ISOXAZOLE DERIVATIVES AS NUCLEAR RECEPTOR AGONISTS AND USES THEREOF

Technical Field

[1] The present application claims priority to Korean Patent Application No. 10-2017-0047393 filed on April 12, 2017 and Korean Patent Application No. 10-2018-0042545 filed April 12, 2018, the disclosures of which are incorporated herein by reference.

[2] The present invention relates to compounds useful as agonists for Farnesoid X receptor (FXR, NR1H4), pharmaceutical formulation comprising such compounds and its study for medicinal uses.

[3]

Background Art

[4] Farnesoid X receptor (FXR, NR1H4) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. FXR is highly expressed in the liver, intestine, kidney, adrenal glands, white adipose tissue and in induced during adipocyte differentiation *in vitro*. (Cariu B. et al., J. Biol. Chem., 2006, 16, 11039-11049).

[5] Not only FXR regulates various physiological processed such as modulates regulrated of bile acid (BA) regulation, lipids/glucose metabolism, inflammation/fibrosis, but recently it has also been linked to the pathology of FXR receptors.

[6] This nuclear receptor is the intracellular bile acid ¡“sensor” and its major physiological role is to protect liver cells from the deleterious effect of bile acids(BA) overload. Intestine is the tissue expressing the first FXR target gene identified. Indeed IBAB-P is expressed in enterocytes and binds bile acids, thus limiting the free concentration of BA intracellularly and consequently their toxicity. (Makishima M, et al., Science, 1999, 284(5418), 1362-1365). FXR is highly expressed in the liver and regulates key genes involved in BA synthesis, metabolism and transport including CYP7A1, UGT2B4, BSEP, MDR3, MRP2, ASBT, NTCP, OST α and OST β in humans. One effect of FXR activation is down regulation of CYP7A1 and thus bile acid synthesis; this is accomplished through induction of SHP (Small Heterodimer Partner) which then represses CYP7A1 transcription (Claude T, et al., Arterioscler. Thromb. Vasc. Biol., 2005, 25, 2020-2031). Altered expression or malfunction of these genes has been described in patients with cholestatic liver disease. FXR agonist 6-ethyl-chenodeoxycholic acid (6EtCDCA) was found to fully reverse the impairment of bile flow and to protect the hepatocytes against liver cell injury caused by the

[86] 3-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-(trifluoromethyl)phenyl)ethynyl)benzoic acid; (I-3)

[87] 4-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-(trifluoromethyl)phenyl)ethynyl)benzoic acid; (I-4)

[88] 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole; (I-5)

[89] 4-((3-chloro-4-(phenylethynyl)phenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole; (I-6)

[90] methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate; (I-7)

[91] methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate; (I-8)

[92] methyl 3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate; (I-9)

[93] methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoate; (I-10)

[94] ethyl (3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)phenyl)carbamate; (I-11)

[95] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzenesulfonamide; (I-12)

[96] N-(3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)phenyl)methanesulfonamide; (I-13)

[97] N-(3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)phenyl)sulfamide; (I-14)

[98] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-15)

[99] 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-16)

[100] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)nicotinic acid; (I-17)

[101] 2-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)isonicotinic acid; (I-18)

[102] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)picolinic acid; (I-19)

[103] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)nicotinic acid; (I-20)

[104] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(dimethylamino)benzoic acid; (I-21)

[105] 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-3-(dimethylamino)benzoic acid; (I-22)

[106] 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-(dimethylamino)benzoic acid; (I-23)

[107] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(diethylamino)benzoic acid; (I-24)

[108] 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-25)

[109] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-(dimethylamino)benzoic acid; (I-26)

[110] 3-chloro-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-27)

[111] 4-chloro-3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-28)

[112] 2-chloro-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-29)

[113] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-fluorobenzoic acid; (I-30)

[114] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(trifluoromethyl)benzoic acid; (I-31)

[115] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-ethynylbenzoic acid; (I-32)

[116] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-cyanobenzoic acid; (I-33)

[117] 3-((2,6-dichloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-34)

[118] 2-chloro-3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-35)

[119] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-fluorobenzoic acid; (I-36)

[120] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-fluorobenzoic acid; (I-37)

[121] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-fluorobenzoic acid; (I-38)

[122] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(trifluoromethoxy)benzoic acid; (I-39)

[123] 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methoxybenzoic acid; (I-40)

[181] 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(2-hydroxy-2-methylpropyl)-1H-indole-6-carboxylic acid; (I-98)

[182] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-indazole-4-carboxylic acid; (I-99)

[183] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2,3-dihydrobenzofuran-7-carboxylic acid; (I-100)

[184] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-indole-4-carboxylic acid; (I-101)

[185] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzo[d]oxazole-7-carboxylic acid; (I-102)

[186] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzo[d]oxazole-7-carboxylic acid; (I-103)

[187] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-ethylbenzo[d]oxazole-7-carboxylic acid; (I-104)

[188] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-propylbenzo[d]oxazole-7-carboxylic acid; (I-105)

[189] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-isopropylbenzo[d]oxazole-7-carboxylic acid; (I-106)

[190] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-(hydroxymethyl)benzo[d]oxazole-7-carboxylic acid; (I-107)

[191] 7-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)quinoxaline-5-carboxylic acid; (I-108)

[192] 7-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2,3-dimethylquinoxaline-5-carboxylic acid; (I-109)

[193] 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-cyclopropylbenzo[d]oxazole-7-carboxylic acid; (I-110)

[194] 2-butyl-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzo[d]oxazole-7-carboxylic acid; (I-111)

[195] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzo[d]oxazole-4-carboxylic acid; (I-112)

[196] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-ethylbenzo[d]oxazole-4-carboxylic acid; (I-113)

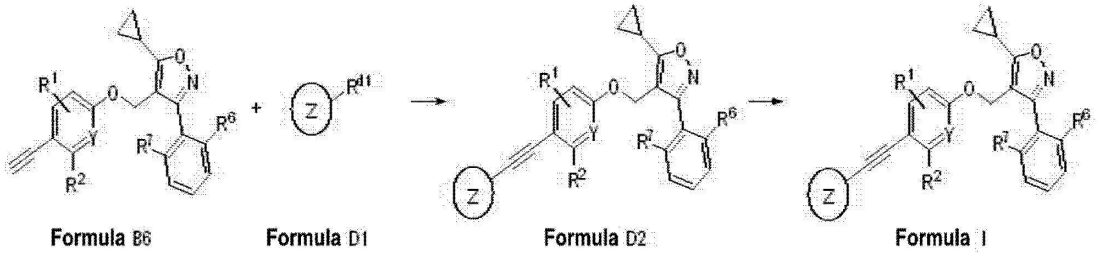
[197] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-propylbenzo[d]oxazole-4-carboxylic acid; (I-114) and

[198] 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-isopropylbenzo[d]oxazole-4-carboxylic acid. (I-115)

[199]

[200] In the present invention, "C_{1-6} alkyl" is a saturated hydrocarbonyl amine with linear or

[330]



[331]

[332] The compound of Formula I, which is a compound of the present invention, may be prepared by series of steps from the compound of Formula B6 as shown in Scheme 3.

[333]

[334] R^1, R^2, R^6, R^7, R^{d1}, Y and Z of Formula I, D1, B2 and B7, illustrated in Scheme 3, are defined as below.

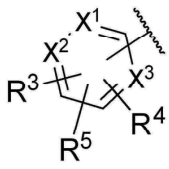
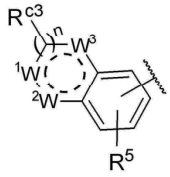
[335]

[336] In the present Formula I,

R^{d1} is bromo or iodo,

[337] Y is carbon or nitrogen,

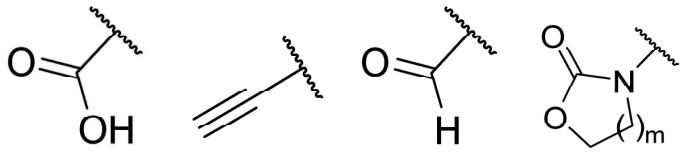
[338] R^1 and R^2 are each independently hydrogen, halo or trifluoromethyl,

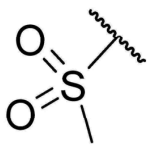
[339] Z is or ,

[340] n is 0, 1 or 2,

[341] X^1, X^2 and X^3 are each independently carbon or nitrogen,

[342] R^3 and R^4 are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl,  , $CONR^{a1}R^{a2}$, $NR^{a1}R^{a2}$, $CH_2NR^{a1}R^{a2}$, CH_2R^{c3}, COR^{a3}, OR^{a3}, $NR^{a4}COR^{a3}$, $NR^{a4}CO_2R^{a3}$, $NHCONHR^{a3}$, $NHSO_2R^{a3}$ or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

[343] wherein, m is 1 or 2,

[344] R^{a1} and R^{a2} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl,  or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

[345]

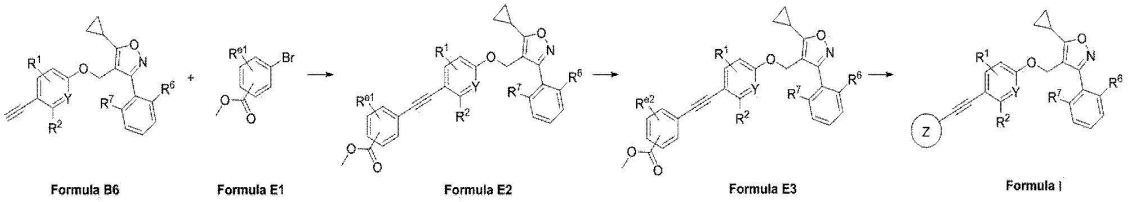
[370]

[371] **Besides, another preparation method of the compound of Formula I according to the present invention is shown in the following reaction scheme 4.**

[372]

[373] [Scheme 4]

[374]



[375] The compound of Formula I, which is a compound of the present invention, may be prepared by series of steps from the compound of Formula B6 as shown in Scheme 4.

[376]

[377] R^1, R^2, R^6, R^7, R^{e1}, R^{e2}, Y and Z of Formula I, B6 and E3, illustrated in Scheme 4, are defined as below:

[378]

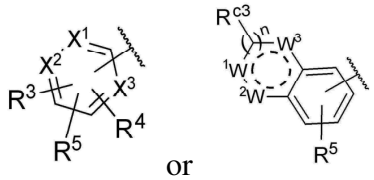
[379] In the present Formula I,

R^{e1} is aldehyde or nitro,

R^{e2} is $CH_2NR^{a1}R^{a2}$ or NH_2,

[380] Y is carbon or nitrogen,

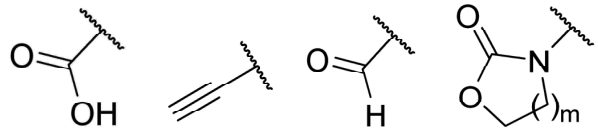
[381] R^1 and R^2 are each independently hydrogen, halo or trifluoromethyl,



[382] Z is or ,

[383] n is 0, 1 or 2,

[384] X^1, X^2 and X^3 are each independently carbon or nitrogen,

[385] R^3 and R^4 are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl,  , $CONR^{a1}R^{a2}$, $NR^{a1}R^{a2}$, $CH_2NR^{a1}R^{a2}$, CH_2R^{c3}, COR^{a3}, OR^{a3}, $NR^{a4}COR^{a3}$, $NR^{a4}CO_2R^{a3}$, $NHCONHR^{a3}$, $NHSO_2R^{a3}$ or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

[386] wherein, m is 1 or 2,

[387] R^{a1} and R^{a2} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl,

[496] The compound of Formula I, which is a compound of the present invention, may be prepared by series of steps from the compound of Formula B6 as shown in Scheme 6.

[497]

[498] R^1, R^2, R^3, R^6, R^7, R^{j1}, Y and Z of Formula I, B6 and J3, illustrated in Scheme 6, are defined as below:

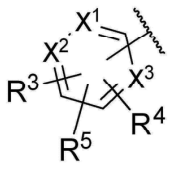
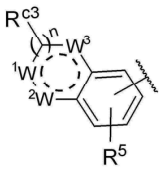
[499]

[500] In the present Formula I,

R^{j1} is H or methyl ester,

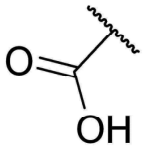
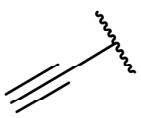
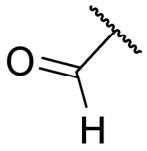
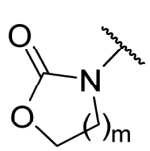
[501] Y is carbon or nitrogen,

[502] R^1 and R^2 are each independently hydrogen, halo or trifluoromethyl,

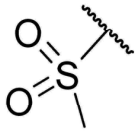
[503] Z is  or ,

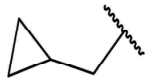
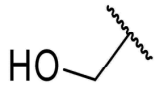
[504] n is 0, 1 or 2,

[505] X^1, X^2 and X^3 are each independently carbon or nitrogen,

[506] R^3 and R^4 are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl, , , , , $CONR^{a1}R^{a2}$, $NR^{a1}R^{a2}$, $CH_2NR^{a1}R^{a2}$, CH_2R^{c3}, COR^{a3}, OR^{a3}, $NR^{a4}COR^{a3}$, $NR^{a4}CO_2R^{a3}$, $NHCONHR^{a3}$, $NHSO_2R^{a3}$ or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

[507] wherein, m is 1 or 2,

[508] R^{a1} and R^{a2} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl,  or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

[509] R^{a3} is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl, , ,  or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

[510] R^{a4} is hydrogen or C_{1-6} alkyl,

[511]

[614]

[615] Trimethylsilylacetylene (2.4ml, 17mmol), bis(triphenylphosphine)palladium(ii) dichloride ($PdCl_2(PPh_3)_2$, 0.6g, 0.85mmol), Copper(I) iodide (0.16g, 0.85mmol), and triethylamine (0.6ml, 4.25mmol) were added to a solution of the intermediate compound (Step 1) (2.8g, 8.5mmol) in *N,N*-dimethylformamide (50ml) and stirred for 12 hours at 80℃. The reaction mixture was diluted with Ethyl acetate and washed with water. The combined organic layers were dried over $MgSO_4$, filtered, evaporated in vacuum and purified using silica chromatography to afford the intermediate compound tert-butyl(4-((trimethylsilyl)ethyl)phenoxy)silane (1.99g, 77%).

[616] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.32 (m, 2H), 6.43 (m, 2H), 0.78 (s, 9H), 0.25 (s, 9H), 0.23 (s, 6H).

[617]

[618] Step 3: Preparation of 4-((trimethylsilly)ethynyl)phenol

[619]

[620] Potassium fluoride (KF, 3.8g, 65mmol) was added to a solution of the intermediate compound (Step 2)(1.99g, 6.5mmol) in methanol (65ml) at 0℃ and stirred for 1 hour. The reaction mixture was diluted with dichloromethane and washed with water. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuum. The resulting 4-((trimethylsilly)ethynyl)phenol was used for next step without any further purification.

[621]

[622] Step 4: Preparation of 5-cyclopropyl-3-(2,6-dichlorophenyl)-4-((4-ethynylphenoxy)methyl)isoxazole

[623]

[624] 4-(bromomethyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxlazole(Intermediate 1)(2.25g, 6.5mmol) and potassium carbonate (1.34g, 9.75mmol) were added to a solution of the intermediate compound(Step 3)(1.25g, 6.5mmol) in *N,N*-dimethylformamide (65ml) stirred for 12 hours at room temperature. The reaction mixture was diluted with Ethyl acetate and washed with water. The combined organic layers were dried over $MgSO_4$, filtered, evaporated in vacuum and purified using silica chromatography to afford the intermediate compound 5-cyclopropyl-3-(2,6-dichlorophenyl)-4-((4-ethynylphenoxy)methyl)isoxazole(2.05g, 82%)

[625] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.30 (m, 5H), 6.83 (d, 1H), 6.66 (dd, 1H), 4.80 (s, 2H), 3.26 (s, 1H), 2.17-2.10 (m, 1H), 1.31-1.27 (m, 2H), 1.23-1.17 (m, 2H).

[626]

[627] Step 5: Preparation of methyl 4-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[628]

[629] 4-iodobenzoate (67mg, 0.52mmol), bis(triphenylphosphine)palladium(ii) dichloride ($PdCl_2(PPh_3)_2$, 42mg, 0.06mmol), Copper(I) iodide(11.4mg, 0.06mmol), and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.4ml, 2.6mmol) were added to a solution of the intermediate compound(Step 4)(200mg, 0.52mmol) in *N,N*-dimethylformamide (5.2ml) and stirred for 4 hours at 80℃. The reaction mixture was diluted with Ethyl acetate and washed with water. The combined organic layers were dried over $MgSO_4$, filtered, evaporated in vacuum and purified using silica chromatography to afford the intermediate compound methyl 4-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate (175mg, 65%).

[630] ^{1}H-NMR (MeOD, 400MHz): δ 8.03 (d, 2H), 8.01-7.40 (m, 7H), 6.83 (d, 2H), 4.94 (s, 2H), 3.93 (s, 3H), 2.37-2.34 (m, 1H), 1.24-1.22 (m, 4H).

[631]

[632] Step 6: Preparation of 4-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol -4-yl)methoxy)phenyl)ethynyl)benzoic acid

[633]

[634] lithium hydroxide (14.2mg, 0.34mmol) was added to a solution of the intermediate compound (Step 5)(175mg, 0.34mmol) in 1,4-dioxane(3ml) and distilled water(0.4ml) and stirred for 18 hours at room temperature. The reaction mixture was acidified to pH=2~3 with 1N HCl and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuum to afford the title compound (133mg, 78%).

[635] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.01 (dd, 2H), 7.55 (dd, 2H), 7.43-7.40 (m, 4H), 7.34-7.32 (m, 1H), 6.79 (d, 2H), 4.83 (s, 2H), 2.20-2.16 (m, 1H), 1.30-1.22 (m, 2H), 1.19-1.13 (m, 2H).

[636]

[637] **<Example 2> 3-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl) methoxy)phenyl)ethynyl)benzoic acid; (I-2)**

[638]

[639] Step 1: Preparation of methyl 3-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[640]

[641] This compound was made using the procedure described for example 1 (Step 5). Thus, this intermediate compound (Step 4 of Example 1)(100mg, 0.26mmol) was reacted with methyl 3-bromobenzoate (56mg, 0.26mmol), bis(triphenylphosphine) palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 21mg, 0.03mmol), Copper(I) iodide(5.7mg, 0.03mmol), and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2ml, 1.3mmol) to afford

21.9mmol) and potassium carbonate (4.54g, 32.9mmol) to afford the title compound (7.15g, 78%).

[711] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.30 (m, 4H), 6.83 (d, 1H), 6.66 (dd, 1H), 4.80 (s, 2H), 3.26 (s, 1H), 2.17-2.10 (m, 1H), 1.31-1.27 (m, 2H), 1.23-1.17 (m, 2H).

[712]

[713] **<Example 6> 4-((3-chloro-4-(phenylethynyl)phenoxy)methyl)-5-cyclopropyl- 3-(2,6-dichlorophenyl)isoxazole; (I-6)**

[714]

[715] Step 1: Preparation of 4-((3-chloro-4-(phenylethynyl)phenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole

[716]

[717] This compound was made using the procedure described for example 1 (Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazole (example 5)(128mg, 0.306mmol) was reacted with bromobenzene (48mg, 0.306mmol), bis(triphenylphosphine)palladium(II) dichloride($PdCl_2(PPh_3)_2$ (21.5mg, 0.031mmol), copper(I) iodide (5.8mg, 0.031mmol) and triethylamine(0.052ml, 0.367mmol) to afford the title compound (7.15g, 78%).

[718] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.54-7.52 (m, 2H), 7.42-7.31 (m, 7H), 6.87-6.86 (d, 1H), 6.69-6.66 (dd, 1H), 4.81 (s, 2H), 2.17-2.04 (m, 1H), 1.29-1.24 (m, 2H), 1.19-1.14 (m, 2H).

[719]

[720] **<Example 7> methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate; (I-7)**

[721]

[722] Step 1: Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[723] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazole (Example 6)(128mg, 0.31mmol) was reacted with methyl 3-iodobenzoate (80mg, 0.31mmol), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 22mg, 0.03mmol), Copper(I) iodide(5.8mg, 0.03mmol) and triethylamine(0.052ml, 0.37mmol) to afford the title compound(107mg, 63%).

[724] ^{1}H-NMR (CDCl3, 400MHz): δ 8.20-8.19 (m, 1H), 8.01-7.98 (m, 1H), 7.72-7.69 (m, 1H), 7.43-7.32 (m, 5H), 6.88-6.87 (m, 1H), 6.71-6.68 (m, 1H), 4.82 (s, 2H), 3.94 (s, 3H), 2.18-2.15 (m, 1H), 1.32-1.28 (m, 2H), 1.20-1.16 (m, 2H).

[725]

[726] **(Example 8) Methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate (I-8)**

[727]

[728] Step 1: Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-nitrobenzoate

[729]

[730] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol(example 5)(3.6g, 8.59mmol) was reacted with methyl 3-bromo-5-nitrobenzoate(2.6g, 10.3mmol), bis(triphenylphosphine)palladium(II) dichloride($PdCl_2(PPh_3)_2$, 302mg, 0.429mmol), copper(I)iodide(81.8mg, 0.429mmol) and triethylamine(1.44ml, 10.3mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol -4-yl)methoxy)phenyl)ethynyl)-5-nitrobenzoate(3.9g, 80%).

[731] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.78 (t, 1H), 8.51 (t, 1H), 8.46 *t, 1H), 7.44-7.40 (m, 3H), 7.36-7.32 (m, 1H), 6.89 (d, 1H), 6.73 (dd, 1H), 4.84 (s, 2H), 4.00 (s, 3H), 2.19-2.13 (m, 1H), 1.32-1.28 (m, 2H), 1.20-1.15 (m, 2H).

[732]

[733] Step 2: Preparation of methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[734]

[735] The intermediate compound(step 1) was dissolved in ethyl acetate(70ml) and ethanol(35ml) and tin(II) chloride dihydrate(15.5g, 68.7mmol) were added. The reaction was stirred at room temperature for 1 day. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to give methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate (3.0g, 77%).

[736] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.59-7.58 (m, 1H), 7.41-7.27 (m, 5H), 7.00-6.99 (m, 1H), 6.87-6.86 (m, 1H), 6.69-6.67 (m, 1H), 4.82 (s, 2H), 3.90 (s,3H), 2.19-2.12 (m, 1H), 1.31-1.28 (m, 2H), 1.20-1.14 (m, 2H).

[737]

[738] Step 3: Preparation of methyl 3-((2-chloro-4-((cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate

[739]

[740] The intermediate compound(step 2) was dissolved in *N,N*-dimethylform amide(8.8ml) and ethylchloroformate(250ul, 2.64mmol), triethylamine(369ul, 2.64mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU, 13 ul, 0.0881mmol) were added. The reaction was stirred at room temperature for 4 hours. The reaction mixture

was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to give the title compound(254mg, 65%).

[741] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 13.42 (br, 1H), 8.03 (d, 1H), 7.82 (t, 1H), 7.65-7.61 (m, 2H), 7.58-7.54 (m, 1H), 7.13 (d, 1H), 6.87 (dd, 1H), 5.01 (s, 2H), 1.05-1.32 (m, 5H).

[742]

[743] **(Example 9) Methyl 3-(tert-butoxycarbonyl)amino)-5-((2-chloro-4-((cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate (I-9)**

[744]

[745] Step 1: Preparation of methyl 3-(tert-butoxycarbonyl)amino)-5-((2-chloro-4-((cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[746]

[747] This compound was made using the procedure described for example 8(Step 3). Thus, methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(500mg, 0.880mmol) was reacted with di-tert-butyl dicarbonate(385mg, 1.76mmol), 4-dimethylaminopyridine(5.4mg, 0.044mmol) and triethylamine(0.2ml, 1.32mmol) to afford the title compound(300mg, 51%).

[748] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.12 (t, 1H), 7.89 (t, 1H), 7.79 (t, 1H), 7.51 - 7.31 (m, 5H), 6.86 (d, 1H), 6.69 (dd, 1H), 6.61(s, 1H), 4.81 (s, 2H), 3.93 (s, 3H), 2.17 (m, 1H), 1.52 (s, 9H), 1.31 1.23 (m, 2H), 1.19 - 1.16 (m, 2H).

[749]

[750] **(Example 10) Methyl 3-((2-chloro-4-((cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoate; (I-10)**

[751]

[752] Step 1 : Preparation of 3-((2-chloro-4- ((cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoate

[753]

[754] The compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino) benzoate (example 8)(220mg, 0.348mmol) was dissolved in *N,N*-dimethylformamide(5ml) and sodiumhydride(25mg, 1.04mmol) and iodomethane(87ul, 1.39mmol) were added. The reaction was stirred at room temperature for 20 hours. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to afford the title compound(113mg, 48%).

[755] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.02 (t, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 7.42-7.38 (m,

Thus, this intermediate compound(Step 1)(47.6mg, 0.086mmol) was reacted with lithium hydroxide(36mg, 0.86mmol) to afford the title compound(27mg, 58%).

[837] ^{1}H-NMR (DMSO, 400MHz): δ 13.73(br, 1H), 8.03 (d, 1H), 7.82 (t, 1H), 7.60 - 7.65 (m, 1 H), 7.58-7.53 (m, 3 H), 7.13 (d, 1H),6.87 (dd, 1H), 5.01 (s, 2H), 1.32-1.03(m, 5H).

[838]

[839] **<Example 19> 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)picolinic acid; (I-19)**

[840]

[841] Step 1 : Preparation of methyl 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)picolinate

[842]

[843] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Eample 5)(100mg, 0.239mmol) was reacted with methyl 6-bromopicolinate(65.9mg, 0.287mmol), bis(triphenylphosphine) palladium(II) dichloride($PdCl_2(PPh_3)_2$, 21mg, 0.03mmol), copper(I) iodide(5.7mg, 0.03mmol) and triethylamine(0.2ml, 1.44mmol) to afford the intermediate compound methyl 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl) methoxy)phenyl)ethynyl)picolinate(60.4mg, 45%).

[844] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.06 (dd, 1H), 7.83 (t, 1H), 7.70 (dd 1H), 7.50 (d, 1H), 7.43-7.39 (m, 2H),7.36-7.31 (m, 1H), 6.88 (d, 1H),6.70 (dd, 1H), 4.83 (s, 2H), 4.49 (q, 2H), 2.18-2.12(m, 1H), 1.45 (t, 3H), 1.30 (dd, 2H), 1.17 (dd, 2H).

[845]

[846] Step 2 : Preparation of 6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)picolinic acid

[847]

[848] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(60.4mg, 0.106mmol) was reacted with lithium hydroxide(44.5mg, 1.06mmol) to afford the title compound(9.7mg, 17%).

[849] ^{1}H-NMR (DMSO, 400MHz): δ 13.42 (br, 1H), 8.03 (d, 1H), 7.82 (t, 1H), 7.65-7.61 (m, 2H), 7.58-7.54 (m, 1H), 7.13 (d, 1H), 6.87 (dd, 1H), 5.01 (s, 2H), 1.05-1.32 (m, 5H).

[850]

[851] **<Example 20> 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)nicotinic acid; (I-20)**

[852]

[853] Step 1 : Preparation of methyl5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)

te(70mg, 42%).

[868] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.55-7.54 (m, 1H), 7.42-7.31 (m, 5H), 7.02-7.01 (m, 1H), 6.87-6.86 (m, 1H), 6.70-6.67 (m, 1H), 4.82 (s, 2H), 3.91 (s, 3H), 3.01 (s, 6H), 2.18-2.14 (m, 1H), 1.32-1.28 (m, 2H), 1.19-1.16 (m, 2H).

[869]

[870] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(dimethylamino)benzoic acid

[871]

[872] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(70mg, 0.118mmol) was reacted with lithium hydroxide(4.9mg, 0.118mmol) to afford the title compound (54mg, 78%).

[873] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.60 (s, 1H), 7.43-7.32 (m, 5H), 7.05-7.04 (m, 1H), 6.88-6.87 (m, 1H), 6.70-6.68 (m, 1H), 4.82 (s, 2H), 3.02 (s, 6H), 2.18-2.14 (m, 1H), 1.32-1.29 (m, 2H), 1.19-1.16 (m, 2H).

[874]

[875] **<Example 22> 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-3-(dimethylamino) benzoic acid; (I-22)**

[876]

[877] Step 1 : Preparation of methyl 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-3-(dimethylamino)benzoate

[878]

[879] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Example 5)(100mg, 0.26mmol) was reacted with methyl 4-bromo-3-(dimethylamino)benzoate(67mg, 0.26mmol), bis(triphenylphosphine) palladium(II) dichloride($PdCl_2(PPh_3)_2$, 21mg, 0.03mmol), copper(I) iodide(5.7mg, 0.03mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2ml, 1.3mmol) to afford the intermediate compound methyl 4-((2-chloro-4-((5-cyclopropyl-3- (2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-3-(dimethylamino)benzoate(80mg, 55%).

[880] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.58 (br, 1H), 7.53 (br, 1H), 7.43-7.41 (m, 3H), 7.35-7.31 (m, 1H), 6.87 (d, 1H), 6.716.68 (dd, 1H), 4.82 (s, 2H), 3.91 (s, 3H), 3.02 (s, 6H), 2.15 (m, 1H), 1.32-1.29 (m, 2H), 1.19-1.14 (m, 2H).

[881]

[882] Step 2 : Preparation of 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-3-(dimethylamino) benzoic acid

[883]

[884] This compound was made using the procedure described for example 1(Step 6).

6.86-6.85 (m, 1H), 6.69-6.68 (m, 1H), 4.81 (s, 2H), 2.16-2.14 (m, 1H), 1.31-1.29 (m, 2H), 1.18-1.15 (m, 2H).

[917]

[918] **<Example 26> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-(dimethylamino)benzoic acid; (I-26)**

[919]

[920] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-(dimethylamino)benzoate

[921]

[922] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Example 5)(100mg, 0.26mmol) was reacted with methyl 3-bromo-4-(dimethylamino)benzoate(67mg, 0.26mmol), bis(triphenylphosphine) palladium(II) dichloride($PdCl_2(PPh_3)_2$, 21mg, 0.03mmol), copper(I) iodide(5.7mg, 0.03mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2ml, 1.3mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3- (2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-(dimethylamino)benzoate(70mg, 48%).

[923] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.14 (d, 1H), 7.87-7.84 (dd, 1H), 7.42-7.38 (m, 3H), 7.35-7.31 (m, 1H), 6.86 (d, 1H), 6.82 (d, 1H), 6.70-6.68 (dd, 1H), 4.82 (s, 2H), 3.88 (s, 3H), 3.14 (s, 6H), 2.16 (m, 1H), 1.30-1.26 (m, 2H), 1.24-1.16 (m, 2H).

[924]

[925] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-(dimethylamino)benzoic acid

[926]

[927] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(70mg, 0.12mmol) was reacted with lithium hydroxide(50.4 mg, 1.2mmol) to afford the title compound(35mg, 53%).

[928] ^{1}H-NMR (DMSO, 400MHz): δ 7.95 (d, 1H), 7.79-7.76 (dd, 1H), 7.64-7.62 (m, 2H), 7.57-7.51 (m, 2H), 7.07 (d, 1H), 6.93 (d, 1H), 6.83-6.80 (dd, 1H), 4.97 (d, 1H), 3.08 (s, 6H), 2.47 (m, 1H), 1.23-1.13 (m, 4H).

[929]

[930] **<Example 27> 3-chloro-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-27)**

[931]

[932] Step 1 : Preparation of methyl 3-chloro-5-((2-chloro-4-((5-cyclopropyl- 3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[933]

[1224]

[1225] **<Example 50> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(morpholinomethyl)benzoic acid; (I-50)**

[1226]

[1227] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(morpholinomethyl)benzoate

[1228]

[1229] This compound was made using the procedure described for example 41(Step 1). Thus methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-formylbenzoate(Step 1 of example 41)(200mg, 0.344mmol) was reacted with acetic acid(21mg, 0.344mmol), morpholine(45mg, 0.516mmol) and sodium cyanoborohydride(65mg, 1.03mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3- (2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(morpholinomethyl)benzoate(99mg, 44%).

[1230] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.09 (s, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.42-7.39 (m, 3H), 7.35-7.31 (m, 1H), 6.88 (d, 1H), 6.70 (dd, 1H), 4.82 (s, 2H), 3.93 (s, 3H), 3.72-3.70 (m, 4H), 3.52 (s, 2H), 2.45-2.44 (m, 4H), 2.17-2.13 (m, 1H), 1.32-1.24 (m, 2H), 1.19-1.14 (m, 2H).

[1231]

[1232] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(morpholinomethyl)benzoic acid

[1233]

[1234] This compound was made using the procedure described for example 1(Step 6). Thus the intermediate compound(Step 1)(99mg, 0.151mmol) was reacted with lithium hydroxide(63mg, 1.51mmol) to afford the title compound(85mg, 96%).

[1235] ^{1}H-NMR (DMSO, 400MHz): δ 7.96-7.76 (m, 3H), 7.64-7.62 (m, 2H), 7.57-7.53 (m, 2H), 7.10 (d, 1H), 6.85 (dd, 1H), 4.99 (s, 2H), 3.78 (s, 2H), 3.30-3.25 (m, 4H), 2.50-2.46 (m, 5H), 1.27-1.11 (m, 4H).

[1236]

[1237] **<Example 51> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((oxetan-3-ylamino)methyl)benzoic acid; (I-51)**

[1238]

[1239] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((oxetan-3-ylamino)methyl)benzoate

[1240]

[1241] This compound was made using the procedure described for example 42(Step 1). Thus methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-

6.91-6.88 (m, 2H), 6.76-6.73 (dd, 1H), 4.39 (s, 2H), 3.88 (s, 3H), 2.79 (s, 3H), 2.34 (m, 1H), 1.28-1.20 (m, 4H).

[1255]

[1256] Step 2 : Preparation of3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylamino)benzoic acid

[1257]

[1258] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(70mg, 0.13mmol) was reacted with lithium hydroxide(54.5mg, 1.3mmol) to afford the title compound(36.8mg, 53%).

[1259] ^{1}H-NMR (DMSO, 400MHz): δ 7.64 (d, 1H), 7.62 (d, 1H), 7.57-7.52 (m, 2H), 7.21 (m, 1H),7.14 (t, 1H), 7.08 (d, 1H), 6.83 (d, 1H), 6.80 (m, 1H), 6.13 (br, 1H), 4.98 (s, 2H), 2.71 (d, 3H), 2.47 (m, 1H), 1.23-1.12 (m, 4H).

[1260]

[1261] **<Example 53> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol -4-yl)methoxy)phenyl)ethynyl)-5-(ethylamino)benzoic acid; (I-53)**

[1262]

[1263] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(ethylamino)benzoate

[1264]

[1265] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Example 5)(100mg, 0.26mmol) was reacted with methyl 3-bromo-5-(ethylamino)benzoate(67mg, 0.26mmol), bis(triphenyl phosphine)palladium(II) dichloride($PdCl_2(PPh_3)_2$, 21mg, 0.03mmol), copper(I) iodide(5.7mg, 0.03mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2ml, 1.3mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5- cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(ethylamino)benzoate(70mg, 48%).

[1266] ^{1}H-NMR (DMSO, 400MHz): δ 7.52-7.39 (m, 4H), 7.34 (t, 1H), 7.21-7.20 (dd, 1H), 6.91-6.88 (m, 2H), 6.76-6.73 (dd, 1H), 4.39 (s, 2H), 3.88 (s, 3H), 3.03 (m, 2H), 2.79 (s, 3H), 2.34 (m, 1H), 1.28-1.20 (m, 4H).

[1267]

[1268] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(ethylamino)benzoic acid

[1269]

[1270] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(70mg, 0.13mmol) was reacted with lithium hydroxide(54.5mg, 1.3mmol) to afford the title compound(37.7mg, 53%).

phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methoxy-3-nitrobenzoate(126.5mg, 61.1%).

[1403] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.13 (s, 1H), 8.02 (s, 1H), 7.43-7.33 (m, 4H), 6.88 (d, 1H), 6.67-6.65 (m, 1H), 4.83 (s, 2H), 4.01 (s, 3H), 3.97 (s, 3H), 2.18-2.13 (m, 1H), 1.33-1.26 (m, 2H), 1.20-1.15 (m, 2H).

[1404]

[1405] Step 2 : Preparation of methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3- (2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methoxy benzoate

[1406]

[1407] This compound was made using the procedure described for example 8(Step 2). Thus, this intermediate compound(Step 1)(126.5mg, 0.2mmol) was reacted with tin(II) chloride dihydrate(225.63mg, 1.0mmol) to afford the intermediate compound methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methoxybenzoate(51mg, 43%).

[1408] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.39-7.33 (m, 5H), 7.05 (s, 1H), 6.86 (s, 1H), 6.68 (dd, 1H), 4.80 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.15-2.05 (m, 1H), 1.29-1.24 (m, 2H), 1.16-1.11 (m, 2H).

[1409]

[1410] Step 3 : Preparation of 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methoxybenzoic acid

[1411]

[1412] This compound was made using the procedure described for example 1(step 6). Thus, this intermediate compound(Step 2)(51mg, 0.09mmol) was reacted with lithium hydroxide(36mg, 0.9mmol) to afford the title compound(37.3mg, 71%).

[1413] ^{1}H-NMR (MeOD, 400MHz): δ 7.55-7.50 (m, 2H), 7.48-7.46 (m, 1H), 7.41 (d, 1H), 7.21 (d, 1H), 7.08 (d, 1H), 6.92 (d, 1H), 6.76 (dd, 1H), 4.95 (s, 2H), 4.13 (s, 3H), 2.38-2.34 (m, 1H), 1.30-1.22 (m, 4H).

[1414]

[1415] **<Example 63> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methylbenzoic acid; (I-63)**

[1416]

[1417] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methylbenzoate

[1418]

[1419] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Example 5)(100mg, 0.239mmol) was reacted with methyl 3-bromo-5-methylbenzoate(65.5mg, 0.287mmol), bis (triphenylphosphine) palladium(II)dichloride($PdCl_2(PPh_3)_2$, 21mg, 0.03mmol), copper(I)iodide(5.7mg, 0.03mmol) and triethylamine(0.2ml, 1.44mmol) to afford the intermediate compound

methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methylbenzoate(87mg, 31%).

[1420] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.00 (s, 1H), 7.82 (s, 1H), 7.53 (s, 1H), 7.42-7.35 (m, 3H), 7.33-7.26 (m, 1H), 6.87 (d, 1H), 6.69 (dd, 1H), 4.82 (s, 2H), 3.92 (s, 3H), 2.40 (s, 3H), 2.22-2.11 (m, 1H), 1.32-1.29 (m, 2H), 1.21-1.15 (m, 2H).

[1421]

[1422] Step 2 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methylbenzoic acid

[1423]

[1424] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound(step1)(87mg, 0.153mmol) was reacted with lithium hydroxide(64.3mg, 1.53mmol) to afford the title compound(28.8mg, 34%).

[1425] ^{1}H-NMR (DMSO, 400MHz): δ 13.43 (br, 1H), 7.81 (d, 1H), 7.65-7.63 (m, 1H), 7.59 (br, 1H), 7.58-7.54 (m, 1H), 7.10 (d, 1H), 6.84 (dd, 1H), 4.99 (s, 2H), 2.39 (s, 3H), 1.21-1.11 (m, 5H).

[1426]

[1427] **<Example 64> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-cyclopropylbenzoic acid; (I-64)**

[1428]

[1429] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-cyclopropylbenzoate

[1430]

[1431] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Example 5)(77.3mg, 0.18mmol)was reacted with methyl 3-cyclopropyl-5-iodobenzoate(55.8mg, 0.18mmol), tetrakis(triphenyl phosphine)palladium(0)($Pd(PPh_3)_4$, 23㎎, 0.02mmol), copper(I) iodide(4mg, 0.02mmol) and *N,N*-diisopropylethylamine(38ul, 0.22mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-cyclopropylbenzoate(45.9mg, 43%).

[1432] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.97 (t, 1H), 7.69 (t, 1H), 7.43-7.38 (m, 4H), 7.36-7.31 (m, 1H), 6.87 (d, 1H), 6.69 (dd, 1H), 4.80 (s, 2H), 3.92 (s, 3H), 2.24-2.12 (m, 1H), 1.98-1.90 (m, 1H), 1.33-1.28 (m, 2H), 1.20-1.14 (m, 2H), 1.05-0.99 (m, 2H), 0.79-0.73 (m, 2H).

[1433]

[1434] Step 2 : Preparation of 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-

4-yl)methoxy)phenyl)ethynyl)-5-isopropylbenzoic acid; (I-66)

[1452]

[1453] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-isopropylbenzoate

[1454]

[1455] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(Example 5)(64.2mg, 0.15mmol) was reacted with methyl 3-iodo-5-isopropylbenzoate(46.6mg, 0.15mmol), tetrakis(triphenylphosphine) palladium(0)($Pd(PPh_3)_4$, 17.3mg, 0.02mmol), copper(I) iodide(2.9mg, 0.02mmol) and *N,N*-diisopropylethylamine(31.3ul, 0.18mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-isopropylbenzoate(76.3mg, 86%).

[1456] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.02 (t, 1H), 7.87 (t, 1H), 7.56 (t, 1H), 7.44-7.39 (m, 3H), 7.36-7.31 (m, 1H), 6.87 (d, 1H), 6.69 (dd, 1H), 4.82 (s, 2H), 3.92 (s, 3H), 3.00-2.91 (m, 1H), 2.20-2.12 (m, 1H), 1.32-1.29 (m, 2H), 1.28 (d, 6H), 1.21-1.14 (m, 2H).

[1457]

[1458] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-isopropylbenzoic acid

[1459]

[1460] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(76.3mg, 0.13mmol) was reacted with lithium hydroxide(53.8 mg, 1.3mmol) to afford the title compound(37mg, 50%).

[1461] ^{1}H-NMR (DMSO, 400MHz): δ 7.84 (d, 2H), 7.65-7.61 (m, 2H), 7.53-7.59 (m, 2H), 7.09 (d, 1H), 6.84 (dd, 1H), 4.89 (s, 2H), 3.06-2.96 (m, 1H), 1.23 (d, 6H), 1.21-1.17 (m, 2H), 1.17-1.15 (m, 2H).

[1462]

[1463] **<Example 67> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol- 4-yl)methoxy)phenyl)ethynyl)-5-iodobenzoic acid; (I-67)**

[1464]

[1465] Step 1 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-iodobenzoic acid

[1466]

[1467] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3- (2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-iodobenzoate (Step 2 of example 56)(108mg, 0.159mmol) was reacted with lithium hydroxide (66.7mg,

[1505] This compound was made using the procedure described for example 1(Step 1). Thus, 2,3-dichloro-4-iodophenol(0.5g, 1.73mmol) was reacted with tert-butyldimethylsilylchloride(TBSCl, 0.39g, 2.60mmol), imidazole(0.23g, 3.46mmol) to afford the intermediate compound tert-butyl(2,3-dichloro-4-iodophenoxy)dimethylsilane(0.61g, 88%).

[1506] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.42 (m, 1H), 6.42 (m, 1H), 0.96 (s, 9H), 0.16 (s, 6H).

[1507]

[1508] Step 2 : Preparation of tert-butyl(2,3-dichloro-4-((trimethylsilyl)ethynyl) phanoxy)dimethylsilane

[1509]

[1510] This compound was made using the procedure described for example 1(Step 2). Thus, this intermediate compound(Step 1)(0.61g, 1.52mmol) was reacted with bis(triphenylphosphine)palladium(II) dichloride(($PdCl_2(PPh_3)_2$, 106.68mg, 0.15mmol), Copper(I) iodide(29mg, 1.22mmol), triethylamine(0.42ml, 3.04mmol), and trimethylsilylacetylene(0.42ml, 3.04mmol), to afford the intermediate compound tert-butyl(2,3-dichloro-4-((trimethylsilyl) ethynyl)phanoxy)dimethylsilane(368.97mg, 65%).

[1511] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.42 (m, 1H), 6.42 (m, 1H), 0.96 (s, 9H), 0.25 (s, 9H), 0.16 (s, 6H).

[1512]

[1513] Step 3 : Preparation of 2,3-dichloro-4-((trimethylsilyl)ethynylphenol

[1514]

[1515] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2)(368.97mg, 0.99mmol)was reacted with Potassium fluoride(KF, 574mg, 9.9mmol) to afford the intermediate compound 2,3-dichloro-4-((trimethylsilyl)ethynylphenol(185mg, 45%) and used directly for the next step without further purification.

[1516]

[1517] Step 4 : Preparation of 5-cyclopropyl-4-((2,3-dichloro-4-ethynylphenoxy) methyl)-3-(2,6-duchlorophenyl)isoxazole

[1518]

[1519] This compound was made using the procedure described for example 1(Step 4). Thus, this intermediate compound(Step 3)(256.6mg, 0.99mmol) was reacted with 4-(bromomethyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole(Intermediate 1)(343.6mg, 0.99mmol) and potassium carbonate(205.2mg, 1.49mmol) to afford the intermediate compound 5-cyclopropyl-4-((2,3-dichloro-4-ethynylphenoxy) methyl)-3-(2,6-duchlorophenyl)isoxazole(345.4mg, 77%).

[1520] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.30 (m, 3H), 6.83 (d, 1H), 6.66 (dd, 1H), 4.80 (s, 2H), 3.26 (s, 1H), 2.17-2.10 (m, 1H), 1.31-1.27 (m, 2H), 1.23-1.17 (m, 2H).

[1521]

[1522] Step 5 : Preparation of methyl 3-((2,3-dichloro-4-((5-cyclopropyl-3- (2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[1523]

[1524] This compound was made using the procedure described for example 1(Step 5). Thus, this intermediate compound(Step 4)(345.4mg, 0.762mmol) was reacted with methyl 3-bromobenzoate(163.9 mg, 0.762mmol), bis(triphenylphosphine)palladium(II) dichloride(($PdCl_2(PPh_3)_2$, 49mg, 0.07mmol), Copper(I) iodide(7mg, 0.035mmol) and 1,8-Diazabicyclo[5.4.0]undec -7-ene(DBU, 0.16ml, 1.05mmol) to afford the intermediate compound methyl 3-((2,3-dichloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl) methoxy)phenyl)ethynyl)benzoate (232.7mg, 52%).

[1525] ^{1}H-NMR (DMSO, 400MHz): δ 8.06 (t, 1H), 8.03-7.78 (m, 2H), 7.96-7.53 (m, 5H), 7.27 (d, 1H), 5.15 (s, 2H), 3.89 (s, 3H), 1.28-1.13 (m, 5H).

[1526]

[1527] Step 6 : Preparation of 3-((2,3-dichloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid

[1528]

[1529] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 5)(232.7mg, 0.40mmol) was reacted with lithium hydroxide(167.8mg, 4mmol) to afford the title compound(133mg, 58%).

[1530] ^{1}H-NMR (DMSO, 400MHz): δ 8.05 (t, 1H), 7.99 (d, 1H), 7.79 (d, 1H), 7.67-7.53 (m, 5H), 7.26 (d, 1H), 5.14 (s, 2H), 1.12-1.26 (m, 5H).

[1531]

[1532] **<Example 70> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazole-4-yl)methoxy)-6-fluorophenyl)ethynyl)benzoic acid (I-70)**

[1533]

[1534] Step 1 : Preparation of tert-butyl(3-chloro-5-fluoro-4-iodophenoxy)dimethyl silane

[1535]

[1536] This compound was made using the procedure described for example 1(Step 1). Thus, 3-chloro-5-fluoro-4-iodophenol(0.5g, 1.84mmol) was reacted with tert-butyldimethylsilyl chloride(TBSCl, 0.39g, 2.60mmol), imidazole(0.23g, 3.46mmol) to afford the intermediate compound tert-butyl(3-chloro-5- fluoro-4-iodophenoxy)dimethylsilane(0.54g, 76%).

[1537] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.69 (d, 1H), 6.97 (d, 1H), 0.96 (s, 9H), 0.16 (s, 6H).

[1538]

[1539] Step 2 : Preparation of tert-butyl(3-chloro-5-fluoro-4-((trimethylsilyl)ethynyl)phenoxy))dimethylsilane

[1540] This compound was made using the procedure described for example 1(Step 2). Thus, this intermediate compound(Step 1)(0.54g, 1.40mmol)was reacted with

bis(triphenylphosphine)palladium(II)dichloride(($PdCl_2(PPh_3)_2$, 106.68mg, 0.14 mmol), copper(I) iodide (29mg, 0.14mmol), triethylamine(0.42ml, 3.04mmol) and trimethylsilylacetylene (0.42ml, 3.04mmol) to afford the intermediate compound tert-butyl(3-chloro-5-fluoro-4- ((trimethylsilyl)ethylnyl)phenoxy)dimethylsilane(239.91mg, 48%).

[1541] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.69 (d, 1H), 6.97 (d, 1H), 0.96 (s, 9H), 0.25 (s, 9H), 0.16 (s, 6H).

[1542]

[1543] Step 3 : Preparation of 3-chloro-5-fluoro-4-((trimethylsilyl)ethylnyl)phenol

[1544]

[1545] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2)(239.91mg, 0.67mmol) was reacted with Potassium fluoride(390mg, 6.7mmol) to afford the intermediate compound 3-chloro-5-fluoro-4-((trimethylsilyl)ethylnyl)phenol without further purification.

[1546]

[1547] Step 4 : Preparation of 4-((3-chloro-4-ethynyl-5-fluorophenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole

[1548]

[1549] This compound was made using the procedure described for example 1(Step 4). Thus, this intermediate compound(Step 3)(162.6mg, 0.67mmol) was reacted with 4-(bromomethyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole(Intermediate 1)(232.5mg, 0.67mmol), potassium carbonate(138.90mg, 1.01mmol) to afford the intermediate compound 4-((3-chloro-4-ethynyl-5-fluorophenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole(210.7mg, 72%).

[1550] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.30 (m, 3H), 6.83 (d, 1H), 6.66 (dd, 1H), 4.80 (s, 2H), 3.26 (s, 1H), 2.17-2.10 (m, 1H), 1.31-1.27 (m, 2H), 1.23-1.17 (m, 2H).

[1551]

[1552] Step 5 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole-4-yl)methoxy)-6-fluorophenyl)ethynyl)benzoate

[1553]

[1554] This compound was made using the procedure described for example 1(Step 5). Thus, this intermediate compound(Step 4)(210.7mg, 0.48mmol) was reacted with methyl 3-bromobenzoate(103.2 mg, 0.48mmol), bis(triphenylphosphine)palladium(II) dichloride(($PdCl_2(PPh_3)_2$, 35mg, 0.05mmol), copper(I) iodide(9.5mg, 0.05mmol), 1,8-Diazabicyclo(5.4.0)undec-7-ene(DBU, 0.36ml, 2.4mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole-4-yl)methoxy)-6-fluorophenyl)ethynyl)benzoate(131.5mg, 48%).

[1555] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.21 (t, 1H), 8.02-7.99 (m, 1H), 7.73-7.71 (m, 1H),

methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzoate (62mg, 62%).

[1572] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.42-7.31 (m, 5H), 6.97 (d, 1H), 6.86 (d, 1H), 6.68 (dd, 1H), 4.81 (s, 2H), 3.89 (s, 3H), 3.76 (s, 2H), 2.35 (s, 3H), 2.17-2.13 (m, 1H), 1.32-1.28 (m, 2H), 1.19-1.15 (m, 2H).

[1573]

[1574] Step 3 : Preparation of 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzoic acid

[1575]

[1576] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound(Step 2)(62mg, 0.106mmol) was reacted with lithium hydroxide(44mg, 1.06mmol) to afford the title compound (53mg, 88%).

[1577] ^{1}H-NMR (DMSO, 400MHz): δ 7.64-7.62 (m, 2H), 7.57-7.48 (m, 2H), 7.06 (dd, 2H), 6.92 (d, 1H), 6.82 (dd, 1H), 5.28 (s, 2H), 4.97 (s, 2H), 2.47 (m, 1H), 2.21 (s, 3H), 1.21-1.19 (m, 2H), 1.14-1.13 (m, 2H).

[1578]

[1579] **<Example 72> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol- 4-yl)methoxy)phenyl)ethynyl)-5-(3-ethylureido) benzoic acid; (I-72)**

[1580]

[1581] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(3-ethylureido) benzoate

[1582]

[1583] The intermediate compound methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(150mg, 0.264mmol) was dissolved in dichlromethane(3ml) and ethylisocyanite(31ul, 0.396mmol) was added. The reaction was stirred at room temperature for 1day. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(3-ethylureido) benzoate(117mg, 69%).

[1584] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.95 (t, 1H), 7.86 (t, 1H), 7.79 (t, 1H), 7.44-7.38 (m, 2H), 7.36-7.30 (m, 2H), 6.85 (d, 1H), 6.67 (dd, 1H), 5.41 (s, 2H), 4.82 (s, 2H), 3.89 (s, 3H), 3.74 (q, 1H), 2.19-2.10 (m, 1 H), 1.24-1.20 (m, 3H), 1.15-1.11 (m, 4H).

[1585]

[1586] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(3-ethylureido) benzoic acid

[1587]

[1588] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound(Step 1)(105mg, 0.165mmol) was reacted with lithium hydroxide(58mg, 1.65mmol) to afford the title compound(20.6mg, 20%).

[1589] ^{1}H-NMR (DMSO, 400MHz): δ 13.12 (br, 1H), 8.82 (s, 1H), 7.93 (s, 1H), 7.88 (s, 1H), 7.64-7.62 (m, 2H), 7.57-7.55 (m, 2H), 7.09 (d, 1H), 6.84 (dd, 1H), 4.99 (s, 2H), 3.11 (s, 2H), 1.24-1.15 (m, 5H), 1.07-1.04 (q, 3H).

[1590]

[1591] **<Example 73> 3-acetamido-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-73)**

[1592]

[1593] Step 1 : Preparation of methyl 3-acetamido-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[1594]

[1595] The intermediate compound methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl- 3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(100mg, 0.176mmol) was dissolved in *N*,*N*-dimethylform amide(1.7ml) and acetylchloride(26ul, 0.264mmol) and triethylamine(55ul, 0.264mmol) were added. The reaction was stirred at room temperature for 1day. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to afford the intermediate compound methyl 3-acetamido-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(44mg, 41%).

[1596] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.23 (t, 1H), 7.91 (dd, 1H), 7.50-7.40 (m, 2H), 7.38-7.32(m, 2H), 6.88 (d, 1H), 6.69 (dd, 1H), 4.82 (s, 2H), 4.27 (q, 1H), 4.26 (q, 2H), 3.94 (s, 3H), 2.31 (s, 3H), 2.19-2.12 (m, 1 H), 1.33-1.24 (m, 2H), 1.23-1.14 (m, 2H).

[1597]

[1598] Step 2 : Preparation of 3-acetamido-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid

[1599]

[1600] The intermediate compound(Step 1) was dissolved in 1,4-dioxane(1.0ml)/ water (0.14ml) and lithium hydroxide(58mg, 0.716mmol) was added. The reaction was stirred at room temperature for 18 hours. The pH of reaction mixture was adjusted 4 to 5 with 1N solution of hydrochloric acid and the reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated to afford the title compound(18.0mg, 42%).

[1601] ^{1}H-NMR (DMSO, 400MHz): δ 13.45 (br, 1H), 10.25 (br, 1H), 8.15 (s, 1H), 8.04 (s, 1H), 7.68 (s, 1H), 7.64-7.20 (m, 2H), 7.58-7.54 (m, 2H), 7.09 (d, 1H), 6.84 (dd, 1H), 4.99 (s, 2H), 2.07(s, 3H), 1.21-1.14 (m, 5H).

[1602]

[1603] **<Example 74> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoic acid; (I-74)**

[1604]

[1605] Step 1 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoic acid

[1606]

[1607] This compound was made using the procedure described for example 1(Step 6). Thus, methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate(Example 8)(55.1mg, 0.086mmol) was reacted with lithium hydroxide(36.1mg, 0.86mmol) to afford the title compound(45.2mg, 84%).

[1608] ^{1}H-NMR (DMSO, 400MHz): δ 13.55 (br, 1H), 9.98 (s, 1H), 8.09 (s, 1H), 7.87 (s, 1H), 7.64-7.62 (m, 3H), 7.58-7.54 (m, 1H), 7.09 (d, 1H), 6.69 (dd, 1H), 4.82 (s, 2H), 4.16 (q, 2H), 1.25(t, 3H), 1.21-1.14 (m, 5H).

[1609]

[1610] **<Example 75> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoic acid; (I-75)**

[1611]

[1612] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate

[1613]

[1614] This compound was made using the procedure described for example 10(Step 1). Thus, methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol- 4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate(Example 8) (50mg, 0.078mmol) was reacted with sodium hydride(5.6mg, 0.234mmol) and iodomethane(6ul, 0.093mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoate(35mg, 69%).

[1615] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.02 (t, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 7.42-7.38 (m, 1H), 7.35-7.31 (m, 1H), 6.87 (d, 1H), 6.70 (dd, 1H), 4.82 (s, 2H), 4.22 (q, 2H), 3.93 (s, 3H), 3.32(s, 3H), 2.17-2.13 (m, 1 H), 1.34(t, 3H), 1.32-1.24 (m, 2H), 1.23-1.14 (m, 2H).

[1616]

[1617] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoic acid

3H), 7.59-7.54 (m, 2H), 7.10 (m, 1H), 6.85-6.82 (m, 1H), 5.02 (s, 2H), 4.09(m, 1H), 1.23-1.14 (m, 6H), 0.72-0.70 (m, 4H).

[1633]

[1634] **<Example 77> 3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl -3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-77)**

[1635]

[1636] Step 1 : Preparation of 3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid

[1637]

[1638] This compound was made using the procedure described for example 1(Step 6). Thus, methyl 3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl -3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Example 9)(300mg, 0.449mmol) was reacted with lithium hydroxide(188mg, 4.49mmol) to afford the title compound(227mg, 77%).

[1639] ^{1}H-NMR (DMSO, 400MHz): δ 13.27 (br, 1H), 8.10(t, 1H), 7.84 (t, 1H), 7.64-7.60 (m, 3H), 7.57-7.56 (m, 2H), 7.09 (d, 1H), 6.84 (dd, 1H), 4.99 (s, 2H), 1.49 (s, 9H), 1.19-1.14 (m, 5H).

[1640]

[1641] **<Example 78> 3-((tert-butoxycarbonyl)(methyl)amino)-5-((2-chloro-4-((5-cyclo propyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-78)**

[1642]

[1643] Step 1 : Preparation of methyl 3-((tert-butoxycarbonyl)(methyl)amino)-5- ((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[1644]

[1645] This compound was made using the procedure described for example 10(Step 1). Thus, methyl 3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(example 9)(220mg, 0.329mmol) was reacted with sodium hydride(24mg, 0.988mmol) and iodomethane(87ul, 1.31mmol) to afford the intermediate compound methyl 3-((tert-butoxycarbonyl)(methyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(102mg, 45%).

[1646] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.98 (t, 1H), 7.88 (t, 1H), 7.60 (s, 1H), 7.42-7.39 (m, 3H), 7.35-7.31 (m, 1H), 6.87 (d, 1H), 6.70 (dd, 1H), 4.82 (s, 2H), 3.93 (s, 3H), 3.29 (s, 3H), 2.17 (m, 1H), 1.46(s, 9H), 1.32 1.24 (m, 2H), 1.19-1.15 (m, 2H).

[1647]

[1648] Step 2 : Preparation of 3-((tert-butoxycarbonyl)(methyl)amino)-5-((2-chloro- 4-((5-cy-

1.13-1.04 (m, 4H), 0.46 (m, 2H), 0.22 (m, 2H).

[1664]

[1665] **<Example 80> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-cyclopropylethoxy)carbonyl)amino)benzoic acid; (I-80)**

[1666]

[1667] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-cyclopropylethoxy)carbonyl)amino)benzoate

[1668]

[1669] This compound was made using the procedure described for example 76(Step 1). Thus, 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(150mg, 0.264mmol), 1,1'-carbonyldiimidazole(47mg, 0.29mmol) and cyclopropylethyl alcohol(43mg, 0.5mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy) phenyl)ethynyl)-5-(((2-cyclopropylethoxy)carbonyl)amino)benzoate(30mg, 17%)).

[1670] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.92 (s, 1H), 7.89 (s, 2H), 7.44-7.32 (m, 4H), 6.87 (m, 1H), 6.70 (m, 1H), 4.82 (s, 2H), 4.27 (m, 2H), 3.92 (s, 3H), 2.17 (m, 1H), 1.60 (m, 2H), 1.33-1.16 (m, 4H), 0.76 (m, 1H), 0.49 (m, 2H), 0.11 (m, 2H).

[1671]

[1672] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-cyclopropylethoxy)carbonyl)amino)benzoic acid

[1673]

[1674] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(30mg, 0.044mmol) was reacted with lithium hydroxide(50mg, 1.2mmol) to afford the title compound(13mg, 44%).

[1675] ^{1}H-NMR (DMSO, 400MHz): δ 9.84 (s, 1H), 7.96 (s, 1H), 7.75 (s, 1H), 7.52 (m, 3H), 7.45 (d, 2H), 6.98 (d, 1H), 6.72 (dd, 1H), 5.64 (s, 2H), 4.87 (s, 2H), 4.06(m, 2H), 1.43 (m, 2H), 0.74-0.65 (m, 4H), 0.30 (m, 2H), 0.01 (m, 2H).

[1676]

[1677] **<Example 81> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-hydroxyethoxy)carbonyl)amino)benzoic acid; (I-81)**

[1678]

[1679]Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-hydroxyethoxy)carbonyl)amino)benzoate

[1680]

[1681] This compound was made using the procedure described for example 78(Step 1). Thus, methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(70mg, 0.123mmol), 1,1'-carbonyldiimidazole(22mg, 0.136mmol) and ethylene glycol (13.6ul, 0.24mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-hydroxyethoxy)carbonyl)amino)benzoate(20mg, 25%)).

[1682] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.94 (m, 1H), 7.90 (m, 1H), 7.42-7.32 (m, 4H), 7.00 (s, 1H), 6.87 (d, 1H), 6.69 (dd, 1H), 4.82 (s, 2H), 4.53 (m, 3H), 4.35 (m, 1H), 3.92 (s, 3H), 2.17 (m, 1H), 1.32-1.16 (m, 4H).

[1683]

[1684] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-hydroxyethoxy)carbonyl)amino)benzoic acid

[1685]

[1686] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(20mg, 0.03mmol) was reacted with lithium hydroxide(50mg, 1.2mmol) to afford the title compound(11mg, 57%).

[1687] ^{1}H-NMR (DMSO, 400MHz): δ 9.93 (s, 1H), 8.03 (s, 1H), 7.78 (s, 1H), 7.64 (m, 3H), 7.54 (m, 2H), 7.09 (d, 1H), 6.83 (dd, 1H), 4.98 (s, 2H), 4.12 (t, 2H), 3.63 (m, 2H), 1.23-1.14 (m, 5H).

[1688]

[1689] **<Example 82> 3-(((azetidin-3-yloxy)carbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-82)**

[1690]

[1691] Step 1 : Preparation of tert-butyl-3-(((3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl-ethynyl)-5-(methoxycarbonyl)phenyl)carbamoyl)oxy)azetidine-1-carboxylate

[1692]

[1693] This compound was made using the procedure described for example 78(Step 1). Thus, methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(170mg, 0.30mmol), tert-butyl 3-hydroxyazetidine -1-carboxylate(120mg, 0.69mmol), N,N-diisopropylethylamine(0.19ml, 1.04mmol) and triphosgene(72mg, 0.24mmol) to afford the intermediate compound tert-butyl-3-(((3-((2-chloro-4-((5- cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl-ethynyl)-5-(methoxycarbonyl)phenyl)carbamoyl)oxy)azetidine-1-carboxylate(80mg, 35%).

[1694] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.94 (m, 2H), 7.86 (s, 1H), 7.43-7.32 (m, 3H), 6.94 (s, 1H), 6.87 (m, 1H), 6.69 (dd, 1H), 5.23 (m, 1H), 4.82 (s, 2H), 4.29 (m, 2H), 3.98 (m, 2H), 3.93 (s, 3H), 2.16 (m, 1H), 1.56 (m, 9H), 1.45-1.15 (m, 4H).

[1695]

[1696] Step 2 : Preparation of 3-(((azetidin-3-yloxy)carbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid

[1697]

[1698] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(30mg, 0.04mmol) was reacted with lithium hydroxide(19mg, 0.46mmol) to afford the title compound(12mg, 61%).

[1699] ^{1}H-NMR (DMSO, 400MHz): δ 13.28 (s, 1H), 10.08 (s, 1H), 8.10 (s, 1H), 7.87 (s, 1H), 7.64 (m, 3H), 7.55 (m, 2H), 7.10 (m, 1H), 6.84 (dd, 1H), 4.99 (s, 2H), 3.95 (d, 2H), 1.24-1.19 (m, 7H), 0.57 (m, 2H), 0.35 (m, 2H).

[1700]

[1701] **<Example 83> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(2-oxooxazolidin-3-yl)benzoic acid; (I-83)**

[1702]

[1703] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(2-oxooxazolidin-3- yl)benzoate

[1704]

[1705] The intermediate compound methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(100mg, 0.176mmol) was dissolved in acetonitrile(2ml) and 2-chlroroethylchloroformate(27.3ul, 0.264mmol) and potassium carbonate (36.5mg, 0.264mmol) was added. The reaction was heated at 80℃for 4 hours. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol -4-yl)methoxy)phenyl)ethynyl)-5-(2-oxooxazolidin-3-yl)benzoate(73mg, 65%).

[1706] H-NMR ($CDCl_3$, 400MHz): δ 8.01 (t, 1H), 7.97 (t, 1H), 7.95 (t, 1H), 7.42-7.40 (m, 3H), 7.35-7.31 (m, 1H), 6.87 (d, 1H), 6.70 (dd, 1H), 4.82 (s, 2H), 4.54 (q, 2H), 4.14 (q, 2H), 3.91 (s, 3H), 2.19 (m, 1H) 1.31-1.27 (m, 2H), 1.201.16 (m, 2H).

[1707]

[1708] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(2-oxooxazolidin-3-yl)benzoic acid

[1709]

[1710] This compound was made using the procedure described for example 1(Step 6).

Thus, the intermediate compound(Step 1)(65mg, 0.101mmol) was reacted with lithium hydroxide(43mg, 1.019mmol) to afford the title compound(21mg, 33%).

[1711] ^{1}H-NMR (DMSO, 400MHz): δ 13.45 (br, 1H), 8.16 (s, 1H), 7.89 (s, 1H), 7.76 (s, 1H), 7.64-7.62 (m, 2H), 7.59-7.53 (m, 2H), 7.10 (d, 1H), 6.85 (dd, 1H), 4.99 (s, 2H), 4.48 (q, 2H), 4.16 (q, 2H), 1.24-1.13 (m, 5H).

[1712]

[1713] **<Example 84> 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)isophthalic acid; (I-84)**

[1714]

[1715] Step 1 : Preparation of dimethyl 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)isophthalate

[1716]

[1717] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(example 5)(196.2mg, 0.47mmol) was reacted with dimethyl 5-iodoisophthalate(150mg, 0.47mmol), tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$, 54.3mg, 0.05mmol), copper(I) iodide(10mg, 0.05mmol) and *N,N*-diisopropylethylamine(0.1ml, 0.56mmol) to afford the intermediate compound dimethyl 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl) methoxy)phenyl)ethynyl)isophthalate(278mg, 97%).

[1718] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.64 (t, 1H), 8.37 (d, 1H), 7.41-7.50 (m, 2H), 7.32-7.40 (m, 3H), 6.90 (d, 1H), 6.73 (d, 1H), 4.85 (s, 2H), 3.98 (s, 6H), 2.13-2.23 (m, 1H), 1.30-1.37 (m, 2H), 1.16-1.24 (m, 2H).

[1719]

[1720] Step 2 : Preparation of 5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)metoxy)phenyl)ethynyl)isophthalic acid

[1721]

[1722] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(278mg, 0.46mmol) was reacted with lithium hydroxide(193mg, 4.6mmol) to afford the title compound(66.6mg, 71.5%).

[1723] ^{1}H-NMR (MeOD, 400MHz): δ 8.61 (t, 1H), 8.30 (d, 2H), 7.55 (d, 1H), 7.53 (d, 1H), 7.50 (d, 1H), 7.48 (d, 1H), 6.96 (d, 1H), 6.80 (d, 1H), 4.97 (s, 2H), 2.33-2.42 (m, 1H), 1.21-1.27 (m, 4H).

[1724]

[1725] **<Example 85> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(piperazine-1-carbonyl)benzoic acid hydrochloride; (I-85)**

[1726]

[1727] Step 1 : Preparation of tert-butyl 4-(3-((2-chloro-4-((5-cyclopropyl-3-(2,6-

dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate

[1728]

[1729] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichloro phenyl)isoxazole(example 5)(115mg, 0.27mmol)was reacted with tert-butyl 4-(3-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate(130mg, 0.27mmol), tetrakis(triphenylphosphine)palladium(0)($Pd(PPh_3)_4$, 34.7mg, 0.03mmol), copper(I) iodide(5.7mg, 0.03mmol), *N,N*-diisopropylethyl amine(56.4ul, 0.32mmol) to afford the intermediate compound tert-butyl 4-(3-((2- chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate(88mg, 43%).

[1730] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.24 (s, 1H), 8.00 (s, 1H), 7.74 (s, 1H), 7.50-7.38(m, 3H), 7.35-7.31 (m, 1H), 6.88 (d, 1H), 6.70 (dd, 1H), 4.83 (s, 3H), 3.99 (s, 3H), 3.85-3.80 (m, 2H), 3.66-3.40(m, 6H), 2.21-2.12 (m, 1H), 1.48 (s, 9H), 1.38-1.32 (m, 2H), 1.20-1.12(m, 2H).

[1731]

[1732] Step 2 : Preparation of 3-(4-(tert-butoxycarbonyl)piperazine-1-carbonyl) -5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid

[1733]

[1734] This compound was made using the procedure described for example 1(Step 6). Thus, this intermediate compound(Step 1)(88mg, 0.12mmol) was reacted with lithium hydroxide(48.3mg, 1.2mmol) to afford the 3-(4-(tert-butoxycarbonyl) piperazine-1-carbonyl)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid(61mg, 67.7%).

[1735] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.28 (s, 1H), 8.05 (s, 1H), 7.79 (s, 1H), 7.45-7.33 (m, 3H), 7.31-7.28(m, 1H), 6.88 (s, 1H), 6.70 (dd, 1H), 4.83 (s, 2H), 3.90-3.82(m, 1H), 3.62-3.30 (m, 6H), 2.30-2.12 (m, 2H), 1.48 (s, 9H), 1.38-1.33 (m, 2H), 1.29-1.16 (m, 2H).

[1736]

[1737] Step 3 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(piperazine-1-carbonyl)benzoic acid hydrochloride

[1738]

[1739] This compound was made using the procedure described for example 57(step 3). Thus, this intermediate compound(Step 2)(61mg, 0.08mmol) was reacted with 5~6N HCl solution(48ul, 0.24mmol) to afford the title compound(35mg, 64%).

[1740] ^{1}H-NMR (DMSO, 400MHz): δ 13.56 (br, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.84 (s,

1H), 7.66-7.60 (m, 2H), 7.58-7.52 (m, 2H), 7.19 (s, 1H), 6.85 (dd, 1H), 4.99 (s, 2H), 3.82-3.74 (m, 3H), 3.42-3.34 (m, 2H), 3.21-3.10 (m, 4H), 1.31-1.19 (m, 4H).

[1741]

[1742] **<Example 86> 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylsulfonamido)benzoic acid; (I-86)**

[1743]

[1744] Step 1 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylsulfonamido)benzoate

[1745]

[1746] The intermediate compound methyl 3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(Step 2 of example 8)(150mg, 0.264mmol) was dissolved in dichloromethane(2ml) /*N,N*-dimethylformamide(1ml) and methylsulfonyl chloride(22.5ul, 0.290mmol) and 1,8-Diazobicyclo[5.4.0]undec-7-ene(DBU, 40ul, 0.264mmol) were added. The reaction was stirred at room temperature for 1day. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylsulfonamido)benzoate(74mg, 44%).

[1747] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.01 (t, 1H), 7.79 (t, 1H), 7.61 (t, 1H), 7.42-7.40 (m, 2H), 7.35-7.31 (m, 1H), 6.88 (d, 1H), 6.71 (dd, 1H), 6.56 (s, 1H), 4.82 (s, 2H), 3.94 (s, 3H), 2.19 (m, 1H) 1.05-1.32 (m, 4H).

[1748]

[1749] Step 2 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylsulfonamido)benzoic acid

[1750]

[1751] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound(step 1)(20mg, 0.031mmol) was reacted with lithium hydroxide(13mg, 0.31mmol) to afford the title compound(16mg, 85%).

[1752] ^{1}H-NMR (DMSO, 400MHz): δ 13.33 (br, 1H), 10.14 (s, 1H), 7.81(s, 1H), 7.73 (s, 1H), 7.64-7.61 (m, 2H), 7.59-7.57 (m, 1H), 7.53 (s, 1H), 7.10 (d, 1H), 6.85 (dd, 1H), 4.98 (s, 2H), 3.06 (s, 3H), 1.05-1.32 (m, 5H).

[1753]

[1754] **<Example 87> 3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid; (I-87)**

[1755]

[1756] Step 1 : Preparation of 2-(trifluoromethyl)benzoaldehyde oxime

[1757]

[1758] This compound was made using the procedure described for Intermediate 1(Step 1). Thus, 2-(trifluoromethyl)benzoaldehyde(11g, 160mmol) was reacted with sodium hydroxide(6.3g, 160mmol), 2,6-dichlorobenzoaldehyde(25g, 140mmol) to afford the intermediate compound 2-(trifluoromethyl)benzo aldehyde oxime(25.9g, 96%).

[1759] ^{1}H-NMR ($CDCl_3$, 400MHz): δ8.53-8.52 (t, 1H), 8.04-8.02 (d, 1H), 7.85 (s, 1H), 7.72-7.70 (d, 1H), 7.60-7.56 (t, 1H), 7.53-7.51 (d, 1H).

[1760]

[1761] Step 2 : Preparation of *N*-hydroxy-2-(trifluoromethyl)bezamidoyl chloride

[1762]

[1763] This compound was made using the procedure described for Intermediate1(Step 2). Thus, the intermediate compound(Step 1)(25.9g, 140mmol) was reacted with *N*-chloro succinimide(NCS, 18.4g, 140mmol) to afford *N*-hydroxy-2-(trifluoro methyl)bezamidoyl chloride(29g) and used without further purification.

[1764] ^{1}H-NMR ($CDCl_3$, 400MHz): δ8.57 (s, 1H), 7.77-7.75 (d, 1H), 7.67-7.58 (m, 3H).

[1765]

[1766] Step 3 : Preparation of ethyl 5-cyclopropyl-3-(2-(trifluoromethyl)phenyl) ioxazol-4-carboxylate

[1767]

[1768] This compound was made using the procedure described for Intermediate1(Step 3). Thus, the intermediate compound(Step 2)(29g, 129mmol) was reacted with ethyl 3-cyclopropyl-3-oxopropanoate(25ml, 194mmol) andtriethylamine(150ml) to afford the intermediate compound ethyl 5-cyclopropyl-3-(2-(trifluoromethyl) phenyl)ioxazol-4-carboxylate(22.37g, 56%).

[1769] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.80-7.78 (m, 1H), 7.66-7.62 (m, 2H), 7.42-7.40 (m, 1H), 3.64 (s, 3H), 2.07-2.03 (m, 1H), 1.16-1.12 (m, 2H), 1.01-0.97 (m, 2H).

[1770]

[1771] Step 4 : Preparation of (5-cyclopropyl-3-(2-(trifluoromethyl)phenyl)isoxazol -4-yl)methanol

[1772]

[1773] This compound was made using the procedure described for Intermediate 1(Step 4). Thus, the intermediate compound(Step 3)(22.37g, 71.7mmol) was reacted with 1M diisobutylaluminium hydride in THF (DIBAL-H, 144ml, 144mmol) to afford the intermediate compound (5-cyclopropyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanol(12.2g, 60%).

[1774] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.81-7.79 (m, 1H), 7.65-7.57 (m, 2H), 7.47-7.45 (m, 1H), 4.40 (s, 2H), 2.19-2.12 (m, 1H), 1.27-1.23 (m, 2H), 1.15-1.10 (m, 2H).

[1775]

[1776] Step 5 : Preparation of 4-(bromomethyl)-5-cyclopropyl-3-(2-(trifluoromethyl)

phenyl)ioxazole

[1777]

[1778] This compound was made using the procedure described for Intermediate 1(Step 5). Thus, the intermediate compound(Step 4)(12.2g, 43.02mmol) was reacted with triphenyl phosphite(TPP, 16.9g, 64.53mmol), tetrabromomethane(21.4g, 64.53mmol) to afford the intermediate compound 4-(bromomethyl)-5- cyclopropyl-3-(2-(trifluoromethyl)phenyl)ioxazole(13.44g, 90%).

[1779] ^{1}H-NMR ($CDCl_3$, 400MHz): δ7.83-7.81 (m, 1H), 7.68-7.62 (m, 2H), 7.55-7.53 (m, 1H), 4.20 (s, 2H), 2.12-2.08 (m, 1H), 1.30-1.25 (m, 2H), 1.24-1.18 (m, 2H).

[1780]

[1781] Step 6 : Preparation of 4-((3-chloro-4-ethynylphenoxy)methyl)- 5-cyclopropyl -3-(2-(trifluoromethyl)phenyl)ioxazole

[1782]

[1783] This compound was made using the procedure described for example 1(Step 4). Thus, the intermediate compound(Step 5)(7.59g, 21.9mmol) was reacted with 3-chloro-4-((trimethylsilyl)ethynyl)phenol(Step 3 of example 5)(4.92g, 21.9mmol), potassium carbonate(4.54g, 32.9mmol) to afford the intermediate compound 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2- (trifluoro methyl)phenyl)ioxazole(7.15g, 78%).

[1784] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.30 (m, 4H), 6.83 (d, 1H), 6.66 (dd, 1H), 4.80 (s, 2H), 3.26 (s, 1H), 2.17-2.10 (m, 1H), 1.31-1.27 (m, 2H), 1.23-1.17 (m, 2H).

[1785]

[1786] Step 7 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoro methyl)phenyl)ioxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[1787]

[1788] This compound was made using the procedure described for example 1(Step 5). Thus, the intermediate compound (Step 6)(128mg, 0.31mmol) was reacted with methyl 3-iodobenzoate(80mg, 0.31mmol), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 22mg, 0.03mmol), copper(I) iodide(5.8mg, 0.03mmol), triethylamine(0.052ml, 0.37mmol) to afford the intermediate compoundmethyl 3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoromethyl)phenyl)ioxazol-4-yl)methoxy)phenyl)ethynyl)benzoate(107mg, 63%).

4-carboxylate

[1809]

[1810] This compound was made using the procedure described for Intermediate 1(Step 3). Thus, the intermediate compound(Step 2)(29g, 129mmol) was reacted with ethyl 3-cyclopropyl-3-oxopropanoate(25ml, 194mmol) and triethylamine(150ml) to afford the intermediate compound 5-cyclopropyl-3-(2-(trifluoromethoxy) phenyl)isoxazol-4-carboxylate(22.37g, 56%).

[1811] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.54-7.48 (m, 2H), 7.41-7.33 (m, 2H), 3.77 (s, 3H), 2.05-2.01 (m, 1H), 1.14-1.10 (m, 2H), 0.99-0.94 (m, 2H).

[1812]

[1813] Step 4 : Preparation of (5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazol -4-yl)methanol

[1814] This compound was made using the procedure described for Intermediate 1(Step 4). Thus, the intermediate compound(Step 3)(22.37g, 71.7mmol) was reacted with 1M diisobutylaluminium hydride in THF(DIBAL-H, 144ml, 144mmol) to afford the intermediate compound (5-cyclopropyl-3-(2-(trifluoromethoxy) phenyl)isoxazol-4-yl)methanol(12.2g, 60%).

[1815] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.58-7.50 (m, 2H), 7.42-7.38 (m, 2H), 4.50 (s, 2H), 2.21-2.16 (m, 1H), 1.27-1.22 (m, 2H), 1.15-1.11 (m, 2H).

[1816]

[1817] Step 5 : Preparation of 4-(bromomethyl)-5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazole

[1818] This compound was made using the procedure described for Intermediate 1(Step 5). Thus, the intermediate compound(Step 4)(12.2g, 43.02mmol) was reacted with triphenyl phosphite(TPP, 16.9g, 64.53mmol), tetrabromomethane(21.4g, 64.53mmol) to afford the intermediate compound 4-(bromomethyl)-5- cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazole(13.44g, 90%).

[1819] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.60-7.53 (m, 2H), 7.45-7.40 (m, 2H), 4.33 (s, 2H), 2.15 (m, 1H), 1.29-1.26 (m, 2H), 1.25-1.20 (m, 2H).

[1820]

[1821] Step 6 : Preparation of 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl -3-(2-(trifluoromethoxy)phenyl)isoxazole

[1822]

[1823] This compound was made using the procedure described for example 1(Step 4). Thus, the intermediate compound(Step 5)(7.59g, 21.9mmol) was reacted with 3-chloro-4-((trimethylsilyl)ethynyl)phenol(Step 3 of Example 5)(4.92g, 21.9mmol) and potassium carbonate(4.54g, 32.9mmol) to afford the intermediate compound 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazole(7.15g, 78%).

[1824] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.30 (m, 4H), 6.83 (d, 1H), 6.66 (dd, 1H), 4.80 (s, 2H), 3.26 (s, 1H), 2.17-2.10 (m, 1H), 1.31-1.27 (m, 2H), 1.23-1.17 (m, 2H).

[1825]

[1826] Step 7 : Preparation of methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate

[1827]

[1828] This compound was made using the procedure described for example 1(Step 5). Thus, the intermediate compound (Step 6)(128mg, 0.31mmol) was reacted with methyl 3-iodobenzoate(80mg, 0.31mmol), bis(triphenylphosphine)palladium(II) dichloride($PdCl_2(PPh_3)_2$, 22mg, 0.03mmol), copper(I) iodide(5.8mg, 0.03mmol) and triethylamine(0.052ml, 0.37mmol) to afford the intermediate compound methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazol -4-yl)methoxy)phenyl)ethynyl)benzoate(107mg, 63%).

[1829] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.20 (s, 1H), 8.00-7.98 (m, 1H), 7.72-7.69 (m, 1H), 7.45-7.37 (m, 4H), 4.88 (s, 2H), 3.93 (s, 3H), 2.16-2.11 (m, 1H), 1.28-1.24 (m, 2H), 1.14-1.13 (m, 2H).

[1830]

[1831] Step 8 : Preparation of 3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoro methoxy)phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid

[1832]

[1833] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound(Step 7)(107mg, 0.20mmol) was reacted with lithium hydroxide(84mg, 2.0mmol) to afford the title compound(92.5mg, 86%).

[1834] ^{1}H-NMR (DMSO, 400MHz): δ 13.6 (s, 1H), 8.02 (s, 1H), 7.97-7.95 (d, 1H) 7.78-7.76 (d, 1H), 7.69-.51 (m, 6H), 7.15 (d, 1H), 6.90-6.88 (dd, 1H), 5.02 (s, 2H), 2.47-2.42 (m, 1H), 1.20-1.15 (m, 2H), 1.14-1.11 (m, 2H).

[1835]

[1836] **<Example 89> 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol -4-yl)methoxy)phenyl)ethynyl)-1*H*-indazole-6-carboxylic acid; (I-89)**

[1837]

[1838] Step 1 : Preparation of 1-(tert-butyl) 6-methyl 4-((2-chloro-4-((5-cyclopropyl -3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1*H*-indazole-1,6-dicarboxylate

[1839]

[1840] This compound was made using the procedure described for example 1(Step 5). Thus, 4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazole(Example 5)(176mg, 0.422mmol) was reacted with 1-(tert-butyl) 6-methyl 4-bromo-1*H*-indazole-1,6-dicarboxylate(100mg, 0.281mmol), copper(I) iodide(5.3mg, 0.028mmol) and bis(triphenylphosphine)palladium(II) dichloride($PdCl_2(PPh_3)_2$, 39.5g,

0.056mmol) to afford the intermediate compound 1-(tert-butyl) 6-methyl-4-((2-chloro-4- ((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl) ethynyl)-1*H*-indazole-1,6-dicarboxylate (107mg, 55%).

[1841] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.70 (s, 1H), 8.62 (s, 1H), 8.17-8.16 (d, 1H), 7.45-7.39 (m, 4H), 7.36-7.32 (m, 1H), 6.89 (d, 1H), 6.73-6.70 (dd, 1H), 4.83 (s, 2H), 4.04 (s, 3H), 2.19-2.13 (m, 1H), 1.74 (s, 9H), 1.33-1.29 (m, 2H), 1.20-1.18 (m, 2H).

[1842]

[1843] Step 2 : Preparation of methyl 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1*H*-indazole-6-carboxylate

[1844]

[1845] Trifluoroacetic acid(0.15ml) was added to a solution of intermediate compound(Step1)(98mg, 0.140mmol) in dichloromethane(3ml) and stirred for 3 days at room temperature. The reaction mixture was concentrated in vacuum, added ethyl acetate and washed with water. The combined organic layers were dried over $MgSO_4$, filtered, evaporated in vacuum and purified using silica chromatography to afford the intermediate compound methyl 4-((2-chloro-4- ((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1*H*-indazole-6-carboxylate (24mg, 28%).

[1846] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 10.47 (s, 1H), 8.59 (s, 1H), 8.08 (d, 1H), 7.87 (s, 1H), 7.45-7.40 (m, 3H), 7.35-7.31 (m, 1H), 6.89-6.88 (d, 1H), 6.72-6.69 (dd, 1H), 4.83 (s, 1H), 4.09 (s, 3H), 2.18-2.13 (m, 1H), 1.32-1.26 (m, 2H), 1.20-1.16 (m, 2H).

[1847]

[1848] Step 3 : Preparation of 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl) isoxazol-4-yl)methoxy)phenyl)ethynyl)-1*H*-indazole-6-carboxylic acid

[1849]

[1850] This compound was made using the procedure described for example 1(Step 6). Thus, the intermediate compound(Step 2)(24mg, 0.04mmol) was reacted with lithium hydroxide(17mg, 0.405mmol) to afford the title compound(20mg, 86%).

[1851] ^{1}H-NMR ($CDCl_3$, 400MHz): δ8.62 (s, 1H), 8.11 (s, 1H), 7.90 (s, 1H), 7.45-7.41 (m, 3H), 7.36-7.32 (m, 1H), 6.89-6.88 (d, 1H), 6.72-6.69 (dd, 1H), 4.83 (s, 2H), 2.02-2.12 (m, 1H), 1.32-1.19 (m, 4H).

[1852]

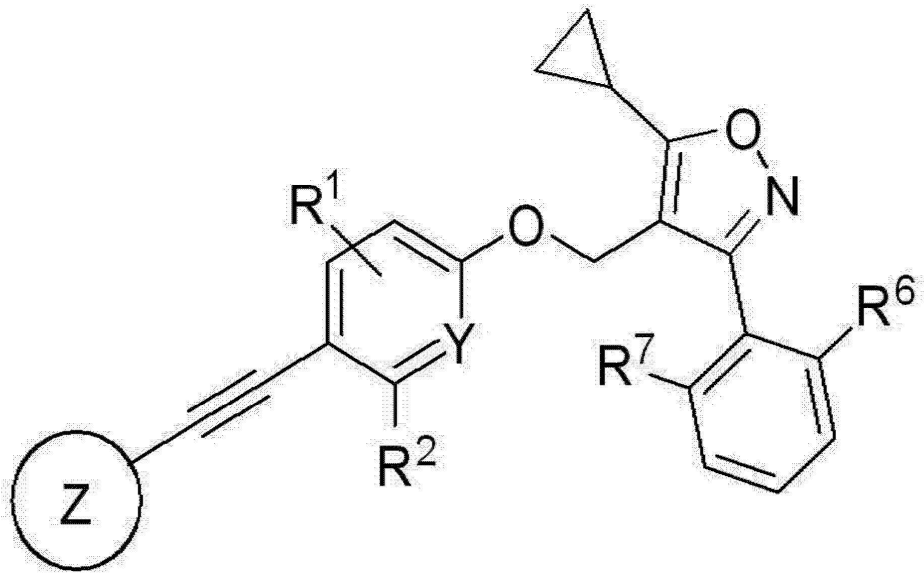
[1853] **<Example 90> 4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-benzo[d]imidazole-6-carboxylic acid; (I-90)**

【CLAIMS】

【Claim 1】

A compound represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

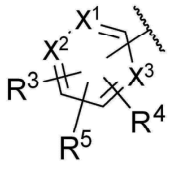
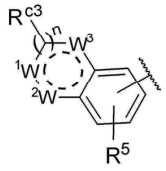
[Formula I]



In the present Formula I,

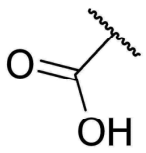
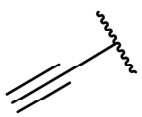
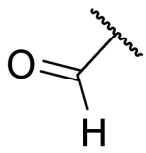
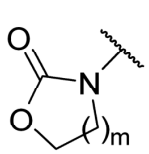
Y is carbon or nitrogen,

R^1 and R^2 are each independently hydrogen, halo or trifluoromethyl,

Z is  or ,

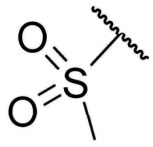
n is 0, 1 or 2,

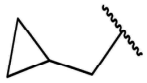
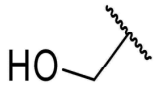
X^1, X^2 and X^3 are each independently carbon or nitrogen,

R^3 and R^4 are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl, , , , , $CONR^{a1}R^{a2}$, $NR^{a1}R^{a2}$, $CH_2NR^{a1}R^{a2}$, CH_2R^{c3}, COR^{a3}, OR^{a3}, $NR^{a4}COR^{a3}$, $NR^{a4}CO_2R^{a3}$,

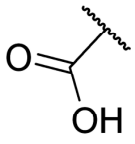
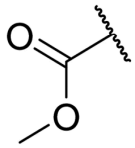
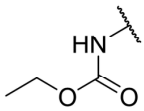
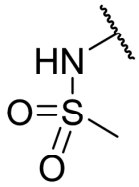
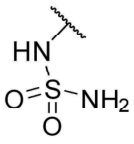
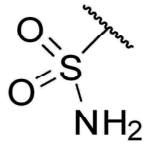
$NHCONHR^{a3}$, $NHSO_2R^{a3}$ or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

wherein, m is 1 or 2,

R^{a1} and R^{a2} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl,  or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

R^{a3} is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl, , ,  or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

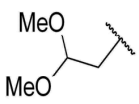
R^{a4} is hydrogen or C_{1-6} alkyl,

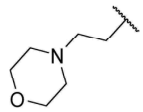
R^5 is hydrogen, , , , ,  or ,

R^6 and R^7 are each independently hydrogen, halo, trifluoromethyl or trifluoromethoxy,

R^{c3} is hydrogen, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl,

W^1, W^2 and W^3 are each independently oxygen, nitrogen, CHR^{w1}, CR^{w1}, NR^{w1} or CO,

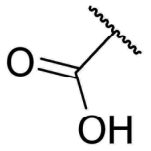
wherein, R^{w1} is hydrogen, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, halo C_{1-6} alkyl, C_{1-6} alkylamine, C_{1-6} alkyl alcohol, 

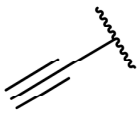
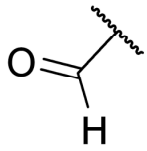
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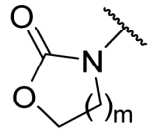
$(CH_2)_p$ heteroaryl or $(CH_2)_p$ aryl, wherein, p is 1, 2 or 3.

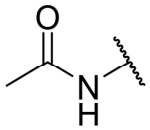
【Claim 2】

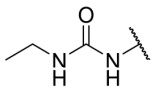
The compound according to claim 1,

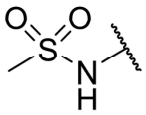
R^3 and R^4 are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, trifluoromethyl, 

, 
, 

, 

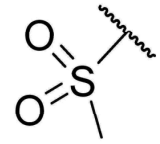
, $NR^{a1}R^{a2}$, $CH_2NR^{a1}R^{a2}$, OR^{a3}, 

, $NR^{a4}CO_2R^{a3}$, 

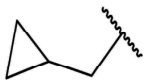
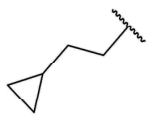
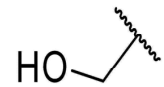
, 

or 3- or 8- membered heterocycles containing one or two oxygen or nitrogen atom(s) therein,

wherein, m is 1 or 2,

R^{a1} and R^{a2} are each independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, trifluoroethyl, 

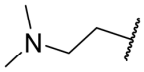
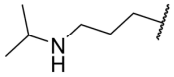
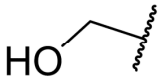
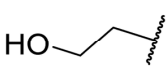
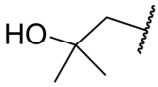
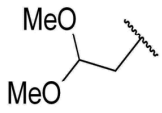
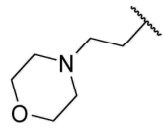
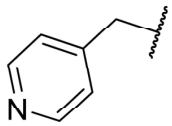
, azetidine or piperidine,

R^{a3} is hydrogen, methyl, ethyl, propyl, tert-butyl, cyclopropyl, trifluoromethyl, 
, 
, 

, azetidine, piperidine, piperazine or morpholine,

R^{a4} is hydrogen or methyl,

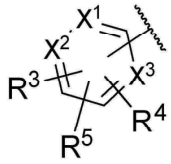
R^{c3} is hydrogen or methyl,

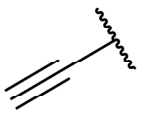
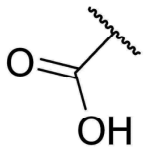
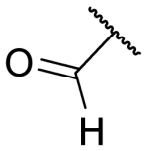
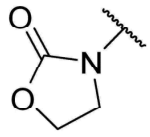
R^{w1} is hydrogen, methyl, ethyl, propyl, cyclopropyl, , , , , , ,  or , Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

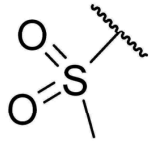
【Claim 3】

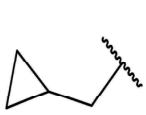
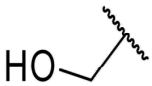
The compound according to claim 1,

R^1 and R^2 are each independently hydrogen, chloro or trifluoromethyl,

wherein, when the Z is ,

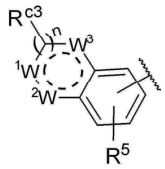
R^3 and R^4 are each independently hydrogen, chloro, fluoro, iodo, cyano, methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, , , , , $NR^{a1}R^{a2}$, $CH_2NR^{a1}R^{a2}$, $NR^{a4}CO_2R^{a3}$, azetidine, piperazine or pyrrolidine,

wherein, R^{a1} and R^{a2} are each independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, trifluoroethyl, , azetidine, piperidine or oxetane,

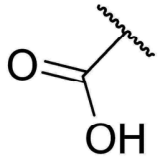
R^{a3} is hydrogen, methyl, ethyl, tert-butyl, cyclopropyl, trifluoromethyl, , , , azetidine, piperidine, piperazine or morpholine, R^{a4} is hydrogen, methyl or ethyl, Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

【Claim 4】

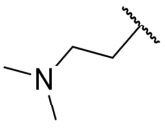
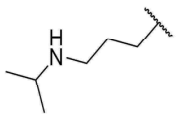
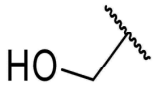
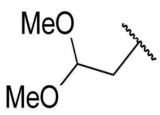
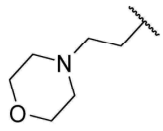
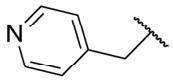
The compound according to claim 1, R^1 and R^2 are each independently hydrogen, chloro or fluoro,

wherein, when the Z is ,

n is 0 or 1,

R^5 is ,

W^1, W^2 and W^3 are each independently oxygen, nitrogen, CR^{w1} or NR^{w1},

wherein, R^{w1} is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, , , , , , or , Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

【Claim 5】

The compound according to claim 1, wherein, the compound represented by Formula I is selected from the group consisting of following compounds and by

Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof:

4-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-(trifluoromethyl)phenyl)ethynyl)benzoic acid;

4-((4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-(trifluoromethyl)phenyl)ethynyl)benzoic acid;

4-((3-chloro-4-ethynylphenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole;

4-((3-chloro-4-(phenylethynyl)phenoxy)methyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole;

methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate;

methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoate;

methyl 3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl- 3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoate;

methyl 3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoate;

ethyl (3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)phenyl)carbamate;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzenesulfonamide;

N-(3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)phenyl)methanesulfonamide;

N-(3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)phenyl)sulfamide;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)nicotinic acid;

2-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)isonicotinic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)picolinic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)nicotinic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(dimethylamino)benzoic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-3-(dimethylamino)benzoic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-(dimethylamino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(diethylamino)benzoic acid;

3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-(dimethylamino)benzoic acid;

3-chloro-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

4-chloro-3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

2-chloro-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-fluorobenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(trifluoromethyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-ethynylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-cyanobenzoic acid;

3-((2,6-dichloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

2-chloro-3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-fluorobenzoic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-fluorobenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-fluorobenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(trifluoromethoxy)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methoxybenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-formylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((cyclopropylamino)methyl)benzoic acid;

3-(azetidin-1-ylmethyl)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((methylamino)methyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethylamino)methyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2,2,2-trifluoroethyl)amino)methyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((isopropylamino)methyl)benzoic acid;

3-((tert-butylamino)methyl)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((dimethylamino)methyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(morpholinomethyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((oxetan-3-ylamino)methyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylamino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(ethylamino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(isopropylamino)benzoic acid;

3-(azetidin-1-yl)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(pyrrolidin-1-yl)benzoic acid;

3-(azetidin-3-ylamino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid hydrochloride;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(piperidin-4-ylamino)benzoic acid hydrochloride;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(piperazin-1-yl)benzoic acid hydrochloride;

3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-methylbenzoic acid;

3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-4-methoxybenzoic acid;

3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methoxybenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-methylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-cyclopropylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-ethylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-isopropylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-iodobenzoic acid;

3-((2,5-dichloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2,3-dichloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-6-fluorophenyl)ethynyl)benzoic acid;

3-amino-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(3-ethylureido)benzoic acid;

3-acetamido-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)amino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((ethoxycarbonyl)(methyl)amino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-((cyclopropoxycarbonyl)amino)benzoic acid;

3-((tert-butoxycarbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((tert-butoxycarbonyl)(methyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((cyclopropylmethoxy)carbonyl)amino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-cyclopropylethoxy)carbonyl)amino)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(((2-hydroxyethoxy)carbonyl)amino)benzoic acid;

3-(((azetidin-3-yloxy)carbonyl)amino)-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(2-oxooxazolidin-3-yl)benzoic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)isophthalic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(piperazine-1-carbonyl)benzoic acid hydrochloride;

3-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-5-(methylsulfonamido)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

3-((2-chloro-4-((5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzoic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-indazole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-benzo[d]imidazole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-indole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(2-(dimethylamino)ethyl)-1H-indole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(3-(isopropylamino)propyl)-1H-indole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(pyridin-4-ylmethyl)-1H-indole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(2-morpholinoethyl)-1H-indole-6-carboxylic acid hydrochloride;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(2,2-dimethoxyethyl)-1H-indole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(2-hydroxyethyl)-1H-indole-6-carboxylic acid;

4-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1-(2-hydroxy-2-methylpropyl)-1H-indole-6-carboxylic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-indazole-4-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2,3-dihydrobenzofuran-7-carboxylic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-1H-indole-4-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzo[d]oxazole-7-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzo[d]oxazole-7-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-ethylbenzo[d]oxazole-7-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-propylbenzo[d]oxazole-7-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-isopropylbenzo[d]oxazole-7-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-(hydroxymethyl)benzo[d]oxazole-7-carboxylic acid;

7-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)quinoxaline-5-carboxylic acid;

7-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2,3-dimethylquinoxaline-5-carboxylic acid;

5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-cyclopropylbenzo[d]oxazole-7-carboxylic acid;

2-butyl-5-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)benzo[d]oxazole-7-carboxylic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-methylbenzo[d]oxazole-4-carboxylic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-ethylbenzo[d]oxazole-4-carboxylic acid;

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-propylbenzo[d]oxazole-4-carboxylic acid; and

6-((2-chloro-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)phenyl)ethynyl)-2-isopropylbenzo[d]oxazole-4-carboxylic acid.

【Claim 6】

A pharmaceutical composition for the treatment, prevention, or amelioration of metabolic diseases, cholestatic Liver Diseases and Organ Fibrosis comprising the compound according to any one of claims 1-5 and represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

【Claim 7】

The pharmaceutical composition according to claim 6,

wherein, the metabolic diseases, cholestatic Liver Diseases and Organ Fibrosis are treated, prevented, or ameliorated by activation of FXR receptors.

【Claim 8】

The pharmaceutical composition according to claim 6,

wherein, the metabolic diseases, cholestatic Liver Diseases and Organ Fibrosis are selected from the group consisting of hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, cholestasis/fibrosis, cholesterol gallstone disease, gastrointestinal disease or condition, hyperglycemia, diabetes, insulin resistance, metabolic inflexibility, nephropathy, liver diseases, atherosclerosis, cancer, inflammatory disorders, osteoporosis and skin aging.