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(54) **Title**: NOVEL BENZIMIDAZOLE COMPOUND, PREPARATION METHOD THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

(57) **Abstract**: The present invention relates to a novel benzimidazole compound, a pharmaceutical composition for preventing or treating an inflammatory disease comprising said compound, a use of a novel benzimidazole compound for the manufacture of a medicament for preventing or treating an inflammatory disease, and a method of preventing or treating an inflammatory disease in a mammal comprising administering to the mammal said compound.

NOVEL BENZIMIDAZOLE COMPOUND, PREPARATION METHOD THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

FIELD OF THE INVENTION

The present invention relates to a novel benzimidazole compound having an excellent inhibitory effect on the microsomal prostaglandin E synthase-1 (mPGES-1) enzyme, a preparation method thereof and a pharmaceutical composition containing the same as an active ingredient.

BACKGROUND OF THE INVENTION

Prostaglandin E2 (PGE2) is a lipid mediator that plays an important role in inflammatory diseases, and the excessive production of PEG2 is observed in the serum or synovia of patients with anflammatory diseases, such as rheumatoid arthritis or osteoarthritis. Thus, the regulation of PGE2 has long been established as an important mechanism in anti-inflammatory therapy.

Prostaglandin is a type of eicosanoid, an oxygenated 20-carbon polyunsaturated fatty acid, and is produced in almost all cells. Cytosolic phospholipase A2 (cPLA2) digests phospholipids in response to various stimuli or substances to secrete arachidonic acid which is then converted to prostaglandin G2 (PGG2) by cyclooxygenase (COX). The PGG2 is metabolized to prostaglandin H2 (PGH2) which is then converted to prostaglandins by prostaglandin D2 synthase (PGDS), prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS), prostaglandin I synthase (PGIS) and tromboxane synthase. As a result, prostaglandin (PGD2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostaglandin I2 (PGI2) and thromboxane A2 (TXA2) are produced.

At least three isozymes of PGE synthase were cloned and identified, and specific examples thereof include cytosolic PGES (cPGES), microsomal PGES-1 (mPGES-1) and microsomal PGES-2 (mPGES-2). cPGES is a glutathione-dependent protein that is continuously expressed in the cytosol. It is functionally associated with COX-1 and contributes to the production of PGE2 for maintaining physiological homeostasis, but is

not influenced by bacterial lipopolysaccharide (LPS). mPGES-1 is expressed by inflammatory agents, is functionally associated with COX-2 and requires glutathione as a cofactor. The expression of mPGES-1 is stimulated by LPS, inflammatory cytokine, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α).

mPGES-2 is expressed in various tissues, responds to acute or chronic inflammation and is functionally associated with COX-1 and COX-2, but is generally more associated with COX-2. mPGES-2 is known to show activity in tissues such as colorectal adenocarcinoma cells, but its physiological and pathological roles are not yet known.

mPGES-1 is a member of the membrane-associated proteins involved in the eicosanoid and glutathione metabolism (MAPEG) superfamily. mPGES-1 was initially identified as homologue to microsomal glutathione S-transferase 1 (MGST1), and since then, it was found to have glutathione-dependent PGE2 synthase activity (Jakobsson PJ, Thoren S, Morgenstern R, Samuelsson B, et al., *Proc Natl. Acad. Sci.* USA 1999, 96: 7220-7225).

A non-steroidal anti-inflammatory drug (NSAID) targeting mPGES-1 that acts in the last stage in the production of PGE2 by an inflammatory agent does not affect the production of other prostaglandins, including PGD2, PGF2α, PGI2 and TXA2. Thus, NSAID targeting mPGES-1 is expected to be a therapeutic agent having less side effects than not only general COX inhibitors but also selective COX2 inhibitors.

According to the results of a previous study, in rats with adjuvant-induced arthritis (AIA), which are an animal model having many characteristics that are clinically or pathologically similar to human rheumatoid arthritis, the expression of mPGES-1 was greatly induced after 5 days of adjuvant treatment, but in rats not treated, no mPGES-1 was found (Mancini JA, Blood K, Guay J, et al., *J Biol Chem* 2001, 276: 4469-4475). According to the results of another study, when rats were treated with an adjuvant, the expression of mPGES-1 was immediately induced (Claveau D, Sirinyan M, Guay J, et al., *J Immunol,* 2003, 170:4738-4744). The increase in mPGES-1 expression was found 4 hours after drug treatment and continued for the first three days and was also continuously observed during the progression of inflammation. Particularly, the increase in mPGES-1 was consistent with the increase in COX-2 and the production of PGE2, but did not substantially affect the expression of cPGES, mPGES-2 and COX-1.

Also, according to the results of an animal experiment conducted using mPGES-

1-defocient (mPGES-/-) mice, any particular difference from wild-type animals was not shown, but PGE2 production that is induced by LPS was not substantially observed in *in vivo* and *in vitro* experiments, and also the production of TNF-α and IL-6 was not substantially influenced, suggesting that mPGES-1 is essential for PGE2 production (Uematsu S, Matsumoto M, Takeda K, et al., *J Immunol,* 2002, 168:5811-5816). Furthermore, in an animal model with collagen-induced arthritis, inflammatory responses and inflammatory pain are decreased in mPGES-/-mice. Such results indicate that mPGES-1 is involved in both an acute and a chronic inflammatory response (Trebino CE, Stock JL, Gibbons CP, et al., *Proc Natl Acad Sci* U S A, 2003, 100:9044-9049).

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a novel compound having an excellent inhibitory effect on the microsomal prostaglandin E synthase-1 (mPGES-1) enzyme.

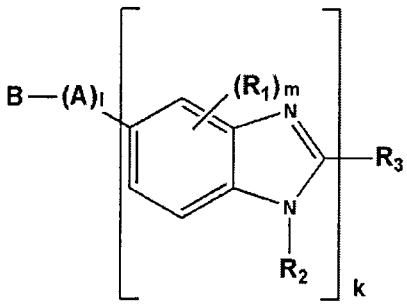
It is another object of the present invention to provide a pharmaceutical composition for preventing or treating an inflammatory disease comprising said compound.

It is a further object of the present invention to provide a use of a benzimidazole compound for the manufacture of a medicament for preventing or treating an inflammatory disease.

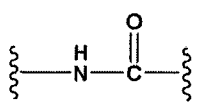
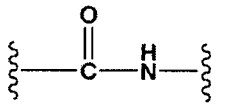
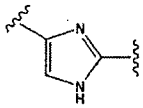
It is a still further object of the present invention to provide a method of preventing or treating an inflammatory disease in a mammal comprising administering said compound to a mammal.

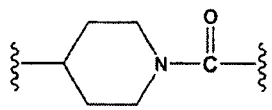
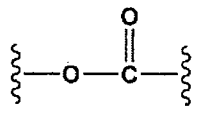
In accordance with one aspect of the present invention, there is provided a compound selected from the group consisting of a compound of formula 1 and a pharmaceutically acceptable salt, an isomer, a hydrate and a solvate thereof:

[Formula 1]



wherein

A is phenylene,  ,  ,  ,

 or  ;

B is C_1-C_5 alkyl, C_2-C_6 alkynyl, C_6-C_{12} aryl, C_2-C_{13} heteroaryl, C_3-C_{13} heterocycloalkyl, sulfonyl or aminocarbonyl, wherein said alkyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, sulfonyl and aminocarbonyl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy) C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy, halo(C_1-C_5 alkyl)(C_6-C_{12} aryl) , C_1-C_5 alkylsulfonyl, C_6-C_{12} haloaryl and cyano, provided that, if k is 0, B is benzimidazolyl optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy)C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkloxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

k is 0 or 1;

l is 0 or 1;

m is an integer ranging from 0 to 3;

R_1 is each independently halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy or carboxyl;

R_2 is hydrogen or C_1-C_5 alkyl; and

R_3 is amino, C_6-C_{12} aryl or C_2-C_{13} heteroaryl, wherein said amino, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, amino, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 haloalkoxy, halo(C_1-C_5 alkoxy)(C_6-C_{12} aryl) and C_6-C_{12} haloaryl.

In accordance with another aspect of the present invention, there is provided a pharmaceutical composition for preventing or treating an inflammatory disease comprising said compound.

In accordance with a further aspect of the present invention, there is provided a use of a compound of formula 1, or a pharmaceutically acceptable salt, an isomer, a hydrate or a solvate thereof for the manufacture of a medicament for preventing or treating an inflammatory disease.

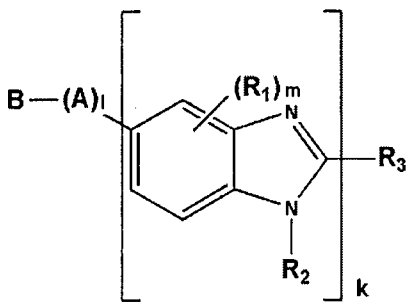
In accordance with a still further aspect of the present invention, there is provided a method of preventing or treating an inflammatory disease in a mammal comprising administering said compound to the mammal.

DETAILED DESCRIPTION OF THE INVENTION

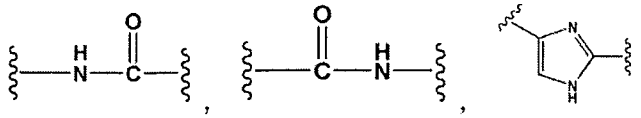
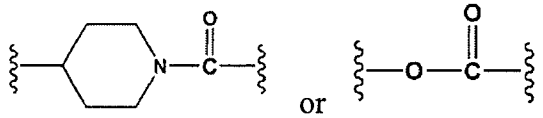
Hereinafter, the present invention will be described in detail.

The present invention provides a compound selected from a compound of formula 1 and a pharmaceutically acceptable salt, an isomer, a hydrate and a solvate thereof:

[Formula 1]



wherein

A is phenylene,  ,  or ;

B is C_1-C_5 alkyl, C_2-C_6 alkynyl, C_6-C_{12} aryl, C_2-C_{13} heteroaryl, C_3-C_{13} heterocycloalkyl, sulfonyl or aminocarbonyl, wherein said alkyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, sulfonyl and aminocarbonyl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy) C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy, halo(C_1-C_5 alkyl)(C_6-C_{12} aryl) , C_1-C_5 alkylsulfonyl, C_6-C_{12} haloaryl and cyano, provided that, if k is 0, B is benzimidazolyl optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy)C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkloxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

k is 0 or 1;

l is 0 or 1;

m is an integer ranging from 0 to 3;

R_1 is each independently halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy or carboxyl;

R_2 is hydrogen or C_1-C_5 alkyl; and

R_3 is amino, C_6-C_{12} aryl or C_2-C_{13} heteroaryl, wherein said amino, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, amino, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 haloalkoxy, halo(C_1-C_5 alkoxy)(C_6-C_{12} aryl) and C_6-C_{12} haloaryl.

As used herein, the term "halogen" means fluoro, bromo, chloro or iodo.

As used herein, the term "alkyl" means a linear or branched saturated C_1-C_6 hydrocarbon radical. Specific examples thereof include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl and isopentyl.

As used herein, the term "alkynyl" refers to a divalent hydrocarbon group derived from the removal of two hydrogen atoms from alkyn. Specific examples thereof include, but are not limited to, ethynyl and propynyl.

As used herein, the term "aryl" is intended to include fused groups, such as naphthyl and phenanthrenyl, as well as monocyclic or bicyclic aromatic rings, such as phenyl and substituted phenyl. Specific examples thereof include, but are not limited to, phenyl, tolyl, xylyl, biphenyl and naphthyl.

As used herein, the term "heteroaryl" means a monocyclic or polycyclic aromatic group containing one or more heteroatoms selected from among oxygen, nitrogen and sulfur. Examples of monocyclic heteroaryl include, but are not limited to, furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4- oxadiazolyl, 1,2,3- oxadiazolyl, 1,3,5-thiazolyl, 1,2,3- thiazolyl, 1,2,4-thiazolyl, pyridyl, pyrimidyl, pyrizinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3- triazinyl, 1,3,5-triazinyl, cinolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyridinyl, etc. Examples of bicyclic heteroaryl include, but are not limited to, 5,6,7,8-tetrahydro-quinolin-3-yl, benzo[d][1,3]dioxolyl, benzoxazolyl, benzothiazolyl, benzo[b]thiophenyl, benzothiazolyl, benzoisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, pyrazolo[3,4-b]pyridinyl, benzoxazinyl, etc.

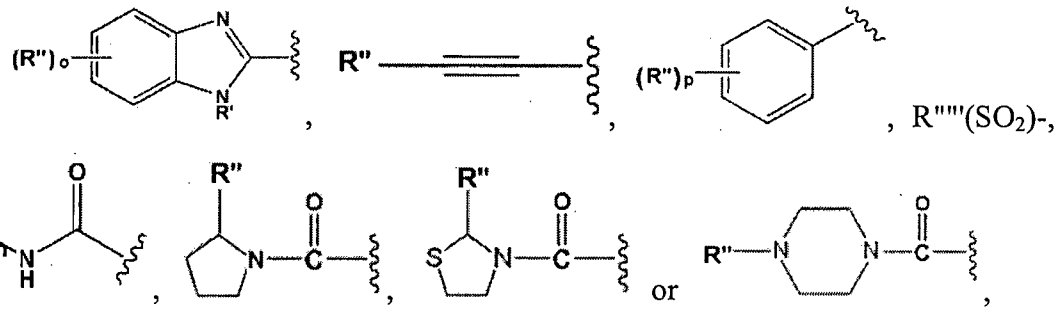
As used herein, the term "cycloalkyl" refers to cyclic alkyl. Specific examples thereof include, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, etc.

As used herein, the term "heterocycloalkyl" refers to a monocyclic or polycyclic alkyl containing one or more heteroatoms selected from among oxygen, nitrogen and sulfur. Examples of mono heterocycloalkyl include, but are not limited to, piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, etc.

As used herein, the term "alkoxy" means an $-OR_a$ wherein R_a is alkyl as defined above. Specific examples thereof include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, etc.

As used herein, the term "substituted" means substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy)alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

Preferably, the present invention provides the compound of formula 1, wherein B is



wherein

R' is hydrogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl or (C_1-C_5 alkoxy)alkyl;

R" is each independently halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, hydroxyl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, (C_1-C_5 alkoxy) C_1-C_5 alkyl, C_1-C_5 hydroxyalkyl, hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy or halo(C_1-C_5 alkyl)(C_6-C_{12} aryl);

X is hydrogen; C_1-C_4 alkyl; C_1-C_4 alkyl optionally substituted with one or more substituents selected from the group consisting of (C_1-C_5 alkoxy)carbonyl, hydroxyl(C_6-C_{12} aryl), carboxyl, C_6-C_{12} aryl, halo C_6-C_{12} aryl, hydroxyl, C_1-C_3 alkylsulfanyl and C_2-C_{13} heteroaryl; C_3-C_8 cycloalkyl; naphthalenyl; C_6-C_{12} aryl; C_2-C_{13} heteroaryl; or C_2-C_{13} heteroaryl optionally substituted with one or more substituents selected from the group consisting of C_1-C_4 alkyl, hydroxyl(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, carboxyl, halo C_6-C_{12} aryl, C_1-C_5 alkoxy, thiol, halogen and C_6-C_{12} aryl;

n is an integer ranging from 0 to 3; o is an integer ranging from 0 to 4; and p is an integer ranging from 0 to 5.

Preferably, R_1 is each independently chloro, bromo, methoxy, methyl or carboxyl.

Preferably, R_2 is hydrogen or methyl.

Preferably, wherein R_3 is phenyl, imidazopyrindinyl, amino, or imidazolyl which is unsubstituted or substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, t-butyl, trifluoromethoxy and 2-chloro-6-fluorophenyl. More preferably, R_3 is imidazopyrindinyl or imidazolyl substituted with 2-chloro-6-fluorophenyl, or amino substituted with bromophenyl.

Preferably, if l is 0 or k is 0; and B is benzimidazolyl which is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy) C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

In the present invention, representative examples of the benzimidazole compound include:

(1) 5-chloro-2-(2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-6-yl)-1H-benzo[d]imidazole;

(2) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]-5-trifluoromethyl-1H-benzo-[d]imidazole;

(3) 2'-(2-chloro-6-fluorophenyl)-1-chclohexyl-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(4) 2'-(2-chloro-6-fluorophenyl)-1-(1-ethylpropyl)-6-methyl-1H,1'H-[2,5'] bibenzimidazolyl;

(5) 1-butyl-2'-(2-chloro-6-fluorophenyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(6) 2'-(2-bromophenyl)-5-chloro-1H,1'H-[2,5']bibenzimidazolyl;

(7) 2'-(2-bromophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(8) 2'-(2-bromophenyl)-1-(1-ethylpropyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(9) 2-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)benzonitrile;

(10) 2-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)benzonitrile;

(11) 2'-(4-tert-butylphenyl)-5-chloro-1H,1'H-[2,5']bibenzimidazolyl;

(12) 2'-(4-tert-butylphenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(13) 2'-(4-tert-butylphenyl)-1-cyclohexyl-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(14) 1-butyl-2'-(4-tert-butylphenyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(15) 2'-(4-trifluoromethoxyphenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(16) 1-cyclohexyl-6-methyl-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl;

(17) 1-(1-ethylpropyl)-6-methyl-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl;

(18) 2'-(2-chloro-6-fluorophenyl)-5-iodo-1H,1'H-[2,5']bibenzimidazolyl;

(19) 2'-(2-bromophenyl)-5-iodo-1H,1'H-[2,5']bibenzimidazolyl;

(20) 5-iodo-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl;

(21) (4-bromophenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(22) (4-trifluoromethoxyphenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(23) (4-tert-butylphenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(24) (4-tert-butylphenyl)-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(25) (5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)-(4-trifluoromethoxyphenyl)amine;

(26) (4-bromophenyl)-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(27) 2'-(2-chloro-6-fluorophenyl)-6'-methyl-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(28) 2'-(2-chloro-6-fluorophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-6'-carboxylic acid;

(29) 6'-bromo-2'-(2-chloro-6-fluorophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(30) 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(31) 5-chloro-2'-(2-chloro-6-fluorophenyl)-1H,1'H-[2,5']bibenzimidazolyl-6'-carboxylic acid;

(32) 2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]phenyl}-5-trifluoromethyl-1H-benzo[d]imidazole;

(33) 5-chloro-2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]phenyl}-1H-benzo[d]imidazole;

(34) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-chlorophenyl)-amide;

(35) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-trifluoromethylphenyl)-amide;

(36) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2,5-dichlorophenyl)-amide;

(37) 4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]-2-methyl-3-butyn-2-ol;

(38) 2-(2-chloro-6-fluorophenyl)-5-(4-trifluoromethylphenylethynyl)-1H-benzimidazole;

(39) 2-chloro-N-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]-benzoamide;

(40) 2'-(2-chloro-6-fluorophenyl)-5-methoxy-1,6'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(41) 2'-(2-chloro-6-fluorophenyl)-1,5,6'-trimethy-1H,1'H-[2,5']bibenzimidazolyl;

(42) 5-chloro-2'-(2-chloro-6-fluorophenyl)-1,6'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(43) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)amide;

(44) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)amide;

(45) 1-cyclohexyl-6-methyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide;

(46) 1-methyl-5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide;

(47) 1-(1-ethylpropyl)-6-methyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-flurophenyl)-1H-benzimidazol-5-yl]amide;

(48) 5-triofluoromethyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1-methyl-1H-benzimidazol-5-yl]amide;

(49) 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide;

(50) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester;

(51) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid;

(52) benzene-1,2-disulfonic acid 1-amide 2-{[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]amide};

(53) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester;

(54) benzene-1,2-disulfonic acid 1-amide 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amide};

(55) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid;

(56) 2-{[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(57) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-ylcarbamoyl]-1H-benzimidazole-5-carboxylic acid methyl ester;

(58) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]amino}-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester;

(59) 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(60) 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]amino}-1-methyl-1H-benzimidazol-5-carboxylic acid methyl ester;

(61) 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester;

(62) 2-{[2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carbonyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(63) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(64) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid

(1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(65) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(66) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(67) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazol-2-yl)-amide;

(68) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(69) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(70) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(71) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(72) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(73) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(74) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(75) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(76) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazol-2-yl)-amide;

(77) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-propyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(78) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(79) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid [1-(2-methoxyethyl)-5-trifluoromethyl-1H-benzimidazol-2-yl]-amide;

(80) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-(3-hydroxy-3-methyl-1-butynyl)-1H-benzimidazol-2-yl]-amide;

(81) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-dimethylamino-1H-benzimidazol-2-yl)-amide;

(82) 2-(2-chloro-6-fluorpophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid [5-dimethylamino-1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-amide;

(83) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [6-methyl-1-(1-methyl-piperidin-4-yl)-1H-benzimidazol-2-yl]-amide;

(84) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-hydroxy-1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-amide;

(85) acetic acid 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazol-5-yl ester;

(86) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(87) 4-(2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-6-methyl-benzoimidzol-1-yl)-piperidine carboxylic acid ethyl ester;

(88) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [6-methyl-1-(2-morpholin-4-ylethyl)-1H-benzimidazol-2-yl]amide;

(89) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (6-methyl-1-piperidin-4-yl-1H-benzimidazol-2-yl)amide;

(90) 2'-(2-chloro-6-fluorophenyl)-7'-methyl-5-trifluoromethyl-1H,1'H-[2,5]bibenzimidazolyl;

(91) 5-chloro-2'-(2-chloro-6-fluorophenyl)-7'-methyl-1H,1'H-[2,5]-bibenzimidazolyl;

(92) 2'-(2-chloro-6-fluoro)-1-cyclohexyl-6,7'-dimethyl-1H,1'H-[2,5]-bibenzimidazolyl;

(93) 2'-(2-chloro-6-fluorophenyl)-5-methoxy-1,7'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(94) 5-chloro-2'-(2-chloro-6-fluorophenyl)-1,7'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(95) 2-(2-chloro-6-fluorophenyl)-7-methyl-6-(5-trifluoromethyl-1H-benzimidazol-2-yl)-3H-imidazo[4,5-b]pyridine;

(96) 2'-(2-chloro-6-fluorophenyl)-6'-methoxy-5-trifluoromethyl-1H,1'H-[2,5]bibenzimidazolyl;

(97) 2'-(2-chloro-6-fluorophenyl)-6'-methoxy-1-methyl-5-methyl-1H,1'H-

[2,5]bibenzimidazolyl;

(98) 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methoxy-1-methyl-1H,1'H-[2,5]bibenzimidazolyl;

(99) 2-[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzoimidzol-5-ylcarbomyl]-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester;

(100) 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid-[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazol-5-ylamide;

(101) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-propyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(102) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxyl acid [1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(103) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cycohexyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(104) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-carboxylic acid [5-dimethylamino-1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-amide;

(105) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(106) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(107) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid-(1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(108) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzoimdazole-5-carboxylic acid-(1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(109) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid-(1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(110) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-(1-methyl-piperidin-4-yl)-6-methyl-1H-benzimidazol-2-yl)-amide;

(111) 7-chloro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(112) 7-choro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(113) 7-chloro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(6-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(114) 7-chloro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(6-methyl-1H-benzimidazol-2-yl)-amide;

(115) 4-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino-piperidine-1-carboxylic acid tert-butyl ester;

(116) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid piperidin-4-ylamide;

(117) 2-(2-chloro-6-fluorophenyl)-6-methoxy-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole;

(118) 2-(2-chloro-6-fluorophenyl)-5-[4-(4-chlorophenyl)-1H-imidazol-2-yl]-6-methoxy-1H-benzimidazole;

(119) 2-(2-chloro-6-fluorophenyl)-6-methoxy-5-(4-phenyl-1H-imidazol-2-yl)-1H-benzimidazole;

(120) 2-(2-chloro-6-fluorophenyl)-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole;

(121) 2-[3-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]-3-(5-trifluoromethyl-benzimidazol-2-yl)-4-benzimidazole;

(122) 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-carbonyl]-piperidine-4-carboxylic acid butylamide;

(123) 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide;

(124) 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide;

(125) 1-[7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide;

(126) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-1H-benzimidazol-2-yl)-amide;

(127) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-iropropyl-1H-benzimidazol-2-yl)-amide;

(128) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-5-methoxy-1H-benzimidazol-2-yl)-amide;

(129) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-1-isopropyl-1H-benzimidazol-2-yl)-amide;

(130) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid

[1-cyclopentyl-6-(2-hydroxyethoxy)-1H-benzimidazol-2-yl]-amide;

(131) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-cyclopropylethoxy)-1H-benzimidazol-2-yl]-amide;

(132) 4-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-benzoic acid-tert-butyl ester;

(133) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-hydroxy-1H-benzimidazol-2-yl)amide;

(134) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)amide;

(135) 2-(2-chloro-6-fluorophenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-yl)amide;

(136) 2-(2-chloro-6-fluorophenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)amide;

(137) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-4-carboxylic acid [1-cyclopentyl-6-(2-hydroxy-ethoxy)-1H-benzimidazol-2-yl]amide;

(138) 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid [1-cyclopentyl-5-(1-hydroxy-ethyl)-1H-benzimidazol-2-yl]-amide;

(139) 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(1-hydroxy-ethyl)-1-isopropyl-1H-benzimidazol-2-yl]-amide;

(140) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid 1-tert-butoxycarbonyl-piperidin-3-yl methyl ester;

(141) 4-({[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

(142) 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-5-(1-hydroxy-1-methyl-ethyl)-1H-benzimidazol-2-yl]-amide;

(143) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid-2-(1-tert-butoxycarbonyl-piperidin-2-yl)-ethyl ester;

(144) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid-1-tert-butoxycarbonyl-piperidin-3-yl ester;

(145) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid ethyl ester;

(146) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester;

(147) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid;

(148) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid ethyl ester;

(149) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(1-hydroxy-1-methyl-ethyl)-1-isopropyl-1H-benzimidazol-2-yl] -amide;

(150) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid;

(151) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid;

(152) 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid methyl ester;

(153) 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid;

(154) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid 1-tert-butoxycarbonyl-piperidin-2-yl methyl ester;

(155) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methylsulfanyl-butyric acid methyl ester;

(156) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(1H-imidazol-4-yl)-propionic acid methyl ester;

(157) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-fluoro-phenyl)-acetic acid methyl ester;

(158) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester;

(159) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methylsulfanyl-butyric acid;

(160) 4-benzyl-1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperazine-2-carboxylic acid tert-butyl ester;

(161) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperazine-2-carboxylic acid tert-butyl ester;

(162) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-fluoro-phenyl)-acetic acid;

(163) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-

piperidine-2-carboxylic acid;

(164) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(2-hydroxy-2-methyl-propyl)-1-cyclopentyl-1H-benzimidazol-2-yl] -amide;

(165) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(2-hydroxy-2-methyl-propyl)-1-isopropyl-1H-benzimidazol-2-yl] -amide;

(166) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [4-cyano-1-(2-oxo-butyl)-1H-pyrazol-3-yl]-amide;

(167) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-hydroxymethyl-3-methylsulfanyl-propyl)-amide;

(168) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methanesulfinyl-butyric acid methyl ester;

(169) 3-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-5-methylsulfanyl-pentanoic acid methyl ester;

(170) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid tert-butyl ester;

(171) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid methyl ester;

(172) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid;

(173) Sodium 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylate;

(174) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-benzofuran-5-carboxylic acid ethyl ester;

(175) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid thiazol-2-ylamide;

(176) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (5-methyl-thiazol-2-yl)-amide;

(177) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide;

(178) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide;

(179) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid pyrimidin-4-ylamide;

(180) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (3-methyl-pyridin-2-yl)-amide;

(181) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-imidazol-2-yl)-amide;

(182) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid pyridin-2-ylamide;

(183) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-chloro-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide;

(184) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-ethyl-5-methyl-2H-pyrazol-3-yl)-amide;

(185) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-methoxy-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide;

(186) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-propyl-2H-pyrazol-3-yl)-amide;

(187) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-propyl-1H-pyrazol-3-yl)-amide;

(188) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-fluoro-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide;

(189) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-isopropyl-2H-pyrazol-3-yl)-amide;

(190) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-pyrazol-3-yl)-amide;

(191) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-mercapto-1H-benzimidazol-5-yl)-amide;

(192) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid adamantan-1-ylamide;

(193) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-trifluoromethyl-1H-benzimidazol-5-yl)-amide;

(194) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-phenyl-propyl)-amide;

(195) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-1H-imidazol-2-yl)-amide;

(196) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid

(1-thiazol-2-yl-ethyl)-amide;

(197) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

(198) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-pyridin-4-yl-ethyl)-amide;

(199) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-indan-1-yl)-amide;

(200) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(3-methoxy-phenyl)-ethyl]-amide;

(201) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-o-tolyl-cyclopropyl)-amide;

(202) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(4-chloro-phenyl)-ethyl]-amide;

(203) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(4-hydroxy-phenyl)-propyl]-amide;

(204) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide;

(205) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid;

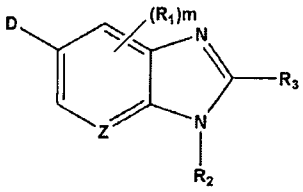
(206) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid tert-butyl ester;

(207) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid methyl ester; and

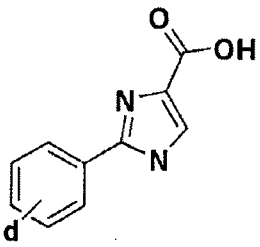
(208) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid ethyl ester.

The compound of formula 1 according to the present invention can be prepared by allowing a compound of formula 2 or 3 to react with a compound selected from the group consisting of compounds of formula 4 to 10:

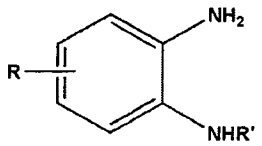
[Formula 2]



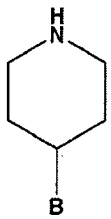
[Formula 3]



[Formula 4]

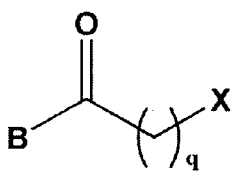


[Formula 5]

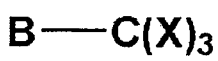


[Formula 6]

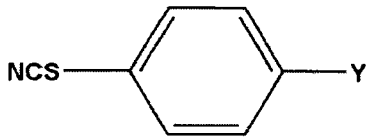
[Formula 7]



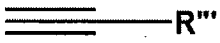
[Formula 8]



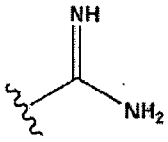
[Formula 9]



[Formula 10]



wherein D is selected from the group consisting of formyl, amino, carboxyl,



, phenyl having formyl, and halogen;

R is each independently selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, hydroxyl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkoxy)alkyl, C_1-C_5 hydroxyalkyl and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl);

X is halogen;

Y is halogen, C_1-C_5 haloalkoxy or C_1-C_5 alkyl;

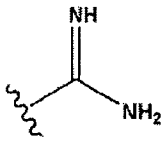
Z is CH or Z;

d is halogen, cyano, C_1-C_5 alkyl, halo(C_1-C_5 alkyl) or halo(C_1-C_5 alkoxy);

q is 0 or 1; and

B, R_1, R_2, R_3, R', R''' and m are as defined above.

Preferably, the compound of formula 2 is allowed to react with the compound of formula 4 when D in formula 2 is formyl or phenyl having formyl; with the compound of formula 5 or 6 when D is carboxyl; with the compound of formula 7 when D is



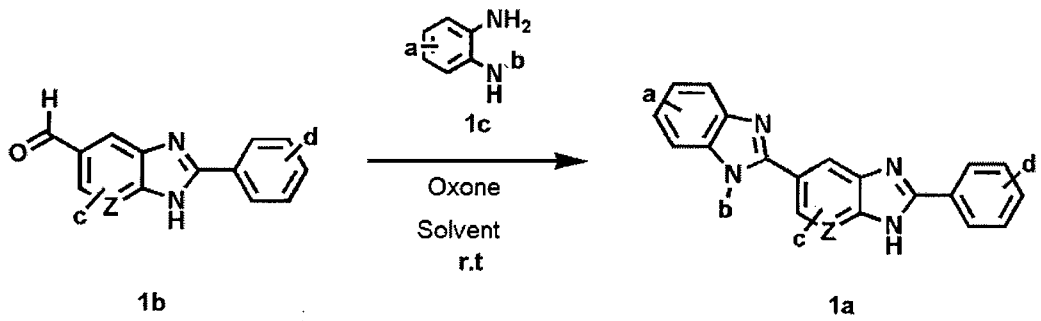
; with the compound of formula 8 when D is amino; with the compound of

formula 10 when D is halogen; and with the compound of formula 9 when R_3 in formula 2 is diaminophenyl. Also, the compound of formula 3 is preferably allowed to react with the compound of formula 6.

Specifically, the compound of formula 1 according to the present invention can be chemically synthesized by the methods shown in reaction schemes 1 to 10, but the scope of the present invention is not limited only to these examples.

In one example of preparing the compound of formula 1 according to the present invention, a compound of formula 1a can be prepared by the reaction shown in the Reaction scheme 1:

[Reaction Scheme 1]



wherein a is halogen, alkoxy, haloalkyl, alkyl, alkyloxycarbonyl or carboxyl, and is preferably CH_3O, Cl, CH_3, I or CF_3; b is hydrogen, alkyl, cycloalkyl or alkoxyalkyl, and is preferably hydrogen, butyl, isobutyl or cyclohexyl; c is hydrogen, alkyl or alkoxy, and is preferably hydrogen or methyl; d is halogen, cyano, alkyl, haloalkyl or haloalkoxy, and is preferably F, Cl, Br, CN, CF_3, t-butyl or OCF_3; Z is CH or N; and r.t is room temperature.

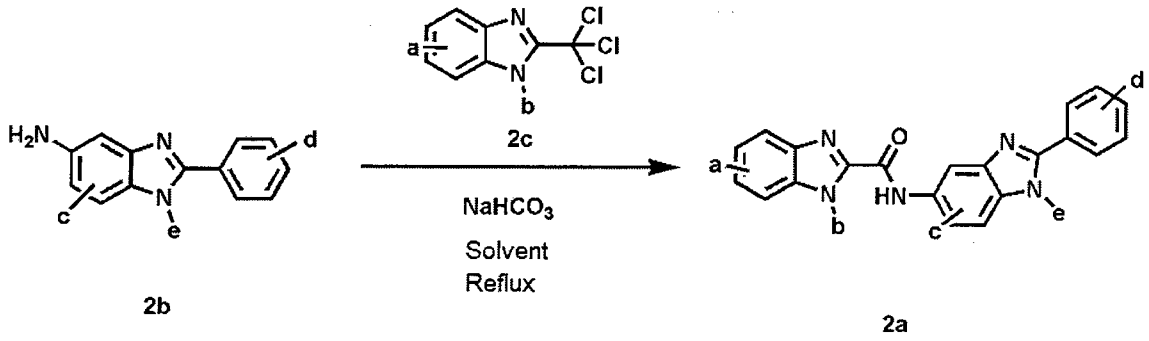
As shown in reaction scheme 1 above, the compound of formula 1a is prepared by allowing the compound of formula 1b to react with 1,2-phenylenediamine of formula 1c.

The compound of formula 1c is preferably used in an amount of 1.0 to 1.2 moles based on 1 mole of the compound of formula 1e.

In one example of preparing the compound of formula 1 according to the present

invention, a compound of formula 2a can be prepared by the reaction shown in the Reaction scheme 2:

[Reaction Scheme 2]



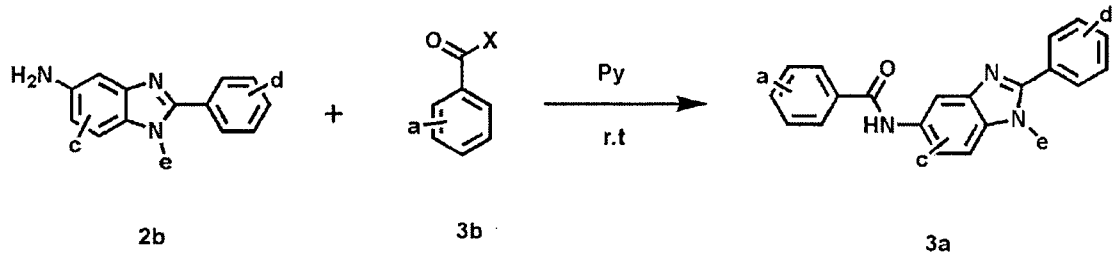
wherein a, b, c and d are as defined above. Preferably, a is methoxy, trifluoromethyl, methyl, methyloxycarbonyl or carboxyl; b is methyl, cyclohexyl or methoxyethyl; c is hydrogen, methyl or methoxy; d is F or Cl; and e is hydrogen or alkyl.

Specifically, the compound of formula 2a can be prepared by dissolving the compound of formula 2b in a mixed solvent of distilled water and a solvent such as tetrahydrofuran or ketone, and then allowing the reaction mixture to react with sodium hydrogen carbonate and the compound of formula 2c.

The compound of formula 2c is preferably used in an amount of 1.0 to 1.2 moles based on 1 mole of the compound of formula 2b.

In a method similar to the above method, as shown in the Reaction scheme 3, a compound of formula 3a can be prepared by dissolving the compound of formula 2b in a solvent, such as pyridine, tetrahydrofuran or toluene, and then allowing the compound of formula 2b to react with a compound of formula 3b:

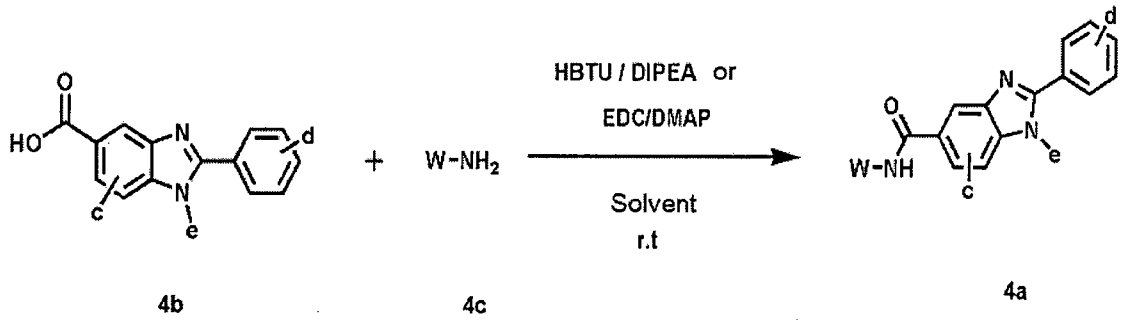
[Reaction Scheme 3]



wherein a, c, d and e are as defined above; x is halogen, preferably chloro, and Py is pyridine.

In one example of preparing the compound of formula 1 according to the present invention, a compound of formula 4a can be prepared by the reaction shown in the Reaction scheme 4:

[Reaction Scheme 4]



4b 4c 4a

wherein c, d and e are as defined above; and W is substituted or unsubstituted benzimidazolyl, phenyl or 1,2-diaminosulfonylphenyl.

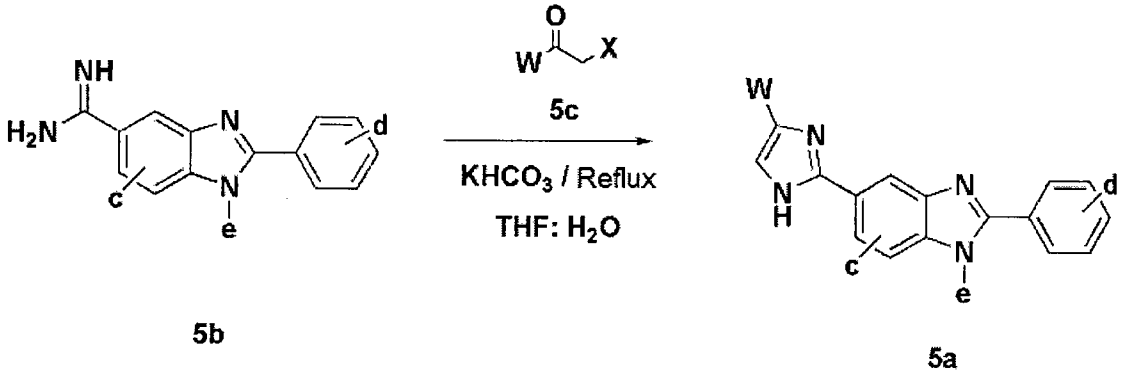
The compound of formula 4a can be prepared by dissolving the compound of formula 4b, diisopropylethylamine (DIPEA) and O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) in a solvent such as N,N-dimethylformamide or N,N-dimethylacetamide to prepare a reaction mixture, and then allowing the mixture to react with a compound of formula 4c, such as 2-chloroaniline.

Herein, each of DIPEA and HBTU is preferably used in an amount of 1.0 to 1.2 moles based on 1 mole of the compound of formula 4b.

Also, the compound of formula 4c is preferably used in an amount of 1.0-1.2 moles based on 1 mole of the compound of formula 4b.

In one example of preparing the compound of formula 1 according to the present invention, a compound of formula 5a can be prepared by the reaction shown in the Reaction scheme 5:

[Reaction Scheme 5]

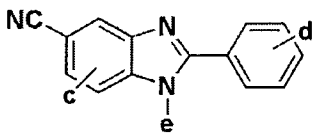


wherein c, d, e, x and w are as defined above; and x is preferably bromo.

Specifically, the compound of formula 5a is prepared by allowing the compound of formula 5b to react with the compound of formula 5c. The compound of formula 5c is preferably used in an amount of 1.2 to 1.5 moles based on 1 mole of the compound of formula 5b.

The compound of formula 5b that is used herein can be prepared by dissolving a compound of the following formula 5d in a solvent such as anhydrous ethanol, adding HCl gas to the solution, diluting the resulting reaction mixture in anhydrous ether, filtering the dilution under reduced pressure, adding the filtrate to a solution of ammonia in methanol, and refluxing the resulting solution for 4 hours:

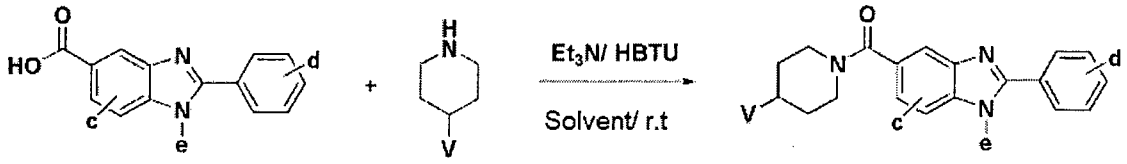
[Formula 5d]



wherein c, d and e are as defined above.

In one example of preparing the compound of formula 1 according to the present invention, a compound of formula 6a can be prepared by the reaction shown in the Reaction scheme 6:

[Reaction Scheme 6]



4b 6c 6a

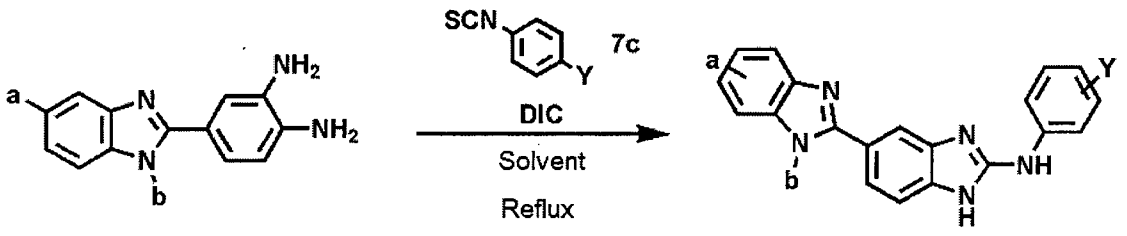
wherein c, d and e are as defined above; and v is alkylaminocarbonyl, arylaminocarbonyl or cycloalkylaminocarbonyl, and preferably pentylaminocarbonyl, naphthalen-1-ylethylaminocarbonyl or cyclopentylaminocarbonyl.

Specifically, the compound of formula 6a is prepared by allowing the compound of formula 4b and the compound of formula 6c to react with each other in the presence of HBTU and triethylamine in a solvent such as N,N-dimethylformamide.

Herein, the compound of formula 6c is preferably used in an amount of 1.0 to 1.2 moles based on 1 mole of the compound of formula 4b.

In one example of preparing the compound of formula 1 according to the present invention, a compound of formula 7a can be prepared by the reaction shown in the Reaction scheme 7:

[Reaction Scheme 7]



7b 7a

wherein a and b are as defined above; Y is halogen, haloalkoxy or alkyl, and is preferably bromo, tert-butyl or trifluoromethoxy, and DIC is diisopropylcarbodiimide.

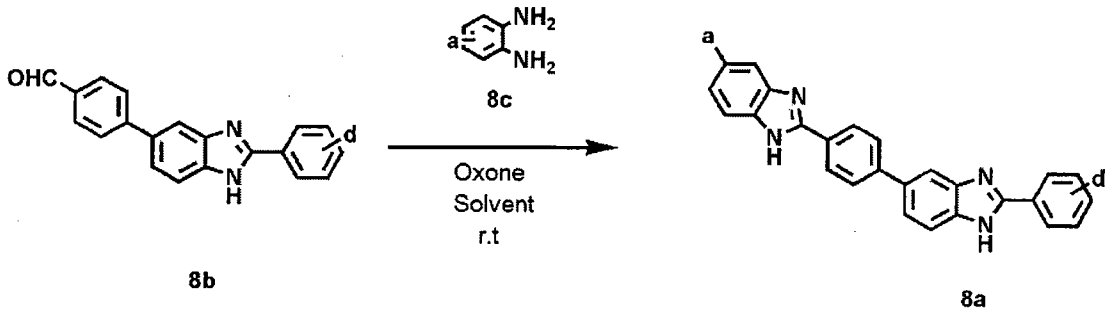
Specifically, the compound of formula 7a is prepared by dissolving the compound of formula 7b in a solvent such as tetrahydrofuran or ether, and then heating and refluxing the solution with phenyl isothiocyanate of formula 7c in the presence of

diisopropylcarbodiimide (DIC).

Herein, the compound of formula 7c and DIC are preferably used in amounts of 0.9 to 1.2 moles and 1.0 to 5.0 moles, respectively, bases on 1 mole of the compound of formula 7b.

In another example of preparing the compound of formula 1 according to the present invention, a compound of formula 8a can be prepared by the reaction shown in the Reaction scheme 8:

[Reaction Scheme 8]



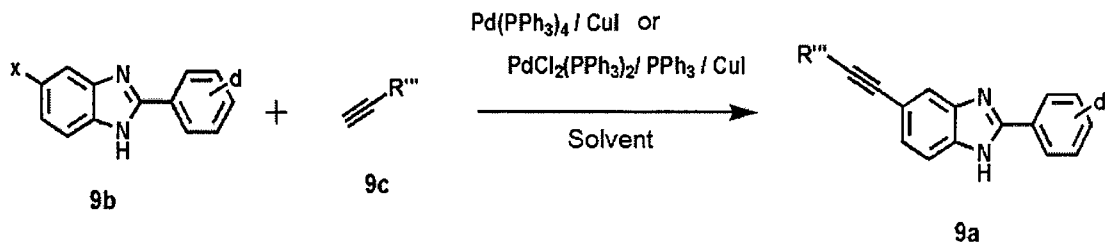
wherein a and d are as defined above.

Specifically, the compound of formula 8a is prepared by allowing a compound of formula 8b to react with 1,2-phenylenediamine compound of formula 8c.

Herein, the compound of formula 8c is preferably used in an amount of 1.0 to 1.2 moles based on 1 mole of the compound of formula 8b.

In another example of preparing the compound of formula 1 according to the present invention, a compound of formula 9a can be prepared by the reaction shown in the Reaction scheme 9:

[Reaction scheme 9]

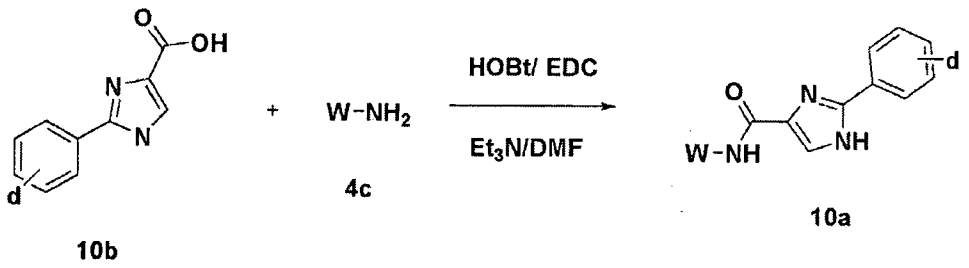


wherein d, R''' and x are as defined above.

Specifically, the compound of formula 9a is prepared by dissolving a compound of formula 9b in a solvent such as N,N-dimethylformamide or tetrahydrofuran, adding thereto tetrakistriphenylphosphin palladium ($Pd(PPh_3)_4$) and copper iodide (CuI), or dichlorobis(triphenylphosphine)palladium ($PdCl_2(PPh_3)_2$), copper iodide and triphenylphosphin, and allowing the mixture to react with the compound of formula 9c in the presence of a base such as diisopropylethylamine or triethylamine.

In another example of preparing the compound of formula 1 according to the present invention, a compound of formula 10a can be prepared by the reaction shown in the Reaction scheme 10:

[Reaction Scheme 10]



wherein d and W are as defined above.

Specifically, the compound of formula 10a can be prepared by allowing a compound of formula 10b to react with a compound of formula 4c in the presence of hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).

The compound of formula 1 according to the present invention may be used in the form of pharmaceutically acceptable salts derived from inorganic acids or organic acids. Examples of such pharmaceutically acceptable salts include acid addition salts formed by acids capable of forming non-toxic acid addition salts containing pharmaceutically acceptable anions, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid or hydroiodic acid, organic carbonic acids such as tartaric acid, formic acid, citric acid, acetic acid,

trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid or maleic acid, sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acid, particularly preferably acid addition salts formed by sulfonic acid, methanesulfonic acid or halogen acid.

Pharmaceutically acceptable salts of the compound of formula 1 can be prepared from the compound of formula 1 using conventional methods. Specifically, the pharmaceutically acceptable salt according to the present invention can be prepared by dissolving the compound of formula 1 in a water-miscible organic solvent, such as acetone, methanol, ethanol or acetonitrile, and adding an excess of organic acid or an aqueous solution of inorganic acid thereto, followed by precipitation or crystallization. Then, an acid addition salt may be prepared by evaporating the solvent or excess acid from the mixture and drying the remaining material. The precipitated salt may also be filtered by suction.

The compound of formula 1 according to the present invention 1 may also be used in the form of a hydrate or a solvate which can be prepared therefrom.

Because the compound of formula 1 according to the present invention may have an asymmetric carbon center, the scope of the present invention encompasses a pharmaceutically acceptable salt of the compound of formula 1, as well as an R or S isomer, a racemic mixture, a diastereoisomeric mixture, and an individual diastereoisomer, which can be prepared therefrom. Also, solvates, hydrates, isomers and mixtures thereof are also included within the scope of the present invention.

The compound of formula 1, or a pharmaceutically acceptable salt, an isomer, a hydrate and a solvate thereof have an excellent inhibitory effect against mPGES-1, and thus can be used for the treatment of diseases caused by the overexpression of mPGES-1. Accordingly, the present invention provides an inhibitor of mPGES-1 activity and a pharmaceutical composition for preventing or treating diseases caused by the overexpression of mPGES-1 and therefore the overproduction of PGE, which contain, as an active ingredient, a compound selected from the group consisting of the compound of formula 1, a pharmaceutically acceptable salt, an isomer, a hydrate and a solvate thereof.

The diseases include all diseases that can be caused by the overexpression of mPGES-1 and therefore the overproduction of PGE2, and specific examples thereof include, but are not limited to, inflammatory diseases, such as rheumatoid arthritis and osteoarthritis.

The pharmaceutical composition may also comprise a pharmaceutically acceptable carrier or vehicle.

The pharmaceutical composition of the present invention can be formulated according to conventional methods. It can be formulated in oral dosage forms, including tablets, pills, powders, capsules, syrups, emulsions and microemulsions, or parenteral dosage forms, including intramuscular, intravenous and subcutaneous dosage forms.

For solid formulations for oral administration, examples of carriers that can be used in the present invention include starch, calcium carbonate, sucrose, lactose, gelatin, magnesium stearate, talc, etc.

For liquid formulations for oral administration, including suspensions, internal solutions, emulsions or syrups, examples of carriers that can be used in the present invention include simple diluents such as water or liquid paraffin, wetting agents, sweeteners, aromatics, and preservatives.

Formulations for parenteral administration include sterile aqueous solutions, non-aqueous solvents, suspensions, emulsions, lyophilized preparations, and suppositories. For non-aqueous solutions and suspensions, examples of carriers that can be used in the present invention include propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable esters such as ethyl oleate. For suppositories, examples of carriers that can be used in the present invention include Witepsol, macrogol, Tween 61, cacao oil, laurin oil, glycerol, and gelatin.

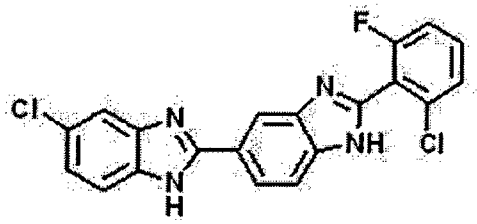
Also, it should be understood that the daily dose should be determined in light of various relevant factors including the conditions to be treated, including age, body weight, sex, administration route, health state and disease severity. A proposed daily dose of the compound of the present invention for administration to a human (of approximately 70 kg body weight) is about from 0.01 mg/day to 1000 mg/day, more preferably about from 1 mg/day to 500 mg/day, and the inventive composition may be administered in a single dose or in divided doses per day.

The present invention provides also a use of a benzimidazole compound for the manufacture of a medicament for preventing or treating an inflammatory disease.

The present invention provides also a method of preventing or treating an inflammatory disease in a mammal comprising administering said compound to the mammal.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Example 1: Preparation of 5-chloro-2-(2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-6-yl)-1H-benzo[d]imidazole



Step 1: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonitrile

To a solution of 3,4-diaminobenzonitrile (0.40 g, 3.00 mmol) in N,N-dimethylformamide (10 ml), 2-fluoro-6-chlorobenzaldehyde (0.52 g, 3.30 mmol) was added followed by oxone (1.20 g, 1.95 mmol). The mixture was stirred for 2 hr at room temperature and then added dropwise with vigorous stirring into a mixture of 2M K_2CO_3 and H_2O. The precipitate was extracted with ethyl acetate, and the extract was washed successively with H_2O and brine. After drying over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude residue was purified by chromatography on silica gel column eluted with 50% ethyl acetate/hexane to give the title compound (0.58 g, 71 %).

^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) 10.26 (s, 1H'), 10.11 (s, 1H), 8.18 (s, 1H), 7.94 (d, J=8.7Hz, 1H'), 7.84 (s, 1H'), 7.57-7.60 (m, 1H+2H'), 7.37-7.50 (m, 2H+2H'), 7.16-7.22 (m, 2H).

Step 2: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbaldehyde

Raney-nickel (2.24 g) was added to a solution of 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonitrile (0.58 g, 2.13 mmol) in formic acid (30 ml) and H_2O (10 ml). The reaction mixture was heated at 95 ℃ for 6 hr. The hot mixture was filtered

through a bed of celite, and the reaction flask and celite bed were rinsed with water. The aqueous solution was concentrated to dryness. After addition of H_2O to this residue, a white precipitate formed. The pH of this suspension was adjusted to 9 by the dropwise addition of 2 N NaOH. The product was obtained by extraction with ethyl acetate. The ethyl acetate extract was dried (Na_2SO_4) and con centrated in vacuo to give the title compound (0.58 g, 100 %).

^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ(ppm) 10.07 (s, 1H+1H'), 8.32 (s, 1H), 8.08 (s, 1H'), 7.87-8.08 (m, 2H'+1H'), 7.61-7.64 (m, 1H), 7.42-7.49 (m, 2H+2H'), 7.14-7.21 (m, 2H)

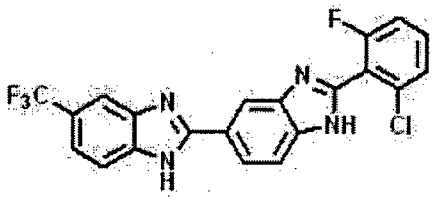
Step 3: Preparation of 5-chloro-2-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-6-yl]-1H-benzo[d]imidazole

The title compound (0.12 g, 86 %) was obtained using the method described in Example 1, Step 1 using 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbaldehyde and 4-chloro-1,2-phenylendiamine .

Mw: 397

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.41 (s, 1H), 8.10 (d, J=8.7Hz, 1H), 7.82 (d, J=8.1Hz, 1H), 7.57-7.66 (m, 3H), 7.50 (d, J=8.1Hz, 1H), 7.34 (dd, J_1=J_2=9.3Hz, 1H), 7.26 (dd, J_1=1.8Hz, J_2=8.7Hz, 1H)

Example 2: Preparation of 2-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]-5-trifluoromethyl-1H-benzo-[d]imidazole

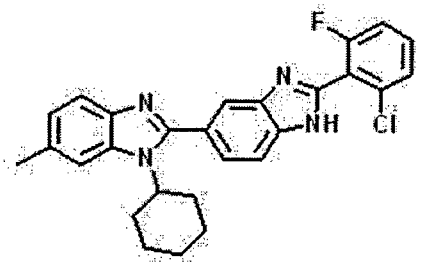


The title compound (0.12 g, 77 %) was obtained using the method described in Example 1, Step 3 using 4-trifluoromethyl-1,2-phenylendiamine.

Mw: 431

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.45 (s,1H), 8.90 (d, J=8.1Hz,1H), 7.70-7.90 (m,3H), 7.50-7.60 (m,2H), 7.44 (d, J=8.1Hz, 1H), 7.29 (dd, J_1=J_2=8.7Hz, 1H)

Example 3: Preparation of 2'-(2-chloro-6-fluorophenyl)-1-chclohexyl-6-methyl-1H,1'H-[2,5']bibenzimidazolyl

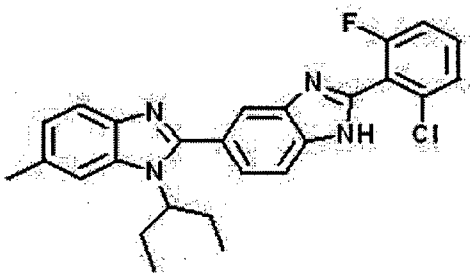


The title compound (0.03 g, 36 %) was obtained using the method described in Example 1, Step 3 using N-cyclohexyl-5-methyl-1,2-phenylendiamine.

Mw: 459

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 7.82 (s, 1H), 7.75 (d, J=8.1Hz, 1H), 7.45-7.55 (m, 4H), 7.39 (d, J=8.1Hz, 1H), 7.20-7.26 (m, 1H), 7.03 (d, J=8.1Hz, 1H), 4.27-4.35 (m, 1H), 2.42 (s, 3H), 2.26-2.38 (m, 2H), 1.80-2.04 (m, 4H), 1.58-1.62 (m, 1H), 1.18-1.34 (m, 3H)

Example 4: Preparation of 2'-(2-chloro-6-fluorophenyl)-1-(1-ethylpropyl)-6-methyl-1H,1'H-[2,5'] bibenzimidazolyl

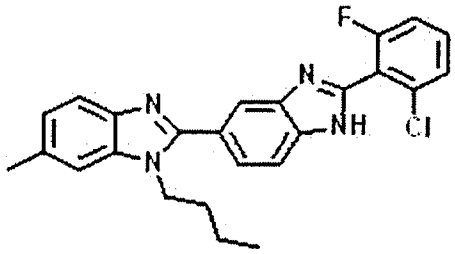


The title compound (0.07 g, 88 %) was obtained using the method described in Example 1, Step 3 using N-isobutyl-5-methyl-1,2-phenylendiamine.

Mw: 447

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.25 (d, J=8.7Hz, 2H), 7.85 (s, 1H), 7.80 (d, J=8.1Hz, 1H), 7.60 (d, J=8.1Hz, 1H), 7.44-7.53 (m, 4H), 7.16 (d, J=8.4Hz, 1H), 4.24-4.35 (m, 1H),2.51 (s, 3H), 2.20-2.48 (m, 2H), 1.92-2.18 (m, 2H), 0.76 (t, J=7.2Hz, 6H)

Example 5: Preparation of 1-butyl-2'-(2-chloro-6-fluorophenyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl

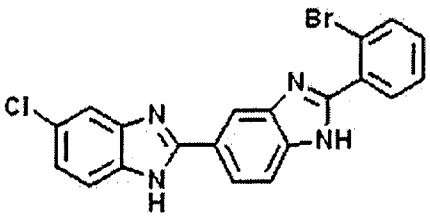


The title compound (0.07 g, 92%) was obtained using the method described in Example 1, Step 3 using N-butyl-5-methyl-1,2-phenylendiamine.

Mw: 433

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 7.99 (s, 1H), 7.84 (d, J=7.8Hz, 1H), 7.57-7.66 (m, 3H), 7.48 (d, J=8.1Hz, 1H), 7.38 (s, 1H), 7.32 (t, J=8.7HZ, 1H), 7.15 (d, J=8.1Hz, 1H), 4.31 (t, J=7.2Hz, 2H), 2.52 (s, 3H), 1.70-1.80 (m, 2H), 1.15-1.25 (m, 2H), 0.8 (t, J=7.5Hz, 3H)

Example 6: 2'-(2-bromophenyl)-5-chloro-1H,1'H-[2,5']bibenzimidazolyl

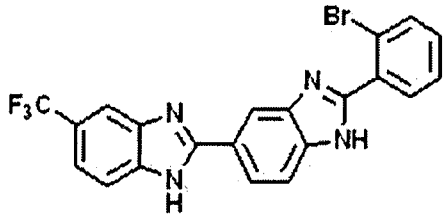


The title compound (0.07 g, 51 %) was obtained using the method described in Example 1, Step 3 using 4-chloro-1,2-phenylendiamine and 2-bromo-1H-benzimidazole-5-carbaldehyde.

Mw: 424

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.39 (s, 1H), 8.07 (d, J=8.4Hz, 1H), 7.75-7.84 (m, 3H), 7.45-7.60 (m, 4H), 7.25 (dd, J_1=1.8Hz, J_2=8.4Hz, 1H)

Example 7: Preparation of 2'-(2-bromophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl

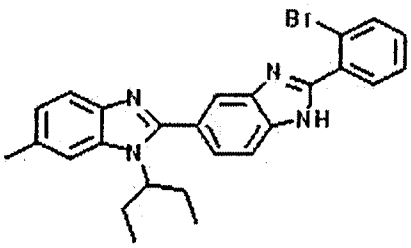


The title compound (0.14 g, 94 %) was obtained using the method described in Example 1, Step 3 using 4-trifluoromethyl-1,2-phenylendiamine and 2-bromo-1H-benzimidazole-5-carbaldehyde.

Mw: 457

^{1}H NMR (CD_3OD+$CDCl_3$, 300 MHz): δ(ppm) 8.33 (s, 1H), 7.23-7.97 (m, 9H)

Example 8: Preparation of 2'-(2-bromophenyl)-1-(1-ethylpropyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl

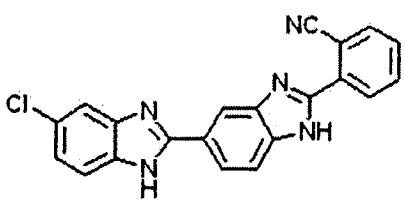


The title compound (0.11 g, 72 %) was obtained using the method described in Example 1, Step 3 using N-isobutyl-5-methyl-1,2-phenylendiamine and 2-bromo-1H-benzimidazole-5-carbaldehyde.

Mw: 473

^{1}H NMR (CD_3OD+$CDCl_3$, 300 MHz): δ(ppm) 7.88 (s, 1H), 7.75-7.82 (m, 3H), 7.52-7.64 (m, 4H), 7.45 (td, J_1=1.5Hz, J_2=7.6Hz, 1H), 7.15 (d, J=8.1Hz, 1H), 4.25-4.35 (m, 1H), 2.51 (s, 3H), 2.17-2.32 (m, 2H), 1.91-2.02 (m, 2H), 0.75 (t, J=7.2Hz, 6H)

Example 9: Preparation of 2-(5-chloro-1H,1'H-[2,5'-bibenzimidazol]-2'-yl)benzonitrile

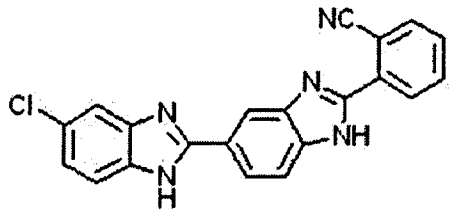


To a DMF (4 ml) solution of 2'-(2-bromophenyl)-5-chloro-1H,1'H-2,5'-bibenzo[d]imidazole (0.1 g, 0.24 mmol) was added NaCN (0.02 g, 0.47 mmol), CuI (0.02 g, 0.12 mmol). The reaction mixture was stirred overnight at 120℃ for 48 hr, cooled down to room temperature. The mixture was diluted with ethyl acetate and filtered. The filterate was washed with water and 5% NH_4OH. The organic phase was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by chromatography on silica gel column eluted with 50% ethyl acetate/hexane to give the title compound (0.06 g, 69 %).

Mw: 370

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.32 (s, 1H), 7.88-8.00 (m, 3H), 7.72-7.85 (m, 2H), 7.60-7.66 (m, 1H), 7.40-7.59 (m, 2H), 7.14-7.25 (m, 1H)

Example 10: Preparation of 2-(5-trifluoromethyl-1H,1'H-[2,5'-bibenzimidazol]-2'-yl)benzonitrile

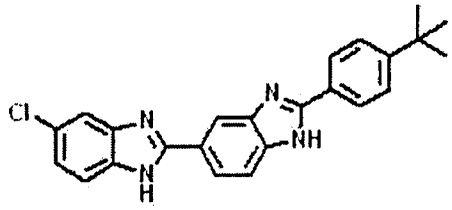


The title compound (0.035 g, 56 %) was obtained using the method described in Example 9, using 2'-(2-bromophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazole.

Mw: 403

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.48-8.58 (m, 1H), 7.71-8.23 (m, 8H), 7.58-7.68 (m, 1H)

Example 11: 2'-(4-tert-butylphenyl)-5-chloro-1H,1'H-[2,5']bibenzimidazolyl

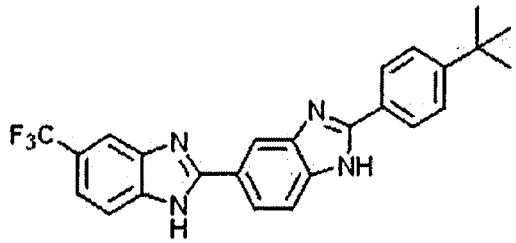


The title compound (0.088 g, 67 %) was obtained using the method described in Example 1, Step 3, using 4-chloro-1,2-phenylendiamine and 4-tert-butyl-1H-benzimidazole-5-carbaldehyde.

Mw: 401

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.17 (s, 1H), 7.94 (d, J=8.4Hz, 2H), 7.87 (d, J=8.4Hz, 1H), 7.61 (d, J=8.1Hz, 1H), 7.45-7.54 (m, 4H), 7.14 (dd, J1=1.8Hz, J2=8.7Hz, 1H)

Example 12: Preparation of 2'-(4-tert-butylphenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl

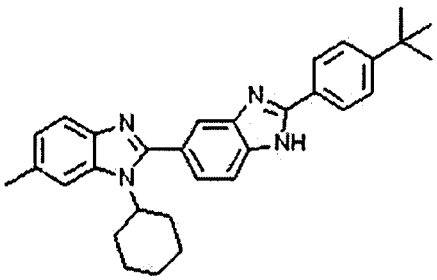


The title compound (0.13 g, 94 %) was obtained using the method described in Example 11, using 4-trifluoromethyl-1,2-phenylendiamine.

Mw: 434

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.26 (s, 1H), 7.93-7.98 (m, 3H), 7.86 (s, 1H), 7.66-7.68 (m, 2H), 7.46-7.58 (m, 3H), 1.33 (s, 9H)

Example 13: Preparation of 2'-(4-tert-butylphenyl)-1-cyclohexyl-6-methyl-1H,1'H-[2,5']bibenzimidazolyl

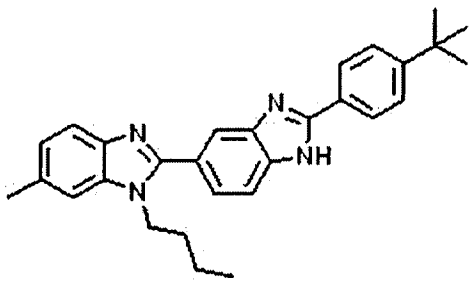


The title compound (0.04 g, 54 %) was obtained using the method described in Example 11, using N-cyclohexyl-5-methyl-1,2-phenylendiamine.

Mw: 463

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.00 (d, J=8.1Hz, 2H), 7.76-7.94 (m, 2H), 7.52-7.62 (m, 1H), 7.46 (s, 1H), 7.26-7.35 (m, 3H), 7.05-7.09 (m, 1H)

Example 14: Preparation of 1-butyl-2'-(4-tert-butylphenyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl

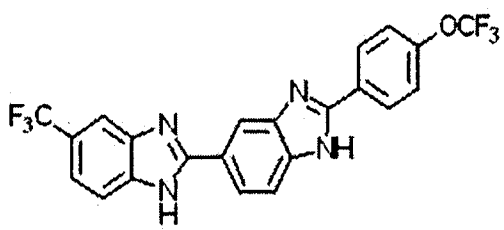


The title compound (0.07 g, 89 %) was obtained using the method described in Example 11, using N-butyl-5-methyl-1,2-phenylendiamine.

Mw: 437

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.00-8.03 (m, 2H), 7.35-7.50 (m, 3H), 7.19-7.25 (m, 3H), 7.02-7.04 (m, 2H), 4.00-4.25 (m, 2H), 2.50 (s, 3H), 1.65-1.82 (m, 2H), 1.24 (s, 11H), 0.72-0.85 (m, 3H)

Example 15: Preparation of 2'-(4-trifluoromethoxyphenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl



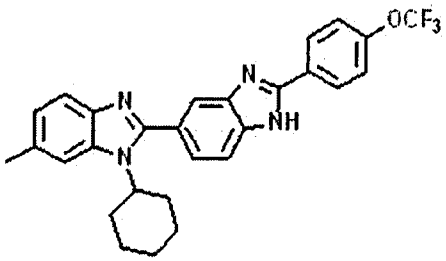
The title compound (0.13 g, 87 %) was obtained using the method described in Example 1, Step 3, using 4-trifluoromethyl-1,2-phenylendiamine and 4-trifluoromethoxy-1H-benzimidazole-5-carbaldehyde.

Mw: 462

^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ(ppm) 8.08 (s, 1H), 7.96-8.06 (m,

2H), 7.82 (dd, J1=1.2Hz, J2=8.7Hz, 1H), 7.76 (s,1H), 7.53-7.60 (m,2H), 7.38 (d, J=8.4Hz, 1H), 7.27 (d, J=9.0Hz, 2H)

Example 16: Preparation of 1-cyclohexyl-6-methyl-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl

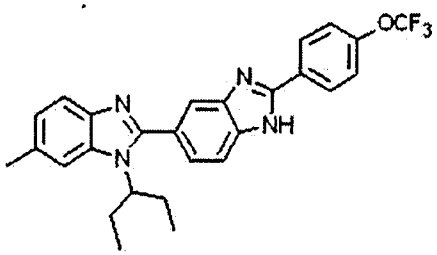


The title compound (0.09 g, 53 %) was obtained using the method described in Example 15, using N-cyclohexyl-5-methyl-1,2-phenylendiamine.

Mw: 491

^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ(ppm) 8.25 (d, J=9.0Hz, 2H), 7.88 (s, 1H), 7.82 (d, J=8.4Hz, 1H), 7.53-7.63 (m, 5H), 7.13 (d, J=8.1Hz, 1H), 4.38-4.46 (m, 1H), 2.54 (s, 3H), 2.40-2.47 (m, 2H), 1.92-1.99 (m, 4H), 1.70-1.73 (m, 1H), 1.30-1.44 (m, 3H)

Example 17: Preparation of 1-(1-ethylpropyl)-6-methyl-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl

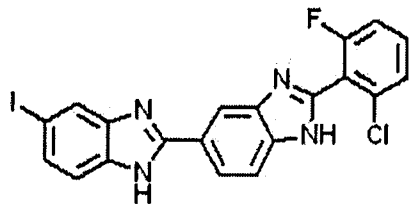


The title compound (0.11 g, 71 %) was obtained using the method described in Example 15, using N-isobutyl-5-methyl-1,2-phenylendiamine.

Mw: 479

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.25 (d, J=8.7Hz, 2H), 7.85 (s, 1H), 7.80 (d, J=8.1Hz, 1H), 7.60 (d, J=8.1Hz, 1H), 7.44-7.53 (m, 4H), 7.16 (d, J=8.4Hz, 1H), 4.24-4.35 (m, 1H), 2.51 (s, 3H), 2.20-2.48 (m, 2H), 1.92-2.18 (m, 2H), 0.76 (t, J=7.2Hz, 6H)

Example 18: Preparation of 2'-(2-chloro-6-fluorophenyl)-5-iodo-1H,1'H-[2,5']bibenzimidazolyl

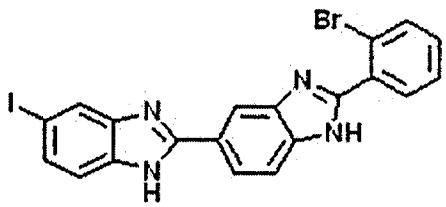


The title compound (0.07 g, 76 %) was obtained using the method described in Example 1, Step 3, using 4-iodo-1,2-phenylendiamine.

Mw: 515

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.42 (s, 1H), 8.10 (d, J=7.8Hz, 1H), 7.98 (s, 1H), 7.35 (d, J=8.4Hz, 1H), 7.32-7.64 (m, 5H)

Example 19: Preparation of 2'-(2-bromophenyl)-5-iodo-1H,1'H-[2,5']bibenzimidazolyl

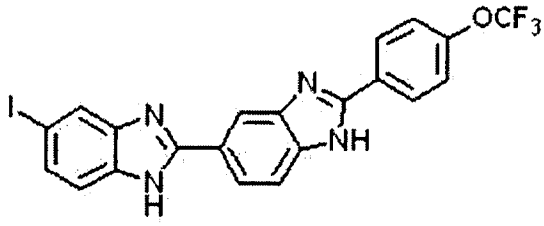


The title compound (0.20 g, 91 %) was obtained using the method described in Example 6, using 4-iodo-1,2-phenylendiamine.

Mw: 515

^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ(ppm) 8.28 (s, 1H), 7.98 (s, 1H), 7.86 (d, J=7.5Hz, 1H), 7.73 (dd, J1=1.2Hz, J2=7.95Hz, 2H), 7.44-7.54 (m, 3H), 7.34-7.39 (m, 2H)

Example 20: Preparation of 5-iodo-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl



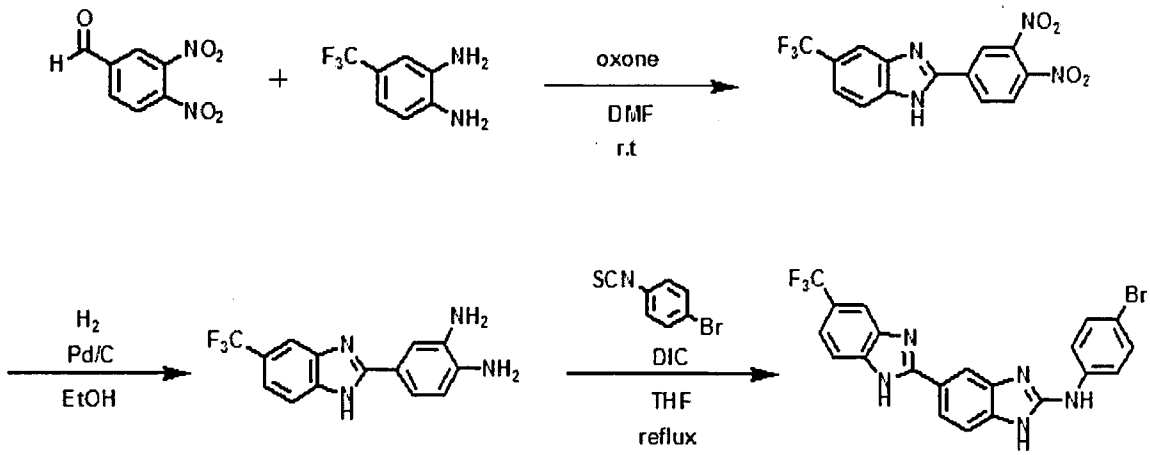
The title compound (0.08 g, 92 %) was obtained using the method described in Example 15, using 4-iodo-1,2-phenylendiamine.

Mw: 520

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.24 (s, 1H), 8.16 (d, J=8.7Hz, 2H), 7.89-7.97 (m, 2H), 7.69 (s, 1H), 7.49 (dd, J_1=1.2Hz, J_2=8.4Hz, 1H), 7.44 (d, J=8.4Hz, 2H), 7.35(d, J=8.4Hz, 1H)

Example 21: Preparation of (4-bromophenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine

The title compound was prepared as follows:



Step 1: Preparation of 5-trifluoromethyl-2-(3,4-dinitrophenyl)-1H-benzimidazole

The title compound (0.29 g, 100 %) was obtained using the method described in Example 1, Step 3, using 4-trifluoromethyl-1,2-phenylendiamine and 3,4-dinitrobenzaldehyde.

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 8.73 (s, 1H), 8.59 (d, J=8.4Hz, 1H), 8.08 (d,

J=8.1Hz, 1H), 7.70-8.00 (m, 1H), 7.66-7.86 (m, 1H), 7.59 (d, J=8.4Hz, 1H)

Step 2: Preparation of 4-(5-trifluoromethyl-1H-benzimidazole-2-yl)-benzene-1,2-diamine

10% Pd/C (0.07 g) was added to solution of 5-trifluoromethyl-2-(3,4-dinitrophenyl)-1H-benzimidazole (0.29 g, 0.83 mmol) in ethanol (10 ml). The reaction mixture was hydrogenated at an hydrogen pressure (10psi), filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound (0.21 g, 87 %).

Mw: 293.9

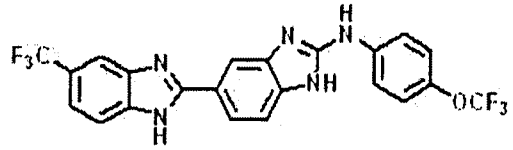
Step 3: Preparation of (4-bromophenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzo[d]imidazolyl-2'-yl)amine

4-bromophenyl isothiocyanate(0.05 g, 0.24 mmol) and diisoproylcarbodiimide (0.15 ml, 0.96 mmol) are added to a solution of 4-(5-trifluoromethyl-1H-benzimidazole-2-yl)-benzene-1,2-diamine (0.07 g, 0.24 mmol) in THF (5 ml). The reaction mixture was heated under reflux for 24hr then cooled down to room temperature and concentrated under reduced pressure. The residue was taken up in ethyl acetate and water. After decanting and extracting, the combined organic phase are washed with brine, dried over Na_2SO_4 then evaporated. The crude residue was purified by chromatography on silica gel column eluted with dichloromethane/methanol (20/1) to give the title compound (0.05 g, 44 %).

Mw: 472

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.14 (s, 1H), 11.29 (s, 1H), 9.78 (s, 1H), 8.13 (d, J=9Hz, 1H), 7.62-7.91 (m, 5H), 7.47 (d, J=8.1Hz, 4H)

Example 22: Preparation of (4-trifluoromethoxyphenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine

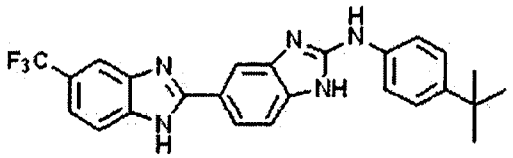


The title compound (0.05 g, 43 %) was obtained using the method described in Example 21, Step 3, using 4-(5-trifluoromethyl-1H-benzimidazole-2-yl)-benzene-1,2-diamine and 4-trifluoromethoxyphenylisothiocyanate.

Mw: 477

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.07 (s, 1H), 7.84-7.86 (m, 2H), 7.63-7.69 (m, 3H), 7.45-7.52 (m, 2H), 7.26 (d, J=8.4Hz, 2H)

Example 23: Preparation of (4-tert-butylphenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine

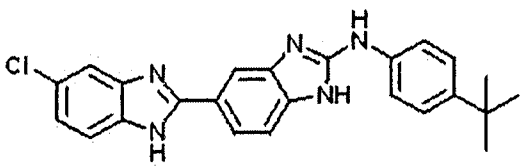


The title compound (0.02 g, 33 %) was obtained using the method described in Example 21, Step 3, using 4-(5-trifluoromethyl-1H-benzimidazole-2-yl)-benzene-1,2-diamine and 4-tert-butylphenylisothiocyanate.

Mw: 416

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.12 (s, 1H), 11.18 (s, 1H), 9.50 (s, 1H), 8.12 (s, 1H), 7.75-7.94 (m, 3H), 7.58-7.65 (m, 2H), 7.40-7.45 (m, 2H), 7.34 (d, J=8.4Hz, 2H), 1.27 (s, 9H)

Example 24: Preparation of (4-tert-butylphenyl)-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine

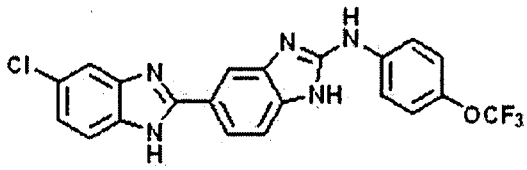


The title compound (0.02 g, 33 %) was obtained using the method described in Example 21, Step 3, using 4-(5-chloro-1H-benzimidazole-2-yl)-benzene-1,2-diamine and 4-tert-butylphenylisothiocyanate.

Mw: 416

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.07 (brs, 1H), 11.34 (s, 1H), 9.67 (s, 1H), 8.27 (s, 1H), 7.36-8.02 (m, 9H), 1.46 (s, 9H)

Example 25: Preparation of (5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)-(4-trifluoromethoxyphenyl)amine

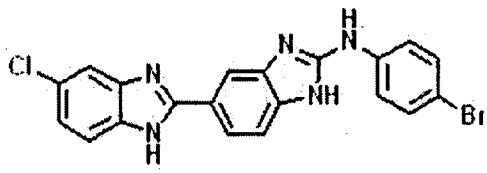


The title compound (0.04 g, 49%) was obtained using the method described in Example 1, Step 3, using 4-(5-chloro-1H-benzimidazole-2-yl)-benzene-1,2-diamine and 4-trifluoromethoxyphenylisothiocyanate.

Mw: 444

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 12.89 (brs, 1H), 11.31 (brs, 1H), 9.82 (brs, 1H), 8.13 (s, 1H), 7.17-7.87 (m, 9H)

Example 26: Preparation of (4-bromophenyl)-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine

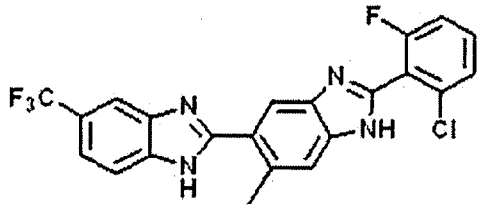


The title compound (0.08 g, 88 %) was obtained using the method described in Example 1, Step 3, using 4-(5-chloro-1H-benzimidazole-2-yl)-benzene-1,2-diamine and 4-bromophenylisothiocyanate.

Mw: 439

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 12.99 (brs, 1H), 11.43 (brs, 1H), 9.91 (s, 1H), 7.23-8.20 (m, 10H)

Example 27: 2'-(2-chloro-6-fluorophenyl)-6'-methyl-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl

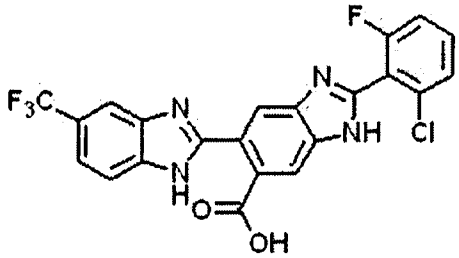


The title compound (0.12 g, 100 %) was obtained using the method described in Example 1, Step 3, using 4-trifluoromethyl-1,2-phenylendiamine and 2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carbaldehyde.

Mw: 445

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.03 (s, 1H), 7.92-8.07 (m, 1H), 7.75 (brs, 1H), 7.49-7.69 (m, 2H), 6.84-7.46 (m, 4H), 2.71 (s, 3H)

Example 28: Preparation of 2'-(2-chloro-6-fluorophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-6'-carboxylic acid

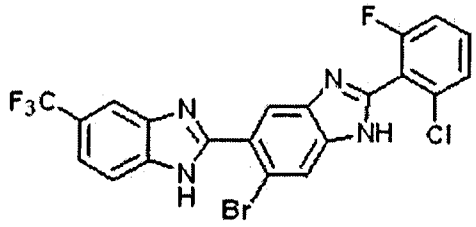


2'-(2-chloro-6-fluorophenyl)-6'-methyl-5-(trifluoromethyl)-1H,1'H-2,5'-bibenzo[d]imidazole (0.1 g, 0.23 mmol) and $KMnO_4$ (0.17 g, 1.12 mmol) in H_2O/BuOH(1/1, 5 ml) was stirred at 80℃ for 7-10hr, filtered through a celite pad and washed with ethyl acetate. The filterate was concentrated under reduced pressure and the crude residue was purified by chromatography on silica gel column eluted with dichloromethane/methanol (5/1) to give the title compound (0.06 g, 56 %).

Mw: 475

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.10 (s, 1H), 8.42 (s, 1H), 8.19 (s, 1H), 7.92 (s, 1H), 7.62-7.73 (m, 2H), 7.55 (d, J=8.1Hz, 1H), 7.41-7.49 (m, 2H)

Example 29: Preparation of 6'-bromo-2'-(2-chloro-6-fluorophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl

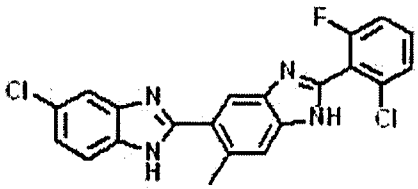


The title compound (0.03 g, 33 %) was obtained using the method described in Example 1, Step 3, using 4-trifluoromethyl-1,2-phenylendiamine and 6-bromo-2-(2-chloro-6-fluoromethylphenyl)-1H-benzimidazole-5-carbaldehyde.

Mw: 510

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.09 (s, 1H), 8.04 (s, 1H), 7.97 (s, 1H), 7.80 (d, J=8.4Hz, 1H), 7.58-7.66 (m, 2H), 7.50 (d, J=8.4Hz, 1H), 7.34 (t, J=8.4Hz, 1H)

Example 30: Preparation of 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methyl-1H,1'H-[2,5']bibenzimidazolyl

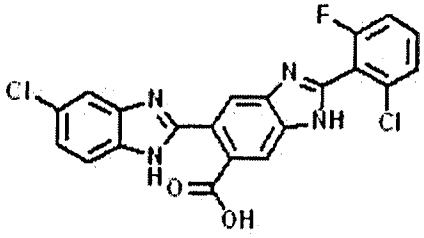


The title compound (0.11 g, 70 %) was obtained using the method described in Example 27, using 4-chloro-1,2-phenylendiamine.

Mw: 411

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 8.01 (brs, 1H), 7.49-7.69 (m, 5H), 7.46 (t, J=9.3Hz, 1H), 7.21 (dd, J1=2.1Hz, J2=8.55Hz, 1H)

Example 31: Preparation of 5-chloro-2'-(2-chloro-6-fluorophenyl)-1H,1'H-[2,5']bibenzimidazolyl-6'-carboxylic acid



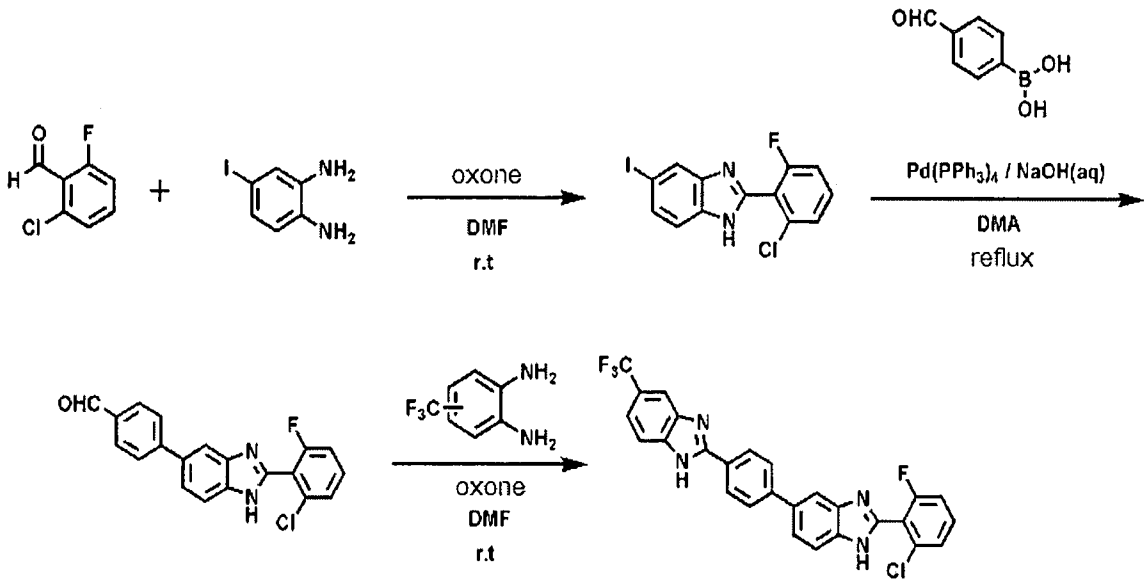
The title compound (0.03 g, 30 %) was obtained using the method described in Example 28, using 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methyl-1H,1'H-2,5'-bibenzo[d]imidazole.

Mw: 441

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.24 (s, 1H), 8.07-8.44 (m, 2H), 7.49-7.75 (m, 5H), 7.18 (d, J=8.4Hz, 1H)

Example 32: Preparation of 2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]phenyl}-5-trifluoromethyl-1H-benzo[d]imidazole

The title compound was prepared as follows:



Step 1: Preparation of 2-(2-chloro-6-fluorophenyl)-5-iodo-1H-benzimidazole

The title compound (0.56 g, 93 %) was obtained using the method described in Example 1, Step 1, using 4-iodo-1,2-phenylendiamine and 2-chloro-6-

fluorobenzaldehyde.

^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) 8.00 (s, 1H), 7.54-7.63 (m, 2H), 7.45 (d, J=9Hz, 2H), 7.30 (t, J=8.4Hz, 1H)

Step 2: Preparation of 4-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]-benzaldehyde

A suspension of 4-formylphenylboronic acid (0.07 g, 0.48 mmol), 2-(2-chloro-6-fluoro-phenyl)-5-iodo-1H-benzimidazole (0.15 g, 0.4 mmol), $Pd(PPh_3)_4$ (0.02 g, 0.02 mmol) and NaOH (0.03 g, 0.80 mmol) in DME/H_2O (3/1) was refluxed for 24hr . The solvent was evaporated, ethyl acetate was added and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (2/1) to give the title compound (0.05 g, 36 %).

^{1}H NMR (CD_3OD,300 MHz): δ(ppm) 10.02 (s, 1H), 7.97-8.01 (m, 3H), 7.91 (d, J=8.4Hz, 2H), 7.76 (d, J=8.4Hz, 1H), 7.69 (dd, J_1=1.8Hz, J_2=8.5Hz, 1H), 7.56-7.61(m, 1H), 7.46-7.49 (m, 1H), 7.29-7.35 (m, 1H)

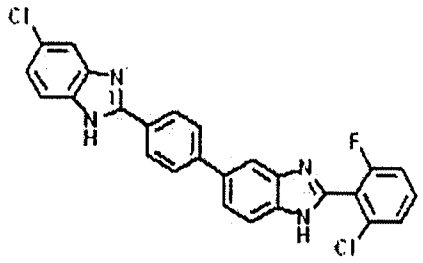
Step 3: Preparation of 2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazole-5-yl]phenyl}-5-trifluoromethyl-1H-benzo[d]imidazole

The title compound (0.04 g, 54 %) was obtained using the method described in Example 1, Step 1, using 4-trifluoromethyl-1,2-phenylendiamine and 4-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-yl]-benzaldehyde.

Mw: 507

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.20 (d, J=8.4Hz, 2H), 7.96 (s, 1H), 7.91 (s, 1H), 7.89 (d, J=8.1Hz, 2H), 7.67-7.73 (m, 3H), 7.46-7.62 (m, 3H), 7.31 (t, J=8.1Hz, 1H)

Example 33: Preparation of 5-chloro-2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]phenyl}-1H-benzo[d]imidazole

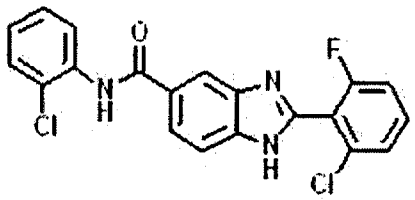


The title compound (0.1 g, 85 %) was obtained using the method described in Example 32, Step 3, using 4-chloro-1,2-phenylendiamine.

Mw: 473

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.05 (d, J=7.8Hz, 2H), 7.88 (s, 1H), 7.74 (d, J=8.1Hz, 2H), 7.66-7.68 (m, 1H), 7.40-7.57 (m, 5H), 7.26 (d, J=8.7Hz, 1H), 7.15 (d, J=8.4Hz, 1H)

Example 34: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-chlorophenyl)-amide



Step 1: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid methyl ester

The title compound (2.11 g, 77%) was obtained using the method described in Example 1, Step 1, using 3,4-diaminobenzoic acid methyl ester.

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 13.21 (s, 1H), 8.24 (brs, 1H), 7.89-7.92 (m, 1H), 7.47 (brs, 1H), 7.18-7.26 (m, 1H), 7.12 (d, J=8.1Hz, 1H), 6.91 (t, J=8.4Hz, 1H), 3.88 (s, 3H)

Step 2: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid

2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid methyl ester (2.11 g, 6.94 mmol) was dissolved in MeOH/THF (2/1, 60 ml) and added NaOH (1.38 g, 34.70 mmol). The reaction mixture was refluxed for 12hr and cooled to room temperature. The reaction mixture was acidified with 1N HCl and evaporated. The reaction mixture was extracted with ethyl acetate, dried (Na_2SO_4), filtered and evaporated to give the title compound (1.40 g, 70 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 13.26 (brs, 1H), 8.23 (s, 1H), 7.87 (d, J=8.1Hz, 1H), 7.62-7.69 (m, 2H), 7.55 (d, J=8.1Hz, 1H), 7.46 (t, J=9Hz, 1H)

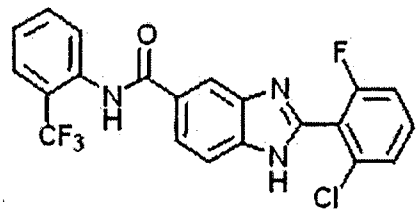
Step 3: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-chlorophenyl)-amide

To a solution of 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.25 g, 0.86 mmol) in DMF (5 ml) was added DIPEA (0.22 ml, 1.29 mmol) and HBTU (0.32 g, 0.86 mmol). The mixture was stirred for 30 minutes at room temperature, then 2-chloroaniline (0.09 ml, 0.86 mmol) was added. This reaction mixture was stirred overnight at room temperature, then the solvent was evaporated, and the residue stirred with sat-K_2CO_3 (aq) solution was added, and the mixture was then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexnae (2/1) to give the title compound (0.32 g, 93 %).

Mw: 400

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 8.66 (d, J=1.2Hz, 1H), 8.20 (dd, J1=1.5Hz, J2=8.7Hz, 1H), 8.09 (d, J=8.4Hz, 1H), 7.84 (d, J=8.4Hz, 1H), 7.33-7.64 (m, 5H), 7.12 (t, J=9.3Hz, 1H)

Example 35: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-trifluoromethylphenyl)-amide

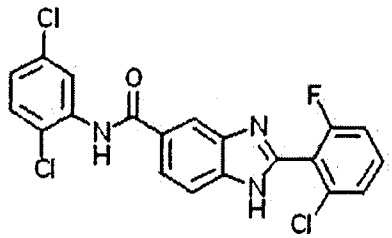


The title compound (0.21 g, 56 %) was obtained using the method described in Example 34, Step 3, using 2-trifluoromethylaniline.

Mw: 434

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.68 (d, J=1.5Hz, 1H), 8.26 (dd, J1=1.5Hz, J2=8.7Hz, 1H), 8.04 (d, J=8.4Hz, 1H), 7.90 (d, J=8.4Hz, 1H), 7.84 (d, J=8.1Hz, 1H), 7.60-7.74 (m, 3H), 7.43-7.59 (m, 2H), 7.36 (t, J=9Hz, 1H)

Example 36: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2,5-dichlorophenyl)-amide



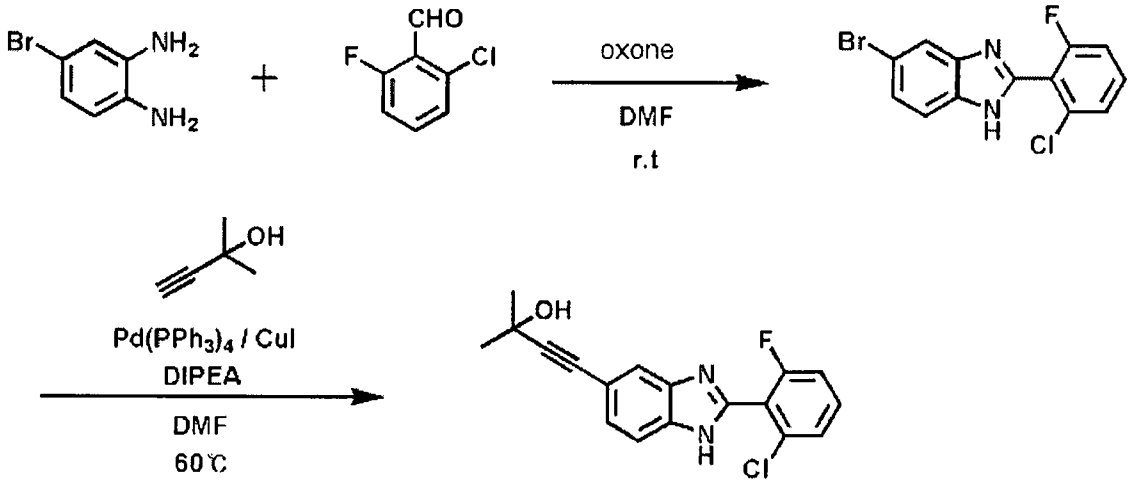
The title compound (0.23 g, 64 %) was obtained using the method described in Example 34, Step 3, using 2,5-dichloroaniline.

Mw: 435

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.70 (s, 1H), 8.28 (dd, J1=1.5Hz, J2=8.4Hz, 1H), 8.09 (d, J=8.4Hz, 1H), 7.87-7.91 (m, 1H), 7.60-7.74 (m, 3H), 7.46-7.57 (m, 2H), 7.36 (t, J=8.4Hz, 1H)

Example 37: Preparation of 4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazole-5-yl]-2-methyl-3-butyn-2-ol

The title compound was prepared as follows:



Step 1: Preparation of 5-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole

The title compound (2.00 g, 77 %) was obtained using the method described in Example 1, Step 3, using 4-bromo-1,2-phenylendiamine and 2-chloro-6-fluorobenzaldehyde.

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 7.78 (brs, 1H), 7.51 (brs, 1H), 7.38-7.51 (m, 2H), 7.33 (d, J=7.5Hz, 1H), 7.13 (t, J=8.1Hz, 1H)

Step 2: Preparation of 4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazole-5-yl]-2-methyl-3-butyn-2-ol

To a solution of 5-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole (0.30 g, 0.92 mmol) in DMF (15 ml) was added 2-methyl-3-butyn-2-ol (0.18 ml, 1.84 mmol), tetrakis(triphenylphosphine)palladium (0.06 g, 0.06 mmol), copper iodide (0.04g, 0.18 mmol) and diisopropylethylamine (0.18 ml, 1.29 mmol). The mixture was stirred at 60℃ for 3 days and cooled to room temperature. The mixture was extracted with ethyl acetate and the organic layer dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (2/1) to give the title compound (0.17 g, 56 %).

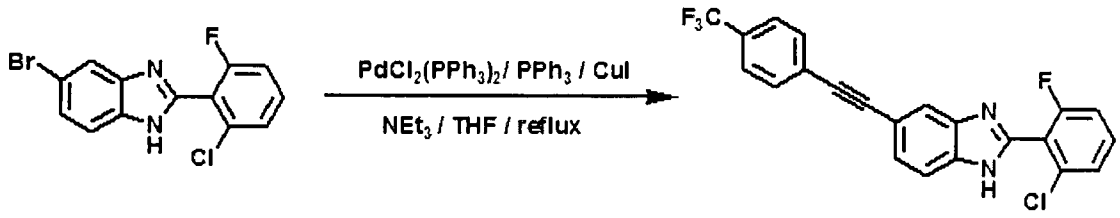
Mw: 329

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 7.54-7.67 (m, 3H), 7.46 (d, J=8.1Hz, 1H),

7.27-7.37 (m, 2H), 1.58 (s, 6H)

Example 38: Preparation of 2-(2-chloro-6-fluorophenyl)-5-(4-trifluoromethylphenyletynyl)-1H-benzimidazole

The title compound was prepared as follows:

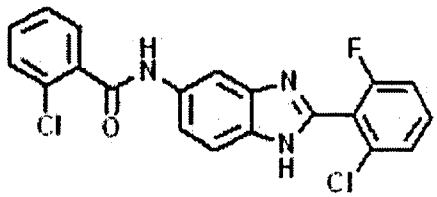


To a solution of 2-(2-chloro-6-fluoro-phenyl)-5-bromo-1H-benzimidazole (0.30 g, 0.92 mmol) and 4-ethynyl-α, α, α-trifluorotoluene (0.30 ml, 1.84 mmol) in anhydrous THF (10 ml). Added triethylamine (0.30 ml, 1.84 mmol), CuI (0.01 g, 0.05 mmol), dichlorobis(triphenylphosphine)palladium (0.03 g, 1.84 mmol), triphenylphosphine (0.02 g, 0.09 mmol). The reaction mixture was refluxed overnight. The reaction mixture was added to water and ethyl acetate. The organic layer washed brine and dried over Na_2SO_4, and concerntrated. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (2/1) to give the title compound (0.26 g, 70 %).

Mw: 415

^{1}H NMR (CDCl3, 300 MHz): δ(ppm) 11.46 (brs, 1H), 7.58-7.90 (m, 5H), 7.24-7.48 (m, 4H), 7.04 (t, J=8.7Hz, 1H)

Example 39: Preparation of 2-chloro-N-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-yl]-benzamide



Step 1: Preparation of 5-amino-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole

2-(2-chloro-6-fluoro-phenyl)-5-nitro-1H-benzimidazole (0.79 g, 2.80 mmol) in

EtOH/ethyl acetate (4/1, 25 ml)) was added $SnCl_2 \cdot 2H_2O$ (2.43 g, 10.81 mmol). The reaction was refluxed for 5 hours and then cooled to room temperature. Being cooled to 0℃ on an ice bath and basified with a 50% NaOH solution. The precipitate was filtered and extracted with ethyl acetate. After concentration, The crude residue was purified by chromatography on silica gel column eluted with dichloromethane/methanol (20/1) to give the title compound (0.50 g, 71 %).

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 7.52 (dd, J_1=6Hz, J_2=8.25Hz, 1H), 7.39-7.46 (m, 2H), 7.26-7.34(m, 1H), 6.93 (d, J=1.5Hz, 1H), 6.80 (dd, J_1=2.1Hz, J_2=8.4Hz, 1H)

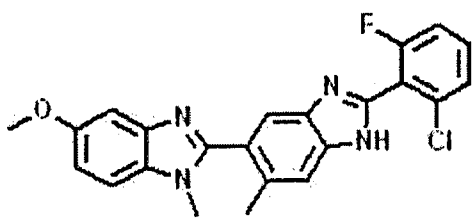
Step 2: Preparation of 2-chloro-N-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-yl]-benzoamide

2-chlorobenzoylchloride (0.06 ml, 0.46 mmol) was added to a stirring solution of 5-amino-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole (0.10 g, 0.38 mmol) in pyridine (5 ml), and the reaction mixture stirred at room temperature for 24 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with dilute HCl and sat-brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (1/1) to give the title compound (0.08 g, 54 %).

Mw: 400

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 12.83 (s, 1H), 10.58 (s, 1H), 8.24 (s, 1H), 7.34-7.66 (m, 9H)

Example 40: Preparation of 2'-(2-chloro-6-fluorophenyl)-5-methoxy-1,6'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl

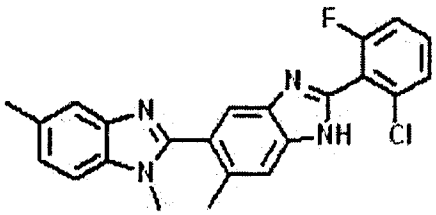


The title compound (0.088 g, 95%) was obtained using the method described in Example 1, Step 3, using 4-methoxy-N1-methylbenzene-1,2-diamine and 2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carbaldehyde.

Mw: 421

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 6.27 (d, J=8.4Hz, 1H), 6.19 (d, J=3.0Hz, 1H), 6.07 (dd, J_1=8.4Hz, J_2=2.7Hz, 1H), 4.5 (s, 2H), 4.10 (s, 1H), 3.56 (s, 3H), 2.62 (s, 3H)

Example 41: Preparation of 2'-(2-chloro-6-fluorophenyl)-1,5,6'-trimethy-1H,1'H-[2,5']bibenzimidazolyl

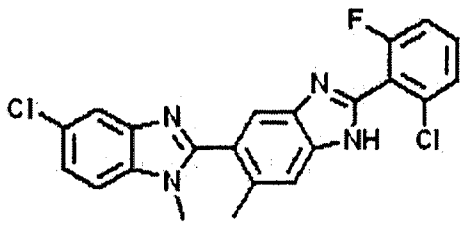


The title compound (0.09 g, 100 %) was obtained using the method described in Example 40, using 4-methyl-N1-methylbenzene-1,2-diamine.

Mw: 405

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.03 (s, 1H), 7.61-7.73 (m, 2H), 7.55 (d, J=8.1Hz, 2H), 7.39-7.47 (m, 3H), 7.10 (d, J=8.4Hz, 1H), 3.58 (s, 3H), 2.43 (s, 3H), 2.25 (s, 3H)

Example 42: Preparation of 5-chloro-2'-(2-chloro-6-fluorophenyl)-1,6'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl

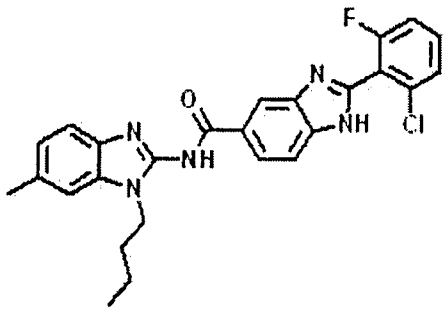


The title compound (0.07 g, 78 %) was obtained using the method described in Example 40, using 4-chloro-1,2-phenylendiamine.

Mw: 425

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.08 (s, 1H), 7.31-7.74 (m, 8H), 3.63 (s, 3H), 2.26 (s, 3H)

Example 43: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)amide



Step 1: 1-butyl-6-methyl-1H-benzimidazole-2-ylamine

To a solution of 5-methyl-N1-butylbenzene-1,2-diamine (0.72 g, 4.04 mmol) in EtOH was added BrCN (3M in CH_2Cl_2, 1.88 ml, 5.65 mmol) and stirred at room temperature for 5hr. The reaction mixture was added sat-$NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give the title compound (0.74 g, 91%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 7.30 (d, J=7.8Hz, 1H), 6.93 (d, J=8.1Hz, 1H), 6.89 (s, 1H), 3.87 (t, J=6.9Hz, 2H), 2.44 (s, 3H), 1.70-1.80 (m, 2H), 1.36-1.44 (m, 2H), 0.95 (t, J=7.2Hz, 3H)

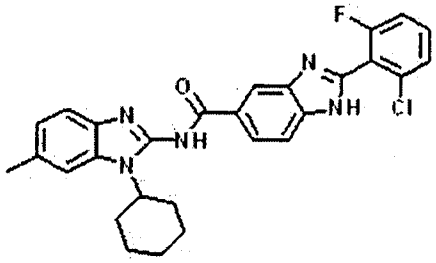
Step 2: 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid(1-butyl-6-methyl-1H-benzimidazole-2-yl)amide

The title compound (0.20 g, 61 %) was obtained using the method described in Example 34, Step 3, using 1-butyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 476

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.53-8.72 (brd, 1H), 8.30 (d, J=8.4Hz, 1H), 7.49-7.71 (m, 2H), 7.48 (d, J=8.4Hz, 1H), 7.29-7.37 (m, 2H), 7.24 (s, 1H), 7.08 (d, J=7.8Hz, 1H), 4.33 (t, J=6.9Hz, 2H), 2.46 (s, 3H), 1.85-1.92 (m, 2H), 1.43-1.50 (m, 2H), 1.01 (t, J=7.2Hz, 3H)

Example 44: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazole-2-yl)amide

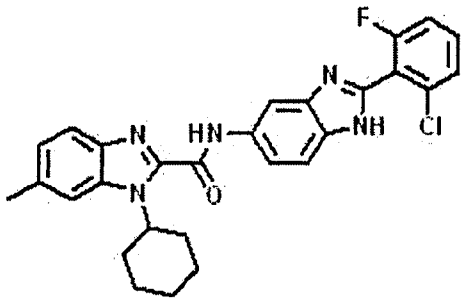


The title compound (0.25 g, 71%) was obtained using the method described in Example 34, Step 3, using 1-cyclohexyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 502

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.63 (brs, 1H), 8.28 (d, J=8.4Hz, 1H), 7.67 (brs, 1H), 7.53-7.58 (m, 1H), 7.45 (d, J=8.1Hz, 1H), 7.26-7.38 (m, 3H), 7.04 (d, J=8.4Hz, 1H), 2.45-2.48 (m, 2H), 2.45 (s, 3H), 1.63-2.14 (m, 6H), 1.43-1.59 (m, 3H)

Example 45: Preparation of 1-cyclohexyl-6-methyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-yl]amide



Step 1: Preparation of 1-cyclohexyl-6-methyl-2-trichloromethyl-1H-benzimidazole

Methyl 2,2,2-trichloroacetimidate (0.36 ml, 2.93 mmol) was added portion wise to a solution of 5-methyl-N1-cyclohexylbenzene-1,2-diamine (0.50 g, 2.45 mmol) in acetic acid (10 ml). The mixture was stirred at room temperature for 4hr room temperature then poured into ice, basified with 2M Na_2CO_3 and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and the solvent was

evaporated to give the title compound (0.45 g, 56 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 7.75 (d, J=8.4Hz, 1H), 7.41 (s, 1H), 7.12 (d, J=8.4Hz, 1H), 4.95-5.03 (m, 1H), 2.52 (s, 3H), 2.23-2.36 (m, 2H), 1.97-2.09 (m, 4H), 1.83-1.86 (m, 1H), 1.40-1.55 (m, 3H)

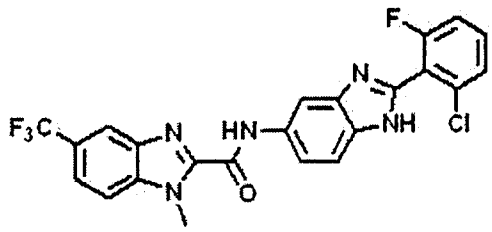
Step 2: Preparation of 1-cyclohexyl-6-methyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-yl]amide

A solution of 1-cyclohexyl-6-methyl-2-trichloromethyl-1H-benzimidazole (0.10 g, 0.33 mmol) in THF/H_2O (1/1, 10 ml) were slowly added to a mixture containing 5-amino-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole (0.09 g, 0.33 mmol), $NaHCO_3$ (0.28 g, 3.33 mmol). The mixture was refluxed vigorously overnight and then cooled to room temperature, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$-solution. The aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (1/1) to give the title compound (0.03 g, 20 %).

Mw: 502

^{1}H NMR (CD_3OD,300 MHz): δ(ppm) 8.32 (s, 1H), 7.55-7.66 (m, 5H), 7.48 (d, J=7.8Hz, 1H), 7.31 (t, J=.7Hz, 1H), 7.20 (d, J=8.7Hz, 1H), 5.41-5.49 (m, 1H), 2.53 (s, 3H), 2.34-2.49 (m, 2H), 1.97-2.14 (m, 4H), 1.79-1.89 (m, 1H), 1.42-1.59 (m, 3H)

Example 46: Preparation of 1-methyl-5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide

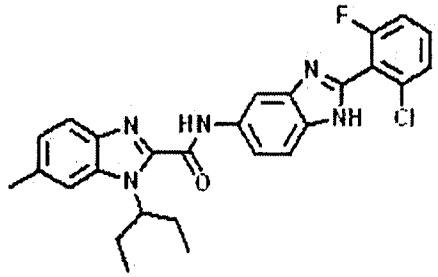


The title compound (0.07 g, 17%) was obtained using the method described in Example 45, Step 2, using 1-methyl-2-trichloromethyl-5-trifluoromethyl-1H-benzimidazole.

Mw: 488

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.33 (s, 1H), 8.13 (s, 1H), 7.84 (d, J=9Hz, 1H), 7.55-7.72 (m, 4H), 7.48 (d, J=8.1Hz, 1H), 7.31 (d, J=8.7Hz, 1H), 4.30 (s, 3H)

Example 47: Preparation of 1-(1-ethylpropyl)-6-methyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide

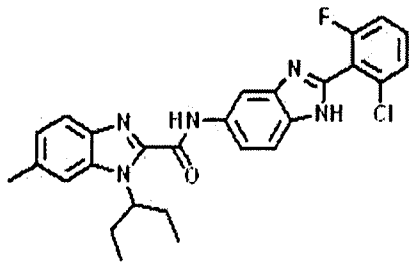


The title compound (0.09 g, 56 %) was obtained using the method described in Example 45, Step 2, using 41-(1-ethylpropyl)-6-methyl-2-trichloromethyl-1H-benzimidazole.

Mw: 490

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.31 (s, 1H), 7.68 (d, J=8.4Hz, 2H), 7.52-7.62 (m, 3H), 7.46 (d, J=8.1Hz, 1H), 7.31 (t, J=8.4Hz, 1H), 7.21 (d, J=8.1Hz, 1H), 5.40-5.56 (m, 1H), 2.51 (s, 3H), 2.23-2.49 (m, 2H), 1.96-2.09 (m, 2H), 0.81 (t, J=7.5Hz, 6H)

Example 48: Preparation of 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluorophenyl)-1-methyl-1H-benzimidazole-5-yl]amide

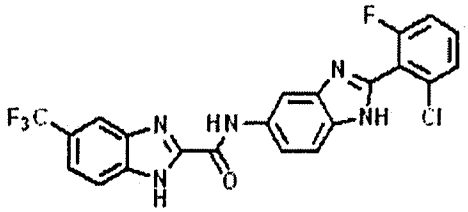


The title compound (0.06 g, 37 %) was obtained using the method described in Example 45, Step 2, using 2-trichloromethyl-5-trifluoromethyl-1H-benzimidazole and 2-(2-chloro-6-fluorophenyl)-1-methyl-1H-benzimidazole-5-ylamine.

Mw: 488

^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ(ppm) 8.39 (s, 1H), 8.05 (s, 1H), 7.84 (d, J=7.8Hz, 1H), 7.63-7.77 (m, 4H), 7.53 (d, J=8.1Hz, 1H), 7.38 (t, J=8.1Hz, 1H), 3.70 (s, 3H)

Example 49: Preparation of 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-yl]amide

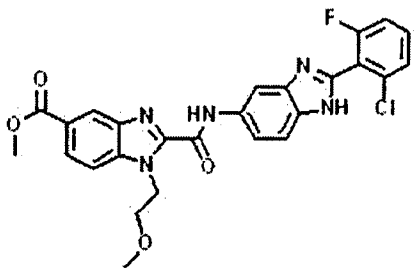


The title compound (0.07 g, 48 %) was obtained using the method described in Example 45, Step 2, using 2-trichloromethyl-5-trifluoromethyl-1H-benzimidazole.

Mw: 474

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.35 (s, 1H), 8.06 (brs, 1H), 7.84 (brs, 1H), 7.55-7.65 (m, 4H), 7.48 (d, J=8.4Hz, 1H), 7.31 (t, J=8.4Hz, 1H)

Example 50: Preparation of 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester



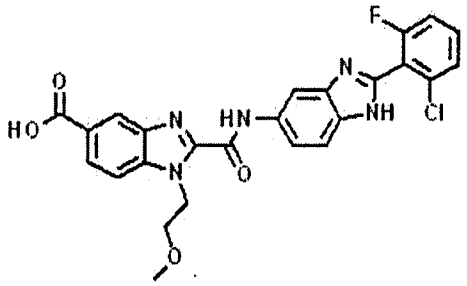
The title compound (0.067 g, 34 %) was obtained using the method described in Example 45, Step 2, using 1-(2-methoxyethyl)-2-trichloromethyl-1H-benzimidazole-5-carboxylic acid methyl ester.

Mw: 522

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 8.54 (d, J=0.9Hz, 1H), 8.13-8.29 (m, 1H),

8.10 (dd, J1=1.2Hz, J2=8.55Hz, 1H), 7.63-7.85 (m, 1H), 7.61 (d, J=8.7Hz, 1H), 7.31-7.46 (m, 3H), 7.13 (td, J_1=1.8Hz, J_2=9.45Hz, 1H), 4.95 (t, J=4.8Hz, 2H), 3.97 (s, 3H), 3.87 (t, J=5.1Hz, 2H), 3.28 (s, 3H)

Example 51: Preparation of 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid

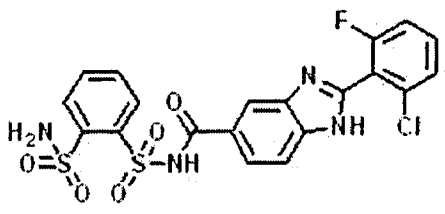


2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (0.06 g, 0.12 mmol) was dissolved in THF/MeOH (2/1, 3 ml) and added NaOH (0.01g, 0.34 mmol). The reaction mixture was stirred at 50℃ for 8hr and cooled to room temperature. The reaction mixture was acidified with 1N HCl and evaporated to give the title compound (0.05 g, 86 %).

Mw: 508

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 12.91 (brs, 1H), 11.05 (brs, 1H), 8.36 (s, 1H), 8.26 (s, 1H), 8.00 (dd, J_1=1.5Hz, J_2=8.55Hz, 1H), 7.82 (d, J=9Hz, 1H), 7.62-7.83 (m,3H), 7.54 (d, J=7.8Hz, 1H), 7.44 (t, J=9.3Hz, 1H), 4.90 (t, J=5.1Hz, 2H), 3.74 (t, J=5.1Hz, 2H), 3.17 (s, 3H)

Example 52: Preparation of benzene-1,2-disulfonic acid 1-amide 2-{[2-(2-chloro-6-fluorophenyl -1H-benzimidazole-5-carbonyl]amide}

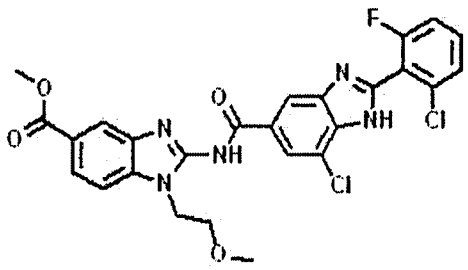


Benzene-1,2-disulfonamide (0.067 g, 0.29 mmol), 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.08 g, 0.28 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.08 g, 0.40 mmol), 4-dimethylaminopyridine (0.09 g, 0.71 mmol) were mixed in DMF (4 ml) and the reaction mixture was stirred at 50 ℃ for 24 hr. The reaction mixture was diluted with water and filtered. The filterate was purified by chromatography on silica gel column eluted with dichloromethane/methanol (10/1) to give the title compound (0.12 g, 83 %).

Mw: 509

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.48 (dd, J_1=3.3Hz, J_2=6Hz, 1H), 8.29 (d, J=1.2Hz, 1H), 8.25 (dd, J_1=3.3Hz, J_2=5.85Hz, 1H), 7.87 (dd, J_1=1.5Hz, J_2=8.7Hz, 1H), 7.81 (dd, J_1=3.6Hz, J_2=5.85Hz, 1H), 7.69 (d, J=8.4Hz, 1H), 7.51-7.58 (m, 1H), 7.41(d, J=8.1Hz, 1H), 7.26 (t, J=8.4Hz, 1H)

Example 53: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester

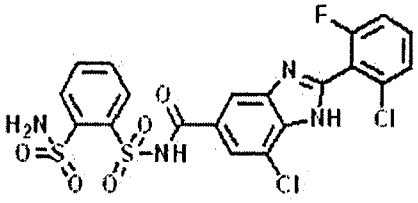


The title compound (0.11 g, 54 %) was obtained using the method described in Example 34, Step 3, using 2-amino-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid.

Mw: 556

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 13.52-13.62 (br, 1H), 12.96 (brs, 1H), 8.41 (s, 1H), 8.18 (s, 1H), 8.11 (s, 1H), 7.88 (dd, J_1=1.5Hz, J_2=8.4Hz, 1H), 7.56-7.69 (m, 3H), 7.48 (t, J=8.7Hz, 1H), 4.48 (t, J=7.8Hz, 2H), 3.85 (s, 3H), 3.80 (t, J=5.4Hz, 2H), 3.25 (s, 3H)

Example 54: Preparation of benzene-1,2-disulfonic acid 1-amide 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amide}

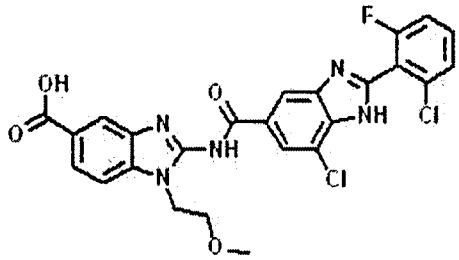


The title compound (0.08 g, 80 %) was obtained using the method described in Example 52, using 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid.

Mw: 543

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 8.28-8.31 (m, 1H), 8.18 (s, 1H), 8.07-7.93 (m, 1H), 7.80-7.93 (m, 1H), 7.63-7.71 (m, 1H), 7.56 (d, J=7.8Hz, 1H), 7.43-7.50 (m, 2H), 7.25 (s, 1H)

Example 55: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid



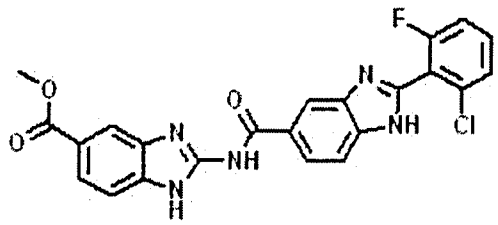
The title compound (0.05 g, 55%) was obtained using the method described in Example 51, using 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester.

Mw: 542

^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ(ppm) 13.00 (s, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 7.96 (d, J=8.4Hz, 1H), 7.46-7.68 (m, 4H), 7.36 (t, J=8.7Hz, 1H), 4.56 (t, J=4.8Hz, 2H), 3.90 (t, J=5.1Hz, 2H), 3.32 (s, 3H)

Example 56: Preparation of 2-{[2-(2-chloro-6-fluorophenyl)-1H-

benzimidazole-5-carbonyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester

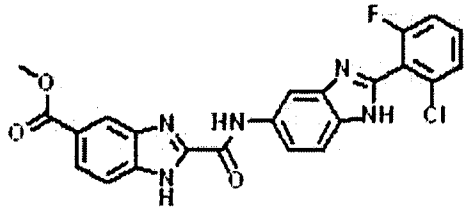


The title compound (0.10 g, 41%) was obtained using the method described in Example 34, Step 3, using 2-amino-1H-benzimidazole-5-carboxylic acid methyl ester and 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid.

Mw: 464

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.45 (s, 1H), 8.18 (s, 1H), 8.08 (d, J=8.7Hz, 1H), 7.90 (dd, J_1=1.8Hz, J_2=8.55Hz, 1H), 7.80 (brs, 1H), 7.48-7.65 (m, 3H), 7.34 (td, J1=1.2Hz, J2=9Hz, 1H), 3.92 (s,3H)

Example 57: Preparation of 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-ylcarbamoyl]-1H-benzimidazole-5-carboxylic acid methyl ester



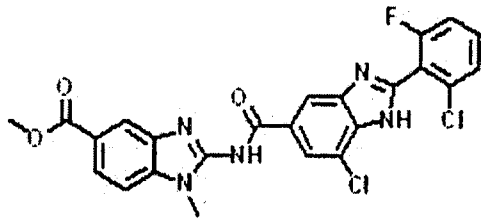
The title compound (0.05 g, 34%) was obtained using the method described in Example 45, Step 2, using 2-trichloromethyl-1H-benzimidazole-5-carboxylic acid methyl ester and 5-amino-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole.

Mw: 464

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.42 (s, 1H), 8.35 (s, 1H), 8.03 (dd, J_1=1.5Hz, J_2=8.55Hz, 1H), 7.55-7.76 (m, 4H), 7.47 (d, J=8.1Hz, 1H), 7.31 (t, J=8.7Hz, 1H), 3.95 (s, 3H)

Example 58: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-

benzimidazole-5-carbonyl]amino}-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester

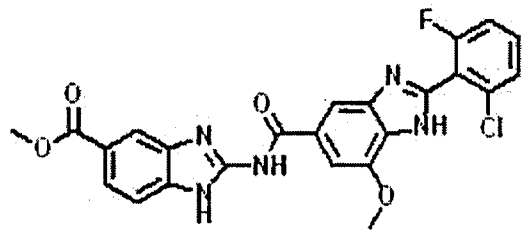


The title compound (0.05 g, 39%) was obtained using the method described in Example 34, Step 3, using 2-amino-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid.

Mw: 512

^{1}H NMR (CD_3OD+$CDCl_3$, 300 MHz): δ(ppm) 8.35 (s, 1H), 8.16 (s, 1H), 8.01-8.04 (m, 1H), 7.86 (s, 1H), 7.58-7.63 (m, 1H), 7.50-7.57 (m, 2H), 7.33 (t, J=9Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H)

Example 59: Preparation of 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]amino}-1H-benzimidazole-5-carboxylic acid methyl ester

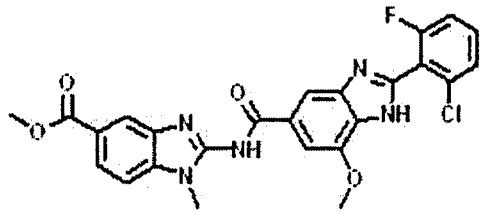


The title compound (0.10 g, 69%) was obtained using the method described in Example 34, Step 3, using 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid and 2-amino-1H-benzimidazole-5-carboxylic acid methyl ester.

Mw: 494

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.03 (s, 1H), 7.95 (s, 1H), 7.82 (dd, J_1=0.9Hz, J_2=8.55Hz, 1H), 7.50-7.60 (m, 2H), 7.42-7.45 (m, 2H), 7.28 (t, J=8.7Hz, 1H), 4.05 (s, 3H), 3.86 (s, 3H)

Example 60: Preparation of 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]amino}-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester

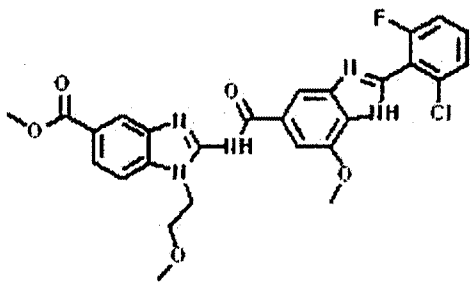


The title compound (0.12 g, 83 %) was obtained using the method described in Example 34, Step 3, using 2-amino-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester and 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid.

Mw: 508

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.4 (s, 1H), 13.09 (s, 1H), 7.68-8.60 (m, 8H), 3.97 (s, 3H), 3.52 (s, 3H), 2.68 (s, 3H)

Example 61: Preparation of 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester



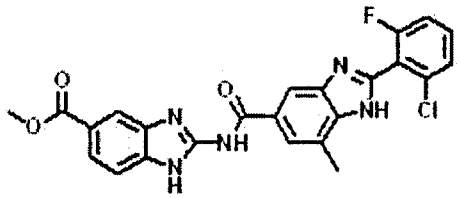
The title compound (0.12 g, 77 %) was obtained using the method described in Example 34, Step 3, using 2-amino-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester and 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid.

Mw: 552

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.23 (s, 1H), 7.96 (s, 1H), 7.78-7.84 (m,

1H), 7.65 (s, 1H), 7.52-7.59 (m, 1H), 7.43 (d, J=8.1Hz, 1H), 7.23-7.30 (m, 2H), 4.38-4.48 (m, 2H), 3.96 (s, 3H), 3.7 (s, 3H), 3.82-3.90 (m, 2H), 3.32 (s, 3H)

Example 62: Preparation of 2-{[2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carbonyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester

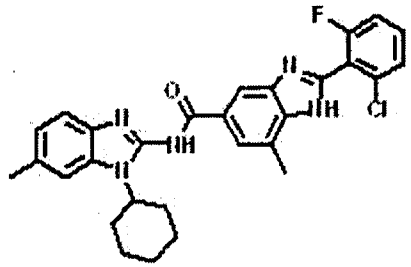


The title compound (0.10 g, 72%) was obtained using the method described in Example 34, Step 3, using 2-amino-1H-benzimidazole-5-carboxylic acid methyl ester and 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid.

Mw: 478

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.28 (s,1H), 7.90 (dd, J_1=1.2Hz, J_2=8.4z, 1H), 7.87 (s, 1H), 7.51-7.63 (m, 3H), 7.34 (t, J=9Hz, 1H), 3.92 (s, 3H), 2.69 (s, 3H)

Example 63: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazole-2-yl)-amide



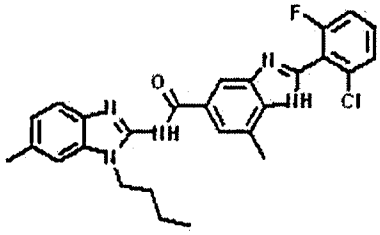
The title compound (0.03 g, 45 %) was obtained using the method described in Example 62, using 1-cyclohexyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 516

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.35-8.58 (m, 1H), 8.08 (s, 1H), 7.56-7.64 (m, 1H), 7.48 (d, J=8.1Hz, 1H), 7.42 (s, 1H), 7.29-7.38 (m, 2H), 7.08 (d, J=7.8Hz, 1H),

4.80-4.86 (m, 1H), 2.48-2.69 (m, 5H), 2.48 (s, 6H), 1.63-1.96 (m, 5H), 1.48-1.59 (m, 3H)

Example 64: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazole-2-yl)-amide

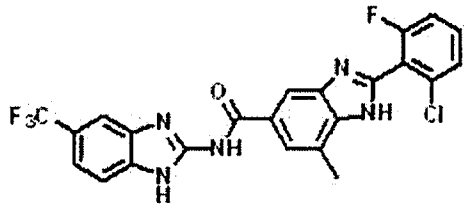


The title compound (0.045 g, 61 %) was obtained using the method described in Example 62, using 1-butyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 490

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.47 (s, 1H), 8.09 (s, 1H), 7.50-7.61 (m, 1H), 7.39-7.47 (m, 2H), 7.26 (s, 1H), 7.09 (d, J=8.4Hz, 2H), 4.34-4.40 (m, 2H), 2.66 (s, 3H), 2.48 (s, 3H), 1.89-2.00 (m, 2H), 1.47-1.60 (m, 2H), 1.01-1.06 (m, 3H)

Example 65: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazole-2-yl)-amide



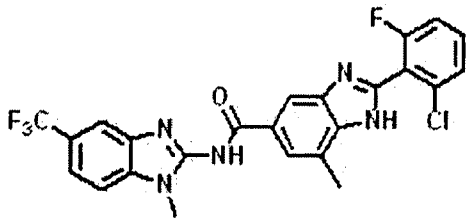
The title compound (0.08 g, 52 %) was obtained using the method described in Example 62, using 2-amino-5-trifluoromethyl-1H-benzimidazole.

Mw: 488

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.27 (s, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.58-7.71 (m, 2H), 7.44-7.53 (m, 2H), 7.33 (t, J=8.7Hz, 1H), 2.67 (s, 3H)

Example 66: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazole-2-

yl)-amide

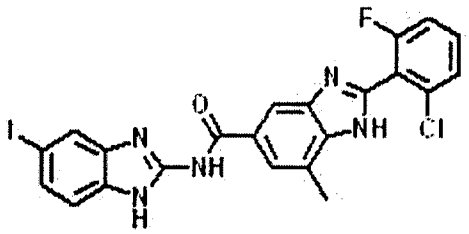


The title compound (0.01 g, 27 %) was obtained using the method described in Example 62, using 1-methyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 502

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.39-8.60 (brd, 1H), 8.12 (s, 1H), 7.80 (s, 1H), 7.59-7.65 (m, 3H), 7.49 (d, J=8.1Hz, 1H), 7.33 (t, J=8.7Hz, 1H), 3.85 (s, 3H), 2.65 (s, 3H)

Example 67: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazole-2-yl)-amide

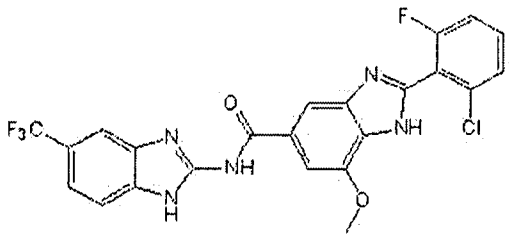


The title compound (0.21 g, 65 %) was obtained using the method described in Example 62, using 5-iodo-1H-benzimidazole-2-ylamine.

Mw: 546

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.26 (s, 1H), 7.85 (d, J=8.1Hz, 1H), 7.83 (s, 1H), 7.58-7.64 (m, 1H), 7.83 (s, 1H), 7.58-7.64 (m, 1H), 7.46-7.51 (m, 2H), 7.29-7.37 (m, 2H), 2.69 (s, 3H)

Example 68: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazole-2-yl)-amide

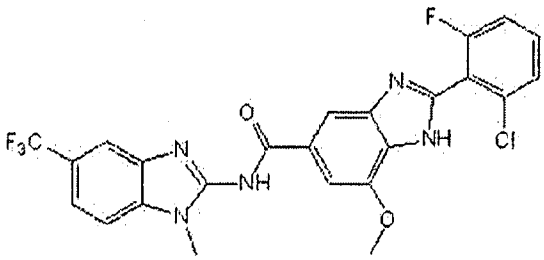


The title compound (0.04 g, 62 %) was obtained using the method described in Example 59, using 5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 504

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.08 (s, 1H), 7.80 (s, 1H), 7.57-7.66 (m, 3H), 7.46-7.49 (m, 2H), 7.32 (t, J=9Hz, 1H), 4.12 (s, 3H)

Example 69: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazole-2-yl)-amide

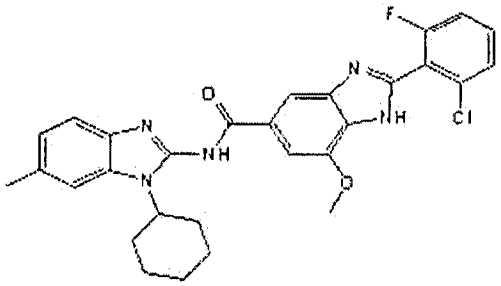


The title compound (0.05 g, 68 %) was obtained using the method described in Example 59, using 1-methyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 518

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.10-8.38 (brd, 1H), 7.77 (s, 2H), 7.45-7.62 (m, 4H), 7.30 (t, J=9Hz, 1H), 4.07 (s, 3H), 3.81 (s, 3H)

Example 70: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazole-2-yl)-amide

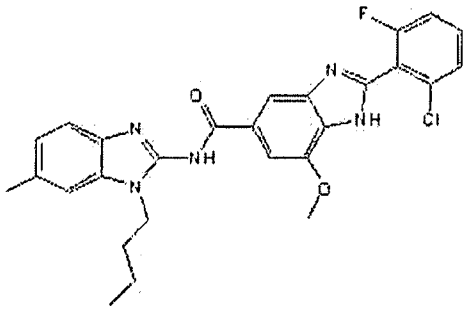


The title compound (0.07 g, 98 %) was obtained using the method described in Example 59, using 1-cyclohexyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 532

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.28 (s, 1H), 7.80 (s, 1H), 7.50-7.62 (m, 1H), 7.27-7.50 (m, 4H), 7.08 (d, J=8.1Hz, 1H), 4.80-5.00 (m, 1H), 4.10 (s, 3H), 2.47 (s, 3H), 2.27-2.55 (m, 2H), 1.61-2.04 (m, 5H), 1.45-1.61 (m, 3H)

Example 71: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazole-2-yl)-amide

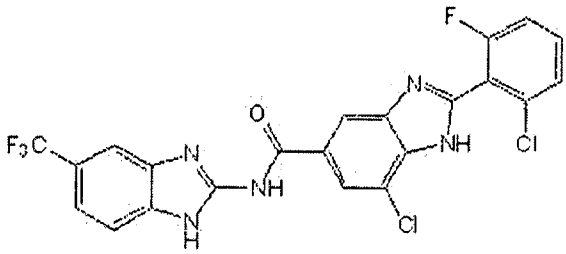


The title compound (0.05 g, 70 %) was obtained using the method described in Example 59, using 1-butyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 506

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.28 (s, 1H), 7.80 (s, 1H), 7.45-7.62 (m, 2H), 7.24-7.37 (m, 3H), 7.08 (d, J=8.1Hz, 1H), 4.30-4.40 (m, 2H), 4.08 (s, 3H), 2.46 (s, 3H), 1.82-1.90 (m, 2H), 1.48 (q, J=7.2Hz, 2H), 1.02 (t, J=7.2Hz, 3H)

Example 72: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazole-2-yl)-amide

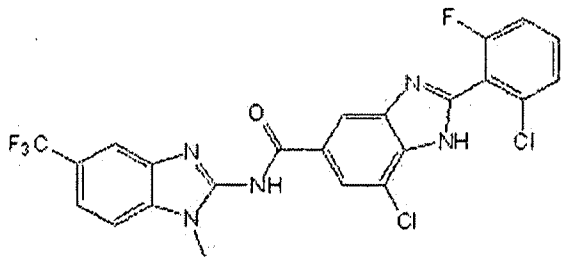


The title compound (0.05 g, 77 %) was obtained using the method described in Example 58, using 5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 508

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.39 (s, 1H), 8.10 (s, 1H), 7.76 (s, 1H), 7.53-7.65 (m, 2H), 7.48 (s, 1H), 7.45-7.54 (m, 2H), 7.30-7.40 (m, 1H),

Example 73: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazole-2-yl)-amide

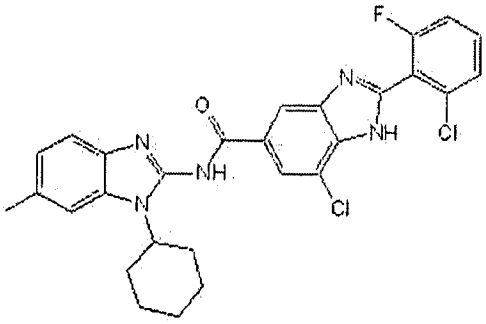


The title compound (0.05 g, 77 %) was obtained using the method described in Example 58, using 1-methyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 522

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.56 (s, 1H), 8.33 (s, 1H), 7.80 (s, 1H), 7.59-7.64 (m, 3H), 7.50 (d, J=8.1Hz, 1H), 7.34 (t, J=9.3Hz, 1H), 3.85 (s, 3H)

Example 74: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazole-2-yl)-amide

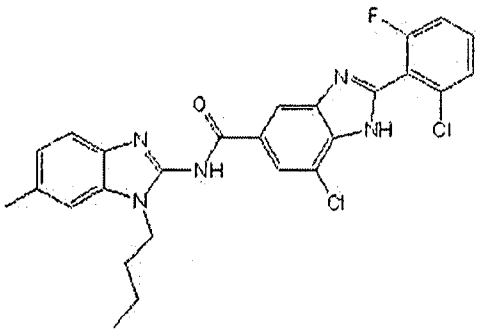


The title compound (0.06 g, 80 %) was obtained using the method described in Example 58, using 1-cyclohexyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 536

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.44-8.64 (m, 1H), 8.28 (s, 1H), 7.58-7.65 (m, 1H), 7.49 (d, J=8.1Hz, 1H), 7.30-7.41 (m, 3H), 7.08 (d, J=8.1Hz, 1H), 4.87-4.98 (m, 1H), 2.47-2.55 (m, 3H), 2.47 (s, 3H), 1.84-2.15 (m, 4H), 1.47-1.67 (m, 3H)

Example 75: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazole-2-yl)-amide



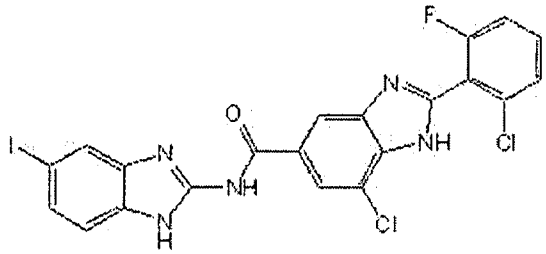
The title compound (0.06 g, 77 %) was obtained using the method described in Example 58, using 1-butyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 510

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.50 (s, 1H), 8.27 (s, 1H), 7.53-7.65 (m, 1H), 7.49 (d, J=8.1Hz, 1H), 7.30-7.47 (m, 2H), 7.20 (s, 1H), 7.06 (d, J=8.1Hz, 1H), 4.30 (t, J=6.6Hz, 2H), 2.44 (s, 3H), 1.86-1.98 (m, 2H), 1.40-1.52 (m, 2H), 1.02 (t, J=7.2Hz, 3H)

Example 76: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-

benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazole-2-yl)-amide

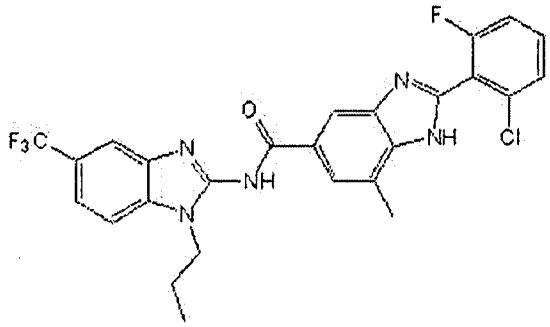


The title compound (0.25 g, 79 %) was obtained using the method described in Example 58, using 5-iodo-1H-benzimidazole-2-ylamine.

Mw: 566

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.38 (s, 1H), 8.12 (s, 1H), 7.84 (s, 1H), 7.60-7.68 (m, 1H), 7.51 (d, J=7.8Hz, 2H), 7.29-.40 (m, 2H)

Example 77: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-propyl-5-trifluoromethyl-1H-benzimidazole-2-yl)-amide



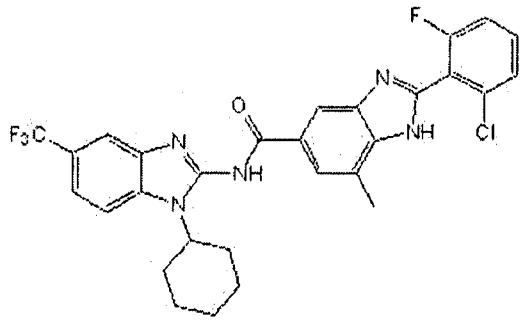
The title compound (0.06 g, 69 %) was obtained using the method described in Example 62, using 1-propyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 530

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 8.61 (s, 1H), 8.14 (s, 1H), 7.72 (d, J=7.2Hz, 1H), 7.53-7.59 (m, 3H), 7.22-7.35 (m, 2H), 7.16 (d, J=8.1Hz, 1H), 6.97 (t, J=9.3Hz, 1H), 4.28 (t, J=6.9Hz, 2H), 2.72 (s, 3H), 1.96 (q, J=9.9Hz, 2H), 1.04 (t, J=7.5Hz, 3H)

Example 78: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-5-trifluoromethyl-1H-

benzimidazole-2-yl)-amide

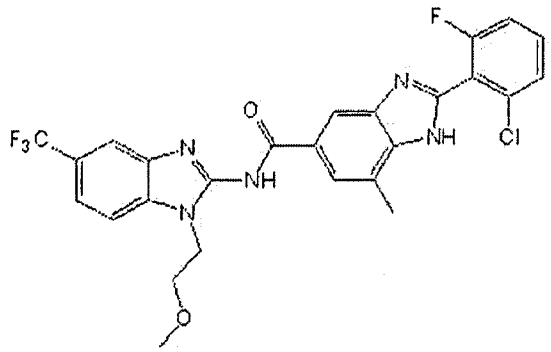


The title compound (0.03 g, 35 %) was obtained using the method described in Example 62, using 1-cyclohexyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 570

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.42 (brs, 1H), 7.87 (s, 1H), 7.60-7.82 (m, 2H), 7.45-7.55 (m, 2H), 7.38 (d, J=8.1Hz, 1H), 7.23 (t, J=9Hz, 1H), 4.80-4.84 (m, 1H), 2.57 (s, 3H), 2.41-2.52 (m, 2H), 1.74-2.05 (m, 5H), 1.43-1.67 (m, 3H)

Example 79: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid [1-(2-methoxyethyl)-5-trifluoromethyl-1H-benzimidazole-2-yl] -amide

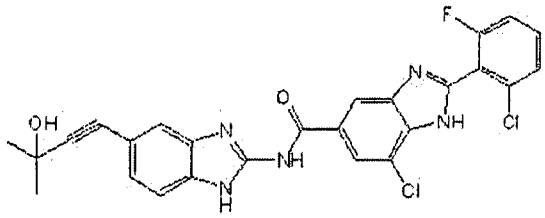


The title compound (0.05 g, 59 %) was obtained using the method described in Example 62, using 1-(2-methoxyethyl)-5-trifluoromethyl-1H-benzimidazole-2-ylamine.

Mw: 546

^{1}H NMR ($CDCl_3$,300 MHz): δ(ppm) 8.59 (s, 1H), 7.73 (d, J=7.5Hz, 1H), 7.45-7.54 (m, 2H), 7.22-7.36 (m, 4H), 7.15 (d, J=8.1Hz, 1H), 6.95 (t, J=8.7Hz, 1H), 4.25-4.40 (m, 2H), 3.70-3.80 (m, 2H), 3.28 (s, 3H), 2.55 (s, 3H)

Example 80 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-(3-hydroxy-3-methyl-1-butynyl)-1H-benzimidazole-2-yl]-amide

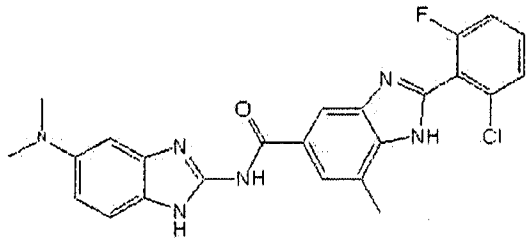


The title compound (0.04 g, 22 %) was obtained using the method described in Example 37, Step 2, using 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazole-2-yl)-amide.

Mw: 522

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.13 (s, 1H), 7.71-7.86 (m, 3H), 7.56-7.65 (m, 2H), 7.24-7.63 (m, 6H), 1.58 (s, 6H)

Example 81: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-dimethylamino-1H-benzimidazole-2-yl)-amide

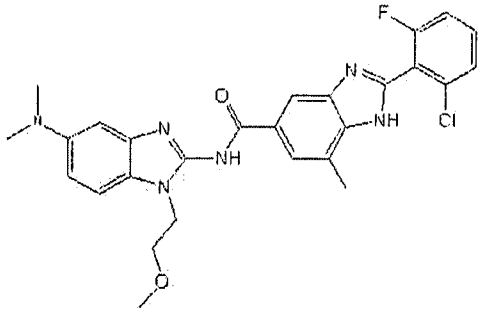


The title compound (0.02 g, 10 %) was obtained using the method described in Example 62, using 5-N,N-dimethyl-1H-benzimidazole-2-ylamine.

Mw: 463

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.28 (brs, 1H), 7.88 (s, 1H), 7.58-7.65 (m, 1H), 7.48 (d, J=7.8Hz, 1H), 7.30-7.47 (m, 2H), 6.93 (s, 1H), 6.85 (d, J=8.7Hz, 1H), 2.92 (s, 6H), 2.67 (s, 3H)

Example 82: Preparation of 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid [5-dimethylamino-1-(2-methoxyethyl)-1H-benzimidazole-2-yl]-amide

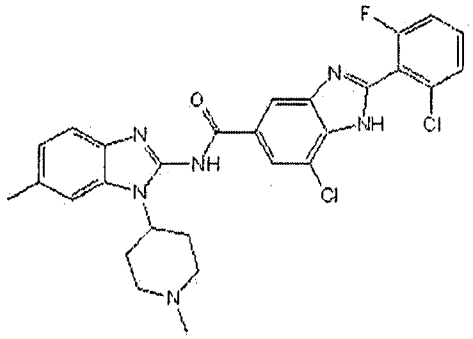


The title compound (0.07 g, 60 %) was obtained using the method described in Example 62, using 1-(2-methoxy-ethyl)-5-N,N-dimethyl-1H-benzimidazole-2-ylamine.

Mw: 521

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.45 (s, 1H), 8.07 (s, 1H), 7.55-7.62 (m, 1H), 7.47 (d, J=8.1Hz, 1H), 7.26-7.34 (m, 2H), 6.85 (s, 1H), 6.75-6.79 (m, 1H), 4.41-4.44 (m, 2H), 3.82-3.85 (m, 2H), 3.34 (s, 3H), 2.89 (s, 6H), 2.64 (s, 3H)

Example 83: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [6-methyl-1-(1-methyl-piperidine-4-yl)-1H-benzimidazole-2-yl] -amide

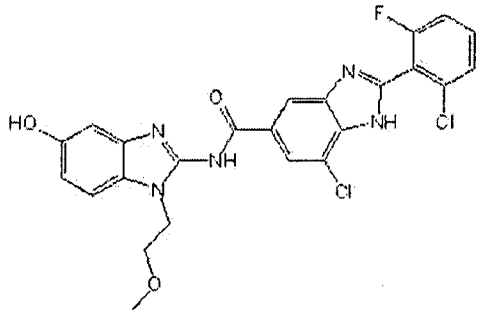


The title compound (0.10 g, 59 %) was obtained using the method described in Example 58, using 1-(methyl-piperidine-4-yl)-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 551

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 13.50 (brd, 1H), 12.85 (s, 1H), 9.46 (s, 1H), 8.15-8.34 (m, 1H), 7.45-7.72 (m, 5H), 7.07 (d, J=7.8Hz, 1H), 5.02-5.25 (m, 1H), 3.62-3.80 (m, 2H), 3.22-3.43 (m, 2H), 3.30 (s, 3H), 2.62-2.80 (m, 2H), 2.44 (s, 3H), 2.10 (d, J=10.5Hz, 2H)

Example 84: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-hydroxy-1-(2-methoxyethyl)-1H-benzimidazole-2-yl]-amide



Step 1: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-benzyloxy-1-(2-methoxyethyl)-1H-benzimidazole-2-yl]-amide

The title compound (0.30 g, 81 %) was obtained using the method described in Example 58, using 5-benzyloxy-1-(2-methoxyethyl)-1H-benzimidazole-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.52 (s, 1H), 8.29 (s, 1H), 7.87 (d, J=8.4Hz, 1H), 7.73 (d, J=8.1Hz, 1H), 7.30-7.66 (m, 9H), 7.15 (d, J=2.1Hz, 1H), 6.97 (dd, J_1=2.1Hz, J_2=8.7Hz, 1H), 5.12 (s, 2H), 4.49 (t, J=6.0Hz, 2H), 3.86 (t, J=5.4Hz, 2H), 3.35 (s, 3H)

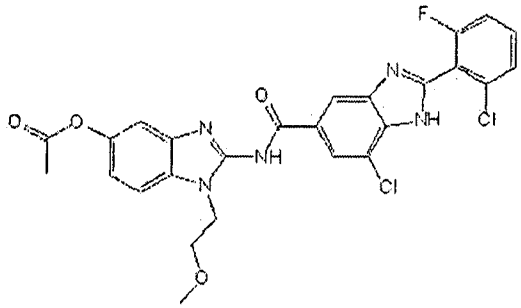
Step 2: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-hydroxy-1-(2-methoxyethyl)-1H-benzimidazole-2-yl]-amide

10% Pd/C (0.05 g) was added to solution of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-benzyloxy-1-(2-methoxyethyl)-1H-benzimidazole-2-yl]-amide (0.3 g, 0.5 mmol) in ethanol (10 ml). The reaction mixture was hydrogenated at an hydrogen pressure (50psi), filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound (0.22 g, 45 %).

Mw: 514

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.51 (s, 1H), 8.28 (s, 1H), 7.86 (d, J=8.1Hz, 1H), 7.73 (d, J=8.1Hz, 1H), 7.45-7.65 (m, 3H), 7.30-7.47 (m, 2H), 6.95 (s, 1H), 6.76-6.95 (m, 1H), 4.48-4.66 (m, 2H), 3.70-3.90 (m, 2H), 3.30 (s, 3H)

Example 85: Preparation of acetic acid 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazol-5-yl ester

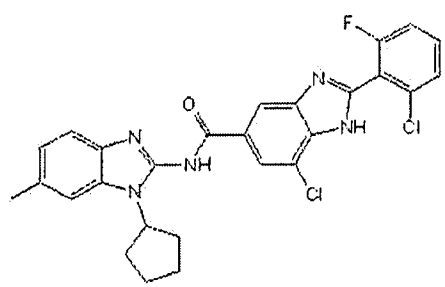


A solution of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-hydroxy-1-(2-methoxyethyl)-1H-benzimidazole-2-yl]-amide (0.07 g, 0.10 mmol) in anhydrous CH_2Cl_2 was added acetic anhydride (0.02 ml, 0.19 mmol), pyridine (0.06 ml, 0.74 mmol) and stirred at room temperature for 1hr. The reaction mixture was refluxed for 3hr and cooled room temperature, extracted with CH_2Cl_2. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo to gice title compound (0.04 g, 47 %).

Mw: 556

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.18-8.36 (m, 2H), 7.55-73 (m, 1H), 7.45-7.58 (m, 1H), 7.24-7.37 (m, 2H), 7.18 (s, 1H), 6.91-6.94 (m, 1H), 4.38-4.42 (m, 2H), 3.80-3.92 (m, 2H), 3.32 (s, 3H), 2.23 (s, 3H)

Example 86: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-methyl-1H-benzimidazole-2-yl)-amide

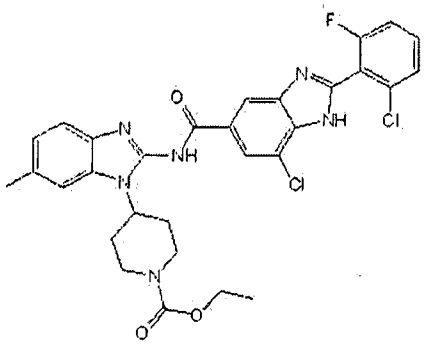


The title compound (0.11 g, 75 %) was obtained using the method described in Example 58, using 1-cyclopentyl-6-methyl-1H-benzimidazole-2-ylamine.

Mw: 522

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.52 (brs, 1H), 8.29 (d, J=1.2Hz, 1H), 7.59-7.64 (m, 1H), 7.50 (d, J=8.1Hz, 1H), 7.31-7.41 (m, 3H), 7.10 (d, J=8.1Hz, 1H), 5.42-5.49 (m, 1H), 2.48 (s, 3H), 2.31-2.41 (m, 2H), 2.10-2.18 (m, 4H), 1.88-2.00 (m, 2H)

Example 87: Preparation of 4-(2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-6-methyl-benzimidazole-1-yl)-piperidine carboxylic acid ethyl ester

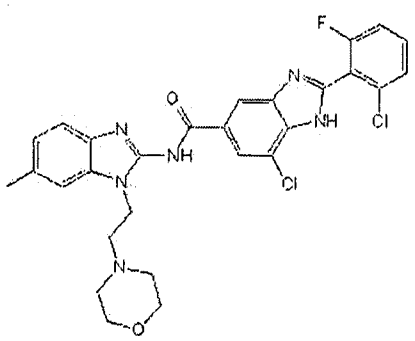


The title compound (0.14 g, 82 %) was obtained using the method described in Example 58, using 4-(2-amino-6-methyl-benzimidazole-1-yl)-piperidine-1-carboxylic acid ethyl ester.

Mw: 609

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.46 (brs, 1H), 8.25 (s, 1H), 7.58-7.66 (m, 1H), 7.50 (d, J=8.1Hz, 1H), 7.31-7.39 (m, 3H), 7.10 (d, J=8.1Hz, 1H), 5.02-5.15 (m, 1H), 4.42 (d, J=13.5Hz, 2H), 4.21 (q, J=7.2Hz, 2H), 3.11 (t, J=13.5Hz, 2H), 2.71-2.75 (m, 2H), 2.47 (s, 3H), 1.95 (d, J=11.7Hz, 2H), 1.29 (t, J=7.2HZ, 3H)

Example 88: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [6-methyl-1-(2-morpholine-4-ylethyl)-1H-benzimidazole-2-yl]amide

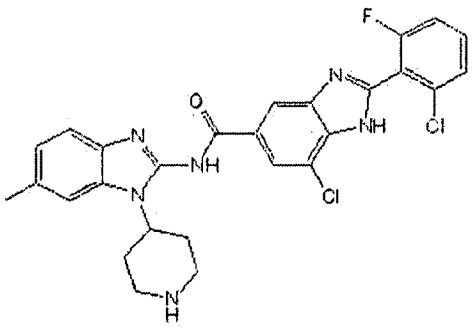


The title compound (0.07 g, 44 %) was obtained using the method described in Example 58, using 6-methyl-1-(2-morpholine-4-yl-ethyl)-1H-benzimidazole-2-ylamine.

Mw: 567

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.48 (brs, 1H), 8.29 (s, 1H), 7.58-7.66 (m, 1H), 7.50 (d, J=8.1HZ, 1H), 7.31-7.36 (m, 2H), 7.26 (s, 1H), 7.08 (d, J=8.4Hz, 1H), 4.46 (t, J=6.6Hz, 2H), 3.58-3.61 (m, 4H), 2.85 (t, J=6.6Hz, 2H), 2.45-2.64 (m, 4H), 2.45 (s, 3H)

Example 89: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (6-methyl-1-piperidine-4-yl-1H-benzimidazole-2-yl)amide



4-(2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-6-methyl-benzimidazole-1-yl)-piperidinecarboxylic acid ethyl ester (0.05 g, 0.09 mmol) was suspended in a 2.5M aq. NaOH (2ml). The suspension was refluxed for 15hr and then allowed to cool. The solution was acidified with 6M HCl (pH=2) and then the pH was carefully adjusted to pH=8.5 using 2.5M aq. NaOH. The resultion precipitate was collected by filtration, washed with cold water and then dried under vacumn to give

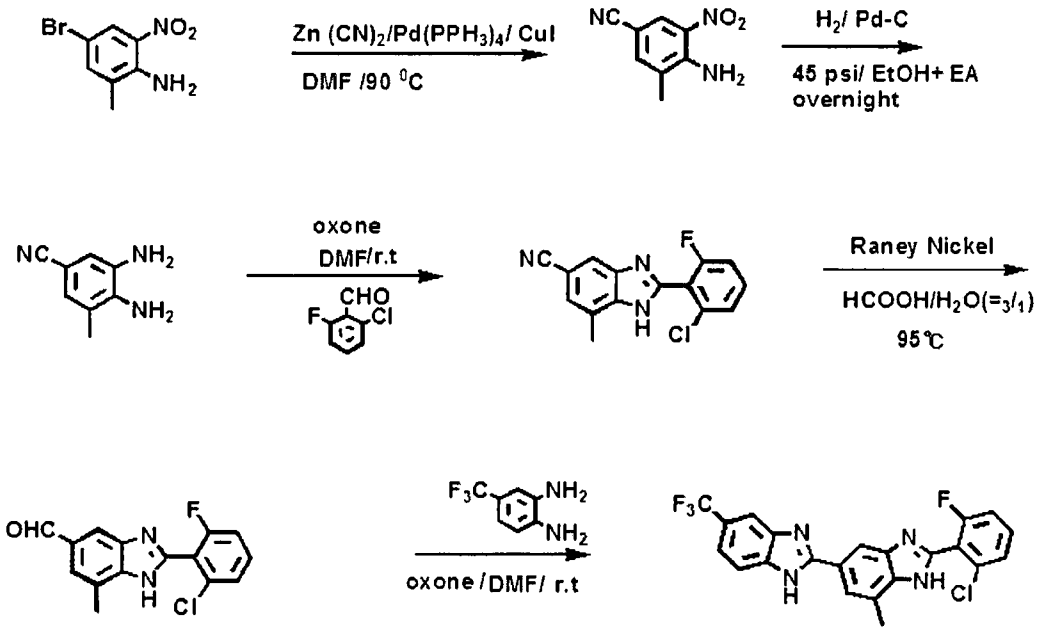
the title compound (0.04 g, 80 %).

Mw: 537

^{1}H NMR (DMSO-d_6, 300 MHz): δ(ppm) 9.09 (s, 1H), 8.01-8.33 (m, 1H), 7.42-7.80 (m, 5H), 6.88-7.05 (m, 4H), 5.00-5.20 (m, 1H), 4.00-4.45 (m, 2H), 3.23-3.37 (m, 2H), 2.67-2.80 (m, 2H), 2.00-2.23 (m, 2H), 2.37 (s, 3H)

Example 90: Preparation of 2'-(2-chloro-6-fluorophenyl)-7'-methyl-5-trifluoromethyl-1H,1'H-[2,5]bibenzimidazolyl

The title compound was prepared as follows:



Step 1: Preparation of 4-amino-3-methyl-5-nitro-benzonitrile

A suspension of 4-bromo-5-methyl-2-nitro-phenylamine (2.50 g, 10.8 mmol), zinc cyanide (1.66 g, 14.04 mmol), and copper iodide (0.10 g, 0.54 mmol) in DMF was stirred at room temperature under nitrogen for 45 min and then treated with $Pd(PPh_3)_4$(4.90g, 4.32 mmol). The mixture was stirred 90℃ for 18hr, filtered through a celite, concentrated under reduced pressure and purified by flash chromatography on silica gel (eluent Hex:EtOAc =3:1) to give the title compound: 1.20 g (63%).

^{1}H NMR (300 MHz, $CDCl_3$) :δ(ppm) 8.40 (s, 1H) 7.48 (s, 1H) 2.30 (s, 3H)

Step 2: Preparation of 3,4-diamino-5-methyl-benzonitrile

A solution of 4-amino-3-methyl-5-nitro-benzonitrile (1.20 g, 3.57 mmol) in ethanol was reduced using 10% Pd-OH (0.12g). The mixture is subsequently hydrogenated at an hydrogen pressure. The mixture was filtered through celite and the bed washed with ethanol. The organic layer was concentrated in vacuo to give the title compound: 0.63g (64%).

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 6.95 (s, 1H) 6.82 (s, 1H) 2.16 (s, 3H)

Step 3: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methyl-1H-benzimidazole-5-carbonitrile

To a solution of 3,4-diamino-5-methyl-benzonitrile (0.53g, 3.53 mmol) in DMF, 2-chloro-6-florobenzaldehyde (0.81 g, 4.80 mmol) was added followed by oxone (1.43 g, 2.32 mmol). The mixture was stirred for 2h at r.t and then added dropwise with vigorous stirring into a mixture of 1M K_2CO_3 and H_2O.

The precipitate was extracted with EtOAc, and the extract was washed successively with H_2O and brine. After drying over Na_2SO_4, the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel (Hex:EtOAc=2:1) to give the title compound: 0.63 g (63%).

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.94-7.11(m, 10H), 2.72 (s, 3H), 2.58 (s, 3H)

Step 4: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methyl-1H-benzimidazole-5-carbaldehyde

The compound of Step 3 (0.53 g, 3.57 mmol) and Ni-Al (Raney nickel) were dissolved in formic acid and H_2O (4:1). The reaction mixture was heated at 95℃ for 6 h. The hot mixture was filtered through a bed of celite, and the reaction flask and celite bed were rinsed with water. The aqueous solution was concentrated to dryness. After addition of H_2O to this residue, a white precipitate formed. The pH of this suspension was adjusted to 9 by the dropwise addition of 2N NaOH (aq). The product was obtained by

extraction with EtOAc. The EtOAc extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography with hexane and ethyl acetate (2:1) to give the title compound: 0.64 g (63 %)

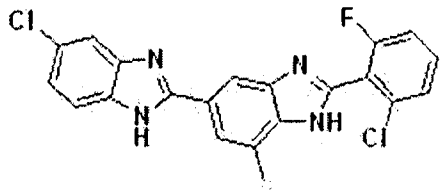
^{1}H NMR (DMSO-d_6, 300,MHz) : δ(ppm) 10.06 (s, 1H), 8.06-7.12 (m, 5H), 2.70 (s, 3H)

Step 5: Preparation of 2'-(2-chloro-6-fluorophenyl)-7'-methyl-5-(trifluoromethyl)-1H,1'H-2,5'-bibenzo[d]imidazole

The title compound (0.20 g, 93%) was prepared from 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carbaldehyde (0.22 g, 0.46 mmol) and 4-trifluoromethyl-benzene-1,2-diamine (0.06 g, 0.38 mmol) in a manner similar to Example 90, Step 3.

Mw: 445

Example 91: Preparation of 5-chloro-2'-(2-chloro-6-fluorophenyl)-7'-methyl-1H,1'H-[2,5]- bibenzimidazolyl

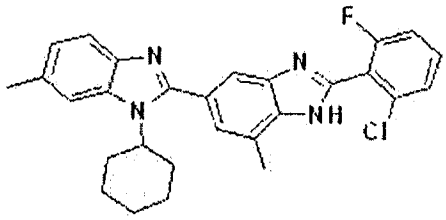


The title compound (0.02 g, 15%) was prepared from 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carbobenzaldehyde (0.08 g,0.27 mmol) and 4-chloro-benzene-1,2-diamine (0.03 g, 0.23 mmol) in a manner similar to Example 90, Step 3.

Mw: 411

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.30 (s, 1H) 8.01 (s, 1H), 7.98-7.23 (m, 6H), 2.71 (s, 3H)

Example 92: Preparation of 2'-(2-chloro-6-fluorophenyl)-1-cyclohexyl-6,7'-dimethyl-1H,1'H-[2,5]-bibenzimidazolyl

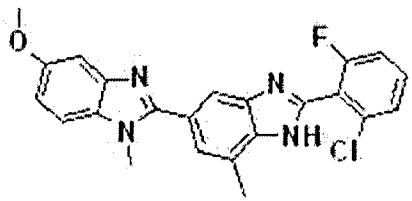


The title compound (0.02 g, 18%) was prepared from 2-(2-chloro-6-fluoro-phenyl)-7-methyl-1H-benzimidazole-5-carbobenzaldehyde (0.07 g,0.24 mmol) and N-cyclohexyl-4-methyl-benzene-1,2-diamine (0.04 g, 0.22 mmol) in a manner similar to Example 90, Step 3.

Mw: 473

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 13.03 (s, 1H), 7.71-7.01 (m, 6H), 2.65 (s, 3H), 2.49 (s, 3H), 1.96-1.73 (m, 3H), 1.35-1.24 (m, 8H)

Example 93: Preparation of 2'-(2-chloro-6-fluorophenyl)-5-methoxy-1,7'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl

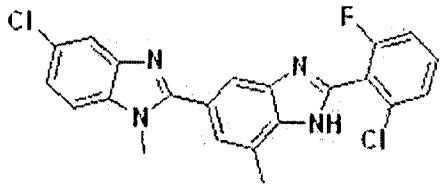


The title compound (0.05 g, 45%) was prepared from 2-(2-chloro-6-fluoro-phenyl)-7-methyl-1H-benzimidazole-5-carbobenzaldehyde and 4-methoxybenzene-1,2-diamine in a manner similar to Example 90, Step 3.

Mw: 421

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.30 (s, 1H), 8.01 (s, 1H), 7.98-7.23 (m, 6H), 3.96 (s, 3H), 2.71 (s, 3H), 2.15 (s, 3H)

Example 94: Preparation of 5-chloro-2'-(2-chloro-6-fluorophenyl)-1,7'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl



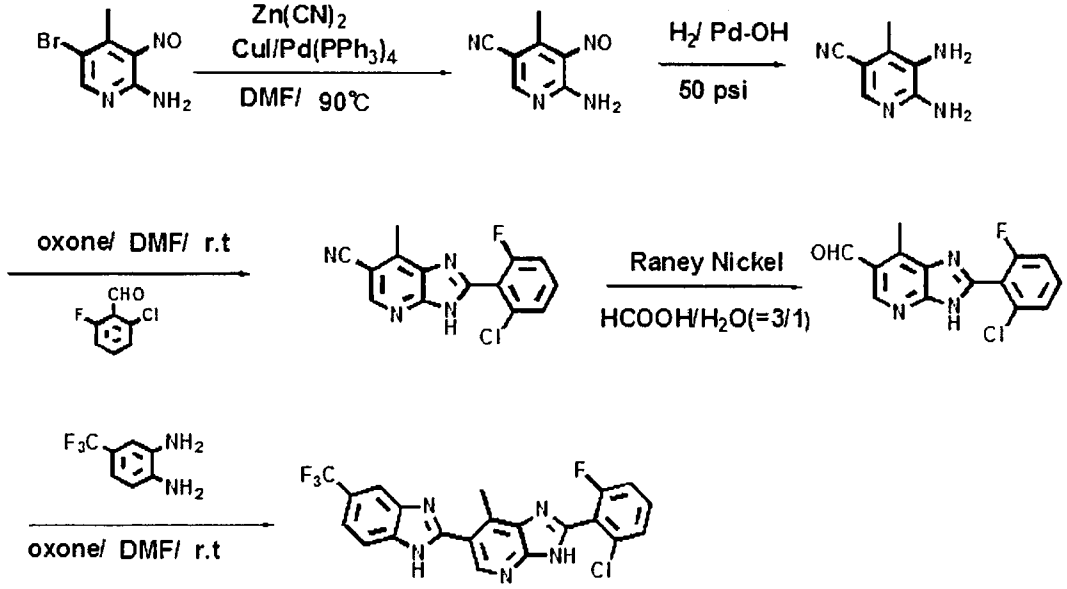
The title compound (0.05 g, 48%) was prepared from 2-(2-chloro-6-fluoro-phenyl)-7-methyl-1H-benzimidazole-5-carbobenzaldehyde and 4-chloro-N-methyl-benzene-1,2-diamine in a manner similar to Example 90, Step 3.

Mw: 425

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.30 (s, 1H), 8.01 (s, 1H), 7.98-7.23 (m, 6H), 2.71 (s, 3H), 2.15 (s, 3H)

Example 95: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methyl-6-(5-trifluoromethyl-1H-benzimidazol-2-yl)-3H-imidazo[4,5-b]pyridine

The title compound was prepared as follows:



Step 1: Preparation of 6-amino-4-methyl-5-nitroso-nicotinonitrile

The title compound (0.37 g, 37%) was prepared from 5-bromo-4-methyl-3-nitro-pyidine-2-ylamine in a manner similar to Example 90, Step 1.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 7.32-6.74 (m, 4H), 2.89-2.19 (m, 9H), 1.44 (s, 9H)

Step 2: Preparation of 5,6-diamino-4-methyl-nicotinonitrile

The title compound (0.28 g, 88 %) was prepared from 6-amino-4-methyl-5-nitroso-nicotinonitrile in a manner similar to Example 90, Step 2.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 8.41 (s, 1H), 6.52 (brs, NH_2), 2.70 (s, 3H)

Step 3: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methyl-3H-imidazo[4,5-b]pyridine-6-carbonitrile

The title compound (0.21 g, 15 %) was prepared from 5,6-diamino-4-methyl-nicotinonitrile in a manner similar to Example 90, Step 3.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 7.54-7.22 (m, 4H), 3.11 (s,3H)

Step 4: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methyl-3H-imidazo[4,5-b]pyridine-6-carboaldehyde

The title compound (0.05 g, 27 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-7-methyl-3H-imidazo[4,5-b]pyridine-6-carbonitrile in a manner similar to Example 90, Step 4.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 10.41 (s, 1H), 7.54-7.22 (m, 4H), 3.11 (s, 3H)

Step 5: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methyl-6-(5-trifluoromethyl-1H-benzimidazol-2-yl)-3H-imidazo[4,5-b]pyridine

The title compound (0.20 g, 93 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-7-methyl-3H-imidazo[4,5-b]pyridine-6-carbaldehyde (0.22g, 0.46 mmol) and 4-trifluoromethyl-1,2-benzen-diamine in a manner similar to Example 90, Step 3.

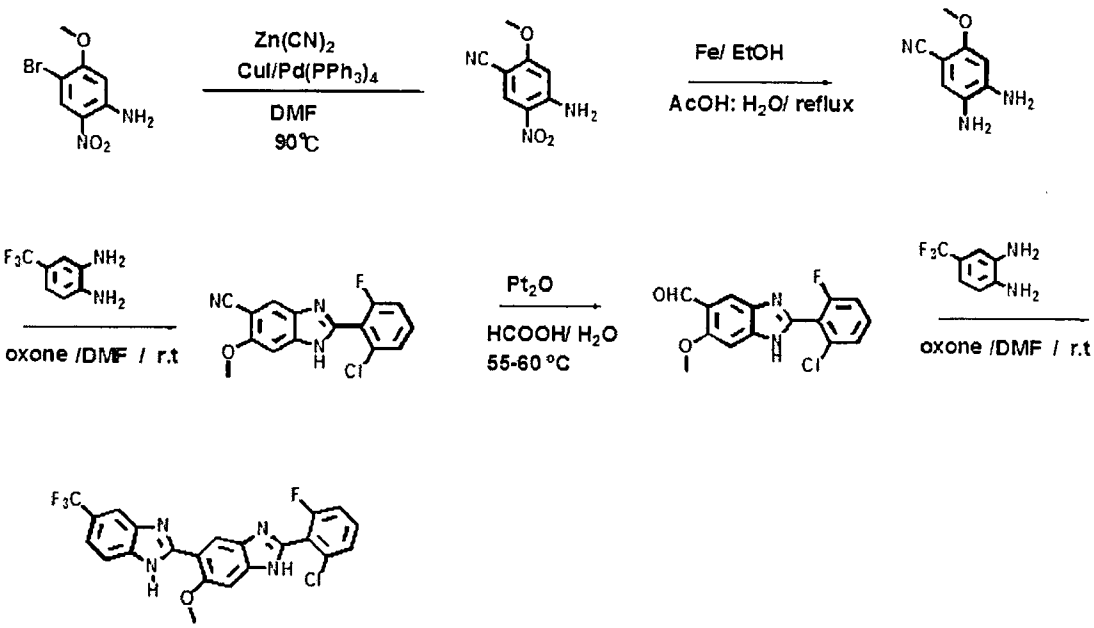
Mw: 446

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.30 (s, 1H) 8.01 (s, 1H), 7.98-7.23 (m,

6H), 2.71 (s, 3H), 2.15 (s, 3H)

Example 96: Preparation of 2'-(2-chloro-6-fluoro-phenyl)-6'-methoxy-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl

The title compound was prepared as follows:



Step 1: Preparation of 4-amino-2-methoxy-5-nitro-benzonitrile

The title compound (2.30 g, 86 %) was prepared from N-(4-bromo-5-methoxy-2-nitro-phenyl)acetamide prepared by the method described in [*J. Heterocyclic chem.*, 32, 1541, 1992] in a manner similar to Example 90, Step 1.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 8.32 (s, 1H), 6.20 (s, 1H), 4.01 (s, 3H)

Step 2: Preparation of 4,5-diamino-2-methoxy-benzonitrile

A solution of 4-amino-5-nitro-2-trifluoromethyl-benzonitrile (2.30 g, 11.90 mmol) in ethanol was reduced using Fe (2.1 g) added acetic acid (10 ml), water (10 ml). The mixture was refluxed for 2h The mixture was filtered through celite and the bed washed with ethanol. The organic layer was concentrated in vacuo. The residue was chromatographed on silica gel column. Elution with a mixture of n-hexane and ethyl

acetate (1:3) to give the title compound: 1.52 g, 80 %

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 7.38 (s, 1H), 6.08 (s, 1H), 3.84 (s, 3H)

Step 3: Preparation of 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carbonitrile

The title compound (1.00 g, 37 %) was prepared from 4,5-diamino-2-methoxy-benzonitrile in a manner similar to Example 90, Step 3.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 7.45-7.17 (m, 5H), 3.98 (s, 3H)

Step 4 : Preparation of 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carboaldehyde

2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carbonitrile (0.42g, 1.39 mmol), platinum (IV) oxide (10mol%) in formic acid (80% solution). The reaction mixture was heated at 55-60 °C for 18 h. The hot mixture was filtered through a bed of celite, and the reaction flask and celite bed were rinsed with water. The aqueous solution was concentrated to dryness. The product was obtained by extraction with EtOAc. The EtOAc extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography with hexane and ethyl acetate (1: 1) to give the title compound: 0.18g (43 %).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 10.57 (s, 1H), 8.16-8.11 (m, 2H), 7.36-7.13 (m, 3H), 3.95 (s, 3H)

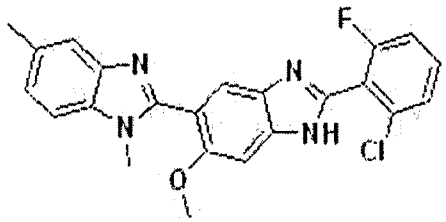
Step 5: Preparation of 2'-(2-chloro-6-fluoro-phenyl)-6'-methoxy-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl

The title compound (0.03 g, 46 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carboaldehyde (0.05 g, 0.16 mmol) and 4-trifluoromethyl-benzene-1,2-diamine in a manner similar to Example 90, Step 3.

Mw: 461

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.30 (s, 1H), 7.34- 6.98 (m, 7H), 3.83 (s, 3H)

Example 97: Preparation of 2'-(2-chloro-6-fluorophenyl)-6'-methoxy-1,5-dimethyl-1H,1'H-2,5'-bibenzo[d]imidazole

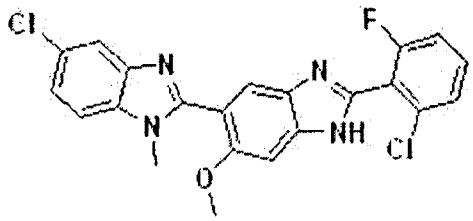


The title compound (0.03 g, 39 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carbaldehyde (0.06g, 0.19 mmol) and N-methyl-4-methyl-benzen-1,2-diamine in a manner similar to Example 90, Step 3.

Mw: 421

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.01-6.98 (m, 8H), 3.64 (s, 3H), 2.95 (s, 3H), 2.46 (s, 3H)

Example 98: Preparation of 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methoxy-1-methyl-1H,1'H-[2,5]bibenzimidazolyl



The title compound (0.04 g, 38 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carboaldehyde (0.06g, 0.20 mmol) and N-methyl-4-chloro-benzen-1,2-diamine in a manner similar to Example 90, Step 3.

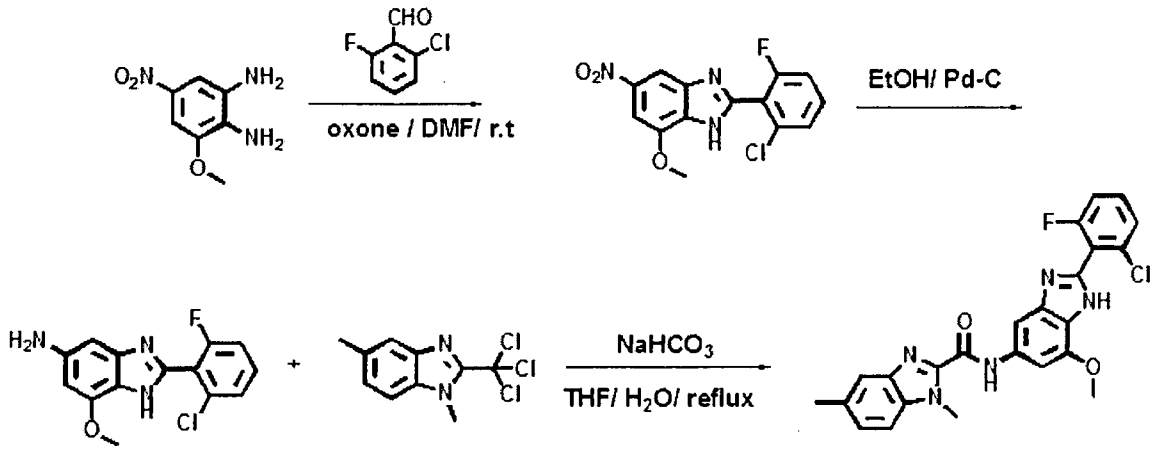
Mw: 441

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.84-7.10 (m, 8H), 3.86 (s, 3H), 3.68 (s, 3H)

Example 99: Preparation of 2-[2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazol-5-ylcarbamoyl]-1-methyl-1H-benzimidazole-5-carboxylic acid methyl

ester

The title compound was prepared as follows:



Step 1: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methoxy-5-nitro-1H-benzimidazole

The title compound (0.6g, 85 %) was prepared from 3-methoxy-5-nitro-benzene-1,2-diamine in a manner similar to Example 90, Step 3.

^{1}H NMR (CD_3OD, 300MHz) : δ(ppm) 8.25 (s, 1H) 7.74 (s, 1H) 7.65-7.30 (m, 3H) 4.11 (s, 3H)

Step 2: Preparation of 2-(2-chloro-6-fluoro-phenyl)-7-methoxy-1H-benzimidazol-5-ylamine

A solution of 2-(2-chloro-6-fluoro-phenyl)-7-methoxy-5-nitro-1H-benzimidazole (0.7 g, 2.18 mmol) in methanol/ethyl acetate (1/1, 50 ml) was reduced using 10% Pd/C (0.12 g). The mixture is subsequently hydrogenated at 45 psi an hydrogen pressure for 2h. The mixture was filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound: 0.2 g (35 %).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.25 (s, 1H), 7.75 (s, 1H), 7.60-7.30 (m, 3H), 4.17 (s, 3H)

Step 3: Preparation of 2-[2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazol-5-

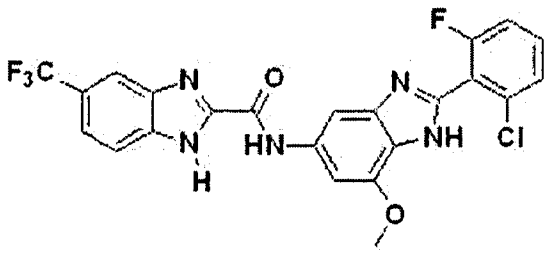
ylcarbamoyl]-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester

A solution of 1-methyl-2-trichloromethyl-1H-benzimidazole-5-carboxylic acid methyl ester (0.11 g, 0.38 mmol) in THF were slowly added to a mixture containing 2-(2-chloro-6-fluoro-phenyl)-7-methoxy-1H-benzimidazol-5-ylamine (0.53 g, 0.42 mmol), $NaHCO_3$ (1.5 eq), THF/H_2O(3/1). The mixture was refluxed vigorously overnight and then cooled to r.t, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$-solution. The aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hex: EA=2:1) to give the title compound: 0.11 g (63 %).

Mw: 508

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.42(s, 1H,), 8.15 (s, 1H), 7.82-7.42(m, 6H), 3.89 (m, 3H), 3.85 (s,3H), 2.25 (s, 3H)

Example 100: Preparation of 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid [2-(2-chloro-6-fluoro-phenyl)-7-methoxy-1H-benzimidazol-5-yl]-amide



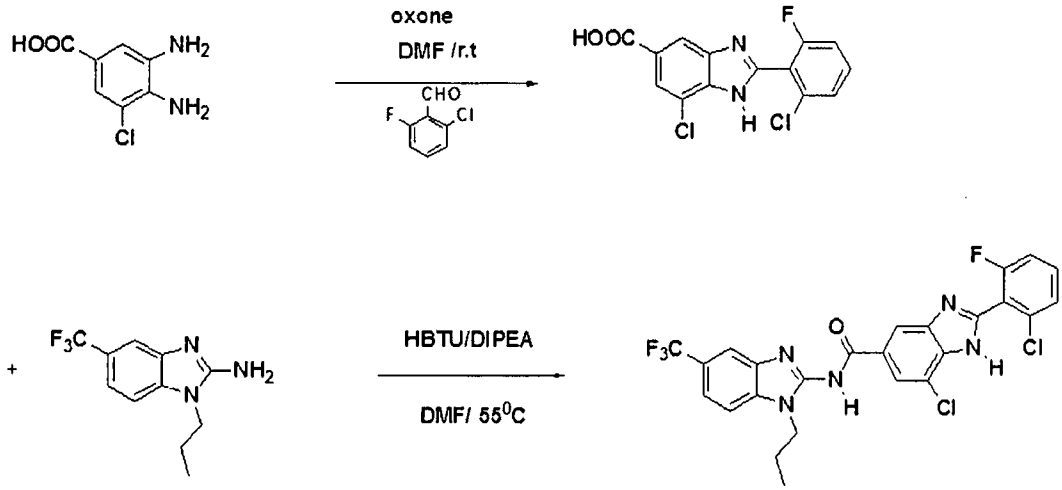
The title compound (0.20 g, 93 %) was prepared from 2-trichloromethyl-5-trifluoromethyl-1H-benzimidazole and 2-(2-chloro-6-fluoro-phenyl)-7-methoxy-5-nitro-1H-benzimidazole (0.22 g, 0.46 mmol) in a manner similar to Example 99, Step 2.

Mw: 504

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.42(s, 1H), 8.15 (s, 1H), 7.82-7.42(m, 6H), 3.89 (m, 3H)

Example 101: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid(1-propyl-5-trifluoromethyl-1H-benzimidazole-2-yl)-amide

The title compound was prepared as follows:



Step 1: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid

The title compound (0.20g, 25 %) was prepared from 3,4-diamino-5-chloro-benzoic acid (0.05 g) and 2-chloro-6-fluorobenzaldehyde in a manner similar to Example 90, Step 3.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.70-7.49 (m, 3H)

Step 2: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid(1-propyl-5-trifluoromethyl-1H-benzimidazole-2-yl)-amide

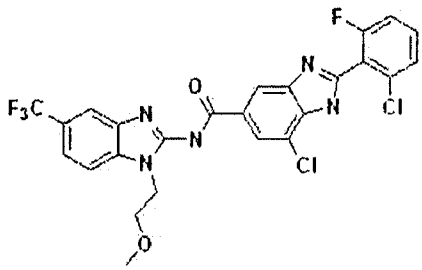
To a solution of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.21 mmol) in N,N-dimethylformamide (5 ml) was added diisoproylethylamine (0.16 ml, 0.96 mmol) and HBTU (O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluro-phosphate) (0.08mg, 0.25 mmol). The mixture was stirred for 30 minutes at rt, then 1-propyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine (0.05 g, 0.25 mmol) was added. This reaction mixture was stirred overnight at rt, then the solvent was evaporated, and the residue stirred with sat-K_2CO_3 (aq) solution was added, and the mixture was then extracted with ethyl acetate. The organic phase was

separated, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (Hex:EA=1:3) to give the title compound: 0.05 g (43 %).

Mw: 550

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.42-7.46 (m, 8H), 4.30 (t, J=7.50 Hz, 2H), 1.97-1.84 (m, 2H), 0.95 (t, J=7.18 Hz, 3H)

Example 102: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzimidazol-2-yl]-amide

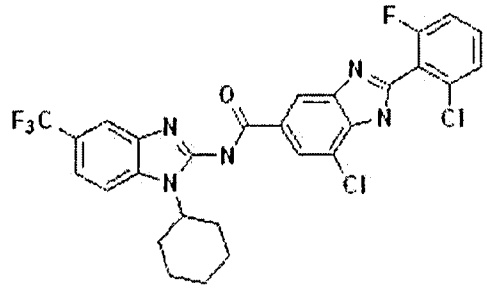


The title compound (0.09g, 76 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.21 mmol) and 1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 566

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.41-7.49 (m, 8H), 4.50 (t, J=7.20 Hz, 2H), 3.82 (t, J=7.20 Hz, 2H), 3.25 (s, 3H)

Example 103: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

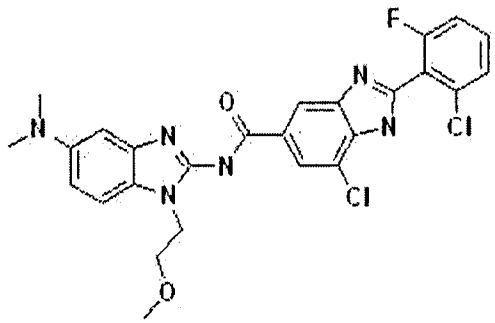


The title compound (0.06g, 48 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylicacid (0.07 g, 0.21 mmol) and 1-(cyclohexyl)-5-trifluoromethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 590

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.41-7.03 (m, 8H), 3.64-3.60 (m, 1H), 1.84-1.44 (m, 10H)

Example 104 : Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-dimethylamino-1-(2-methoxy-ethyl)-1H-benzimidazol-2-yl]-amide

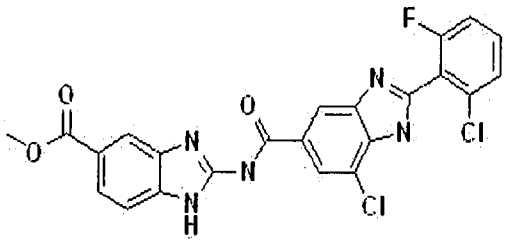


The title compound (0.03g, 24 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.21 mmol) and 1-(2-methoxy-ethyl)-5-N,N-dimethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 541

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.41-7.49 (m, 8H), 4.50 (t, J=7.20 Hz, 2H), 3.82 (t, J=7.20 Hz, 2H), 3.25 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H)

Example 105: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester



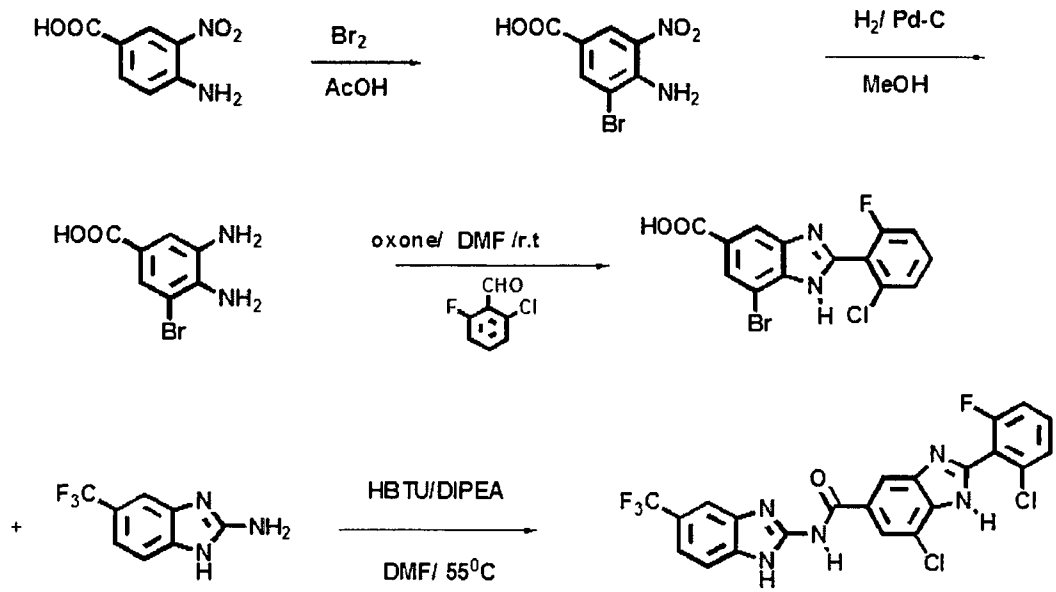
The title compound (0.20g, 94 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.22 g, 0.52 mmol) and 2-amino-1H-benzimidazole-5-carboxylic acid methyl ester in a manner similar to Example 101, Step 2.

Mw: 498

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.70-7.49 (m, 3H)

Example 106 : Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

The title compound was prepared as follows:



Step 1 : Preparation of 3-bromo-4-amino -5-nitro-benzoic acid

4-amino-3-nitrobenzoic acid (3g, 16.47 mmol) was dissolved in AcOH and Bromine (0.9 ml, 18.11 mmol) was added. The mixture was stirred for 3h at rt, after stirring for an additional 1h at rt, the reaction mixture was poured over ice and the precipitated solid collected by filtration to give the title compound: 3.9g (95%).

^{1}H NMR (DMSO-D_6, 300 MHz) : δ(ppm) 8.30 (s, 1H) 7.76 (s, 1H)

Step 2: Preparation of 3,4-diamino -5-bromo-benzoic acid

The compound (1.70 g, 94 %) was prepared from 3-bromo-4-amino-5-nitro-benzoic acid (2.00 g, 7.66 mmol) in a manner similar to Example 90, Step 2.

^{1}H NMR (DMSO-D_6, 300 MHz) : δ(ppm) 6.92 (s, 1H) 6.80 (s, 1H)

Step 3: Preparation of 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid

The title compound (0.80 g, 28 %) was prepared from 3,4-diamino-5-bromo-benzoic acid (1.70 g, 7.35 mmol) and 2-chloro-6-fluorobenzaldehyde in a manner similar to Example 90, Step 3.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.69-7.46 (m, 3H)

Step 4: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

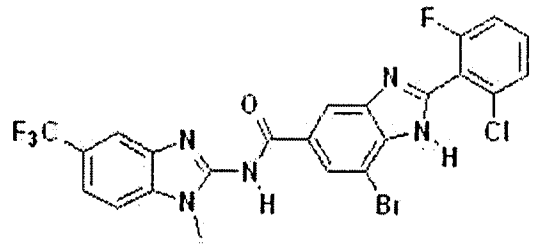
The title compound (0.20 g, 94 %) was prepared from 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.22 g, 0.52 mmol) and 5-trifluoromethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 553

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.69-7.46 (m, 6H)

Example 107: Preparation of 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-

benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

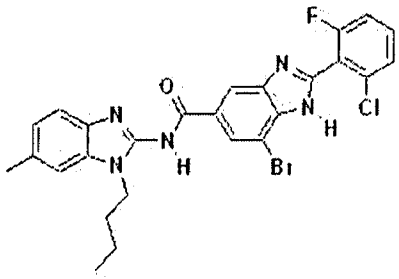


The title compound (0.02 g, 25 %) was prepared from 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.14 mmol) and1-methyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 567

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.69-7.46 (m, 6H), 3.78 (s, 3H)

Example 108: Preparation of 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide



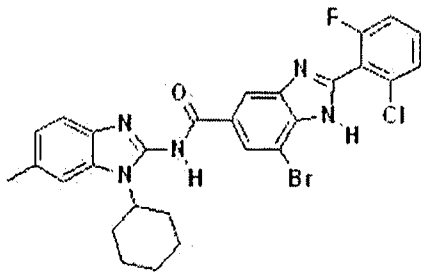
The title compound (0.03 g, 39 %) was prepared from 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.14 mmol) and 1-methyl-6-butyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 555

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.69-7.46 (m, 6H), 4.26 (t, J=6.89 Hz, 2H), 1.97-1.76 (m, 4H), 0.96 (q, J= 7.80 Hz, 3H)

Example 109: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-

amide

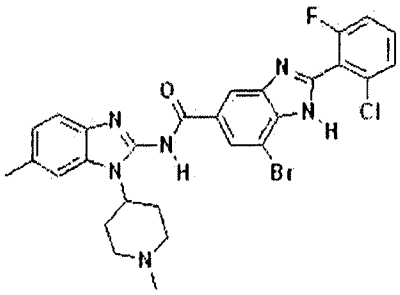


The title compound (0.03 g, 37 %) was prepared from 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.14 mmol) and 1-(cyclohexyl)-6-methyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 581

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.41-7.03 (m, 8H), 3.64-3.60 (m, 1H), 2.42 (s, 3H), 1.84-1.44 (m, 10H)

Example 110: Preparation of 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-(1-methyl-piperidin-4-yl)-6-methyl-1H-benzimidazol-2-yl)-amide



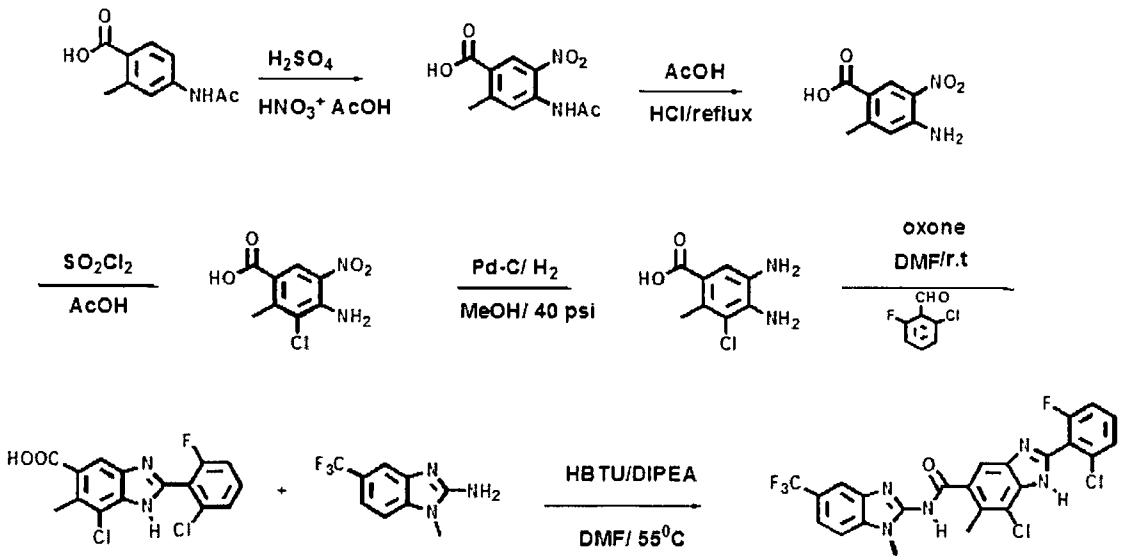
The title compound (0.02 g, 20 %) was prepared from 7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.17 mmol) and 1-(methyl-piperidine-4-yl)-6-methyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 596

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.41-7.03 (m, 8H), 3.64-3.60 (m, 1H), 2.42 (s, 3H), 2.06 (s, 3H), 1.84-1.74 (m, 8H)

Example 111: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

The title compound was prepared as follows:



Step 1: Preparation of 4-acetylamino-2-methyl-5-nitro-benzoic acid

15ml con. H_2SO_4 was allowed to cool between 0- 5℃ with ice bath added 3.3 g of 4-acetylamino-2-methyl-benzoic acid (3.30 g). Added acetic acid 10 ml and con. HNO_3 1.6 ml. The reaction mixture was stirred 3h at room temperature. The solution was added ice water, filtration to give the title compound: 1.20 g (30 %)

^{1}H NMR ((DMSO-d_6, 300 MHz) : δ(ppm) 10.10 (br, OH), 7.78 (d, J=8.7 Hz, 1H), 7.70-7.45 (m, 2H), 2.47 (s, 3H), 2.04 (s, 3H)

Step 2: Preparation of 4-amino-2-methyl-5-nitro-benzoic acid

Hydrolysis of the amide (1.20 g) was accomplished by boiling it under reflux with a mixture of 10ml of 12 M HCl and 30 ml AcOH for 1h. After addition of water filter, dried to give the title compound: 0.50 g (96 %)

^{1}H NMR (DMSO-D_6, 300 MHz) : δ(ppm) 8.12 (s, 1H) 7.68-7.49 (m, 3H) 2.65 (s, 3H)

Step 3: Preparation of 4-amino-3-chloro-2-methyl-5-nitro-benzoic acid

4-amino-2-methyl-5-nitro-benzoic acid (0.45 g) was dissolved in AcOH (5 ml) and sulfuryl chloride (0.2 ml) was added. The mixture was stirred for 2h at rt, after stirring for an additional 1h at rt, the reaction mixture was poured over ice and the precipitated solid collected by filtration to give the title compound: 0.5 g (96 %).

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.56 (s, 1H), 7.73 (NH, 2H), 2.64 (s, 3H)

Step 4: Preparation of 4,5-diamino-3-chloro-2-methyl-benzoic acid

The title compound (0.35 g) was prepared from 4-amino-3-chloro-2-methyl-5-nitro-benzoic acid (0.05 g) in a manner similar to Example 99, Step 2.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.12 (s, 1H), 2.43 (s, 3H)

Step 5: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid

The title compound (0.13 g, 22 %) was prepared from 4-amino-3-chloro-2-methyl-5-nitro-benzoic acid in a manner similar to Example 90, Step 3.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.27 (s, 1H), 7.97-7.44 (m, 3H), 2.65 (s, 3H)

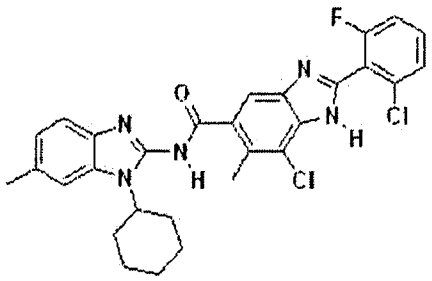
Step 6: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

The title compound (0.03 g, 35 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.16 mmol) and 1-(methyl-5-trifluoromethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 536

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.27 (s, 1H), 7.97-7.44 (m, 6H), 3.72 (s, 3H), 2.48(s, 3H)

Example 112: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide

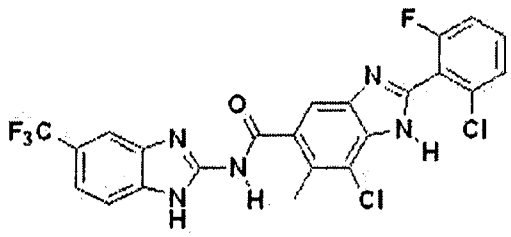


The title compound (0.03 g, 35 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.16 mmol) and 1-(cyclohexyl)-6-methyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 550

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.27 (s, 1H), 7.97-7.44 (m, 6H), 4.40-4.20 (m, 1H), 3.72 (s, 3H), 2.48 (s, 3H)

Example 113: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide

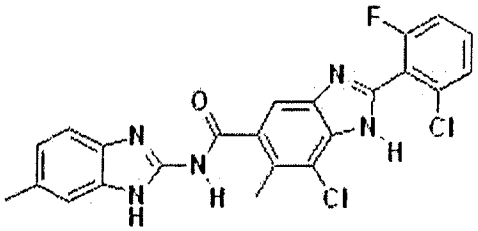


The title compound (0.03 g, 38 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.16 mmol) and 5-trifluoromethyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 522

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.27 (s, 1H), 7.97-7.44 (m, 6H), 2.48 (s, 3H)

Example 114: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (6-methyl-1H-benzimidazol-2-yl)-amide



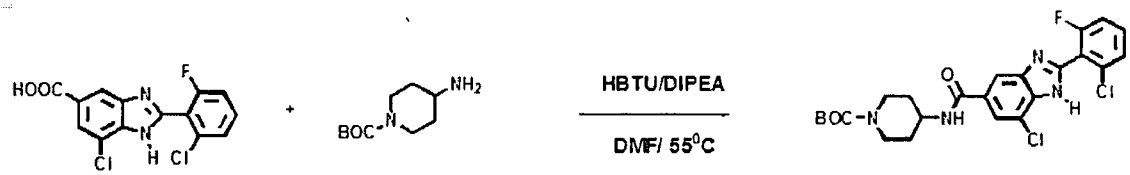
The title compound (0.04 g, 38 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (0.06 g, 0.16 mmol) and 6-methyl-1H-benzimidazole-2-ylamine in a manner similar to Example 101, Step 2.

Mw: 468

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.27 (s, 1H), 7.97-7.44 (m, 6H), 4.40-4.20 (m, 1H), 3.72 (s, 3H), 2.48 (s, 3H)

Example 115: Preparation of 4-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-piperidine-1-carboxylic acid-tert-butyl ester

The title compound was prepared as follows:



Wherein, Boc is tert-butyloxycarbonyl.

The title compound (0.20 g, 94 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid (0.17 g, 0.52 mmol) and 4-amino-piperidine-1-carboxylic acid tert-butyl ester (0.1 g, 0.52 mmol) in a manner

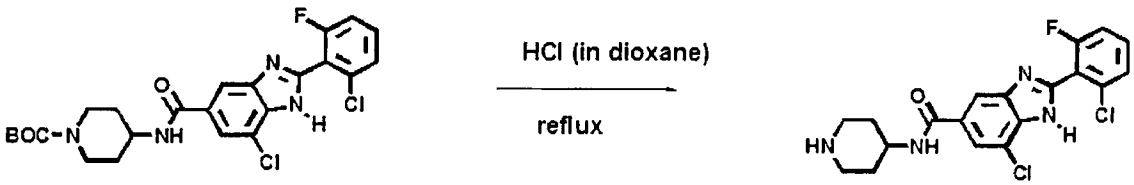
similar to Example 101, Step 2.

Mw: 507

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.89 (s, 1H), 7.97-7.44 (m, 4H), 2.90-1.84 (m, 9H), 1.42 (s, 9H)

Example 116: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid piperidin-4-ylamide

The title compound was prepared as follows:



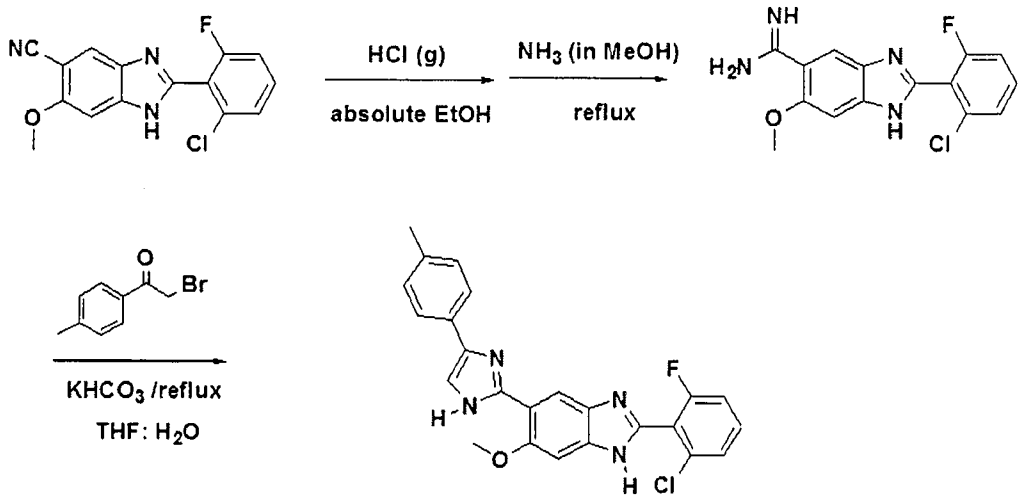
A solution of 4-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (0,16 g, 0.67 mmol) in a mixture of 5 ml HCl in dioxane. The mixture was reflux for 1h. The mixture was then concentrated in vacuo, the residue dissolved in ethanol (2 ml) and ether (3 ml) and solution was refluxed for 30 min then concentrated in vacuo to give the title compound: 0.09 g (69 %).

Mw: 407

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.18 (s, 1H), 7.92 (s, 1H), 7.72-7.48 (m, 3H), 3.70-1.84 (m, 9H)

Example 117: Preparation of 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole

The title compound was prepared as follows:



Step 1 : Preparation of 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carboxamidine

2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carbonitrile (0.5 g, 1.65 mmol) were suspended in absolute EtOH (15 ml), cooled in a ice-salt bath, and dry HCl gas was then passed through the solution for 40 min. The stoppered flask was stirred at room temperature for 3h. The solution was duilted with dry ether. The imidate esters were precipitated washed with ether, dried under vacuum. The solid was suspended in MeOH ammonia solution (10 ml) and heated for 4h. The solution was cooled on an ice bath, and the resulting precipitate was collected by filteration washed with ether to give the title compound: 0.30 g (69 %)

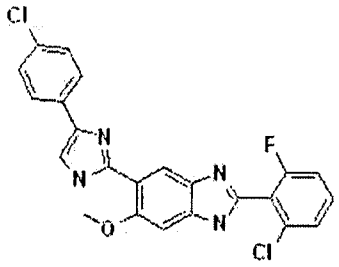
Step 2: Preparation of 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole

A mixture of 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzo-imidazole-5-carboxamidine (0.07 g) and 2-bromo-4'-methylacetophenone (0.03 g) and $KHCO_3$ (0.02 g) in 15ml THF and 5ml water was heated at reflux for 12h. After cooled to room temperature, the reaction mixture was added to water (10 ml) and ethyl acetate. The organic layer washed brain and dried with magnesium sulfate, and concentrated. The residue was chromatographed on silica gel column. Elution with a mixture of n-hexane and ethyl acetate (3:1) to give the title compound: 0.05 g (68 %)

Mw: 433

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.02-7.27 (m, 10H), 4.36-4.29 (m, 1H), 4.02 (s, 3H), 2.46 (s, 3H)

Example 118: Preparation of 2-(2-chloro-6-fluoro-phenyl)-5-[4-(4-chloro-phenyl)-1H-imidazol-2-yl]-6-methoxy-1H-benzimidazole

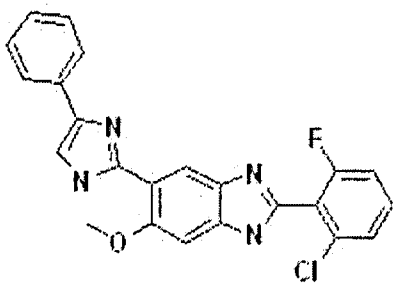


The title compound (0.20 g, 29 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carboxamidine(0.06g, 0.18mmol) and 2-bromo-4'-chloroacetophenone in a manner similar to Example 101, Step 2.

Mw: 453

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.02-7.27 (m, 9H), 4.36-4.29 (m, 1H), 4.02 (s, 3H)

Example 119: Preparation of 2-(2-chloro-6-fluorophenyl)-6-methoxy-5-(4-phenyl-1H-imidazol-2-yl)-1H-benzimidazole



The title compound (0.20 g, 25 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-6-methoxy-1H-benzimidazole-5-carboxamidine (0.06g, 0.18mmol) and 2-bromo-acetophenone in a manner similar to Example 101, Step 2.

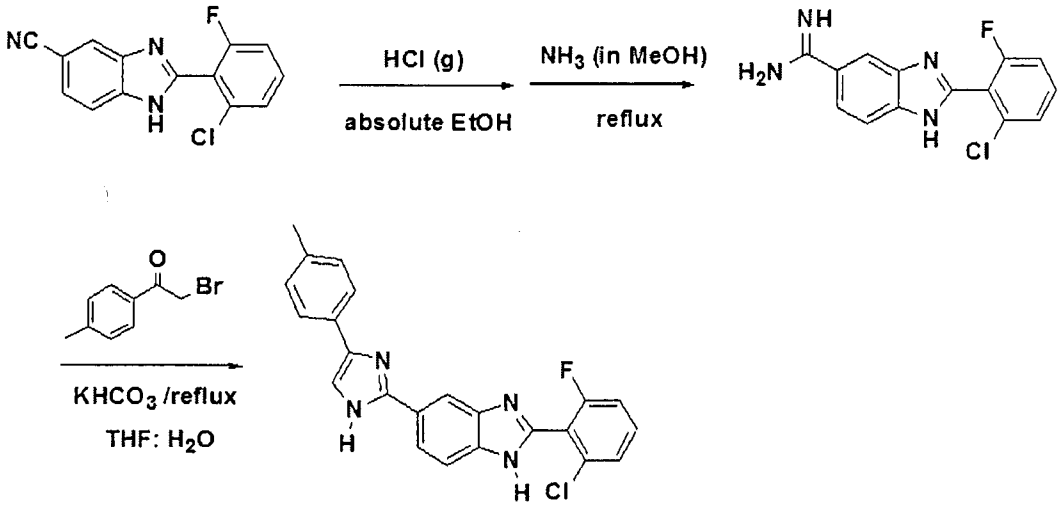
Mw: 419

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.02-7.27 (m, 10H), 4.36-4.29 (m, 1H),

4.02 (s, 3H)

Example 120: Preparation of 2-(2-chloro-6-fluoro-phenyl)-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole

The title compound was prepared as follows:

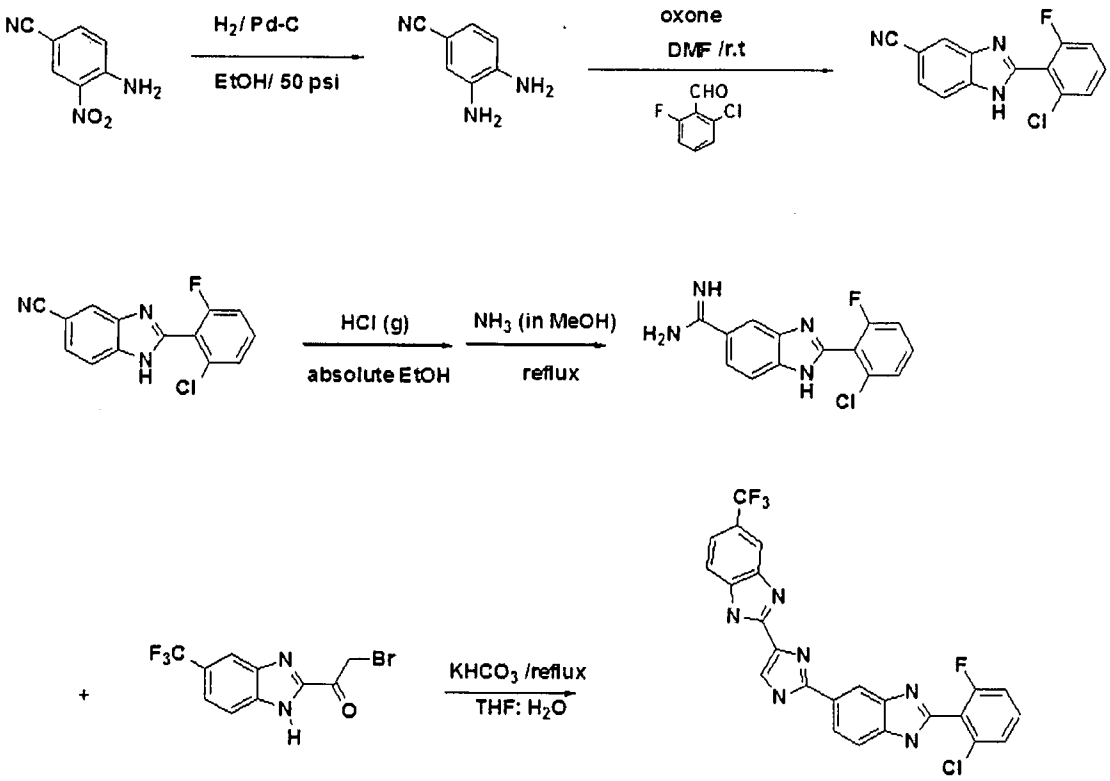


The title compound (0.20 g, 25 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxamidine and 2-bromo-4'-methylacetophenone in a manner similar to Example 117.

Mw: 403

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.02-7.27 (m, 10H), 4.36-4.29 (m, 1H), 2.64 (s, 3H)

Example 121: Preparation of 2-[3-(2-chloro-6-fluoro-phenyl)-1H-benzimidazol-5-yl]-3-(5-trifluoromethyl-benzimidazole-2-yl)-4-benzimidazole



Step 1: Preparation of 3,4-diamino-benzonitrile

The title compound (1.00 g, 83 %) was prepared from 4-amino-3-nitro-benzonitrile (1.40 g, 8.58 mmol) in a manner similar to Example 90, Step 2.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 6.95 (s, 1H) 6.82 (s, 1H) 6.70 (s, 1H)

Step 2: Preparation of 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonitrile

The title compound (1.40 g, 70 %) was prepared from 3,4-diamino-benzonitrile (1.00 g, 7.51 mmol) in a manner similar to Example 90, Step 3.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.21 (s, 1H) 7.97-7.17(m, 5H), 2.72 (s, 3H), 2.58 (s, 3H)

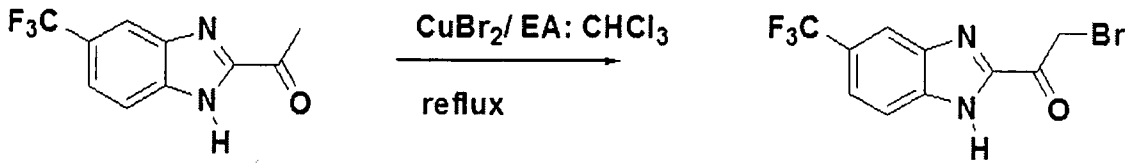
Step 3: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxamidine

The title compound (0.34 g, 64 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonitrile (0.50 g, 1.84 mmol) in a manner similar to Example 117, Step 1.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.74-7.16 (m, 6H)

Step 4: Preparation of 2-bromo-1-(5-trifluoromethyl-1H-benzimidazol-2-yl)-ethanone

The title compound was prepared as follows:



1-(5-trifluoromethyl-1H-benzimidazol-2-yl)-ethanone (0.07 g, 0.24 mmol) was dissolved in EA:CH_2Cl_2 (1:1)(20 ml), after which $CuBr_2$ (0.17 g, 0.78 mmol) and mixture heated under reflux for 3hr. After cooled to room temperature, the reaction mixture was filter and evaporation of the solvent, the residue was dissolved in 15ml dichloromethane and washed with water. The organic layer washed brain and dried with magnesium sulfate, and concentrated. The residue was chromatographed on silica gel column. Elution with a mixture of n-hexane and ethyl acetate (1:1) to give the title compound: 0.18 g (45 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 7.76-7.39 (m, 3H) 4.84 (s, 2H)

Step 5: Preparation of 2-[3-(2-chloro-6-fluoro-phenyl)-1H-benzimidazol-5-yl]-3-(5-trifluoromethyl-benzimidazole-2yl)-4-benzimidazole

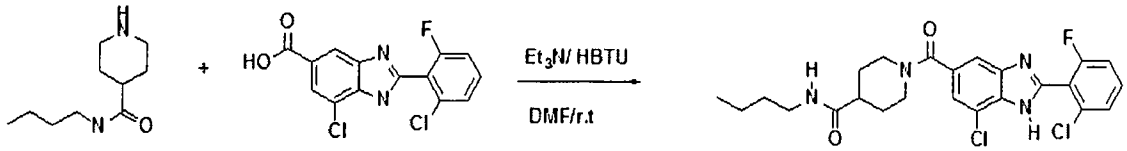
The compound (0.02 g, 29 %) was prepared from 2-bromo-1-(5-trifluoromethyl-1H-benzimidazol-2-yl)-ethanone (0.07 g, 0.24 mmol) and 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxamidine (0.08 g, 0.28 mmol) in a manner similar to Example 117, Step 2.

Mw: 497

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.29-7.20 (m, 10H)

Example 122: Preparation of 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-carbonyl]-piperidine-4-carboxylic acid butylamide

The title compound was prepared as follows:



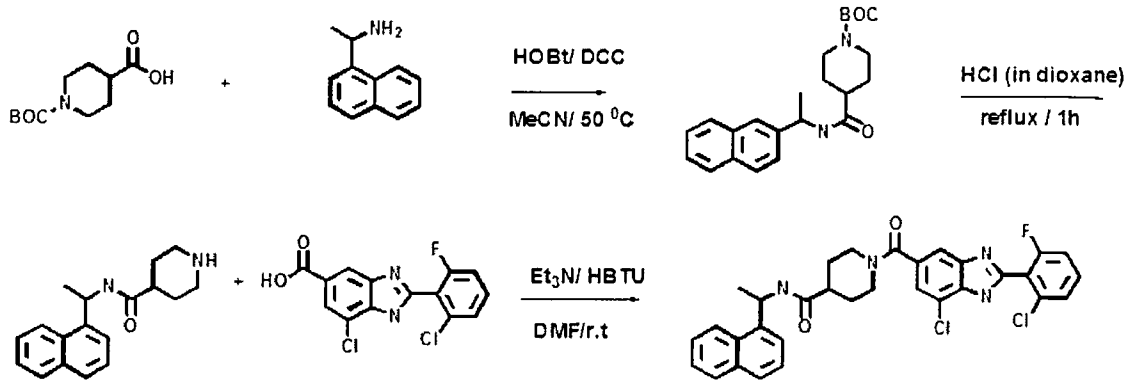
To a solution of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.21 mmol) in N,N-dimethylformamide was added Et_3N(0.07 ml, 0.52 mmol) and HBTU (O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate)(0.08 g, 0.25 mmol), piperidine-4-carboxylic acid butylamide(0.04 g, 0.25 mmol). This reaction mixture was stirred overnight at rt, then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (Hex: EA= 1/5) :0.05 g (48 %)

Mw: 491

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.79-7.32 (m, 5H), 3.00-2.87 (m, 4H), 2.40-2.34 (m 4H), 1.76-1.81 (m, 9H)

Example 123: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide

The title compound was prepared as follows:



Step 1: Preparation of 4-(1-naphthalen-2-yl-ethylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester

To a solution piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (0.30 g, 1.30 mmol) in acetonitrile was added DCC(0.26g, 1.30 mmol) and HOBT (0.19g, 1.43 mmol), 1-naphthalen-1-yl-ethylamine (0.25 ml, 1.57 mmol). This reaction mixture was stirred overnight at 50 ℃, then the solvent was evaporated, and the residue stirred with sat-$NaHCO_3$(aq) solution was added, and the mixture was then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (Hex/EA=2/1) to give the title compound: 0.45 g (92 %).

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.05-7.43 (m, 7H), 5.87 (q, J=8.5 Hz, 1H), 2.75-1.60 (m, 8H), 1.67 (d, J=7.5 Hz, 3H), 1.43 (s, 9H)

Step 2: Preparation of piperidine-4-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide

The title compound (0.13 g, 93 %) was prepared from 4-(1-Naphthalen-2-yl-ethylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester (0.20 g, 0.52 mmol) in a manner similar to Example 115.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.05-7.43 (m, 7H), 5.87 (q, J=8.5 Hz, 1H), 2.75-1.60 (m, 8H), 1.67 (d, J=7.5 Hz, 3H)

Step 3: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-

benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide

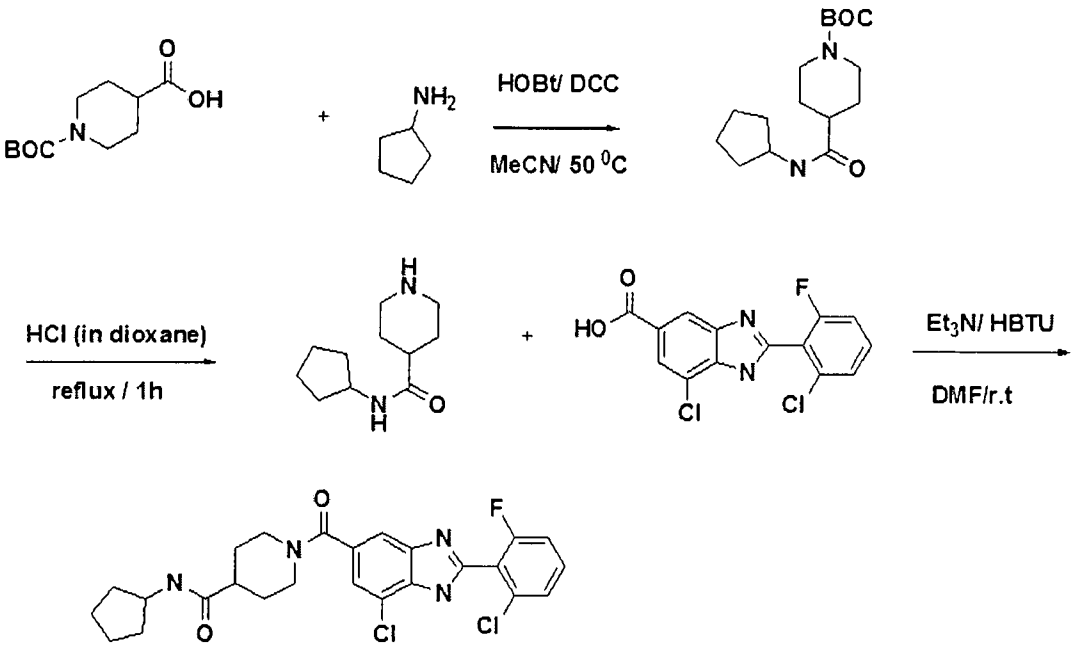
The title compound (0.07 g, 61 %) was prepared from piperidine-4-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide (0.07 g, 0.25 mmol) in a manner similar to Example 122.

Mw: 590

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.20-7.43 (m, 12H), 5.87 (q, J=8.5 Hz, 1H), 2.75- 1.60 (m, 8H), 1.67 (d, J=7.5 Hz, 3H)

Example 124: Preparation of 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide

The title compound was prepared as follows:



Step 1: Preparation of 4-cyclopentylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester

The title compound (0.06 g, 93 %) was prepared from 1-(tert-butoxycarbonyl)-4-piperidinecarboxylic acid (0.5g, 2.08 mmol) and cyclopentylamine (0.25 ml, 2.61 mmol) in a manner similar to Example 123, Step 1.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 4.23-4.10 (m, 6H), 3.49-3.46 (m, 1H), 3.48-1.20 (m, 10H), 1.45 (s, 9H)

Step 2: Preparation of piperidine-4-carboxylic acid cyclopentylamide

The title compound (0.09 g, 69 %) was prepared from 4-cyclopentylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester (0.20 g, 0.52 mmol) in a manner similar to Example 115.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 4.23-4.10 (m, 6H) 3.49-3.46 (m, 1H) 3.48-1.20 (m, 8H)

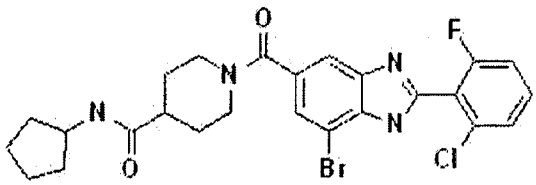
Step 3: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide

The title compound (0.08 g, 76 %) was prepared from piperidine-4-carboxylic acid cyclopentylamide (0.07 g, 0.21 mmol) in a manner similar to Example 122.

Mw: 503

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.93 (s, 1H), 7.75-7.32 (m, 5H), 3.98-3.89 (m, 1H), 2.87-1.12 (m, 16H)

Example 125: Preparation of 1-[7-bromo-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide

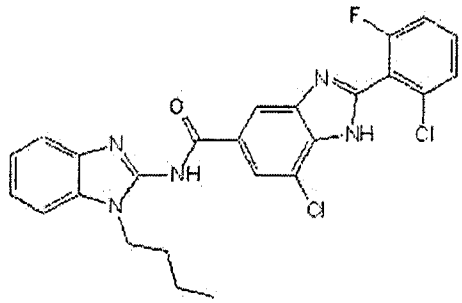


The title compound (0.02 g, 35 %) was prepared from piperidine-4-carboxylic acid cyclopentylamide (0.06 g, 0.14 mmol) and 3-bromo-4-amino-5-nitro-benzoic acid in a manner similar to Example 115.

Mw: 549

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.98 (s, 1H), 7.75-7.32 (m, 5H), 3.98-3.89 (m, 1H), 2.87-1.12 (m, 16H)

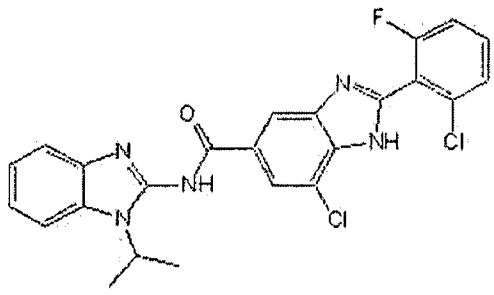
Example 126: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-1H-benzimidazole-2-yl)-amide



The title compound (0.17 g, 43%) was obtained using the method described in Example 58, using 1-butyl-1H-benzimidazole-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.29 (s, 1H), 8.04 (s, 1H), 7.60-7.67 (m, 1H), 7.50 (d, J=7.5Hz, 1H), 7.35 (t, J=8.7Hz, 1H), 7.15-7.22 (m, 2H), 6.82 (d, J=8.4Hz, 1H), 6.72 (t, J=7.5Hz, 1H), 3.16 (t, J=6.9Hz, 2H), 1.51-1.68 (m, 2H), 1.39-1.46 (m, 2H), 0.96 (t, J=7.5Hz, 3H)

Example 127: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-benzimidazole-2-yl)-amide

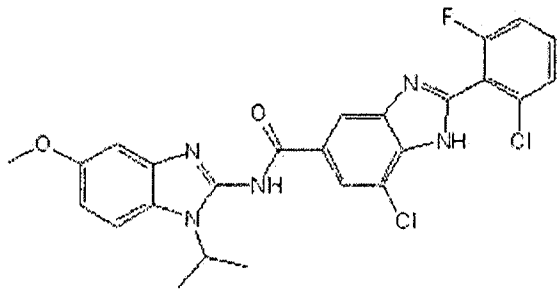


The title compound (0.02 g, 14%) was obtained using the method described in Example 58, using 1-isopropyl-1H-benzimidazole-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.32 (brs, 1H), 8.03 (s, 1H), 7.60-7.68 (m, 1H), 7.51 (d, J=8.1Hz, 1H), 7.32-7.38 (m, 1H), 7.21-7.30 (m, 2H), 6.85 (d, J=8.1Hz, 1H), 6.72 (t, J=7.5Hz, 1H), 3.64-3.72 (m, 1H), 1.22 (d, J=6.3Hz, 6H)

Example 128: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-

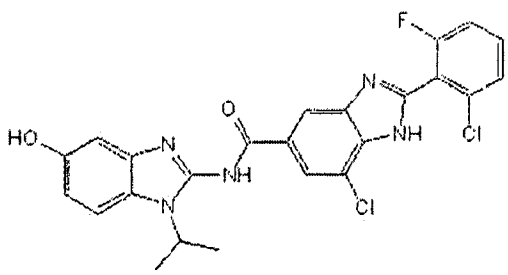
benzimidazole-5-carboxylic acid (1-isopropyl-5-methoxy-1H-benzimidazole-2-yl)-amide



To a solution of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.1 g, 0.30 mmol) in DMF (4 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.06 g, 0.34 mmol), 1-hydroxybenzotriazol monohydrate (0.009 g, 0.06 mmol) and 1-isopropyl-5-methoxy-1H-benzimidazol-2-ylamine (0.07 g, 0.34 mmol). The mixture was stirred for 4hr at room temperature, then the solvent was evaporated, and the mixture was then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (1/1) to give the title compound (0.035 g, 25%).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.42-8.60 (brd, 1H), 8.29 (s, 1H), 7.58-7.63 (m, 1H), 7.50 (d, J=8.7Hz, 1H), 7.33 (t, J=8.7Hz, 1H), 7.10 (d, J=2.1Hz, 1H), 6.88 (dd, J1=2.1Hz, J2=8.7Hz, 1H), 5.33-5.37 (m, 1H), 3.83 (s, 3H), 1.70 (d, J=6.9Hz, 6H)

Example 129: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-1-isopropyl-1H-benzimidazole-2-yl)-amide

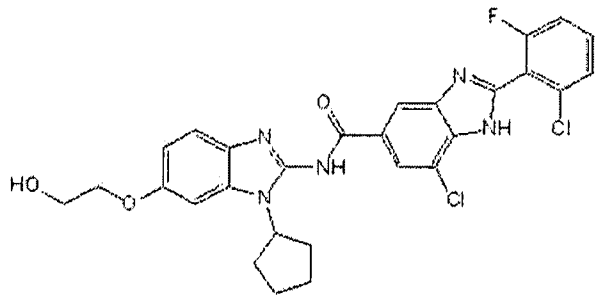


To a solution of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-

carboxylic acid (1-isopropyl-5-methoxy-1H-benzimidazol-2-yl)-amide (0.035 g, 0.068 mmol) in CH_2Cl_2 was added BBr_3 (1M CH_2Cl_2, 2 ml, 2 mmol) at room temperature. The reaction mixture was stirred for 2hr and concentrated in vacuo to give the title compound (0.03 g, 83%).

^1H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.41 (s, 1H), 8.19 (s, 1H), 7.48-7.54 (m, 1H), 7.39 (d, J=8.1Hz, 1H), 7.31 (d, J=8.7Hz, 1H), 7.23 (t, J=8.7Hz, 1H), 6.87 (d, J=2.1Hz, 1H), 6.68 (dd, J1=8.4Hz, J2=2.1Hz, 1H), 5.19-5.39 (m, 1H), 1.60 (d, J=6.9Hz, 6H)

Example 130: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-hydroxyethoxy)-1H-benzimidazole-2-yl]-amide



Step 1: Preparation of 2-(3-fluoro-4-nitrophenoxy)-ethanol

A mixture 3-fluoro-4-nitrophenol (1 g, 6.36 mmol), 2-bromoethanol (0.45 ml, 6.36 mmol) and K_2CO_3 (0.96 g, 7 mmol) in acetone was refluxed for 20hr. The reaction mixture was then diluted with water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer were washed with water, brine, dried over (Na_2SO_4) and concentrated to give the title compound (0.85 g, 67 %).

^1H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 8.07-8.13 (m, 1H), 6.79-6.84 (m, 2H), 4.16-4.19 (m, 2H), 4.02 (t, J=4.5Hz, 2H)

Step 2: Preparation of 2-(3-cyclopentylamino-4-nitrophenoxy)-ethanol

To a solution of 2-(3-fluoro-4-nitrophenoxy)-ethanol (0.85 g, 4.24 mmol) in toluene was added K_2CO_3 (0.93 g, 6.78 mmol), potassium iodide (0.007 g, 0.04 mmol),

cyclopentylamine (0.42 ml, 4.24 mmol) and refluxed for 4hr. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, evaporated to give the title compound (1.06 g, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 8.33 (brd, J=5.4Hz, 1H), 8.10 (d, J=10.5Hz, 1H), 6.20-6.24 (m, 2H), 4.10-4.53 (m, 2H), 3.99 (t, J=4.5Hz, 2H), 3.87-3.92 (m, 1H), 3.03 (s, 1H), 2.04-2.17 (m, 1H), 1.61-1.81 (m, 7H)

Step 3: Preparation of 2-(4-amino-3-cyclopentylamino-phenoxy)-ethanol

10% Pd/C (0.25 g) was added to solution of 2-(3-cyclopentylamino-4-nitrophenoxy)-ethanol (1 g, 4 mmol) in ethanol (10 ml). The reaction mixture was hydrogenated at a hydrogen pressure (55psi), filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound (0.88 g, 86 %).

^{1}H NMR (CDCl3, 300 MHz) : δ(ppm) 6.63 (d, J=8.4Hz, 1H), 6.30 (d, J=2.7Hz, 1H), 6.17 (dd, J1=2.7Hz, J2=8.2Hz, 1H), 4.01 (t, J=4.8Hz, 2H), 3.92 (t, J=4.8Hz, 2H), 3.68-3.75 (m, 1H), 1.52-2.02 (m, 8H)

Step 4: Preparation of 2-(2-amino-3-cyclopentyl-3H-benzimidazole-5-yloxy)-ethanol

To a solution of 2-(4-amino-3-cyclopentylamino-phenoxy)-ethanol (0.88 g, 3.72 mmol) in EtOH was added BrCN (3.0M in CH_2Cl_2, 1.48 ml, 4.46 mmol) and stirred at room temperature for 6hr. The reaction mixture was added sat-$NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4, evaporated. The crude residue was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (1/1) to give the title compound (0.1 g, 58 %).

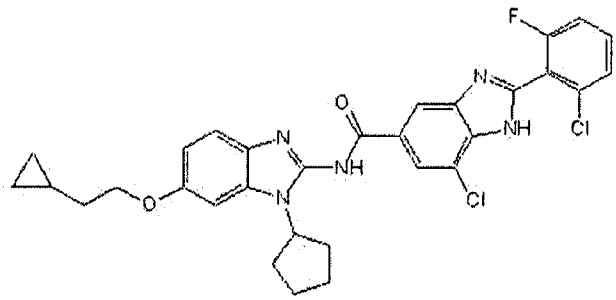
^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 7.12 (d, J=8.7Hz, 1H), 6.85 (d, J=2.4Hz, 1H), 6.72 (dd, J1=2.4Hz, J2=8.4Hz, 1H), 4.64-4.70 (m, 1H), 4.03 (t, J=4.5Hz, 2H), 3.86 (st, J=4.8Hz, 2H), 1.99-2.17 (m, 6H), 1.77-1.81 (m, 2H)

Step 5: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-hydroxyethoxy)-1H-benzimidazole-2-yl]-amide

The title compound (0.098 g, 58%) was obtained using the method described in Example 3, using 2-(2-amino-3-cyclopentyl-3H-benzimidazole-5-yloxy)-ethanol.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.50 (brs, 1H), 8.28 (s, 1H), 7.58-7.74 (m, 1H), 7.48 (d, J=8.4Hz, 1H), 7.40 (d, J=8.7Hz, 1H), 7.33 (t, J=8.7Hz, 1H), 7.08 (d, J=2.1Hz, 1H), 6.92 (dd, J1=2.1Hz, J2=8.7Hz, 1H), 5.39-5.45 (m, 1H), 4.09 (t, J=4.8Hz, 2H), 3.90 (t, J=4.8Hz, 2H), 1.87-2.44 (m, 8H)

Example 131: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-cyclopropylethoxy)-1H-benzimidazole-2-yl] -amide



Step 1: Preparation of 4-(2-cyclopropylethoxyl)-2-fluoro-1-nitrobenzene

The title compound (1.43 g, 100 %) was obtained using the method described in Example 130, Step 1, using 2-cyclopropylethyl methanesulfonate.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 8.06 (t, J=8.7Hz, 1H), 6.71-6.79 (m, 2H), 4.11 (t, J=6.6Hz, 2H), 1.73 (q, J=6.9Hz, 2H), 0.82-0.89 (m, 1H), 0.48-0.54 (m, 2H), 0.11-0.16 (m, 2H)

Step 2: Preparation of cyclopentyl-[5-(2-cyclopropylethoxy)-2-nitrophenyl]-amine

The title compound (1.32 g, 72 %) was obtained using the method described in Example 5, Step 2, using 4-(2-cyclopropylethoxyl)-2-fluoro-1-nitrobenzene.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 8.37 (d, J=4.2Hz, 1H), 8.13 (d, J=9.6Hz, 1H), 6.17-6.24 (m, 2H), 4.08 (q, J=6.9Hz, 2H), 3.89-3.95 (m, 1H), 2.05-2.13 (m, 1H), 1.63-1.79 (m, 9H), 0.80-0.87 (m, 1H), 0.49-0.53 (m, 2H), 0.12-0.14 (m, 2H)

Step 3: Preparation of N-2-cyclopentyl-4-(2-cyclopropylethoxy)-benzene-1,2-diamine

The title compound (0.8 g, 67 %) was obtained using the method described in Example 5, Step 3, using cyclopentyl-[5-(2-cyclopropylethoxy)-2-nitrophenyl]-amine.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 6.62 (d, J=8.1Hz, 1H), 6.28 (d, J=2.1H, 1H), 6.17 (dd, J1=2.4Hz, J2=8.1Hz, 1H), 3.99-4.10 (m, 2H), 3.73-3.79 (m, 1H), 1.99-2.09 (m, 2H), 1.45-1.82 (m, 8H), 0.77-0.88 (m,, 1H), 0.41-0.53 (m, 2H), 0.08-0.14 (m, 2H)

Step 4: Preparation of 1-cyclopentyl-6-(2-cyclopropylethoxy)-1H-benzimidazole-2-ylamine

The title compound (0.6 g, 61 %) was obtained using the method described in Example 5, Step 4, using N-2-cyclopentyl-4-(2-cyclopropylethoxy)-benzene-1,2-diamine.

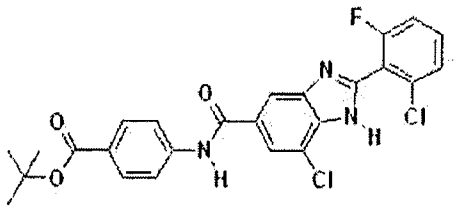
^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 7.17 (d, J=8.7Hz, 1H), 6.70-6.89 (m, 1H), 4.7-4.93 (m, 1H), 3.94 (t, J=6.6Hz, H), 1.89-2.07 (m, 5H), 1.63-1.75 (m, 5H), 1.63-1.75 (m, 2H), 1.55 (q, J=6.6Hz, 2H), 0.76-0.80 (m, 1H), 0.35-0.40 (m, 2H), 0.00-0.048 (m, 2H)

Step 5: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-cyclopropylethoxy)-1H-benzimidazole-2-yl] – amide

The title compound (0.045 g, 25 %) was obtained using the method described in Example 5, Step 5, using 1-cyclopentyl-6-(2-cyclopropylethoxy)-1H-benzimidazole-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.16-8.44 (m, 1H), 8.16 (s, 1H), 7.46-7.53 (m, 1H), 7.37 (d, J=8.1Hz, 1H), 7.18-7.26 (m, 2H), 6.86 (d, J=1.5Hz, 1H), 6.73 (dd, J1=1.5Hz, J2=8.7Hz, 1H), 5.28 (t, J=8.4Hz, 1H), 3.95 (t, J=6.6Hz, 2H), 2.25-2.88 m, 2H), 2.03-2.25 (m, 4H), 1.53-1.76 (m, 2H), 1.56 (q, J=6.6Hz, 2H), 0.71-0.80 (m, 1H), 0.34-0.39 (m, 2H), 0.01-0.05 (m, 2H)

Example 132: Preparation of 4-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-benzoic acid-tert-butyl ester

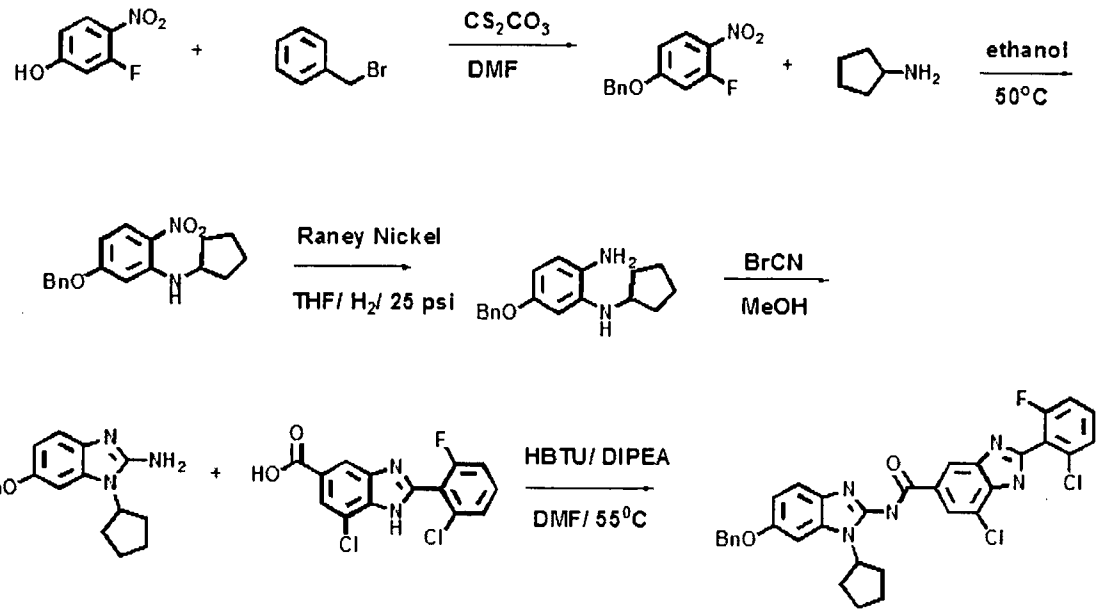


The title compound (0.06 g, 30 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.46 mmol) and tert-butyl-4-aminobenzoate (0.05 g, 0.25 mmol) in a manner similar to Example 101, Step 2.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.02-7.50 (m, 5H) 4.10-3.90 (m, H) 2.50 (s, 4H) 2.02-1.80 (m, 4H) 1.42 (s, 9H)

Example 133: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-hydroxy-1H-benzimidazol-2-yl)amide

The title compound was prepared as follows:



Step 1: Preparation of 4-benzyloxy-2-fluoro-1-nitro-benzene

A solution of 3-fluoro-4-nitrophenol (5.0 g, 31.84 mmol) in DMF were added CS_2CO_3 (11.4 g, 34.99 mmol), tetrabutylammoniumiodide (cat), benzylbromide (4.1 ml, 25.03 mmol). The mixture was stirred overnight and added water. The solution was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hex/EA=1/1) to give the title compound: 7.0 g (90 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 8.09 (t, J=9.09Hz, 1H) 7.42-7.37 (m, 5H), 6.85-6.78 (m, 2H), 5.14 (s, 2H)

Step 2: Preparation of (5-benzyloxy-2-nitro-phenyl)-cyclopentyl-amine

4-benzyloxy-2-fluoro-1-nitro-benzene (0.5 g, 2.01 mmol) was dissolved in EtOH and cyclopentylamine (0.25 ml, 2.62 mmol) was added. The mixture was stirred for 24h at 50℃. The reaction mixture was concentrated in vacuo. Purification by column chromatography on silica gel (Hex/ EA=1/1) to give the title compound: 0.32 g (50 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 8.09 (t, 1H, J=9.09 Hz), 7.42-7.37 (m, 5H), 6.85-6.78 (m, 2H), 5.14 (s, 2H), 3.89-3.81 (m, 1H), 2.06-1.59 (m, 8H)

Step 3: Preparation of 4-benzyloxy-N2-cyclopentyl-benzene-1,2-diamine

A solution of (5-benzyloxy-2-nitro-phenyl)-cyclopentyl-amine (0.32 g, 1.02 mmol) in THF was reduced using Ra-Nickel (10 mmol%). The mixture is subsequently hydrogenated at 30 psi a hydrogen pressure for 4h. The mixture was filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo. Purification by column chromatography on silica gel (Hex/ EA=1/1) to give the title compound: 0.16 g (57 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 7.42-7.37 (m, 5H), 6.85-6.78 (m, 2H), 6.63-6.42 (m, 1H), 4.97 (s, 2H), 3.89-3.81 (m, 1H), 2.06-1.59 (m, 8H)

Step 4: Preparation of 6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-ylamine

4-benzyloxy-N2-cyclopentyl-benzene-1,2-diamine (0.42 g, 1.48 mmol) was dissolved in MeOH and cyanobromide (3.0 M solution, 0.22 ml, 0.67 mmol) was added.

The mixture was stirred for 24h at r.t. The reacetion mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hex: EA= 1:5) to give the title compound: 0.13 g (28 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 8.12 (d, 1H, J=8.90 Hz), 7.42- 7.26 (m, 5H), 6.30- 6.23 (m, 2H), 5.12 (s, 2H), 3.85-3.81 (m, 1H), 1.98-1.57 (m, 8H)

Step 5: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-yl)-amide

The title compound (0.05 g, 26 %) was prepared from 6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-ylamine (0.19 g, 0.59 mmol) in a manner similar to Example 101, Step 2.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.87 (s, 1H), 8.34 (s, 1H), 7.47- 6.88 (m, 11H), 5.52-5.41 (m, 1H), 5.14 (s, 2H), 2.17-1.68 (m, 8H)

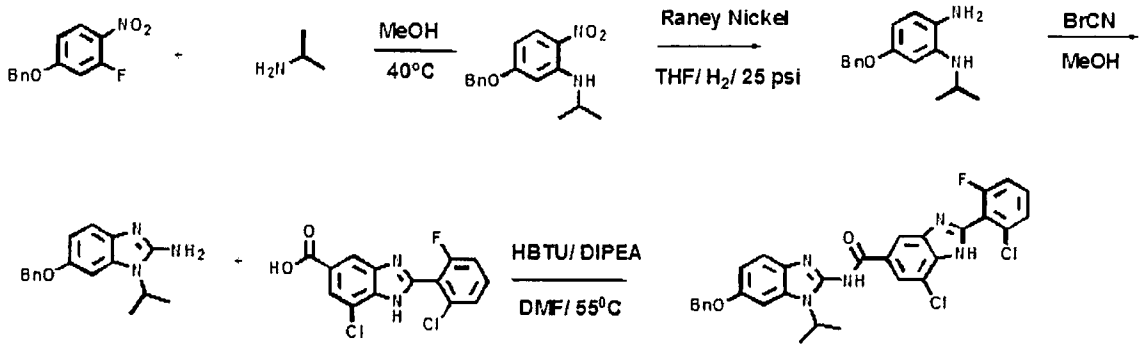
Step 6: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-hydroxy-1H-benzimidazol-2-yl)-amide

The title compound (1.0 g, 63 %) was prepared from 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-yl)-amide (1.90 g, 3.62 mmol) in a manner similar to Example 90, Step 2.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.87 (s, 1H), 8.34 (s, 1H), 7.47- 6.88 (m, 6H), 5.52-5.41 (m, 1H), 2.17- 1.68 (m, 8H)

Example 134: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)-amide

The title compound was prepared as follows:



Step 1: Preparation of (5-benzyloxy-2-nitro-phenyl)-isopropyl-amine

The title compound (0.6 g, 60 %) was prepared from 4-benzyloxy-2-fluoro-1-nitro-benzene (1.0 g, 4.03 mmol) and isopropylamine (0.56 ml, 6.45 mmol) in a manner similar to Example 133, Step 2.

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 7.79-7.32 (m, 5H), 6.67 (d, J=8.01 Hz, 1H), 6.39-6.20 (m, 2H), 5.03 (s, 2H), 3.59-3.52 (m, 1H), 1.53 (d, J=7.00 Hz, 6H)

Step 2: Preparation of 4-benzyloxy-N2-isopropyl-benzene-1,2-diamine

The title compound (0.32 g, 60 %) was prepared from (5-benzyloxy-2-nitro-phenyl)-isopropyl-amine (0.6 g, 2.34 mmol) in a manner similar to Example 133, Step 3.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 7.74-7.29 (m, 5H), 6.64 (d, 1H, J=8.01 Mz) 6.39-6.20 (m , 2H) 5.02 (s, 2H) 3.59- 3.52 (m, 1H) 1.56 (d, 6H, J=7.00 Hz)

Step 3: Preparation of 6-benzyloxy-1-isopropyl-1H-benzimidazol-2-ylamine

The title compound (0.17 g, 51 %) was prepared from 4-benzyloxy-N2-isopropyl-benzene-1,2-diamine (0.32 g, 0.12 mmol) in a manner similar to Example 133, Step 4.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.48-6.81 (m, 8H), 5.08 (s, 2H), 4.41-4.37 (m, 1H), 1.56 (d, 6H, J=7.00 Hz)

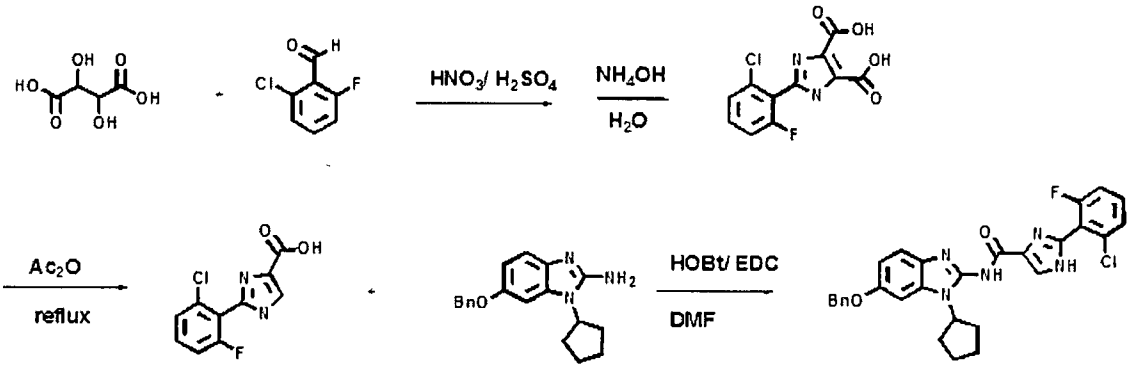
Step 4: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)-amide

The title compound (0.20 g, 57 %) was prepared from 6-benzyloxy-1-isopropyl-1H-benzimidazol-2-ylamine (0.17g, 0.60 mmol) in a manner similar to Example 133, Step 5.

^{1}H NMR (DMSO-d_6, 300 MHz) : δ(ppm) 8.78-6.78 (m, 13H), 5.29-5.22 (m, 1H), 5.04 (s, 2H), 1.55 (d, J=7.00 Hz, 6H)

Example 135: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-yl)-amide

The title compound was prepared as follows:



Step 1: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4,5-dicarboxylic acid

To tartaric acid (4g, 26.65 mmol) was added 70% nitric acid 13 ml, 98% nitric acid 13ml, con, sulfuric acid 24 ml. The mixture was left to stand for 2h in ice bath. The precipitate was filtered on Buchner funnel and transferred into flask containing 85g of crushed ice, cooled to -18 ℃. The resulting solution was neutralized with a con. ammonia solution. When the PH value attained 7-8, 14 ml of an ammonia solution and 2-chloro-6-fluoro-benzaldehyde was added, the mixture was stirred for 20h. The mixture was acidified with con. HCl to pH 3. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel to give the title compound (3g, 40%).

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 6.90-7.20 (m, 3H)

Step 2: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid

To a solution of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4,5-dicarboxylic acid (3g, 11.98 mmol) in acetic anhydride the mixture was reflux for 4h. The mixture was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel to give the title compound (2.3g, 83%).

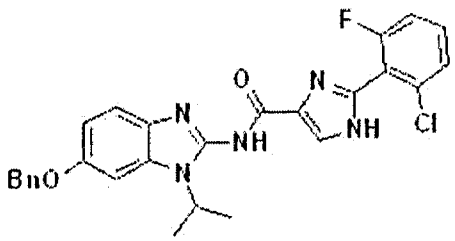
^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.35 (d, J=7.04 Hz, 1H), 7.30-7.15 (m, 3H)

Step 3: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-yl)-amide

To a solution of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (0.49g, 2.07 mmol) in DMF was added EDC(0.33g, 2.48 mmol) and HOBT (0.27g, 2.07 mmol), 6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-ylamine (0.70 g, 2.48 mmol). This reaction mixture was stirred overnight at r.t, then the solvent was evaporated, and the residue stirred with sat-$NaHCO_3$(aq) solution was added, and the mixture was then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (Hex/EA=1/3) to give the title compound: 0.10 g (28 %).

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.86 (s, 1H), 8.58 (s, 1H), 8.31 (d, 1H), 7.39-6.90 (m, 9H), 5.29-5.25 (m, 1H), 5.05 (s, 2H), 1.98-1.65 (m, 8H)

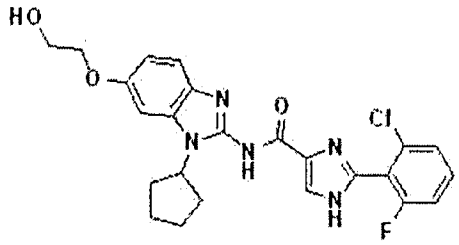
Example 136: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)-amide



The title compound (0.10 g, 25 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid(0.20 g, 0.83 mmol) and 6-benzyloxy-1-isopropyl-1H-benzimidazole-2-ylamine (0.23 g, 0.83 mmol) in a manner similar to Example 135, Step 3.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.86 (s, 1H), 8.58 (s, 1H), 8.31 (d, 1H), 7.39-6.90 (m, 9H), 5.29-5.25 (m, 1H), 5.05 (s, 2H), 1.65 (d, J=6.93 Hz, 6H)

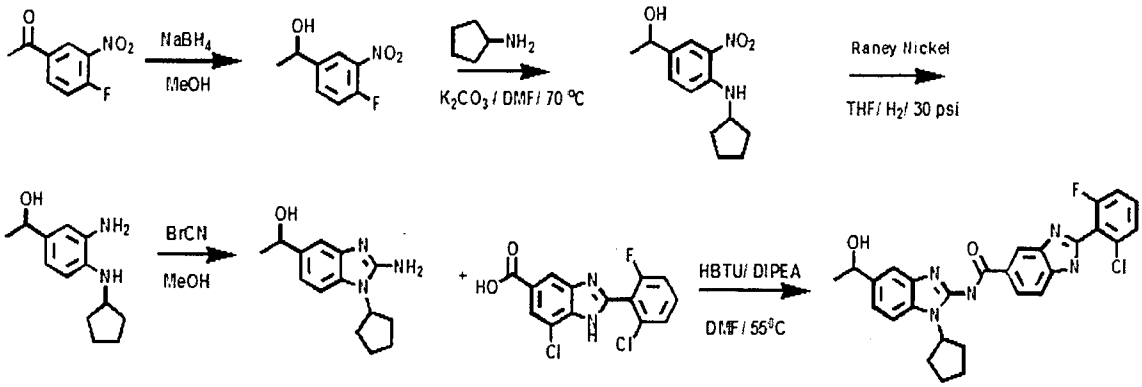
Example 137: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid [1-cyclopentyl-6-(2-hydroxy-ethoxymethyl)-1H-benzimidazol-2-yl]-amide



The title compound (0.14 g, 59 %) was prepared from 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid(0.11 g, 0.49 mmol) and 2-(2-amino-3-cyclopentyl-3H-benzimidazole-5-yloxy)-ethanol(0.13 g, 0.49 mmol) in a manner similar to Example 135, Step 3.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.20 (s, 1H), 7.97 (s, 1H), 7.25-6.92 (m, 5H), 5.20-5.10 (m, 1H), 3.96 (t, J=5.60 Hz, 2H), 3.71 (t, J=5.60 Hz, 2H), 1.88-1.63 (m, 8H)

Example 138: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid [1-cyclopentyl-5-(1-hydroxy-ethyl)-1H-benzimidazol-2-yl]-amide



Step 1: Preparation of 1-(4-fluoro-3-nitro-phenyl)-ethanol

To a solution of 1-(4-fluoro-3-nitro-phenyl)-ethanone (4g, 21,84 mmol) in MeOH added $NaBH_4$ (2.40 g, 3eq), the mixture was stirred for 1h at r.t. The mixture was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hex/EA=1/1) to give the title compound: 3.60 g (90%).

1H NMR (300 MHz, $CDCl_3$) :δ(ppm) : 8.10-7.16 (m, 3H) 5.42-5.35 (m, 1H) 1.52 (d, 3H, J= 6.46 HZ)

Step 2: Preparation of 1-(4-cyclopentylamino-3-nitro-phenyl)-ethanol

A solution of 1-(4-Fluoro-3-nitro-phenyl)-ethanol (1.6g, 8.64 mmol) in DMF were added K_2CO_3 (1.43 g, 10.35 mmol), cyclopentylamine(1.0 ml, 10.36 mmol). The mixture was stirred at 45 ℃ overnight and added water. The solution was extracted with ethylacetate and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hex:EA=5:1) to give the title compound: 1.73g (80%).

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.10-7.16 (m, 3H) 5.42-5.35 (m, 1H) 3.65- 3.60 (m, 1H) 1.98-1.20 (m, 8H) 1.52 (d, 3H, J= 6.46 Hz)

Step 3: Preparation of 1-(3-amino-4-cyclopentylamino-phenyl)-ethanol

A solution of 1-(4-cyclopentylamino-3-nitro-phenyl)-ethanol (1.73g, 6.91 mmol)

in THF was reduced using Ra-Ni. The mixture is subsequently hydrogenated at 30 psi an hydrogen pressure for 4h. The mixture was filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound: 1.06g (70%).

^{1}H NMR (300 MHz, DMSO-d_6) :δ(ppm) 6.52-6.31 (m, 3H) 4.43 (NH, 2H) 4.10-4.05 (m, 1H) 3.65-3.62 (m, 1H) 1.96-1.45 (m,8H) 1.20 (d, 3H, J=6.30 Hz)

Step 4: Preparation of 1-(2-amino-1-cyclopentyl-1H-benzimidazol-5-yl)-ethanol

1-(3-amino-4-cyclopentylamino-phenyl)-ethanol (1.06 g, 4.84 mmol) was dissolved in MeOH and cyanobromide (3.0 M in CH_2Cl_2, 1.93 ml, 5.80 mmol) was added. The mixture was stirred for 24h at r.t. The reacetion mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by columnchromatography on silica gel (Hex/ EA= 1/5) to give the title compound:0.30 g (32 %).

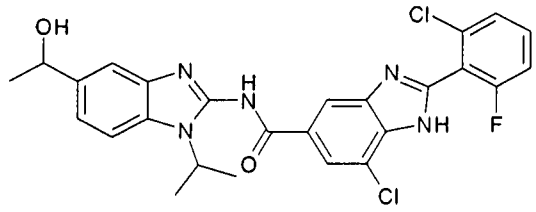
^{1}H NMR (300 MHz, DMSO-d_6) : δ(ppm) 7.20-6.27 (m, 1H) 4.72-4.62 (m, 1H) 4.24-4.18 (m, 1H) 1.96-1.45 (m,8H) 1.20 (d, 3H, J=6.30 Hz)

Step 5: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid[1-cyclopentyl-5-(1-hydroxy-ethyl)-1H-benzimidazol-2-yl]-amide

To a solution of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.49g, 1.50 mmol) in DMF was added DIPEA (1.2 ml, 6.9 mmol) and HBTU (0.74g, 2.25 mmol). The mixture was stirred for 30 minutes at rt, then 1-(2-amino-1-cyclopentyl-1H-benzimidazol-5-yl)-ethanol (0.37g, 1.50 mmol) was added. This reaction mixture was stirred overnight at 50 ℃, then the solvent was evaporated, and the residue stirred with sat-K_2CO_3 (aq) solution was added, and the mixture was then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (Hex/EA=1/3) to give the title compound: 60 mg (10%)

^{1}H NMR (300 MHz, DMSO-d_6) : δ(ppm) 8.40-7.03 (m, 8H) 5.42-5.32 (m, 1H) 4.40-4.23 (m, 1H) 2.20-2.06 (m, 1H) 2.05-1.75 (m, 8H) 1.33 (d, 3H, J=6.31 Hz)

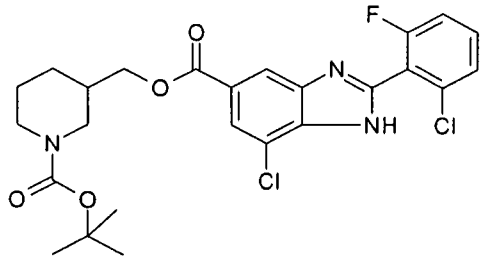
Example 139: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(1-hydroxy-ethyl)-1-isopropyl-1H-benzimidazol-2-yl]-amide



The title compound (0.12 g, 25 %) was prepared from 1-(2-amino-1-isopropyl-1H-benzimidazole-5-yl)-ethanol (0.20 g, 0.91mmol) in a manner similar to Example 138.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.38-7.19 (m, 8H) 5.40-5.28 (m, 1H) 4.78-4.70 (m, 1H)

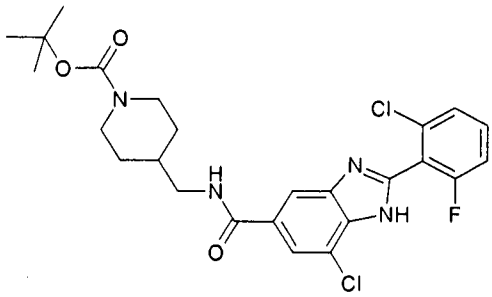
Example 140: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid 1-tert-butoxycarbonyl-piperidin-3-ylmethyl ester



The title compound (0.12 g, 25 %) was prepared from 3-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (0.10 g, 0.46 mmol) and 7-chloro-2- (2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.18 g, 0.55 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.52-7.12 (m, 5H) 3.50 (s, 2H) 3.60-2.30 (m, 9H) 1.45 (s, 9H)

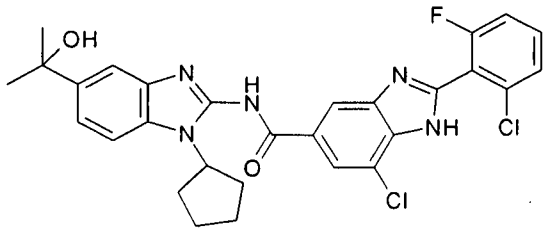
Example 141: Preparation of 4-({[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester



To a solution of 4-aminomethyl-piperidine-1-carboxylic acid tert-butyl ester (0.11 ml, 0.55 mmol) in DMF was added EDC(0.14 g, 0.59 mmol) and hydroxyl benzotriazole (0.06 g, 0.50 mmol), 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.46 mmol). This reaction mixture was stirred overnight at r.t, then the solvent was evaporated, and the residue stirred with sat-$NaHCO_3$(aq) solution was added, and the mixture was then extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (Hex/EA=1/3) to give the title compound: 0.14 g (59 %)

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.63-7.45 (m, 5H) 4.40 (s, 2H) 3.80-2.30 (m, 8H) 1.20 (s, 9H)

Example 142: Preparation of 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-5-(1-hydroxy-1-methyl-ethyl)-1H-benzimidazol-2-yl]-amide

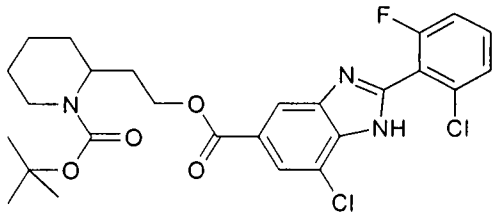


The title compound (0.13 g, 54 %) was prepared from 2-(2-amino-1-cyclopentyl-1H-benzimidazole-5-yl)-propan-2-ol (0.08 g, 0.31 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.12 g, 0.37 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.10-7.78 (m, 8H) 5.30-5.20 (m, 1H)

1.56 (s, 6H) 1.45 (d, 6H, J=7.92 Hz)

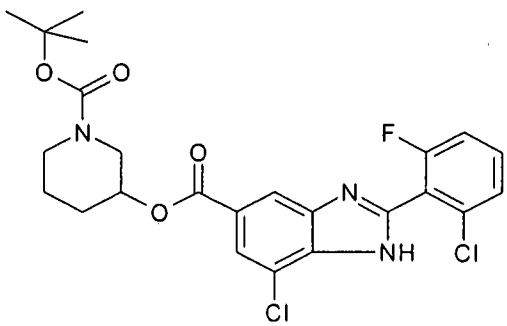
Example 143: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid-2-(1-tert-butoxycarbonyl-piperidin-2-yl)-ethyl ester



The title compound (0.19 g, 70 %) was prepared from 2-(2-hydoxy-ethyl)-piperidine-1-carboxyli acid tert-butyl ester (0.11 ml, 0.51 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.63-7.45 (m, 5H) 4.20 (t, 2H, J= 7.20 Hz) 3.80 (t, 2H, J=7.20 Hz) 3.60-2.30 (m, 9H) 1.27 (s, 9H)

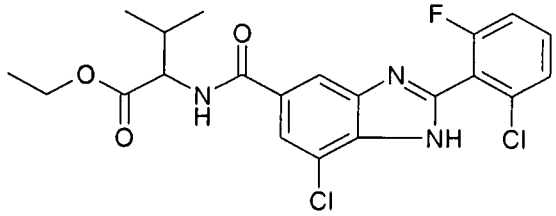
Example 144: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid-1-tert-butoxycarbonyl-piperidin-3-yl ester



The title compound (0.12 g, 52 %) was prepared from 3-hydroxy-1-piperidine-1-carboxylic acid tert-butyl ester (0.09 g, 0.46 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 8.52-7.12 (m, 5H) 3.60-2.30 (m, 9H) 1.45 (s, 9H)

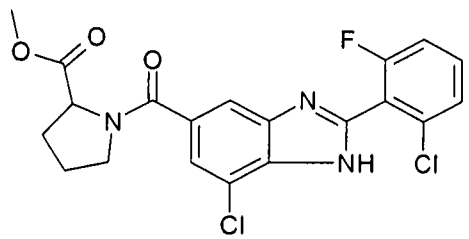
Example 145: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid ethyl ester



The title compound (0.16 g, 77 %) was prepared from 2-amino-3-methyl-butyric acid ethyl ester (0.07 g, 0.46 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.46 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.38-7.46 (m, 5H) 4.12 (t, 1H, J=6.89 Hz) 4.17-4.10 (m, 2H) 2.23-2.16 (m, 1H) 1.19 (t, 3H, J=7.19 Hz) 0.97 (dd, H, J= 6.75 Hz)3H)

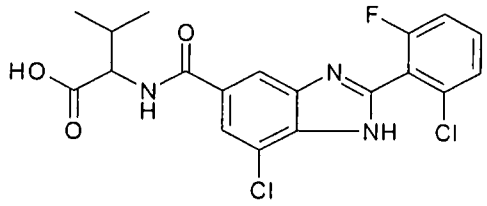
Example 146: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester



The title compound (0.11 g, 55 %) was prepared from L-pyrroline methyl ester (0.07 g, 0.46 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.46 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.72-7.45 (m, 5H) 4.60-4.45 (m, 1H) 3.80 (s, 3H) 2.27-1.80 (m, 6H)

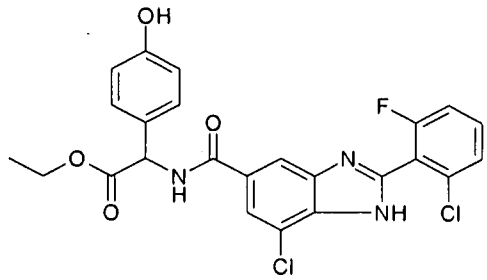
Example 147: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid



To the 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid ethyl ester (0.14 g, 0.30 mmol) in THF/methanol (2/1, 3 ml) was added NaOH (0.01 g, 0.34 mmol) dissolved in water (1 ml). The resulting mixture was stirred at 30 ℃ for 4h and was then acidified with 1N HCl to pH 3-4. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound: 0.10 g (78 %).

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.65-7.46 (m, 5H) 4.12 (t, 1H, J=6.89 Hz) 2.23-2.16 (m, 1H) 0.97 (dd, H, J= 6.75 Hz)

Example 148: Preparation of {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid ethyl ester

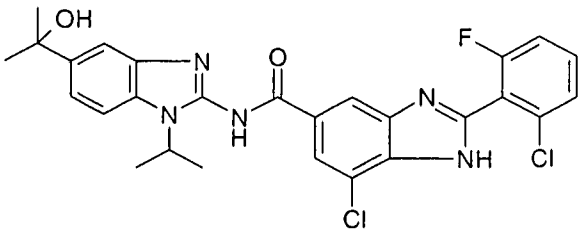


The title compound (0.09 g, 60 %) was prepared from amino-(4-hydroxy-phenyl)-actic acid ethyl ester (0.06 g, 0.30 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.10 g, 0.30 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (CD_3OD, 300MHz) : δ(ppm) 7.69-6.75 (m, 9H) 5.48 (d, 1H, J=6.45 Hz) 4.13-4.08 (m, 2H) 0.97 (t, 3H, J=7.00 Hz)

Example 149: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(1-hydroxy-1-methyl-ethyl)-1-isopropyl-1H-

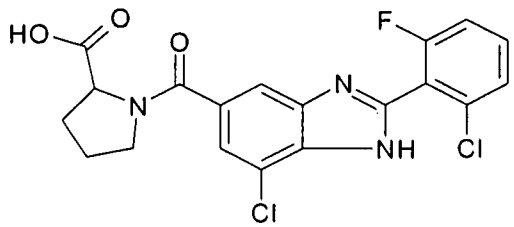
benzimidazol-2-yl] –amide



The title compound (0.01 g, 35 %) was prepared from 2-(2-amino-1-isopropyl-1H-benzimidazole-5-yl)-propan-2-ol (0.07 g, 0.30 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.09 g, 0.30 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) : 8.10-7.78 (m, 8H) 5.30-5.20 (m, 1H) 1.56 (s, 6H) 1.45 (d, 6H, J=7.92 Hz)

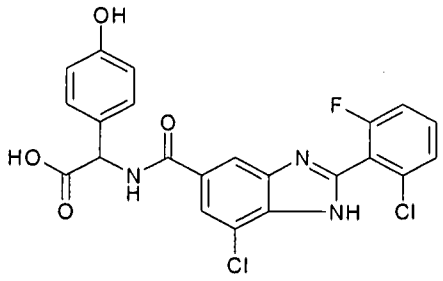
Example 150: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid



The title compound (0.06 g, 65 %) was prepared from 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (0.10 g, 0.22 mmol) in a manner similar to Example 147.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.72-7.45 (m, 5H) 4.60-4.45 (m, 1H) 2.27-1.80 (m, 6H)

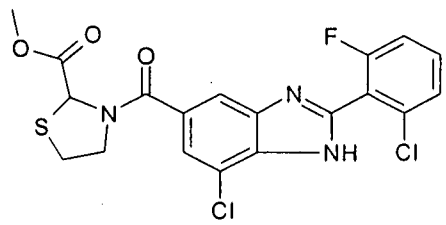
Example 151: Preparation of {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid



The title compound (0.06 g, 65 %) was prepared from {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid ethyl ester (0.10 g, 0.22 mmol) in a manner similar to Example 147.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.41-7.03 (m, 8H) 3.64-3.60 (m, 1H) 1.84-1.44 (m, 10H)

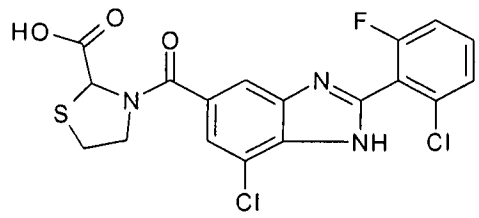
Example 152: Preparation of 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid methyl ester



The title compound (0.05 g, 38 %) was prepared from thiazolidine-2-carboxylic acid methyl ester (0.06 g, 0.30 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.10 g, 0.30 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.75-7.44 (m, 5H) 4.18-4.00 (m, 1H) 3.36 (s, 3H) 3.22-2.75 (m, 4H)

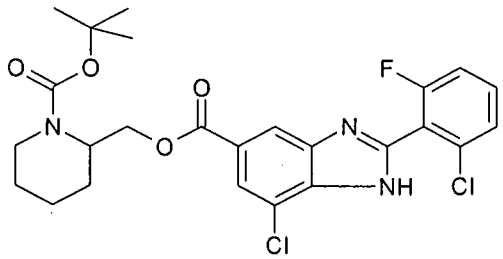
Example 153: Preparation of 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid



The title compound (0.02 g, 52 %) was prepared from 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid methyl ester (0.05 g, 0.11 mmol) in a manner similar to Example 147.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.75-7.44 (m, 5H) 4.18-4.00 (m, 1H) 3.22-2.75 (m, 4H)

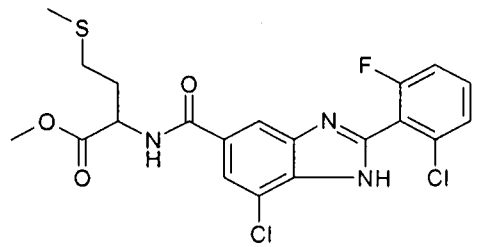
Example 154: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid 1-tert-butoxycarbonyl-piperidin-2-yl methyl ester



The title compound (0.13 g, 54 %) was prepared from 2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (0.10 g, 0.46 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.18 g, 0.55 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.52-7.12 (m, 5H) 3.50 (s, 2H) 3.60-2.30 (m, 9H) 1.45 (s, 9H)

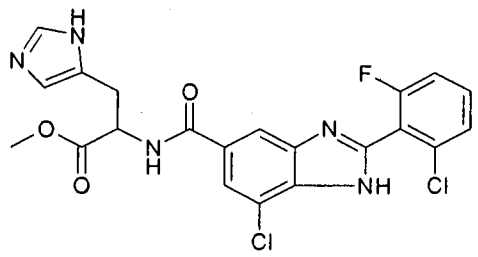
Example 155: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methylsulfanyl-butyric acid methyl ester



The title compound (0.13 g, 59 %) was prepared from amino-(4-methylsulfanyl)-butyric acid (0.08 g, 0.46 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.46 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.10- 7.46 (m, 5H) 4.64-4.57 (m, 1H) 3.65 (s, 3H) 2.72- 2.48 (m, 4H) 2.05 (s, 3H)

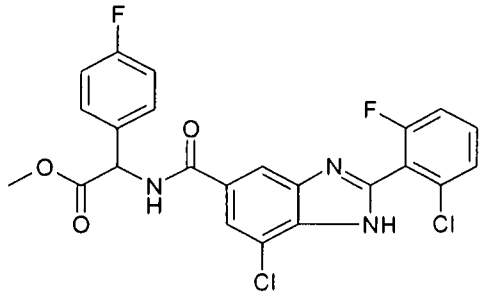
Example 156: Preparation of {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-(1H-imidazol-4-yl)-propionic acid methyl ester



The title compound (0.13 g, 70 %) was prepared from 3-amino-2-(1H-imidazole-4-yl)-propionic acid methyl ester (0.08 g, 0.46 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.13 g, 0.39 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.93 - 6.80 (m,7H) 4.80 - 4.60 (m, 1H) 3.15 (d, 2H, J= 6.00 Hz) 3.42 (s, 3H)

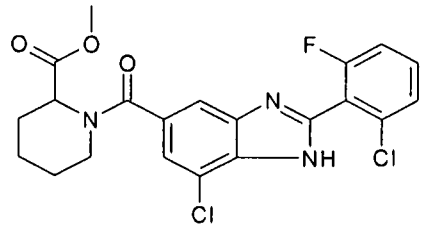
Example 157: Preparation of {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-fluoro-phenyl)-acetic acid methyl ester



The title compound (0.13 g, 70 %) was prepared from amino-4-(fluoro-phenyl)-acetic acid methyl ester (0.08 g, 0.46 mmol) and 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (0.13 g, 0.39 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.15-7.27 (m, 9H) 5.73 (d, 1H, J=6.89 Hz) 3.67 (s, 3H)

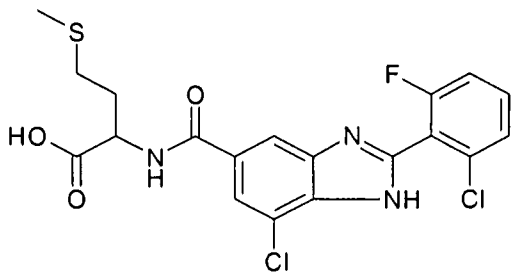
Example 158: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester



The title compound (0.17 g, 82 %) was prepared from piperidine-2-carboxylic acid methyl ester (0.06 g, 0.46 mmol) and in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.72-7.31 (m, 5H) 5.20-5.16 (m, 1H) 3.73 (s, 3H) 3.20-3.00 (m, 2H) 2.38-2.19 (m, 2H) 1.72- 1.13 (m, 4H)

Example 159: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methylsulfanyl-butyric acid

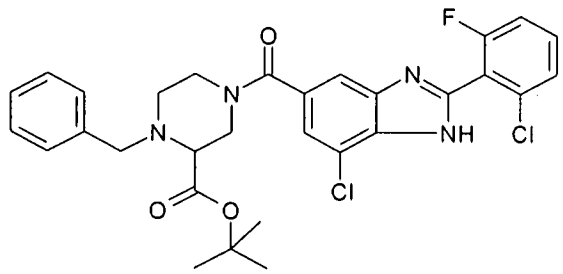


The title compound (0.05 g, 60 %) was prepared from 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid methyl ester(0.09 g, 0.19 mmol) in a manner similar to Example 147.

^{1}H NMR ((DMSO-d_6, 300MHz) : δ(ppm) 8.10- 7.46 (m, 5H) 4.64-4.57 (m, 1H)

2.72- 2.48 (m, 4H) 2.05 (s, 3H)

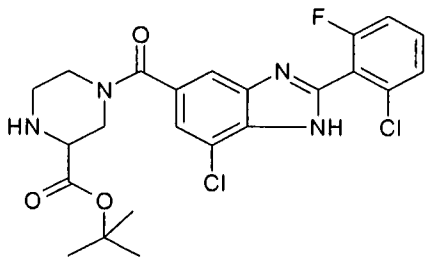
Example 160: Preparation of 4-benzyl-1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperazine-2-carboxylic acid tert-butyl ester



The title compound (0.19 g, 45 %) was prepared from 4-benzyl-piperazine-2-carboxylic acid tert-butyl ester (0.20 g, 0.72mmol) in a manner similar to Example 138 Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.75-7.32 (m, 10H) 4.98 (s, 2H) 3.00-2.21 (m, 7H) 1.37 (s, 9H)

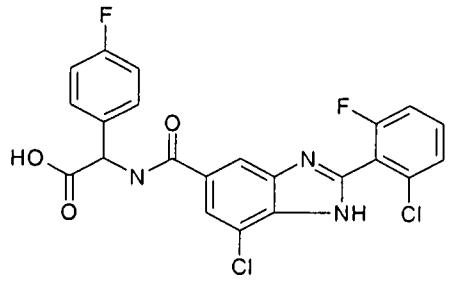
Example 161: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperazine-2-carboxylic acid tert-butyl ester



A solution of 4-benzyl-1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperazine-2-carboxylic acid tert-butyl ester(0.16 g, 0.27 mmol) in MeOH + THF and added Pd-C (10 mol%). The mixture is subsequently hydrogenated at 40 psi an hydrogen pressure for 20h. The mixture was filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound: 0.04 g (30 %).

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.75-7.32 (m, 5H) 3.00-2.21 (m, 7H) 1.37 (s, 9H)

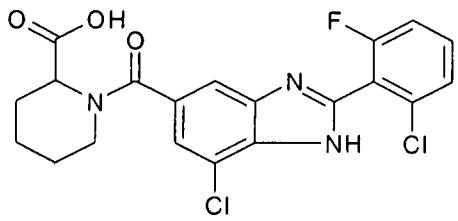
Example 162: Preparation of {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-fluoro-phenyl)-acetic acid



The title compound (0.07 g, 80 %) was prepared from {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-(1H-imidazole-4-yl) propionic acid methyl ester (0.10 g, 0.20 mmol) in a manner similar to Example 147.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.15-7.27 (m, 9H) 5.73 (d, 1H, J=6.89 Hz)

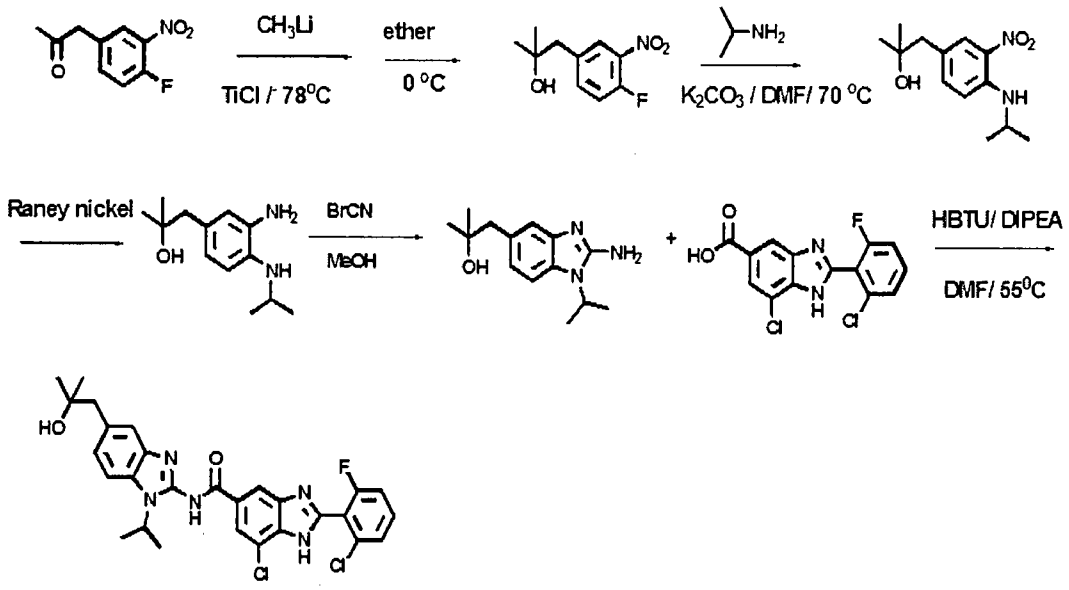
Example 163: Preparation of 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-2-carboxylic acid



The title compound (0.10 g, 75 %) was prepared from 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester (0.14 g, 0.31 mmol) in a manner similar to Example 147.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 7.72-7.31 (m, 5H) 5.20-5.16 (m, 1H) 3.20-3.00 (m, 2H) 2.38-2.19 (m, 2H) 1.72- 1.13 (m, 4H)

Example 164: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(2-hydroxy-2-methyl-propyl)-1-cyclopentyl-1H-benzimidazol-2-yl] –amide



Step 1: Preparation of 1-(4-fluoro-3-nitro-phenyl)-2-methyl-propan-2-ol

To a round flask at - 78℃ charged with $TiCl_4$ (1 M in CH_2Cl_2, 36 ml), was added methyllithium (1.6 M in diethyl ester, 22.8 ml). The resulting deep red solution was stirred at -78 ℃ for 15 min and then added via cannula to a 0 ℃ solution of 1-(4-Fluoro-3-nitro-phenyl)-propan-2-one (1.8g, 9.1 mmol) in diethyl ether (10 ml). The resulting mixture was stirred at 0 ℃ for 3h, then quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hex:EA=5:1) :1.20 g (63 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 7.95- 7.19 (m, 3H) 2.89 (s, 2H) 1.25 (s, 6H)

Step 2: Preparation of 1-(4-cyclopentylamino-3-nitro-phenyl)-2-methyl-propan-2-ol

A solution of 1-(4-fluoro-3-nitro-phenyl)-2-methyl-propan-2-ol (0.9 g, 4.22 mmol) in DMF were added K_2CO_3 (0.69g, 5.06 mmol), cychloropentylamine (0.5ml, 5.06 mmol). The mixture was stirred at 70 ℃ overnight and added water. The solution was extracted with ethylacetate and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on

silica gel (Hex:EA=5:1) to give the title compound: 1.09 g (85 %).

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 8.02 (s, 1H) 7.32 (d, 1H, J=8.80 Hz) 6.83 (d, 1H, J=8.80 Hz) 3.99-3.93 (m, 1H) 2.67 (s, 2H) 2.17-1.61 (m, 8H) 1.23 (s, 6H)

Step 3: Preparation of 1-(3-amino-4-cyclopentylamino-phenyl)-2-methyl-propan-2-ol

The title compound (0.70 g, 78 %) was prepared from 1-(4-cyclopentylamino-3-nitro-phenyl)-2-methyl-propan-2-ol (1.0 g, 3.59 mmol) in a manner similar to Example 138, Step 3.

^{1}H NMR ($CDCl_3$, 300MHz) : δ(ppm) 6.63 (s, 2H) 6.57 (s, 1H) 3.79-3.75 (m, 1H) 2.62 (s, 2H) 2.06-1.41 (m, 8H) 1.21 (s, 6H)

Step 4: Preparation of 1-(2-amino-1-cyclopentyl-1H-benzimidazol-5-yl)-2-methyl-propan-2-ol

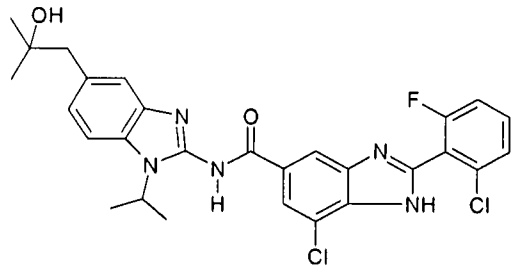
The title compound (0.15 g, 20 %) was prepared from 1-(3-amino-4-cyclopentylamino-phenyl)-2-methyl-propan-2-ol (0.70 g, 2.81 mmol) in a manner similar to Example 138, Step 4.

Step 5: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-5-(2-hydroxy-2-methyl-propyl)-1H-benzimidazol -2-yl] -amide

The title compound (0.06 g, 10 %) was prepared from 1-(2-amino-1-cyclopentyl-1H-benzimidazol-5-yl)-2-methyl-propan-2-ol (0.12 g, 0.43 mmol) in a manner similar to Example 138, Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.22-7.01 (m, 8H) 4.91-4.81 (n, 1H) 2.87 (s, 2H) 2.19-1.41 (m, 8H) 1.20 (s, 6H)

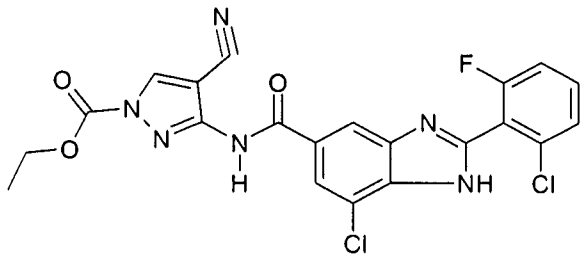
Example 165: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(2-hydroxy-2-methyl-propyl)-1-isopropyl-1H-benzimidazol-2-yl] –amide



The title compound (0.13 g, 40 %) was prepared from 1-(2-amino-1-isopropyl-1H-benzimidazole-5-yl)-2-methyl-propan-2-ol (0.15 g, 0.60 mmol) in a manner similar to Example 138.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.40- 7.46 (m, 8H) 5.30-5.28 (m, 1H) 2.68 (s, 2H) 1.63 (d, 6H, J=6.75 Hz) 1.08 (s, 6H)

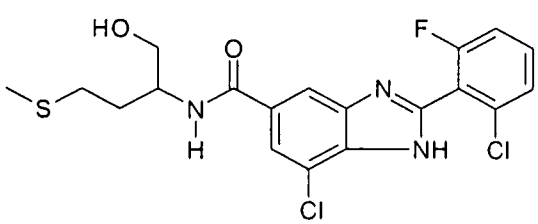
Example 166: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [4-cyano-1-(2-oxo-butyl)-1H-pyrazol-3-yl]-amide



The title compound (0.01 g, 7 %) was prepared from 3-amino-1-(2-oxo-butyl)-1H-pyrazole-4-carbonitrile (0.05 g, 0.30 mmol) in a manner similar to Example 138 Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) : 8.27- 6.90 (m, 6H) 4.12 (q, 2H, J=8.32 Hz) 1.32 (t, 3H, J=8.32 Hz)

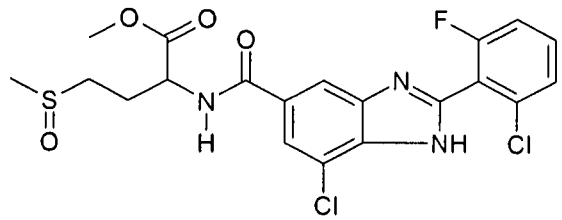
Example 167: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-hydroxymethyl-3-methylsulfanyl-propyl)-amide



The title compound (0.25 g, 38 %) was prepared from L-methioninol (0.20 g, 1.47 mmol) in a manner similar to Example 138 Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.29- 7.47 (m, 5H) 4.79 (t, 1H, J=5.87 Hz) 4.08-4.01 (m, 2H) 3.52-3.39 (m, 2H) 2.05 (s, 3H) 1.98-1.75 (m, 2H)

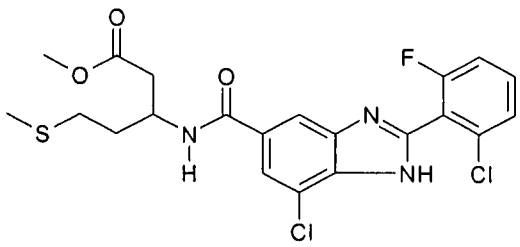
Example 168: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methanesulfinyl-butyric acid methyl ester



The title compound (0.08 g, 23 %) was prepared from 2-amino-4-methanesulfinyl-butyric acid methyl ester (0.13 g, 0.72 mmol) in a manner similar to Example 138 Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 9.02-7.47 (m, 5H) 4.63-4.58 (m, 1H) 3.69 (s, 3H) 2.89-2.69 (m, 2H) 2.50 (s, 3H) 2.28-2.18 (m, 2H)

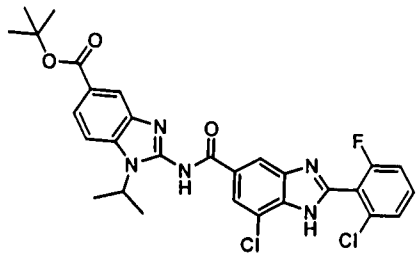
Example 169: Preparation of 3-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-5-methylsulfanyl-pentanoic acid methyl ester



The title compound (0.17 g, 49 %) was prepared from 3-amino-5-methylsulfanyl-pentanoic acid methyl ester (0.21 g, 1.18mmol) in a manner similar to Example 138 Step 5.

^{1}H NMR (DMSO-d_6, 300MHz) : δ(ppm) 8.48-7.48 (m,5H) 4.44-4.3. (m, 1H) 3.57 (s, 3H) 2.78-2.60 (m, 4H) 2.04 (s, 3H) 1.98-1.84 (m, 2H)

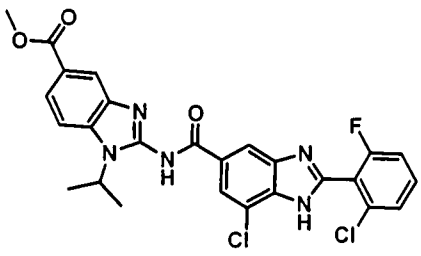
Example 170: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid tert-butyl ester



To a solution of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (0.2 g, 0.61 mmol) in DMF(10 ml) was added DIPEA (0.42 ml, 2.57 mmol) and O-benzotriazole-N,N,N',N'-tetramethyl uranium hexafluoro phosphate (0.25 g, 0.67 mmol). The mixture was stirred for 30 minutes at room temperature, then 2-amino-1-isopropyl-1H-benzimidazole-5-carboxylic acid tert-butyl ester (0.15 g, 0.56 mmol) was added. This reaction mixture was stirred overnight at room temperature, then the solvent was evaporated, and the residue stirred with sat-K_2CO_3(aq) solution was added, and the mixture was then extracted with ethylacetate. The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel column eluted with ethyl acetate/hexane (1/1) to give the title compound (0.18 g, 56 %) as a brown solid.

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.67 (s, 1H), 8.33-8.34 (m, 1H), 7.92-7.80 (m, 2H), 7.43 (d,J=9Hz, 1H), 7.24-7.36 (m, 1H), 7.18 (d,J=8.1Hz, 1H), 6.99 (t,J=8.4Hz, 1H), 5.32-5.41 (m, 1H), 1.68 (d,J=7.2Hz, 6H), 1.60 (s,9H)

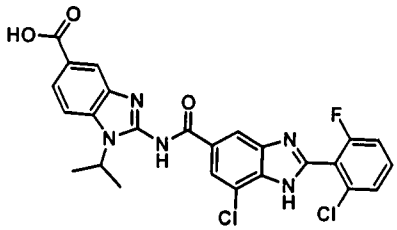
Example 171: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid methyl ester



The title compound (0.49 g, 65%) was obtained using the method described in Example 170, using 2-amino-1-isopropyl-1H-benzimidazole-5-carboxylic acid methyl ester.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.66 (s, 1H), 8.34 (d,J=1.2Hz, 1H), 7.96-8.03 (m,2H), 7.45 (d,J=8.4Hz, 1H), 7.28-7.35 (m, 1H), 7.18 (d,J=8.1z,1H), 6.99 (t,J=8.4Hz, 1H), 5.32-5.42 (m, 1H), 3.91 (s,3H), 1.69 (d,J=7.2Hz, 6H)

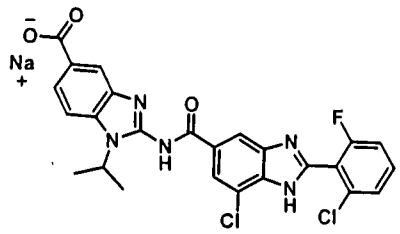
Example 172: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid



2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid methyl ester (0.45 g, 0.83 mmol) was dissolved in THF/MeOH (2/1)(15 ml) and added NaOH (0.16 g, 4.16 mmol). The reaction mixture was stirred at 50℃ for 8hr and cooled to room temperature. The reaction mixture was acidified with 1N HCl and evaporated. The reaction mixture was extracted with dichloromethane and the organic layer were dried (Na_2SO_4), filtered and the solvent was removed in vacuo to give the title compound (0.37 g, 85 %).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.63 (s, 1H), 8.46 (s, 1H), 8.36 (s, 1H), 8.15 (d, J=8.4Hz, 1H), 7.70-8.00 (m, 2H), 7.65 (d, J=8.1Hz, 1H), 7.48-7.60 (m, 1H), 5.31-5.38 (m, 1H), 1.80 (d, J=6.9Hz, 6H)

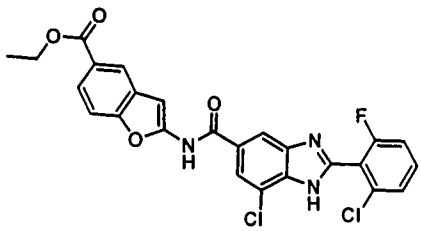
Example 173: Preparation of Sodium 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylate



2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-isopropyl-1H-benzimidazole-5-carboxylic acid (0.05 g, 0.095 mmol) was dissolved in methanol and added NaOH (0.004g, 0.095 mmol). The reaction mixture was stirred at room temperature for 10 hr and evaporated to give the title compound (0.05 g, 100 %).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.56 (s, 1H), 8.31 (s, 1H), 8.14 (s, 1H), 7.95 (d, J=8.1Hz, 1H), 7.56-7.69 (m, 3H), 7.46-7.54 (m, 1H), 7.24-7.40 (m, 2H), 5.38-5.42 (m, 1H), 1.75 (d, J=6.9Hz, 6H)

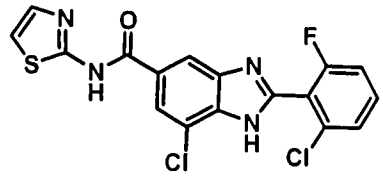
Example 174: Preparation of 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-benzofuran-5-carboxylic acid ethyl ester



The title compound (0.22 g, 40%) was obtained using the method described in Example 170, using 2-amino-benzofuran-5-carboxylic acid ethyl ester.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.26 (s, 1H), 8.20 (d, J=1.8Hz, 1H), 8.01 (s, 1H), 7.75 (dd, J1=1.5Hz, J2=8.7Hz, 1H), 7.60-7.65 (m, 3H), 7.51 (d, J=8.1Hz, 1H), 7.35 (t, J=8.7Hz, 1H), 4.42 (q, J=7.5Hz, 2H), 1.41 (t, J=7.2Hz, 3H)

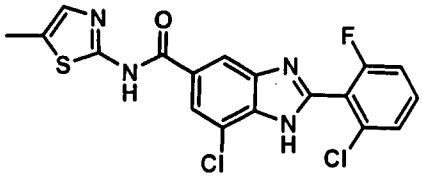
Example 175: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid thiazol-2-ylamide



The title compound (0.17 g, 70%) was obtained using the method described in Example 170, using thiazol-2-ylamine

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.28-8.50 (brs, 1H), 8.06 (s, 1H), 7.59-7.70 (m, 1H), 7.42-7.51 (m, 2H), 7.33 (t, J=9Hz, 1H), 7.16 (d, J=3.9Hz, 1H)

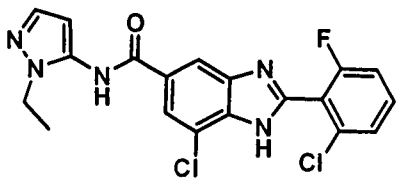
Example 176: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (5-methyl-thiazol-2-yl)-amide



The title compound (0.07 g, 27%) was obtained using the method described in Example 170, using 5-methyl-thiazol-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.30 (s, 1H), 8.03 (s, 1H), 7.33-7.86 (m, 3H), 7.14 (s, 1H), 2.41 (s, 3H)

Example 177: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide

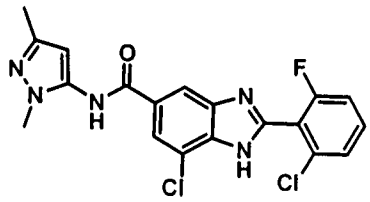


The title compound (0.017 g, 10%) was obtained using the method described in Example 170, using 2-ethyl-2H-pyrazol-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.27(s, 1H),8.01(s, 1H),7.60-7.68(m, 1H),7.38-7.52(m,2H),7.35(t,J=9Hz, 1H),6.30(d,J=1.8Hz, 1H),4.13(q,J=7.5Hz,

2H),1.43(t,J=7.2Hz, 3H)

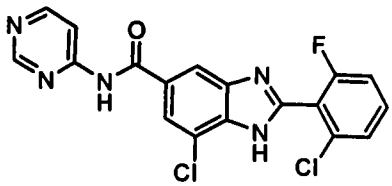
Example 178: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide



The title compound (0.1 g, 49%) was obtained using the method described in Example 170, using 2,5-dimethyl-2H-pyrazol-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.27(s, 1H), 8.00(s, 1H), 7.61-7.67(m, 1H), 7.50(d,J=8.1Hz, 1H), 7.36(t,J=9Hz, 1H), 6.10(s, 1H), 3.71(s,3H), 2.22(s,3H)

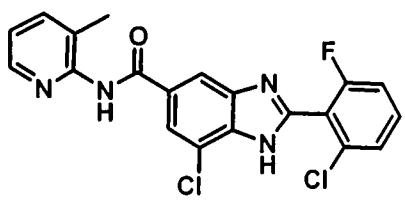
Example 179: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid pyrimidin-4-ylamide



The title compound (0.02 g, 13%) was obtained using the method described in Example 170, using pyrimidin-4-ylamine.

^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 8.89(s, 1H), 8.67(d,J=5.7Hz, 1H), 8.36(dd, J1=1.2Hz, J2=9Hz, 1H), 8.30(brs, 1H), 8.02(s, 1H), 7.60-7.71(m, 1H), 7.50(d,J=8.1Hz, 1H), 7.35(t,J=9Hz, 1H)

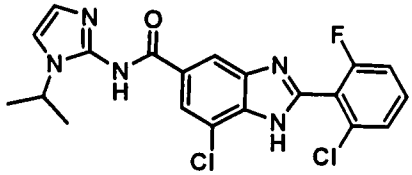
Example 180: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (3-methyl-pyridin-2-yl)-amide



The title compound (0.062 g, 39%) was obtained using the method described in Example 170, using 3-methyl-pyridin-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm)8.14-8.30(m, 1H), 7.95(s, 1H), 7.73(d,J=7.8Hz, 1H), 7.51-7.58(m, 1H), 7.42(d,J=8.1Hz, 1H), 7.22-7.29(m, 1H), 2.26(s,3H)

Example 181: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-imidazol-2-yl)-amide



Step 1: Preparation of 1-isopropyl-2-nitro-1H-imidazole

2-iodopropane (0.86 ml, 8.62 mmol) and K_2CO_3 (2.04 g, 14.77 mmol) were added to solution of 2-nitroimidazole (0.55 g, 4.92 mmol) in DMF (10 ml). The reaction mixture was stirred at 60℃ for 5hr. The reaction mixture was cooled to room temperature and water was added. The reaction mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtered and the solvent was removed in vacuo to give 1-isopropyl-2-nitro-1H-imidazole (0.76 g, 100%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) 6.73 (s, 1H), 6.56 (s, 1H), 4.22-4.30 (m, 1H), 1.35 (d, J=6.6Hz, 6H)

Step 2: Preparation of 1-isopropyl-1H-imidazole-2-ylamine

Ammonium hydroxide (3.54 ml) and 10% Pd/C (0.6 g) were added to solution of 1-isopropyl-2-nitro-1H-imidazole (1 g, 6.44 mmol) in methanol (60 ml). The reaction mixture was hydrogenated at an hydrogen pressure (80 psi), filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give 1-isopropyl-1H-imidazole-2-ylamine(0.87 g, 100 %).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 6.73 (s, 1H), 6.56 (s, 1H), 4.22-4.30 (m,

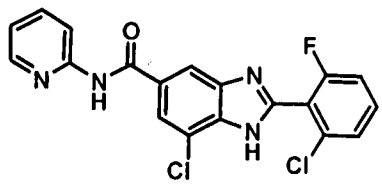
1H), 1.35 (d,J=6.6Hz, 6H)

Step 3: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-imidazol-2-yl)-amide

The title compound (0.16 g, 34%) was obtained using the method described in Example 170, using 1-isopropyl-1H-imidazole-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.39 (brs, 1H), 8.22 (s, 1H), 7.58-7.65 (m, 1H), 7.48 (d,J=8.1Hz, 1H), 7.33 (t,J=8.7Hz, 1H), 6.95 (s, 1H), 7.09 (s, 1H), 4.89-5.00 (m, 1H), 1.49 (d,J=6.9Hz, 6H)

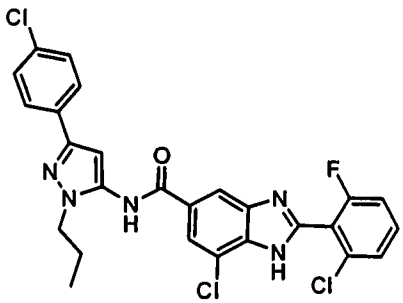
Example 182: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid pyridin-2-ylamide



The title compound (0.07 g, 36%) was obtained using the method described in Example 170, using pyridin-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.36-8.38 (m, 1H), 8.28 (brs, 1H), 8.23 (d, J=8.4Hz, 1H), 8.02 (s, 1H), 7.82-7.88 (m, 1H), 7.60-7.67 (m, 1H), 7.50 (d, J=8.1Hz, 1H), 7.35 (t, J=9Hz, 1H), 7.18 (dd, J1=4.8Hz, J2=8.4Hz, 1H)

Example 183: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole -5-carboxylic acid [5-(4-chloro-phenyl)-2-propyl-2H-pyrazol-3-yl] -amide



Step 1: Preparation of 4-amino-3-chloro-N-[5-(4-chlorophenyl)-2-propyl-2H-pyrazole-3-yl]-5-nitrobenzamide

To a solution of 4-amino-3-chloro-5-nitro-benzoic acid (0.57 g, 2.65 mmol) in DMF (10 ml) were added 5-(4-chlorophenyl)-2-propyl-2H-pyrazole-3-ylamine (0.33 g, 1.32 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.5 g, 2.64 mmol), 1-hydroxybenzotriazole hydrate (0.35 g, 2.64 mmol), 4-methylmorpholine (2.9 ml, 26.4 mmol). The reaction mixture was stirred at 60℃ overnight, quenched with water and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by chromatography on silica gel column eluted with 50% hexane/ethyl acetate to give the title compound (0.41 g, 71%).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.81 (d, J=2.1Hz, 1H), 8.21 (d, J=2.16Hz, 1H), 7.74 (d, J=8.6Hz, 2H), 7.39 (d, J=8.6Hz, 2H), 6.61 (s, 1H), 4.02-4.10 (m, 2H), 1.85-1.92 (m, 2H), 0.89-0.94 (m, 3H)

Step 2: Preparation of 3,4-diamino-5-chloro-N-[5-(4-chlorophenyl)-2-propyl-2H-pyrazole-3-yl]benzamide

10% Pd/C (0.04 g) was added to solution of 4-amino-3-chloro-N-[5-(4-chlorophenyl)-2-propyl-2H-pyrazole-3-yl]-5-nitrobenzamide (0.41 g, 0.94 mmol) in ethanol (10 ml). The reaction mixture was hydrogenated at an hydrogen pressure (10psi), filtered through celite and the bed washed with methanol. The organic layer was concentrated in vacuo to give the title compound (0.15 g, 39%).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ(ppm) 7.83 (s, 1H), 7.66 (d, J=8.7Hz, 2H), 7.29-7.33 (m, 2H), 7.11 (d, J=2.1Hz, 1H), 6.50 (s, 1H), 3.96 (t, J=7.2Hz, 2H), 1.88 (q, J=7.2Hz, 2H), 0.91 (t, J=7.5Hz, 3H)

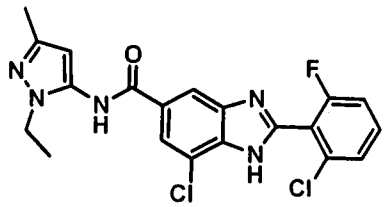
Step 3: Preparation of 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-chlorophenyl)-2-propyl-2H-pyrazole-3-yl]-amide

To a solution of 3,4-diamino-5-chloro-N-[5-(4-chlorophenyl)-2-propyl-2H-

pyrazole-3-yl]benzamide (0.15 g, 0.37 mmol) in DMF, 2-chloro-6-fluorobenzaldehyde (0.06 g, 0.41 mmol) was added followed by oxone (0.15 g, 0.24 mmol). The mixture was stirred for 1 h at room temperature and then added dropwise with vigorous stirring into a mixture of 1M K_2CO_3 and H_2O. The precipitate was extracted with ethyl acetate, and the extract was washed successively with H_2O and brine. After drying over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude residue was purified by chromatography on silica gel column eluted with 50% hexane/ethyl acetate to give the title compound (0.08 g, 39%).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.30 (s, 1H), 8.03 (d,J=1.2Hz, 1H), 7.79 (d,J=8.7Hz, 2H), 7.61-7.66 (m, 1H), 7.52 (d,J=8.4Hz, 1H), 7.40 (d,J=8.7Hz, 2H), 7.35 (d,J=8.1Hz, 1H), 6.69 (s, 1H), 4.12 (t,J=6.9Hz, 2H), 1.88-2.00 (m,2H), 0.96 (t,J=7.5Hz, 3H)

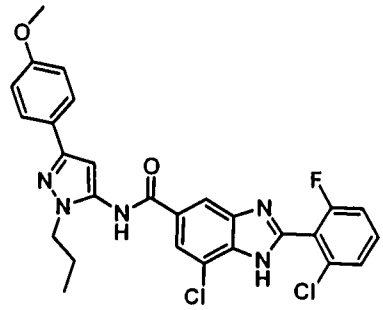
Example 184: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-ethyl-5-methyl-2H-pyrazol-3-yl)-amide



The title compound (0.032 g, 16%) was obtained using the method described in Example 170, using 2-ethyl-5-methyl-2H-pyrazole-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.28(s, 1H),8.01(d,J=1.2Hz, 1H),7.64-7.69(m, 1H),7.52(d,J=8.1Hz, 1H),7.36(t,J=8.1Hz, 1H),6.11(s, 1H),4.05-4.12(m,2H),2.27(s,3H),1.41(t,J=7.2Hz, 3H)

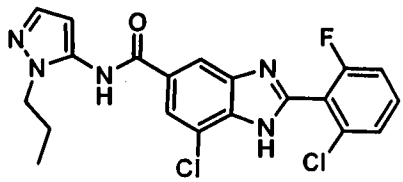
Example 185: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-methoxy-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide



The title compound (0.005 g, 25%) was obtained using the method described in Example 183, Step 3, using 3,4-diamino-5-chloro-N-[5-(4-methoxyphenyl)-2-propyl-2H-pyrazole-3-yl]benzamide.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.31(brs, 1H), 8.04(d,J=1.5Hz, 1H), 7.73(d,J=8.7Hz, 2H), 7.60-7.69(m, 1H), 7.53(d,J=8.4Hz, 1H), 7.32-7.43(m, 1H), 7.00(d,J=8.7Hz, 2H), 6.60(s, 1H), 4.07-4.15(m,2H), 3.84(s,3H), 1.90-1.97(m,2H), 0.93-1.00(m,3H)

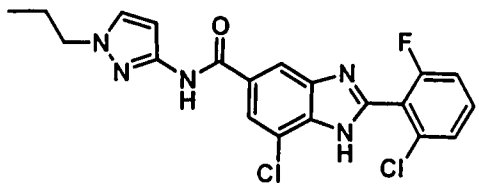
Example 186: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-propyl-2H-pyrazol-3-yl)-amide



The title compound (0.19 g, 39%) was obtained using the method described in Example 170, using 2-propyl-2H-pyrazol-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.19-8.34(m, brd, 1H), 8.00(s, 1H), 7.51-7.66(m, 3H), 7.36(t,J=9Hz, 1H), 6.65(d,J=2.1Hz, 1H), 4.07(t,J=6.9Hz, 2H), 1.88(q,J=6.9Hz, 2H), 0.93(t,J=7.2Hz, 3H)

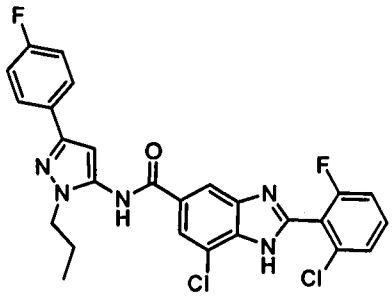
Example 187: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-propyl-1H-pyrazol-3-yl)-amide



The title compound (0.04 g, 9%) was obtained using the method described in Example 170, using 2-propyl-1H-pyrazol-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.24-8.38(m, brd, 1H), 7.90-7.95(m, 1H), 7.67-7.90(m, 1H), 7.57-7.67(m, 1H), 7.51(d,J=8.4Hz, 1H), 7.32-7.38(m, 1H), 6.66(d,J=2.1Hz, 1H), 4.07(t,J=6.9Hz, 2H), 1.90(q,J=7.2Hz, 2H), 0.93(t,J=7.5Hz, 3H)

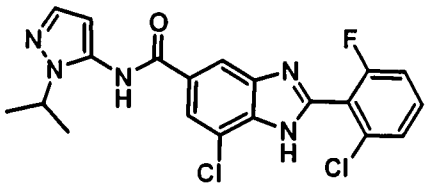
Example 188: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-fluoro-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide



The title compound (0.027 g, 36%) was obtained using the method described in Example 183, Step 3 using 3,4-diamino-5-chloro-N-[5-(4-fluorophenyl)-2-propyl-2H-pyrazole-3-yl]benzamide.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.20-8.40 (brd,1H), 8.03 (d,J=1.2Hz, 1H), 7.80-7.84 (m,2H), 7.62-7.67 (m, 1H), 7.53 (d,J=8.1Hz, 1H), 7.37 (t,J=9Hz, 1H), 7.12-7.18 (m, 1H), 6.66 (s, 1H), 4.12 (t,J=6.9Hz, 2H), 1.93 (q,J=7.59Hz, 2H), 0.97 (t,J=7.5Hz, 3H)

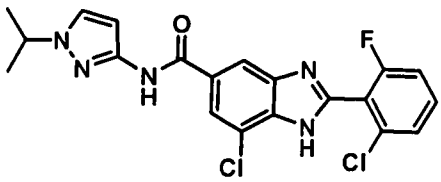
Example 189: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-isopropyl-2H-pyrazol-3-yl)-amide



The title compound (0.11 g, 30%) was obtained using the method described in Example 170, using 2-isopropyl-2H-pyrazol-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.25(s, 1H), 8.00(d,J=1.2Hz, 1H), 7.61-7.66(m, 1H), 7.52(d,J=8.1Hz, 1H), 7.36(t,J=8.1Hz, 1H), 6.65(d,J=2.4Hz, 1H), 4.45-4.50(m, 1H), 1.51(d,J=6.6Hz, 6H)

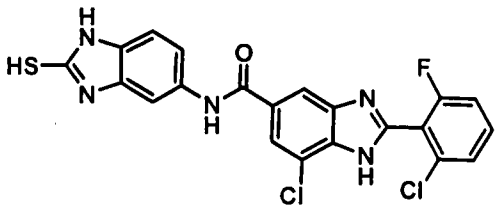
Example 190: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-pyrazol-3-yl)-amide



The title compound (0.04 g, 12%) was obtained using the method described in Example 170, using 2-isopropyl-1H-pyrazol-3-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.34(s, 1H), 7.97(d,J=8.4Hz, 1H), 7.75(brd,2H), 7.58-7.66(m, 1H), 7.50(d,J=8.1Hz, 1H), 7.31-7.37(m, 1H), 6.66(d,J=2.1Hz, 1H), 4.45-4.50(m, 1H), 1.51(d,J=6.6Hz, 6H)

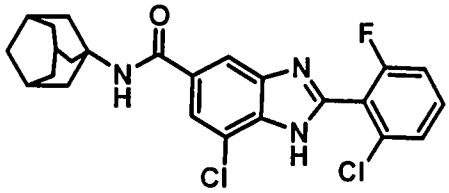
Example 191: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-mercapto-1H-benzimidazol-5-yl)-amide



The title compound (0.11 g, 39%) was obtained using the method described in Example 170, using 5-amino-1H-benzimidazole-2-thiol.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 6.96 (s, 1H), 6.71 (d, J=1.05Hz, 1H), 6.52 (d, J=1.8Hz, 1H), 6.31-6.36 (m, 1H), 6.22 (d, J=8.1Hz, 1H), 6.13 (dd, J1=1.8Hz, J2=8.5Hz, 1H), 6.03-6.08 (m, 1H), 5.92 (d, J=8.6Hz, 1H)

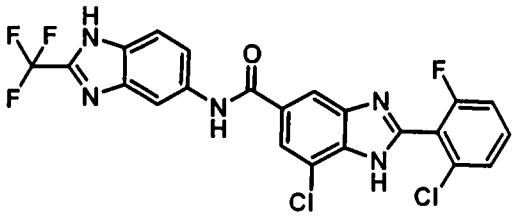
Example 192: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid adamantan-1-ylamide



The title compound (0.12 g, 90%) was obtained using the method described in Example 170, using adamantan-1-ylamine (0.038 g, 0.26 mmol).

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.00 (s, 1H), 7.80 (s, 1H), 7.60-7.22 (m, 1H), 7.52 (d, J=8.1Hz, 1H), 7.34-7.43 (m, 1H), 2.22 (brs, 6H), 2.14 (brs, 3H), 1.80 (brs, 6H)

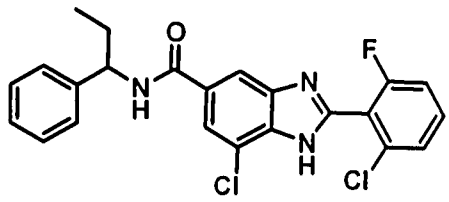
Example 193: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-trifluoromethyl-1H-benzimidazol-5-yl)-amide



The title compound (0.071 g, 55%) was obtained using the method described in Example 170, using 2-trifluoromethyl-1H-benzimidazol-5-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : δ(ppm) 8.34 (s, 1H), 8.29 (s, 1H), 8.04 (d, J=1.5Hz, 1H), 7.62-7.75 (m, 4H), 7.53 (d, J=8.1Hz, 1H), 7.37 (t, J=9Hz, 1H)

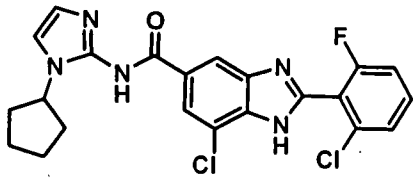
Example 194: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-phenyl-propyl)-amide



The title compound (0.15 g, 88%) was obtained using the method described in Example 170, using α-ethylbenzylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.20 (s, 1H), 7.98 (s, 1H), 7.28-7.65 (m, 8H), 5.20-5.28 (m, 1H), 1.80-2.00 (m, 2H), 0.80-1.00 (m, 3H)

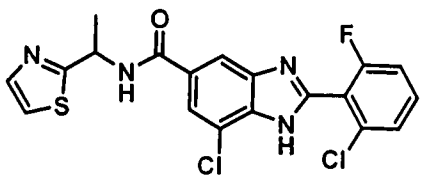
Example 195: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-1H-imidazol-2-yl)-amide



The title compound (0.099 g, 45%) was obtained using the method described in Example 170, using 1-cyclopentyl-1H-imidazol-2-ylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.36 (s, 1H), 8.23 (s, 1H), 7.5807.70 (m, 1H), 7.44-7.56 (m, 1H), 7.30-7.40 (m, 1H), 7.08 (s, 1H), 6.95-6.96 (m, 1H), 5.00-5.20 (m, 1H), 2.20-2.40 (m, 2H), 1.68-2.00 (m, 6H)

Example 196: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-thiazol-2-yl-ethyl)-amide

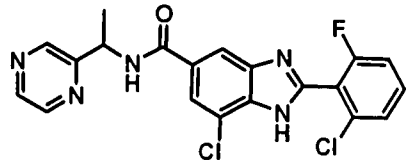


The title compound (0.11 g, 66%) was obtained using the method described in Example 170, using 1-thiazol-2-yl-ethylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.23-8.29 (m, 1H), 7.95 (s, 1H), 7.77 (d, J=3.3Hz,

1H), 7.61-7.67 (m, 1H), 7.50-7.53 (m, 1H), 7.50-7.53 (m, 2H), 7.36 (t, J=8.1Hz, 1H), 5.61 (q, J=6.9Hz, 1H), 1.76 (d, J=7.2Hz, 3H)

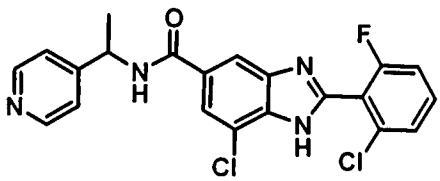
Example 197: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide



The title compound (0.09 g, 54%) was obtained using the method described in Example 170, using 1-pyrazin-2-yl-ethylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.73 (s, 1H), 8.61 (s, 1H), 8.50 (d, J=2.4Hz, 1H), 8.19 (brs, 1H), 7.93 (s, 1H), 7.59-7.66 (m, 1H), 7.49 (d, J=8.4Hz, 1H), 7.33 (t, J=8.7Hz, 1H), 5.35-5.42 (m, 1H), 1.68 (d, J=7.2Hz, 3H)

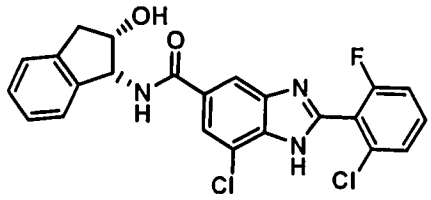
Example 198: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-pyridin-4-yl-ethyl)-amide



The title compound (0.16 g, 65%) was obtained using the method described in Example 170, using 1-pyridin-4-yl-ethylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.51 (d, J=6Hz, 2H), 8.19 (brs, 1H), 7.94 (d, J=1.2Hz, 1H), 7.60-7.67 (m, 1H), 7.48-7.51 (m, 3H), 7.34 (t, J=8.7Hz, 1H), 5.27 (q, J=6.9Hz, 1H), 1.63 (d, J=7.2Hz, 3H)

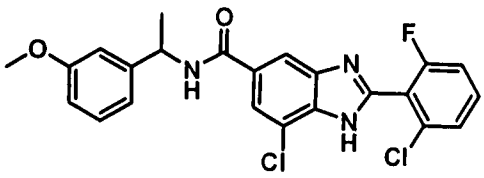
Example 199: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-indan-1-yl)-amide



The title compound (0.16 g, 90%) was obtained using the method described in Example 170, using (1S,2R)-(-)-cis-1-amino-2-indanol .

^{1}H NMR (CD_3OD, 300 MHz) : 8.48 (d, J=8.4Hz, 1H), 8.23 (s, 1H), 7.99 (d, J=1.2Hz, 1H), 7.60-7.70 (m, 1H), 7.51 (d, J=8.4Hz, 1H), 7.20-7.40 (m, 5H), 5.59-5.64 (m, 1H), 4.70-4.86 (m, 1H), 3.20-3.40 (m, 2H), 3.00-3.06 (m, 1H)

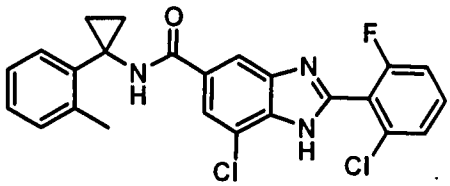
Example 200: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(3-methoxy-phenyl)-ethyl]-amide



The title compound (0.13 g, 74%) was obtained using the method described in Example 170, using 1-(3-methoxy-phenyl)-ethylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 8.96 (d, J=8.1Hz, 1H), 8.15 (s, 1H), 7.90-7.91 (m, 1H), 7.56-7.68 (m, 1H), 7.50 (d, J=8.4Hz, 1H), 7.21-7.40 (m, 2H), 6.98-7.40 (m, 2H), 6.79-6.84 (m, 1H), 5.20-5.30 (m, 1H), 3.80 (s, 3H), 1.60 (d, J=6.9Hz, 3H)

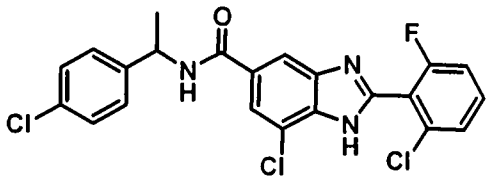
Example 201: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-o-tolyl-cyclopropyl)-amide



The title compound (0.07 g, 40%) was obtained using the method described in Example 170, using 1-(2-methylphenyl)-cyclopropanamine .

^{1}H NMR (CD_3OD, 300 MHz) : 9.20 (s, 1H), 8.04 (d, J=1.2Hz, 1H), 7.80 (d, J=1.2Hz, 1H), 7.59-7.72 (m, 2H), 7.46 (d, J=8.4Hz, 1H), 7.31 (t, J=9Hz, 1H), 7.11-7.14 (m, 3H), 2.60 (s, 3H), 1.18-1.34 (m, 4H)

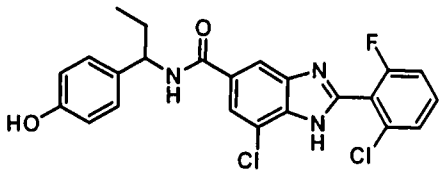
Example 202: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(4-chloro-phenyl)-ethyl]-amide



The title compound (0.1 g, 50%) was obtained using the method described in Example 170, using 1-(4-chloro-phenyl)-ethylamine.

^{1}H NMR (CD_3OD, 300 MHz) : 9.00 (d, J=7.5Hz, 1H), 8.16 (d, J=1.2Hz, 1H), 7.91 (d, J=1.2Hz, 1H), 7.55-7.68 (m, 1H), 7.48 (d, J=8.1Hz, 1H), 7.30-7.43 (m, 5H), 5.21-5.28 (m, 1H), 1.59 (d, J=7.2Hz, 3H)

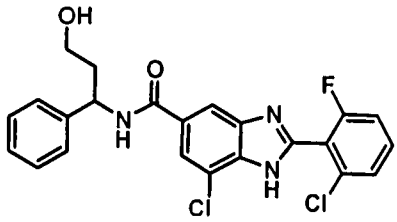
Example 203: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(4-hydroxy-phenyl)-propyl]-amide



The title compound (0.9 g, 50%) was obtained using the method described in Example 170, using 4-(1-aminopropyl)phenol hydochloride.

^{1}H NMR (CD_3OD, 300 MHz) : 8.84 (d, J=8.4Hz, 1H), 8.13 (s, 1H), 7.88 (d, J=1.2Hz, 1H), 7.50-7.64 (m, 1H), 7.46 (d, J=8.4Hz, 1H), 7.31 (t, J=8.7Hz, 1H), 7.25 (d, J=8.4Hz, 2H), 6.78 (d, J=8.4Hz, 2H), 4.80-5.01 (m, 1H), 1.80-2.01 (m, 2H), 0.98 (t, J=7.2Hz, 3H)

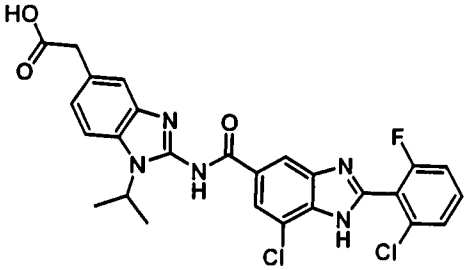
Example 204: Preparation of 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide



The title compound (0.03 g, 17%) was obtained using the method described in Example 170, using 3-amino-3-phenylpropan-1-ol.

^{1}H NMR (CD_3OD, 300 MHz) : 8.23 (s, 1H), 8.07 (s, 1H), 7.89 (d, J=1.2Hz, 1H), 7.63-7.71 (m, 1H), 7.40-7.60 (m, 3H), 7.20-7.41 (m, 4H), 5.30-5.35 (m, 1H), 3.63-3.71 (m, 2H), 2.11-2.20 (m, 2H)

Example 205: Preparation of (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid

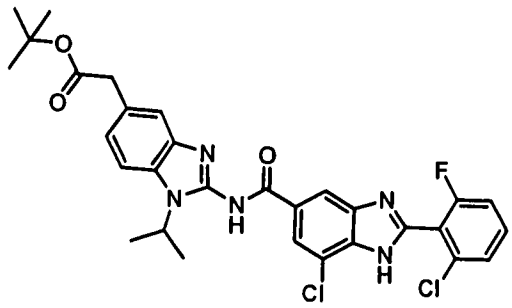


(2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid tert-butyl ester (0.15 g, 0.25 mmol) was dissolved in THF/MeOH (3/1) and added NaOH (0.1 g, 2.5 mmol). The reaction mixture was stirred at 60℃ for 10hr and cooled to room temperature. The reaction mixture was acidified with 1N HCl and evaporated. The reaction mixture was extracted with dichloromethane, dried (Na_2SO_4), filtered and evaporated. The crude residue was purified by chromatography on silica gel column eluted with 10% methanol/dichloromethane to give the title compound (0.08 g, 60%).

^{1}H NMR (CD_3OD, 300 MHz) : 8.40 (s, 1H), 8.20 (s, 1H), 7.33-7.68 (m, 4H), 7.24 (t, J=8.4Hz, 1H), 7.13 (d, J=8.7Hz, 1H), 5.25-5.30 (m, 1H), 3.60 (s, 2H), 1.62 (d, J=6.9Hz, 6H)

Example 206: Preparation of (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid

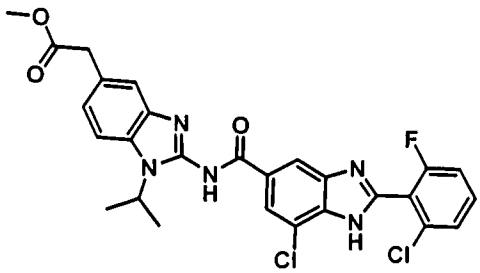
tert-butyl ester



The title compound (0.25 g, 15%) was obtained using the method described in Example 170, using (2-amino-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid tert-butyl ester.

^{1}H NMR (CD_3OD, 300 MHz) : 8.57 (s, 1H), 8.32 (s, 1H), 7.26-7.35 (m, 4H), 7.05-7.13 (m, 2H), 5.25-5.35 (m, 1H), 3.62 (s, 2H), 1.63 (d, J=6.9Hz, 6H), 1.45 (s, 9H)

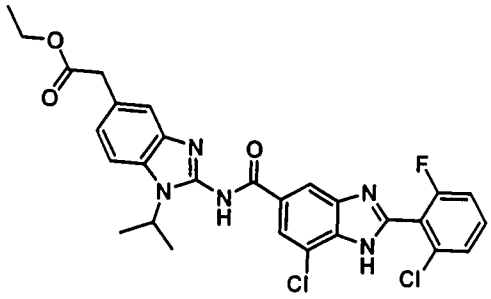
Example 207: Preparation of (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid methyl ester



The title compound (0.35 g, 74%) was obtained using the method described in Example 170, using (2-amino-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid methyl ester .

^{1}H NMR (CD_3OD, 300 MHz) : 8.60 (s, 1H), 8.31 (s, 1H), 7.34 (d, J=8.4Hz, 1H), 7.11-7.28 (m, 4H), 6.95 (t, J=8.4Hz, 1H), 5.27-5.36 (m, 1H), 3.70 (s, 5H), 1.63 (d, J=7.2Hz, 6H)

Example 208: Preparation of (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid ethyl ester



The title compound (0.35 g, 65%) was obtained using the method described in Example 170, using (2-amino-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid ethyl ester. ^{1}H NMR (CD_3OD, 300 MHz) : 8.50 (s, 1H), 8.32 (s, 1H), 7.48-7.65 (m, 4H), 7.36 (t, J=9Hz, 1H), 7.23 (d, J=8.4Hz, 1H), 5.38-5.42 (m, 1H), 4.18 (q, J=7.2Hz, 2H), 3.76 (s, 2H), 1.75 (d, J=7.2Hz, 6H), 1.27 (t, J=7.2Hz, 3H)

Test Example 1: mPGES-1 assay

Virus with human mPGES-1 cDNA plasmid was obtained by use of the transfection into insect cell, SF9 cells (invitrogen), according to manufacturer's instructions (Ouellet M, et al., Purification and characterization of recombinant microsomal prostaglandin E synthase-1, *Protein Expr Purif.*, 2002; 26: 489-495). 3 x10^5 cells/ml of insect High5 (invitrogen) were cultured to reach 2 x10^6 cells/ml at 27 ℃ in shaking incubator (85 rpm) for 48hr. The cells were infected with virus (5x10^8 pfu/ml) and incubated to express maximal mPGES-1 protein at 27 ℃ in shaking incubator (85rpm) for 48hr. After High 5 insect cells were homogenized using dounce homogenizer, the remaining cell debris were removed by further centrifugation and the microsome expressed human mPGES-1 were obtained.

To measure the inhibitory effects of compounds towards human mPGES-1, microsome (3ug/ml) were diluted in 100mM potasium phosphate (pH7.0), 2mM EDTA (ethylene-diamine tetraacetic acid) and 2.5mM reduced glutathione (GSH). 25ul microsome and compound in 3.7% (v/v) DMSO were prechilled on ice for 10 min. The reaction was initiated by the addition of 1ml PGH2 (1uM) diluted by isopropanol and incubated on ice for 10 min. The reaction was stopped by 12.5ul of 11mg/ml $SnCl_2$ in 1N HCl. The reactants were diluted 625-fold with assay buffer from PGE2 Enzyme Immunoassay (EIA) kit (Assay Designs). 100ul diluted reactants, PEG2 tracer and PEG2

antibody were added into the well in the assay plate and incubated at R.T. for 2 hr. After the incubation, the plates were washed and p-nitrophenylphosphate (p-NPP) was added. The absorbance for producing PGE2 was measured at 405nm. The inhibition of compound was determined by IC_{50} value. The results were shown in Table 1.

Test Example 2: mPGES-1 whole cell assay

We carried out the experiments both inhibition of PGE2 production and selectivity of PGF2a production in human A549 epithelial lung carcinoma cells. This assay was performed as reported previously (*Riendeau D, et al., Bioorg Med Chem Lett.*, 2005, 15: 3352-3355). It incubated in A549 cells with IL-1b for 12 hr for mPGES-1 specific expression. A549 cells were seeded in 96 well plates at a density of 25,000 cells/well and incubated for 20 hr in DMEM (Dulbeco's modified eagle's medium) medium supplemented with 2% fetal bovine serum (FBS). The cells were then incubated with 10 ng/ml IL-1b for 24 hr in the presence of a vehicle or inhibitors. A Negative control is the sample without IL-1b and positive control is with IL-1b and DMSO solution. After incubation with IL-1b or not inhibitor, 30ul of supernatants medium is used for PGE2 measurement and 90ul is for PGF2α. Concentrations of PGE2 and PGF2α, in the cell free medium were measured by EIA (Assay Designs Inc.). EC_{50} values of PGE2 were derived from inhibition of PGE2 production. The selectivity of mPGES-1 inhibitor was determined increase of PGF2α production. The results were shown in table 1.

<Table 1>

Example	IC_{50}(μM)	EC_{50}(μM)	Selectivity
1	0.37	0.61	x
2	0.14	0.65	o
6	0.29	0.30	x
7	0.25	0.80	o
9	0.91	1.0	o
10	0.70	2.0	o
18	0.12	0.51	o

19	0.11	0.30	x
27	1.2	5.8	o
29	0.90	20	o
33	0.23	0.60	x
38	0.36	2.6	o
43	0.70	0.82	x
44	0.35	0.65	x
45	0.12	10	o
49	0.60	1.3	x
53	0.58	3.0	x
54	0.75	>10	o
58	0.18	0.30	o
59	0.34	0.24	x
63	0.057	0.21	o
64	0.19	0.17	o
65	0.24	0.30	o
66	0.69	0.13	x
67	0.16	0.21	o
68	0.096	0.20	x
69	0.91	0.21	x
70	0.18	0.060	x
71	0.29	0.13	x
72	0.041	0.30	o
73	0.16	0.30	o
74	0.007	0.21	o
75	0.011	0.23	o
76	0.026	1.4	o
77	0.36	0.30	o
78	0.07	0.21	o
80	0.35	2.0	o
84	0.18	1.9	x
85	0.55	1.0	x

86	0.0075	0.24	o
87	0.081	0.14	x
88	0.44	0.24	x
90	0.080	2.0	o
91	0.21	0.65	o
100	0.20	0.045	x
101	0.033	0.43	o
102	0.096	0.59	o
103	0.017	0.34	o
104	0.23	0.23	o
105	0.21	0.30	o
106	0.042	2.4	o
107	0.048	0.28	o
108	0.012	0.21	o
109	0.0095	0.070	o
110	0.70	0.64	o
111	0.32	0.39	x
112	0.12	0.80	o
113	0.46	2.2	o
114	0.48	1.3	o
126	0.95	2.0	o
127	0.56	0.65	o
128	0.022	0.40	o
129	0.026	0.22	o
130	0.025	0.29	o
131	0.0078	0.50	o
132	0.29	5.9	o
133	0.0080	0.26	o
134	0.033	0.69	o
138	0.036	0.35	o
139	0.095	0.50	o
142	0.095	0.23	o

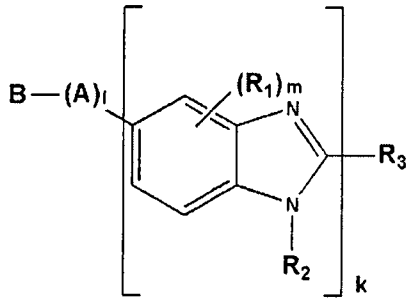
152	0.080	1.0	o
154	0.1	1.0	o
155	0.012	0.50	o
164	0.21	1.6	o
165	0.036	0.17	o
166	1.0	2.0	o
167	0.65	1.5	o
170	0.019	0.40	o
171	0.026	1.4	o
181	0.21	0.31	o
183	0.050	1.0	o
184	0.30	10	o
185	0.22	0.75	o
186	3.9	7.5	o
187	0.18	2.5	o
188	0.75	3.0	o
190	0.40	2.0	o
192	0.98	3.8	o
193	0.91	0.52	o
195	0.90	1.5	o

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

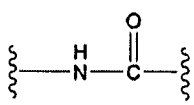
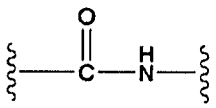
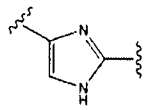
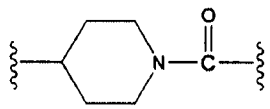
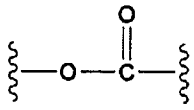
WHAT IS THE CLAIMED IS

1. A compound selected from the group consisting of a compound of formula 1 and a pharmaceutically acceptable salt, an isomer, a hydrate and a solvate thereof:

[Formula 1]



wherein

A is phenylene,  ,  ,  ,  or  ;

B is C_1-C_5 alkyl, C_2-C_6 alkynyl, C_6-C_{12} aryl, C_2-C_{13} heteroaryl, C_3-C_{13} heterocycloalkyl, sulfonyl or aminocarbonyl, wherein said alkyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, sulfonyl and aminocarbonyl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy) C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy, halo(C_1-C_5 alkyl)(C_6-C_{12} aryl) , C_1-C_5 alkylsulfonyl, C_6-C_{12} haloaryl and cyano, provided that, if k is 0, B is benzimidazolyl optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy)C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5

alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkloxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

k is 0 or 1;

l is 0 or 1;

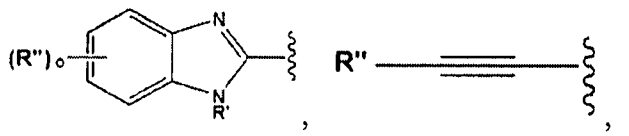
m is an integer ranging from 0 to 3;

R_1 is each independently halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy or carboxyl;

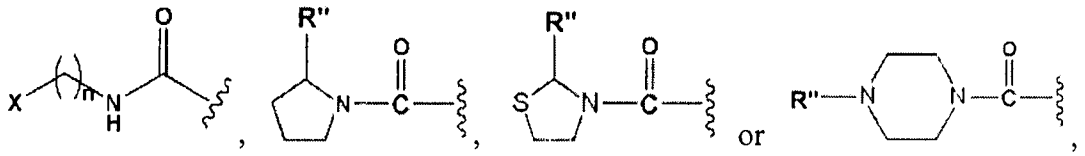
R_2 is hydrogen or C_1-C_5 alkyl; and

R_3 is amino, C_6-C_{12} aryl or C_2-C_{13} heteroaryl, wherein said amino, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, amino, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 haloalkoxy, halo(C_1-C_5 alkoxy)(C_6-C_{12} aryl) and C_6-C_{12} haloaryl.

2. The compound of claim 1, wherein B is



, R""'(SO$_2$)-,



wherein

R' is hydrogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl or (C_1-C_5 alkoxy)alkyl;

R" is each independently halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, hydroxyl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, (C_1-C_5 alkoxy) C_1-C_5 alkyl, C_1-C_5 hydroxyalkyl, hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy or halo(C_1-C_5 alkyl)(C_6-C_{12} aryl);

X is hydrogen; C_1-C_4 alkyl; C_1-C_4 alkyl optionally substituted with one or more substituents selected from the group consisting of (C_1-C_5 alkoxy)carbonyl, hydroxyl(C_6-C_{12} aryl), carboxyl, C_6-C_{12} aryl, halo C_6-C_{12} aryl, hydroxyl, C_1-C_3 alkylsulfanyl and C_2-C_{13} heteroaryl; C_3-C_8 cycloalkyl; naphthalenyl; C_6-C_{12} aryl; C_2-C_{13} heteroaryl; or C_2-C_{13} heteroaryl optionally substituted with one or more substituents selected from the group consisting of C_1-C_4 alkyl, hydroxyl(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, carboxyl, halo C_6-C_{12} aryl, C_1-C_5 alkoxy, thiol, halogen and C_6-C_{12} aryl;

n is an integer ranging from 0 to 3;

o is an integer ranging from 0 to 4; and

p is an integer ranging from 0 to 5.

3. The compound of claim 1, wherein R_1 is each independently chloro, bromo, methoxy, methyl or carboxyl.

4. The compound of claim 1, wherein R_2 is hydrogen or methyl.

5. The compound of claim 1, wherein R_3 is phenyl, imidazopyrindinyl, amino, or imidazolyl which is unsubstituted or substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, t-butyl, trifluoromethoxy and 2-chloro-6-fluorophenyl.

6. The compound of claim 1, wherein l is 0 or k is 0; and B is benzimidazolyl which is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy) C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

7. The compound of claim 1, which is selected from the group consisting of:

(1) 5-chloro-2-(2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-6-yl)-1H-benzo[d]imidazole;

(2) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]-5-trifluoromethyl-1H-benzo-[d]imidazole;

(3) 2'-(2-chloro-6-fluorophenyl)-1-chclohexyl-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(4) 2'-(2-chloro-6-fluorophenyl)-1-(1-ethylpropyl)-6-methyl-1H,1'H-[2,5'] bibenzimidazolyl;

(5) 1-butyl-2'-(2-chloro-6-fluorophenyl)-6-methyl-1H,1'H-

[2,5']bibenzimidazolyl;

(6) 2'-(2-bromophenyl)-5-chloro-1H,1'H-[2,5']bibenzimidazolyl;

(7) 2'-(2-bromophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(8) 2'-(2-bromophenyl)-1-(1-ethylpropyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(9) 2-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)benzonitrile;

(10) 2-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)benzonitrile;

(11) 2'-(4-tert-butylphenyl)-5-chloro-1H,1'H-[2,5']bibenzimidazolyl;

(12) 2'-(4-tert-butylphenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(13) 2'-(4-tert-butylphenyl)-1-cyclohexyl-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(14) 1-butyl-2'-(4-tert-butylphenyl)-6-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(15) 2'-(4-trifluoromethoxyphenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(16) 1-cyclohexyl-6-methyl-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl;

(17) 1-(1-ethylpropyl)-6-methyl-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl;

(18) 2'-(2-chloro-6-fluorophenyl)-5-iodo-1H,1'H-[2,5']bibenzimidazolyl;

(19) 2'-(2-bromophenyl)-5-iodo-1H,1'H-[2,5']bibenzimidazolyl;

(20) 5-iodo-2'-(4-trifluoromethoxyphenyl)-1H,1'H-[2,5']bibenzimidazolyl;

(21) (4-bromophenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(22) (4-trifluoromethoxyphenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(23) (4-tert-butylphenyl)-(5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(24) (4-tert-butylphenyl)-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(25) (5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)-(4-trifluoromethoxyphenyl)amine;

(26) (4-bromophenyl)-(5-chloro-1H,1'H-[2,5']bibenzimidazolyl-2'-yl)amine;

(27) 2'-(2-chloro-6-fluorophenyl)-6'-methyl-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(28) 2'-(2-chloro-6-fluorophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl-6'-carboxylic acid;

(29) 6'-bromo-2'-(2-chloro-6-fluorophenyl)-5-trifluoromethyl-1H,1'H-[2,5']bibenzimidazolyl;

(30) 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methyl-1H,1'H-[2,5']bibenzimidazolyl;

(31) 5-chloro-2'-(2-chloro-6-fluorophenyl)-1H,1'H-[2,5']bibenzimidazolyl-6'-carboxylic acid;

(32) 2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]phenyl}-5-trifluoromethyl-1H-benzo[d]imidazole;

(33) 5-chloro-2-{4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]phenyl}-1H-benzo[d]imidazole;

(34) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-chlorophenyl)-amide;

(35) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2-trifluoromethylphenyl)-amide;

(36) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (2,5-dichlorophenyl)-amide;

(37) 4-[2-(2-chloro-6-fluorophenyl)-1H-benzo[d]imidazol-5-yl]-2-methyl-3-butyn-2-ol;

(38) 2-(2-chloro-6-fluorophenyl)-5-(4-trifluoromethylphenylethynyl)-1H-benzimidazole;

(39) 2-chloro-N-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]-benzoamide;

(40) 2'-(2-chloro-6-fluorophenyl)-5-methoxy-1,6'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(41) 2'-(2-chloro-6-fluorophenyl)-1,5,6'-trimethy-1H,1'H-[2,5']bibenzimidazolyl;

(42) 5-chloro-2'-(2-chloro-6-fluorophenyl)-1,6'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(43) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)amide;

(44) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)amide;

(45) 1-cyclohexyl-6-methyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide;

(46) 1-methyl-5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide;

(47) 1-(1-ethylpropyl)-6-methyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-flurophenyl)-1H-benzimidazol-5-yl]amide;

(48) 5-triofluoromethyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1-methyl-1H-benzimidazol-5-yl]amide;

(49) 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]amide;

(50) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester;

(51) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-ylcarbamoyl]-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid;

(52) benzene-1,2-disulfonic acid 1-amide 2-{[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]amide};

(53) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester;

(54) benzene-1,2-disulfonic acid 1-amide 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amide};

(55) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid;

(56) 2-{[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(57) 2-[2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-ylcarbamoyl]-1H-benzimidazole-5-carboxylic acid methyl ester;

(58) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]amino}-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester;

(59) 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(60) 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]amino}-1-methyl-1H-benzimidazol-5-carboxylic acid methyl ester;

(61) 2-{[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carbonyl]-

amino}-1-(2-methoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester;

(62) 2-{[2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carbonyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(63) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(64) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(65) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(66) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(67) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazol-2-yl)-amide;

(68) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(69) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(70) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(71) 2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(72) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(73) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(74) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(75) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(76) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-iodo-1H-benzimidazol-2-yl)-amide;

(77) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-propyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(78) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (1-cyclohexyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(79) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid [1-(2-methoxyethyl)-5-trifluoromethyl-1H-benzimidazol-2-yl]-amide;

(80) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-(3-hydroxy-3-methyl-1-butynyl)-1H-benzimidazol-2-yl]-amide;

(81) 2-(2-chloro-6-fluorophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid (5-dimethylamino-1H-benzimidazol-2-yl)-amide;

(82) 2-(2-chloro-6-fluorpophenyl)-7-methyl-1H-benzimidazole-5-carboxylic acid [5-dimethylamino-1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-amide;

(83) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [6-methyl-1-(1-methyl-piperidin-4-yl)-1H-benzimidazol-2-yl]-amide;

(84) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [5-hydroxy-1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-amide;

(85) acetic acid 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-(2-methoxyethyl)-1H-benzimidazol-5-yl ester;

(86) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(87) 4-(2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-6-methyl-benzoimidzol-1-yl)-piperidine carboxylic acid ethyl ester;

(88) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [6-methyl-1-(2-morpholin-4-ylethyl)-1H-benzimidazol-2-yl]amide;

(89) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (6-methyl-1-piperidin-4-yl-1H-benzimidazol-2-yl)amide;

(90) 2'-(2-chloro-6-fluorophenyl)-7'-methyl-5-trifluoromethyl-1H,1'H-[2,5]bibenzimidazolyl;

(91) 5-chloro-2'-(2-chloro-6-fluorophenyl)-7'-methyl-1H,1'H-[2,5]-bibenzimidazolyl;

(92) 2'-(2-chloro-6-fluoro)-1-cyclohexyl-6,7'-dimethyl-1H,1'H-[2,5]-bibenzimidazolyl;

(93) 2'-(2-chloro-6-fluorophenyl)-5-methoxy-1,7'-dimethyl-1H,1'H-[2,5']bibenzimidazolyl;

(94) 5-chloro-2'-(2-chloro-6-fluorophenyl)-1,7'-dimethyl-1H,1'H-

[2,5']bibenzimidazolyl;

(95) 2-(2-chloro-6-fluorophenyl)-7-methyl-6-(5-trifluoromethyl-1H-benzimidazol-2-yl)-3H-imidazo[4,5-b]pyridine;

(96) 2'-(2-chloro-6-fluorophenyl)-6'-methoxy-5-trifluoromethyl-1H,1'H-[2,5]bibenzimidazolyl;

(97) 2'-(2-chloro-6-fluorophenyl)-6'-methoxy-1-methyl-5-methyl-1H,1'H-[2,5]bibenzimidazolyl;

(98) 5-chloro-2'-(2-chloro-6-fluorophenyl)-6'-methoxy-1-methyl-1H,1'H-[2,5]bibenzimidazolyl;

(99) 2-[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzoimidzol-5-ylcarbomyl]-1-methyl-1H-benzimidazole-5-carboxylic acid methyl ester;

(100) 5-trifluoromethyl-1H-benzimidazole-2-carboxylic acid-[2-(2-chloro-6-fluorophenyl)-7-methoxy-1H-benzimidazol-5-ylamide;

(101) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-propyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(102) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxyl acid [1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(103) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cycohexyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(104) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-carboxylic acid [5-dimethylamino-1-(2-methoxyethyl)-1H-benzimidazol-2-yl]-amide;

(105) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxyl]-amino}-1H-benzimidazole-5-carboxylic acid methyl ester;

(106) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(107) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid-(1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(108) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzoimdazole-5-carboxylic acid-(1-butyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(109) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid-(1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(110) 7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-(1-methyl-piperidin-4-yl)-6-methyl-1H-benzimidazol-2-yl)-amide;

(111) 7-chloro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(1-methyl-5-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(112) 7-choro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(1-cyclohexyl-6-methyl-1H-benzimidazol-2-yl)-amide;

(113) 7-chloro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(6-trifluoromethyl-1H-benzimidazol-2-yl)-amide;

(114) 7-chloro-2-(2-chloro-6-fluorophenyl)-6-methyl-1H-benzimidazole-5-carboxylic acid-(6-methyl-1H-benzimidazol-2-yl)-amide;

(115) 4-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino-piperidine-1-carboxylic acid tert-butyl ester;

(116) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid piperidin-4-ylamide;

(117) 2-(2-chloro-6-fluorophenyl)-6-methoxy-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole;

(118) 2-(2-chloro-6-fluorophenyl)-5-[4-(4-chlorophenyl)-1H-imidazol-2-yl]-6-methoxy-1H-benzimidazole;

(119) 2-(2-chloro-6-fluorophenyl)-6-methoxy-5-(4-phenyl-1H-imidazol-2-yl)-1H-benzimidazole;

(120) 2-(2-chloro-6-fluorophenyl)-5-(4-p-tolyl-1H-imidazol-2-yl)-1H-benzimidazole;

(121) 2-[3-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-yl]-3-(5-trifluoromethyl-benzimidazol-2-yl)-4-benzimidazole;

(122) 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazol-5-carbonyl]-piperidine-4-carboxylic acid butylamide;

(123) 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide;

(124) 1-[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide;

(125) 1-[7-bromo-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-piperidine-4-carboxylic acid cyclopentylamide;

(126) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-butyl-1H-benzimidazol-2-yl)-amide;

(127) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid

(1-iropropyl-1H-benzimidazol-2-yl)-amide;

(128) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-5-methoxy-1H-benzimidazol-2-yl)-amide;

(129) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-1-isopropyl-1H-benzimidazol-2-yl)-amide;

(130) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-hydroxyethoxy)-1H-benzimidazol-2-yl]-amide;

(131) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-6-(2-cyclopropylethoxy)-1H-benzimidazol-2-yl]-amide;

(132) 4-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-benzoic acid-tert-butyl ester;

(133) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-6-hydroxy-1H-benzimidazol-2-yl)amide;

(134) 7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)amide;

(135) 2-(2-chloro-6-fluorophenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-cyclopentyl-1H-benzimidazol-2-yl)amide;

(136) 2-(2-chloro-6-fluorophenyl)-1H-imidazole-4-carboxylic acid (6-benzyloxy-1-isopropyl-1H-benzimidazol-2-yl)amide;

(137) 2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-4-carboxylic acid [1-cyclopentyl-6-(2-hydroxy-ethoxy)-1H-benzimidazol-2-yl]amide;

(138) 2-(2-chloro-6-fluoro-phenyl)-1H-imidazole-4-carboxylic acid [1-cyclopentyl-5-(1-hydroxy-ethyl)-1H-benzimidazol-2-yl]-amide;

(139) 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(1-hydroxy-ethyl)-1-isopropyl-1H-benzimidazol-2-yl]-amide;

(140) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid 1-tert-butoxycarbonyl-piperidin-3-yl methyl ester;

(141) 4-({[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

(142) 2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-cyclopentyl-5-(1-hydroxy-1-methyl-ethyl)-1H-benzimidazol-2-yl]-amide;

(143) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid-2-(1-tert-butoxycarbonyl-piperidin-2-yl)-ethyl ester;

(144) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid-1-tert-butoxycarbonyl-piperidin-3-yl ester;

(145) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid ethyl ester;

(146) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester;

(147) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-3-methyl-butyric acid;

(148) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid ethyl ester;

(149) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(1-hydroxy-1-methyl-ethyl)-1-isopropyl-1H-benzimidazol-2-yl] -amide;

(150) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-pyrrolidine-2-carboxylic acid;

(151) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-hydroxy-phenyl)-acetic acid;

(152) 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid methyl ester;

(153) 3-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-thiazolidine-2-carboxylic acid;

(154) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid 1-tert-butoxycarbonyl-piperidin-2-yl methyl ester;

(155) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methylsulfanyl-butyric acid methyl ester;

(156) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(1H-imidazol-4-yl)-propionic acid methyl ester;

(157) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-fluoro-phenyl)-acetic acid methyl ester;

(158) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester;

(159) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methylsulfanyl-butyric acid;

(160) 4-benzyl-1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-

carbonyl]-piperazine-2-carboxylic acid tert-butyl ester;

(161) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperazine-2-carboxylic acid tert-butyl ester;

(162) {[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-(4-fluoro-phenyl)-acetic acid;

(163) 1-[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-piperidine-2-carboxylic acid;

(164) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(2-hydroxy-2-methyl-propyl)-1-cyclopentyl-1H-benzimidazol-2-yl] -amide;

(165) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(2-hydroxy-2-methyl-propyl)-1-isopropyl-1H-benzimidazol-2-yl] -amide;

(166) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [4-cyano-1-(2-oxo-butyl)-1H-pyrazol-3-yl]-amide;

(167) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-hydroxymethyl-3-methylsulfanyl-propyl)-amide;

(168) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-4-methanesulfinyl-butyric acid methyl ester;

(169) 3-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-5-methylsulfanyl-pentanoic acid methyl ester;

(170) 2-{[7-chloro-2-(2-chloro-6-fluorophenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid tert-butyl ester;

(171) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid methyl ester;

(172) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylic acid;

(173) Sodium 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazole-5-carboxylate;

(174) 2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-benzofuran-5-carboxylic acid ethyl ester;

(175) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid thiazol-2-ylamide;

(176) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (5-methyl-thiazol-2-yl)-amide;

(177) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide;

(178) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide;

(179) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid pyrimidin-4-ylamide;

(180) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (3-methyl-pyridin-2-yl)-amide;

(181) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-imidazol-2-yl)-amide;

(182) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid pyridin-2-ylamide;

(183) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-chloro-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide;

(184) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-ethyl-5-methyl-2H-pyrazol-3-yl)-amide;

(185) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-methoxy-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide;

(186) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-propyl-2H-pyrazol-3-yl)-amide;

(187) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-propyl-1H-pyrazol-3-yl)-amide;

(188) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [5-(4-fluoro-phenyl)-2-propyl-2H-pyrazol-3-yl]-amide;

(189) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-isopropyl-2H-pyrazol-3-yl)-amide;

(190) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-isopropyl-1H-pyrazol-3-yl)-amide;

(191) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-mercapto-1H-benzimidazol-5-yl)-amide;

(192) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid adamantan-1-ylamide;

(193) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid

(2-trifluoromethyl-1H-benzimidazol-5-yl)-amide;

(194) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-phenyl-propyl)-amide;

(195) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-cyclopentyl-1H-imidazol-2-yl)-amide;

(196) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-thiazol-2-yl-ethyl)-amide;

(197) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-pyrazin-2-yl-ethyl)-amide;

(198) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-pyridin-4-yl-ethyl)-amide;

(199) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-indan-1-yl)-amide;

(200) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(3-methoxy-phenyl)-ethyl]-amide;

(201) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (1-o-tolyl-cyclopropyl)-amide;

(202) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(4-chloro-phenyl)-ethyl]-amide;

(203) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid [1-(4-hydroxy-phenyl)-propyl]-amide;

(204) 7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide;

(205) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid;

(206) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid tert-butyl ester;

(207) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid methyl ester; and

(208) (2-{[7-chloro-2-(2-chloro-6-fluoro-phenyl)-1H-benzimidazole-5-carbonyl]-amino}-1-isopropyl-1H-benzimidazol-5-yl)-acetic acid ethyl ester.

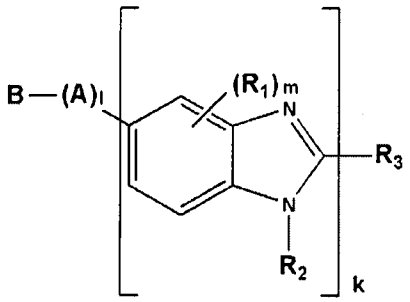
8. A pharmaceutical composition for preventing or treating inflammatory disease

comprising the compound of claim 1, or a pharmaceutically acceptable salt, an isomer, a hydrate or a solvate thereof.

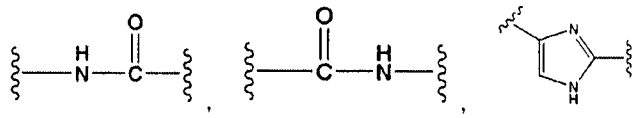
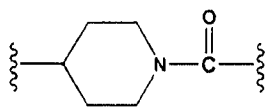
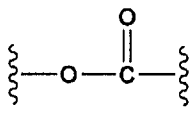
9. The composition of claim 8, wherein the inflammatory disease is rheumatoid arthritis, or osteoarthritis.

10. A use of a compound of formula 1, or a pharmaceutically acceptable salt, an isomer, a hydrate or a solvate thereof for the manufacture of a medicament for preventing or treating an inflammatory disease:

[Formula 1]



wherein

A is phenylene,  ,  or  ;

B is C_1-C_5 alkyl, C_2-C_6 alkynyl, C_6-C_{12} aryl, C_2-C_{13} heteroaryl, C_3-C_{13} heterocycloalkyl, sulfonyl or aminocarbonyl, wherein said alkyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, sulfonyl and aminocarbonyl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy) C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkoxy), C_6-C_{12} aryloxy, halo(C_1-C_5 alkyl)(C_6-C_{12} aryl) , C_1-C_5 alkylsulfonyl, C_6-C_{12} haloaryl and cyano, provided that, if k is 0, B is

benzimidazolyl optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_8 cycloalkyl, hydroxyl, C_6-C_{12} aryl, C_1-C_5 alkoxy, (C_1-C_5 alkoxy)carbonyl, carboxyl, amino, (C_1-C_5 alkyl)amino, piperidinyl, (C_1-C_5 alkoxy)C_1-C_5 alkyl, morpholinyl, aminocarbonyl, morpholinyl(C_1-C_5 alkyl), (C_1-C_5 alkyl)piperidinyl, (C_1-C_5 alkoxy)carbonylpiperidinyl, hydroxy(C_1-C_5 alkyl), hydroxy(C_1-C_5 alkoxy), (C_3-C_8 cycloalkyl)(C_1-C_5 alkloxy), C_6-C_{12} aryloxy and halo(C_1-C_5 alkyl)(C_6-C_{12} aryl).

k is 0 or 1;

l is 0 or 1;

m is an integer ranging from 0 to 3;

R_1 is each independently halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy or carboxyl;

R_2 is hydrogen or C_1-C_5 alkyl; and

R_3 is amino, C_6-C_{12} aryl or C_2-C_{13} heteroaryl, wherein said amino, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, amino, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 haloalkoxy, halo(C_1-C_5 alkoxy)(C_6-C_{12} aryl) and C_6-C_{12} haloaryl.

11. The use of claim 10, wherein the inflammatory disease is rheumatoid arthritis, or osteoarthritis.