 4-(trifluoromethoxy)phenylboronic acid (52 mg, 0.242

mmol) and 1 M aqueous solution of potassium carbonate (56 mg, 0.405 mmol). The reaction mixture was purged with nitrogen for 30 min. Tetrakis(triphenylphosphine) Pd(0) (12 mg, 0.010 mmol) was added to the reaction mixture and it was heated to 80-90 °C for 16 h. The reaction mixture was cooled to room temperature. The reaction was diluted with water (20 ml) and extracted with ethyl acetate (25 ml x 2). The organic layer was washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and concentrated to yield the crude product which was further purified by silica gel column chromatography to yield 20 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50-7.62 (m, 3H), 7.77 (t, J = 8.7 Hz, 2H), 7.86-7.93 (m, 4H), 8.18 (s, 1H), 8.88 (s, 1H), 12.94 (br s, 1H); ESI (m/z) 417 $(M+H)^+$.

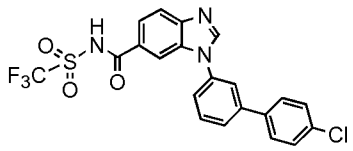
Examples 43 and 44 were prepared as described in Example 42 using appropriate aryl halide and substituted phenylboronic acid via Suzuki coupling reaction

Table 3: Chemical structure, name and analytical data of Examples 43 - 44

Example no.	Structure & nomenclature	Analytical Data
43	 1-(4'-Chlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.78-7.84 (m, 3H), 7.87-7.95 (m, 3H), 8.01-8.07 (m, 2H), 8.17 (s, 1H), 9.26 (br s, 1H).
44	 5-Fluoro-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1H-benzimidazole-6-carboxylic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 8.1 Hz, 2H), 7.69-7.78 (m, 3H), 7.80-7.87 (m, 1H), 7.95 (d, J = 8.4 Hz, 2H), 8.01-8.09 (m, 2H), 8.91 (s, 1H), 12.20 (br s, 1H); ESI (m/z) 414 $(M-H)^-$

Example 45

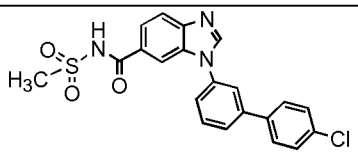
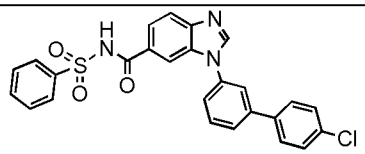
1-(4'-Chlorobiphenyl-3-yl)-*N*-[(trifluoromethyl)sulfonyl]-1*H*-benzimidazole-6-carboxamide



To a stirred solution of 1-(4'-Chlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid (Example 43) (60 mg, 0.163 mmol) in dichloromethane (5 ml) were added 1,1,1-trifluoromethanesulfonamide (30 mg, 0.201 mmol), DMAP (N,N-dimethylaminopyridine; 22 mg, 0.179 mmol) and DCC (N,N'-Dicyclohexylcarbodiimide; 50 mg, 0.244 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with ammonium chloride solution (25 ml) and extracted with ethyl acetate (2 x 25 ml). The combined organic layer was washed with water (25 ml), brine (25 ml), dried (Na_2SO_4) and concentrated to yield the crude product which was further purified by silica gel column chromatography to yield 50 mg of the pure product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56 (d, J = 8.4 Hz, 2H), 7.72-7.77 (m, 4H), 7.83-7.89 (m, 2H), 7.92-7.99 (m, 2H), 8.21 (s, 1H), 8.76 (s, 1H), 12.14 (br s, 1H); ESI (*m/z*) 478 $(M-H)^-$.

Examples 46 and 47 were prepared by coupling appropriate sulphonamide with Example 43 as described above using DCC as coupling agent.

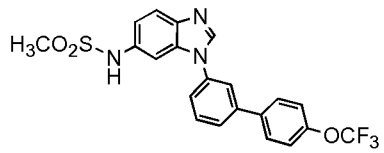
Table 4: Chemical structure, name and analytical data of Examples 46 - 47

Example no.	Structure & nomenclature	Analytical Data
46	 1-(4'-Chlorobiphenyl-3-yl)-*N*-(methylsulfonyl)-1*H*-benzimidazole-6-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 3H), 7.57 (d, J = 9.0 Hz, 2H), 7.80-7.90 (m, 7H), 8.02 (s, 1H), 8.29 (s, 1H), 8.88 (s, 1H), 12.25 (br s, 1H); ESI (*m/z*) 426 $(M+H)^+$.
47	 1-(4'-Chlorobiphenyl-3-yl)-*N*-(phenylsulfonyl)-1*H*-benzimidazole-6-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 (d, J = 8.7 Hz, 3H), 7.53 (d, J = 7.8 Hz, 2H), 7.57-7.68 (m, 6H), 7.88 (d, J = 8.4 Hz, 2H), 8.06 (s, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.88 (s, 1H), 12.10 (br s, 1H);

		ESI (*m/z*) 486 $(M-H)^-$.

Example 48

N-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}methanesulfonamide



Step 1: *tert*-Butyl [1-(3-bromophenyl)-1*H*-benzimidazol-6-yl]carbamate: To a well-stirred solution of 1-(3-Bromophenyl)-1*H*-benzimidazole-6-carboxylic acid (1.5 g, 4.731 mmol) and triethylamine (0.9 ml, 6.623 mmol) in *tert*-butanol (15 ml), was added diphenylphosphoryl azide (1.2 ml, 5.678 mmol) drop-wise over 5 min and was heated at 100 °C for 2 h. The solvent was distilled out under reduced pressure and the residue was purified by silica gel column chromatography to yield 930 mg of the pure product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (s, 9H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.57-7.63 (m, 2H), 7.64-7.72 (m, 2H), 7.90 (s, 2H), 8.44 (s, 1H), 9.40 (s, 1H).

Step 2: *tert*-butyl {1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1H-benzimidazol-6-yl}carbamate: This intermediate was prepared by Suzuki coupling reaction of Step 1 intermediate (900 mg, 2.319 mmol) with 4-trifluoromethoxyphenyl boronic acid (717 mg, 3.479 mmol) using Tetrakis(triphenylphosphine) Pd(0) (134 mg, 0.115 mmol) in presence of 1 M aqueous solution of potassium carbonate (3.5 ml, 3.479 mmol) in dry DMF (10 ml) as described in step 2 of Example 42 to yield 907 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.44 (s, 9H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.54-7.66 (m, 3H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.93-7.98 (m, 3H), 8.52 (s, 1H), 9.46 (s, 1H).

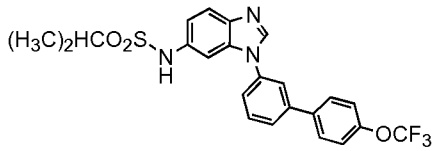
Step 3: 1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-amine: To the Step 2 intermediate (900 mg, 1.918 mmol) was added a solution of TFA (2 ml) in dichloromethane (8 ml) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The excess of solvent was distilled under reduced pressure and the residue obtained was diluted with saturated sodium bicarbonate solution (25 ml). The compound was extracted with chloroform (2 x 100 ml) and the combined organic layer was washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and concentrated to yield the crude product which was further purified by silica gel column

chromatography to yield 610 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.19 (br s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.81 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.48-7.58 (m, 2H), 7.62-7.68 (m, 1H), 7.71-7.78 (m, 2H), 7.89-7.95 (m, 3H), 8.30 (s, 1H).

Step 4: To a stirred mixture of Step 3 intermediate (100 mg, 0.271 mmol), in dichloromethane (2 ml) were sequentially added triethylamine (0.07 ml, 0.542 mmol) and methanesulphonyl chloride (0.02 ml, 0.298 mmol) at 0 °C and the resulting mixture was stirred at the same temperature for 1 h. The mixture was diluted with water (20 ml) and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with water (20 ml), brine (20 ml), dried (Na_2SO_4), and concentrated to yield the crude product which was further purified by silica gel column chromatography to yield 40 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.93 (s, 3H), 7.20 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.69-77.73 (m, 2H), 7.75-7.82 (m, 2H), 7.91-7.96 (m, 3H), 8.63 (s, 1H), 9.70 (s, 1H); ESI (*m/z*) 448 $(M+H)^+$.

Example 49

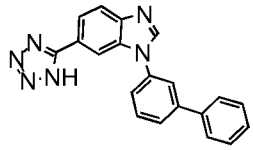
N-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}propane-2-sulfonamide



To the well-stirred solution of 1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-amine (50 mg, 0.135 mmol) in dry pyridine (1 ml) was added isopropylsulphonyl chloride (0.18 ml, 0.162 mmol) at 0 °C and was stirred at room temperature for 5 h. The reaction mixture was quenched with 1N HCl and extracted with ethyl acetate (2 x 25 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (Na_2SO_4),filtered and concentrated to yield the crude product which was further purified by silica gel column chromatography to yield 20 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.19 (d, J = 6.9 Hz, 6H), 3.22 (br s, 1H), 7.21 (d, J = 6.9 Hz, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.59 (s, 1H), 7.65-7.73 (m, 2H), 7.74-7.82 (m, 2H), 7.93 (d, J = 7.8 Hz, 3H), 8.61 (s, 1H), 9.80 (s, 1H); ESI (*m/z*) 476 $(M+H)^+$.

Example 50

1-(Biphenyl-3-yl)-6-(1*H*-tetrazol-5-yl)-1*H*-benzimidazole



Step 1: 3-(Biphenyl-3-ylamino)-4-nitrobenzonitrile: This intermediate was prepared by coupling reaction of 3-fluoro-4-nitrobenzonitrile (0.5 g, 3.012 mmol) with biphenyl-3-amine (0.560 g, 3.313 mmol) using sodium hydride (0.180 g, 4.518 mmol) in DMSO (10 ml) as described in Step 1 of Example 1 to yield 0.175 g of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.23 (d, J = 9.0 Hz, 1H), 7.30-7.55 (m, 6H), 7.62 (s, 1H), 7.68 (d, J = 9.3 Hz, 2H), 8.22 (d, J = 9.0 Hz, 1H), 9.53 (s, 1H), 11.82 (br s, 1H); ESI (*m/z*) 315 $(M+H)^+$.

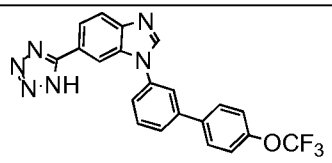
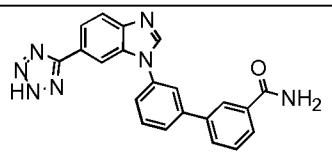
Step 2: *N*-[2-Nitro-5-(1*H*-tetrazol-5-yl)phenyl]biphenyl-3-amine: To a well stirred solution of Step 1 intermediate (170 mg, 0.539 mmol) in DMF (2 ml), was added ammonium chloride (37.52 mg 0.701 mmol) and sodium azide (46 mg, 0.701 mmol) and stirred at 80 °C at inert atmosphere overnight. The solvent was distilled out under reduced pressure and the residue obtained was diluted with water (50 ml). The product was extracted with ethyl acetate (3 x 75 ml). The combined organic layer was washed with brine (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.14 g of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32-7.60 (m, 6H), 7.65-7.75 (m, 3H), 8.00 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 9.61 (s, 2H); ESI (*m/z*) 357 $(M-H)^-$.

Step 3: N^2-(Biphenyl-3-yl)-4-(1*H*-tetrazol-5-yl)benzene-1,2-diamine: This intermediate was prepared by catalytic reduction of nitro group of Step 2 intermediate (0.125 g, 0.349 mmol) using H_2, Pd/C (0.040 g) in methanol (10 ml) as described in procedure of step 2 of Example 1 to yield 0.102 g of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.40-5.48 (m, 3H), 6.79 (d, J = 7.8 Hz, 2H), 6.86 (d, J = 7.2 Hz, 2H), 6.95-7.05 (m, 1H), 7.20-7.60 (m, 7H), 7.77 (s, 1H), 16.21 (br s, 2H); ESI (*m/z*) 329 $(M+H)^+$.

Step 4: This title compound was prepared by reaction of Step 3 intermediate (0.125 g, 0.381 mmol) with triethyl orthoformate (0.095 ml, 0.572 mmol) and sulphamic acid (3.70 mg, 0.038 mmol) in methanol (2 ml) as described in step 3 of Example 1 to yield 80 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40-7.47 (m, 1H), 7.50-7.57 (m, 2H), 7.76-7.82 (m, 2H), 7.83-7.92 (m, 3H), 7.99-8.07 (m, 3H), 8.34 (s, 1H), 8.68 (s, 1H), 16.78 (br s, 1H); APCI (*m/z*) 339 $(M+H)^+$.

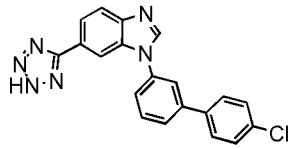
Examples 51 and 52 were prepared in four steps from 3-fluoro-4-nitrobenzonitrile and appropriate biphenyl amine compounds as described in Example 50.

Table 5: Chemical structure, name and analytical data of Examples 51 – 52

Example no.	Structure & nomenclature	Analytical Data
51	 6-(1*H*-Tetrazol-5-yl)-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 7.8 Hz, 2H), 7.78-7.89 (m, 3H), 7.95-8.06 (m, 5H), 8.34 (s, 1H), 8.86 (s, 1H), 16.81 (br s, 1H); ESI (m/z) 423 $(M+H)^+$.
52	 3'-[6-(2*H*-Tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.80-7.85 (m, 3H), 7.90-8.02 (m, 4H), 8.12 (s, 2H), 8.31 (d, *J* = 10.8 Hz, 2H), 8.86 (s, 1H), 16.95 (br s, 1H); ESI (*m/z*) 382 $(M+H)^+$.

Example 53

1-(4'-Chlorobiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole



Step 1: 3-[(3-Iodophenyl)amino]-4-nitrobenzonitrile: To a well-stirred solution 3-fluoro-4-nitrobenzonitrile (3.5 g, 21.084 mmol) in DMF were added 3-iodoaniline (6.9 g, 31.624 mmol) and DIPEA (54 ml, 42.168 mmol) and the reaction mixture was heated to 80 °C for 16 h. The reaction mixture was quenched with water (150 ml), diluted with methanol (50 ml) and stirred for 30 min. The precipitate obtained was filtered to yield 5.8 g of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (t, *J* = 7.8 Hz, 1H), 7.29-7.38 (m, 2H), 7.56 (d, *J* = 5.4 Hz, 2H), 7.70 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 9.39 (s, 1H).

Step 2 *N*-(3-Iodophenyl)-2-nitro-5-(2*H*-tetrazol-5-yl)aniline: This intermediate was prepared by reaction of Step 1 intermediate (4 g, 10.958 mmol) with sodium azide (926 mg, 14.246 mmol) in the presence of ammonium chloride (760 mg 14.246 mmol) in DMF (30 ml) as described in step 2 of Example 50 to yield 4.9 g of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.22 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H), 7.88 (s, 1H), 8.24 (d, *J* = 8.7 Hz, 1H), 9.43 (s, 1H).

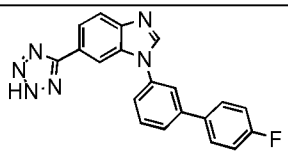
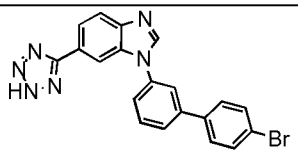
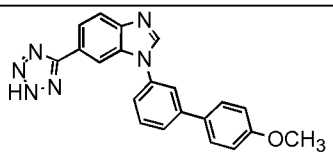
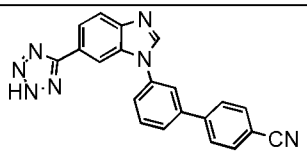
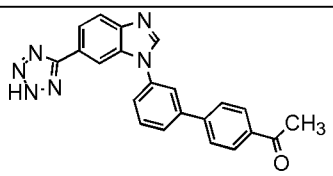
Step 3: N^2-(3-Iodophenyl)-4-(2*H*-tetrazol-5-yl)benzene-1,2-diamine: To the well stirred solution of Step 2 intermediate (3.6 g, 8.823 mmol) in ethanol (36 ml) was added aqueous ammonium chloride solution (4.72 g, 88.255 mmol) and the reaction mixture was refluxed. At the reflux temperature, iron powder (1.47 g, 26.47 mmol) was added portion-wise to the reaction mixture and it was further refluxed for 0.5 h. The reaction mixture was diluted with ethyl acetate (500 ml) and filtered. The filtrate was washed with water (2 x 50 ml), brine (50 ml), dried (Na_2SO_4) and concentrated to yield 2.2 g of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.50 (s, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.86-6.6.95 (m, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 7.50 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H).

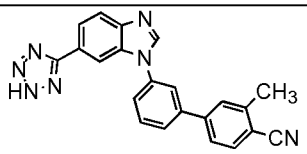
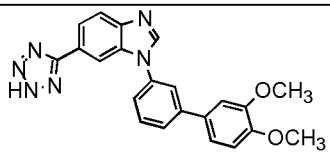
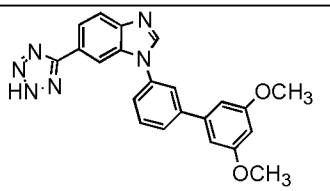
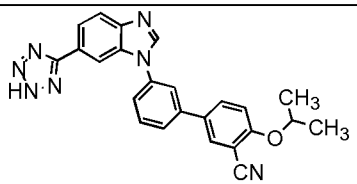
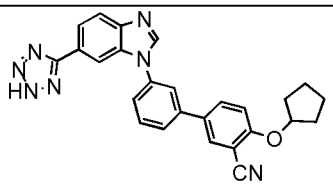
Step 4: 1-(3-Iodophenyl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole: This intermediate was prepared by reaction of Step 3 intermediate (2.2 g, 5.820 mmol) with triethyl orthoformate (1.6 ml, 8.730 mmol) and sulphamic acid (57 mg, 0.582 mmol) in methanol (100 ml) as described in Step 3 of Example 1 to yield 2 g of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.91-8.02 (m, 2H), 8.12 (s, 1H), 8.23 (s, 1H), 8.73 (s, 1H), 16.82 (br s, 1H).

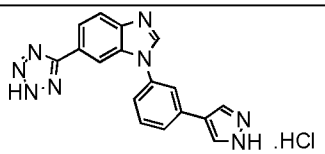
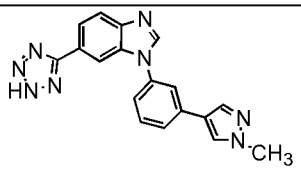
Step 5: The title compound was prepared by Suzuki coupling reaction of Step 4 intermediate (70 mg, 0.179 mmol) with 4-chlorophenylboronic acid (37 mg, 0.236 mmol) using Tetrakis(triphenylphosphine) Pd(0) (10 mg, 0.0089 mmol) in presence of 1 M aqueous solution of potassium carbonate (50 mg, 0.361 mmol) in DMF (5 ml) as described in step 2 of Example 42 to yield 30 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 5.1 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 3H), 7.96-8.04 (m, 3H), 8.32 (s, 1H), 8.85 (s, 1H), 16.91 (br s, 1H); APCI (*m/z*) 373 $(M+H)^+$.

Examples 54-65 shown below were prepared by Suzuki coupling reaction of 1-(3-iodophenyl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole with substituted phenylboronic acids as described in Example 53.

Table 6: Chemical structure, name and analytical data of Examples 54 – 65

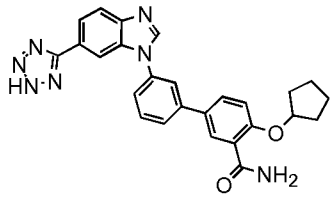
Example no.	Structure & nomenclature	Analytical Data
54	 1-(4'-Fluorobiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33 (d, J = 9.0 Hz, 2H), 7.74-7.79 (m, 2H), 7.83-7.90 (m, 3H), 7.95-8.04 (m, 3H), 8.31 (s, 1H), 8.82 (s, 1H), 16.81 (br s, 1H); APCI (*m/z*) 357 $(M+H)^+$.
55	 1-(4'-Bromobiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 (d, J = 8.4 Hz, 2H), 7.78-7.83 (m, 4H), 7.88 (br s, 1H), 7.98-8.04 (m, 3H), 8.32 (s, 1H), 8.84 (s, 1H), 16.88 (br s, 1H); ESI (*m/z*) 417 $(M+H)^+$.
56	 1-(4'-Methoxybiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 7.07 (d, J = 8.7 Hz, 2H), 7.67-7.72 (m, 1H), 7.74-7.84 (m, 4H), 7.96 (s, 1H), 8.01-8.05 (m, 2H), 8.33 (s, 1H), 8.84 (s, 1H), 16.90 (br s, 1H); APCI (*m/z*) 369 $(M+H)^+$.
57	 3'-[6-(2*H*-Tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (br s, 2H), 7.93-8.08 (m, 7H), 8.12 (s, 1H), 8.31 (s, 1H), 8.81 (s, 1H), 16.87 (br s, 1H); ESI (*m/z*) 362 $(M-H)^-$.
58	 1-(4'-Acetylbiphenyl-3-yl)-6-(2*H*-	^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 3H), 7.83 (br s, 2H), 7.96-8.07 (m, 5H), 8.09-8.13 (m, 3H), 8.33 (s, 1H), 8.86 (s, 1H), 16.85 (br s, 1H);

	tetrazol-5-yl)-1*H*-benzimidazole	ESI (*m/z*) 381 $(M+H)^+$.
59	 3-Methyl-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile	^{1}H NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3H), 7.82-7.93 (m, 4H), 7.99-8.03 (m, 4H), 8.13 (s, 1H), 8.32 (s, 1H), 8.86 (s, 1H), 16.95 (br s, 1H); APCI (*m/z*) 378 $(M+H)^+$.
60	 1-(3',4'-Dimethoxybiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 3.85 (s, 3H), 7.08 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.68-7.77 (m, 2H), 7.85 (d, *J* = 7.5 Hz, 1H), 8.02 (br s, 3H), 8.34 (s, 1H), 8.85 (s, 1H), 16.68 (br s, 1H); APCI (*m/z*) 399 $(M+H)^+$.
61	 1-(3',5'-Dimethoxybiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 6H), 6.54 (s, 1H), 6.94 (s, 2H), 7.74 (br s, 2H), 7.85 (br s, 1H), 7.97-8.01 (m, 3H), 8.31 (s, 1H), 8.84 (s, 1H), 16.75 (br s, 1H); APCI (*m/z*) 399 $(M+H)^+$.
62	 4-(Propan-2-yloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carbonitrile	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (d, *J* = 5.7 Hz, 6H), 4.84-4.91 (m, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.76 (br s, 2H), 7.89 (br s, 1H), 7.98-8.03 (m, 2H), 8.05-8.14 (m, 2H), 8.26 (s, 1H), 8.33 (s, 1H), 8.85 (s, 1H), 16.89 (br s, 1H); APCI (*m/z*) 420 $(M-H)^-$.
63	 4-(Cyclopentyloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (br s, 1H), 1.76 (br s, 5H), 1.97 (br s, 2H), 5.09 (br s, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.76 (br s, 2H), 7.89 (br s, 1H), 7.99-8.05 (m, 2H), 8.06-8.14 (m, 2H), 8.26 (s, 1H),

	yl]biphenyl-3-carbonitrile	8.33 (s, 1H), 8.85 (s, 1H), 16.90 (br s, 1H); APCI (*m/z*) 448 $(M+H)^+$.
64	 1-[3-(1*H*-Pyrazol-4-yl)phenyl]-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 8.01-8.07 (m, 3H), 8.14 (d, *J* = 9.0 Hz, 1H), 8.24 (s, 2H), 8.36 (s, 1H), 9.12 (br s, 1H), 16.79 (br s, 1H); ESI (*m/z*) 329 $(M+H)^+$.
65	 1-[3-(1-Methyl-1*H*-pyrazol-4-yl)phenyl]-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.95 (s, 1H), 7.99-8.06 (m, 2H), 8.32 (s, 3H), 8.78 (s, 1H), 16.90 (br s, 1H); APCI (*m/z*) 343 $(M+H)^+$.

Example 66

4-(Cyclopentyloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carboxamide

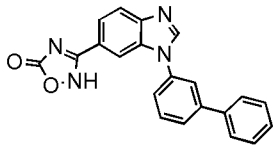


To 4-(cyclopentyloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carbonitrile (Example 63) (60 mg, 0.134 mmol) was added a solution of sulphuric acid (0.2 ml) in TFA (0.6 ml) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with ice cold water (25 ml) and was extracted with chloroform (2 x 25 ml). The combined organic layer was washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and concentrated to yield the crude product which was further purified by silica gel column chromatography to yield 15 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (br s, 4H), 1.68 (br s, 2H), 1.93 (br s, 2H), 4.27 (br s, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.70-7.80 (m, 2H),

7.88 (br s, 2H), 7.97-8.06 (m, 2H), 8.30 (d, *J* = 7.8 Hz, 2H), 8.74 (d, *J* = 6.9 Hz, 1H), 8.82 (s, 1H), 12.97 (s, 1H), 16.68 (br s, 1H); APCI (*m/z*) 466 $(M+H)^+$.

Example 67

3-[1-(Biphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one



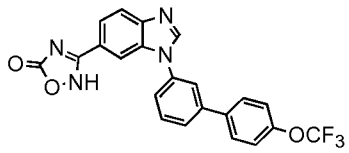
Step 1: 1-(Biphenyl-3-yl)-1*H*-benzimidazole-6-carbonitrile: The title compound was prepared by coupling 3-fluoro-4-nitrobenzonitrile (360 mg, 2.168 mmol) and biphenyl-3-amine (400 mg, 2.366 mmol) followed by reduction and cyclization as described in Example 1 to yield 250 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40-7.46 (m, 1H), 7.49-7.54 (m, 2H), 7.74 (br s, 3H), 7.83 (d, *J* = 7.2 Hz, 3H), 7.97 (d, *J* = 9.3 Hz, 2H), 8.26 (s, 1H), 8.96 (s, 1H).

Step 2: 1-(Biphenyl-3-yl)-*N*-hydroxy-1*H*-benzimidazole-6-carboximidamide: To the well stirred solution of Step 1 intermediate (250 mg, 0.847 mmol) in DMF (6 ml) was added hydroxylamine.hydrochloride (220 mg, 3.165 mmol) followed by DIPEA (0.53 ml, 3.120 mmol) and the reaction mixture was stirred at 60-70 °C for 18 h. The reaction mixture was diluted with water and stirred for 30 min. The precipitate obtained was filtered, washed with water and dried to yield 220 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.88 (s, 1H), 7.38-7.43 (m, 1H), 7.50 (d, *J* = 6.9 Hz, 2H), 7.65-7.72 (m, 3H), 7.75-7.81 (m, 3H), 7.93 (s, 1H), 8.69 (s, 1H), 9.58 (s, 1H).

Step 3: To the well stirred solution of Step 2 intermediate (220 mg, 0.670 mmol) in DMF (6 ml) was added CDI (1,1'-carbonyldiimidazole; 110 mg, 0.670 mmol) and the reaction mixture was heated at 100°C for 8 h. The reaction mixture was diluted with water and stirred for 30 min. The precipitate obtained was filtered, washed with water and dried to yield the crude product which was further purified by silica gel column chromatography to yield 110 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40-7.46 (m, 1H), 7.49-7.54 (m, 2H), 7.72-7.79 (m, 3H), 7.82-7.88 (m, 3H), 7.95 (s, 1H), 8.00 (br s, 1H), 8.14 (s, 1H), 8.87 (s, 1H), 13.02 (br s, 1H); APCI (*m/z*) 355 $(M+H)^+$.

Example 68

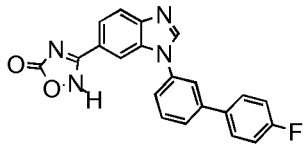
3-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}-1,2,4-oxadiazol-5(2*H*)-one



The title compound was prepared by reaction of 3-fluoro-4-nitrobenzonitrile (580 mg, 3.493 mmol) with 4'-(trifluoromethoxy)biphenyl-3-amine (972 mg, 3.843 mmol) followed by reduction of nitro group, cyclization and subsequent oxadiazolone formation as described in Example 67 to yield 40 mg of the product; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.77-7.82 (m, 3H), 7.88 (br s, 1H), 7.97 (d, *J* = 8.1 Hz, 3H), 8.04 (s, 1H), 8.14 (s, 1H), 8.87 (s, 1H), 13.02 (br s, 1H); ESI (*m/z*) 439 $(M+H)^+$.

Example 69

3-[1-(4'-Fluorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2H)-one



Step 1: 4-Amino-3-[(3-bromophenyl)amino]benzonitrile: The title compound was prepared by coupling 3-fluoro-4-nitrobenzonitrile (5 g, 30.12 mmol) and 3-bromoaniline (5.7 g, 33.132 mmol) followed by reduction and cyclization as described in Example 1 to yield 4.6 g of the product; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.59 (d, *J* = 9.3 Hz, 1H), 7.69-7.80 (m, 3H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 2H), 8.03 (s, 1H), 8.22 (s, 1H), 8.87 (s, 1H).

Step 2: 1-(3-Bromophenyl)-*N*-hydroxy-1*H*-benzimidazole-6-carboximidamide: This intermediate was prepared by reaction of Step 1 intermediate (1.5 g, 5.033 mmol) with hydroxylamine.hydrochloride (1.3 g, 18.624 mmol) in DMSO (20 ml) using DIPEA (3.2 ml, 18.624 mmol) as described in procedure of step 2 of Example 67 to yield 1.56 g of product; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 5.92 (br s, 2H), 7.55-7.80 (m, 5H), 7.89 (s, 1H), 7.99 (s, 1H), 8.62 (s, 1H), 9.63 (s, 1H); APCI (*m/z*) 331 $(M+H)^+$.

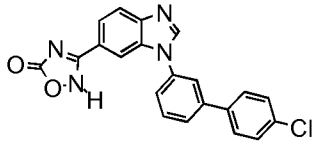
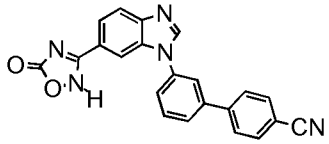
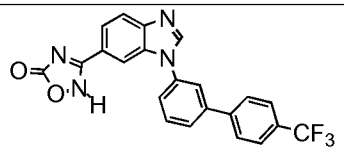
Step 3: 3-[1-(3-Bromophenyl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one: This intermediate was prepared by reaction of Step 2 intermediate (1.5 g, 4.531 mmol) with CDI (1,1'-carbonyldiimidazole; 810 mg, 4.90 mmol) in DMF (15 ml) as described in procedure of step 3 of Example 67 to yield 1.3 g of the product; ^{1}H NMR

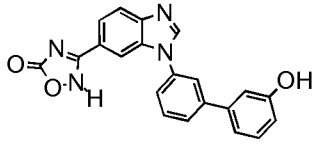
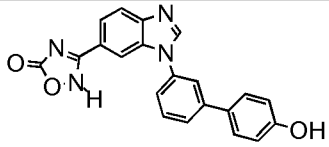
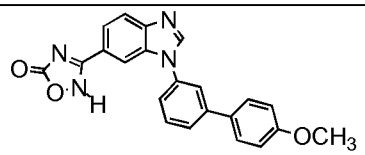
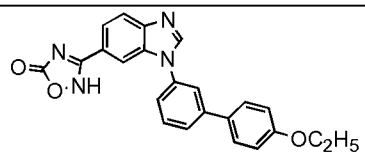
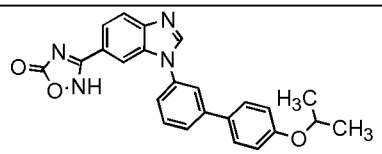
(300 MHz, DMSO-d_6) δ 7.55-7.69 (m, 1H), 7.70-7.78 (m, 4H), 7.96 (s, 2H), 8.62 (s, 1H); APCI (*m/z*) 357 $(M+H)^+$.

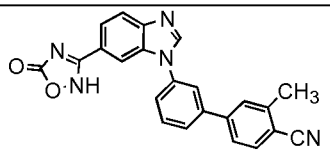
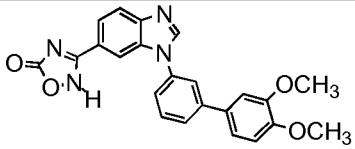
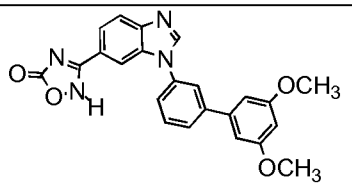
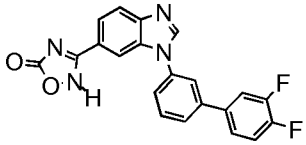
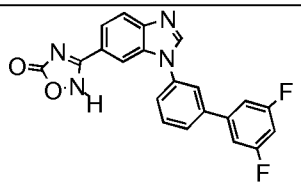
Step 4: The title compound was prepared by Suzuki coupling reaction of Step 3 intermediate (100 mg, 0.280 mmol) with 4-fluorophenylboronic acid (45 mg, 0.336 mmol) using Tetrakis(triphenylphosphine) Pd(0) (17 mg, 0.014 mmol) in presence of 1 M aqueous solution of potassium carbonate (0.6 ml, 0.57 mmol) in dry DMF (5 ml) as described in procedure in step 2 of Example 42 to yield 50 mg of product, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35 (t, J = 9.0 Hz, 2H), 7.74-8.00 (m, 8H), 8.14 (s, 1H), 8.87 (s, 1H), 13.01 (br s, 1H); ESI (*m/z*) 371 $(M-H)^-$.

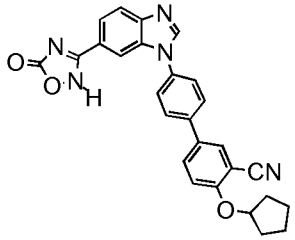
Examples 70-83 were prepared by Suzuki coupling reaction of 3-[1-(3-bromophenyl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one with substituted phenylboronic acids as described in Example 69.

Table 7: Chemical structure, name and analytical data of Examples 70 - 83

Example no.	Structure & nomenclature	Analytical Data
70	 3-[1-(4'-Chlorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.12-8.02 (m, 8H), 8.14 (s, 1H), 8.87 (s, 1H), 13.01 (br s, 1H); ESI (*m/z*) 387 $(M-H)^-$.
71	 3'-[6-(5-Oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80-7.89 (m, 3H), 7.96-8.14 (m, 8H), 8.89 (s, 1H), 13.02 (br s, 1H) ESI (*m/z*) 378 $(M-H)^-$.
72	 3-{1-[4'-(Trifluoromethyl)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79-7.85 (m, 3H), 7.88 (d, J = 7.8 Hz, 2H), 7.94-8.00 (m, 2H), 8.02-8.09 (m, 3H), 8.15 (s, 1H), 8.89 (s, 1H), 13.01 (br s, 1H); ESI (*m/z*) 423 $(M+H)^+$.

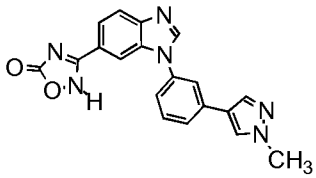
73	 3-[1-(3'-Hydroxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.82 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.24-7.33 (m, 2H), 7.72-7.81 (m, 4H), 7.91-7.99 (m, 2H), 8.13 (s, 1H), 8.86 (s, 1H), 9.62 (s, 1H), 13.03 (br s, 1H); APCI (*m/z*) 371 $(M+H)^+$.
74	 3-[1-(4'-Hydroxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.89 (d, J = 7.8 Hz, 2H), 7.61-7.73 (m, 3H), 7.77-7.83 (m, 3H), 7.89 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 8.14 (s, 1H), 8.85 (s, 1H), 9.69 (s, 1H), 13.03 (br s, 1H); APCI (*m/z*) 371 $(M+H)^+$.
75	 3-[1-(4'-Methoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 7.05 (d, J = 8.4 Hz, 2H), 7.60-7.79 (m, 6H), 7.92-8.00 (m, 2H), 8.12 (s, 1H), 8.84 (s, 1H), 13.01 (br s, 1H); ESI (*m/z*) 383 $(M-H)^-$.
76	 3-[1-(4'-Ethoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2H)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (t, J = 6.9 Hz, 3H), 4.08 (q, J = 6.9 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 7.60-7.81 (m, 6H), 7.90-7.98 (m, 2H), 8.14 (s, 1H), 8.85 (s, 1H), 13.01 (br s, 1H); APCI (*m/z*) 399 $(M+H)^+$.
77	 3-(1-(4'-Isopropoxy-[1,1'-biphenyl]-3-yl)-1H-benzo[d]imidazol-6-yl)-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (d, J = 5.4 Hz, 6H), 4.62-4.70 (m, 1H), 7.02 (d, J = 8.1 Hz, 2H), 7.58-7.80 (m, 6H), 7.90-7.98 (m, 2H), 8.12 (s, 1H), 8.83 (s, 1H), 12.99 (br s, 1H); APCI (*m/z*) 413 $(M+H)^+$.

78	 3-Methyl-3'-[6-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile	^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57 (s, 3H), 7.79-7.87 (m, 4H), 7.90-7.98 (m, 4H), 8.11 (d, *J* = 7.5 Hz, 2H), 8.87 (s, 1H), 13.01 (br s, 1H); APCI (*m/z*) 392 $(M-H)^-$.
79	 3-[1-(3',4'-Dimethoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 3.85 (s, 3H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.33-7.40 (m, 2H), 7.64-7.75 (m, 4H), 7.92-7.99 (m, 2H), 8.14 (s, 1H), 8.86 (s, 1H), 13.01 (br s, 1H); ESI (*m/z*) 413 $(M-H)^-$.
80	 3-[1-(3',5'-Dimethoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 6H), 6.54 (s, 1H), 6.93 (s, 2H), 7.70-7.83 (m, 4H), 7.93-8.00 (m, 2H), 8.12 (s, 1H), 8.85 (s, 1H), 13.00 (br s, 1H); ESI (*m/z*) 413 $(M-H)^-$.
81	 3-[1-(3',4'-Difluorobiphenyl-3-yl)-1H-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2H)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56-7.64 (m, 1H), 7.70-7.79 (m, 4H), 7.82-7.90 (m, 1H), 7.94-8.06 (m, 3H), 8.14 (s, 1H), 8.88 (s, 1H), 13.02 (br s, 1H); APCI (*m/z*) 391 $(M+H)^+$.
82	 3-[1-(3',5'-Difluorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26-7.35 (m, 1H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.75-7.85 (m, 3H), 7.94-8.01 (m, 2H), 8.13 (d, *J* = 7.5 Hz, 2H), 8.89 (s, 1H), 13.02 (br s, 1H); ESI (*m/z*) 391 $(M+H)^+$.

83	 4-(Cyclopentyloxy)-3'-[6-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carbonitrile	^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (s, 1H), 1.60-1.67 (m, 2H), 1.73-1.80 (m, 3H), 1.94-2.01 (m, 2H), 5.06-5.13 (m, 1H), 7.38 (d, *J* = 9.3 Hz, 1H), 7.70-7.82 (m, 3H), 7.85-7.97 (m, 3H), 8.05-8.15 (m, 2H), 8.26 (s, 1H), 8.87 (s, 1H), 13.02 (br s, 1H); ESI (*m/z*) 464 $(M+H)^+$.

Example 84

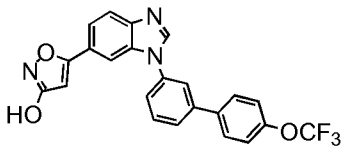
3-{1-[3-(1-Methyl-1*H*-pyrazol-4-yl)phenyl]-1*H*-benzimidazol-6-yl}-1,2,4-oxadiazol-5(2*H*)-one



To a mixture of sodium carbonate (62 mg, 0.597 mmol) and palladium acetate (7 mg, 0.029 mmol), was added polyethylene glycol 200 (2 ml) followed by water (3 ml), and nitrogen gas was purged into it. The reaction mixture was heated to 50-60 °C for 30 min. To the reaction mixture was added 3-[1-(3-bromophenyl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one (100 mg, 0.290 mmol), followed by N-methyl-1*H*-pyrazole 4-boronic acid pinacol ester (78 mg, 0.370 mmol) in polyethylene glycol 200 (2 ml) and heated to 80-85 °C for 16 h. The solvent was distilled out under reduced pressure to obtain crude residue. To this residue, methanol (10 ml) was added and evaporated under reduced pressure. The crude solid was purified by column chromatography to yield 20 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30-3.53 (m, 3H), 4.55-4.63 (m, 2H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.72-7.85 (m, 3H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 8.08 (s, 1H), 8.79 (s, 1H), 13.03 (s, 1H); ESI (*m/z*) 357 $(M-H)^-$.

Example 85

5-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}-1,2-oxazol-3-ol



Step 1: 1-(3-Bromophenyl)-1*H*-benzimidazole-6-carboxylic acid: This intermediate was prepared by coupling reaction of 3-fluoro-4-nitrobenzoic acid (5 g, 27.011 mmol) with 3-bromoaniline (3.529 ml, 32.413 mmol) furnished the amino nitro intermediate, which upon reduction to diamine and cyclisation to the corresponding benzimidazole using triethyl orthoformate as described in Example 1 affords 4.5 g of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, *J* = 7.8 Hz, 1H), 7.70-7.79 (m, 2H), 7.89 (dd, *J* = 9.0 Hz, 22.5 Hz, 2H), 8.01 (s, 1H), 8.11 (s, 1H), 8.78 (s, 1H), 12.98 (br s, 1H) ; ESI (*m/z*) 317 $(M)^+$.

Step 2: 1-(3-Bromophenyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-6-carboxamide: *N,O*-dimethylhydroxylamine hydrochloride (0.692 g, 7.098 mmol) was added to a stirred mixture of Step 1 intermediate (1.50 g, 4.732 mmol), hydroxybenzotriazole (0.959 g, 7.098 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.36 g, 7.098 mmol) in dry DMF (20 ml) at 0 °C and the suspension was stirred for 15 min. To this suspension *N*-methyl morpholine (2.09 ml, 18.927 mmol) was added and the resultant mixture was stirred at room temperature overnight. The reaction was quenched with water (75 ml) and extracted with ethyl acetate (3 x 75 ml). The combined organic layer was washed with water (150 ml), brine (150 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography to yield 1.6 g of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.56 (s, 3H), 7.40-7.52 (m, 2H), 7.59-7.66 (m, 1H), 7.69-7.75 (m, 2H), 7.84-7.92 (m, 2H), 8.19 (s, 1H).

Step 3: 1-[1-(3-Bromophenyl)-1*H*-benzimidazol-6-yl]ethanone: To a cooled solution of Step 2 intermediate (1.1 g, 3.055 mmol) in dry THF (20 ml), methyl magnesium bromide (2.55 ml, 7.638 mmol) was drop wise added and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was slightly warmed to room temperature and was quenched with saturated solution of ammonium chloride (50 ml). The mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with water (100 ml), brine (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude solid was purified by column chromatography to yield 715 mg of product; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3H), 7.50 (d, *J* = 6.9 Hz,

2H), 7.63-7.71 (m, 2H), 7.95 (dd, *J* = 8.7 Hz, 19.8 Hz, 2H), 8.16 (s, 1H), 8.23 (s, 1H); ESI (*m/z*) 315 $(M)^+$.

Step 4: Methyl 3-[1-(3-bromophenyl)-1*H*-benzimidazol-6-yl]-3-oxopropanoate: To a cooled solution of Step 3 intermediate (700 mg, 2.220 mmol) in dry THF (20 ml), was added sodium hydride (355 mg, 8.888 mmol) and the resulting suspension was stirred at 0 °C for 20 min. To this suspension dimethyl carbonate (0.281 ml, 3.330 mmol) was drop wise added and the reaction mixture was gradually heated to 85 °C for 4 h. The reaction mixture was cooled to room temperature and quenched with saturated solution of ammonium chloride (25 ml). The mixture was extracted with ethyl acetate (2 x 100 ml). The combined organic layer was washed with water (100 ml), brine (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude solid was purified by column chromatography to yield 635 mg of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.08 (s, 2H), 7.49 (d, *J* = 6.0 Hz, 2H), 7.62-7.71 (m, 2H), 7.93 (s, 2H), 8.15-8.27 (m, 2H); ESI (*m/z*) 373 $(M)^+$.

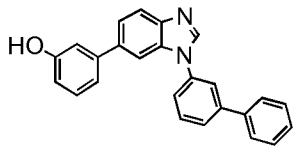
Step 5: 5-[1-(3-Bromophenyl)-1*H*-benzimidazol-6-yl]-1,2-oxazol-3-ol: To a cooled solution of sodium hydroxide (142 mg, 3.547 mmol) in methanol (2 ml) and water (2 ml), was drop wise added suspension of Step 4 intermediate (630 mg, 1.689 mmol) in methanol (2 ml) at -20 °C. The reaction mixture was stirred for 20 min at 0 °C, then freshly prepared hydroxylamine (235 mg, 3.378 mmol) was added at -30 °C and was stirred for 2 h at same temperature. To the mixture was added acetone (7 ml) followed by the addition of concentrated hydrochloric acid (18 ml) and the resulting mixture was heated to 80 °C for 1 h. The reaction mixture was cooled to room temperature and was poured in saturated solution of sodium bicarbonate (50 ml). The mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic extract was washed with water (100 ml), brine (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography to yield 120 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.63 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.70-7.82 (m, 3H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.95 (s, 1H), 8.02 (s, 1H), 8.71 (s, 1H), 11.36 (s, 1H); ESI (*m/z*) 356 $(M)^-$.

Step 6: The title compound was prepared by Suzuki coupling reaction of Step 5 intermediate (50 mg, 0.140 mmol) with 4-trifluoromethoxyphenylboronic acid (43 mg, 0.211 mmol) using Tetrakis(triphenylphosphine) Pd(0) (24 mg, 0.021 mmol) in presence of 1 M aqueous solution of potassium carbonate (0.7 ml, 0.702 mmol) in dry

DMF (2 ml) as described in procedure in step 2 of Example 42 to yield 15 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.62 (s, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.78 (s, 1H), 7.86-8.02 (m, 8H), 8.80 (s, 1H), 11.36 (s, 1H); ESI (m/z) 438 $(M+H)^+$.

Example 86

3-(1-([1,1'-Biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)phenol



Step 1: *N*-(5-Bromo-2-nitrophenyl)biphenyl-3-amine: This intermediate was prepared by coupling reaction of 4-bromo-2-fluoro-1-nitrobenzene (1 g, 4.545 mmol) with 3-phenylaniline (840 mg, 4.97 mmol) using sodium hydride (290 mg, 7.272 mmol) in DMSO (20 ml) as described in procedure of step 1 of Example 1 to yield 500 mg of the product.

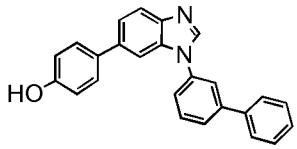
Step 2: 3'-(Biphenyl-3-ylamino)-4'-nitrobiphenyl-3-ol: This intermediate was prepared by Suzuki coupling reaction of Step 1 intermediate (200 mg, 0.909 mmol) with 3-hydroxyphenylboronic acid (140 mg, 0.99 mmol) using Tetrakis(triphenylphosphine) Pd(0) (52 mg, 0.045 mmol) in presence of 1 M aqueous solution of potassium carbonate (1.8 ml, 1.80 mmol) in dry DMF (5 ml) as described in procedure in step 2 of Example 42 to yield 87 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.80-6.88 (m, 1H), 6.92 (s, 1H), 7.06-7.15 (m, 1H), 7.20-7.30 (m, 3H), 7.35-7.45 (m, 4H), 7.65-7.72 (m, 2H), 7.98 (d, J = 9.3 Hz, 1H), 8.21 (d, J = 9.9 Hz, 1H), 9.57 (s, 1H), 9.65-9.72 (m, 2H), 11.06 (br s, 1H); APCI (m/z) 383 $(M+H)^+$.

Step 3: 4'-Amino-3'-(biphenyl-3-ylamino)biphenyl-3-ol: This intermediate was prepared by nitro group reduction of Step 2 intermediate (85 mg) using Pd/C (20 mg) in methanol (7 ml) as described in Step 2 of Example 1 to yield 63 mg of product.

Step 4: The title compound was prepared by reaction of Step 3 intermediate (60, 0.170 mmol) with triethyl orthoformate (50 µl, 0.255 mmol) using sulfamic acid (2 mg, 0.018 mmol) in methanol (4 ml) as described in step 3 of Example 1 to yield 10 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.69-6.80 (m, 1H), 7.03-7.14 (m, 2H), 7.24 (t, J = 6.9 Hz, 1H), 7.39-7.58 (m, 5H), 7.72-7.85 (m, 6H), 7.99 (s, 1H), 8.72 (s, 1H), 9.50 (s, 1H); APCI (m/z) 363 $(M+H)^+$.

Example 87

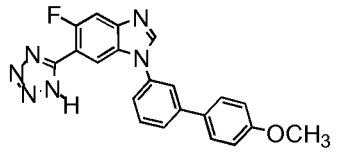
4-(1-([1,1'-Biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)phenol



The title compound was prepared by coupling reaction of *N*-(5-Bromo-2-nitrophenyl)biphenyl-3-amine with 4-hydroxyphenylboronic acid followed by nitro group reduction and subsequent cyclization as described in Example 86 to yield 160 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.83 (d, J = 8.4 Hz, 2H), 7.38-7.53 (m, 6H), 7.69-7.84 (m, 7H), 7.97 (s, 1H), 8.67 (s, 1H), 9.51 (s, 1H); APCI (*m/z*) 363 $(M+H)^+$.

Example 88

5-Fluoro-1-(4'-methoxybiphenyl-3-yl)-6-(1*H*-tetrazol-5-yl)-1*H*-benzimidazole



Step 1: 5-Fluoro-1-(4'-methoxybiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid: The title compound was prepared by Suzuki coupling reaction of 1-(3-bromophenyl)-5-fluoro-1*H*-benzimidazole-6-carboxylic acid (215 mg, 0.642 mmol) with 4-methoxyphenylboronic acid (117 mg, 0.770 mmol) in 1,4-dioxane (5 ml) using Tetrakis(triphenylphosphine) Pd(0) (74 mg, 0.064 mmol) in presence of 1 M aqueous solution of potassium carbonate (177 mg, 1.284 mmol) as described in procedure in Step 2 of example 42 to yield 215 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 7.06 (d, J = 8.7 Hz, 2H), 7.65-7.78 (m, 6H), 7.93 (s, 1H), 8.02 (d, J = 6.9 Hz, 1H), 8.87 (s, 1H), 13.00 (br s, 1H); APCI (*m/z*) 363 $(M+H)^+$.

Step 2: 5-Fluoro-1-(4'-methoxybiphenyl-3-yl)-1*H*-benzimidazole-6-carboxamide: The title compound was prepared by reaction of Step 1 intermediate (200 mg, 0.580 mmol) with ammonium chloride (95 mg, 1.740 mmol) using BOP reagent (310 mg, 0.696 mmol) in presence of DIPEA (290 µl, 1.70 mmol) in DMSO (5 ml) as described in Example 40 to yield 143 mg of the product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 7.06 (d, J = 8.7 Hz, 2H), 7.60-7.82 (m, 8H), 7.85-7.92 (m, 2H), 8.85 (s, 1H); APCI (*m/z*) 362 $(M+H)^+$.

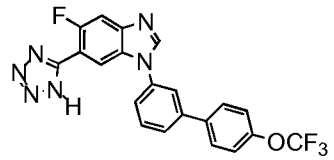
Step 3: 5-Fluoro-1-(4'-methoxybiphenyl-3-yl)-1*H*-benzimidazole-6-carbonitrile: To a stirred solution of Step 2 intermediate (140 mg, 0.385 mmol) in dichloromethane (5

ml) was added triethylamine (160 µl, 1.157 mmol) at 0-5 °C followed by drop wise addition of trifluoroacetic anhydride (0.1 ml, 0.577 mmol) and the resultant mixture was stirred for 1 h. The reaction mixture was diluted with water (15 ml) and stirred for 10 min. The reaction mixture was extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with water (100 ml), brine (75 ml), dried (Na_2SO_4) and concentrated under reduced pressure to yield 80 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 7.06 (d, J = 8.7 Hz, 2H), 7.64-7.72 (m, 2H), 7.73-7.82 (m, 3H), 7.90-7.98 (m, 2H), 8.34 (d, J = 6.9 Hz, 1H), 9.00 (s, 1H); APCI (m/z) 344 $(M+H)^+$.

Step 4: The title compound was prepared by reaction of Step 3 intermediate (75 mg, 0.218 mmol) with sodium azide (50 mg, 0.76 mmol) using ammonium chloride (41 mg, 0.76 mmol) in DMF (5 ml) as described in step 2 of Example 50 to yield 7 mg of product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.18 (s, 3H), 7.06 (d, J = 8.4 Hz, 2H), 7.66-7.85 (m, 5H), 7.89-7.98 (m, 2H), 8.23 (d, J = 6.0 Hz, 1H), 8.91 (s, 1H), 16.31 (br s, 1H); APCI (m/z) 385 $(M-H)^-$.

Example 89

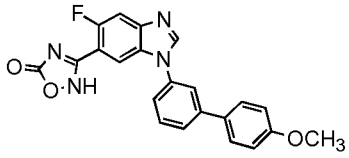
5-Fluoro-6-(1*H*-tetrazol-5-yl)-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole



The title compound was prepared in 3 steps using 5-Fluoro-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1H-benzimidazole-6-carboxylic acid (Example 44) as described in Example 88 to yield 22 mg of product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15-7.25 (m, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.72-7.81 (m, 1H), 7.90-8.00 (m, 4H), 8.22 (d, J = 7.2 Hz, 1H), 8.91 (s, 1H), 16.89 (br s 1H); APCI (m/z) 441 $(M+H)^+$.

Example 90

3-(5-Fluoro-1-(4'-methoxy-[1,1'-biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)-1,2,4-oxadiazol-5(2*H*)-one



The title compound was prepared by reaction of 5-Fluoro-1-(4'-methoxybiphenyl-3-yl)-1*H*-benzimidazole-6-carbonitrile (100 mg, 0.290 mmol) with hydroxylamine hydrochloride (75 mg, 1.078 mmol) followed by oxadiazolone ring formation using CDI (1,1'-carbonyldiimidazole; 36 mg, 0.22 mmol) in DMF (4 ml) as described in steps 2 and 3 of Example 67 to yield 16 mg of the product; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 7.06 (d, J = 9.0 Hz, 2H), 7.63-7.95 (m, 7H), 8.05 (d, J = 5.7 Hz, 1H), 8.93 (s, 1H), 12.92 (s, 1H); APCI (*m/z*) 403 $(M+H)^+$.

Pharmacological activity

The illustrative examples of the present invention are screened for COT kinase activity according to procedure described in Jia Y et al., *Analytical Biochemistry*. 350 (12), pp. 268-276, 2006 using the non-radioactive method by homogeneous time resolved fluorescence (HTRF) with the Cisbio assay kit.

In-vitro screening assay for COT kinase inhibitors:

COT kinase catalyzes the inactive biotin-MEK1/2 causing its phosphorylation at Ser217 and S221 sites in presence of ATP that is detected by a detection complex that contains the donor molecule Europium cryptate molecule complex by anti-phospho-MEK1/2-specific antibody that recognizes the phosphorylation sites on the MEK1/2 peptide and an acceptor molecule XL-665 complex by streptavadin that binds to the biotin tag on the N-terminal region of MEK1/2 peptide. On excitation of the donor molecule at 337nm causes a resonance energy transfer to the acceptor molecule at 620nm that emits at 665nm and can be recorded as an HTRF signal. The signal obtained is proportional to the extent of substrate phosphorylation (MEK1/2) by COT kinase. Inhibition of COT kinase enzyme activity produces a low level of this energy transfer as compared to the control determining the percentage of inhibition of the respective inhibitor.

Test or reference compounds were dissolved in dimethylsulfoxide (DMSO) to prepare 10 mM stock solution and diluted suitably to get the desired concentration. Final concentration of DMSO in the reaction was 5 % (v/v). Substrate mixture was prepared by mixing 1mM ATP (Sigma) and 5 μM Biotin-MEK1/2 (American Peptide Company) in order to get 100μM and 500nM final concentrations of each respectively in the assay buffer containing 50 mM Tris –HCL (pH 7.5), 10 mM $MgCl_2$, 1mM EGTA, 2mM DTT, 0.01% Brij, and 5mM β-phosphoglycerate. Streptavidin- XL

(Cisbio) and anti-Phospho MEK1/2(Ser217/221)-cryptate (Cisbio) were prepared in the Revelation buffer containing 30mM HEPES, pH 7.0, 0.06% BSA, 0.006% Tween 20, 0.24M Potassium Fluoride. The assay was carried out using suitably dilution of COT kinase enzyme (BPS Biosciences) to get around 2.5 fold conversion of MEK1/2 to Phospho-MEK1/2 to ensure linear reaction kinetics.

COT kinase assay was carried out in 40 µL reaction volume by addition of assay buffer containing test compound and substrate mixture and initiated with the required concentration of the enzyme. Reaction mixture was incubated at room temperature for 60 min with constant shaking. The reaction was stopped by adding 10µl of 500mM EDTA to get final concentration of 100mM in the reaction mixture. This was followed by addition of 25 µL of each detection reagents Streptavidin- XL and anti-Phospho MEK1/2(Ser217/221)-cryptate to the reaction mixture. The reaction mixture was kept in cold over night after 10 mins shaking and read the emission (665/620) in the HTRF instrument the next day.

Reaction was measured based on the signal to background ratio of the phosphorylated and non-phosphorylated biotinylated MEK1/2 substrate using the Artemis instrument reader. An enzyme control without test compounds was run to quantitate maximum COT kinase reaction. Inhibition of enzyme activity was calculated as a percent of control reaction. IC_{50} values were calculated from dose response curve by nonlinear regression analysis using GraphPad Prism software.

The compounds prepared were tested using the above assay procedure and the results obtained are given in Table 8. Percentage inhibition at concentrations of 1.0 µM and 10.0 µM are given in the table along with IC_{50} (nM). The IC_{50} (nM) values of the compounds are set forth in Table 8 wherein "A" refers to an IC_{50} value of less than 100 nM, "B" refers to an IC_{50} value in range of 100.01-250 nM, "C" refers to an IC_{50} value in range of 250.01-500 nM and "D" refers to an IC_{50} value of more than 500 nM.

Table 8: In-vitro screening results of compounds of invention

Examples	**% inhibition at**		**IC_{50} value (nM)**
	1 µM	**10 µM**	
1.	1.4	15	-
2.	73.84	97.62	C
3.	77.38	97.22	B
4.	74.5	90.9	C

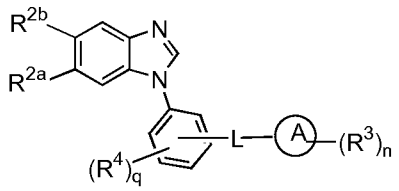
5.	91.1	98.4	A
6.	-	102.82	A
7.	68.44	96.56	C
8.	31.31	68.95	-
9.	0	40.56	-
10.	9.76	39.06	-
11.	74.1	92.7	B
12.	65.3	90.6	D
13.	81.9	92.6	B
14.	80.5	97.3	B
15.	49.04	88.05	-
16.	83.69	96.85	A
17.	85.61	96.16	B
18.	90.2	98.45	A
19.	56.49	85.04	-
20.	0	31.95	-
21.	37.68	73.51	-
22.	-	51.27	-
23.	13	28.68	-
24.	0	37.56	-
25.	15.91	31.54	-
26.	8.11	21.96	-
27.	12.62	28.86	-
28.	6.9	3.9	-
29.	9.4	5.7	-
30.	3.1	9.8	-
31.	17.3	18.8	-
32.	0	23.26	-
33.	-	94.26	B
34.	82.77	99.4	A
35.	0	31.36	-
36.	20.8	43.64	-
37.	10.6	57.1	-
38.	3.6	17.9	-
39.	14.24	38.44	-
40.	27.22	68.06	D
41.	35.49	56.79	-
42.	55.71	81.76	-

43.			
44.	43.03	88.37	-
45.	21.51	63.3	-
46.	3.93	35.5	-
47.	16.08	57.27	-
48.	15.32	11.93	-
49.	10.88	17.03	-
50.	94.7	98.1	A
51.	93.21	98.8	A
52.	92.91	99.24	A
53.	97.37	98.96	A
54.	97.58	99.65	A
55.	97.17	98.26	A
56.	95.37	98.5	A
57.	98.98	100.66	A
58.	93.74	98.23	A
59.	95.95	99.25	A
60.	93.41	100.85	A
61.	93.26	101.34	A
62.	86.05	101.03	A
63.	66.73	92.67	C
64.	86.22	96.69	A
65.	81.5	95.52	A
66.	93.38	102.59	A
67.	86.3	90.1	A
68.	94.04	101.08	A
69.	93.41	100.03	A
70.	99.88	100	A
71.	94.7	95.6	A
72.	95.87	98.6	A
73.	95.04	95.58	A
74.	91.45	98.12	A
75.	96.47	98.45	A
76.	92.48	98.36	A
77.	90.89	98.07	A
78.	97.8	100	A
79.	89.02	97.24	A
80.	93.13	96.97	A

81.	92.83	95.13	A
82.	91.09	95.83	A
83.	63.56	83.51	-
84.	47.47	87.81	-
85.	91.52	96.37	A
86.	11.09	42.63	-
87.	10.67	36.38	-
88.	92.16	99.04	A
89.	84.45	95.33	A
90.	96.17	101.83	A

Claims:

1. A compound of formula II



(II)

or pharmaceutically acceptable salt thereof,

wherein,

'A' is C_{6-14}aryl, 5-14 membered heteroaryl or 3-15 membered heterocyclyl;

'L' is a bond or selected from –O- and -C(O)-;

R^{2a} is independently selected from -COOH, $-C(O)NR^aR^b$, $-C(O)N(R^a)SO_2R^b$, $-N(R^a)SO_2R^b$, substituted or unsubstituted C_{6-14}aryl, substituted or unsubstituted 3-15 membered heterocyclyl ring and substituted or unsubstituted 5-14 membered heteroaryl;

R^{2b} is selected from hydrogen, halogen, nitro, cyano, hydroxyl and substituted or unsubstituted C_{1-8}alkyl;

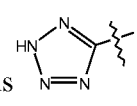
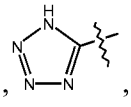
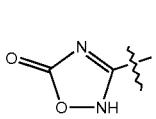
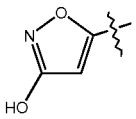
R^3, at each occurrence, is independently selected from halogen, cyano, hydroxyl, $-C(O)R^a$, $-C(O)NR^aR^b$, $-C(O)OR^a$, $-NR^aR^b$, $-NR^aC(O)R^b$, $N(R^a)SO_2R^b$, $-OR^a$, and $SO_2NR^aR^b$, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{1-8}alkoxy, substituted or unsubstituted haloC_{1-8}alkyl, substituted or unsubstituted haloC_{1-8}alkoxy and substituted or unsubstituted C_{3-12}cycloalkyl;

R^4, at each occurrence, is independently selected from halogen, cyano, hydroxyl and substituted or unsubstituted C_{1-8}alkyl;

R^a and R^b, which may be the same or different, are independently selected from hydrogen, hydroxyl, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{1-8}alkoxy, substituted or unsubstituted haloC_{1-8}alkyl, substituted or unsubstituted haloC_{1-8}alkoxy, substituted or unsubstituted C_{3-12}cycloalkyl, substituted or unsubstituted C_{6-14}aryl, substituted or unsubstituted 3-15 membered heterocyclyl, substituted or unsubstituted 5-14 membered heteroaryl and; or R^a and R^b together with the atom to which they are attached, may form cyclic ring, which may be monocyclic, bicyclic or tricyclic rings; substituted or unsubstituted; the cyclic ring may optionally contain one or more hetero atoms selected from O, N or S;

'n' is an integer ranging from 0 to 5, both inclusive; and

'q' is an integer ranging from 0 to 4, both inclusive.

2. The compound according to claim 1, wherein A is phenyl, pyrazolyl or piperidinyl.
3. The compound according to claim 1, wherein L is a bond.
4. The compound according to claim 1, wherein R^{2a} is –COOH.
5. The compound according to claim 1, wherein R^{2a} is $C(O)NR^aR^b$ and R^a is hydrogen and R^b is hydrogen or hydroxyl.
6. The compound according to claim 1, wherein R^{2a} is $-C(O)N(R^a)SO_2R^b$.
7. The compound according to claim 6, wherein R^a is hydrogen and R^b is methyl, trifluoromethyl or phenyl.
8. The compound according to claim 1, wherein R^{2a} is $N(R^a)SO_2R^b$.
9. The compound according to claim 8, wherein R^a is hydrogen and R^b is methyl or isopropyl.
10. The compound according to claim 1, wherein R^{2a} is hydroxyl substituted phenyl.
11. The compound according to claim 1, wherein R^{2a} is  ,  ,  or  .
12. The compound according to claim 1, wherein R^{2b} is hydrogen or fluorine.
13. The compound according to claim 1, wherein R^3 is selected from. F, Cl, Br, cyano, $CONH_2$, $COCH_3$, SO_2NH_2, methyl, methoxy, ethoxy, propran-2-yloxy, trifluoromethyl, and trifluoromethoxy.
14. The compound according to claim 1, wherein R^3 is OR^a and R^a is hydrogen or cyclopentyl.
15. The compound according to claim 1, wherein R^4 is fluorine.
16. The compound according to claim 1 selected from

1-(Biphenyl-2-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(Biphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-[4'-(Trifluoromethyl)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Methoxybiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Cyanobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Cyanobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Sulfamoylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Cyanobiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Cyanobiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3',5'-Dimethylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(2',4'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3',5'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3',4'-Difluorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(2',4'-Dichlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3',5'-Dichlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Chloro-4'-cyanobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Cyano-3'-methylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-[4-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-[6-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-[2-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-(3-Phenoxyphenyl)-1*H*-benzimidazole-6-carboxylic acid,

1-[3-(4-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-(4-Phenoxyphenyl)-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(2-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(3-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(4-Cyanophenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(Piperidin-3-yloxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(Piperidin-4-yloxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[3-(Piperidin-3-yloxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[3-(Piperidin-4-yloxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(Phenylcarbonyl)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Carbamoylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Carbamoylbiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(3'-Carbamoylbiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Carbamoylbiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-[3-(4-Carbamoylphenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-[4-(3-Carbamoylphenoxy)phenyl]-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Carbamoylbiphenyl-4-yl)-1*H*-benzimidazole-6-carboxylic acid,

1-(Biphenyl-3-yl)-1*H*-benzimidazole-6-carboxamide,

1-(3',5'-Difluorobiphenyl-3-yl)-*N*-hydroxy-1*H*-benzimidazole-6-carboxamide,

1-[5-Fluoro-4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Chlorobiphenyl-3-yl)-1*H*-benzimidazole-6-carboxylic acid,

5-Fluoro-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole-6-carboxylic acid,

1-(4'-Chlorobiphenyl-3-yl)-*N*-[(trifluoromethyl)sulfonyl]-1*H*-benzimidazole-6-carboxamide,

1-(4'-Chlorobiphenyl-3-yl)-*N*-(methylsulfonyl)-1*H*-benzimidazole-6-carboxamide,

1-(4'-Chlorobiphenyl-3-yl)-*N*-(phenylsulfonyl)-1*H*-benzimidazole-6-carboxamide,

N-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}methanesulfonamide,

N-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}propane-2-sulfonamide,

1-(Biphenyl-3-yl)-6-(1*H*-tetrazol-5-yl)-1*H*-benzimidazole,

6-(1*H*-Tetrazol-5-yl)-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole,

3'-[6-(2*H*-Tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carboxamide,

1-(4'-Chlorobiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

1-(4'-Fluorobiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

1-(4'-Bromobiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

1-(4'-Methoxybiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

3'-[6-(2*H*-Tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile,

1-(4'-Acetylbiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

3-Methyl-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile,

1-(3',4'-Dimethoxybiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

1-(3',5'-Dimethoxybiphenyl-3-yl)-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

4-(Propan-2-yloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carbonitrile,

4-(Cyclopentyloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carbonitrile,

1-[3-(1*H*-Pyrazol-4-yl)phenyl]-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

1-[3-(1-Methyl-1*H*-pyrazol-4-yl)phenyl]-6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazole,

4-(Cyclopentyloxy)-3'-[6-(2*H*-tetrazol-5-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carboxamide,

3-[1-(Biphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(4'-Fluorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(4'-Chlorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3'-[6-(5-Oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile,

3-{1-[4'-(Trifluoromethyl)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(3'-Hydroxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(4'-Hydroxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(4'-Methoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(4'-Ethoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-(1-(4'-Isopropoxy-[1,1'-biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)-1,2,4-oxadiazol-5(2*H*)-one,

3-Methyl-3'-[6-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-benzimidazol-1-yl]biphenyl-4-carbonitrile,

3-[1-(3',4'-Dimethoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(3',5'-Dimethoxybiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(3',4'-Difluorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

3-[1-(3',5'-Difluorobiphenyl-3-yl)-1*H*-benzimidazol-6-yl]-1,2,4-oxadiazol-5(2*H*)-one,

4-(Cyclopentyloxy)-3'-[6-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-benzimidazol-1-yl]biphenyl-3-carbonitrile,

3-{1-[3-(1-Methyl-1H-pyrazol-4-yl)phenyl]-1*H*-benzimidazol-6-yl}-1,2,4-oxadiazol-5(2H)-one,

5-{1-[4'-(Trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazol-6-yl}-1,2-oxazol-3-ol,

3-(1-([1,1'-Biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)phenol,

4-(1-([1,1'-Biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)phenol,

5-Fluoro-1-(4'-methoxybiphenyl-3-yl)-6-(1*H*-tetrazol-5-yl)-1*H*-benzimidazole,

5-Fluoro-6-(1*H*-tetrazol-5-yl)-1-[4'-(trifluoromethoxy)biphenyl-3-yl]-1*H*-benzimidazole and

3-(5-Fluoro-1-(4'-methoxy-[1,1'-biphenyl]-3-yl)-1*H*-benzo[d]imidazol-6-yl)-1,2,4-oxadiazol-5(2*H*)-one or

pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16, either as a free base or pharmaceutically acceptable salt form and a pharmaceutically acceptable excipient.

18. The pharmaceutical composition according to claim 17, wherein the pharmaceutically acceptable excipient is a carrier or diluents.

19. The compound according to any one of claims 1 to 16 for use in the treatment of conditions in which inhibition of COT kinase is required.

20. The compound according to any one of claims 1 to 16 for use in the treatment of inflammation.

21. A method of treatment of disease, disorder, syndrome or condition selected from the group consisting of asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, pain, inflammatory pain, chronic pain, acute pain, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections, influenza, common cold, herpes zoster, hepatitis C, AIDS, bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies hyperprostaglandin E syndrome, classic Bartter syndrome, synovitis, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, cancer, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis and multiple sclerosis, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, and sarcoidosis by administration of a compound according to any one of claims 1 to 16.

22. The method according to claim 21, wherein the symptoms of a disease or condition is associated with pain

23. The method according to claim 21, wherein the symptoms of a disease or condition is associated with rheumatoid arthritic pain.

24. A method of treatment of cancer by administration of a compound according to any one of claims 1 to 16.

25. The method of claim 24, wherein the cancer is selected from lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cancers of the tongue, mouth, pharynx, and oral cavity, melanoma, cutaneous or intraocular melanoma, BRAF resistant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, or carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lynphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma

of the renal pelvis, pediatric malignancy, neoplasms of the central nervous system, primary CNS lymphoma, spinal axis tumors, brain stem glioma or pituitary adenomas, cancers of the bloodsuch as acute myeloid leukemia, chronic mueloid leukemia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/050756

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D235/-, C07D403/-, C07D413/-, A61K31/-, A61P25/-, A61P29/-, A61P35/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNPAT, CNKI, CAPLUS, CA: benzimidazo+, cot, cancer, kinase, pain, inflammat+, neurodegenerative

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP0563001A1 (NEUROSEARCH A/S) 29 Sept. 1993(29.09.1993) pages 3-8 of the description, Table 1, especially compounds 3a, 8a-80a	1-25
A	CN101193867A(OSI PHARMACEUTICALS, INC.) 04 June 2008(04.06.2008) claims 1-26	1-25

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 May 2012(03.05.2012)	**14 Jun. 2012 (14.06.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer DAI, Nianzhen Telephone No. (86-10)82246703

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/050756

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-25
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 21-25 are directed to the methods for treatment of human or animal body by therapy. But the search has been carried out and based on the following subject matter: the use of a compound according to any one of claims 1-16 in the preparation of medicaments for treatment of diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/050756

Continuation of: CLASSIFICATION OF SUBJECT MATTER:

C07D235/06(2006.01)i

C07D235/04(2006.01)i

C07D403/04(2006.01)i

C07D403/02(2006.01)i

C07D403/12(2006.01)i

C07D413/02(2006.01)i

C07D413/04(2006.01)i

A61K31/535(2006.01)i

A61K31/53(2006.01)i

A61K31/4184(2006.01)i

A61P25/00(2006.01)i

A61P35/00(2006.01)i

A61P29/00(2006.01)i

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2012/050756

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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		TW200633704A	01.10.2006
		EP1831206B1	24.08.2011